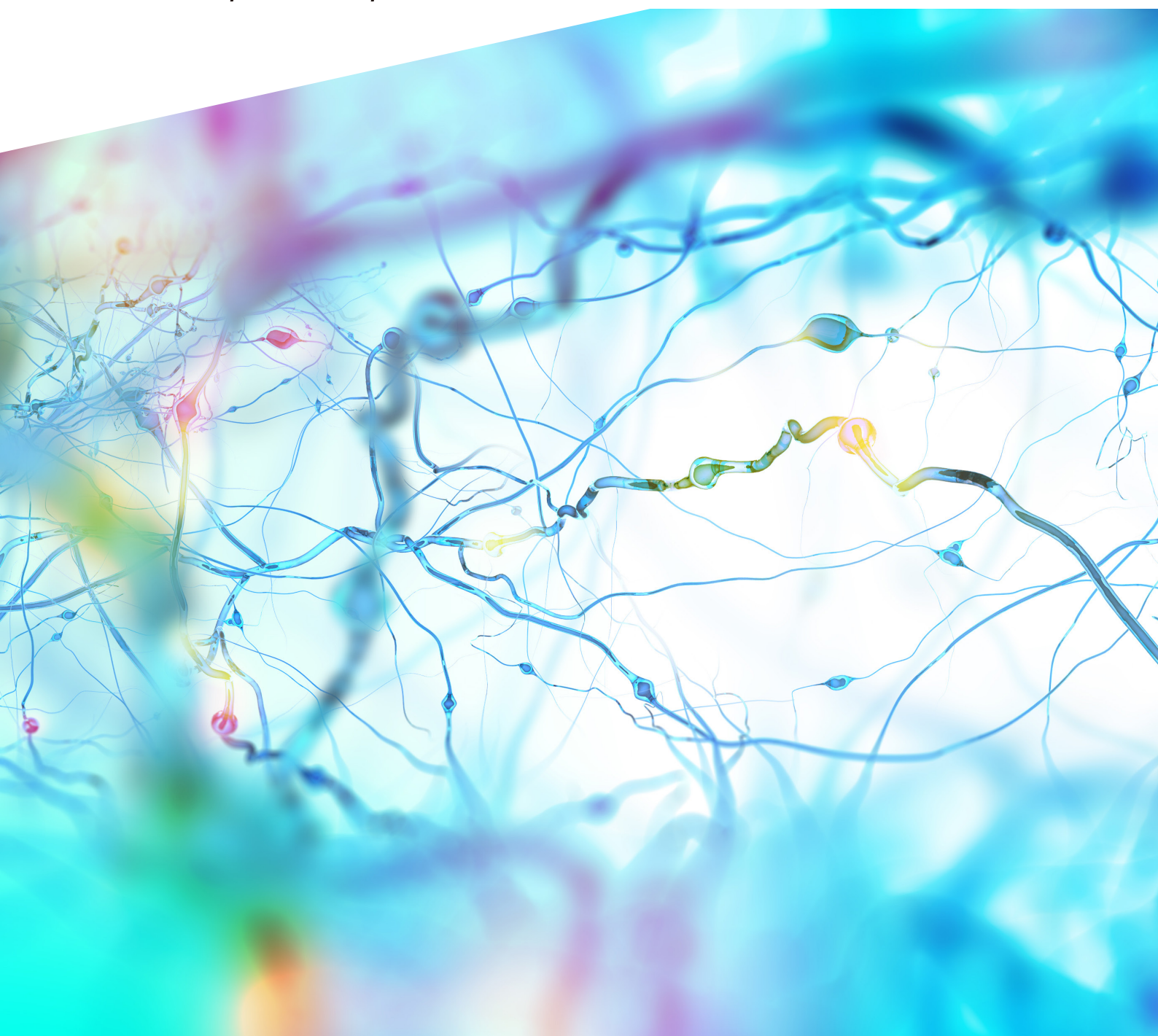




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The Ewha Medical Journal

Vol. 47, No. 4, 2024





Aims & Scope

Aims: The Ewha Medical Journal aims to provide medical professionals with essential healthcare information and fundamental medical knowledge. The journal will contribute to improving and serving human society based on the Christian values of education, truth, goodness, and beauty. Additionally, the journal strives to nurture young editors, enabling them to demonstrate exceptional women's editorial leadership and provide innovative learning methods.

Scope: Its scope includes:

Up-to-date medical knowledge and skills essential for patient care
Preparing for the future of medicine
Effective interprofessional communication
Ensuring gender equity and diversity
Medical education materials
Sharing data and protocols

Regional scope: The journal primarily focuses on Korea but welcomes submissions from researchers worldwide.

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Tel: 82-2-6986-6013, E-mail: mediewha@ewha.ac.kr, Homepage: <http://www.ewhamed.ac.kr>

Editorial office Ewha Medical Research Institute

25, Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea

Tel: 82-2-6986-6092, E-mail: E600091@ewha.ac.kr, Homepage: <http://www.e-emj.org>

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Editorial

Halted medical education in Korea amid Nobel Prizes in deep learning and machine learning research, tribute to a leader of Ewha Womans University College of Medicine, and highlights from this issue

Sun Huh

Obituary

Keun Lee (October 10, 1942 – May 14, 2024): a pioneering pediatrician in the field of developmental screening tests in Korea and a beloved teacher at Ewha Womans University College of Medicine

Su Jin Cho

Original Article

Standardization of the Denver Developmental Screening Test for children in Seoul: a validity study

Keun Lee

Special topic: cutting-edge technologies in radiation therapy

Editorial

Cutting-edge technologies in external radiation therapy

Jun Won Kim

Reviews

Clinical indications and future directions of carbon-ion radiotherapy: a narrative review

Seo Hee Choi, Woong Sub Koom, Hong In Yoon, Kyung Hwan Kim, Chan Woo Wee, Jaeho Cho, Yong Bae Kim, Ki Chang Keum, Ik Jae Lee

FLASH radiotherapy: bridging revolutionary mechanisms and clinical frontiers in cancer treatment – a narrative review

Jae Sik Kim, Hak Jae Kim

Challenges and opportunities to integrate artificial intelligence in radiation oncology: a narrative review

Chiyoung Jeong, YoungMoon Goh, Jungwon Kwak

Special topic: recent management strategies for liver cancer

Reviews

The histopathological and molecular heterogeneity of hepatocellular carcinoma: a narrative review

Wonju Chung, Haeryoung Kim

Pathogenesis and management of metabolic dysfunction-associated steatohepatitis-related hepatocellular carcinoma: a narrative review

Han Ah Lee

Imaging findings of intrahepatic cholangiocarcinoma for prognosis prediction and treatment decision-making: a narrative review

Jun Gu Kang, Taek Chung, Dong Kyu Kim, Hyungjin Rhee

Current perspectives on the pharmacological treatment of advanced hepatocellular carcinoma: a narrative review

Hye-Jin Yoo, Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

Reviews

Update on sexually transmitted infections in Korea: a narrative review

Chung-Jong Kim

Clinical outcomes and future directions of enhanced recovery after surgery in colorectal surgery: a narrative review

Ji Hyeong Song, Minsung Kim

Gender and healthcare issues related to the Protected Birth Act in Korea

Jiah Jeong

Original Articles

Exploration of the interaction between remote ischemic preconditioning and anesthetic-induced preconditioning using sevoflurane in isolated perfused rabbit heart

Seung-Hee Yoo, Sooyoung Cho, Yoonsun Won, Jong Wha Lee

Early detection of patients with narcotic use disorder using a modified morphine equivalent daily dose score based on an analysis of real-world prescription patterns: a retrospective cohort study

Yi-Jun Kim, Kye Hwa Lee

Reduced cardiovascular events through dynamic lifestyle modification in individuals with prediabetes or prehypertension in Korea: a nationwide cohort study

Yeji Kim, Shinjeong Song, Chang Mo Moon, Hye Ah Lee, Junbeom Park

Comparison of the long-term outcomes of cast immobilization methods in distal radius fractures: a systematic review of randomized controlled trials

Maria Florencia Deslivia, Claudia Santosa, Sherly Desnita Savio, Erica Kholinne, Made Bramantya Karna, Anak Agung Gde Yuda Asmara

Prevalence and associated factors of ADHD-like symptoms among pharmacy students at Prince of Songkla University, Thailand in 2024: a cross-sectional study

Krittiya Rakchat, Saranan Eadcharoen, Amarawan Pentrakan

Adequacy of the physician workforce for preparing for future society in Korea: an English translation

Yun-Chul Hong

맥커스커 주관적 인지 장애 검사(McSCI): 지각된 인지 저하의 새 측정 도구

The McCusker Subjective Cognitive Impairment Inventory (McSCI): a novel measure of perceived cognitive decline – a Korean translation

Hamid R. Sohrabi, Brandon E. Gavett, Michael Weinborn, Craig P. Speelman, Romola S. Bucks, Ralph N. Martins

Case Report

Septic cerebral embolism following lumbar spine surgery in a 69-year-old man with a lumbar epidural abscess in Korea: a case report

Yo Seob Lee

Correspondences

How should medical students and young physicians prepare to be National Assembly members in Korea?

Hyun-Yung Shin

Could I become a physician in the pharmaceutical industry?: practical insights from a 12-year veteran in pharma

Yoenjung Lee

The leitmotifs we shared

Minyoung Kim



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Guidelines

Clinical practice guidelines for the diagnosis and treatment of scabies in Korea: Part 1. Epidemiology, clinical manifestations, and diagnosis — a secondary publication

Jin Park, Soon-Hyo Kwon, Young Bok Lee, Hei Sung Kim, Jie Hyun Jeon, Gwang Seong Choi; on behalf of the Scabies Study Group of Korean Dermatological Association

Clinical practice guidelines for the diagnosis and treatment of scabies in Korea: Part 2. Treatment and prevention — a secondary publication

Jin Park, Soon-Hyo Kwon, Young Bok Lee, Hei Sung Kim, Jie Hyun Jeon, Gwang Seong Choi; on behalf of the Scabies Study Group of Korean Dermatological Association

의학학술지에 게재되는 학술 저작물의 생산, 보고, 편집 및 출판에 대한 권고안(2024년 1월 개정)

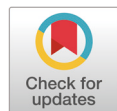
Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals (revised in January 2024): a Korean translation

국제의학학술지편집인위원회

International Committee of Medical Journal Editors



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Halted medical education in Korea amid Nobel Prizes in deep learning and machine learning research, tribute to a leader of Ewha Womans University College of Medicine, and highlights from this issue

Sun Huh 

Institute of Medical Education, Hallym University College of Medicine, Chuncheon, Korea



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Corresponding author

Sun Huh
Institute of Medical Education, Hallym
University College of Medicine, 1
Hallimdaehak-gil, Chuncheon 24252,
Korea
E-mail: shuh@hallym.ac.kr

Nobel Prizes awarded for machine learning and deep learning during a halt in Korean medical education

The Royal Swedish Academy of Sciences has awarded the 2024 Nobel Prize in Physics to John J. Hopfield of Princeton University, NJ, USA, and Geoffrey E. Hinton of the University of Toronto, Canada. They are recognized "for foundational discoveries and inventions that enable machine learning with artificial neural networks" [1]. Additionally, the Academy has bestowed the 2024 Nobel Prize in Chemistry upon David Baker of the University of Washington and the Howard Hughes Medical Institute, USA, "for computational protein design." The other half of the prize has been awarded jointly to Demis Hassabis and John M. Jumper of Google DeepMind, London, UK, "for protein structure prediction" [2].

Machine learning and deep learning are profoundly impacting individual lives and medical research. Modern technological systems, equipped with these capabilities, are increasingly being integrated into medical research, marking an inevitable trend. A search on PubMed using the terms "((artificial intelligence) OR (machine learning)) OR (deep learning) OR (deep neural network)" reveals a significant increase in related articles (Fig. 1).

Integrating machine learning and deep learning into medical education is now necessary. The National Health Insurance Service of Korea has already started to reimburse for radiology image classification tools that utilize deep learning [3]. This area is advancing rapidly through collaborations between medical faculty and venture companies in Korea. Thus, it is crucial to incorporate machine learning and deep learning into medical curricula. Many Korean medical schools have already begun to introduce these topics. However, since the start of the new semester in March, medical education—including resident training in hospitals—has been disrupted due to the Korean government's policy to increase medical school admissions by 2,000 slots. As a result, most medical students are currently not attending classes, and numerous residents have resigned from their positions [4]. It is regrettable that education, particularly at a time when machine learning and deep learning are increasingly important, is being interrupted. I hope we can soon find a way through this tragic situation, but resolving the ongoing conflict

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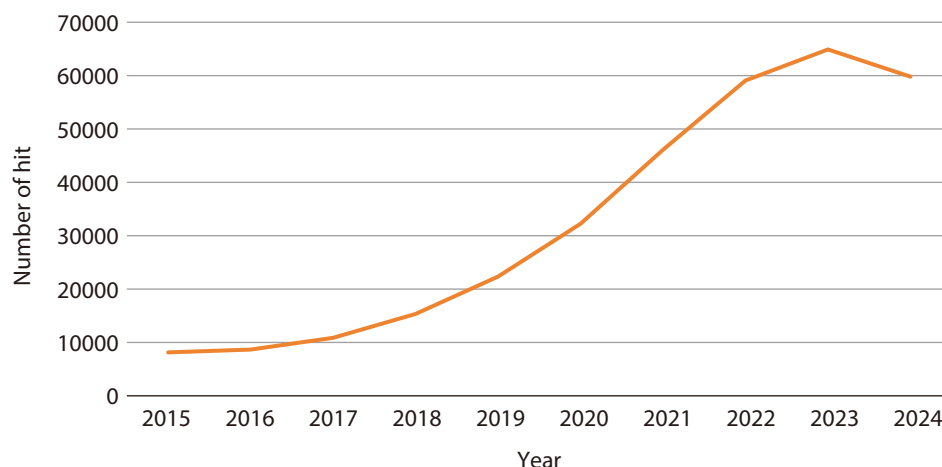


Fig. 1. Number of articles in PubMed with search terms including "((artificial intelligence) OR (machine learning)) OR (deep learning) OR (deep neural network)."

between the Korean government and medical societies appears challenging. Despite Korea's strengths in science, government officials have yet to provide scientific evidence to support their policies on medical school quotas [5]. In the Jewish discussion method known as Havruta, peers engage in debate from opposing viewpoints. Such discussions could lead to better mutual understanding and more scientific thinking if both parties participate.

Remembering a great leader

Dr. Keun Lee, a pediatrician at Ewha Womans University College of Medicine, passed away on May 14, 2024, in the United States at the age of 81 after a seven-year battle with vascular dementia. I vividly remember her from attending the annual meetings of the Korean Society of Medical Education in the 1990s. Her love for medical students and dedication to education were evident in her speeches and discussions with society members. Dr. Su Jin Cho, her student, wrote a beautiful obituary [6]. To commemorate her pioneering work in developmental screening studies, we have included her 1987 article from the *Journal of the Korean Pediatric Society* in this issue after English translation [7]. This article describes her extensive efforts to introduce the Denver Developmental Screening Test to Korea by testing 2,140 children, providing pediatricians with a tool to directly observe and assess children's developmental progress. All students of Ewha Womans University College of Medicine who learned from her will remember her as an excellent researcher and beloved educator.

Special topics on radiation therapy and liver cancer

This issue contains invited articles on two particular topics: cutting-edge technologies in radiation therapy and recent management strategies for liver cancer. Dr. Jun Won Kim wrote a guest editorial on the former topic [8], introducing three articles on particle therapy, FLASH radiation therapy, and artificial intelligence in radiation therapy. This will provide an excellent opportunity for our readers to gain insights into the latest advancements in radiation therapy.

A leading research group specializing in liver cancer, headed by Dr. Haeryoung Kim, a

pathologist at Seoul National University Hospital, has published four review articles. These articles cover a range of topics including the histopathological and molecular heterogeneity of hepatocellular carcinoma; the pathogenesis and management of metabolic dysfunction-associated steatohepatitis-related hepatocellular carcinoma; imaging findings of intrahepatic cholangiocarcinoma for prognosis prediction and treatment decision-making; and the pharmacological treatment of advanced hepatocellular carcinoma. Despite liver cancer being the second leading cause of death in Korea, mortality rates have been steadily declining [9]. Access to the latest knowledge and technologies for managing liver cancer is invaluable for readers.

Specially invited articles

"The leitmotifs we share" is an essay by a student from Ewha Womans University College of Medicine that received the grand prize at the 2024 Korean Medical Student Essay Competition on September 28, 2024. Her essay, originally written in Korean, was noted for its exceptional quality, especially for a student. It is presented here in English translation, accompanied by the original Korean text as a supplement [10]. Readers worldwide will connect deeply with the delicate leitmotifs she shares with patients.

"Gender and healthcare issues related to the Protected Birth Act in Korea" [11] by Prof. Jiah Jeong of Chungnam National University has been selected for secondary publication following its translation into English from the original Korean article in *Women's Health Nursing*. This legislation is designed to prevent infanticide and child abandonment by mandating the reporting of births and allowing anonymous births for women in crisis pregnancies. The paper examines the gender and healthcare consequences of the Act, highlighting its role in perpetuating discrimination against unmarried pregnancies and reinforcing traditional family values. With Korea currently holding the lowest birth rate in the world, the primary goal of this legislation is to provide genuine protection to women facing crisis situations. Additionally, it could help increase the birth rate by improving social support systems.

Clinical practice guidelines for diagnosing and treating scabies in Korea are divided into two parts: Part 1 addresses epidemiology and clinical manifestations [12], and Part 2 discusses treatment and prevention [13]. These guidelines have been translated into English and are published as secondary publications with permission from the editor of the original journal, the *Korean Journal of Dermatology*. They are intended to assist dermatologists and general physicians in diagnosing and treating patients with scabies. The prevalence of scabies in Korea decreased from 97.6 per 100,000 person-years in 2010 to 43.4 in 2021. Despite this decline, the incidence of scabies remains relatively high among elderly populations in long-term care facilities [14].

An excellent article on a novel measure of perceived cognitive decline was translated into Korean with Dr. Hamid R. Sohrabi, co-authors, and the publisher's permission [15]. The authors named this measurement tool the McCusker Subjective Cognitive Impairment Inventory (McSCI). I hope Korean physicians use this tool to detect the cognitive impairment of visitors more conveniently.

The Korean translation of the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (revised in January 2024) [16] has been released with assistance from the Korean Association of Medical Journal Editors (KAMJE). This translation will greatly benefit many medical editors in Korea by providing them with immediate access to these guidelines. I would like to express my gratitude to Dr. Dong Soo Han, president

of KAMJE, for permitting the publication of this invaluable document.

Retirement of an esteemed editor

Dr. Ryung-Ah Lee retired from Ewha Womans University College of Medicine in August. Since 2011, she has been a significant contributor to the *Ewha Medical Journal*. Under her 14-year editorship, the journal achieved international recognition as a bilingual publication in Korean and English. She also collaborated with me at KAMJE for many years. When we first met at the KAMJE annual meeting in 2007, I immediately recognized her as a prominent leader at her medical school and within her academic society. Her active engagement and dedication were particularly striking. In 2008, I invited her to join the Committee for Information Management at KAMJE while I was the committee chair. Later, she supported me as the chair of the Committee for Planning and Administration at KAMJE during my presidency from April 2020 to March 2023. I owe her a great deal. This is the reason I agreed to take on the editorship of the *Ewha Medical Journal*, despite my retirement in February 2024. I simply could not turn down her request for assistance with the journal. Dr. Lee is renowned as an outstanding colon cancer surgeon and researcher, and her commitment to resident training is widely recognized. In September, she transitioned to a biotechnology company, CorestemChem Inc., where she now focuses on stem cell therapy and non-clinical research projects as the manager of the Research and Development Innovation Headquarters. I am confident that she will achieve excellent results in patient care, leveraging her extensive clinical and surgical expertise. To mark her retirement, some members of the editorial board gathered for a farewell party on August 26, 2024, in downtown Seoul (Fig. 2).



Fig. 2. Photo from the farewell party for Dr. Ryung-Ah Lee at Joyang Korean Restaurant in Gangnam, Seoul. From the first row, left to right, in the counter-clockwise direction: Ryung-Ah Lee, Sun Huh, Ji Yeon Byun, Hyungju Kwon, Sohyun Ahn, and Hae-Sun Chung.

Progress of applying to PubMed Central, Scopus, and Directory of Open Access Journals

Although the *Ewha Medical Journal* has been indexed in the Emerging Sources Citation Index and Embase since 2016, being searchable in PubMed Central (PMC)/PubMed and Scopus is essential. Additionally, inclusion in the Directory of Open Access Journals (DOAJ) is critical for international recognition as an open-access journal. With the assistance of Ms. Yoonjin Kim from Infolumi Co., Korea (<https://infolumi.co.kr/>), and the support of our editorial board, we have refined our publishing policies, research and publication ethics, best practices, and author guidelines. We have also introduced new publishing policies that include article sharing, preprint options, procedures for handling corrections and retractions, CrossMark, and advertising policies.

On August 21, 2024, we submitted our application to PMC, initiating the review process. The progress of this review can be monitored through the PMC Publisher Portal [17]. Since September 5, 2024, the journal has been in the scientific quality review stage (Fig. 3). The application form is included in Supplement 1. During our previous PMC application on July 13, 2021, we received feedback from reviewers on March 12, 2022. This feedback pointed out several issues, including article quality, study design, methods description, adherence to guidelines, clarity of writing, conflict of interest statements, and diversity among authors and editors. Despite the editorial team's diligent efforts to address these issues, meeting the scientific quality standards required by PMC reviewers continues to be a significant challenge.

We also applied to Scopus on August 21, 2024 (Supplement 2). After applying, I received a letter from the Scopus Title Evaluation Specialist, noting that the *Ewha Medical Journal* had been suggested for inclusion in Scopus as of March 31, 2015. The decision letter, dated January 3, 2017, noted that although the journal was readily accessible online, it did not meet other criteria

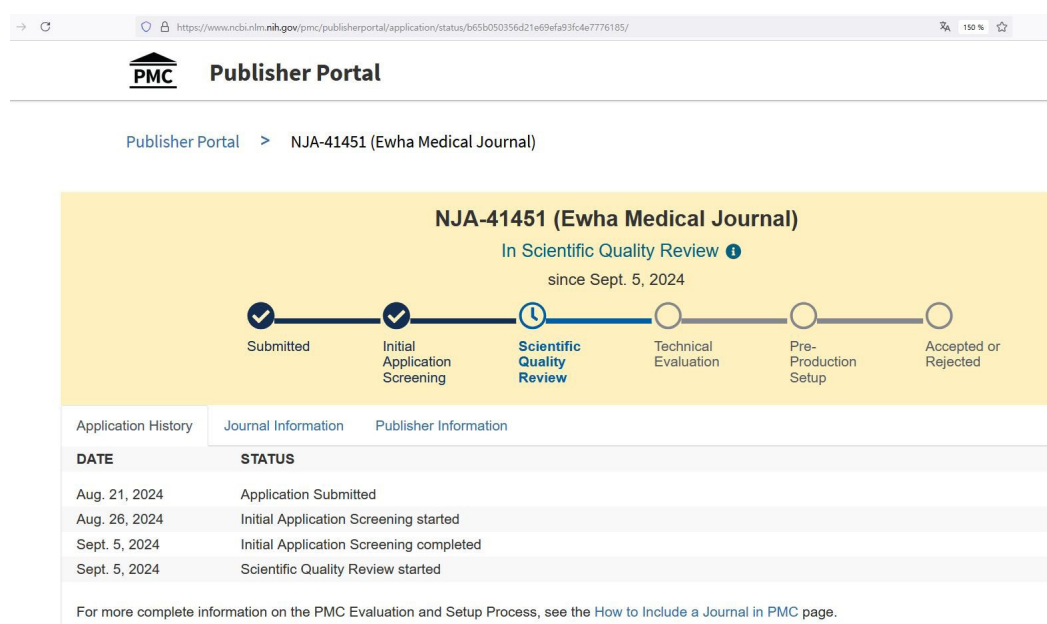


Fig. 3. Snapshot of application status of *Ewha Medical Journal* to PubMed Central at the PMC Publisher Portal [cited 2024 Oct 13].

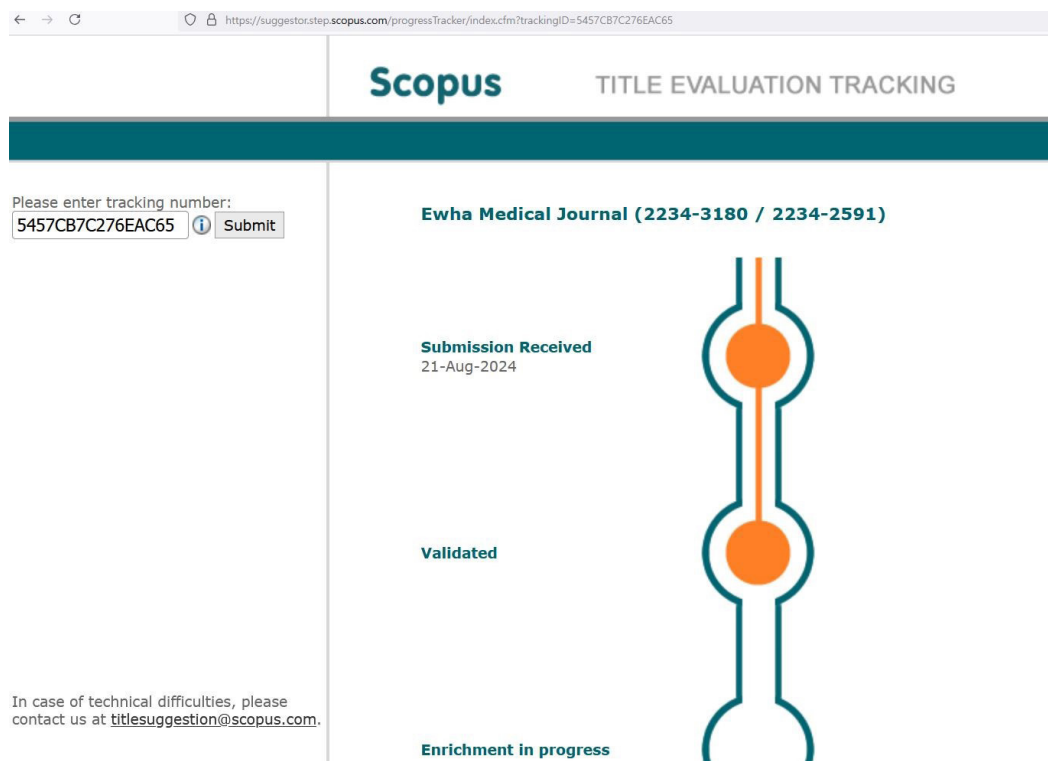


Fig. 4. Snapshot of the progress of *Ewha Medical Journal* in the Scopus Title Evaluation Tracking system [cited 2024 Oct 13].

due to low citation rates in Scopus and insufficient international diversity among its authors and editors. I have addressed these issues in my responses (Supplement 3). The progress of the review process can be monitored via the Scopus Title Evaluation Tracking [18]. As of August 2024, the process is still in the pre-enrichment stage (Fig. 4), and the final decision may take 4 to 12 months.

We applied to DOAJ on August 24, 2024 (Supplement 4) and are awaiting the outcome of the review.

Editing this journal to fully satisfy readers with engaging and unique topics is a challenging task. Our primary audience includes the members of Ewha Womans University College of Medicine and Ewha Womans University hospitals. Additionally, our secondary audience comprises individuals worldwide who are interested in Korean medicine. Maintaining the journal's uniqueness and providing valuable content continue to be challenges for editors. Our editors have exerted their utmost effort to meet the readers' demands, and we hope that you enjoy this issue.

ORCID

Sun Huh: <https://orcid.org/0000-0002-8559-8640>

Authors' contributions

All work was done by Sun Huh.

Conflict of interest

Sun Huh has edited the *Ewha Medical Journal* since September 2023. However, he was not involved in the peer review process or decision-making. No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials are available from: <https://doi.org/10.12771/emj.2024.e71>.

Supplement 1. Application form of *Ewha Medical Journal* reviewed by PubMed Central

Supplement 2. Application form of *Ewha Medical Journal* to Scopus

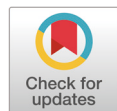
Supplement 3. Responses from *Ewha Medical Journal* to Scopus regarding the 2015 application

Supplement 4. Application form of *Ewha Medical Journal* to the Directory of Open Access Journals

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Keun Lee (October 10, 1942 – May 14, 2024): a pioneering pediatrician in the field of developmental screening tests in Korea and a beloved teacher at Ewha Womans University College of Medicine

Su Jin Cho

Department of Pediatrics, Ewha Womans University College of Medicine, Seoul, Korea

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Corresponding author

Su Jin Cho
Department of Pediatrics, Ewha Womans
University College of Medicine, 1071,
Anyangcheon-ro, Yangcheon-gu, Seoul
07985, Korea
E-mail: sujin-cho@ewha.ac.kr



Fig. 1. Photo of the late Dr. Keun Lee
(courtesy of her family).

It is with profound sadness that we announce the passing of Dr. Keun Lee (Fig. 1), a trailblazer in pediatric developmental screening, a staunch advocate for breastfeeding, and a cherished medical educator. Dr. Lee passed away on May 14, 2024, in Fullerton, California, USA, at the age of 81, after a seven-year battle with vascular dementia, which developed following a stroke in 2017.

Early life and education

Dr. Lee was born on October 10, 1942, in Seoul, Korea, as the second child and only daughter in a family of six children. She received her M.D. from Ewha Womans University College of Medicine in February 1967. She pursued further medical training in the United States, completing an internship at Long Island College Hospital in New York from 1967 to 1968, followed by residencies at the University of Iowa Hospital from 1968 to 1969 and at Vanderbilt University Hospital from 1970 to 1971. In 1972, she achieved board certification in pediatrics in the United States and completed a fellowship at New York University Hospital from 1972 to 1974. She obtained her Ph.D. in Medicine from Seoul National University in 1981.

Professional achievements

In March 1976, Dr. Lee began her tenure as a professor at Ewha Womans University College

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of Medicine, where she served until February 2008 before being named an emeritus professor. Her most notable contribution was the introduction of developmental screening tests for children in Korea. In 1987, she introduced the Denver Developmental Screening Test to Korea, providing pediatricians with a tool to directly observe and assess the developmental progress of children [1]. Her landmark study, which involved 2,144 children, demonstrated that the behavioral development of Korean children often exceeded that of their counterparts in the United States and Japan. The findings of this study were also featured in a newspaper — Korean children's behavioral development is faster than that of children in the United States and Japan. Newspaper, DongA Ilbo, November 7, 1986.

Over the years, Dr. Lee made significant contributions to several areas of pediatrics. In 1989, she conducted research on asthma severity using the Child Symptom Checklist and DSM-III Axis levels [2]. By 1991, she had developed a language development screening method for Korean children aged 0 to 3 years, designed for use by pediatricians without the need for specialized training [3]. In 1999, she highlighted the importance of integrating parental concerns into developmental screenings during immunization visits [4]. Her study in 2000 resulted in the creation of a user-friendly developmental screening test tailored for pediatricians [5]. In 2002, she introduced the Ewha Infant Development Screening Test (EDST) for infants aged 1 to 48 months [6]. These accomplishments established the groundwork for the Ewha Birth and Growth Study [7], positioning the Ewha Womans University College of Medicine as a leader in cohort research in the field of pediatrics.

Leadership and advocacy

Dr. Lee held several prominent positions, including:

- President of the Korean Society of Medical Education (1997–1999)

- President of the Korean Pediatric Society (2003)

- Founding President of the Korean Society of Breastfeeding Medicine (2006–2008)

In 2007, she played a pivotal role in changing the term “pediatrics” [소아과학] to “pediatrics and adolescent medicine” [소아청소년의학], reflecting a broader commitment to child and adolescent health. She was also a vocal advocate for breastfeeding, meticulously organizing relevant information and teaching how to provide breastfeeding counseling.

Emphasizing that breastfeeding is a fundamental right of newborns, she highlighted its advantages and importance. As the inaugural president of the Korean Society of Breastfeeding Medicine from 2006 to 2008, she addressed the benefits and significance of breastfeeding from an academic perspective, promoting it in terms that were easily understandable to mothers.

From 1992 to 1996, she served as a committee member on the UNICEF Korea Committee's initiative to establish baby-friendly hospitals and was later the chairperson from 1997 to 2004. Through her leadership, she played a pivotal role in the development of baby-friendly hospitals in our country. Following her retirement, she managed the Ewha Infant and Child Health Counseling Center from March 2008 to January 2010.

Dr. Lee expressed concerns in various media outlets about adopting American-style parenting practices. She emphasized the importance of the first year of life for a child, stating, “During the first year of life, it's crucial for a child to form basic trust correctly with the primary caregiver to foster harmonious relationships in the future. Neglecting a child's needs too early under the guise of promoting independence may lead the child to unconsciously harbor distrust” [8]. In addition to her media appearances, she has been an active writer for the general public. Her

publications include *To the Overwhelmed Mothers* in 1989 [9], *Smart Mothers Raise Their Children with Breast Milk* in 2003 [10], and *Raise Your Child Like a Kangaroo: 111 Questions and Answers from the Child Growth Clinic* in 2010 [11].

Personal reflections

As a student in 1994, I vividly recall Dr. Lee's charismatic presence during our first pediatrics lecture. She captivated us for two hours without the aid of slides or handouts, vividly bringing the subject to life by mimicking various breath sounds—wheezing, stridor, grunting—as if she were performing in an opera. Her innovative teaching methods made a lasting impression on all of us. Starting my residency in 1998, I observed Dr. Lee's unique approach to admitting patients by listing symptoms rather than diagnoses. This method compelled us to consult textbooks, collaborate on diagnostic plans, and engage deeply in research, providing invaluable experience in diagnosing rare syndromes. Dr. Lee was fearless and formidable when necessary, a strong woman who made significant scholarly and public contributions. Yet, to me and many others, she was also a warm and genuine mentor. Her smile was always gentle, tinged with playfulness, making her someone with whom we could discuss anything.

Dr. Lee passed away in the United States, where she was lovingly cared for by her family throughout her illness. She is survived by her three sons, three daughters-in-law, four grandsons, and two granddaughters. Her legacy continues to inspire not only those who had the privilege of knowing her but also countless others who have been impacted by her work.

We remember and will long cherish the legacy of our esteemed teacher, Dr. Keun Lee. Her contributions have left an indelible mark on pediatrics and medical education in Korea. Her dedication to her patients, students, and the field of pediatrics will continue to influence and inspire future generations.

ORCID

Su Jin Cho: <https://orcid.org/0000-0002-3851-9073>

Authors' contributions

All work was done by Su Jin Cho.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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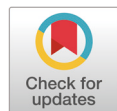
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Supplementary materials

Not applicable.

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Standardization of the Denver Developmental Screening Test for children in Seoul: a validity study

Keun Lee

Department of Pediatrics, Ewha Womans University College of Medicine, Seoul, Korea

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Corresponding author

Keun Lee, deceased on May 14, 2024.

*This is an English translation of the author's article originally published in 1987. It has been republished as a secondary publication with permission from Dr. Man Yong Han, Editor-in-Chief of *Clinical and Experimental Pediatrics*. This journal is the successor to the *Korean Journal of Pediatrics* (ISSN 1738-1061; 2004–2019) and the *Journal of the Korean Pediatric Society* (ISSN 0560-3560; 1958–2003). Also, the family of the late Dr. Keun Lee agreed with the secondary publication of this article. The original article was published under the following citation: Lee K. Standardization of the Denver Developmental Screening Test on Seoul Children. *J Korean Pediatr Soc* 1987;30(9):958-971. This publication is dedicated to the memory of the late Dr. Keun Lee, who was a pioneer in the area of developmental screening tests in Korea. English translation was done by the editorial office of the *Ewha Medical Journal*.

Keywords

Child; Denver Developmental Screening Test; Reproducibility of results; Seoul; Tokyo

Objectives: This study aimed to evaluate the applicability of the Denver Developmental Screening Test (DDST) for Korean children and to develop a Korean version reflecting the developmental characteristics of children in Seoul.

Methods: The DDST was administered to 2,140 children, aged 2 weeks to 6 years and 4 months, in Seoul between July 1985 and September 1986. Participants were recruited from the pediatric departments and counseling centers of several hospitals, excluding those with conditions affecting development. Certain test items were aligned with the Korean context. Inter-examiner reliability was evaluated based on 32 children, while validity was assessed with 30 children using standard developmental scales. The Probit method was employed for statistical analysis.

Results: Children from Seoul exhibited more rapid development than their counterparts in Denver and Tokyo across all four developmental domains: personal-social, fine motor-adaptive, language, and gross motor. Specifically, Korean children displayed earlier development for 10 items within the personal-social domain, eight within fine motor-adaptive, seven in language, and seven in the gross motor domain. This advanced development was consistent across age groups. Inter-examiner reliability averaged 97.3%, and validity tests demonstrated high concordance with established developmental scales.

Conclusion: The rapid development of Korean children may be attributed to close attention paid by parents and early exposure to educational materials. However, the potential role of genetic differences cannot be denied. The occupational distribution of the fathers in the sample did not differ significantly from that of the Seoul population; thus, these findings were applied to establish a standardized Korean DDST.

Introduction

Background

Early detection of developmental delays in children is crucial for evaluating their growth and development. Prompt identification of these delays and the implementation of appropriate interventions can either lessen their impact or address underlying causes to support normal development [1–4]. While accurate assessment of a child's developmental status typically requires

complex testing by highly trained specialists [5–7], such methods are too time-consuming and impractical for general pediatric practice. Simpler, time-efficient screening tests that can be easily administered by pediatricians are more useful in clinical settings [8–10]. The Denver Developmental Screening Test (DDST) [11,12] is the most widely used of these tests and is also employed in Korea. A pediatrician can conduct this test in about 20 minutes without special training. However, the DDST was developed based on children in Denver, a city in the United States, and may not be fully suitable for assessing the development of Korean children.

Objectives

In this study, we administered the DDST to 2,140 boys and girls ranging in age from 2 weeks to 6 years and 4 months, all residing in Seoul. We compared the results with those obtained from children in Denver and Tokyo. Based on these findings, we developed a Korean version of the DDST.

Methods

Ethics statement

Neither institutional review board approval nor informed consent was obtained for this study. In 1985, systems for ethical oversight, such as ethics statements, were not yet established in Korea.

Study design

This validity study was aimed at adapting a measurement tool originally developed in the United States for use in Korea.

Setting

From July 1985 to September 1986, a period of approximately 14 months, the DDST was administered to 2,140 children, both boys and girls (Tables 1, 2). The DDST manual and test forms [13] were translated into Korean and underwent several revisions (Supplement 1). Examiners were thoroughly trained using the translated materials through repeated explanations, discussions, and demonstrations. After the test was administered to 32 children, inter-examiner reliability was established. To ensure the accuracy of the results, two examiners worked as a team: one administered the test while the other recorded the results.

Participants

Children ranging in age from 2 weeks to 6 years and 4 months, as defined by the DDST, were included in the study. The participants were selected from those attending pediatric departments and child counseling centers at Ewha University Hospital, Red Cross Hospital, National Medical Center, Hanyang University Hospital, and Bangzi Hospital. In accordance with DDST guidelines, we excluded premature infants, twins, breech deliveries, adopted children, and children with visual or hearing impairments, central nervous system disorders, cleft palate, Down syndrome, or any acute or chronic illnesses. The team of examiners consisted of 15 individuals, including the researcher, medical students, pediatric residents, and students majoring in early childhood education.

Variables

A total of 104 items from the DDST observer's checklist were used as variables.

Table 1. Distribution of sample by age

Age (months)	Age range (days)	Number	Percent
1	16–45	73	3.4
2	46–75	90	4.2
3	76–105	91	4.3
4	106–135	86	4
5	136–165	72	3.4
6	166–195	100	4.7
7	196–225	93	4.3
8	226–255	79	3.7
9	256–285	83	3.9
10	286–315	76	3.6
11	316–345	75	3.5
12	346–375	82	3.8
13	376–405	72	3.4
14	406–435	74	3.5
15	436–495	91	4.3
18	496–585	105	4.9
21	586–675	74	3.5
24	676–810	91	4.3
30 (2.5 y)	811–990	97	4.5
36 (3 y)	991–1,170	101	4.7
42 (3.5 y)	1,171–1,350	90	4.2
48 (4 y)	1,351–1,530	79	3.7
54 (4.5 y)	1,531–1,710	90	4.2
60 (5 y)	1,711–1,980	93	4.3
72 (6 y)	1,981–2,340	83	3.9
Total		2,140	100.0 (%)

Table 2. Distribution of sample by sex

Sex	Number	Percent
Male	1,162	54.3
Female	978	45.7
Total	2,140	100

Data sources/measurement

The testing materials used aligned with those specified in the manual. However, certain test items were modified, as follows.

In the language domain, “Uses plurals” was excluded because plural and singular forms are not distinguished in spoken Korean. For “Defines words,” the passing criterion was adjusted from correctly defining six out of nine words to three out of nine. In “Object drawing,” a child was

considered to pass if at least one of the three items was correct, rather than requiring all three to be correct. These modifications were based on preliminary studies that revealed differences in language expression among Korean children. Similar adjustments were made in the development of the Japanese version of the DDST [14].

Reliability and validity were evaluated. Prior to beginning the study, inter-examiner reliability was established. One examiner administered the test while another observed and independently recorded the results; then, the level of agreement was calculated. Overall, 32 children, ranging in age from 3 months to 5 years, were assessed to determine reliability. The inter-examiner reliability scores varied from 93.8% to 100%, with an average of 97.3%.

To assess validity, the DDST was administered to 30 children ranging in age from 3 months to 5 years. Subsequently, these children were evaluated using either the Bayley Scales of Infant Development or the Korea University–Binet Intelligence Test [15]. As shown in Table 3, all three children who scored an intelligence quotient of ≤ 75 or ≤ 69 on these respective tests were rated as either “questionable” or “abnormal” on the DDST, demonstrating high concordance despite the small sample size.

Bias

Participants were selected after applying the exclusion criteria mentioned above. No additional selection bias was identified.

Statistical methods

Statistical analysis was performed using the Probit method in SAS (SAS Institute, Cary, NC, USA).

Results

Participating children

The DDST was administered to a total of 2,140 boys and girls. Tables 1, 2 detail the distributions of their ages and sexes. The occupational distribution of the participants’ fathers (Table 4) did not significantly differ from that of the general population in Seoul, as recorded in the 25th Seoul Statistical Yearbook, published in December 1985 ($P>0.05$).

Main results

Results of test items by city

The ages at which 25%, 50%, 70%, and 90% of children passed each of the 104 test items

Table 3. Relationships among the results of the DDST, Binet Intelligence Scale, and Bayley Scales of Infant Development

DDST	Binet IQ	≥ 92	76–91	≤ 75
	Bayley DQ	≥ 90	70–89	≤ 69
Normal		20	0	0
Questionable		1	5	2
Abnormal		0	1	1

DDST, Denver Developmental Screening Test; IQ, intelligence quotient; DQ, developmental quotient.

Table 4. Occupations of fathers of participants compared with the general population of Seoul

Occupation	Sample (%)	Seoul general population (%) ¹⁾
Administrative, managerial, or professional	13.1	11.9
Clerical and related workers	40.4	22.7
Commerce	21.3	25.6
Service	4.3	8.7
Agriculture, livestock, forestry, fishery	0.6	0.7
Production, transportation	23.5	30.9
Unknown, military, student, unemployed	7.5	0

P>0.05.

¹⁾ The 25th Seoul Statistics annual report, published in December 1985.

(Supplement 2) were calculated. These findings were then compared with the results of children from Denver and Tokyo. A difference exceeding 20% was considered significant. The percentage difference was determined using the following formula:

$$[(\text{Result of children in Seoul}) - (\text{Result of children in Denver})] / (\text{Result of children in Seoul}) \times 100$$

Comparison between children in Seoul and Denver

Test items exhibiting a difference of more than 20% are compared in Supplement 3.

Personal-social domain: For 10 of the 23 items, children from Seoul demonstrated more rapid development than their counterparts from Denver. Both 50% and 90% passing ages were earlier for four items: "Resists when a toy is taken away," "Plays peek-a-boo," "Attempts to reach distant toys," and "Plays ball." Only one item, "Easily separates from mother," was achieved earlier by the Denver children.

Fine motor-adaptive domain: Of the 30 items, relative to their counterparts from Denver, children from Seoul demonstrated faster development for eight. This was evident in both 50% and 90% passing ages for three items: "Regards raisin," "Picks up raisin with thumb and forefinger," and "Copies a square." Conversely, the Denver group exhibited more rapid development for three items.

Language domain: Of the 20 items, children from Seoul demonstrated faster development than the Denver children in seven. These items included "Says 'mama,' 'dada' (non-specific)," "Turns head to voice," and "Follows simple commands." The item "Defines words" was not included in the comparison due to changes in the scoring criteria.

Gross motor domain: For seven of the 31 items, children from Seoul demonstrated more rapid development than those in Denver. They reached both the 50% and 90% passing ages more quickly for "Bears weight on legs when held upright" and "Head lag disappears when pulled to sit." The Denver children did not exhibit faster development for any items.

Comparison between children in Seoul and Tokyo (Supplement 4)

Personal-social domain: Children from Seoul demonstrated faster development for 11 of the 23 items, reaching both the 50% and 90% passing ages more quickly for five of these items. The children from Tokyo outpaced their Seoul counterparts for only one item.

Fine motor-adaptive domain: Children from Seoul displayed faster development for 12 of the

31 items, reaching both the 50% and 90% passing ages earlier for three items. The Tokyo group exhibited more rapid development for one item.

Language domain: Children from Seoul exhibited faster development for 10 of the 20 items, reaching both the 50% and 90% passing ages earlier for two items. The Tokyo children displayed more rapid development for two items.

Gross motor domain: Children from Seoul demonstrated faster development for 14 of the 31 items, attaining both the 50% and 90% passing ages earlier for six items.

In Supplement 5, we superimposed the average ages of children from Seoul onto the original DDST chart to facilitate direct comparison with children from Denver. Dark shading on the left side of the bar indicates that the Seoul children achieved a milestone earlier, while shading on the right side signifies later achievement. As shown, the children from Seoul were ahead in many test items across all four domains and age groups.

Supplement 6 presents the Korean version of the DDST, developed based on the average data from the children in Seoul (Supplement 2). This version can replace the original DDST for the developmental screening of Korean children and should be used in conjunction with standardized testing materials and appropriate training. As explained, the Korean children demonstrated more rapid development for many test items across all domains and ages.

Discussion

Key results

In this study, the DDST was administered to 2,140 boys and girls ranging in age from 2 weeks to 6 years and 4 months, all residing in Seoul. When comparing the results with those from Denver and Tokyo, children from Seoul demonstrated more advanced development in multiple test items across all four developmental domains. Specifically, they were ahead in 10 out of 23 items in the personal-social domain, eight out of 30 items in the fine motor-adaptive domain, seven out of 20 items in the language domain, and seven out of 31 items in the gross motor domain. These differences were observed across all age groups.

Interpretation/comparison with previous studies

Developmental delays in children can arise from various causes, including congenital or genetic disorders, complications during childbirth, and environmental factors after birth. Early detection is crucial for identifying the underlying causes and initiating interventions that can mitigate delays. Detection also enables parents to understand the delay and thus engage in more constructive childcare and educational practices [1–4,9].

Historically, a variety of methods have been developed to assess child development, each with advantages and disadvantages. Many of these methods are complex and time-consuming, rendering them impractical for use by general pediatricians [5–7]. Consequently, simple screening tests for developmental delays have been emphasized [8–10,16].

The DDST [11–13,17–19] is the most widely used screening tool. General pediatricians, nurses, or medical students can administer the DDST without specialized training, and it takes only 15–20 minutes to complete. This instrument was developed based on a population of children from Denver, and while it has been claimed to be applicable in other regions, studies have indicated differences among children from other countries [20–26], as detailed below.

Cardiff: A study by Bryant et al. [20] revealed that infants in Cardiff exhibited advanced development in the personal-social and language domains but delays in gross motor

development compared to their counterparts in Denver. Employing the original DDST could thus lead to the misclassification of normal gross motor development as delayed [27].

Tokyo: Ueda [26] observed that infants in Tokyo display relatively delayed gross motor development and preschool children exhibit delayed language development, which can be attributed to environmental factors such as childcare practices. For instance, Japanese infants are often not placed in a prone position, potentially leading to delays in the ability to lift the head or chest.

Hong Kong: A study by Fung and Lau [21] indicated that Chinese infants in Hong Kong exhibited delayed gross motor development, which normalized post-infancy. Contributing to this delay were cultural practices such as swaddling and a tendency towards overprotective parenting.

Differences stemming from childcare methods have also been observed in African [24,28] and Mexican infants [23]. Furthermore, economic factors can affect development; children from low-income families may exhibit delays in language and conceptual thinking tasks [29,30].

In this study, children from Seoul exhibited more rapid development across all domains compared to their counterparts in Denver and Tokyo. This trend was observed consistently among age groups. Two aspects of Korean childcare practices may contribute to this phenomenon. First, close physical contact is near-constant; Korean mothers often maintain close physical contact with their infants, frequently carrying or holding them, even during sleep. Sensory stimulation through skin-to-skin contact is known to facilitate development [4,31]. Second, a high value is placed on education. Korean parents emphasize educational achievement, providing educational materials at an early age and enrolling their children in preschools and academies. Nonetheless, genetic factors could also play a role in development, warranting further investigation.

Given the numerous test items for which Seoul children outperformed their counterparts, applying the original DDST to Korean children is unsuitable, as children with developmental delays could be misclassified as developmentally normal. The occupations of the fathers in our sample were comparable to those of the broader population of Seoul (Table 4), and the inter-examiner reliability was high. Validity tests demonstrated high concordance with established developmental scales (Table 3). Therefore, the establishment of a Korean version of the DDST based on our results is justified.

Accordingly, we developed the Korean version of the DDST (Supplement 6), tailored to the assessment of Korean children. Adequate training and standardized administration are essential for accurate results.

Limitations

This study has several limitations. First, it was restricted to children visiting specific institutions in Seoul, which may not be representative of the broader pediatric population of the city. Second, children who visit hospitals and counseling centers might not fully reflect the health status of the general pediatric population, potentially impacting the generalizability of the findings. Third, the sample sizes for testing inter-examiner reliability (32 children) and validity (30 children) were relatively small, possibly affecting the statistical reliability of the results.

Conclusion

Using the DDST, we examined the developmental progress of 2,140 children—both boys and girls—ranging in age from 2 weeks to 6 years and 4 months. The following results were obtained.

1. Overall advancement: Children in Seoul exhibited faster development than their counterparts in Denver and Tokyo across all domains and age groups.
2. Personal-social domain (23 items): Children from Seoul displayed slower attainment of only one item compared to both Denver and Tokyo children, while they exhibited faster development regarding 11 items.
3. Fine motor-adaptive domain (30 items): Compared to children in Denver, those in Seoul exhibited slower development regarding three items and faster development for eight. Compared to children in Tokyo, they were slower for one item and faster for 12.
4. Language domain (20 items): Children from Seoul displayed more rapid development for seven items compared to children from Denver. Relative to their counterparts in Tokyo, the Seoul group exhibited slower development for two items and faster attainment for 10.
5. Gross motor domain (31 items): Children from Seoul exhibited faster development for seven items compared to their counterparts in Denver and for 14 items compared to children from Tokyo.

The findings indicate that environmental factors and ethnic differences may contribute to the accelerated development observed in children from Seoul. To address these distinctions, we have developed and presented a Korean version of the DDST, which was informed by the study results. This research is anticipated to aid in the early detection of developmental delays and the implementation of appropriate interventions by offering an assessment tool tailored to the developmental evaluation of Korean children.

ORCID

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Authors' contributions

All work was done by Keun Lee.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Not applicable.

Supplementary materials

Supplementary materials are available from: <https://doi.org/10.12771/emj.2024.e61>.

Supplement 1. Korean translation of the Denver Developmental Screening Test (DDST)

Supplement 2. Age at which a given percentage of the Seoul sample passes various items

Supplement 3. Comparison of children from Seoul and Denver regarding the ages at which 50% and 90% of the sample pass various items

Supplement 4. Comparison of children from Seoul and Tokyo regarding the ages at which 50% and 90% of the sample pass various items

Supplement 5. Comparison of the original Denver Developmental Screening Test (DDST) with its Korean version

Supplement 6. The Korean version of the Denver Developmental Screening Test (DDST), developed using the average data of children from Seoul as shown in Supplement 2

Editor's note

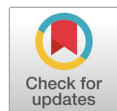
This secondary publication has been modified during the English translation process to align with the style and format of the *Ewha Medical Journal*. The abstract, which was originally quite short, has been expanded to approximately 250 words. An ethics statement has been incorporated; however, ethical approval and informed consent were not obtained, as Korea lacked an established system for such declarations in 1985. Nonetheless, this study posed no harm to children, as it was observational and involved no interventions. Additional sections on study design, variables, bias, key results, and limitations have been introduced. Reference number 17, which was not present in the main text of the original Korean article, has now been incorporated. Tables 5–7 from the original article were in Korean. Since the Korean texts of the items in these tables are meaningful, they have been moved to the Supplement without English translation. Throughout the translation and editing process, great care has been taken to preserve the core message of the original article.

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Cutting-edge technologies in external radiation therapy

Jun Won Kim

Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author

Jun Won Kim
Department of Radiation Oncology,
Gangnam Severance Hospital, Yonsei
University College of Medicine, 211,
Eonju-ro, Gangnam-gu, Seoul 06273,
Korea
E-mail: junwon@yuhs.ac

Radiation therapy (RT) is a key component of cancer treatment, complementing surgery and chemotherapy. While some technological advancements are still far from clinical application, others have been quickly adopted in the field of radiation oncology. This special issue features three reviews that highlight recent advancements in RT technologies, specifically particle therapy [1], FLASH RT [2], and artificial intelligence (AI) [3]. These articles also discuss the future prospects of these technologies.

Photons (X-rays) produced by linear accelerators are commonly used for the irradiation of tumors. However, the use of charged particles, such as protons and heavy ions (typically carbon), is on the rise [1]. The benefits of charged-particle therapy (CPT) stem from a physical phenomenon known as the Bragg peak. Unlike X-rays, which lose energy through attenuation as they pass through tissues, CPT allows the energy deposited per unit track to increase with depth. This results in a sharp and narrow peak of maximum energy deposition near the end of the particle's range. Consequently, the radiation dose delivered to the surrounding normal tissue is lower with CPT than with photons, offering better protection to organs at risk located near the target.

Another advantage of CPT is that it interacts with cells differently than photons. Linear energy transfer (LET) is the amount of energy transferred by an ionizing particle to the material it passes through per unit of distance as it penetrates tissues. Heavy ions, such as carbon and helium ions, have a high LET. Radiation with high LET, like that from heavy ions, exhibits greater relative biological effectiveness (RBE) than low-LET radiation. The RBE for photons is set at a reference value of 1, while protons have an accepted RBE value of 1.1. Carbon ions, in contrast, can have RBE values ranging from 2.0 to 3.5. Despite these benefits, CPT has faced criticism for its high cost/benefit ratio, primarily due to its significantly higher costs and the lack of level-1 evidence compared to conventional photon treatments such as intensity-modulated radiotherapy, which is commonly used to treat solid tumors. However, the growing number of CPT centers worldwide in recent years has led to an accumulation of clinical evidence suggesting that CPT can reduce toxicity and improve survival in selected cases.

Limiting toxicity to normal tissues has always posed a significant challenge in RT. FLASH-RT, an external beam RT technology, administers ultra-high doses in a very short duration [2]. Instead of administering treatment in multiple fractions over days or weeks, a large total radiation dose is delivered rapidly in a single fraction. Remarkably, these high dose rates (over 40 Gy per second) result in less damage to normal tissue compared to conventional dose rates (2–10 Gy per minute), while still preserving the radiation's ability to kill tumor cells. The underlying mechanism

remains poorly understood. The most widely accepted theory for the FLASH effect is the oxygen depletion hypothesis, which suggests that the local oxygen depletion process occurs more quickly than reoxygenation during FLASH-RT. Consequently, normal tissue becomes more radioresistant under FLASH irradiation. This could represent a major advancement in RT; however, the clinical application of FLASH-RT still faces significant challenges and is far from routine use. Although initial results from animal and preclinical studies are promising, further research and clinical trials are necessary to translate these findings into effective cancer treatments.

In the field of radiation oncology, the application of AI is becoming increasingly widespread, with growing acceptance in clinical practice [3]. One of the most time-consuming aspects of the RT process is the segmentation or contouring of targets and normal structures in medical images, which is prone to significant intra- and interobserver variability. Deep learning models have significantly advanced as tools for the automated segmentation of organs at risks and are showing promise in contouring target volumes. Researchers are exploring the use of AI algorithms for automated treatment planning to reduce planning time, improve plan quality, and decrease interobserver variability. MRI offers superior soft-tissue contrast but lacks the electron density information required for RT planning. Deep learning models have been developed to generate CT images from MRI scans, and the resulting pseudo-CT images are useful for dose estimations in RT planning. Another emerging application of AI models is in predicting treatment outcomes. Traditional TNM prediction primarily focuses on cancer cells to forecast prognosis, but often falls short in accuracy. There is an increasing interest in employing radiomics signatures to predict overall and disease-free survival following cancer treatment. AI models have also shown potential in predicting RT-related side effects. The integration of AI with modern RT technologies could lead to significant transformations in the field of radiation oncology. However, there are ongoing concerns about the stability and generalizability of AI applications that need to be addressed before they can be fully integrated into clinical practice.

The authors of this special issue provide a comprehensive review of the recent developments and future prospects of these new technologies in radiation oncology.

ORCID

Jun Won Kim: <https://orcid.org/0000-0003-1358-364X>

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Clinical indications and future directions of carbon-ion radiotherapy: a narrative review

Seo Hee Choi[✉], Woong Sub Koom[✉], Hong In Yoon[✉], Kyung Hwan Kim[✉], Chan Woo Wee[✉],
Jaeho Cho[✉], Yong Bae Kim[✉], Ki Chang Keum[✉], Ik Jae Lee[✉]

Department of Radiation Oncology, Heavy Ion Therapy Research Institute, Yonsei Cancer Center, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author

Ik Jae Lee
Department of Radiation Oncology,
Heavy Ion Therapy Research Institute,
Yonsei Cancer Center, Yonsei University
Health System, Yonsei University
College of Medicine, 50-1 Yonsei-ro,
Seodaemun-gu, Seoul 03722, Korea
E-mail: ikjae412@yuhs.ac

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Carbon-ion radiotherapy (CIRT) offers superior dose distributions and greater biological effectiveness than conventional photon-based radiotherapy (RT). Due to its higher linear energy transfer and relative biological effectiveness, CIRT is particularly effective against radioresistant tumors and those located near critical organs. Since the first dedicated CIRT facility was established in Japan in 1994, CIRT has demonstrated remarkable efficacy against various malignancies, including head and neck tumors, skull base and upper cervical spine tumors, non-small-cell lung cancer, hepatocellular carcinoma, pancreatic cancer, prostate cancer, and bone and soft tissue sarcomas. This narrative review provides a comprehensive overview of the current status of CIRT, highlighting its clinical indications and future directions. According to clinical studies, CIRT achieves high local control rates with manageable toxicity across multiple cancer types. For instance, in head and neck tumors (e.g., adenoid cystic carcinoma and mucosal melanoma), CIRT has achieved local control rates exceeding 80%. In early-stage non-small-cell lung cancer, CIRT has resulted in local control rates over 90% with minimal toxicity. Moreover, CIRT has shown promise in treating challenging cases of hepatocellular carcinoma and pancreatic cancer, where conventional therapies are limited. Nonetheless, the global adoption of CIRT remains limited due to high costs and complexity. Future directions include conducting randomized controlled trials to establish high-level evidence, integrating new technologies such as ultrahigh-dose-rate (FLASH) therapy, and expanding CIRT facilities globally with strategic planning and cost-effectiveness analyses. If these challenges are addressed, CIRT is poised to play a transformative role in cancer treatment, improving survival rates and the quality of life.

Introduction

Background

Radiotherapy (RT) has long been a cornerstone of cancer treatment. It employs ionizing radiation to damage the DNA in tumor cells, initiating a series of biochemical reactions that result in cell death. Among the various types of ionizing radiation, X-rays and gamma rays are most commonly used, with X-ray therapy being the standard in clinical settings. Despite its prevalent use, X-ray therapy faces significant challenges, particularly in avoiding damage to healthy tissues near the tumor, especially when these tissues are close to vital organs. These challenges have

spurred the development of alternative RT methods that offer more favorable dose distributions and improved biological effects.

In recent years, charged particle beam therapy, often referred to as particle therapy, has become a significant advancement in the field of RT. This innovative method includes proton and carbon-ion radiotherapy (CIRT), offering substantial physical and biological advantages over traditional photon-based therapies. Notably, carbon ions have a higher linear energy transfer and relative biological effectiveness (RBE) than protons, enhancing their effectiveness in controlling tumors, particularly those that are radioresistant or situated near critical organs [1,2]. The establishment of the first dedicated CIRT facility in Japan in 1994 was a pivotal moment in the history of RT. This development was inspired by earlier research that recognized the therapeutic potential of high-linear energy transfer radiation. Since then, CIRT has been successfully implemented in a limited number of countries, including China, Germany, Italy, Japan, and Korea, where it has shown remarkable efficacy in treating various malignancies. A recent meta-analysis also confirmed that CIRT is a safe and effective option for achieving local control (LC) in patients with solid tumors [3].

In Korea, the Yonsei Cancer Center has been at the forefront of adopting CIRT, marking a significant milestone in the nation's medical advancement. The planning for the Heavy Ion Therapy Center at Yonsei Cancer Center began in 2013, leading to the establishment of Korea's first CIRT facility, which became operational in April 2023. This center is globally recognized for its state-of-the-art infrastructure, including the world's first configuration with a fixed beam and two superconducting gantries dedicated to CIRT. The Heavy Ion Therapy Center at the Yonsei Cancer Center represents a decade of meticulous planning and collaboration, with over 200 prostate cancer patients successfully treated by mid-2024. The center has expanded its treatment offerings to include CIRT for pancreatic, liver, and lung cancers starting in May 2024. The Yonsei Cancer Center's commitment to advancing CIRT not only enhances treatment options for Korean patients but also positions the center as a leading institution in the global CIRT community.

Despite the clear therapeutic benefits of CIRT, its global adoption remains limited primarily due to the high costs and complexity associated with establishing such facilities. However, the increasing number of CIRT centers and ongoing clinical research are expanding its applications and accessibility.

Objectives

This review aimed to provide a comprehensive overview of the current status of CIRT, encompassing its physical and biological characteristics, clinical indications, and future directions. By exploring the progress and potential of CIRT, this study sought to highlight its crucial role in advancing cancer treatment and the need for wider implementation of this advanced technology.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Head and neck tumors

Surgical resection is the primary treatment for head and neck malignancies. However, the

complexity of this region often makes it challenging to achieve complete resection without significant morbidity. Consequently, RT is frequently used as either primary or adjuvant therapy. CIRT is particularly effective in these cases due to its superior dose distribution and enhanced biological efficacy. It enables precise targeting of the tumor while sparing radiosensitive structures such as the salivary glands, cranial nerves, and brainstem. CIRT has shown favorable outcomes, especially in treating radioresistant tumors like adenoid cystic carcinoma (ACC) and chordomas, achieving high LC rates with manageable toxicity. Although direct comparative studies with conventional treatments are limited, both CIRT and proton therapy have been successfully used as primary and postoperative treatments, either alone or in combination with photon therapy.

ACC in the head and neck poses significant treatment challenges due to its propensity for perineural invasion and involvement of the skull base, which complicates achieving complete surgical resection. CIRT has emerged as a promising treatment option for managing ACC, especially in patients with postoperative residual disease or unresectable tumors. An initial study [4] from the Heavy Ion Research Center (GSI) in Heidelberg reported 1- and 3-year LC rates of 80.8% and 64.6%, respectively, for patients treated with a combination of photon therapy and a CIRT boost, totaling 72 Gy(RBE). At the National Institute of Radiological Sciences (NIRS) in Japan, a dose-escalation trial identified the maximum tolerated dose as 70.2 Gy(RBE) in 18 fractions, resulting in a 5-year LC rate of 73% [5]. The COSMIC trial, a phase II study in Heidelberg, reported a 3-year LC rate of 81.9% for ACC, with higher control rates observed in patients with residual disease post-resection [6]. Large-scale studies at the GSI [7] and NIRS [8] confirmed these findings, with 3- and 5-year LC rates of approximately 81% and 73%, respectively, and low incidence of severe toxicity. Additionally, a sub-analysis of a Japanese multicenter study (1402 HN) by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) [9] reported 2- and 5-year LC rates of 88% and 68%, respectively. Meanwhile, the 2- and 5-year overall survival (OS) rates were 94% and 74%, respectively, with 15% of the patients experiencing grade 3 or higher toxicities, such as osteoradionecrosis and vision loss. These studies highlight the effectiveness of CIRT in managing ACC, particularly in challenging cases involving residual disease.

CIRT has also shown significant effectiveness in treating head and neck mucosal melanoma, a notably aggressive and radioresistant cancer. Various studies, including both prospective and retrospective analyses from institutions such as the NIRS [5,8], Hyogo Ion Beam Medical Center [10], National Centre for Oncological Hadrontherapy in Italy [11], Gunma University Heavy Ion Medical Center [12], and Heidelberg Ion Beam Therapy Center (HIT) in Germany [13], have documented the benefits of CIRT in this context. A multicenter retrospective study [14] in Japan, which included 260 patients with mucosal melanoma, reported a 2-year LC rate of 83.9% and an OS rate of 69.4%, with grade 3 or higher toxicities occurring in 19% of the patients. At the NIRS, dose adjustments over time, from 70.2 Gy(RBE) in 18 fractions to 57.6 Gy(RBE) in 16 fractions, resulted in a 5-year LC rate of 75% and an OS rate of 35% [5,8]. The HIT in Germany reported a 3-year LC rate of 58.3% and an OS rate of 16.2% for paranasal sinus melanoma [13], highlighting the challenges in treating this type of tumor. In cases of choroidal melanoma, NIRS reported a 5-year LC rate of 92.8% and an OS rate of 80.4%, although 31.6% of patients experienced neovascular glaucoma as a late toxicity [15,16]. These findings demonstrate the potential of CIRT to achieve high LC rates in challenging melanoma cases, particularly in anatomically complex regions such as the head, neck, and choroid.

Skull base and upper cervical spine tumors

Several studies have demonstrated the effectiveness of CIRT in treating tumors located at the skull base and upper spine, particularly in patients with sarcoma where surgical resection is challenging or incomplete. A prospective study [17] involving 27 patients with unresected sarcomas of mixed histology reported a 3-year LC rate of 91.8% following CIRT administration at a dose of 70.4 Gy(RBE) in 16 fractions. However, 23.1% of these patients experienced late radiation-related complications of grade 3 or higher. Similarly, another prospective study [18] conducted at Gunma University included 10 patients with unresectable bone or soft tissue sarcomas at the skull base. These patients received CIRT at the same dosage and reported a 3-year LC rate of 72.9%. These studies underscore the potential of CIRT to achieve substantial LC in regions that are difficult to treat, although concerns about late toxicity remain unresolved.

Chordomas and chondrosarcomas of the skull base have been significant targets for charged-particle therapy due to their complex anatomical locations and the high radiation doses needed for effective treatment [19,20]. At HIT, a retrospective study [21] conducted in 155 patients with skull base chordomas treated with 60 Gy(RBE) in 20 fractions reported 5-year and 10-year LC rates of 72% and 54%, respectively. Another follow-up study [22] at HIT involving 111 patients treated with 66 Gy(RBE) in 22 fractions reported a 5-year LC rate of 65%. In Italy, a study carried out at the National Centre for Oncological Hadrontherapy reported a 5-year LC rate of 71% in 135 patients treated with 70.4 Gy(RBE) in 16 fractions for skull base chordoma [23]. For chondrosarcoma, German studies [24–26] demonstrated a 3-year LC rate of 96.2% and a 10-year LC rate of 88% in patients treated with 60 Gy(RBE) in 20 fractions, with a low incidence of severe toxicity. These findings underscore the efficacy of CIRT in managing these rare but challenging tumors, providing long-term control with an acceptable safety profile.

Non-small-cell lung cancer

RT is a crucial treatment modality for lung cancer and the second most common treatment in Korea [27]. CIRT has become a viable and effective treatment option for localized non-small-cell lung cancer (NSCLC), especially in patients who are not suitable candidates for surgery due to comorbidities or advanced age. Since its introduction for NSCLC in November 1994, CIRT has shown effectiveness in treating early-stage NSCLC, particularly in tumors located peripherally and in selected cases of central tumors. CIRT offers potential advantages over traditional treatments for patients who need to minimize radiation exposure to the lungs, such as those suffering from interstitial lung disease (ILD). Multiple studies have confirmed the efficacy of CIRT in improving LC with an acceptable toxicity profile (Table 1).

At the NIRS in Japan, several hypofractionation and dose-escalation studies explored the optimal dosing regimens for CIRT in stage I NSCLC. An initial dose of 59.4 Gy(RBE) in 18 fractions was progressively refined to 72 Gy(RBE) in nine fractions, 52.8 Gy(RBE) in four fractions, and even a single-fraction dose of 50 Gy(RBE). These studies [28–32] reported a 3-year OS rate of approximately 70%–80% and a 3-year LC rate exceeding 90% in patients with stage IA tumors, although the LC rate was lower in patients with stage IB tumors. The incidence of grade 2 or higher toxicity was less than 2%. Recent phase I/II Japanese studies [31] and other recent studies [33] have identified 50 Gy(RBE) as the optimal dose for dose-escalated, single-fraction CIRT, demonstrating its feasibility as a treatment option with high LC and low toxicity rates. In a Japanese multicenter study (J-CROS-LUNG) [34], 95 patients with inoperable stage I NSCLC

Table 1. Clinical studies and outcomes of patients with NSCLC treated with CIRT

Author	Study design	No. of patients	CIRT dose	LC	OS	Acute toxicity	Late toxicity
Early-stage NSCLC							
Miyamoto et al. [28]	Phase I/II	81	59.4–95.4 Gy(RBE)/9–18 fr	First trial: 64% Second trial: 84%	5-yr 42%	Gr3 RP=3	
Miyamoto et al. [29]	Phase II	50	72 Gy(RBE)/9 fr	5-yr 94.7%	5-yr 50% (IA 55.2%, IB 42.9%)	No Gr3≤toxicity Gr 2 skin=1, Gr 2 RP=1	Gr 3 skin=1 Gr 2 skin=1 Gr 2 lung=2
Miyamoto et al. [30]	Phase II	79	52.8 Gy(RBE)/4 fr for stage IA, 60 Gy(RBE)/4 fr for stage IB	5-yr 90%	Overall: 5-yr 45%, stage IA: 5-yr 62%, stage IB: 25%	No Gr3≤toxicity Gr 2 skin=5 Gr 2 lung=1	No Gr3≤toxicity Gr 2 skin=1 Gr 2 lung=1
Yamamoto et al. [31]	Phase I/II	218	28–50 Gy(RBE)/1 fr	36–50 Gy(RBE): 3-yr 84.2%, 5-yr 80.5% 28–34 Gy(RBE): 3-yr 63.7%, 5-yr 54.4%	36–50 Gy(RBE): 3-yr 76.2%, 5-yr 56.8% 28–34 Gy(RBE): 3-yr 50.7%, 5-yr 32.8%	No Gr3≤toxicity Gr 2 toxicity=2% Gr 3 chest wall pain=1 (50 Gy(RBE))	
Saitoh et al. [32]	Phase II	37	52.8–60 Gy(RBE)/4 fr	Overall: 2-yr 91.2%, 5-yr 88.1% T1: 2-yr 91.3%, 5-yr 86.7% T2: 2-yr 90%, 5-yr 90%	Overall: 2-yr 91.9%, 5-yr 74/9% T1: 5-yr 80% T2: 66.7%	No Gr 4≤toxicity, Gr 3 RP=1, Gr 2 RP=1	
Ono et al. [33]	Retrospective	57	50 Gy(RBE)/1 fr	3-yr 96.4%, 5-yr 91.8%	3-yr 91.2%, 5-yr 81.7%	No Gr 3≤toxicity Gr 2 rib fracture=4 (7.0%) Gr 2 peripheral motor neuropathy=2 (3.5%)	
Kubo et al. (J-CROS-LUNG) [34]	Multicenter prospective observational registry study	95	72 Gy(RBE)/16 fr–50 Gy(RBE)/1 fr	3-yr 87.3%	3-yr 59.3%	No Gr 4≤toxicity, 3-yr Gr2≤ RP rate=3.2%, Risk factor for RP=FEV1<0.9L, dose≥67 Gy(RBE)	
Locally advanced NSCLC							
Takahashi et al. [37]	Phase I/II	62	68–76 Gy(RBE)/16 fr	2-yr 93.1% (cT3–4N0 only: 2-yr 100%)	2-yr 51.9% (cT3–4N0 only: 2-yr 69.3%)	Gr 2 RP=6.5% Gr 3 RP=1.6%	Gr 3 tracheoesophageal fistula=1 No grade 4/5 toxicity
Hayashi et al. [38]	Retrospective	141	54–76 Gy(RBE)/12–16 fr	2-yr 80.3%, 3-yr 75.4%	2-yr 58.7%, 3-yr 47.5%	Gr 2 skin=13.5%	Gr 4 mediastinal hemorrhage=0.7% Gr 3 RP=3.5% Gr 3 bronchial fistula=7%
Karube et al. [39]	Retrospective	64	52.8–60 Gy(RBE)/4 fr, 64–70.4 Gy(RBE)/16 fr	2-yr 81.8%	Overall: 2-yr 62.2% N0: 2-yr 67.8% N1–N2: 2-yr 62.2%	Gr 2 lung infection=3 Gr 2 lung reaction=4 Gr 2 skin reaction=3 Gr 2 chest wall pain=1	NR

Table 1. Continued

Author	Study design	No. of patients	CIRT dose	LC	OS	Acute toxicity	Late toxicity
Anzai et al. [40]	Retrospective	24	64–76 Gy(RBE)/16 fr	2-yr 73.9%, 3-yr 70.2%	2-yr 54.9%, 3-yr 42%	No Gr 3≤toxicity	Gr 4 mediastinal hemorrhage=1 Gr 3 RP=4 Gr 3 bronchial fistula=1

NSCLC, non-small-cell lung cancer; CIRT, carbon-ion radiotherapy; LC, local control; OS, overall survival; RBE, relative biological effectiveness; fr, fractions; yr, year; Gr, grade; RP, radiation pneumonitis; FEV1, forced expiratory volume in 1 s; J-CROS, Japan Carbon-Ion Radiation Oncology Study Group; NR, not reported.

received CIRT using regimens such as 64–72 Gy(RBE) in 12–16 fractions, 54–64 Gy(RBE) in four fractions, and 50 Gy(RBE) in one fraction. This study reported a 3-year LC rate of 87.3%, an OS rate of 59.3%, and a 3-year cumulative incidence of grade 2 or higher radiation pneumonitis of 3.2%. A retrospective, single-institutional study [35] directly comparing CIRT and stereotactic body RT for early-stage NSCLC found that CIRT achieved significantly higher 3-year OS rates (80.1% vs. 71.6%) and LC rates (87.7% vs. 79.1%) than stereotactic body RT. Furthermore, a cost-effectiveness analysis at Gunma University [36] suggested that while CIRT is cost-effective for stage I NSCLC, careful resource management could enhance its economic viability. These outcomes highlight CIRT's potential to achieve high LC with low toxicity, particularly in patients with limited surgical options.

CIRT has shown promising results in treating locally advanced NSCLC (LA-NSCLC), despite the inherent challenges associated with this stage of the disease. In a phase I/II study [37] at NIRS involving 62 patients with stage IIA–IIIA NSCLC treated with CIRT at a dose of 76 Gy(RBE), the 2-year LC and OS rates were 93% and 52%, respectively. Notably, patients with N0 disease exhibited a 2-year LC rate of 100% and an OS rate of 69%, with cases of no grade 3 or higher toxicity observed following treatment with 72 Gy(RBE). A retrospective study [38] of 141 patients with LA-NSCLC treated with a median dose of 72 Gy(RBE) in 16 fractions reported 2-year LC and OS rates of 80.3% and 58.7%, respectively. In a Japanese multicenter study [39] of patients with LA-NSCLC, the 2-year LC and OS rates were 81.8% and 62.2%, respectively, with no reported adverse effects higher than grade 2. Similarly, Anzai et al. [40] analyzed 65 patients with stage III NSCLC treated at NIRS with a median dose of 72 Gy(RBE), resulting in 2-year LC and OS rates of 74% and 55%, respectively. These studies suggest that CIRT, even without concurrent chemotherapy, may be a viable treatment option for patients with LA-NSCLC, achieving substantial LC and survival rates. However, further research is needed to clarify the role of CIRT in combination with systemic treatments, such as chemotherapy or immunotherapy.

Treating NSCLC in patients with ILD presents significant challenges due to the risk of acute exacerbation. However, recent research indicates that proton therapy [41] or CIRT may be safe and effective options. A retrospective study [42] of 124 patients with stage I NSCLC, including 26 with ILD, found that although patients with ILD had a lower OS (59.7% vs. 83.2%), CIRT did not significantly increase the incidence of severe side effects. Additionally, a multi-institutional study [43] of 30 patients with ILD reported a 3-year LC rate of 88.1%, with only 3.3% experiencing grade 2 or higher radiation pneumonitis. These findings suggest that CIRT could be a viable treatment for early-stage NSCLC in patients with ILD.

Hepatocellular carcinoma

CIRT has demonstrated significant potential in treating hepatocellular carcinoma (HCC), proving effective not only in early-stage cases but also in more complex situations where alternative treatments are limited. It is particularly beneficial for patients with large tumors, tumors in difficult anatomical locations such as near the porta hepatis or major blood vessels, and for those with compromised liver function. In cases where surgical resection or photon therapy may present significant risks, CIRT offers a safer alternative. Moreover, CIRT is a viable treatment option for patients experiencing recurrent HCC following previous interventions like transarterial chemoembolization or radiofrequency ablation (RFA), where it is critical to minimize additional liver damage.

In 2004, the NIRS conducted a prospective phase I trial [44] to explore the impact of increasing the dose from 49.5 Gy(RBE) to 79.5 Gy(RBE) in 15 fractions. The trial found no severe adverse effects and reported an 81% LC rate at both 3 and 5 years. Subsequent phase I and II trials [45] established 52.8 Gy(RBE) in four fractions as the recommended dose, with no cases of dose-limiting toxicity. Gunma University reported a 92.3% LC rate at 2 years and 76.5% at 4 years using doses of 52.8 Gy(RBE) and 60 Gy(RBE) in four fractions, with only grade 3 hepatobiliary toxicity reported in two patients [46,47]. A multi-institutional retrospective study [48] conducted by the J-CROS Group in 174 patients with HCC treated with CIRT (48–60 Gy(RBE) in two to four fractions) reported a 3-year LC rate of 81.0% and a 3-year OS rate of 73.3%, with only a few patients experiencing grade 3 or higher acute or late toxicity. Recent studies have refined the dosing strategy, using two or four fractions for tumors distant from the gastrointestinal tract and 12 or more fractions for those closer to the gastrointestinal tract to minimize adverse effects [49–52].

The majority of existing literature on CIRT has focused primarily on its usage, with only a limited number of small retrospective studies comparing it to other treatment modalities. Shiba et al. [50] compared CIRT with transarterial chemoembolization after propensity score matching. They found that CIRT led to significantly better 3-year OS (88% vs. 58%, $P < 0.05$) and LC (80% vs. 26%, $P < 0.01$) rates. Fujita et al. [53] compared the efficacy of CIRT and RFA in early-stage HCC in a study of 560 patients. CIRT was associated with significantly lower cumulative intrasubsegmental recurrence rates than RFA (2 years: 12.6% vs. 31.7%; 5 years: 15.5% vs. 49.6%), although the local recurrence, progression-free survival, and OS rates were similar between the groups. Notably, no grade 3 or higher adverse events were reported in the CIRT group, while 1.2% of the patients in the RFA group experienced grade 3 adverse events. Additionally, a comparative study by Komatsu et al. [54] reported similar outcomes between CIRT and proton beam therapy, with 5-year LC and OS rates of 93% and 36.3%, respectively, for CIRT.

CIRT has demonstrated significant potential in managing complex HCC cases, where conventional RT may pose considerable risks. Studies have demonstrated that CIRT can effectively minimize radiation-induced liver disease while still achieving high LC rates, even in patients with compromised liver function or large tumors. Hiroshima et al. [55] reported a low incidence of grade 3 toxicity in patients with Child-Pugh B liver function treated with CIRT. Meanwhile, Tomizawa et al. [52] reported no grade 4 toxicity in patients who underwent re-irradiation with CIRT for intrahepatic HCC recurrence. Furthermore, CIRT has proven effective in treating HCC located near critical structures such as the caudate lobe and porta hepatis, maintaining high LC rates and reducing the incidence of adverse effects in these challenging scenarios [56,57].

Pancreatic cancer

Pancreatic cancer is known for its resistance to conventional RT and its generally poor prognosis, underscoring the urgency for more effective treatment approaches. The pancreas's close proximity to radiosensitive organs like the stomach and bowel restricts the amount of radiation that can be safely administered using photon therapy. CIRT has not only shown a strong biological rationale *in vitro* [58,59], but has also yielded promising clinical results, especially in cases of locally advanced pancreatic cancer. Recent studies have further investigated the potential of CIRT in treating resectable and borderline resectable pancreatic cancers, aiming to improve surgical outcomes and decrease recurrence rates.

CIRT has emerged as a promising alternative for treating locally advanced pancreatic cancer, where conventional treatments often show limited efficacy. A phase 1/2 prospective clinical trial conducted at the NIRS [60] assessed the maximum tolerated dose of CIRT combined with gemcitabine. The study reported a 2-year local progression-free rate of 83% and a 2-year OS rate of 48% for patients receiving more than 45.6 Gy(RBE). A multicenter study (J-CROS 1403) [61] reported a median survival of 21.5 months, with a 2-year OS rate of 46% and a 2-year local recurrence rate of 24%. Notably, only 1% of patients experienced late grade 3 gastrointestinal toxicity, and no cases of severe toxicity were observed. Additionally, a study from Gunma University [62], which analyzed patients treated with concurrent chemotherapy ($\pm$ neoadjuvant or adjuvant multiagent chemotherapy), reported a 2-year LC rate of 76.1%, a 2-year OS rate of 56.6%, and a median survival of 29.6 months. These findings suggest that CIRT may improve outcomes in patients with locally advanced pancreatic cancer. However, further research is needed to comprehensively define its role and determine the optimal combination strategies with chemotherapy.

For resectable or borderline resectable pancreatic cancers, CIRT has been investigated as a preoperative treatment to enhance surgical outcomes and decrease recurrence rates. Promising results have emerged from studies conducted by Japan's NIRS. A phase I trial [63] demonstrated that 90% of patients could undergo R0 resection after receiving CIRT at 30–36.8 Gy(RBE) in eight fractions, with no local recurrences reported. The 5-year OS rate of patients who underwent surgery was 52%. Based on these findings, a subsequent phase II study [64] reported that 89% of patients underwent surgery after receiving CIRT, with a 5-year LC rate of 92.3% and an OS rate of 49%. Ongoing trials, such as the PLOPPO study in Italy [65], will further explore the efficacy of CIRT combined with chemotherapy in improving surgical outcomes for this group of patients.

Prostate cancer

For prostate cancer, RT is crucial for achieving optimal tumor control while minimizing gastrointestinal and genitourinary toxicities. While photon therapy is widely used, charged-particle therapies such as proton therapy and CIRT offer improved dose distribution and a lower incidence of side effects. This advantage is similar to what is observed in breast cancer [66,67]. The low alpha/beta ratio in prostate cancer makes it particularly amenable to hypofractionated treatment schedules [68]. Hypofractionated CIRT has shown high rates of biochemical recurrence-free survival (bRFS) with reduced toxicity compared to photon therapy. Although direct comparisons are limited, current studies suggest that CIRT may offer significant benefits in the treatment of prostate cancer.

Since 1995, CIRT has been administered to over 4,100 prostate cancer patients in Japan, with its use refined through numerous clinical trials. Initial phase I/II trials at NIRS escalated the doses from 54 Gy(RBE) to 72 Gy(RBE) across 20 fractions [69,70]. The second trial (protocol 9703) established 66 Gy(RBE) as the recommended dose [70,71]. A subsequent phase II trial (protocol 9904) [72] validated this regimen and reported 4-year bRFS rates of 87% in low-risk patients and 88% in high-risk patients. In this group, 5% experienced grade 2 genitourinary toxicity, 2% had gastrointestinal toxicity, and there were no grade 3 or higher events. Further research led to a reduction in dose to 63 Gy(RBE) in 20 fractions and subsequently to 57.6 Gy(RBE) in 16 fractions, achieving a 5-year bRFS rate of 88.5% with fewer cases of grade 2 genitourinary toxicity [73]. In 2010, protocol 1002 [74] adopted 51.6 Gy(RBE) in 12 fractions as the standard, with 5-year bRFS rates of 95.1%, 90.9%, and 91.1% in low-, intermediate-, and high-risk groups, respectively, and late grade 2 genitourinary and gastrointestinal toxicity in only 6.3% and 0.4% of patients, respectively. A Japanese multicenter study (J-CROS1501PR) [75] involving 2,157 patients further validated these outcomes, with 5-year RFS rates of 92%, 89%, and 92% in the respective risk groups and a lower incidence of grade 2 genitourinary and gastrointestinal toxicity.

In Germany and Italy, CIRT for prostate cancer has demonstrated favorable safety and efficacy outcomes. A clinical trial [76] at the HIT in Germany reported that CIRT was associated with a lower incidence of genitourinary and gastrointestinal toxicities compared to proton therapy. Among those treated with CIRT, 28.9% experienced grade 1 cystitis, 13.3% experienced grade 2 cystitis, 11.1% experienced grade 1 proctitis, and 2.2% experienced grade 2 proctitis. In Italy, a trial that combined CIRT with photon therapy for patients at high risk of prostate cancer indicated that this combined approach might offer better outcomes than photon therapy alone [77,78]. Additionally, quality of life assessments from studies conducted in Germany, Japan, and China [76,79,80] showed that CIRT had a minimal long-term impact on the quality of life. These studies reported transient acute genitourinary toxicity and no cases of significant gastrointestinal toxicity, reinforcing its safety and efficacy in prostate cancer.

Bone and soft tissue sarcoma

Sarcomas are known for their radioresistance and often develop in anatomically challenging locations, which complicates surgical resection. As a result, RT plays a pivotal role, especially for patients with unresectable tumors or residual disease. While traditional photon therapy is commonly employed, there is a growing preference for charged-particle therapies, such as CIRT, due to their enhanced efficacy. CIRT has demonstrated effectiveness in treating sarcomas, particularly those that are radioresistant or situated in complex anatomical areas. There is substantial evidence supporting the effectiveness of CIRT in improving LC and OS rates in patients with various types of sarcomas (Table 2).

CIRT has demonstrated significant efficacy in treating various types of bone sarcomas, particularly those that are inoperable or resistant to conventional therapies. In a study involving 188 patients treated with CIRT, Imai et al. [81,82] reported a 5-year LC rate of 77.2% and a 5-year OS rate of 81% in patients treated with CIRT at a dose of 64–73.6 Gy(RBE). More recent studies have also reported a 2-year LC rate exceeding 80% in patients with sacral chordomas or chondrosarcomas [83,84]. Furthermore, Shiba et al. [85] found that patients with inoperable bone sarcomas treated with CIRT exhibited a 3-year LC rate of 62% and an OS rate of 51%. For the treatment of primary spinal sarcomas, Matsunobu et al. [86] demonstrated that CIRT

Table 2. Clinical studies and outcomes of patients with bone and soft tissue sarcomas treated with CIRT

Author	Study design	Tumor type and location	No. of patients	CIRT dose (Gy(RBE))	LC	OS	Acute toxicity	Late toxicity
Bone sarcoma								
Imai et al. [81]	Retrospective	Sacral chordoma	188	64–73.6	5-yr 77.2%	5-yr 81.1%	NR	Gr 3 peripheral nerve toxicity=6, Gr 4 skin=2
Imai et al. [82]	Retrospective	Chondrosarcoma	73	64–73.6	5-yr 53%	5-yr 53%	NR	Gr 3 ≤toxicity=8, Gr 3 skin=3, bone fracture=4, bone necrosis=1
Wu et al. [83]	Retrospective	Chordoma or chondrosarcoma	21	57–80	1-yr 93.8%, 2-yr 85.2%	1-yr 100%, 2-yr 100%	Gr 1 skin=14.2%, Gr 1 myelosuppression=33.3% No Gr 2 ≤toxicity.	No severe late toxicity
Bostel et al. [84]	Retrospective	Primary or recurrent sacrococcygeal chordoma	68	60–70.4	Overall: 1-yr 90%, 2-yr 80%, 3-yr 65%, 5-yr 53% Primary: 1-yr 96%, 2-yr 88%, 3-yr 77%, 5-yr 62% Recurrent: 1-yr 68%, 2-yr 54%, 3-yr 27%, 5-yr 27%	Overall: 1-yr 97%, 2-yr 97%, 3-yr 86%, 5-yr 74%	NR	Radiogenic toxicity=40 (59%, 14 received at least 80 GyE) Gr 3 ≤=21%, Sacral insufficiency fractures=49%
Shiba et al. [85]	Retrospective	Bone sarcoma	53	64–70.4	Overall: 3-yr 88.6%, 5-yr 73.8% Chordoma: 3-yr 92.5%, 5-yr 84.8% Non-chordoma: 3-yr 82.2%, 5-yr 54.8% Osteosarcoma: 3-yr 87.5% Chondrosarcoma: 3-yr 60%	Overall: 3-yr 79.7%, 5-yr 79.7% Chordoma: 3-yr 91.3%, 5-yr 91.3% Non-chordoma: 3-yr 60.7%, 5-yr 60.7% Osteosarcoma: 3-yr 36.5% Chondrosarcoma: 3-yr 59.3%	No Gr 3 ≤toxicity Gr 1 dermatitis=21 Gr 2 dermatitis=6 Gr 1 neuropathy=6 Gr 2 neuropathy 2	Gr 3 dermatitis=5 Gr 3 GI tract=1 Gr 3 infection=5 Gr 3 dermatitis=3 Gr 3 GI tract=1 Gr 2 neuropathy=12 Gr 2 urinary=3 Gr 2 bone fracture=4
Matsunobu et al. [86]	Retrospective	Trunk osteosarcoma	78	52.8–73.6	5-yr 62%	5-yr 33%, <70 Gy(RBE)=56% ≥70 Gy(RBE)=27%	Gr 3 skin=3	Gr 3 skin/soft tissue=4 Gr 4 skin/soft tissue=3 Bone fracture requiring surgery=2

Table 2. Continued

Author	Study design	Tumor type and location	No. of patients	CIRT dose (Gy(RBE))	LC	OS	Acute toxicity	Late toxicity
Matsumoto et al. [87]	Retrospective	Primary spinal sarcoma	47	52.8–70.4	5-yr 79%	5-yr 52%	Gr 3 skin=1	Gr 3 skin 1, Gr 4 skin ulcer 1, Vertebral body compression=7 (more common in ≥70.4 GyE) Gr 3 myelopathy=1
Sugahara et al. [88]	Phase I/II	Extremity sarcoma	17	52.8–70.4	3-yr 76%, 5-yr 76%	3-yr 68%, 5-yr 56%	Gr 1 skin=16 (94%)	Gr 2 skin=1 (6%) Gr 2 neuropathy=4 (24%)
Pediatric/young adult sarcoma								
Mohamad et al. [89]	Retrospective	Unresectable truncal osteosarcoma	26	52.8–73.6	3-yr 70%, 5-yr 63%	3-yr 50%, 5-yr 42%	None	Gr 3–4=4 (1 Gr 3 skin, 1 Gr 4 skin, 2 neuropathy)
Combs et al. [90]	Retrospective	Skull base chordoma or chondrosarcoma	17	60–66.6	Only 1 tumor progression (60 months after CIRT)	NR	Only mild (Gr 1 or 2) Focal alopecia=1 (6%), skin=1 (6%)	No severe late toxicity, 2 hormone deficiency requiring hormone substitution, No secondary malignancy
Soft tissue sarcoma								
Serizawa et al. [91]	Retrospective	Unresectable retroperitoneal sarcoma	24	52.8–73.6	2-yr 77%, 5-yr 69%	2-yr 75%, 5-yr 50%	Gr 1 skin=83%, Gr 2 skin=17%	Gr 2 neurotoxicity=21% No Gr 3 toxicity
Imai et al. [92]	Phase I/II	Unresectable axial soft tissue sarcoma (deep 96%, subdeep 4%)	128	64–73.6	3-yr 68%, 5-yr 65%	3-yr 60%, 5-yr 46%	NR	Gr 3≤4 Gr 3 spinal cord injury=1 Gr 3 peripheral nerve injury=1 Gr 4 colon injury=1 Gr 3 skin=1

CIRT, carbon-ion radiotherapy; Gy(RBE), gray (relative biological effectiveness); LC, local control; OS, overall survival; yr, year; NR, not reported; Gr, grade; GI, gastrointestinal.

delivered at a dose of 64 Gy(RBE) in 16 fractions achieved a 5-year LC rate of 79% and an OS rate of 52%. The effectiveness of CIRT has also been prospectively evaluated in primary spinal sarcomas [87] or localized primary sarcomas of the extremities [88]. Moreover, it has shown potential in pediatric and young adult patients with bone tumors [89,90], providing effective treatment without significant growth disturbances or secondary malignancies, as observed in studies from the NIRS in Japan and HIT in Germany. These results collectively illustrate CIRT's ability to provide effective tumor control with a manageable toxicity profile across various challenging bone sarcomas.

CIRT has shown promising results in treating retroperitoneal sarcoma, a particularly challenging subtype of soft tissue sarcomas due to their proximity to critical structures like the gastrointestinal tract. Since 1997, CIRT has been used at the NIRS to manage unresectable retroperitoneal sarcomas that are not extensively attached to the intestines and measure less than 20 cm, employing a dose of 70.4 Gy(RBE) delivered in 16 fractions over 4 weeks. Serizawa et al. [91] reported a 5-year LC rate of 69% and an OS rate of 50% in patients with unresectable retroperitoneal sarcomas with no gastrointestinal complications or grade 2 or higher toxicity. This finding suggests that CIRT is an effective treatment option for these cases. Additionally, Imai et al. [92] evaluated 128 patients with unresectable axial soft tissue sarcomas treated with CIRT at doses of 64–73.6 Gy(RBE). They reported a 5-year LC rate of 54% and a 5-year OS rate of 46%, with grade 3 or higher late adverse events occurring in four patients.

Although the administration of high-dose CIRT is associated with the risk of late toxicity, particularly osteoradionecrosis and soft tissue necrosis, its ability to achieve high LC rates in both bone and soft tissue sarcomas makes it an invaluable treatment option. The use of surgical spacers for tumors located near the gastrointestinal tract has proven to be an effective strategy for reducing the risk of severe complications [93,94], thereby enabling safer delivery of CIRT and improving patient outcomes.

Future directions

CIRT has demonstrated significant clinical efficacy across various types of malignancies and offers distinct advantages over conventional therapies due to its unique physical and biological properties. However, the lack of high-level evidence, especially from randomized controlled trials, challenges the establishment of CIRT's superiority over conventional therapies. To further solidify CIRT's role in modern oncology, it is crucial to address these gaps by conducting well-designed randomized controlled trials that directly compare CIRT with conventional therapies. In addition to these trials, adopting a multifaceted approach that includes long-term clinical cohort studies and the establishment of robust multicenter registries is essential. These initiatives will provide a deeper understanding of CIRT's clinical benefits across diverse patient populations, refine patient selection criteria, and optimize treatment protocols. Moreover, future advancements in CIRT will be influenced by translational research. Key areas of exploration include the integration of ultrahigh-dose-rate (FLASH) therapy, which could further enhance the therapeutic window of CIRT by reducing the risk of normal tissue toxicity. Additionally, investigating the immunogenic effects of particle therapy could reveal potential synergies with emerging immunotherapies. As CIRT facilities continue to expand globally, particularly in leading countries such as Japan, the United States, Europe, and Korea, this growth must be managed through strategic planning and comprehensive cost-effectiveness analyses. These efforts should be complemented by initiatives to standardize treatment protocols and facilitate international collaboration to ensure

that the benefits of CIRT are accessible to a broad range of patients worldwide. By addressing these challenges and capitalizing on new research opportunities, CIRT is expected to play a transformative role in cancer treatment.

Conclusion

The establishment of Korea's first CIRT center at the Yonsei Cancer Center, along with the development of additional CIRT centers in Korea and abroad, offers a significant opportunity to gather compelling evidence that could substantiate the clinical advantages of CIRT and broaden its uses. By coordinating clinical and translational research with carefully devised expansion strategies, CIRT is well-positioned to improve survival rates, enhance the quality of life for cancer patients, and potentially decrease the risk of secondary malignancies. These advancements highlight the pivotal role of CIRT as a critical modality in modern cancer treatment, setting the stage for its incorporation into worldwide oncological practices.

ORCID

Seo Hee Choi: <https://orcid.org/0000-0002-4083-6414>

Woong Sub Koom: <https://orcid.org/0000-0002-9435-7750>

Hong In Yoon: <https://orcid.org/0000-0002-2106-6856>

Kyung Hwan Kim: <https://orcid.org/0000-0002-6713-1350>

Chan Woo Wee: <https://orcid.org/0000-0002-0631-7549>

Jaeho Cho: <https://orcid.org/0000-0001-9966-5157>

Yong Bae Kim: <https://orcid.org/0000-0003-4884-2330>

Ki Chang Keum: <https://orcid.org/0000-0003-4123-7998>

Ik Jae Lee: <https://orcid.org/0000-0001-7165-3373>

Authors' contributions

Project administration: Lee IJ

Conceptualization: Choi SH, Lee IJ

Methodology & data curation: Choi SH, Koom WS, Yoon HI, Kim KH, Wee CW, Cho J, Kim YB, Keum KC, Lee IJ

Funding acquisition: Choi SH, Lee IJ

Writing – original draft: Choi SH

Writing – review & editing : Choi SH, Koom WS, Yoon HI, Kim KH, Wee CW, Cho J, Kim YB, Keum KC, Lee IJ

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Supplementary materials

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FLASH radiotherapy: bridging revolutionary mechanisms and clinical frontiers in cancer treatment – a narrative review

Jae Sik Kim¹, Hak Jae Kim^{2,3}

¹Department of Radiation Oncology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

²Department of Radiation Oncology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

³Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author

Hak Jae Kim
Department of Radiation Oncology,
Seoul National University Hospital, Seoul
National University College of Medicine,
101 Daehak-ro, Jongno-gu, Seoul 03080,
Korea
E-mail: khjae@snu.ac.kr

Keywords

FLASH radiotherapy; Radiobiology;
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FLASH radiotherapy (FLASH-RT) is an innovative approach that delivers ultra-high dose rates exceeding 40 Gy in less than a second, aiming to widen the therapeutic window by minimizing damage to normal tissue while maintaining tumor control. This review explores the advancements, mechanisms, and clinical applications of FLASH-RT across various radiation sources. Electrons have been predominantly used due to technical feasibility, but their limited penetration depth restricts clinical application. Protons, offering deeper tissue penetration, are considered promising for treating deep-seated tumors despite challenges in beam delivery. Preclinical studies demonstrate that FLASH-RT reduces normal tissue toxicity in the lung, brain, skin, intestine, and heart without compromising antitumor efficacy. The mechanisms underlying the FLASH effect may involve oxygen depletion leading to transient hypoxia, reduced DNA damage in normal tissues, and modulation of immune and inflammatory responses. However, these mechanisms are incompletely understood, and inconsistent results across studies highlight the need for further research. Initial clinical studies, including treatment of cutaneous lymphoma and bone metastases, indicate the feasibility and potential benefits of FLASH-RT in patients. Challenges for clinical implementation include technical issues in dosimetry accuracy at ultra-high dose rates, adaptations in treatment planning systems, beam delivery methods, and economic considerations due to specialized equipment requirements. Future directions will involve comprehensive preclinical studies to optimize irradiation parameters, large-scale clinical trials to establish standardized protocols, and technological advancements to overcome limitations. FLASH-RT holds the potential to revolutionize radiotherapy by reducing normal tissue toxicity and improving therapeutic outcomes, but significant research is required for real-world clinical applications.

Introduction

Background

Radiotherapy (RT) is a crucial component of antitumor therapies, and approximately 30% of cancer patients in Korea undergo RT [1]. RT must strike a balance between efficiently killing tumor cells and minimizing damage to normal tissue [2]. This constraint complicates the administration of an adequate tumoricidal dose, presenting a significant challenge, especially in the context of

repeated RT [3,4]. Although numerous biological studies have been conducted to prevent or mitigate RT-induced acute and late toxicities, there have also been significant advancements in radiation technology over the past few decades, such as intensity-modulated RT, stereotactic body RT, and adaptive RT [5–10]. Moreover, technologies aided by artificial intelligence have been integrated into these advancements [11]. Despite these improvements, the radiation oncology community continues to explore new methods to expand the therapeutic window, as there remain unmet medical needs.

One of these innovative approaches is FLASH radiotherapy (FLASH-RT), which delivers irradiation at an ultra-high dose rate (UHDR) exceeding 40 Gy in less than a second [12]. This method can significantly shorten treatment times compared to conventional RT. In 1959, Dewey and Boag first observed that the radiosensitivity of *Serratia marcescens* decreased when exposed to 1.5 MV X-rays at a UHDR of 10–20 kilorads/2 μ s, thereby protecting the bacteria compared to exposure at conventional dose rates—a phenomenon now known as the FLASH effect [13]. The term FLASH-RT was first introduced in a 2014 study by Favaudon et al. [14]. Subsequent preclinical experiments with mammalian cells and animal models have shown that UHDR irradiation, compared to conventional RT, provides a similar antitumor effect while also protecting normal tissue [12]. In 2019, a case report detailed the treatment of a patient with T-cell cutaneous lymphoma using FLASH-RT, noting that the approach was feasible and resulted in favorable outcomes for both the lymphoma and normal skin [15].

When cells and tissues are irradiated, a series of physical, chemical, and biological reactions occur. However, after FLASH-RT, these reactions do not advance to the biochemical phase [16]. Several radiobiological hypotheses have been proposed to explain the differential effects of FLASH-RT on normal and tumor tissues, including oxygen depletion, DNA damage, and the immune/inflammatory response [17]. Nevertheless, the exact mechanism of action of FLASH-RT is still not well understood.

Objectives

The purpose of this review is to explore the revolutionary advancements and underlying mechanisms of FLASH-RT in cancer treatment. By integrating findings from both preclinical and clinical studies, this review aims to highlight the therapeutic potential and challenges of FLASH-RT, ultimately bridging the gap between cutting-edge radiobiological research and clinical application.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

FLASH radiotherapy beam delivery devices

FLASH-RT is theoretically feasible with all contemporary RT equipment; however, most research has primarily utilized pulsed electron beams [18]. In this session, we will introduce the characteristics of FLASH-RT according to different radiation sources. However, implementing FLASH-RT in clinical settings using current RT modalities presents technical challenges, including the need for multiple beam directions to ensure tumor conformity [19].

Electrons

The initial studies on FLASH-RT were performed using low-energy electrons (~25 MeV) from either experimental or medical linear accelerators [20]. Conventional C-arm and intraoperative RT devices have also been successful in achieving UHDR [21]. These devices are readily available for UHDR, and several vendors are developing electron beam FLASH-dedicated linear accelerators [18]. However, the clinical application of this technology is restricted by the inherent properties of electrons, which include a low penetration depth of only a few centimeters, a short source-target distance (~50 cm), and a significant lateral penumbra [18,21]. Consequently, only skin cancers or tumors located within 2–3 cm of the body surface are currently suitable for treatment with FLASH-RT [22].

The use of very high energy electrons (VHEE, 50–250 MeV) has been suggested as an effective method for delivering therapeutic doses to tumors deep within the body using external electron beam FLASH-RT [22]. VHEE beams demonstrate relative insensitivity to body inhomogeneities compared to protons [23]. Although VHEE beams are associated with high entrance and exit doses, employing multi-directional beams can offer a benefit by sparing the skin [23,24]. However, due to the technical challenges associated with electron acceleration, VHEE research is limited to a few facilities, including the Photo Injector Test facility at Deutsches Elektronen-Synchrotron in Zeuthen and the European Organization for Nuclear Research Linear Electron Accelerator for Research facility [21].

Photons

Currently used linear accelerators in RT are unsuitable for photon beam-based FLASH-RT [18]. The primary reason is the high inefficiency in converting the electron beam to a photon beam, largely due to electron heat deposition [21,22]. This inefficiency necessitates the generation of a factor of 1,000 more electrons than current equipment can handle, presenting a significant challenge that must be overcome. Furthermore, technology that can accelerate this vast quantity of electrons and convert them into photons is also required [22].

Unlike high-energy beams, X-rays with energies <1 MeV can achieve FLASH conditions through a synchrotron [18]. The European Synchrotron Radiation Facility was the first to demonstrate that a UHDR synchrotron light source could reduce brain injury in mice following whole-brain irradiation [25]. Johns Hopkins University successfully achieved UHDR (40–240 Gy/s) using two 150 kVp fluoroscopy systems [26]. Development projects for new accelerators specifically designed for conventional, high-energy photon UHDR beams are currently in progress. Notable examples include the superconductive linac (6–8 MeV) from the Chengdu THz Free Electron Laser group and the Pluridirectional High-energy Agile Scanning Electronic RT platform from the Stanford Linear Accelerator Center [18,21].

Protons

Protons, unlike electrons and photons, possess a unique physical property known as the Bragg peak, where they deposit most of their energy at a specific depth just before stopping. This characteristic enables proton therapy to concentrate the dose on the tumor site while reducing exposure beyond the Bragg peak, thereby minimizing the risk of side effects [27]. Clinical isochronous cyclotrons utilized in proton therapy can deliver intensities exceeding 60 Gy/s at a fixed energy [18]. With proton energies surpassing 200 MeV, these cyclotrons are capable of treating deep-seated tumors [21]. As a result, protons are considered the most advanced technology for the clinical application of FLASH therapy [18].

Proton therapy employs pencil beam scanning to accurately target tumor volumes. However, a significant limitation of proton-based FLASH therapy stems from this method of beam delivery, as existing technology cannot accommodate the rapid energy modulation needed. In clinical settings, it is difficult to achieve FLASH conditions across the entire tumor due to the current speed of 3D volumetric scanning. Each energy change in the scanning process takes about one second, which is too slow to satisfy FLASH criteria. To achieve FLASH conditions throughout the entire tumor, the scanning speed must be increased by at least two orders of magnitude [18].

Researchers are actively working to overcome this challenge and bring this technology into routine clinical use. Hybrid active-passive systems featuring patient-specific 3D range modulators are currently being tested in clinical facilities and offer extremely rapid irradiation times (<1 s). Additionally, laser-driven accelerators are under development at Helmholtz-Zentrum Dresden-Rossendorf [18].

Heavy ions

The depth-dose distribution of heavy ions exhibits a Bragg peak similar to that observed with protons; however, unlike protons, heavy ions also display a tail region [21]. Heavy ions offer additional advantages in RT, including a sharper lateral penumbra and higher relative biological effectiveness [18,21]. Despite these advantages, the global number of heavy ion centers remains limited. Consequently, research on FLASH-RT using heavy ions has been relatively sparse, partly due to the technical challenges associated with the synchrotron accelerators needed to achieve UHDR [21]. Currently, the Heidelberg Ion Beam Therapy Center has achieved dose rates exceeding 50 Gy/s using both helium and carbon ions. Meanwhile, Gunma University Hospital has reached dose rates up to 195 Gy/s with carbon ions, and the GSI Helmholtz Center for Heavy Ion Research has exceeded 100 Gy/s [18].

In vivo studies on FLASH radiotherapy

The burgeoning interest in UHDR FLASH-RT is driven by recent preclinical studies that have shown its potential to protect various normal tissues (Table 1). These promising results have sparked a surge of *in vivo* research focused on understanding the underlying mechanisms and improving clinical applications. RT often results in significant toxicity, which complicates the administration of high doses to tumors [28–30]. Given FLASH-RT's ability to preserve normal tissues, it could facilitate dose escalation, thus improving tumor control while maintaining similar levels of normal tissue toxicity. However, it is crucial to acknowledge that not all studies have demonstrated the FLASH effect, with some yielding negative outcomes. This underscores the urgent need for additional research to better comprehend the factors that affect the efficacy of FLASH-RT.

Lung

The first groundbreaking proof of concept study in 2014, using a lung fibrosis mouse model, demonstrated that 17 Gy FLASH-RT prevented lung fibrosis and radiation-induced acute apoptosis in blood vessels and bronchi. At 30 Gy, FLASH-RT was less fibrogenic than conventional RT, although it still caused some pulmonary fibrosis [14]. The morphology of lung tissue exposed to 20 Gy of either single or 10-pulse (fractionated) FLASH resembled that of non-irradiated tissue, with only minimal neutrophil infiltration [31]. This finding was consistent with observations from 30 Gy FLASH whole-thorax irradiation [32]. In contrast, the conventional

Table 1. Summary of *in vivo* studies demonstrating the effect of FLASH on normal tissues

Irradiated site	Model	FLASH source (energy)	FLASH dose rate (Gy/s)	FLASH dose ¹⁾ (Gy)	Main assessment	Reference
Lung	Mouse	Electrons (4.5 MeV)	60	17 or 30	Pulmonary fibrosis Apoptosis	Favaudon et al. [14]
Lung	Mouse	Electrons (4.5 MeV)	60	17	Pulmonary fibrosis Cell proliferation RNA sequencing DNA damage Radiation-induced senescence	Fouillade et al. [33]
Lung	Mouse	Photons (8 MeV)	1,200	30	Survival Pathological analysis	Gao et al. [32]
Lung	Mouse	Photons (1.25 MeV)	200	20 (1 or 10 pulses)	Pathological analysis	Dai et al. [31]
Brain	Mouse	Electrons (4.5 or 6 MeV)	5.6M ²⁾	10	Cognitive function Neurogenesis	Montay-Gruel et al. [34]
Brain	Mouse	Electrons (6 MeV)	>100	10	Cognitive function Neuroinflammation Neuronal morphology	Montay-Gruel et al. [36]
Brain	Mouse	Electrons (16 or 20 MeV)	200 or 300	30	Cognitive function Neuroinflammation Neuronal morphology Cytokine assay	Simmons et al. [41]
Brain	Mouse	Electrons (6 MeV)	2.5K	10 or 25	Cerebrovascular structure Apoptosis within neurogenic regions	Allen et al. [44]
Brain	Mouse	Electrons (6 MeV)	5.6M	10	Astrogliosis Astrocytic/microglial expression	Montay-Gruel et al. [35]
Brain	Mouse	Electrons (6 MeV)	2.5K–7.8M	10, 14, 25 ³⁾ , 14/4 Fx, 14/2 Fx, or 30/3 Fx,	Cognitive function	Montay-Gruel et al. [40]
Brain	Mouse	Electrons (6 MeV)	1.6M	30/10 Fx	Long-term potentiation	Limoli et al. [42]
Brain	Mouse	Photons (102 keV)	37	10	Cognitive function Neurogenesis Neuroinflammation	Montay-Gruel et al. [25]
Brain	Mouse	Protons (146.6 MeV)	120	10	Neuroinflammation DNA damage Cerebrovascular structure HMGB1 expression	Dokic et al. [37]
Brain	Mouse, juvenile	Electrons (6 MeV)	4.4M	8	Cognitive function Neurogenesis Neuroinflammation Pituitary function	Alaghband et al. [38]
Brain	Mouse, juvenile	Electrons (6 MeV)	5.6M	20/2 Fx	Cognitive function Neuroinflammation Neuronal morphology Long-term potentiation Cerebrovascular structure	Allen et al. [39]
Brain	Rat	Electrons (10 MeV)	≥429	20–30	Hair loss	Liljedahl et al. [67]
Brain	Rat	Protons (226 MeV)	257	25	Cognitive function Neuroinflammation Circulating immune cell	Iturri et al. [43]
Skin	Mouse	Electrons (16 MeV)	180	10–40	Survival Skin damage	Soto et al. [45]
Skin	Mouse	Protons (250 MeV)	57 or 115	35	Skin damage Leg contracture TGF-β1 expression Cytokine assay	Cunningham et al. [47]

Table 1. Continued

Irradiated site	Model	FLASH source (energy)	FLASH dose rate (Gy/s)	FLASH dose ¹⁾ (Gy)	Main assessment	Reference
Skin	Mouse	Protons (230 MeV)	69–124	30	Survival Skin/muscle/bone damage Skin inflammation Lymphedema RNA sequencing TGF- β 1 expression	Velalopoulou et al. [46]
Skin	Mouse	Protons (250 MeV)	71–89	40–60	Skin damage Fibrosis	Sørensen et al. [49]
Skin	Mouse	Protons (230 MeV)	~130	25–45	Skin damage	Zhang et al. [48]
Skin	Mouse	Protons (20 MeV)	930	23 or 33	Skin damage Ear swelling/inflammation Cytokine assay	Rudigkeit et al. [50]
Skin	Mini-pig	Electrons (4.5 or 6 MeV)	~300	22–34	Skin damage	Vozenin et al. [51]
Skin	Mini-pig	Electrons (6 MeV)	150	31	Skin damage	Rohrer Bley et al. [52]
Abdomen	Mouse	Electrons (16 MeV)	216	14 or 16	Survival Body weight Intestinal damage Intestinal crypts Stool pellets Apoptosis DNA damage	Levy et al. [57]
Abdomen	Mouse	Electrons (6 MeV)	2M–6M	5–19.9	Intestinal crypts Fecal microbiome analysis	Ruan et al. [54]
Abdomen	Mouse	Photons (6 MV)	110–120	13 or 25/5 Fx	Intestinal crypts Fibrosis Immune cell infiltration cGAS-STING activation	Shi et al. [58]
Abdomen	Mouse	Photons (6 MV)	>150	10 or 15	Survival Body weight Intestinal damage Intestinal crypts Immune cell infiltration Complete blood count Cytokine assay ROS, antioxidant enzyme, and lipid peroxidation response	Zhu et al. [59]
Abdomen	Mouse	Photons (8 MeV)	700 or 937	12 or 15	Survival Pathological analysis	Gao et al. [32]
Abdomen	Mouse	Protons (230 MeV)	94 (whole-abdomen) or 63 (focal abdomen)	15 (whole-abdomen) or 18 (focal abdomen)	Intestinal crypts Fibrosis	Diffenderfer et al. [55]
Abdomen	Mouse	Protons (230 MeV)	106.2–108.2 (SOBP) or 107.1–118.5 (entrance region)	15	Intestinal crypts	Kim et al. [56]
Heart	Mouse	Protons (230 MeV)	122.65	40	DNA damage RNA sequencing TGF- β 1/TNF- α / α SMA expression Myocardial fibrosis Echocardiography	Kim et al. [60]

K, 10^3 ; M, 10^6 ; HMGB1, high mobility group box protein 1; cGAS, cyclic guanosine monophosphate–adenosine monophosphate synthase; STING, stimulator of interferon genes; ROS, reactive oxygen species; SOBP, spread-out Bragg peak; TNF, tumor necrosis factor; SMA, smooth muscle actin.

¹⁾ Used to assess the effects on normal tissue.

²⁾ To investigate the differences in FLASH-induced neuropreservation at various dose rates, intermediate dose rates of 1, 3, 10, 30, 100, and 500 Gy/s were also used.

³⁾ Delivered only to the right hemisphere.

RT group showed additional changes, including thickening of the alveolar septum and interstitial hemorrhage [31].

The study conducted by Fouillade et al. provides compelling evidence that FLASH irradiation offers protective effects on lung tissue compared to conventional RT [33]. The researchers observed that FLASH irradiation significantly reduced DNA damage in irradiated lung tissues and decreased the proliferation of lung progenitor cells following injury. Through single-cell RNA sequencing and histological analyses, it was revealed that FLASH reduced the activation of pro-inflammatory genes, diminished progenitor cell proliferation, and curtailed stem cell senescence, all factors contributing to lung fibrosis. Notably, lungs treated with FLASH showed a greater potential for tissue regeneration, exhibiting fewer signs of persistent DNA damage and senescence compared to those treated with conventional RT. However, these protective effects were absent in *Terc*^{-/-} mice, which have notably shortened telomeres and deficient telomerase activity, underscoring the critical role of telomere integrity and progenitor cell populations in harnessing the full benefits of FLASH.

In a study comparing thorax-irradiated mice, the FLASH group exhibited an 81% lower risk of mortality compared to the conventional group [32]. By the end of the follow-up period, survival rates were 100% in the control group, 90% in the FLASH group, and 50% in the conventional group.

Brain

Montay-Gruel et al. were the first to show that after 10 Gy whole-brain irradiation in mice, spatial memory was impaired at conventional dose rates, but remained unchanged at dose rates of ≥ 100 Gy/s [34]. This preservation of memory was attributed to the reduced impact of FLASH-RT on neurogenesis in the subventricular zone of the hippocampus compared to conventional dose rates. Montay-Gruel and colleagues also demonstrated this neuroprotective effect using synchrotron-generated X-rays for FLASH-RT [25]. Additionally, radiation-induced reactive astrogliosis was less severe following FLASH treatment than with conventional RT [25,35]. In later experiments, FLASH-RT was associated with long-term neurocognitive benefits over a 6-month period, reduced neuroinflammation, and preserved neuronal structure [36]. Not only was astrogliosis less pronounced in the FLASH group compared to conventional RT, but there was also no significant increase in the number of activated microglia in the hippocampus or brain cortex [36,37]. The dendritic area, branches, and length, which were significantly reduced after conventional RT compared to the control, were maintained in the FLASH-irradiated brain [36]. Similar results were observed in the number, density, and volume of dendritic spines.

Although the juvenile mouse brain is known to be radiosensitive, the FLASH effect was still observed [38,39]. Further research has shown that FLASH-RT not only spares the neurogenic niche but also preserves pituitary function, as evidenced by stable growth hormone levels [38]. Even with hypofractionated regimens, it prevented radiation-induced neurocognitive complications in the normal brain [39,40]. Other researchers have also validated the relationship between FLASH-RT and reduced cognitive deficits in both spatial and non-spatial object recognition, as well as associated neurodegeneration, at the electrophysiological, molecular, and structural levels [39,41,42].

In experiments involving proton-based FLASH, no significant differences were observed in locomotion, exploratory behavior, spontaneous activity, or anxiety levels among the control, FLASH, and conventional RT groups [43]. However, in the object recognition task used to assess memory, both the control and FLASH groups demonstrated good recall of the familiar object,

in contrast to the rats that received conventional RT. Analysis of the immune cell populations in the brain parenchyma revealed that infiltration of peripheral immune cells (CD45^{high}) occurred irrespective of the dose rate. Additionally, there was a 4-fold reduction in microglia compared to non-irradiated tissue, with no variations noted across different dose rates.

These beneficial effects of FLASH might result from reduced production of reactive oxygen species or less pronounced increases in pro-inflammatory cytokines following FLASH-RT [36,41]. They may be associated with the preservation of cerebrovascular integrity through the protection of tight junctions or aquaporin-4 levels [37,39,44].

Skin

FLASH-RT has the potential to mitigate radiation-induced skin reactions, which could significantly reduce both acute and late skin reactions in the treatment of head and neck cancers and extremity soft tissue sarcoma when integrated into future clinical practice [45–48]. When murine skin was subjected to UHDR proton therapy, the skin reaction score was lower compared to that observed with conventional proton therapy [45–47]. There were fewer instances of epidermal necrosis, skin stem cell depletion, hair follicle atrophy, inflammation, epidermal hyperplasia, myofiber atrophy, and bone remodeling [46,47,49,50]. The potential benefits of FLASH-RT have also been demonstrated in mini-pigs; however, severe late skin necrosis, which was volume-dependent, developed but eventually resolved [51,52]. Regarding lymphedema, no differences were noted in the incidence or progression between the dose rates; however, the severity was greater in mice that received conventional RT [46]. This reduction in side effects translated into a survival benefit for mice that received ≤ 40 Gy, although no survival difference was observed between the two dose rates at the 45 Gy dose [45,46].

Zhang et al. reported the oxygen dependence of the FLASH effect [48]. FLASH irradiation improved skin contraction (25–30 Gy), epidermal thickness (25 Gy), and collagen deposition (25 Gy). However, when irradiation occurred in a 100% oxygen environment or under hypoxic conditions induced by restricting blood flow through leg constriction, the tissue-sparing effect of FLASH was lost.

In transcriptome analysis, pathways such as apoptotic signaling, keratinocyte differentiation, and cornification were upregulated in the group that received conventional proton therapy. Conversely, these changes were not observed in the UHDR group [46]. TGF- β 1 expression was also observed at lower levels following FLASH-RT [46,47]. The levels of chemokine ligand-1 and granulocyte-colony stimulating factor increased, while those of granulocyte-macrophage colony-stimulating factor decreased following conventional RT [47]. The granulocyte-macrophage colony-stimulating factor/granulocyte-colony stimulating factor ratio, which inversely correlates with tissue toxicity, was reduced in the conventional group, suggesting increased tissue toxicity [53]. In the FLASH group, IL-6 levels rose, although no significant differences in IL-6 levels were noted between the 57 Gy/s and 115 Gy/s dose rates [47]. However, when proton irradiation was delivered at 930 Gy/s, no differences were observed in the levels of TGF- β 1, IL-1 α , IL-1 β , and tumor necrosis factor- α in the blood [50].

Intestines

FLASH experiments using electrons demonstrated more favorable crypt survival at doses between 7.5–12.5 Gy after whole-abdominal irradiation than after conventional dose rate irradiation [54]. However, this sparing effect decreased as the number of FLASH pulses increased or as the interval between pulses extended, leading to a longer delivery time. When 15

Gy of proton irradiation was administered to the whole abdomen, there was a smaller reduction in proliferating cells within the jejunum crypts in the FLASH group than in the conventional RT group [55,56]. After intestinal irradiation at 15 or 18 Gy, the extent of intestinal fibrosis was similar to that observed in non-irradiated tissue [32,55].

Some studies have shown that abdominal FLASH irradiation reduces mortality in mice suffering from radiation-induced gastrointestinal syndrome compared to conventional irradiation [32,57]. This protective effect is believed to stem from FLASH irradiation's ability to decrease chromosomal damage and apoptosis in the crypt base columnar cells of the jejunum, thereby helping to preserve intestinal function and epithelial integrity [57]. Additionally, the beneficial impact of FLASH X-rays may be associated with differing inflammatory responses, including reduced activation of the cyclic guanosine monophosphate–adenosine monophosphate synthase–stimulator of interferon genes (cGAS–STING) pathway and changes in the redox status within the intestinal crypts [58,59].

Fecal samples were utilized for gut microbiome analysis, revealing that overall α -diversity and evenness declined across all irradiated groups, although richness decreased solely in the conventional group [54]. In the β -diversity analysis, the cluster of the FLASH-treated group was closer to that of the control group, suggesting fewer alterations in the microbiome.

Heart

The impact of FLASH-RT on the heart remains largely unexplored. Until recently, research in this area continued to be scarce, with the heart being an uncharted area in FLASH-RT studies. It was not until 2024 that the first study addressing the effects of FLASH-RT on cardiac tissue was published, marking a significant advancement in our understanding of how this innovative RT might influence cardiac function.

A recent study investigated the impact of proton FLASH-RT aimed specifically at the cardiac apex, delivering a precise 40 Gy dose [60]. The research utilized γ H2AX staining to evaluate DNA damage, which was found to be limited to the lower third of the heart, with no impact on adjacent tissues. Bulk RNA sequencing of cardiac tissue revealed distinct pathway regulations based on the treatment approach. In the FLASH-RT group, pathways related to cytoplasmic translation, mitochondrion organization, and adenosine triphosphate synthesis were upregulated. In contrast, pathways involved in tissue morphogenesis and the regulation of developmental growth were downregulated. A key finding was that FLASH-RT reduced cardiac inflammation and profibrotic responses, leading to decreased myocardial fibrosis. Unlike conventional RT, FLASH-RT maintained heart functionality at levels similar to those of non-irradiated controls.

Tumors

Tumor cell killing was not altered, as reported by Favaudon et al., who found that both xenograft human tumor and syngeneic orthotopic lung tumor models exhibited equivalent tumor growth inhibition when comparing FLASH-RT (4.5 MeV electrons, 60 Gy/s) with conventional RT [14]. Similarly, other studies employing various tumor models and FLASH sources have demonstrated comparable levels of histological tumor cell damage, regardless of the dose rate and fractionation [31,40,43,46,47,49,55–57,61–67]. In some instances, tumor growth was even more delayed with FLASH-RT than with conventional RT [32]. In a separate study using 250 MeV proton beams, no difference in lung tumor diameter was observed between 18 Gy FLASH (60 Gy/s) and conventional irradiation; however, there was a significant reduction in proliferating

tumor cells following FLASH, indicating a meaningful decrease in lung tumor burden [68]. The survival of tumor-bearing mice was found to be equivalent to or better with FLASH-RT compared to conventional RT [14,32,40,56,66].

Although numerous studies have explored the interaction between the tumor immune microenvironment (TIME) and FLASH-RT, the results have so far been varied and inconsistent [43, 61, 62, 65, 68]. Some researchers have observed that FLASH retains its antitumor efficacy even in severely immunodeficient mice, suggesting the existence of an antitumor mechanism that may function independently of the immune response [65]. FLASH-RT has been shown to enhance cytotoxic T-cell infiltration into tumors and reverse the immunosuppressive phenotype [68]. There was an increase in CD8⁺ T-cell recruitment to the tumor, accompanied by a decrease in the infiltration of immunosuppressive regulatory T-cells (Treg). Additionally, macrophage polarization shifted towards an M1-like phenotype, which facilitated increased lymphocyte infiltration in lung tumors. Furthermore, FLASH-RT suppressed the expression of programmed death-1 (PD-1) and its ligand (PD-L1).

In an orthotopic glioma rat model, tumor-infiltrating lymphocytes, including CD4⁺ and CD8⁺ T-cells, increased at both conventional dose rates and UHDR (226 MeV proton, 257 Gy/s) [43]. Interestingly, Treg levels also increased in both groups. Additionally, there were observed increases in natural killer cells and B cells, suggesting that cranial irradiation activates adaptive immunity. However, in the FLASH group, no increase in tumor myeloid cells was noted.

A very recent study using an orthotopic syngeneic mouse model of brainstem diffuse midline glioma explored high-resolution profiling of the TIME following FLASH (9 MeV electron, 90 Gy/s) and conventional dose-rate RT [61]. The methods employed included single-cell RNA sequencing and flow cytometry. Analysis of CD45⁺ cells revealed that both the FLASH and conventional groups displayed similar proportions of immune subsets, with microglia as the predominant population. As an acute effect of RT, both FLASH and conventional irradiation triggered a type 1 interferon (IFN1) response in microglia. However, by day 10 post-RT, the FLASH group exhibited a dose-rate-dependent reduction in the IFN1 response in microglia, indicating a distinct temporal pattern and suggesting that microglial activation by FLASH was transient during the early stages. Regarding non-resident myeloid cells, such as macrophages and dendritic cells, which represented a minor fraction of the TIME, an early IFN1 response was observed in the conventional group, but in the FLASH group, this response was not clearly defined until day 10 post-RT. Despite these temporal immune changes, no significant differences in tumor control were noted between the dose rates, highlighting an area for future research.

Several trials have explored FLASH-RT in animals with cancer, using electrons in the 4.5–12 MeV range [51,52,69–71]. In one study, seven cats with T1/2N0M0 squamous cell carcinoma of the nasal planum received 30 Gy of radiation [52]. All remained tumor-free for one year, with only one case showing progression thereafter. Another trial involved six cats with locally advanced T2/T3N0M0 tumors treated with 25–41 Gy, achieving an 84% progression-free survival rate at 16 months [51]. Additionally, a collaborative effort between researchers from Denmark and Sweden applied FLASH-RT to canine cancer patients with superficial malignant tumors [69–71]. The treatment was effective, although it was associated with a potential risk of osteoradionecrosis.

Clinical studies with FLASH radiotherapy

The clinical application of FLASH-RT was first demonstrated in 2018 when a 75-year-old patient with multi-resistant CD30⁺ T-cell cutaneous lymphoma received treatment at Lausanne

University Hospital in Switzerland (Table 2) [15]. A skin tumor measuring 3.5 cm was exposed to 15 Gy of radiation in just 90 milliseconds using a 5.6-MeV linac. The tumor began to shrink 10 days after treatment with FLASH-RT, achieving a complete response by day 36, which was sustained for five months. Regarding adverse effects, the patient experienced asymptomatic grade 1 epithelitis and grade 1 edema in the surrounding skin, which had previously undergone extensive RT. Optical coherence tomography showed no reduction in epidermal thickness or disruption of the basal membrane, except for a slight increase in vascularization. Subsequently, the patient underwent two additional treatments of 15 Gy each at different sites on the same day (dose rates, 166 Gy/s and 0.08 Gy/s, respectively) [72]. Over the next 2 years, both treatment sites exhibited similar levels of acute and late skin toxicity, with no differences in tumor response noted (Table 2).

The FAST-01 trial, a pioneering first-in-human study of FLASH-RT, involved 10 patients with symptomatic bone metastasis [73]. This trial, presented at the 2022 Annual Meeting of the American Society for Radiation Oncology, suggested that FLASH-RT could be a promising treatment for particularly resistant tumors. It targeted one to three painful bone metastases in the extremities, administering an 8 Gy single fraction to 12 metastatic sites using a FLASH-enabled proton therapy system at a dose rate of ≥ 40 Gy/s. The primary outcomes, which included workflow feasibility and radiation-related toxicities, demonstrated favorable results comparable to those of conventional RT (as detailed in Table 2). Among the 12 treated metastatic lesions, pain was completely alleviated at six sites, and symptoms partially improved at two sites.

Several clinical trials involving FLASH-RT have recently been initiated and are currently recruiting patients: NCT04986696 (phase I, metastatic melanoma), NCT05524064 (phase I, bone metastases, FAST-02), and NCT05724875 (phase II, skin cancers; Table 3). These trials mark a significant step forward in investigating the safety and efficacy of FLASH-RT, potentially providing cancer patients with faster and less toxic treatment options.

Biological mechanisms behind FLASH radiotherapy

The biological mechanisms by which FLASH irradiation reduces damage to non-malignant tissues while maintaining effective tumor control, as compared to conventional irradiation, remain under active investigation and are not yet fully understood. Several hypotheses have been proposed to explain these differential effects, each with its own limitations. In this section, we introduce three key biological mechanisms: oxygen depletion, DNA damage, and immune/inflammatory response. Additionally, other emerging hypotheses, such as minimal mitochondrial damage or the preservation of normal flora induced by FLASH, are also under consideration [74]. A deeper understanding of these mechanisms is essential for optimizing FLASH-RT and successfully translating its benefits into clinical practice.

Oxygen depletion hypothesis

The oxygen depletion hypothesis is currently the most widely accepted theory. It is based on the principle that oxygen acts as a critical radiosensitizer in RT; thus, tissues with a high oxygen supply are more radiosensitive [75]. FLASH irradiation rapidly depletes oxygen, leaving insufficient time for oxygen to be replenished from the surrounding circulating blood [74]. This results in acute hypoxic conditions that lead to transient radioresistance, thereby sparing normal tissue [76]. Conversely, tumors, with their inherently abnormal blood vessels, are already

Table 2. Clinical experiences with FLASH radiotherapy

Authors	Cancer	Design	Population	No. of patients	Radiation source (energy, dose rate)	Treatment	Main outcomes
Bourhis et al. [15]	Lymphoma	Case report	Multi-resistant CD30 ⁺ T-cell cutaneous lymphoma	1	Electrons (5.6 MeV, 166 Gy/s)	15 Gy in a single fraction	- Follow-up of 5 months - Rapid, complete, and durable tumor response - Grade 1 epithelitis and edema - Intact epidermis and basal membrane - Limited increased vascularization
Gaide et al. [72]	Lymphoma	Case report	Multi-resistant CD30 ⁺ T-cell cutaneous lymphoma	1 (2 sites)	Electrons (5.6 MeV, 166 Gy/s)	15 Gy in a single fraction - Right elbow: 0.08 Gy/s - Left distal arm: 166 Gy/s	- Follow-up of 2 years - Rapid, complete, and durable tumor response - Grade 1 acute epithelitis at both treated sites - Mild late radiodermatitis at both treated sites
Mascia et al. [73]	Bone metastasis	Prospective Single arm Feasibility study	1–3 symptomatic bone metastases in the extremities (except for the feet, hands, or wrists)	10 (12 sites)	Protons (250 MeV, 51–61 Gy/s)	8 Gy in a single fraction	- Median follow-up of 4.8 months (range, 2.3–13.0) - Average patient time on the treatment couch 18.9 minutes (range, 11–33) - No device-related treatment delays - Transient pain flares (2–9 days post-FLASH) in 4 of the 12 sites (33%) - Pain relief in 8 of the 12 sites (67%) - No pain in 6 of the 12 sites (50%) - No grade ≥ 3 FLASH-related toxicity

Table 3. Overview of ongoing clinical trials involving FLASH radiotherapy

NCT identifier	Cancer	Design	Population	Estimated enrollment	Radiation source	Treatment	Primary endpoint	Status ¹⁾ (study start date)
NCT04986696	Malignant melanoma	Phase I Non-randomized Dose escalation	Multiple skin metastases PD after systemic treatment	46	Electrons	7 dose levels (22, 24, 26, 28, 30, 32, and 34 Gy in a single fraction)	MTD or RP2D	Recruiting (July 1, 2021)
NCT05524064	Bone metastasis	Phase I Single arm	1–3 symptomatic bone metastasis in the thorax	10	Protons	8 Gy in a single fraction	Toxicity Patient-reported pain relief Pain medication use	Recruiting (March 8, 2023)
NCT05724875	Skin cancer	Phase II Randomized	T1-2N0M0 cutaneous squamous cell carcinoma or basal cell carcinoma	60	Electrons	FLASH-RT vs. Conventional RT (T1, 22 Gy in a single fraction; T2, 30 Gy in 5 fractions)	Skin toxicity ($\geq$ grade 3) Local control rate	Recruiting (June 22, 2023)

NCT, National Clinical Trial; PD, progressive disease; MTD, maximum tolerated dose; RP2D, recommended phase II dose; RT, radiotherapy.

¹⁾ From <https://clinicaltrials.gov/> (accessed on July 26, 2024).

adapted to hypoxic conditions. This adaptation explains why the dose rate does not significantly impact the tumor cells' susceptibility to radiation [17].

A limitation of this hypothesis is that while FLASH-RT resulted in greater oxygen consumption compared to conventional RT, it did not completely deplete all the oxygen [77]. Furthermore, the oxygen levels associated with higher cell survival rates following FLASH-RT vary significantly across experiments, ranging from severely hypoxic conditions (<0.5%) to oxygen-rich environments like those found in the lungs [74]. This variability suggests that the oxygen depletion hypothesis may not fully explain the FLASH effect.

An alternative explanation has been proposed, suggesting that reactive oxygen species, which serve dual roles as signaling and damaging agents within cells, may interact with molecules involved in redox metabolism. This interaction could potentially play a pivotal role in the FLASH effect [18].

DNA damage hypothesis

Cell fate after irradiation is primarily determined by DNA damage, specifically unrepaired DNA double-strand breaks [78]. Several studies have shown that DNA damage is less severe after FLASH irradiation [33,37,57]. This reduction in DNA damage helps preserve stem and progenitor cells across various tissues, consequently decreasing toxicity [33,34,38,46,55,56]. However, while this effect accounts for the sparing of normal tissue, it does not completely explain the sustained antitumor activity. Although the precise mechanisms are still not fully understood, it is possible that differences in the activation of downstream pathways after DNA damage—such as DNA repair pathways, the cGAS-STING pathway, or the immune system—between normal and tumor cells could contribute [17].

Immune and inflammatory hypothesis

FLASH significantly reduces the duration of radiation exposure, which is anticipated to decrease the volume of irradiated blood and aid in preserving circulating immune cells from depletion [50,79]. However, several *in vivo* studies have yielded negative results, showing no significant difference in the circulating immune cell populations between FLASH and conventional dose rates [43,59,80]. Instead, while further detailed research is necessary, it is generally observed that there is an increase in cytotoxic T-cell infiltration into tumors [43,68]. Conversely, the persistence of the antitumor effect in immunocompromised animals suggests that this effect cannot be solely attributed to the immune response [65].

FLASH also reduces TGF- β and pro-inflammatory gene expression, as well as the release of pro-inflammatory cytokines, thereby mitigating stress response and inflammation [33,41,46,47,58–60,81]. This contributes to the preservation of normal tissue, exemplified by the reduction of neuroinflammation in the normal brain, which in turn supports the maintenance of neurological function [25,35–37]. Given that the TGF- β pathway is a pharmacological target in cancer therapy, the reduction of TGF- β expression induced by FLASH could enhance antitumor activity, similar to the effects of TGF- β antagonists [82].

Current cancer treatment is witnessing a revival of interest in immunotherapy, particularly in its integration with RT [83]. In this context, the immune response elicited by FLASH provides compelling insights that may herald a new phase in radioimmunotherapy. First, FLASH reduces the expression of PD-1 and PD-L1, thereby inhibiting the tumor's ability to evade the immune system [68,84]. In a study using an ovarian cancer mouse model, abdominopelvic irradiation followed by PD-1 therapy led to enhanced tumor control in both conventional and UHDR

settings, without an increase in toxicity compared to using FLASH alone [85]. This treatment also resulted in a lower Treg-to-T-effector ratio and a higher level of CD8⁺ T-cell infiltration within the tumor. While immunotherapy alone often yields only modest response rates, these findings are noteworthy as they indicate that FLASH-RT can significantly improve the effectiveness of PD-1/PD-L1 inhibitors.

Challenges in the clinical application of FLASH radiotherapy: current issues and future directions

Recent preclinical studies and ongoing clinical trials have advanced the clinical application of FLASH-RT significantly. However, numerous challenges must be overcome before it can be routinely implemented in clinical settings. Key considerations for preclinical studies include: (i) research has been limited to a small number of normal tissues, which may lead to unexpected side effects when FLASH-RT is used clinically; (ii) the extent of the protective effect varies based on tissue type and physical parameters; (iii) there are inconsistent results among different studies; and (iv) most studies have utilized high single doses, necessitating further research to determine if the FLASH effect is achievable with lower doses and fractionated regimens [17,81]. Addressing these issues is essential for the successful integration of FLASH-RT into standard clinical protocols.

In addition to these challenges, it is important to note that some studies have not observed the beneficial effects of FLASH [80, 86-88]. One study compared high dose-rate synchrotron broad-beam RT (37–41 Gy/s) with a mean photon energy of 124 keV to conventional RT (0.05–0.06 Gy/s) with 93 keV [86]. It found that synchrotron broad-beam RT did not demonstrate the FLASH effect of sparing normal tissue compared to conventional RT [86]. The irradiated mice exhibited weights below normal compared to control mice and experienced disruption of normal crypt-villus units following abdominal irradiation. Additionally, cranial irradiation led to neurological deficits, while thoracic partial irradiation caused inflammatory responses and long-term lung damage.

In a mouse model investigating radiation-induced lymphopenia, both cardiac and splenic irradiation were administered using 20 MeV electron FLASH-RT (35 Gy/s) and conventional RT (0.1 Gy/s) [80]. For both cardiac and splenic irradiation, researchers employed a multi-fraction regimen of 2 Gy (or 1 Gy) per day over 5 days, as well as a single fraction of 10 Gy (or 5 Gy). The findings indicated a decrease in CD3⁺, CD4⁺, CD8⁺, and CD19⁺ lymphocytes, regardless of the dose rate or fractionation regimen used. Notably, the FLASH-RT group showed a more significant reduction in lymphocyte counts following splenic irradiation compared to the conventional RT group. In a model of gastrointestinal mucosal injury following whole-abdominal irradiation, acute gastrointestinal toxicity was more severe in the FLASH-RT group after a 16 Gy single fraction. All mice in the FLASH-RT group died within 7 days, whereas those in the conventional RT group survived until day 15.

A recent study demonstrated the absence of tissue-protective effects with FLASH-RT [87]. After partial abdominal FLASH proton irradiation at a rate of 120 Gy/s, survival rates were notably lower in the FLASH group compared to those in the conventional RT group at doses ranging from 15.1 to 18 Gy. Additionally, measurements of proliferating crypt cells and the thickness of the muscularis externa revealed no significant differences. Similarly, there were no variations in circulating lymphocyte counts. These findings indicate that the effectiveness of FLASH irradiation may be subject to multiple influencing factors and that FLASH irradiation could

potentially result in adverse outcomes if not properly managed.

When using zebrafish embryos and proton-based FLASH irradiation, no significant protective effect was observed [88]. A comparison of FLASH irradiation (100 Gy/s) using 224 MeV protons with conventional RT (5 Gy/min) revealed no differences in embryonic survival attributable to the varying proton dose rates. Apart from a decreased incidence of pericardial edema following FLASH irradiation, there were no differences in the rate of embryo malformations, specifically spinal curvature, between the two irradiation methods.

The negative results observed in these studies underscore the importance of thoroughly examining the underlying factors. It is possible that the low dose rates and the specific experimental setup played a role in these outcomes [89]. Determining the optimal dose rate to preserve the integrity of normal tissue remains an unresolved issue. Future research should focus on identifying the most effective dose, dose rate, pulse, and fraction size to reduce complications in normal tissues for specific organs [80]. These experiments should be carefully designed to mirror clinical treatment scenarios, ensuring that the results are relevant to real-world applications. Given these challenges, ongoing research and sustained attention are crucial to effectively address these issues and advance the field.

One technical issue pertains to dosimetry. Current dosimetry protocols and equipment, designed for much lower dose rates than those used in FLASH, struggle with accurate measurements at UHDR [90]. The ion chambers typically employed in clinical settings are significantly affected by ion recombination at UHDR, resulting in substantial uncertainties [21,90]. Another challenge involves the development of treatment plans that can accurately deliver the desired dose at UHDR to the specific target location. To address this, modifications are necessary in the treatment planning system to not only calculate and display the dose distribution in patients but also evaluate the 3D dose rate distribution [21]. Additionally, the beam delivery system needs further development. For optimal conformity to the RT target, beams are usually delivered from multiple angles, which requires the use of rotating gantry systems instead of fixed gantry setups in FLASH-RT [19].

From an economic perspective, FLASH-RT is currently available at only a few institutions, and the equipment required for proton therapy, suitable for treating deep tumors, is extremely expensive. Electron therapy, on the other hand, is only effective for superficial tumors. Photon equipment, which is more widely used globally and less costly than proton therapy, can treat deep-seated tumors. Therefore, it is essential to develop photon-based FLASH-RT equipment to make this treatment more accessible and economically viable [12].

Conclusions

FLASH-RT represents an exciting avenue for improving therapeutic outcomes in oncology, characterized by its ability to deliver UHDR radiation while minimizing damage to normal tissues. This approach has shown promise in both preclinical and initial clinical studies, offering efficacy in tumor control and reduced toxicity. Despite these positive findings, numerous biological and technical challenges remain. The precise mechanisms underlying the FLASH effect are complex and not yet fully understood, necessitating further investigation into the oxygen depletion hypothesis and other potential explanations. Additionally, implementing FLASH-RT in clinical settings requires improvements in dosimetry, treatment planning, and beam delivery systems to meet the specific requirements of UHDR. Future research and clinical trials are essential to address these challenges and validate the long-term safety and effectiveness of FLASH-

RT across a broader range of cancers. As this technology evolves, it holds the potential to revolutionize RT, offering more effective and less toxic treatment options for patients.

ORCID

Jae Sik Kim: <https://orcid.org/0000-0002-0039-8667>

Hak Jae Kim: <https://orcid.org/0000-0003-3602-2263>

Authors' contributions

Project administration: Kim HJ

Conceptualization: Kim HJ

Methodology & data curation: not applicable

Funding acquisition: Kim HJ

Writing - original draft: Kim JS

Writing - review & editing: Kim JS, Kim HJ

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

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Supplementary materials

Not applicable.

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Challenges and opportunities to integrate artificial intelligence in radiation oncology: a narrative review

Chiyoung Jeong^{ORCID}, YoungMoon Goh^{ORCID}, Jungwon Kwak^{ORCID}

Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Corresponding author

Jungwon Kwak
Department of Radiation Oncology,
Asan Medical Center, University of Ulsan
College of Medicine, 88 Olympic-ro 43-
gil, Songpa-gu, Seoul 05505, Korea
E-mail: sea1101@amc.seoul.kr

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Artificial intelligence (AI) is rapidly transforming various medical fields, including radiation oncology. This review explores the integration of AI into radiation oncology, highlighting both challenges and opportunities. AI can improve the precision, efficiency, and outcomes of radiation therapy by optimizing treatment planning, enhancing image analysis, facilitating adaptive radiation therapy, and enabling predictive analytics. Through the analysis of large datasets to identify optimal treatment parameters, AI can automate complex tasks, reduce planning time, and improve accuracy. In image analysis, AI-driven techniques enhance tumor detection and segmentation by processing data from CT, MRI, and PET scans to enable precise tumor delineation. In adaptive radiation therapy, AI is beneficial because it allows real-time adjustments to treatment plans based on changes in patient anatomy and tumor size, thereby improving treatment accuracy and effectiveness. Predictive analytics using historical patient data can predict treatment outcomes and potential complications, guiding clinical decision-making and enabling more personalized treatment strategies. Challenges to AI adoption in radiation oncology include ensuring data quality and quantity, achieving interoperability and standardization, addressing regulatory and ethical considerations, and overcoming resistance to clinical implementation. Collaboration among researchers, clinicians, data scientists, and industry stakeholders is crucial to overcoming these obstacles. By addressing these challenges, AI can drive advancements in radiation therapy, improving patient care and operational efficiencies. This review presents an overview of the current state of AI integration in radiation oncology and insights into future directions for research and clinical practice.

Introduction

Background

Radiation oncology has seen significant advancements in recent decades, driven by the introduction of several innovative technologies. These include intensity-modulated radiation therapy, stereotactic radiosurgery, stereotactic body radiation therapy, image-guided radiation therapy (IGRT), and respiratory beam control. These technologies have increased the precision of treatments [1], reduced side effects [2,3], and improved patient outcomes [4–6]. Furthermore, the advent of various imaging modalities such as CT, MRI, and PET scans, coupled with significant developments in computational resources, has greatly expanded the capabilities of radiation

oncology. These imaging modalities provide complementary information: CT scans deliver detailed anatomical information, MRI offers exceptional soft tissue contrast, and PET scans provide metabolic insights into tumors. By integrating these modalities, radiation oncologists can achieve more accurate tumor localization, more precise treatment planning, and better treatment adaptation, thereby further improving patient care and outcomes.

Intensity-modulated radiation therapy enables the modulation of radiation beams to conform more precisely to the shape of the tumor, thereby protecting surrounding healthy tissues and reducing complications [7–9]. However, this technique requires meticulous treatment planning and the implementation of rigorous quality assurance protocols, which can be challenging [10,11]. Stereotactic radiosurgery and stereotactic body radiation therapy administer high doses of radiation with sub-millimeter accuracy to treat small, well-defined tumors in the brain and body, respectively. The primary challenge in these therapies is managing patient movement and ensuring accurate targeting. These issues can be addressed using advanced imaging technologies and motion management techniques [12,13]. IGRT employs advanced imaging technologies to enhance the precision of radiation delivery by compensating for patient movement and anatomical changes during treatment [14]. The advantage of IGRT is its ability to adapt treatment in real-time. However, challenges include integrating imaging and treatment systems and maintaining consistent image quality [15]. Respiratory gating aligns radiation delivery with the patient's breathing cycle, minimizing exposure to moving organs such as the lungs and liver. The main challenges associated with respiratory gating include the need for advanced equipment and software, as well as requiring patient cooperation [16].

Integrating artificial intelligence (AI) into radiation oncology is becoming increasingly important due to various social and healthcare trends [17]. The global population is aging, which leads to a higher incidence of cancer in older age groups. As life expectancy increases, so does the demand for effective and efficient cancer treatments, placing significant burdens on healthcare systems worldwide [18]. To manage the increasing patient load effectively, it is essential to adopt advanced technologies [19].

Moreover, healthcare systems are under pressure to improve patient outcomes while controlling costs [20]. AI has the potential to meet these challenges by improving the accuracy of radiation therapy, shortening treatment durations, and reducing side effects. This can result in better resource utilization and heightened patient satisfaction [21]. Additionally, AI supports personalized medicine by offering treatments customized to the unique characteristics of each patient. By analyzing extensive datasets from diverse sources, AI can assist in creating more effective treatment plans that are specifically tailored to the genetic, phenotypic, and lifestyle factors of individual patients [22,23].

The necessity and justification for AI in radiation oncology extend beyond these practical improvements. The complexity and variability inherent in cancer treatments require sophisticated decision-making tools capable of analyzing vast amounts of data in real time—capabilities that surpass human limits. AI excels in integrating and interpreting multi-dimensional data from various imaging modalities and patient records, significantly enhancing clinical decision-making. This reduces errors and improves treatment outcomes. Additionally, AI supports continuous learning and adaptation in treatment protocols, allowing them to evolve with new medical insights and tailored to individual patient responses. Therefore, the integration of AI not only enhances efficiency but also elevates the standard of personalized patient care, rendering it an essential component in contemporary radiation oncology.

Objectives

This review provides a comprehensive overview of the current state of AI integration in radiation oncology, exploring both the benefits and challenges associated with its implementation.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Opportunities for artificial intelligence integration

Treatment planning

AI offers significant opportunities in various facets of radiation oncology, such as treatment planning, image analysis, adaptive radiation therapy (ART), and predictive analytics. In these domains, AI can enhance clinical workflows, shorten treatment durations, and deliver more personalized and effective treatments.

AI can optimize radiation treatment planning by automating complex tasks, reducing planning time, and enhancing accuracy [24]. Machine learning algorithms can analyze extensive datasets to identify optimal treatment parameters, potentially leading to personalized treatment plans that maximize efficacy while minimizing side effects [25]. Over the past few decades, AI has been progressively integrated into radiation treatment planning. Initially, simple rule-based systems supported clinical decision-making. As computational power and data availability have increased, more sophisticated machine learning algorithms, including artificial neural networks, have been developed. These algorithms, which initially supported basic tasks, have now evolved to handle complex treatment planning scenarios. Current research in AI for radiation treatment planning focuses on developing algorithms that can analyze large datasets to identify optimal treatment parameters. Machine learning models are trained using historical treatment data, patient outcomes, and imaging data to enhance the precision and accuracy of treatment plans [26]. Studies have demonstrated that AI can significantly reduce the time required for planning while maintaining or improving the quality of the plans. Research is also exploring how to integrate AI with ART to continuously update treatment plans based on real-time patient data [27]. The automated generation of radiation fluence is a critical component of treatment planning, determining the intensity and distribution of radiation beams to achieve the desired dose distribution within the target area while sparing healthy tissues. AI has played a crucial role in improving the accuracy and efficiency of fluence map optimization. Deep learning techniques can predict optimal fluence patterns based on patient-specific anatomical and dosimetric data, reducing the complexity and time required for manual adjustments [28,29].

Several commercial products have incorporated AI into radiation treatment planning. For example, Varian's Ethos Therapy [30,31] and Elekta's MOSAIQ Plaza [32] utilize AI to improve treatment planning and adaptive therapy. These systems automate aspects of the planning process, optimize dose distribution, and adjust treatment plans in response to anatomical changes or variations in tumor size during treatment.

Image analysis

AI-driven image analysis can significantly enhance the accuracy of tumor detection and

segmentation [33]. Deep learning algorithms are capable of processing imaging data from various modalities, including CT, MRI, and PET scans, to provide precise tumor delineation, which is crucial for effective radiation targeting [34,35]. The journey of AI-based image analysis in radiation oncology is marked by significant milestones. Initially, basic image processing techniques were employed to improve image quality and enhance tumor visualization. With the advent of machine learning, more advanced algorithms were developed to automate tumor detection and segmentation tasks. Early methodologies heavily relied on handcrafted features, but they were soon surpassed by deep learning algorithms capable of autonomously learning features from data [36]. Current research in AI-based image analysis focuses on increasing the precision and efficiency of tumor detection and segmentation [37,38]. Deep learning models, particularly convolutional neural networks, are widely used to analyze imaging data from CT, MRI, and PET scans [39]. These models have demonstrated an exceptional ability to distinguish tumors from adjacent healthy tissues, often surpassing the accuracy and consistency of human experts [40]. Additionally, research in multimodal image analysis indicates that AI can combine data from various imaging modalities to enhance diagnostic accuracy and inform treatment planning [41].

The segmentation of tumors and surrounding normal organs is a critical task in radiation therapy, requiring accurate delineation of tumor boundaries and normal tissues to ensure effective treatment planning [42]. Manual segmentation is traditionally labor-intensive and prone to inter-observer variability. However, AI-based segmentation techniques streamline this process, providing consistent and rapid results. Advanced algorithms, such as U-Net and its variants, have become the standard for medical image segmentation, known for their ability to accurately identify tumor boundaries [43]. These models utilize an encoder-decoder architecture to capture the complex spatial hierarchies within images, ensuring precise segmentation. Commercial applications of AI-based image analysis in radiation oncology are already making an impact. For example, IBM Watson for Oncology leverages AI to analyze medical images and provide insights for treatment planning [44]. Similarly, Varian's ARIA oncology information system integrates AI to enhance treatment planning and execution [45]. Siemens Healthineers also offers AI-based tools for advanced image analysis and interpretation within its syngo.via platform [46].

Adaptive radiation therapy

In ART, treatment plans are adjusted based on changes in patient anatomy and tumor size throughout the course of treatment. AI improves ART by swiftly analyzing imaging data and making real-time adjustments to the treatment plan, thus increasing the accuracy and effectiveness of the treatment. The concept of ART has significantly evolved over the past few decades. Initially, radiation treatment plans were static and did not accommodate anatomical changes during the treatment course. As technology progressed, the necessity for more adaptive approaches became apparent, leading to the development of ART [47]. Early implementations of ART involved periodic imaging and manual adjustments, which were time-consuming and could not be performed in real-time. Current research and development in ART focus on utilizing AI to automate and improve the adaptability of treatment plans [48]. AI-based ART systems employ advanced imaging technologies, such as daily cone-beam CT scans, to monitor tumor size and anatomical changes in patients. Machine learning algorithms then analyze these imaging data to predict anatomical changes and adjust radiation dose distributions accordingly. This capability for real-time adaptation ensures that radiation doses

are precisely targeted to the tumor, minimizing exposure to surrounding healthy tissues and enhancing overall treatment outcomes [49–51].

Several commercial products have integrated AI to improve ART. Notably, Varian's Ethos Therapy system and Elekta's Unity system stand out. Varian's Ethos utilizes AI to analyze daily imaging and dynamically adjust treatment plans, offering personalized therapy for each session [49]. Similarly, Elekta's Unity combines a high-field MRI scanner with a linear accelerator to provide real-time imaging and adaptation during treatment sessions [52]. These systems mark significant progress in the field of commercial ART, facilitating more accessible and practical real-time adaptive therapy. As we look to the future, ART is poised to continue its evolution through the further integration of AI and advanced imaging technologies.

Predictive analytics

AI can analyze historical patient data to predict treatment outcomes and potential complications. Predictive analytics can guide clinical decision-making, allowing for more informed and personalized treatment strategies [53,54]. The application of predictive analytics in radiation oncology has advanced significantly over the years. Initially, treatment decisions were primarily based on empirical data and clinical experience. With the advent of data collection and storage technologies, large databases became available, enabling the identification of patterns and correlations through statistical methods. However, traditional methods were limited in handling complex, high-dimensional data. Current predictive analytics research focuses on leveraging AI to analyze large-scale historical patient data [55]. Machine learning algorithms, including deep learning and ensemble methods, are used to predict various clinical outcomes, including tumor response, survival rates, and potential side effects. These models process diverse data types, including demographic information, genetic profiles, imaging data, and treatment histories, to provide comprehensive predictions. Studies have shown that AI-based predictive models can outperform traditional statistical methods in terms of accuracy and robustness [56].

Several commercial products have integrated AI-based predictive analytics to support clinical decision-making in radiation oncology. For instance, IBM Watson for Oncology utilizes AI to analyze patient data and provide evidence-based treatment recommendations [57]. Similarly, the RayStation treatment planning system employs machine learning models to predict patient-specific treatment outcomes and optimize treatment plans [58]. Looking ahead, predictive analytics is poised to revolutionize clinical practice in radiation oncology. Researchers are focusing on improving the interpretability of AI models, which will enable clinicians to better understand and trust their predictions. Furthermore, the integration of predictive analytics with other AI-based technologies, such as image analysis and ART, is expected to streamline treatment workflows and improve efficiency. The adoption of federated learning, which allows AI models to be trained on data from multiple institutions without the need to share patient data, is anticipated to improve the generalizability and reliability of predictive models. The elements discussed in the "Opportunities for AI Integration" section are depicted in Fig. 1.

Challenges in artificial intelligence integration

Integrating AI into radiation oncology involves multiple challenges that need to be addressed to fully harness its potential. These challenges encompass technical, clinical, and ethical aspects, necessitating collaboration among researchers, clinicians, and policymakers.

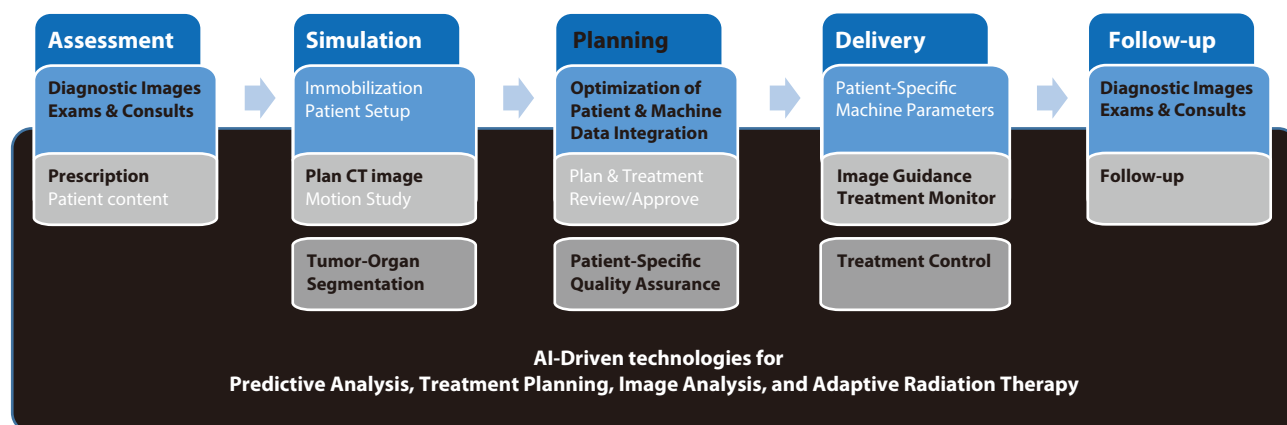


Fig. 1. The radiation therapy procedures, tasks performed during the procedures, and subsequent related tasks. The black background signifies the aspects related to opportunities for AI integration, indicating that these AI integrations are influencing the entire radiation therapy process. The tasks within the radiation therapy process that are expected to change or be affected by AI in the near future are presented in black text. AI, artificial intelligence.

Data quality and quantity

The effectiveness of AI models is heavily influenced by the quality and quantity of the data used for training [59–61]. Challenges such as inconsistent data quality, missing data, and limited access to large annotated datasets are significant obstacles [62]. AI algorithms depend on robust datasets that accurately reflect diverse patient populations and clinical scenarios. However, acquiring such datasets is often challenging due to privacy concerns, variations in data collection protocols, and the absence of standardized data formats. Research has indicated that biases in training data can result in AI models that fail to generalize effectively across different patient groups. It is crucial to ensure data quality and to develop techniques for managing missing or incomplete data to build dependable AI systems. Moreover, large datasets from multiple institutions are necessary to train models that are effective in various clinical environments. Collaborative initiatives to share data while safeguarding patient privacy are vital for the progress of AI in radiation oncology [63].

Interoperability and standardization

Radiation oncology systems frequently utilize various software and data formats, which can lead to interoperability issues [64]. To facilitate the seamless integration of AI tools across different platforms and institutions, it is crucial to standardize data formats and protocols [65]. The lack of interoperability may impede the efficient deployment of AI technologies, as it poses challenges in integrating and analyzing data from disparate systems. These interoperability challenges are further exacerbated by the use of diverse imaging modalities, treatment planning systems, and electronic health records in radiation oncology. Developing common data standards, such as Digital Imaging and Communications in Medicine (DICOM), is essential for enabling data exchange and integration [66,67]. Encouraging the widespread adoption of these standards throughout the industry will help surmount obstacles to AI implementation and enhance the effectiveness of AI tools in clinical settings.

Regulatory and ethical considerations

Integrating AI into radiation oncology introduces several regulatory and ethical challenges,

including concerns about patient privacy [68], data security, and the necessity for rigorous validation of AI models. Regulatory frameworks need to adapt to address these issues and ensure AI is used safely and effectively in clinical settings. Current regulations may not adequately capture the complexities of AI technologies, necessitating updates to existing guidelines and the creation of new standards. Ethical considerations are also paramount in the integration of AI [69–71]. It is crucial to obtain patient consent and safeguard data privacy, particularly when handling sensitive health information. Additionally, the potential for AI to reinforce existing biases in healthcare must be addressed, as biased algorithms could worsen health disparities. Developing AI models that are transparent and explainable will foster trust between clinicians and patients, facilitating their understanding and acceptance of AI-driven decisions.

Clinical implementation and adoption

Adopting AI tools in clinical settings necessitates significant changes in workflows and staff training. Resistance to change and skepticism regarding the reliability of AI can impede adoption [72]. It is crucial to implement comprehensive training programs and clearly communicate the benefits of AI to overcome these barriers. Research indicates that involving clinicians in the development and implementation of AI tools is essential for meeting clinical needs and ensuring seamless integration into existing workflows [73–75]. Providing ongoing education and support for healthcare professionals can foster trust in AI technologies and promote their adoption. Demonstrating the clinical and economic advantages of AI through pilot studies and real-world applications can also secure support from stakeholders. The issues discussed in the section "Challenges in AI Integration" are illustrated in Fig. 2.

Future directions

The future of AI in radiation oncology promises significant transformations in patient care. As AI technologies advance, several critical areas are poised to propel progress within the field. These

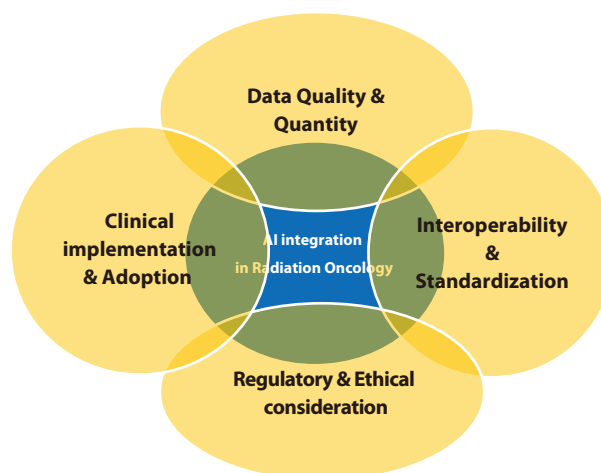


Fig. 2. The challenges involved in integrating AI into radiation oncology, which are likely to be highly complex and closely interconnected. This indicates the need for careful planning and consideration at an early stage to address these issues before they become entangled. AI, artificial intelligence.

areas encompass the creation of more advanced AI models, the integration of AI with other emerging technologies, the development of stringent standards and regulations, and a focus on collaborative and multidisciplinary approaches.

Future AI development will concentrate on creating more sophisticated models that can manage complex, high-dimensional data [76]. Advances in deep learning and reinforcement learning will enable the creation of models capable of predicting treatment outcomes with greater accuracy and adapting to new data in real time. These models will benefit from the ongoing expansion of available data, including multimodal datasets that integrate imaging, genomics, and clinical information. These comprehensive datasets will enable the development of personalized treatment plans specifically tailored to individual patients [77,78].

The integration of AI with other emerging technologies, such as radiomics, genomics, and wearable health devices, is expected to revolutionize radiation oncology [77]. Radiomics extracts a large number of features from medical images, which AI then uses to predict disease progression and treatment responses. Genomics offers insights into the genetic makeup of tumors, facilitating more targeted and effective treatments [79]. Wearable health devices continuously monitor patients' health indicators, supplying data that enables AI to dynamically adjust treatment plans in real-time [80].

To fully realize the potential of AI in radiation oncology, it is crucial to standardize and ensure interoperability across systems and institutions. The development and adoption of common data standards, such as DICOM, will facilitate the exchange and integration of data [81,82]. Additionally, it is essential to establish standardized protocols for the development, validation, and deployment of AI models to ensure that these tools are safe, reliable, and effective [83]. The International Electrotechnical Commission (IEC) is also working to establish standards that ensure the quality, safety, and reliability of AI in medical devices [84].

Collaboration among researchers, clinicians, data scientists, and industry stakeholders is essential for advancing AI in radiation oncology [76,85]. Multidisciplinary teams can leverage diverse expertise to create AI tools that address clinical needs and integrate smoothly into current workflows [86]. Collaborative research initiatives and shared databases facilitate the pooling of data and resources, which accelerates the development of robust AI models [82]. Promoting open science and data sharing while ensuring patient privacy will foster innovation and advance the field [87].

Developing explainable AI models is crucial for fostering trust between clinicians and patients [88]. Explainable AI offers insights into the decision-making processes of AI algorithms, thereby facilitating clinicians' understanding and validation of AI-based recommendations [89]. Increasing the transparency of AI systems will address concerns about bias and errors, ultimately encouraging the adoption of AI technologies in clinical settings [90,91]. AI has the potential to significantly improve the quality of clinical care while increasing efficiency. For instance, studies have demonstrated that AI can reduce the time needed for treatment planning and image analysis, allowing clinicians to devote more attention to patient care [92,93]. AI-based predictive analytics can identify patients at high risk of complications, enabling proactive interventions that improve outcomes [94,95]. Moreover, AI's capacity to continuously learn and adapt from new data ensures that treatment strategies are consistently updated with the latest medical knowledge and technological advancements [96]. In clinical settings, AI technologies have the potential to drive several key advancements in radiation oncology. These advancements include improving diagnostic accuracy, enabling real-time adaptive therapy, enhancing patient monitoring, and developing personalized treatment plans, all of which contribute to better

patient outcomes and operational efficiencies [97–101].

Improving diagnostic accuracy: AI-based image analysis increasing the accuracy of tumor detection and segmentation, thereby improving the precision of radiation targeting. This increased precision minimizes damage to surrounding healthy tissues and increases treatment efficacy.

Enabling real-time adaptive therapy: AI rapidly analyzes daily imaging data and adjusts treatment plans in real time, enhancing the effectiveness of ART. This capability ensures that radiation doses are precisely targeted to the tumor, accommodating anatomical changes or variations in tumor size throughout the treatment course.

Enhancing patient monitoring: Wearable health devices coupled with AI analytics enable continuous monitoring of patients' health indicators. This allows timely interventions when adverse changes are detected. Such a predictive approach aids in managing side effects and enhances overall treatment outcomes.

Developing personalized treatment plans: AI analyzes extensive datasets to identify patterns and predict individual responses to different treatment modalities. This capability allows clinicians to create treatment plans that are tailored to each patient's unique genetic and clinical profile, thereby maximizing efficacy and minimizing side effects.

Looking ahead, integrating AI into clinical practice in radiation oncology necessitates careful consideration of ethical, regulatory, and practical issues. However, the potential benefits, such as improved patient outcomes and operational efficiencies, make it a worthwhile endeavor. Collaborative efforts among multidisciplinary teams, the establishment of robust standards, and the continued advancement of AI technologies will shape the future of radiation oncology, ultimately transforming patient care. The themes explored in the "Future Directions" section are visualized in Fig. 3.

Conclusion

The integration of AI into radiation oncology offers significant opportunities to enhance the

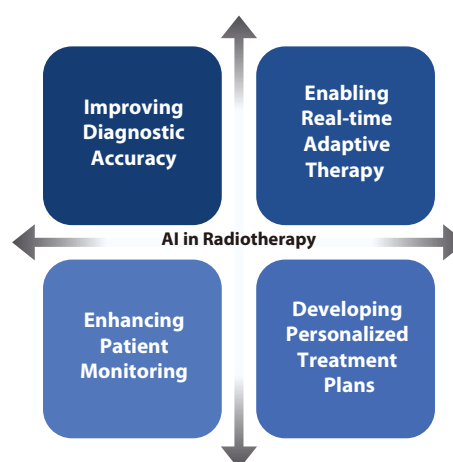


Fig. 3. Advancements anticipated to result from the integration of AI into radiation therapy. These significant advancements are expected to lead to enhanced diagnostic accuracy, seamless patient monitoring, real-time therapeutic adaptations, and the delivery of highly personalized treatment, thereby substantially improving outcomes for many cancer patients. AI, artificial intelligence.

precision, efficiency, and outcomes of treatments. As AI technologies continue to advance, their potential to transform various aspects of radiation therapy becomes increasingly apparent. This review has highlighted key areas where AI can make substantial contributions, including treatment planning, image analysis, ART, and predictive analytics. Each area showcases AI's ability to improve clinical workflows, shorten treatment times, and deliver more personalized and effective treatments.

Despite these promising advancements, several challenges must be addressed to fully realize the potential of AI in radiation oncology. Data quality and quantity are critical issues because robust and comprehensive datasets are necessary for effective AI models. Ensuring interoperability and standardization across different systems and institutions is also essential to facilitate seamless integration and data exchange. Additionally, regulatory and ethical considerations must be carefully addressed to protect patient privacy and ensure the safe deployment of AI technologies in clinical environments.

Collaboration among researchers, clinicians, data scientists, and industry stakeholders is essential for overcoming these challenges. By forming multidisciplinary teams, diverse expertise can be harnessed to create AI tools that not only meet clinical needs but also integrate seamlessly into existing workflows. Initiatives that promote collaborative research and shared databases will facilitate the pooling of data and resources, thereby accelerating the development of robust AI models. Encouraging open science and data sharing, while simultaneously protecting patient privacy, will drive innovation and advance the field. Moreover, the development of explainable AI models is crucial for promoting trust between clinicians and patients. Explainable AI offers insights into the decision-making processes of AI algorithms, enabling clinicians to more easily understand and validate AI-based recommendations. Increasing the transparency of AI systems will address concerns about bias and errors, ultimately encouraging the adoption of AI technologies in clinical practice.

The future of AI in radiation oncology is bright, and ongoing research and development are poised to overcome current challenges and unlock new opportunities. AI-driven improvements in diagnostic accuracy, real-time adaptive therapy, patient monitoring, and personalized treatment plans are poised to revolutionize the field, enhancing patient care and operational efficiencies. By emphasizing collaborative research, continuous learning, and patient-centric approaches, the field can surmount these challenges and realize transformative advancements in radiation therapy.

ORCID

Chiyoun Jeong: <https://orcid.org/0000-0001-5558-2456>

YoungMoon Goh: <https://orcid.org/0000-0003-4934-1730>

Jungwon Kwak: <https://orcid.org/0000-0001-7982-8510>

Authors' contributions

Project administration: Kwak J

Conceptualization: Kwak J

Methodology & data curation: Jeong C, Goh YM, Kwak J

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Writing – original draft: Jeong C, Goh YM, Kwak J

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The histopathological and molecular heterogeneity of hepatocellular carcinoma: a narrative review

Wonju Chung^{ORCID}, Haeryoung Kim^{ORCID}

Department of Pathology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author

Haeryoung Kim
Department of Pathology, Seoul National
University Hospital, Seoul National
University College of Medicine, 103
Daehak-ro, Jongno-gu, Seoul 03080,
Korea
E-mail: haeryoung.kim@snu.ac.kr

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Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related deaths worldwide, with poor clinical outcomes due to challenges in early detection and limited efficacy of current treatments such as receptor tyrosine kinase inhibitors and immunotherapy. HCC exhibits significant heterogeneity at both histopathological and molecular levels, complicating its management but offering potential for personalized therapeutic approaches. This review outlines the morpho-molecular heterogeneity of HCC and summarizes various histological subtypes, including steatohepatitic, clear cell, macrotrabecular-massive, scirrhous, lymphocyte-rich, and fibrolamellar HCCs. Each subtype possesses distinct clinical, histological, and molecular features; for instance, steatohepatitic HCC is associated with metabolic dysfunction and shows IL-6/JAK/STAT activation, while clear cell HCCs often have *IDH1* mutations and favorable prognosis. The macrotrabecular-massive subtype is linked to poor outcomes and *TP53* mutations, whereas scirrhous HCCs express stemness markers and have *TSC1/TSC2* mutations. Lymphocyte-rich HCCs are characterized by immune cell infiltration and better prognosis. *CTNNB1*-mutated HCCs show specific morphological features and may benefit from targeted therapies. Understanding these subtypes and associated molecular alterations is crucial for developing effective diagnostic and therapeutic strategies, including potential predictive biomarkers and personalized treatments. Additionally, the identification of patterns like vessels-encapsulating-tumor-clusters offers prognostic implications and may guide therapeutic decisions. Recent molecular studies have enhanced our comprehension of HCC heterogeneity, laying the groundwork for more personalized approaches. Pathologists play a vital role in recognizing these subtypes, aiding in prognosis prediction and treatment planning. Advances in digital pathology and artificial intelligence may further facilitate biomarker research, ultimately improving patient outcomes in HCC management.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for 75%–80% of primary liver malignancies [1]. HCC mostly develops in the background of chronic liver disease, the most common etiologies being HBV or HCV infection, and chronic alcohol abuse. During the recent year, metabolic syndrome has become another major risk factor for HCC, even in Asian countries [2,3].

The clinical outcome of patients with HCC is generally poor, mainly due to difficulties in early

detection and limited treatment options for advanced disease [4,5]. Currently, systemic therapy, such as receptor tyrosine kinase inhibitors and immunotherapy, is the treatment of choice for the patients with unresectable HCC [5]. However, the efficacy of systemic therapy in HCC is still unsatisfactory with survival benefit of 1–3 months, objective response rate less than 30%, and a high incidence of adverse events [6,7]. In this context, understanding the heterogeneity of HCC will play a key role in developing effective diagnostic and therapeutic strategies, by offering potential predictive biomarkers and personalized approaches for HCC management.

Ethics statement

It is a literature database-based review; therefore, neither approval by the institutional review board nor obtainment of informed consent was required.

Morpho-molecular heterogeneity of hepatocellular carcinoma

HCC is typically composed of tumor cells showing hepatocytic differentiation with variable degrees of atypia [8]. While HCC recapitulates the cytoarchitectural morphology of the liver to varying extents, there are alterations in the hepatic microarchitecture such as loss of portal tracts, reduction or loss of the reticulin framework, and thickening of the hepatic plates. Neoangiogenesis occurs in HCCs, in the form of sinusoidal capillarization and unpaired arteries [8]. These changes also result in the characteristic imaging features, such as the early enhancement on contrast enhanced CT/MRI.

However, there is considerable heterogeneity of HCC, in the microscopic growth patterns, cytological features, and histological grade. About 50% of HCCs demonstrate mixed patterns of growth: trabecular, pseudoglandular, solid, and macrotrabecular (Fig. 1) [9]. In addition, while most HCCs demonstrate cytological features that recapitulate those of normal hepatocytes (i.e. polygonal cells with abundant eosinophilic cytoplasm), some HCCs show extensive areas with

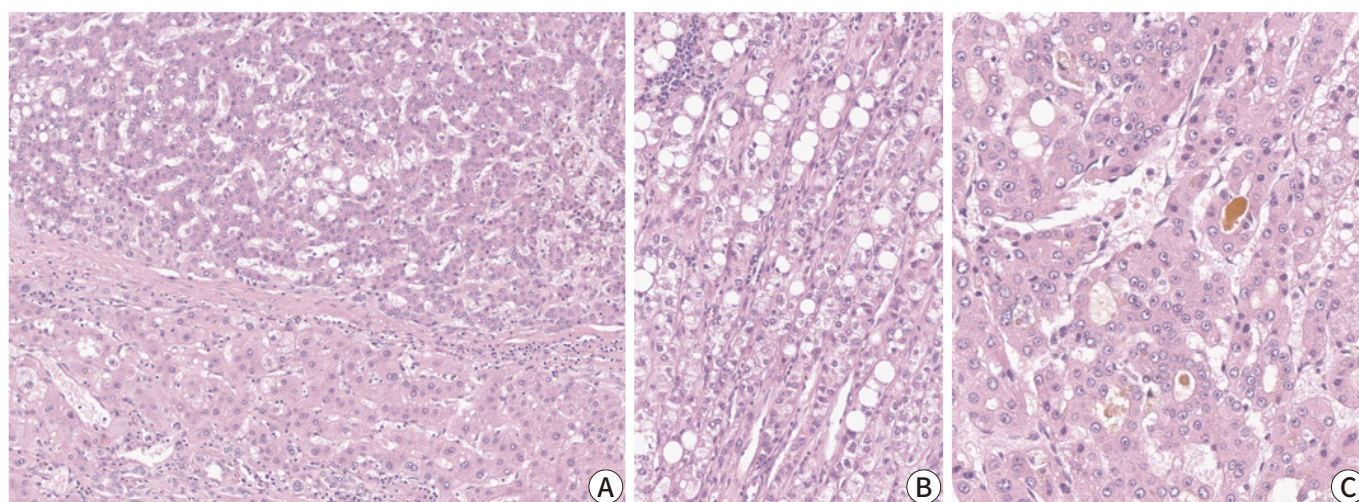


Fig. 1. Microscopic features of a typical hepatocellular carcinoma (HCC). (A) Non-neoplastic hepatocytes (lower half) and HCC tumor cells (upper half) are separated by a fibrous capsule. (B) Trabecular pattern HCC with steatosis. (C) Pseudoglandular pattern HCC with cholestasis (Hematoxylin-Eosin stain, original magnification $\times 100$ [A,B], $\times 200$ [C]).

clear cell change, fatty change, and cholestasis. Cytoplasmic inclusions (e.g., hyaline bodies, Mallory-Denk bodies, and pale bodies) may also be seen in some tumor cells [8]. Histological grading is currently performed according to either the four-tiered modified Edmondson and Steiner system or the three-tiered World Health Organization (WHO) grading system [9–11].

Recent advances in genomic techniques have unraveled the heterogeneity in the mutational landscape of HCC [12,13]. The most frequently mutated genes include *TERT* promoter, *TP53*, *CTNNB1*, *ARID1A*, *ARID2*, *JAK1*, *ALB*, *AXIN1*, *NFE2L2*, and *RPS6KA3* [12]. In addition, gene expression profiling studies have suggested several molecular subclasses of HCC that correlate with the clinicopathological features, providing the foundation for an integrated morphological-molecular classification of HCC [14]. In the past two decades, there have been many efforts to establish a subclassification system that better categorizes HCCs with distinct clinical, histological, and molecular features (Table 1) [13,15–19]. HCC can be subclassified into two major groups, the proliferative class and the non-proliferative class. The proliferative class is characterized by high chromosomal instability and *TP53* mutations, and is associated with poor histological differentiation, frequent vascular invasion, increased alpha-fetoprotein (AFP) level, and overall poor clinical outcome [16,18]. On the other hand, the non-proliferative class displays chromosomal stability and a well-differentiated phenotype with less frequent vascular invasion [16,18]. *CTNNB1*-mutated HCCs belong to the latter group: these demonstrate frequent cholestasis and less immune cell infiltration on histology [14,20].

Currently, approximately 35% of HCC can be further subclassified into histological subtypes with distinct morphological, clinicopathological and molecular characteristics [9]. The following section will summarize the clinicopathological and molecular features of these different subtypes.

Steatohepatic hepatocellular carcinoma

The steatohepatic subtype of HCC demonstrates the key histological features of non-neoplastic steatohepatitis, including steatosis, pericellular fibrosis, cell ballooning, inflammation, and Mallory-Denk bodies, and these features occupy a major portion (>50%) of the tumor (Fig. 2) [21]. This subtype has been more frequently identified in patients with underlying metabolic

Table 1. Integrated morphological-molecular classification of hepatocellular carcinoma

Classification system	Proliferative class	Non-proliferative class
Lee et al. [15]	Cluster A	Cluster B
Boyault et al. [16]	G1, G2, G3	G4, G5, G6
Chiang et al. [17]	Proliferation	Interferon, Poly7, <i>CTNNB1</i>
Hoshida et al. [18]	S1, S2	S3
TCGA Research Network [13]	Immune high and intermediate	Immune excluded
Sia et al. [19]	iClust1, iClust3	iClust2
Clinical features	Poor clinical outcome, high AFP, HBV, frequent vascular invasion	Improved clinical outcome, low AFP, HCV, low vascular invasion
Histological features	Poorly differentiated	Well differentiated
Molecular alterations	Chromosomal instability, <i>TP53</i> mutations, <i>FGF19</i> amplification	Chromosomal stability, <i>CTNNB1</i> mutations, <i>TERT</i> promoter mutations

AFP, alpha-fetoprotein.

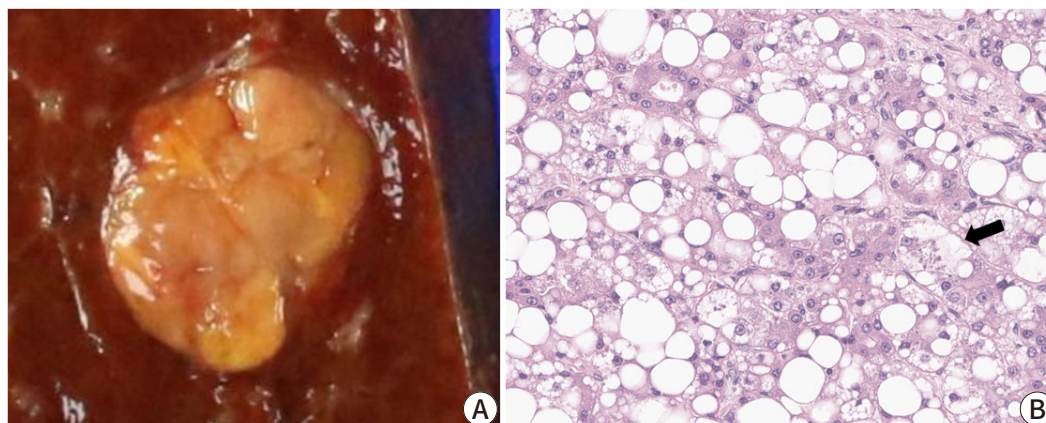


Fig. 2. Steatohepatic hepatocellular carcinoma (HCC). (A) The tumor demonstrates a yellow hue on macroscopy reflecting the lipid component. (B) High power magnification showing the diffuse steatosis of tumor cells, tumor cell ballooning (arrow), some inflammatory cells, and pericellular fibrosis (Hematoxylin-Eosin stain, original magnification ×400).

dysfunction-associated steatotic liver disease and alcohol abuse, and its relative frequency has been reported to be between 5% and 20% [3,21]. Steatohepatic HCC has been associated with less frequent vascular invasion and satellite nodules; however, its prognosis appears to be similar to that of conventional HCC [14]. Key molecular alterations associated with steatohepatic HCC include IL-6/JAK/STAT activation, while *CTNNB1*, *TERT* promoter and *TP53* mutations have been found to be less frequent in these tumors [14].

Clear cell hepatocellular carcinoma

By definition, in clear cell HCCs, more than 80% of tumor cells demonstrate abundant clear cytoplasm (Fig. 3). The clear cytoplasm is a result of glycogen accumulation; however, some tumor cells may appear clear due to lipid droplets, and some degree of steatosis is acceptable for this diagnosis [22]. The relative frequency of clear cell HCC has been estimated to be around 3%–7%. Clear cell HCCs are generally well-differentiated tumors with a favorable prognosis [23]. One study has reported that clear cell HCCs demonstrate higher frequency of *IDH1* mutation, although this mutation is not sufficient to define the subtype [24].

Macrotrabecular-massive hepatocellular carcinoma

The macrotrabecular-massive subtype of HCC is an HCC in which more than 50% of the tumor cells assume a macrotrabecular growth pattern, defined as large trabeculae that are more than 6–10 cells thick (Fig. 4) [25]. This subtype accounts for approximately 5% of all HCCs and has been strongly associated with elevated serum AFP levels, high-grade cytological atypia, extensive lymphovascular invasion, more frequent distant metastasis, and a poor prognosis [25,26]. In addition, the vessels-encapsulating-tumor-clusters (VETC) pattern of neoangiogenesis, which has been associated with metastatic dissemination of HCC, is often enriched in this subtype (Fig. 4) [27,28]. *TP53* mutations and *FGF19* amplifications have been more frequently identified in the macrotrabecular-massive subtype of HCC [14].

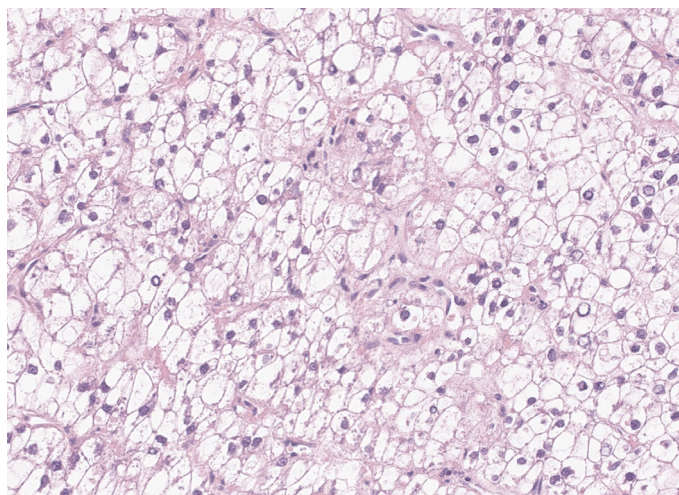


Fig. 3. Clear cell hepatocellular carcinoma (HCC). Most of the tumor cells demonstrate clear cytoplasm due to glycogen accumulation (Hematoxylin-Eosin stain, original magnification $\times 200$).

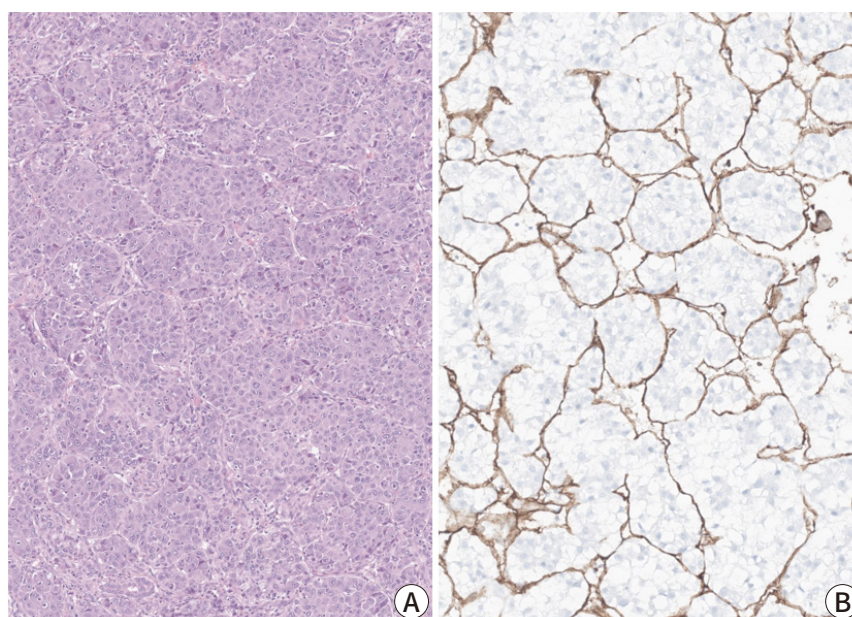


Fig. 4. Macrotrabecular-massive hepatocellular carcinoma (HCC; A) and vessels-encapsulating-tumor clusters (VETC) pattern (B). (A) Macrotrabecular-massive HCC demonstrating thick tumor cell trabeculae, of more than 10-cell thickness (Hematoxylin-Eosin stain, original magnification $\times 100$). (B) CD34 immunostain highlighting the VETC pattern, where the CD34-positive endothelial cells completely surround tumor cell clusters.

Scirrhou hepatocellular carcinoma

This subtype is characterized by dense intratumoral fibrous stroma (Fig. 5). The scirrhou subtype has a relative frequency of 4% and often mimics intrahepatic cholangiocarcinoma on imaging [29]. Expression of immunohistochemical markers associated with stemness (e.g., cytokeratin ([CK]) 7, CK19, and epithelial cell adhesion molecule) is often seen in scirrhou HCCs,

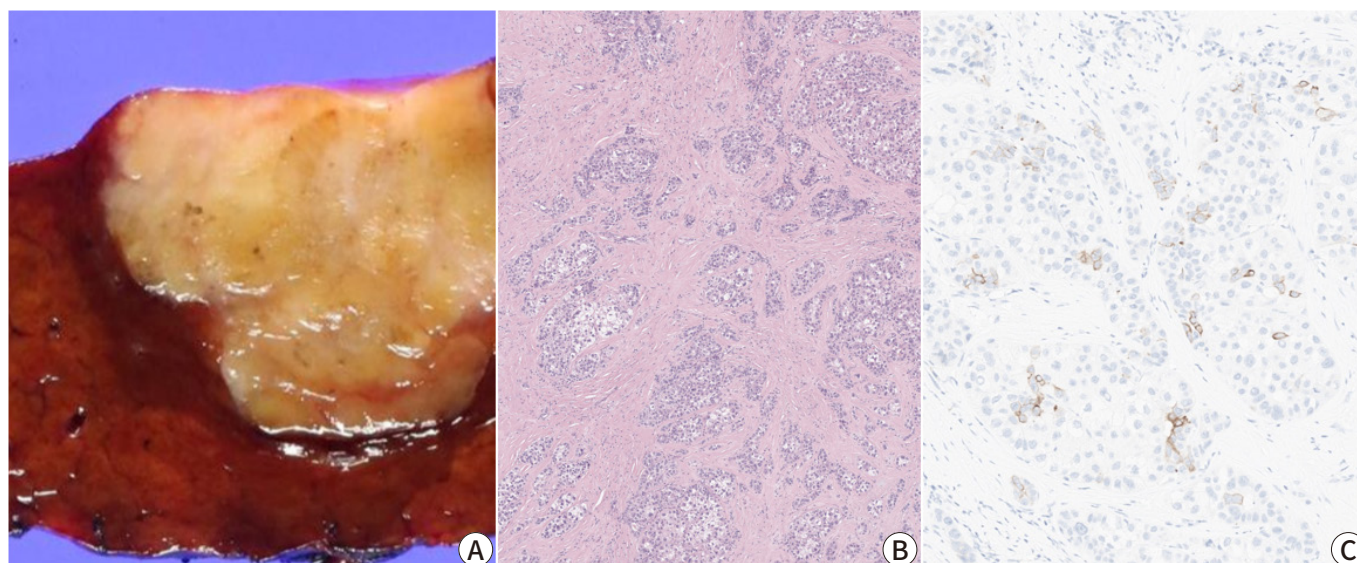


Fig. 5. Scirrhou hepatocellular carcinoma (HCC). (A) The tumor appears as a firm, yellowish-white and lobulated mass on gross examination, mimicking an intrahepatic cholangiocarcinoma. (B) Dense intratumoral fibrosis is evident at low power magnification (Hematoxylin-Eosin stain, original magnification $\times 40$). (C) Immunohistochemical expression of cyokeratin 19 is seen in a few tumor cells.

and increased expression of cholangiocarcinoma-like and stem-cell-like genes have been identified by gene expression profiling, consistent with the intermediate characteristic of this subtype [30,31]. Furthermore, scirrhou HCC is associated with frequent *TSC1/TSC2* mutations and transforming growth factor- β signaling activation [14,30].

Lymphocyte-rich hepatocellular carcinoma

The lymphocyte-rich subtype demonstrates massive intratumoral infiltration of lymphocytes, which outnumber the tumor cells in most microscopic fields. This subtype is rare, accounting for less than 1% of all HCCs, but has received much attention as it has been associated with a favorable clinical outcome [32]. The lymphocyte-rich subtype is associated with increased programmed death-ligand 1 expression and focal amplification of chromosome 11q13.3, which is related to the immune checkpoint signature (CD274, PDCD1, BTLA, CTLA4, HAVCR2, IDO1, and LAG3) [32–35]. Interestingly, although this subtype is also known as “lymphoepithelioma-like HCC”, it is not associated with Epstein-Barr virus infection, unlike the lymphoepithelioma-like tumors arising in other organs, such as the nasopharynx and stomach [32].

Fibrolamellar hepatocellular carcinoma

Fibrolamellar carcinoma, or fibrolamellar HCC, consists of strands of large eosinophilic tumor cells with abundant cytoplasm and prominent nucleoli, and separated by dense intratumoral bands of fibrosis [36]. Fibrolamellar carcinoma accounts for approximately 1% of all HCC, occurs in younger patients (median age of 25 years), and the background liver is non-cirrhotic [37]. The prognosis of fibrolamellar carcinoma appears to be better than that of conventional HCC arising in cirrhotic livers, but similar to that of HCC in non-cirrhotic livers [37]. *DNAJB1-PRKACA* gene fusion has been identified in >95% of cases, and fluorescence *in situ* hybridization for *PRKACA*

gene rearrangement is a useful ancillary test in confirming the diagnosis [38]. Expression of CK7 and CD68 in the tumor cells is another characteristic of fibrolamellar carcinoma [38].

***CTNNB1*-mutated hepatocellular carcinoma**

CTNNB1 mutations have been reported in approximately 20%–40% of HCCs [39]. *CTNNB1* encodes β -catenin, which plays a key role in the WNT signaling pathway that regulates liver function and zonation [40]. In addition, bile salt transporter expression is dysregulated in these tumors, histologically manifested by frequent intratumoral cholestasis. Some *CTNNB1*-mutated HCCs may be diagnosed by gadoxetic acid-enhanced MRI, due to the upregulation of the organic anion transporting polypeptide 1B3 (OATP1B3) [41]. Histologically, *CTNNB1*-mutated HCCs are typically well-differentiated tumors with microtrabecular and/or pseudoglandular growth patterns, intratumoral cholestasis, and less immune cell infiltration compared to non-*CTNNB1*-mutated HCCs [14,20]. However, *CTNNB1*-mutated HCCs are not morphologically homogeneous, with approximately 40% not demonstrating the “classic *CTNNB1* morphology” [42]. Immunohistochemical studies for β -catenin (nuclear expression) and glutamine synthetase (diffuse, strong and homogeneous expression) may serve as useful surrogate markers for *CTNNB1* mutation.

Hepatocellular carcinoma with stemness-related marker expression

HCC with stemness-related marker expression, or progenitor HCC, is defined as HCC expressing stemness-related markers, e.g., CK19, in >5% of the tumor cells [15]. This subset of HCCs differ from combined hepatocellular-cholangiocarcinoma, as they are morphologically compatible with HCC, and there is no evidence of glandular differentiation or mucin production in these tumors. They are associated with increased serum AFP levels, frequent vascular invasion, poor histological differentiation, high recurrence rate, resistance to systemic chemotherapy and locoregional treatment, and overall poor prognosis [43]. HCCs with stemness-related marker expression more frequently demonstrate *TP53* mutations and chromosomal instability, and increased PD-L1 expression [33,34].

Hepatocellular carcinomas with vessels-encapsulating-tumor-clusters pattern

The VETC phenotype is defined by the presence of VETC pattern in more than 55% of the tumor area, characterized by CD34-positive vessels that encapsulate and isolate individual tumor clusters, forming a cobweb-like pattern (Fig. 4) [27,28,44]. The VETC pattern is often found in the macrotrabecular-massive subtype of HCC (7.8%) and is associated with aggressive behavior and metastatic dissemination [27,28]. It has been reported that VETC pattern is related to a novel mechanism of metastasis, independent of epithelial-to-mesenchymal transition [44]. Furthermore, patients with VETC-positive HCC have shown greater survival benefits from sorafenib therapy compared to those with VETC-negative HCC, suggesting that the VETC pattern may serve as a potential predictive marker for sorafenib response [28]. Correlation between the VETC pattern on histology and a rim arterial phase hyperenhancement in arterial phase imaging suggests a role for imaging in the prognostication of HCC [45].

Other rare histological subtypes of HCC have been described. The chromophobe subtype of HCC has tumor cells with clear to pale cytoplasm and mainly bland nuclei with focal areas of striking nuclear atypia [46]. Chromophobe subtype is strongly associated with alternative lengthening of telomeres, a telomerase-independent mechanism of telomere maintenance, which can be detected by fluorescence *in situ* hybridization [46]. Its prognosis is currently known to be similar to that of conventional HCC [47]. Neutrophil-rich HCC is characterized by marked intratumoral neutrophilic infiltration, granulocyte colony-stimulating factor production by tumor cells, and a poor prognosis [47]. The tumor cells are often poorly differentiated, and focal sarcomatoid differentiation can be observed [48].

Conclusion

Recent molecular studies have significantly enhanced our understanding of the morphological and molecular heterogeneity of HCC, providing the foundation for more effective and personalized treatment strategies. Pathologists are becoming increasingly aware of the histomorphological heterogeneity of HCC, and the specification of the various subtypes of HCC has helped pathologists understand the histology of HCC in more detail and the various differential diagnoses and diagnostic pitfalls for each variant. The correlation between the histomorphology and the molecular and biological features suggests the role of histology in the prediction of therapeutic response and prognosis. This may be further facilitated by the recent advances in digital pathology and artificial intelligence-based biomarker research.

ORCID

Wonju Chung: <https://orcid.org/0009-0006-8239-9968>

Haeryoung Kim: <https://orcid.org/0000-0002-4205-9081>

Authors' contributions

Project administration: not applicable

Conceptualization: Chung W, Kim H

Methodology & data curation: not applicable

Funding acquisition: Kim H

Writing – original draft: Chung W

Writing – review & editing: Chung W, Kim H

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

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Supplementary materials

Not applicable.

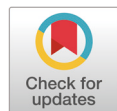
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Pathogenesis and management of metabolic dysfunction-associated steatohepatitis-related hepatocellular carcinoma: a narrative review

Han Ah Lee^{1b}

Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

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Corresponding author

Han Ah Lee
Department of Internal Medicine,
Chung-Ang University College of
Medicine, 102, Heukseok-ro, Dongjak-
gu, Seoul 06973, Korea
E-mail: amelia86@naver.com

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Metabolic dysfunction-associated steatohepatitis (MASH) is increasingly recognized as a leading cause of hepatocellular carcinoma (HCC), the third-leading cause of cancer mortality worldwide, driven by the global obesity epidemic. Projected to become the primary cause of HCC by 2030, MASH-HCC presents unique clinical challenges. This review examines its clinical management, including surveillance strategies and treatment advances, and discusses prospects to overcome existing challenges. MASH-HCC accounts for 10%–20% of HCC cases, particularly in Western countries, with a rising incidence due to obesity. Risk factors include cirrhosis, diabetes, obesity, alcohol, smoking, genetic polymorphisms (e.g., PNPLA3), and microbiome alterations. The pathogenesis involves fibrosis, immune dysfunction (e.g., T-cell impairment), and molecular changes. Prevention focuses on lifestyle modifications. Surveillance in patients with MASH cirrhosis is crucial but is hindered by poor ultrasound sensitivity in obese patients, necessitating alternative methods. Treatment mirrors that of other HCC types, but comorbidities and potentially reduced efficacy of immunotherapy necessitate tailored approaches. MASH is becoming the leading cause of HCC, necessitating lifestyle interventions for prevention. Improved surveillance and early detection are critical but challenging due to obesity-related factors. Treatments align with those for other HCC types, but comorbidities and potential differences in immunotherapy efficacy due to T-cell dysfunction require careful consideration. Key needs include identifying molecular drivers in non-cirrhotic metabolic dysfunction-associated steatotic liver disease, developing preventive therapies, refining surveillance methods, and tailoring treatments. Trials should specifically report MASH-HCC outcomes to enable personalized therapies. Further research is needed to understand T-cell dysfunction, optimize immunotherapies, and identify predictive biomarkers.

Introduction

Background

Primary liver cancer ranks as the third leading cause of cancer-related deaths globally, with nearly 1 million new cases reported annually [1]. Hepatocellular carcinoma (HCC) accounts for approximately 90% of all primary liver cancers. It typically arises in the setting of chronic liver diseases, which may be due to HBV, HCV, alcohol-related liver disease, or metabolic dysfunction-

associated steatotic liver disease (MASLD) [2]. MASLD is estimated to affect around 20%–25% of the global population [3]. Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by more than 5% steatosis, hepatocellular injury (such as "ballooning"), and inflammation, which may occur with or without fibrosis [4]. About 20% of individuals with MASLD develop MASH, which is strongly linked to rising rates of obesity, diabetes, and metabolic syndrome. As MASH progresses, it can lead to severe liver-related complications, including cirrhosis or liver failure, and significantly increases the risk of developing HCC [5].

In patients with MASH-related cirrhosis, the annual incidence of HCC is approximately 2% [6]. Moreover, MASH is the primary cause of HCC in patients who do not have cirrhosis [7]. MASH-related HCC accounts for 20% of HCC cases in the Western world and is projected to become the leading cause of HCC globally by 2030 [8]. The development of MASH-related HCC is characterized by unique mutational, immunological, and microenvironmental features. Although most cases of MASH-related HCC occur in patients with cirrhosis, 30%–40% develop in those with advanced fibrosis but without cirrhosis. This suggests a distinct metabolic environment and the likely involvement of extrahepatic cancer drivers associated with metabolic syndrome [9,10]. Unlike infections with HBV or HCV, MASH more frequently leads to HCC in the absence of cirrhosis, underscoring the need for strengthened surveillance and early detection [11].

Currently, MASH-HCC is managed similarly to other causes of HCC, employing strategies such as transplantation, resection, or locoregional therapies for early- or intermediate-stage disease [12]. MASH is the leading cause of HCC-related liver transplants in the USA; however, approximately 50% of patients undergo systemic therapy as their disease progresses, which includes both combination therapies and single-agent treatments with tyrosine kinase inhibitors or monoclonal antibodies [13]. Nevertheless, it remains uncertain whether immune-based therapies are as effective for non-viral HCC as they are for viral-related HCC [14].

Objectives

In this review, we examine the clinical management of MASH-HCC, focusing on surveillance strategies and recent advancements in treatment. We also discuss the customized application and outcomes of surgical, locoregional, and systemic therapies, examining future prospects and strategies to address current challenges.

Ethics statement

It is a literature database-based review; therefore, neither approval by the institutional review board nor obtaining of informed consent was required.

Epidemiology

Approximately 10% (ranging from 1% to 38%) of all HCC cases are associated with MASLD, with higher rates (>20%) reported in studies from the USA, UK, India, Germany, and the Middle East. In contrast, lower estimates (1%–2%) are reported from China and Japan [15]. The incidence of MASH-related HCC is expected to rise substantially as the obesity epidemic continues to expand [16]. Mathematical models predict a significant increase in the incidence of MASH-HCC from 2016 to 2030, with projected rises of 47% in Japan, 82% in China, 88% in the UK, 117% in France, and 130% in the USA [17]. Compared to patients with HCC due to viral hepatitis (HBV or HCV) or alcohol-related liver disease, those with MASH-HCC typically

have a lower male-to-female ratio (1.2:1), are generally 5–10 years older (mean age 73), and are more likely to have metabolic and cardiovascular comorbidities, such as type 2 diabetes mellitus (DM) and chronic vascular disease. Although the incidence of MASH-HCC is lower than that associated with active viral hepatitis, the increasing prevalence of MASLD, combined with improved treatments for viral hepatitis, is expected to increase both the proportion and rate of HCC attributed to MASLD [18,19].

Risk factors

Liver cirrhosis

A study involving approximately 300,000 patients with MASLD reported an HCC incidence of 0.21 per 1,000 person-years, which is seven times higher than that observed in control individuals without liver disease—specifically, those free from viral hepatitis and with normal alanine aminotransferase levels [20]. The primary risk factor for MASH-HCC is cirrhosis, with incidence rates in cohorts of MASH cirrhosis estimated at about 2% per year, although these rates vary from 0.3% to 4.7% per year [6]. This variability can be attributed to differences in age, metabolic profiles, and the severity of liver decompensation. While HCC can also develop in MASH patients without cirrhosis, the overall incidence in this subgroup is low, ranging between 0.01% and 0.13% per year. It is even lower in the general MASLD population, underscoring the importance of assessing cirrhosis status as the primary risk stratifier for MASLD [21].

Diabetes

In cohort studies from both Europe and the US, type 2 diabetes has been identified as the strongest independent metabolic risk factor for the development of HCC. A retrospective study demonstrated that in patients with MASH-cirrhosis, the presence of DM was associated with a fourfold increase in the risk of developing HCC (hazard ratio [HR], 4.2; 95% CI, 1.2–14.2; $P=0.02$) [19]. Another large study in Europe, which included 136,703 patients with MASLD, found that among the 6,425 (4.7%) patients with advanced fibrosis, DM was the most significant risk factor for HCC [22]. Similarly, a study involving a US cohort of 271,906 MASLD patients, of whom 253 had HCC, reported a strong association between DM and HCC (adjusted HR, 2.77; 95% CI, 2.03–3.77) [23].

Obesity

In a large cohort study involving 296,707 patients, those diagnosed with MASLD and obesity did not show a statistically significant increase in HCC risk ($P=0.06$). However, the risk increased significantly, by 2.6 times, when obesity was accompanied by diabetes, hypertension, and hyperlipidemia [20]. Another recent study, which examined data from 98,090 MASLD patients with severe obesity, found that those who underwent bariatric surgery experienced a reduced risk of HCC. The adjusted HR was 0.48 (95% CI, 0.24–0.89) [24]. Although numerous studies have explored the link between obesity and elevated HCC risk, most have not sufficiently evaluated the presence of MASLD or MASH.

Alcohol

The impact of mild to moderate alcohol consumption on the development of HCC in patients with MASLD is still unclear, as research has produced inconsistent findings. A cohort study in Korea examined the relationship between mild to moderate alcohol intake and the progression

of non-invasive fibrosis scores in 58,927 adults with MASLD who initially had low fibrosis scores over a median period of 4.9 years [25]. Of these participants, 5,303 (9%) progressed from low to intermediate or high fibrosis scores. Moderate drinkers were more likely to experience increased fibrosis compared to nondrinkers, with an HR of 1.29 (95% CI, 1.23). Another study indicated that even mild drinking habits increased the risk of carcinogenesis in patients with MASH-associated cirrhosis, presenting an HR of 3.8 (95% CI, 1.6–8.9; $P=0.002$); however, this study focused solely on patients with decompensated liver disease [26]. Additionally, a recent multivariate analysis of patients with biopsy-proven MASLD across various stages of fibrosis revealed that consuming less than 20 g of alcohol per day heightened the risk of HCC, especially in those with advanced F3–4 fibrosis, with a relative risk of 4.83 ($P=0.04$) [27].

Smoking

Smoking is generally associated with an increased risk of HCC; however, its specific impact on MASLD has not been thoroughly investigated [28].

Coffee

Coffee is rich in antioxidants, including phenolic compounds such as chlorogenic, caffeic, ferulic, and coumaric acids, along with melanoidins and diterpenes such as cafestol and kahweol. These compounds have shown inhibitory effects on the development of HCC [29,30]. Additionally, the beneficial effects of coffee in preventing HCC may be partially attributed to its role in lowering the risk of type 2 DM, which is a known risk factor for HCC [31].

Antidiabetics

Metformin inhibits the mammalian target of the rapamycin pathway, which plays a role in cell proliferation by activating AMP-activated protein kinase (AMPK) [32]. It also inhibits angiogenesis, disrupts the cell cycle, and induces apoptosis independently of p53 [33]. Additionally, metformin promotes moderate weight loss, mitigates the effects of hyperinsulinemia on the cell cycle and inflammation, and improves liver biochemistry and histology in patients with MASLD [34,35]. Research has explored the impact of antidiabetic medications on HCC risk, recognizing diabetes as a significant risk factor. A recent study demonstrated that effective glycemic control was associated with a 31% reduced risk of HCC in patients with MASLD and DM [36]. The study also found that metformin use led to a 20% decrease in HCC risk, whereas insulin use, particularly when combined with other oral antidiabetic medications, increased the risk by 1.6 to 1.7 times. However, a database study of 18,080 MASLD patients without cirrhosis, monitored over an average of 6.3 years, showed no link between metformin use and HCC risk [37]. In a recent nationwide cohort, patients with MASLD and DM who used sodium-glucose cotransporter-2 inhibitors had significantly lower risks of liver and non-liver complications compared to users of other antidiabetic medications, with HRs ranging from 0.76 to 0.97. The risk was further reduced when metformin was also used, with HRs between 0.58 and 0.79 [38].

Statins

Statins exhibit a range of anticancer effects that go beyond their ability to lower cholesterol. They inhibit key oncogenic drivers including MYC, AKT, Rho-dependent kinase, and extracellular signal-regulated kinase 1 and 2 [35,39,40]. Additionally, statins activate protective liver pathways such as AMPK and p38-MAPK, and promote apoptosis through a p53-dependent mechanism [41,42]. These drugs have also been linked to anticarcinogenic effects. A database study from

Taiwan involving 18,080 MASLD patients demonstrated an inverse relationship between statin use and HCC, with an OR of 0.29 (95% CI, 0.12–0.68) [37]. In a retrospective case-control study of 102 MASLD patients, including 34 HCC cases, statins were found to be protective against HCC (OR, 0.20; 95% CI, 0.07–0.60) [43]. Another recent retrospective study showed that statin use significantly and dose-dependently reduced the risk of HCC in patients with NASH cirrhosis [44]. However, a study involving 458 MASLD patients with advanced fibrosis did not find such an association [45]. The uncontrolled and retrospective nature of these studies limits the ability to definitively interpret their findings on the chemopreventive benefits of statins, making it inappropriate to recommend them solely for the prevention of HCC.

Pathogenesis

Liver fibrosis

Approximately 80% of MASLD patients do not develop NASH, prompting research efforts to focus on identifying the factors that differentiate those with inflammation, cell injury, and fibrosis (MASH) from those exhibiting simple steatosis. A critical factor in understanding the progression to MASH is lipotoxicity, which involves hepatocellular injury resulting from disrupted fat metabolism [46]. Lipotoxicity is triggered by various factors, including increased fatty acid delivery to the liver, insulin resistance, and inflammatory signals from dysfunctional adipose tissue [47]. This condition leads to cellular stress, oxidative damage, inflammasome activation, and ultimately, cell death in hepatocytes [48]. These damaging responses are linked to pre-malignant changes, such as oxidative DNA damage and mutations in metabolism-related genes such as *FOXO1*, *CIDEA*, and *GPAM*. Although these genes may help protect hepatocytes from lipotoxicity, they also elevate the risk of malignancy [49,50].

To repair hepatocellular injuries in MASH, developmental pathways such as YAP–TAZ, Notch, and Hedgehog signaling are reactivated in hepatocytes. This reactivation leads to cell proliferation, inflammation, and potentially cancer [51,52]. In advanced MASH, there is a marked decline in hepatocyte proliferation and regenerative capacity. These dysregulated cells exacerbate inflammation and fibrosis [53]. Consequently, this hepatocellular damage fosters a pro-inflammatory environment, perpetuating chronic inflammation and impacting various immune cell types.

The stage of hepatic fibrosis in MASH is a critical determinant of clinical outcomes, as it can progress to cirrhosis and liver failure, and create conditions conducive to cancer development [54]. This process involves the activation or transdifferentiation of resident hepatic stellate cells (HSCs) into fibrogenic, proliferating myofibroblasts, which leads to the accumulation of extracellular matrix or scar tissue. Advanced single-cell sequencing has revealed significant heterogeneity among HSCs in MASH, although the functional implications of this diversity are not yet clear [55]. The exact mechanisms by which MASH–HCC develops without cirrhosis remain poorly understood, but they are likely related to fibrosis. The accumulation of extracellular matrix increases liver stiffness, which can facilitate the emergence and growth of tumor cells [56]. This scar matrix also acts as a reservoir for growth factors that may support the survival of pre-neoplastic hepatocytes, thereby promoting tumor initiation or progression. Additionally, HSCs possess immunoregulatory properties that contribute to the liver's immune tolerance, potentially affecting its response to checkpoint blockade therapies [57].

Angiogenesis is implicated in both MASH and potentially MASH–HCC. Increased CD34 expression in new blood vessels has been observed in previous studies involving both humans

and rodents, indicating enhanced vascularization [58]. Vascular endothelial growth factor (VEGF), a crucial angiogenic signal, shows elevated levels in experimental MASH models. Inhibiting VEGF leads to reduced vascularization, inflammation, and steatosis [59].

The impact of treatments targeting MASH on the risk of MASH-HCC has yet to be determined; however, a decrease in HCC risk has been noted in MASH patients following bariatric surgery, indicating that future medical interventions for MASH could potentially lower the incidence of HCC [60]. Nonetheless, it remains uncertain whether advanced liver fibrosis continues to carry an inherent risk of cancer even if the fibrosis subsequently regresses.

Immune system

The immune system plays a major role in both MASLD and HCC, and distinct immunogenomic classifications have been identified [61]. MASH is characterized by inflammatory responses in the liver, which are pivotal in its progression to fibrosis, cirrhosis, or HCC [62]. Both innate and adaptive immune mechanisms significantly contribute to hepatic inflammation in MASH. Resident Kupffer cells and the recruitment of leukocytes, including neutrophils, monocytes, NK cells, and NKT cells, promote inflammation through the release of cytokines, chemokines, and reactive oxygen species. Elevated levels of CD4⁺ T helper cells, particularly the TH1 and TH17 subsets, have been observed in the livers of mice with MASH [63]. Although T cells exhibit anti-tumorigenic properties, the depletion of CD8⁺ T cells accelerates tumor growth in MASH-driven HCC models. Similarly, the depletion of CD4⁺ T cells promotes tumor growth, impacting the efficacy of immune-based therapies [64].

The disruption of the immune system in MASH and MASH-HCC has been linked to the response to immunotherapies. Both adaptive and innate immune cells, including CD4⁺ T cells, metabolically activated CD8⁺ T cells, platelets, and dendritic cells, play a role in shaping the liver microenvironment as MASH progresses to HCC [65,66]. Neutrophils, in particular, are involved in the transition from fatty liver to steatohepatitis. They contribute to an immunosuppressive environment through the production of extracellular traps and PDL1 signaling, which leads to CD8⁺ T cell exhaustion and affects the response to immunotherapy [67,68]. In MASLD, impaired antigen-specific T-cell function has been observed, partially due to macrophage activity [69]. In advanced HCC, the infiltration of CCR2⁺ and CX3CR1⁺ macrophages is linked to non-responsiveness to immune-checkpoint inhibition. Conversely, pro-inflammatory PDL1-expressing CXCL10⁺ macrophages can drive treatment response. Recent studies indicate that T cells lose functionality in MASLD, which contributes to poor responses to immune checkpoint inhibitor (ICI) therapy [70]. Approaches such as neutrophil reprogramming with CXCR2 antagonists have shown promise in enhancing the effectiveness of ICI therapy in MASH-HCC models by increasing dendritic cell activity and CD8⁺ T cell numbers [68].

In two notable studies involving both mice and humans, the presence of CD8⁺PD1⁺ T cells in the liver increased as MASH progressed. These cells are in an auto-aggressive state, characterized by liver-resident CD8⁺PD1⁺CD103⁺ T cells that, despite being exhausted, display an activated phenotype and express high levels of cytokines such as TNF, CCL2, IL-10, and granzyme B [71,72]. In MASH-HCC mouse models treated with immunotherapy, these CD8⁺PD1⁺ cells exhibited minimal changes in their transcriptomes and proteomes, yet they increased in size over time. This growth contributed to heightened liver inflammation, hepatocyte death, and oncogenic signaling [72]. Instead of eliminating HCC, these cells became dysfunctional in tumor surveillance and even promoted tumor growth. This dysfunction resulted in a lack of response to ICIs in therapeutic settings and accelerated HCC development

in preventive scenarios. Similar characteristics of CD8+ T cells have been observed in human MASH-HCC, indicating that peritumoral and intratumoral CD8+PD1+ T cells could potentially serve as predictors of treatment success or resistance to ICIs. Understanding the immune microenvironment is essential for identifying the most effective therapies in future research.

Microbiome

The gut microbiome plays a crucial role in influencing altered liver responses in MASH by affecting hepatic bile acid metabolism and facilitating the translocation of gut-derived signals through an increasingly permeable gut lining [73]. Throughout all stages of NASH, the gut–liver axis remains active, with interactions between liver damage, regeneration, and heightened gut permeability exacerbating inflammatory, pro-fibrogenic, and pro-carcinogenic pathways [48]. This permeability defect allows for both direct (e.g., bacterial presence) and indirect (e.g., bacterial metabolites) interactions between the gut microbiome and the liver, which in turn impact liver metabolism and contribute to the progression of MASH and HCC.

The gut microbiome has been identified as a key factor in triggering MASLD, driving liver steatosis by enhancing energy harvest, monosaccharide absorption, and abnormal acetate production [74]. A dysbiotic, leaky gut permits the translocation of pathogen-associated and danger-associated molecular patterns into the liver, activating immune cells and Toll-like receptors, which in turn trigger pro-inflammatory and fibrotic pathways [75]. In mice, disruption of the gut vascular barrier by the microbiota is seen as a precursor to NASH [76]. Additionally, inflammatory cells from the gut may migrate to the liver, contributing to bacterial translocation. Several bacterial species, such as Proteobacteria, Enterobacteriaceae, and Escherichia, are associated with MASLD in humans, and levels of Bacteroides are elevated in MASH patients [76,77]. Treatment with non-absorbable antibiotics, such as rifaximin, has shown potential in improving liver function, underscoring the significant role of the gut microbiome in MASH pathogenesis [78].

Molecular alterations

Several single-nucleotide polymorphisms (SNPs) associated with abnormal lipid metabolism in hepatocytes have been linked to an increased risk of MASH and progression to HCC. One of the most well-known SNPs is rs738409 in the *PNPLA3* gene, which encodes the patatin-like phospholipase domain-containing protein 3. This variant interferes with the breakdown of lipid droplets in hepatocytes, leading to decreased triglyceride lipolysis and promoting hepatic steatosis. As a result, it is associated with more than a 2-fold increased risk of MASH and a 2.2-fold higher risk of progressing to MASH HCC compared to those without the variant [79]. Another significant SNP, rs58542926 in the *TM6SF2* gene, plays a role in regulating liver fat metabolism and increases hepatic triglyceride content. This variant is linked to a 1.6-fold increased risk of MASH and a 1.9-fold higher risk of MASH HCC [80].

Additionally, an SNP near the *MBOAT7* gene is associated with increased hepatic triglyceride levels and occurs twice as frequently in patients with MASH-HCC compared to those with MASLD alone [81]. A loss-of-function variant in the *GCKR* gene, which encodes the glucokinase regulator, leads to increased *de novo* lipogenesis and insulin resistance. This variant is linked to a 1.5-fold increased risk of MASH and a 1.8-fold higher risk of MASH-HCC [82]. A polygenic risk score that incorporates these four SNPs has been suggested for HCC risk stratification in patients of European ancestry with NASH cirrhosis. This score has proven to be a more accurate predictor of HCC development than individual SNPs ($P < 10^{-13}$) [83].

MASH-HCC is often associated with an increased presence of ACVR2A and TP53 mutations, as well as the proliferative class S1-WNT/TGF β [84]. A distinct mutational signature, termed MutSigNASH-HCC, has been identified in 25% of MASH-HCC patients, compared to only 2% in those with other causes. This signature is characterized by a higher frequency of C>T and C>A transitions [85]. Furthermore, patients with MASH-HCC exhibit higher levels of hepatic oxidative DNA damage than those with other etiologies, a phenomenon that correlates with a diminished DNA damage response in experimental models [49]. Additionally, epigenetic events that suppress the transcription of genes involved in bile and fatty acid metabolism, while activating proliferative pathways, have been implicated in MASH-HCC. Experimental models have shown that epigenetic reprogramming can reverse hepatocarcinogenesis [86].

A diagram of the pathogenesis of HCC associated with metabolic dysfunction-related steatohepatitis is shown in Fig. 1.

Clinical management

Prevention

Several observational, retrospective, population-based studies have suggested that metformin, statins, coffee, and aspirin might contribute to the prevention of HCC, regardless of the underlying liver disease etiology [87,88]. Due to its generally favorable benefit-to-risk ratio, current guidelines endorse the consumption of coffee for individuals with chronic liver disease [89,90]. However, other agents have not demonstrated sufficient efficacy to be recommended for HCC prevention, and most studies related to this have not been conducted in well-defined populations with MASLD.

For the prevention of MASH-HCC, the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Korean Association for the Study of Liver Diseases (KASL) recommend combining a hypocaloric or Mediterranean

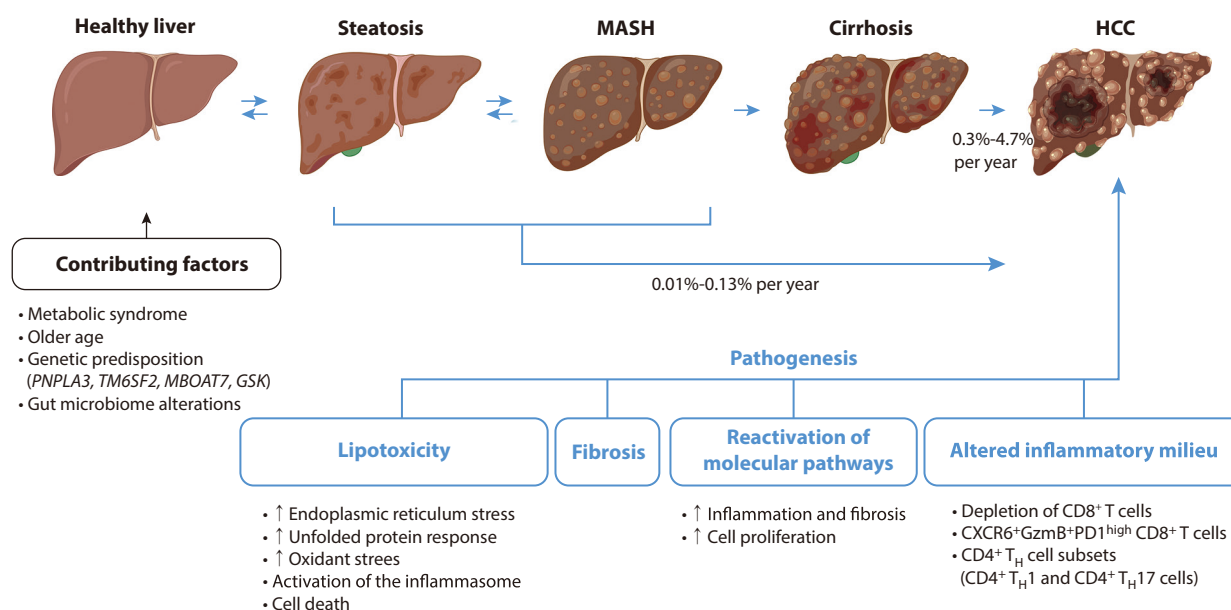


Fig. 1. Pathogenesis and progression of MASH-HCC (drawn by the author). MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; T_H, T helper.

diet with moderate-intensity exercise to achieve and maintain weight loss, as outlined in their practice guidelines [89–91]. Additionally, a large multinational cohort study has demonstrated that physical activity is associated with a reduced risk of HCC [92]. Although there is no direct evidence currently available that weight loss decreases the risk of MASH-HCC, observational studies indicate that weight loss may reverse steatosis and potentially fibrosis in patients with MASH, thereby suggesting a possible benefit of weight loss in reducing the risk of HCC [93,94].

Hepatocellular carcinoma surveillance

The clinical practice guidelines from the AASLD, EASL, and KASL recommend semiannual surveillance for HCC using abdominal ultrasound, with or without α -fetoprotein testing, for all patients with cirrhosis, regardless of the underlying cause. However, only two studies have specifically assessed the potential benefits of such surveillance in patients with MASLD-related cirrhosis.

However, a previous study found no significant association between surveillance and the applicability of curative treatment (45.5% versus 51.5%; $P=0.72$) [95].

Data specifically focusing on patients with MASLD are important, as this group exhibits unique characteristics that pose challenges to traditional HCC surveillance methods. Notably, about one-third of MASLD-HCC cases arise in individuals without cirrhosis, suggesting that these patients are often excluded from the at-risk populations typically targeted for surveillance [21]. Furthermore, at the time of their HCC diagnosis, patients with MASLD are generally less likely to have been previously diagnosed with liver disease or cirrhosis, which likely contributes to their lower rates of surveillance utilization [96]. A meta-analysis revealed that a significantly smaller proportion of patients with MASLD-HCC (32.8%, 95% CI, 12.0–63.7) underwent surveillance compared to patients with HCC from other causes (55.7%, 95% CI, 24.0–83.3; $P<0.0001$) [97].

Second, patients with MASH are more likely to experience inadequate ultrasound visualization and surveillance failure, leading to a higher rate of late-stage HCC diagnoses even when surveillance is performed [98,99]. This suggests that the sensitivity of ultrasound-based surveillance in patients with MASH may be lower than the 63% observed in those with HCC from other causes [100]. This finding underscores the need for alternative imaging methods, such as CT or MRI, and blood-based biomarker strategies for this group [101].

Treatment for metabolic dysfunction-associated steatohepatitis-hepatocellular carcinoma

Patients with MASH-HCC often present with comorbidities, such as cardiovascular disease, which can restrict their access to curative treatments, especially surgery [102,103]. However, a systematic review has shown that despite having more comorbidities and larger tumors at diagnosis, the allocation of treatments for MASLD patients is similar to that for other patients [97]. Moreover, when severe comorbidities are excluded, the outcomes following curative and locoregional treatments for MASH-HCC are comparable to, or even better than, those observed in non-MASH patients. Lastly, immunotherapies may be less effective in non-viral HCC cases, such as MASH-HCC, due to impairments in the immune system [72].

Surgery: Patients with MASLD face a higher risk of intra-operative complications and poorer post-surgical outcomes, largely due to the increased prevalence of metabolic syndrome comorbidities. Obesity and type 2 diabetes have been linked to lower survival rates in cancer patients, including those receiving surgical treatments [104,105]. Research indicates that patients with MASH-HCC are more likely to suffer from hypertension, hyperlipidemia, and ischemic

heart disease compared to those with other causes of HCC, all factors that heighten the risk of post-surgical morbidity and complications [102]. Furthermore, the degree of liver steatosis may correlate with poorer surgical outcomes [106].

However, a systematic review and meta-analysis of 14 studies, which included 7,226 HCC patients—approximately 20% of whom had MASH-HCC—demonstrated that patients with MASH-HCC experienced improved disease-free survival (HR, 0.81) and overall survival (HR, 0.78) compared to those with other causes [107]. Another meta-analysis corroborated these results, suggesting that the better outcomes in MASH-HCC patients might be due to the absence of cirrhosis in many cases and the exclusion of those with severe comorbidities from surgical interventions [108].

Liver transplantation: An analysis of the United Network for Organ Sharing (UNOS) registry from 2002 to 2012 revealed that patients with MASH-HCC had significantly better post-transplant survival outcomes (HR, 0.69; 95% CI, 0.63–0.77) and a lower risk of graft failure (HR, 0.76; 95% CI, 0.69–0.83) compared to those with other causes of HCC. This was despite a higher prevalence of diabetes and cardiovascular disease in the MASH-HCC group [109]. In contrast, data from the European Liver Transplant Registry showed no statistically significant differences in post-transplant survival or graft survival between patients with HCC, regardless of MASLD status. However, there were differences in the causes of mortality [110]. While some single-center studies suggest that patients with MASLD may have a higher risk of post-transplant complications, the overall evidence indicates similar post-transplant survival rates between patients with MASLD and those with other etiologies of HCC [111].

Locoregional therapies: Current evidence on the efficacy of locoregional therapies for MASH-HCC is limited. However, a study using the SEER-Medicare database showed similar overall survival rates following radiofrequency ablation in patients with MASH-HCC compared to those with other HCC etiologies [112]. Additionally, a propensity score-matched study that included patients undergoing transarterial chemoembolization revealed no significant differences in time-to-progression (13.0 vs. 8.5 months; $P=0.25$) or overall survival (23.2 vs. 28.0 months; $P=0.48$) between patients with and without MASLD [113]. Another study comparing MASLD-HCC and HBV-related HCC patients treated with transarterial radioembolization also found no significant differences in treatment-related adverse events or overall survival [114]. These results indicate that transarterial chemoembolization and transarterial radioembolization are likely safe and effective treatments for patients with MASH-HCC, yielding comparable outcomes across different etiologies.

Systemic therapies: Phase III studies of systemic therapies in advanced HCC have predominantly involved patients with compensated liver disease. However, the etiology of liver disease has not been a consideration in treatment decisions or trial designs. Typically, studies report efficacy based on stratification factors such as etiology, often categorized as HBV, HCV, or “non-viral.” The “non-viral” category includes alcohol-related disease, MASH, and other causes (Table 1).

Currently, several agents are approved for the first- and second-line treatment of advanced HCC. These can be broadly categorized into two groups: multi-kinase VEGFR-targeting small molecules and VEGFR2 monoclonal antibody approaches, as well as immunotherapy-based approaches. Regarding overall survival, the efficacy of the first group does not significantly vary based on the etiology of HCC, as evidenced by similar HRs for overall survival in the study versus control arms. This trend is also generally observed in secondary endpoints, such as progression-free survival and objective response rates.

Table 1. Summary of key phase III randomized trials evaluating the efficacy and safety of systemic therapies according to the etiology of hepatocellular carcinoma

Trial	Treatment arms	Subgroup based on etiology (n, %)	Overall survival HR (95% CI)	Progression-free survival HR (95% CI)
Immunotherapy: first line				
IMbrave150 [118]	Atezolizumab plus bevacizumab vs. sorafenib	Overall (501)	0.58 (0.42–0.79)	0.59 (0.47–0.76)
		HBV (240, 48%)	0.51 (0.32–0.81)	0.47 (0.33–0.67)
		HCV (108, 22%)	0.43 (0.22–0.87)	0.69 (0.39–1.20)
		Non-viral (153, 31%)	0.91 (0.52–1.60)	0.71 (0.47–1.08)
COSMIC-312 [119]	Atezolizumab plus cabozantinib vs. sorafenib	Overall (649)	0.90 (0.69–1.18)	0.63 (0.44–0.91)
		HBV (190, 29%)	0.53 (0.33–0.87)	0.46 (0.29–0.73)
		HCV (202, 31%)	1.10 (0.72–1.68)	0.64 (0.38–1.09)
		Non-viral (257, 40%)	1.18 (0.78–1.79)	0.92 (0.60–1.41)
HIMALAYA [120]	Tremelimumab plus durvalumab vs. sorafenib	Overall (782)	0.78 (0.65–0.93)	0.90 (0.77–1.05)
		HBV (241, 31%)	0.64 (0.48–0.86)	-
		HCV (214, 27%)	1.06 (0.76–1.49)	-
		Non-viral (327, 42%)	0.74 (0.57–0.95)	-
	Durvalumab vs. sorafenib	Overall (778)	0.86 (0.73–1.03)	1.02 (0.88–1.19)
		HBV (238, 31%)	0.78 (0.58–1.04)	-
		HCV (211, 27%)	1.05 (0.75–1.48)	-
		Non-viral (329, 42%)	0.82 (0.64–1.05)	-
CheckMate 459 [121]	Nivolumab vs. sorafenib	Overall (743)	0.85 (0.72–1.02)	0.93 (0.79–1.10)
		HBV (233, 31%)	0.77 (0.56–1.05)	-
		HCV (173, 23%)	0.71 (0.49–1.01)	-
		Non-viral (336, 45%)	0.95 (0.74–1.22)	-
RATIONALE-301 [122]	Tislelizumab vs. sorafenib	Overall (674)	0.85 (0.71–1.02)	1.11 (0.92–1.33)
		HBV (427, 63%)	0.91 (0.73–1.14)	-
		HCV (85, 13%)	0.64 (0.38–1.08)	-
		Non-viral (162, 24%)	0.78 (0.55–1.12)	-
LEAP-002 [123]	Pembrolizumab plus lenvatinib vs. lenvatinib	Overall (794)	0.84 (0.71–1.00)	0.83 (0.71–0.98)
		HBV (385, 47%)	0.75 (0.58–0.97)	-
		HCV (181, 22%)	0.86 (0.60–1.24)	-
		Alcohol (251, 31%)	0.84 (0.67–1.05)	-
CARES-310 [124]	Camrelizumab plus rivoceranib vs. sorafenib	Overall (543)	0.62 (0.49–0.80)	0.52 (0.41–0.65)
		HBV (405, 75%)	0.66 (0.50–0.87)	0.57 (0.45–0.72)
		HCV (51, 9%)	0.45 (0.18–1.16)	0.46 (0.21–1.05)
		Non-viral (87, 16%)	0.71 (0.37–1.36)	0.55 (0.33–0.93)
ORIENT-32 [125]	Sintilimab plus IBI305 vs. sorafenib	Overall (571)	0.57 (0.43–0.75)	0.56 (0.46–0.70)
		HBV (538, 94%)	0.58 (0.43–0.76)	0.56 (0.40–0.76)
		Non-HBV (33, 6%)	0.80 (0.22–2.87)	0.38 (0.14–1.06)
Immunotherapy: second line				
KEYNOTE-240 [126]	Pembrolizumab vs. placebo	Overall (413)	0.78 (0.61–1.00)	0.72 (0.57–0.90)
		HBV (101, 24%)	0.57 (0.35–0.94)	0.70 (0.44–1.13)
		HCV (64, 15%)	0.96 (0.48–1.92)	0.46 (0.24–0.90)
		Non-viral (248, 60%)	0.88 (0.64–1.20)	0.75 (0.56–1.01)
KEYNOTE-394 [127]	Pembrolizumab vs. placebo	Overall (453)	0.79 (0.63–0.99)	0.74 (0.60–0.92)
		HBV (360, 79%)	0.78 (0.61–0.99)	0.77 (0.61–0.98)
		Non-HBV (93, 21%)	0.87 (0.53–1.44)	0.58 (0.36–0.94)
Tyrosine kinase inhibitors: first line				
SHARP [128,129]	Sorafenib vs. placebo	Overall (439)	0.69 (0.55–0.87)	-
		HBV (111, 18%)	0.76 (0.38–1.50)	-
		HCV (169, 28%)	0.50 (0.32–0.77)	-
		Alcohol (159, 26%)	0.76 (0.50–1.16)	-
Asia-Pacific [130,131]	Sorafenib vs. placebo	Overall (226)	0.68 (0.50–0.93)	-
		HBV (165, 73%)	0.74 (0.51–1.06)	-
		Non-HBV (61, 27%)	0.57 (0.29–1.13)	-

Table 1. Continued

Trial	Treatment arms	Subgroup based on etiology (n, %)	Overall survival HR (95% CI)	Progression-free survival HR (95% CI)
REFLECT [132]	Lenvatinib vs. sorafenib	Overall (753)	0.92 (0.79–1.06)	0.66 (0.57–0.77)
		HBV (479, 50%)	0.83 (0.68–1.02)	0.62 (0.50–0.75)
		HCV (217, 23%)	0.91 (0.66–1.26)	0.78 (0.56–1.09)
		Alcohol (57, 6%)	1.03 (0.47–2.28)	0.27 (0.11–0.66)
Tyrosine kinase inhibitors: second line				
CELESTIAL [133]	Cabozantinib vs. placebo	Overall (707)	0.76 (0.63–0.92)	0.44 (0.36–0.52)
		HBV (267, 38%)	0.69 (0.51–0.94)	0.31 (0.23–0.42)
		HCV (168, 24%)	1.11 (0.72–1.71)	0.61 (0.42–0.88)
		Non-viral (272, 38%)	0.72 (0.54–0.96)	0.48 (0.36–0.63)
RESORCE [134]	Regorafenib vs. placebo	Overall (573)	0.63 (0.50–0.79)	0.46 (0.37–0.56)
		HBV (216, 38%)	0.58 (0.41–0.82)	0.39 (0.29–0.54)
		HCV (119, 21%)	0.79 (0.49–1.26)	0.59 (0.39–0.90)
		Alcohol (145, 25%)	0.92 (0.61–1.38)	0.53 (0.37–0.77)
REACH-2 [135]	Ramucirumab vs. placebo	Overall (292)	0.71 (0.53–0.95)	0.45 (0.34–0.60)
		HBV (107, 37%)	0.84 (0.52–1.35)	0.43 (0.28–0.68)
		HCV (76, 26%)	0.76 (0.44–1.33)	0.33 (0.19–0.60)
		Other (109, 37%)	0.63 (0.38–1.06)	0.57 (0.35–0.95)

HR, hazard ratio.

Unlike previous treatments, ICIs have not only demonstrated a survival benefit but have also achieved significant response rates with durable responses lasting over 20 months. There is growing interest in evaluating clinical characteristics as markers of benefit, especially those associated with distinct pathogenic pathways and immune profiles linked to different HCC etiologies. Two studies have raised questions about the effectiveness of immunotherapies in metabolic-associated steatohepatitis-HCC (MASH-HCC) compared to viral-related HCC [72,115]. However, none of the phase III randomized controlled trials (RCTs) in advanced HCC have reported the percentage of patients with MASH-HCC. Consequently, indirect analysis of survival effects by etiology has been limited to non-viral HCC cases. A meta-analysis of three RCTs (IMbrave150, CheckMate 459, and Keynote-240) indicated that patients with viral-related HCC responded better to immunotherapies (HR, 0.64; 95% CI, 0.50–0.83) than those with non-viral-related HCC (HR, 0.92; 95% CI, 0.77–1.11; $P=0.2$) [115]. Following the publication of a subgroup analysis from the COSMIC-312 trial, a meta-analysis of four RCTs confirmed a significant difference in efficacy ($P=0.01$) [116]. When the HIMALAYA trial, which assessed a combination of two ICIs, was included in the meta-analysis (five RCTs), the difference remained significant, albeit less pronounced ($P=0.046$) [15]. These findings suggest that immunotherapies may be more effective in viral-related HCC than in other etiologies, supporting observations that MASH-HCC tumors have dysfunctional T cells, which may limit the effectiveness of ICIs [72].

However, these subgroup analyses are not statistically definitive and do not account for other prognostic factors. The term "non-viral etiologies" includes MASH-related, alcohol-related, idiopathic, and other metabolic causes, which complicates the analysis. These findings suggest that future studies should stratify participants based on etiology; however, dedicated prospective studies are necessary to determine the specific role of etiology. Although MASH-HCC is biologically distinct, the current clinical approaches remain consistent with those used for other non-viral etiologies, including alcohol-related HCC. Future trials should specifically identify cases of MASH-related HCC to better understand the impact of immunotherapies on the survival of this subgroup.

Conclusion

MASH is a significant global health issue and is projected to become the leading cause of HCC by 2030. The progression from MASH to HCC is influenced by molecular changes, the stage of fibrosis, the immune microenvironment, and the microbiome. Lifestyle changes are crucial for preventing MASLD progression, and surveillance in patients with MASH cirrhosis enables earlier detection and improves survival. Currently, MASH-HCC is managed similarly to other HCC etiologies, but comorbidities such as obesity and diabetes can complicate treatment.

Key unmet needs include identifying the molecular drivers of HCC in non-cirrhotic MASLD and developing preventive therapies. There is also a need for improved surveillance methods, particularly alternatives to ultrasound for obese patients, and for refining the selection of surgical candidates. It is crucial to report MASH-HCC outcomes separately in trials to facilitate better analysis; thus, it is recommended that MASH-HCC be specifically identified in clinical trials to enable more effective, personalized treatments. Additionally, further studies are required to understand MASH-HCC-related T-cell dysfunction and to identify biomarkers that predict treatment responses [117].

ORCID

Han Ah Lee: <https://orcid.org/0000-0003-4082-1121>

Authors' contributions

All work was done by Han Ah Lee.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

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Imaging findings of intrahepatic cholangiocarcinoma for prognosis prediction and treatment decision-making: a narrative review

Jun Gu Kang^{1,2}, Taek Chung³, Dong Kyu Kim^{1,2}, Hyungjin Rhee^{1,2}

¹Department of Radiology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

²Research Institute of Radiological Sciences, Center for Clinical Imaging Data Science, and Institute for Innovation in Digital Healthcare, Yonsei University College of Medicine, Seoul, Korea

³Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author

Hyungjin Rhee
Department of Radiology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: hjinrhee@yuhs.ac

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Intrahepatic cholangiocarcinoma (iCCA) is a heterogeneous bile duct adenocarcinoma with a rising global incidence and a poor prognosis. This review aims to present a comprehensive overview of the most recent radiological research on iCCA, focusing on its histopathologic subclassification and the use of imaging findings to predict prognosis and inform treatment decisions. Histologically, iCCA is subclassified into small duct (SD-iCCA) and large duct (LD-iCCA) types. SD-iCCA typically arises in the peripheral small bile ducts and is often associated with chronic hepatitis or cirrhosis. It presents as a mass-forming lesion with a relatively favorable prognosis. LD-iCCA originates near the hepatic hilum, is linked to chronic bile duct diseases, and exhibits more aggressive behavior and poorer outcomes. Imaging is essential for differentiating these subtypes and assessing prognostic factors like tumor size, multiplicity, vascular invasion, lymph node metastasis, enhancement patterns, and intratumoral fibrosis. Imaging-based prognostic models have demonstrated predictive accuracy comparable to traditional pathological staging systems. Furthermore, imaging findings are instrumental in guiding treatment decisions, including those regarding surgical planning, lymphadenectomy, neoadjuvant therapy, and the selection of targeted therapies based on molecular profiling. Advancements in radiological research have improved our understanding of iCCA heterogeneity, facilitating prognosis prediction and treatment personalization. Imaging findings assist in subclassifying iCCA, predicting outcomes, and informing treatment decisions, thus optimizing patient management. Incorporating imaging-based approaches into clinical practice is crucial for advancing personalized medicine in the treatment of iCCA. However, further high-level evidence from international multicenter prospective studies is required to validate these findings and increase their clinical applicability.

Introduction

Background

Cholangiocarcinoma (CCA) is an adenocarcinoma characterized by differentiation of the bile duct epithelium. Based on its anatomical location, CCA is classified into intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA) [1,2]. CCAs located more peripherally than the

second confluence of the bile ducts are classified as iCCA, those situated between the second confluence and the cystic duct insertion site on the common bile duct are categorized as pCCA, and those found distal to the cystic duct insertion are classified as dCCA [3]. iCCAs account for 10% to 20% of all CCAs, while pCCAs (50% to 60%) and dCCAs (20% to 30%) are more common [3]. However, while the rates of pCCA and dCCA are decreasing, the age-standardized incidence of iCCA has been rising globally over the past few decades, necessitating closer attention [3]. iCCA is the second most common primary liver cancer after hepatocellular carcinoma (HCC) and has a worse prognosis than HCC [4]. Recently, our understanding of iCCA has improved, and it is now recognized as a heterogeneous tumor with diverse etiology, clinical presentation, pathology, and genetic characteristics. The clinical significance of this heterogeneity is being increasingly recognized.

iCCA often presents as a mass with variable shapes, including lobulated or irregular contours, and may be associated with bile duct dilatation, vascular encasement, and regional lymph node metastasis [5]. The enhancement patterns observed on dynamic CT or MRI are diverse; typically, peripheral enhancement is evident in the arterial phase, followed by centripetal enhancement in later phases [6,7]. On MRI, most iCCAs exhibit high signal intensity on T2-weighted images relative to the surrounding liver parenchyma, display diffusion restriction on diffusion-weighted images, and appear hypointense in the hepatobiliary phase when gadoxetic acid is used as a contrast medium [6–8]. The imaging characteristics of iCCA are heterogeneous, reflecting the recently recognized diversity of the disease. Accumulating evidence suggests that these imaging features can be clinically applied to predict prognosis and guide treatment decisions [9,10].

Objectives

This review provides a comprehensive overview of recent radiological research on iCCA, emphasizing its histopathological subclassification as well as imaging findings that aid in predicting the prognosis of iCCA and in making treatment decisions.

Ethics statement

As this study is based on a review of the literature, neither institutional review board approval nor informed consent was required.

Histopathologic subclassification of intrahepatic cholangiocarcinoma

In the fifth edition of the World Health Organization classification, updated in 2019, a new histological subclassification of iCCA was introduced, delineating small duct (SD-iCCA) and large duct (LD-iCCA) types [11,12]. SD-iCCA and LD-iCCA are distinct not only in their histopathological morphology but also in their etiology, tumor location, gross morphology, histopathological characteristics such as invasiveness and vascularity, molecular features, and prognosis (Table 1).

SD-iCCA typically arises in the small bile ducts within the peripheral liver, often in the context of chronic hepatitis and cirrhosis. It is characterized by an exclusively mass-forming (MF) gross morphology [13]. Histologically, SD-iCCA consists of cuboidal or low columnar cells arranged in a tubular or cord-like glandular pattern. Compared to LD-iCCA, SD-iCCA is less frequently associated with aggressive pathological features, such as perineural invasion, vascular invasion,

Table 1. Comparison of characteristics between small duct and large duct iCCA

Characteristic	Small duct iCCA	Large duct iCCA
Location	Peripheral	Close to hilum
Etiology	Chronic hepatitis, cirrhosis	Hepatolithiasis, PSC
Postulated cell origin	Small bile duct, canal of Hering	Large bile duct, peribiliary gland
Shape of cancer cells	Low columnar to cuboidal	Columnar cells
Precursor lesions	(–)	(+ / BillIN, IPNB)
Gross morphology	Mass-forming type	Various
Perineural invasion	(+/-)	(++)
Lymphovascular invasion	(+/-)	(++)
Lymph node metastasis	(+/-)	(++)
Prognosis	Good	Poor
Molecular marker(s)	NCAM (+), N-cadherin (+)	S100P (+)
Mutation(s)	<i>IDH1/2</i> mutation, <i>FGFR2</i> fusion	<i>KRAS</i> mutation
Vasculature	Arteries (+), high MVD	Arteries (+/-), low MVD
Necrosis	(+/-)	(+)

iCCA, intrahepatic cholangiocarcinoma; PSC, primary sclerosing cholangitis; BillIN, biliary intraepithelial neoplasia; IPNB, intraductal papillary neoplasm of the bile duct; NCAM, neural cell adhesion molecule; N-cadherin, neural cadherin; IDH, isocitrate dehydrogenase; FGFR2, fibroblast growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MVD, microvessel density.

and lymph node metastasis [14]. It also tends to have a higher microvascular density (MVD) and exhibits necrosis less frequently. Overall, SD-iCCA has a more favorable prognosis than LD-iCCA [15,16].

LD-iCCA typically originates in the large bile ducts near the hilum and is often associated with underlying chronic bile duct diseases such as hepatolithiasis, liver fluke infestation, or primary sclerosing cholangitis [13]. LD-iCCA frequently arises from a multistep carcinogenesis process, with well-known precursor lesions including biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct [17]. It usually develops from either periductal-infiltrating or intraductal-growing tumors of the large bile duct [14]. These tumors can further evolve into the MF type or present as a hybrid of the MF and either the periductal-infiltrating or the intraductal-growing type [18]. Compared to the SD-iCCA, LD-iCCA more frequently exhibits perineural invasion, vascular invasion, and lymph node metastasis; it also displays lower MVD and more frequent necrosis [14,19]. LD-iCCA has a poorer prognosis than SD-iCCA due to its high invasiveness, which leads to frequent recurrence after curative surgical resection and resistance to chemotherapy [20,21].

Utilizing imaging findings to predict prognosis in intrahepatic cholangiocarcinoma

Imaging assessment of the American Joint Committee on Cancer, Eighth Edition, tumor-node-metastasis staging system

The prognosis of iCCA in clinical settings is generally stratified using the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. This system incorporates the

tumor, node, metastasis (TNM) classification [22] and was developed and validated through pathological assessment of tumor involvement [22–25]. In iCCA staging, the T category is defined by several factors, including the size of the tumor (with a threshold of 5 cm), the number of tumors present, vascular invasion, visceral peritoneal perforation, and invasion of extrahepatic organs. The N category signifies the presence of regional lymph node metastasis, while the M category indicates distant metastasis. Although TNM staging should be definitively determined through pathological examination of resectable tumors, imaging-based staging is commonly employed to predict prognosis and guide treatment decisions for tumors prior to surgical resection or those deemed unresectable.

The eighth edition of the AJCC provides brief guidance on the clinical TNM classification for iCCA, noting that both contrast-enhanced CT and MRI are valuable for detecting tumors larger than 2 cm and assessing vascular involvement. Additionally, it indicates that magnetic resonance cholangiopancreatography can offer additional insights into the extent of disease. However, recent clinical practice guidelines from the European Association for the Study of the Liver and the International Liver Cancer Association (EASL-ILCA) recommend MRI over CT for the staging of iCCA [2]. This guidance is supported by a multicenter retrospective study that directly compared these modalities and revealed the superiority of MRI in staging MF-iCCAs, especially for tumors classified as T1b, T2, and T3/T4. Specifically, MRI displayed better performance in predicting T category components, such as tumor multiplicity, vascular invasion, and visceral peritoneal invasion [26].

Tumor size and multiplicity

The eighth edition AJCC staging system for iCCA categorizes solitary tumors as T1a or T1b, depending on whether the tumor is larger or smaller than 5 cm. This classification is underpinned by multiple studies demonstrating that tumors exceeding 5 cm are linked to comparatively poor survival outcomes and a high likelihood of recurrence [27–29]. Recent research has confirmed the reliability of preoperative imaging for accurately estimating iCCA tumor size, revealing a median difference of less than 0.5 cm between pathological and radiological measurements [30]. Furthermore, a study comparing the effectiveness of CT and MRI for determining iCCA tumor size reported no significant difference between these modalities [26].

Tumor multiplicity is another key determinant for the T category in the AJCC staging system, with its presence categorizing a tumor as T2. Multiplicity is defined as the presence of satellitosis, multifocal tumors, or intrahepatic metastasis [22]. Studies have demonstrated that tumor multiplicity is linked to poorer overall survival and a higher risk of tumor recurrence after resection [31,32]. As previously noted, a recent study showed MRI to be superior to CT in the imaging assessment of tumor multiplicity [26].

In both CT and MRI dynamic imaging studies, the assessment of tumor size and the detection of satellite nodules in iCCA typically involve the use of the portal venous phase [26,33]. Regarding MRI, hepatobiliary phase and diffusion-weighted imaging are also useful, particularly for detecting small lesions [34,35].

Vascular invasion

Vascular invasion, which includes both macrovascular invasion and microvascular invasion (MiVI) observed on histopathologic examination, is a major prognostic factor for iCCA. Specifically, it assigns a stage of T2 in the eighth edition AJCC system [22]. Research indicates that MiVI in iCCA is significantly linked to poor overall survival. Additionally, macrovascular invasion has been

associated with comparatively low overall and disease-free survival [36,37].

The challenge of clinical staging arises from the inability to directly observe MiVI using CT or MRI. To address this issue, recent research has focused on identifying imaging characteristics that can predict the presence of MiVI in iCCA. Studies have found that MiVI is more commonly associated with larger tumors, lobulated or irregular tumor morphology, thin-rim enhancement during the arterial phase, penetration of the hepatic artery within the tumor, bile duct dilation, and a high apparent diffusion coefficient (ADC) [38–40].

Lymph node metastasis

Lymph node metastasis is widely recognized as a strong prognostic factor for iCCA [31,41]. The conventional criteria for detecting lymph node metastasis on CT and MRI generally involve a lymph node size threshold of 1 cm in short-axis diameter, along with imaging characteristics such as round shape, irregular margins, and internal necrosis [42]. Recent studies have demonstrated that the inclusion of tumor imaging factors—such as arterial phase hypoenhancement, tumor multiplicity, bile duct involvement, periductal infiltrating growth pattern, and a primary tumor located in the left lobe—combined with serum tumor markers like elevated carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) levels, can improve the accuracy of lymph node metastasis detection in iCCA [43–46].

However, the diagnostic accuracy of CT and MRI for detecting lymph node metastases is generally considered to be inadequate. The most recent EASL-ILCA guidelines advise the routine use of 18-fludeoxyglucose positron emission tomography-CT (^{18}F -FDG PET-CT) for patients with apparently resectable iCCA to achieve precise clinical nodal staging [2]. This recommendation stems from a recent meta-analysis, which revealed that MRI has a sensitivity of 64% and a specificity of 69% for identifying lymph node metastases. In contrast, ^{18}F -FDG PET-CT demonstrated a sensitivity of 52% but a notably higher specificity of 92% [47].

Radiological prognosis prediction

Subclassification of intrahepatic cholangiocarcinoma

Subclassifying iCCA based on radiological findings can be useful for predicting prognosis, as LD-iCCA is associated with a poorer prognosis than SD-iCCA. Imaging can be employed to assess the differences in gross morphology between these types of iCCA. SD-iCCA typically exhibits a MF appearance with a round or lobulated shape (Figs. 1, 2) [48]. In contrast, LD-iCCA often displays irregular contours alongside a round or lobulated shape, frequent bile duct involvement that is readily apparent on T2-weighted MRI, and vascular encasement (Fig. 3) [9,10,48]. Recent studies indicate that features such as infiltrative contours, adjacent bile duct dilatation, the absence of arterial phase hyperenhancement, and vascular invasion are associated with LD-iCCA and are correlated with poorer disease-free and overall survival [48,49].

The imaging findings of the two types of iCCA closely align with their pathogenesis and associated liver or bile duct diseases. SD-iCCA is frequently accompanied by chronic hepatitis or cirrhosis, whereas LD-iCCA is commonly associated with chronic bile duct diseases such as primary sclerosing cholangitis, hepatolithiasis, or *Clonorchis sinensis* infection [50–53].

Enhancement pattern of the tumor

The arterial enhancement pattern of iCCA is recognized as a key imaging-based prognostic marker. Studies have shown that iCCA with arterial phase hyperenhancement is associated

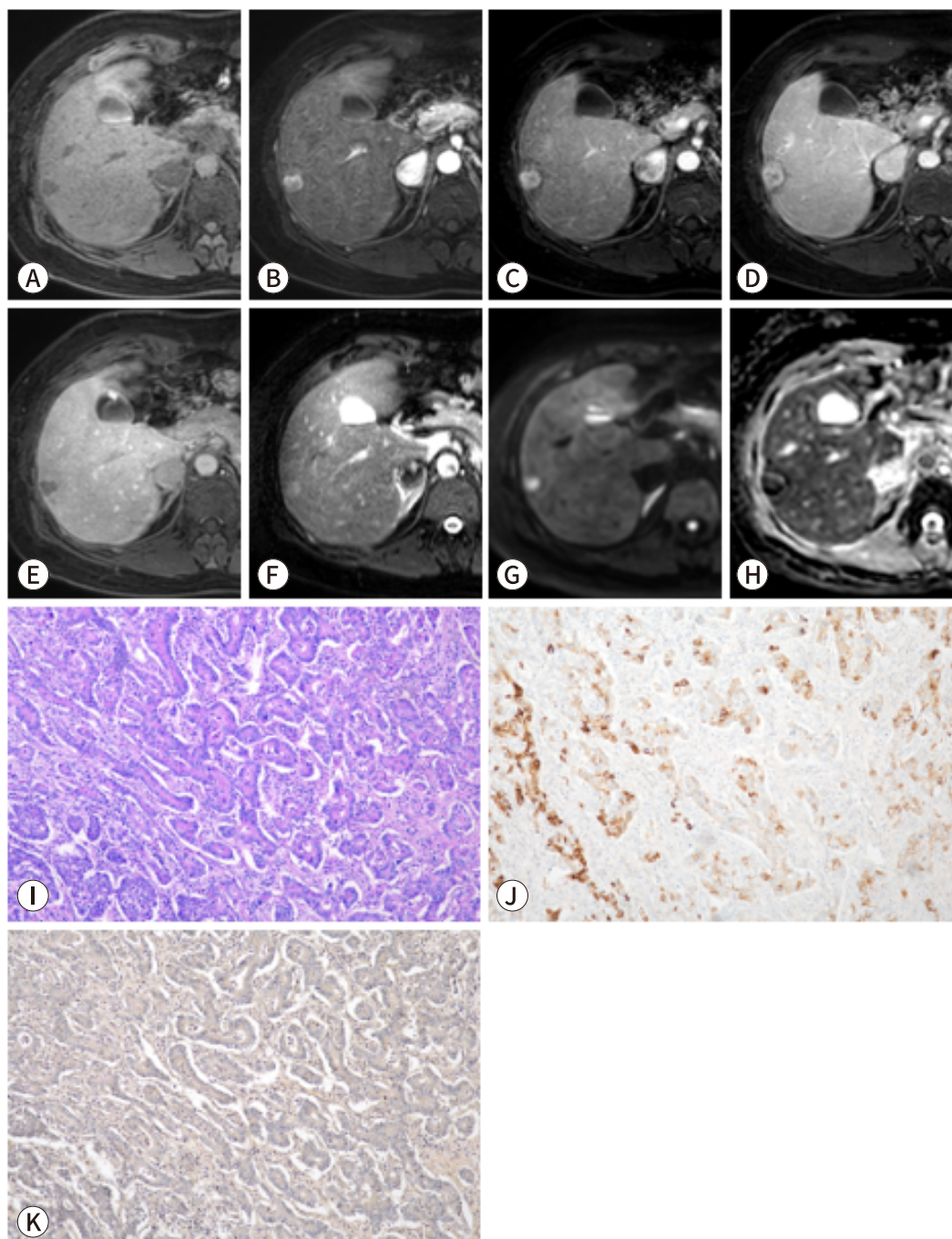


Fig. 1. A 34-year-old female patient with liver cirrhosis and small duct-type intrahepatic cholangiocarcinoma (iCCA). Gadoxetic acid-enhanced MRI: (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) transitional phase, (E) hepatobiliary phase, (F) T2-weighted, and (G) diffusion-weighted ($b=800 \text{ s/mm}^2$) images and (H) apparent diffusion coefficient map. Staining: (I) hematoxylin-eosin, (J) C-reactive protein (CRP) immunohistochemical, and (K) mucicarmine staining (I–K, original magnification $\times 200$). The gadoxetic acid-enhanced MRI reveals a 1.5-cm round mass in the subcapsular area of the right liver. The mass exhibits hyperenhancement in the arterial phase (B), does not show washout in the portal phase (C), and appears hypointense in the hepatobiliary phase (E). Pathological examination confirmed the lesion as a small duct iCCA with positive CRP expression (J) and the absence of mucin under mucicarmine staining (K).

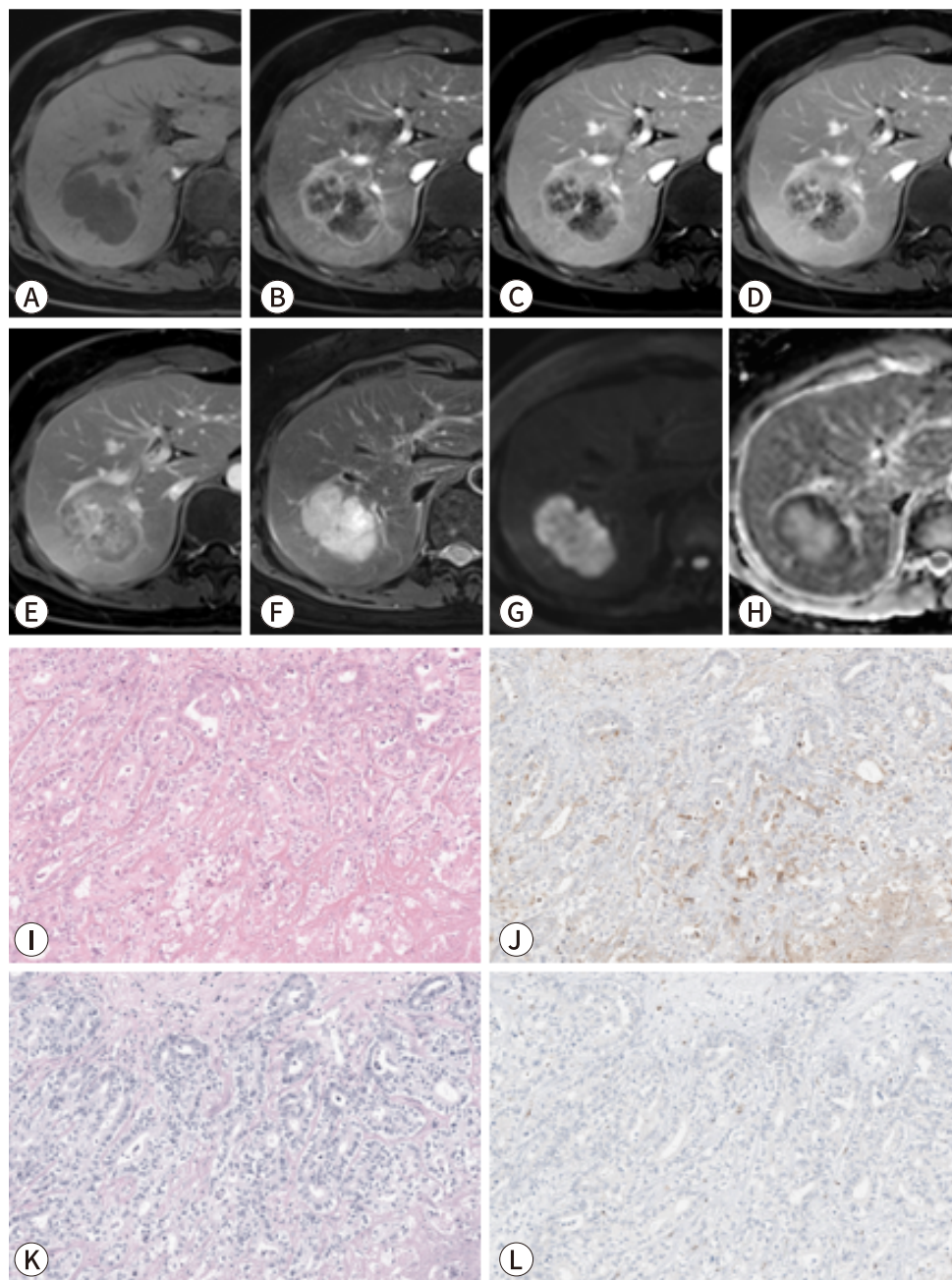


Fig. 2. A 51-year-old female patient with small duct-type intrahepatic cholangiocarcinoma (iCCA). Gadobutrol-enhanced MRI: (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) equilibrium phase, (E) 15-minute delayed phase, (F) T2-weighted, and (G) diffusion-weighted ($b=800 \text{ s/mm}^2$) images and (H) apparent diffusion coefficient (ADC) map. Staining: (I) hematoxylin-eosin, (J) C-reactive protein (CRP) immunohistochemical, (K) Alcian blue/periodic acid-Schiff (AB/PAS), and (L) S100 calcium-binding protein P (S100P) immunohistochemical staining (I–L, original magnification $\times 200$). The mass exhibits rim hyperenhancement in the arterial phase (B) and a progressive centripetal pattern of contrast filling in the portal (C), equilibrium (D), and delayed (E) phases. It also displays moderate hyperintensity on the T2-weighted image (F), and restriction on both the diffusion-weighted image and the ADC map (G,H). No significant bile duct dilatation is evident in the peritumoral area. The patient underwent right lobectomy, and a diagnosis of small duct iCCA was confirmed through immunohistochemical and special staining techniques. Specifically, on pathologic examination, the lesion displayed positive CRP expression (J), absence of mucin on AB/PAS staining (K), and negative staining for S100P expression (L).

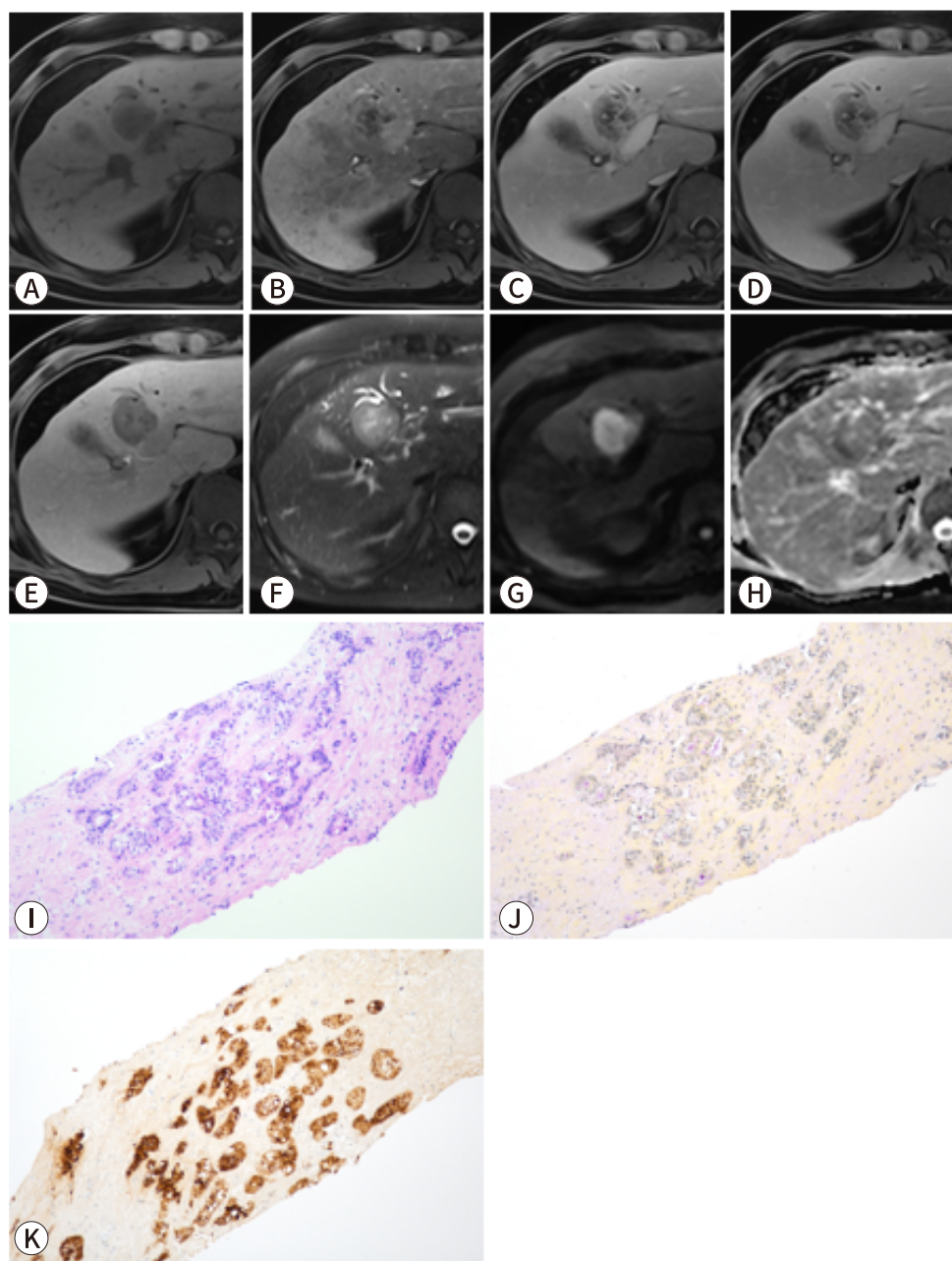


Fig. 3. A 52-year-old male patient with large duct-type intrahepatic cholangiocarcinoma (iCCA). Gadoteric acid-enhanced MRI: (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) transitional phase, (E) hepatobiliary phase, (F) T2-weighted, and (G) diffusion-weighted ($b=800 \text{ s/mm}^2$) images and (H) apparent diffusion coefficient (ADC) map. Staining: (I) hematoxylin-eosin, (J) mucicarmine, and (K) S100 calcium-binding protein P (S100P) immunohistochemical staining (I–K, original magnification $\times 200$). A well-defined 3.2-cm mass is evident in segment 4 of the liver. The mass exhibits diffuse hypovascularity in the arterial phase (B); hypointensity in the portal (C), transitional (D), and hepatobiliary phases (E); adjacent bile duct dilatation on the T2-weighted image (F); and restricted diffusion on both the diffusion-weighted image and the ADC map (G,H). The patient underwent percutaneous biopsy, and a diagnosis of large duct iCCA was confirmed through immunohistochemical and special staining techniques. Specifically, the tumor displayed positive expression of both mucin (J) and S100P (K).

with less invasive histopathological features and better overall survival compared to iCCA with either diffuse hypoenhancement or rim enhancement during the arterial phase (Fig. 1) [54–56]. Radiopathologic correlation studies have additionally established that MVD is linked to arterial enhancement patterns. iCCA with low MVD typically displays low arterial phase enhancement on imaging; furthermore, low MVD is associated with a poor prognosis, along with aggressive pathological features such as tumor multiplicity, MiVI, lymph node metastasis, and low infiltration of CD8+ tumor-infiltrating lymphocytes [57,58].

Moreover, the enhancement pattern of iCCA is suspected to be associated with its subclassification. SD-iCCA often exhibits arterial hyperenhancement, resembling that seen in HCC or combined hepatocellular-CCA [59]. The arterial enhancement patterns in LD-iCCA are more variable, ranging from diffuse hyperenhancement to rim hyperenhancement and diffuse hypoenhancement [48].

Intratumoral fibrous stroma

Most iCCAs exhibit some degree of fibrous stroma. When scirrhous fibrous stroma comprises more than 70% of the tumor area, the iCCA is classified as scirrhous. Scirrhous iCCA is linked to a higher incidence of lymphatic and perineural invasion and is associated with significantly worse survival outcomes compared to non-scirrhous iCCA [60].

Intratumoral fibrosis can be assessed using dynamic CT or MRI. Radiopathologic correlation studies have demonstrated that regions of delayed enhancement are indicative of contrast retention within the fibrous stroma of the tumor [61–63]. Furthermore, the degree of delayed enhancement has been recognized as a prognostic marker for poor outcomes in patients with MF-iCCA. Specifically, iCCAs that exhibit delayed enhancement in more than two-thirds of the tumor on dynamic CT are associated with scirrhous iCCA, a higher incidence of perineural invasion, and relatively low overall survival [64].

Similarly, on gadoxetic acid-enhanced MRI, central intratumoral enhancement observed during the hepatobiliary phase reflects the presence of fibrous stroma within an iCCA lesion (Fig. 4) [65,66]. During this phase, iCCAs containing fibrous stroma exhibit an ill-defined hyperintense region set against a peripheral hypointense area. This pattern is often described as the “EOB-cloud,” a term derived from the chemical name of gadoxetic acid, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) [66,67]. This cloud-like appearance results from the extracellular accumulation of contrast in the central fibrous stroma, while the periphery of the tumor typically contains a higher proportion of tumor tissue and less fibrosis. Notably, MF-iCCAs in which more than 50% of the area appears hyperintense or isointense during the hepatobiliary phase tend to exhibit comparatively poor disease-free and overall survival [68].

Imaging-based prognosis prediction model for intrahepatic cholangiocarcinoma

Recent research has progressed from correlating imaging findings with histopathologic characteristics associated with prognosis to creating models that directly predict prognosis from imaging findings. These imaging-based prognostic models can offer insights into patient outcomes before treatment is initiated, potentially informing critical decisions about therapeutic strategies.

A multicenter study proposed a preoperative prognostic model for resectable iCCA that includes serum CA19-9 levels and three MRI findings: tumor multiplicity, lymph node metastasis, and bile duct invasion [69]. In predicting overall survival, this imaging-based model demonstrated comparable discriminatory performance to traditional pathologic staging systems,

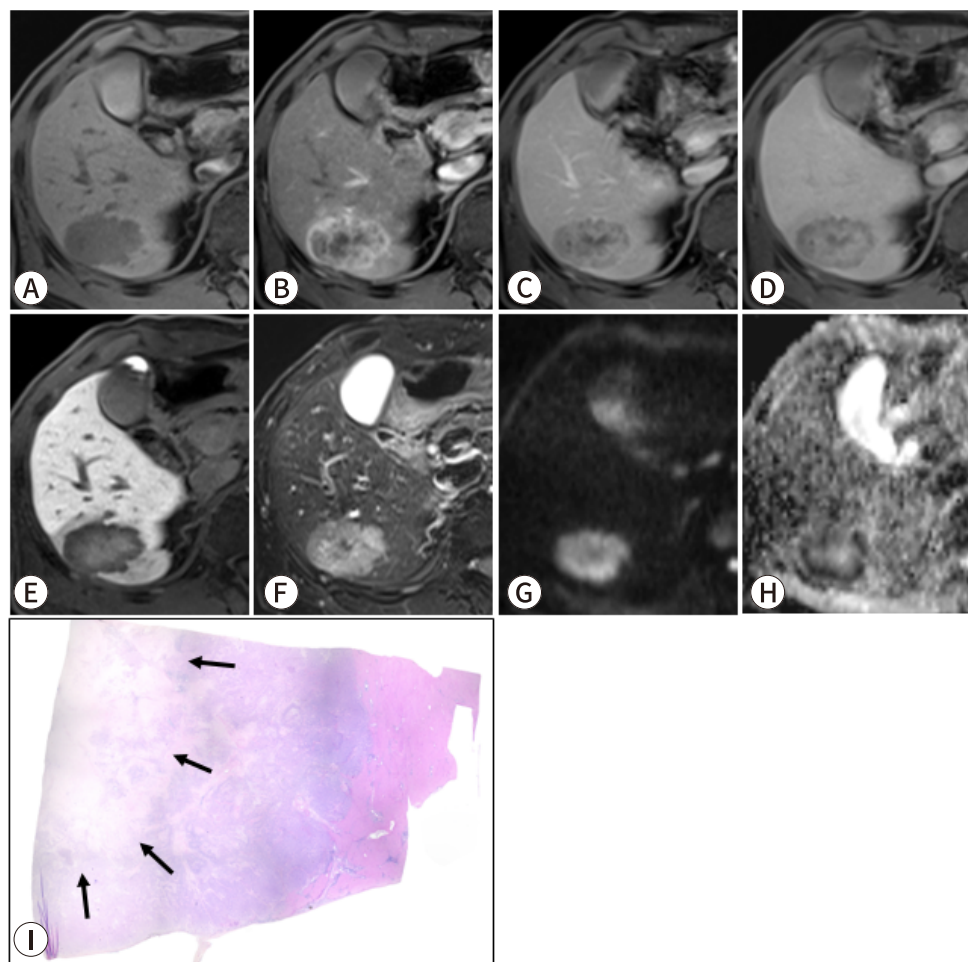


Fig. 4. A 63-year-old male patient with intrahepatic cholangiocarcinoma (iCCA) exhibiting a dense fibrous stroma. Gadobutic acid-enhanced MRI: (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) transitional phase, (E) hepatobiliary phase, (F) T2-weighted, and (G) diffusion-weighted ($b=800 \text{ s/mm}^2$) images and (H) apparent diffusion coefficient map. (I) Scan view image of hematoxylin-eosin staining. MRI revealed an approximately 4.5-cm lobulated mass in the right posterior liver. The mass exhibited thin-rim hyperenhancement in the arterial phase (B), peripheral washout with progressive central enhancement in the portal (C) and transitional (D) phases, and an “EOB-cloud” appearance in the hepatobiliary phase (E), as well as targetoid diffusion restriction (G,H). The patient underwent extended right posterior sectionectomy, and the diagnosis of iCCA was confirmed. The pathology specimen (I) displayed a dense fibrotic area, corresponding to the “EOB-cloud area” observed on MRI.

such as the eighth edition AJCC TNM system, the MEGNA score, and Nathan staging [69–71]. Another recent study introduced a more sophisticated prognostic model for resectable iCCA, combining two serum markers (CA19-9 $>300 \text{ IU/mL}$ and albumin $\leq 40 \text{ g/L}$) and six imaging findings [72]. This model outperformed pathologic staging systems, including the eighth edition AJCC and the MEGNA score, in predicting disease-specific and disease-free survival [72].

Imaging-based models have also been reported for predicting the prognosis of unresectable iCCA. The Fudan score, originally developed from a cohort of patients with resectable iCCA, has been shown to be effective for prognostic prediction in unresectable iCCA as well [73]. This score includes five variables: tumor diameter, the number of intrahepatic tumors, the type of tumor boundary, serum alkaline phosphatase levels, and CA19-9 levels. A recent study proposed

a modified scoring system for unresectable iCCA by incorporating an additional unfavorable prognostic factor—high ADC—which improved the model's performance in predicting survival [74].

Utilizing imaging findings for treatment decision-making in intrahepatic cholangiocarcinoma

Imaging is vital in the treatment decision-making process for iCCA, as it aids not only in assessing resectability but also in determining the need for lymphadenectomy during hepatic resection, deciding whether to administer neoadjuvant therapy, and selecting targeted therapies.

Lymphadenectomy

Lymphadenectomy plays a crucial role in accurate staging and may reduce the risk of recurrence; however, its impact on survival remains unclear. Although the practice of lymph node dissection in patients with clinically positive lymph nodes (cN+) has gained broader acceptance, the routine dissection of lymph nodes in patients who lack clear evidence of lymph node metastases (clinically negative lymph nodes, cN-) remains a topic of ongoing debate [75,76].

The AJCC staging system, EASL-ILCA guidelines, and National Comprehensive Cancer Network (NCCN) clinical practice guidelines all endorse the routine dissection of lymph nodes. The AJCC and EASL-ILCA guidelines specifically recommend the removal of a minimum of six lymph nodes to ensure thorough nodal staging. In comparison, the NCCN guidelines simply advise regional lymphadenectomy of the porta hepatis [2,22,77]. Conversely, Japanese guidelines do not provide a specific recommendation concerning routine lymph node dissection [78].

In clinical practice, lymph node dissection is performed in about half of patients, largely based on the surgeon's discretion [79,80]. When deciding whether to perform lymph node dissection, imaging findings play a key role. One study revealed that a risk score combining serum carcinoembryonic antigen level (≥ 7 ng/mL), lymph nodes deemed suspicious on MRI, and MRI evidence of bile duct invasion was significantly correlated with the presence of pathological lymph node metastasis (Fig. 5) [46]. Moreover, among patients who had a high risk score but did not undergo lymph node dissection, the researchers observed a higher likelihood of nodal recurrence within 3 months after surgery [46]. Imaging results can therefore be instrumental in stratifying the risk of lymph node metastasis, thus guiding the decision of whether to perform lymph node dissection in patients at high risk.

Neoadjuvant therapy

Currently, the literature includes no prospective evidence specifically supporting neoadjuvant therapy for iCCA, and no randomized studies have directly compared neoadjuvant chemotherapy followed by surgery with surgery alone. However, two retrospective studies, both analyzing data from the US National Cancer Database, yielded notable findings.

One study demonstrated that patients with a higher clinical T stage or clinical lymph node metastasis who received neoadjuvant therapy had better survival outcomes than those who underwent upfront surgery [81]. Similarly, another study found that although no survival benefit was observed in a propensity score-matched analysis across all stages of iCCA, neoadjuvant therapy did confer a survival advantage in patients with more advanced disease (stages II-III) [82].

As a result, guidelines vary in their recommendations concerning neoadjuvant therapy for iCCA. The EASL-ILCA guideline states that neoadjuvant systemic chemotherapy can be considered for patients with surgically challenging yet resectable disease, especially when an R1

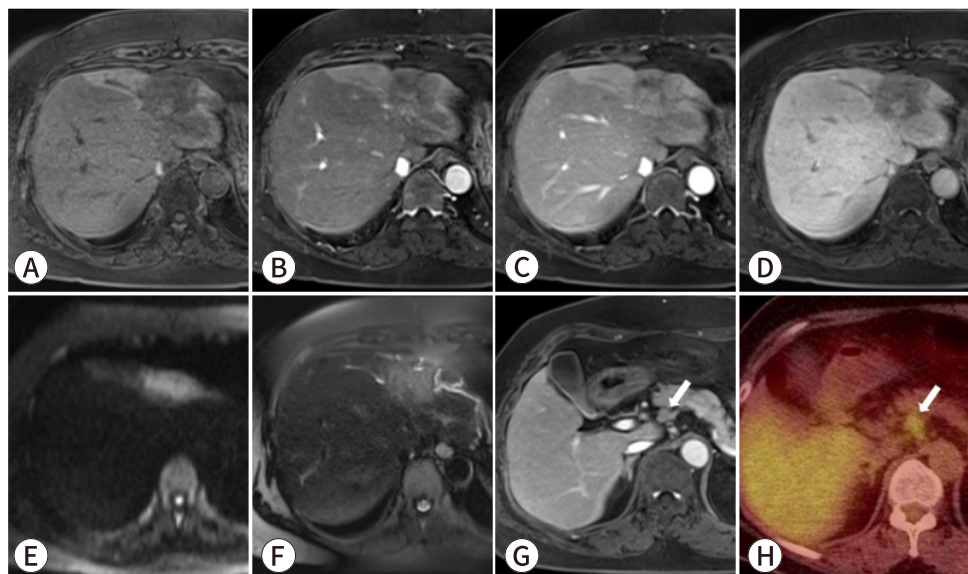


Fig. 5. A 64-year-old female patient with intrahepatic cholangiocarcinoma (iCCA) and lymph node metastasis. Gadoxetic acid-enhanced MRI, comprising (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) hepatobiliary phase, (E) diffusion-weighted ($b=800 \text{ s/mm}^2$), and (F) T2-weighted images, reveals a 3.5-cm infiltrative, poorly enhancing mass in the left lobe, with adjacent bile duct dilatation. Additionally, the (G) portal phase image and (H) ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography-CT display an enlarged lymph node with increased ^{18}F -FDG uptake situated adjacent to the common hepatic artery (white arrows). The patient underwent left hepatic lobectomy with lymph node dissection, and pathological examination confirmed the diagnosis of iCCA with regional lymph node metastases.

resection is anticipated [2]. In contrast, neither the NCCN nor the Japanese guidelines provide specific recommendations for neoadjuvant therapy in the context of iCCA [77,78]. Well-designed prospective trials are necessary to further evaluate the role of neoadjuvant treatment in this context.

Collectively, neoadjuvant therapy has been demonstrated to confer a survival benefit in cases with a high T stage, suspected nodal metastasis, or a high likelihood of positive resection margins. Considering that imaging-based prognostic models are highly effective at predicting postoperative outcomes, the use of imaging to identify high-risk patients who might benefit from neoadjuvant therapy could represent a viable strategy [72].

Molecular profiling for targeted therapy

In recent years, targeted therapy has become increasingly important in the treatment of iCCA [83]. The standard first-line treatment consists of a combination of gemcitabine, cisplatin, and durvalumab. However, targeted therapies are emerging as a viable second-line option for patients with specific genetic mutations [2,77]. These therapies require molecular profiling, often performed through next-generation sequencing, which can be expensive. Molecular profiling is typically recommended for patients with advanced-stage disease who need systemic therapy and for early-stage patients at high risk of recurrence. Imaging findings can be instrumental in identifying and stratifying these high-risk patients.

Currently, approved targeted therapies are available for genetic factors including isocitrate dehydrogenase 1 (*IDH1*) mutation, fibroblast growth factor receptor 2 (*FGFR2*) fusion, *BRAF*

V600E mutation, microsatellite instability-high and mismatch repair-deficient cancers, and epidermal growth factor receptor 2 (*HER2*) overexpression [84–88]. Among these, *IDH1* mutation and *FGFR2* fusion are particularly impactful due to their comparatively high incidence [77]. These mutations are predominantly observed in SD-iCCA [18]. Studies have shown that iCCA with *IDH1/2* mutations often presents with pronounced arterial phase enhancement on imaging, a feature commonly associated with SD-iCCA [89]. Given the higher prevalence of targetable mutations such as *IDH1* and *FGFR2* within the small duct type, molecular profiling may be particularly promising when imaging findings suggest the presence of SD-iCCA (Fig. 6). However, limited research is available to support this recommendation.

Conclusion

iCCA represents a serious and escalating global health concern, with a rising incidence and persistently poor prognosis. However, advancements in pathology and radiology have provided new insights into the disease. The histological subclassification into SD-iCCA and LD-iCCA offers a valuable framework for understanding the heterogeneity of iCCA and improving prognosis prediction. Radiological studies that focus on various imaging findings, such as tumor size, multiplicity, enhancement patterns, the presence of intratumoral fibrous stroma, and suspicious lymph nodes, have demonstrated high utility in the pre-treatment assessment of patients.

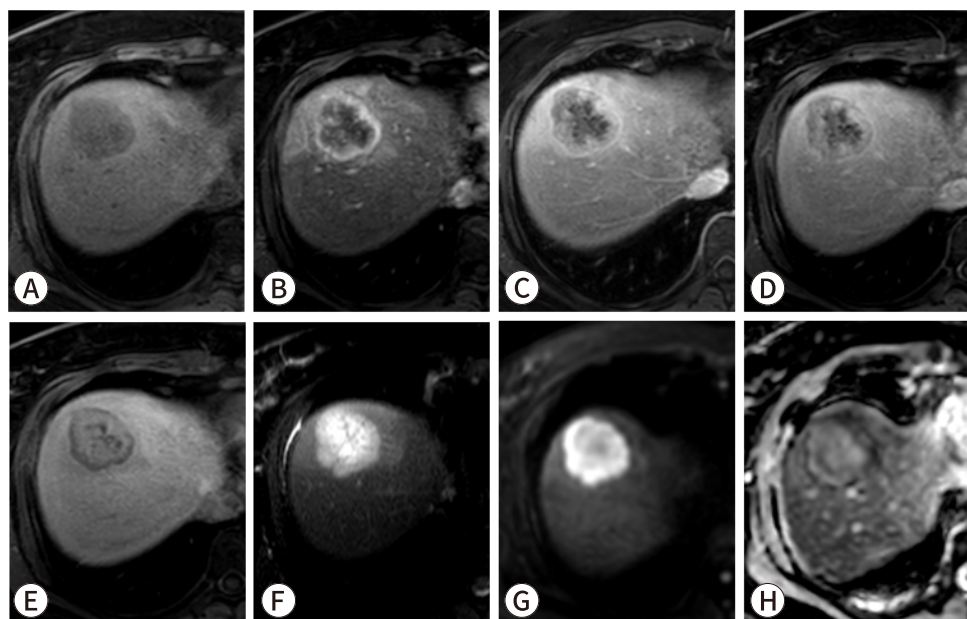


Fig. 6. A 42-year-old female patient with intrahepatic cholangiocarcinoma (iCCA) harboring an isocitrate dehydrogenase 1 (*IDH1*) mutation. Gadoxetic acid-enhanced MRI, comprising (A) pre-contrast T1-weighted, (B) arterial phase, (C) portal phase, (D) transitional phase, (E) hepatobiliary phase, (F) T2-weighted, and (G) diffusion-weighted ($b=800 \text{ s/mm}^2$) images, as well as (H) apparent diffusion coefficient map, reveal a 4.5-cm well-defined mass in the right liver dome. The mass exhibits rim hyperenhancement in the arterial phase (B), a targetoid appearance in the transitional and hepatobiliary phases (D,E), hyperintensity on the T2-weighted image (F), and diffusion restriction (G,H). The lesion is situated peripherally in the liver without evidence of adjacent biliary dilatation. The patient underwent central lobectomy, and iCCA was confirmed. Next-generation sequencing identified an *IDH1* missense mutation.

Importantly, imaging-based prognostic models for resectable iCCA have demonstrated predictive accuracy comparable to that of traditional pathological staging systems. Beyond predicting prognosis, imaging also offers critical insights that may inform decisions about lymphadenectomy and neoadjuvant therapy. Furthermore, radiological findings indicative of SD-iCCA could assist in identifying patients likely to harbor clinically relevant mutations, such as *IDH1* mutations and *FGFR2* fusions.

These imaging-based approaches are essential for improving prognosis and tailoring treatment strategies for patients with iCCA, thereby advancing personalized medicine in this area. Nevertheless, to increase the utilization of imaging findings in predicting prognosis and informing treatment decisions, higher-level evidence from international multicenter prospective studies is necessary.

ORCID

Jun Gu Kang: <https://orcid.org/0000-0002-9275-3194>

Taek Chung: <https://orcid.org/0000-0001-7567-0680>

Dong Kyu Kim: <https://orcid.org/0000-0001-7322-2550>

Hyungjin Rhee: <https://orcid.org/0000-0001-7759-4458>

Authors' contributions

Project administration: Rhee H

Conceptualization: Rhee H

Methodology & data curation: Kang JG, Chung T, Kim DK, Rhee H

Funding acquisition: Rhee H

Writing – original draft: Kang JG, Rhee H

Writing – review & editing: Kang JG, Chung T, Kim DK, Rhee H

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

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Current perspectives on the pharmacological treatment of advanced hepatocellular carcinoma: a narrative review

Hye-Jin Yoo¹, Jeong-Ju Yoo¹, Sang Gyune Kim¹, Young Seok Kim¹

Department of Internal Medicine, Gastroenterology and Hepatology, Soonchunhyang University School of Medicine, Bucheon, Korea

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Corresponding author

Jeong-Ju Yoo
Department of Internal Medicine,
Gastroenterology and Hepatology,
Soonchunhyang University School of
Medicine, 170 Jomaru-ro Wonmigu,
Bucheon 14584, Korea
E-mail: puby17@naver.com

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Hepatocellular carcinoma (HCC) remains a critical health concern in Korea, ranking as the second leading cause of cancer mortality and imposing substantial economic burdens, particularly among the working-age population. This review examines recent advancements in treating advanced HCC, referencing the updated 2022 HCC guidelines and the Barcelona Clinical Liver Cancer system. Historically, first-line systemic therapies included sorafenib and lenvatinib, with regorafenib, cabozantinib, or ramucirumab serving as second-line options. Since 2020, immune checkpoint inhibitors have shown superior overall survival than sorafenib, leading to the adoption of combination therapies such as atezolizumab with bevacizumab and durvalumab with tremelimumab as first-line treatments. The IMbrave150 study demonstrated that atezolizumab–bevacizumab significantly extended median overall survival and progression-free survival, with the longest survival reported in any phase 3 trial for advanced HCC. Similarly, the HIMALAYA study indicated that durvalumab combined with tremelimumab significantly improved survival rates. Second-line therapies now include regorafenib, cabozantinib, ramucirumab, nivolumab with ipilimumab, and pembrolizumab, each offering benefits for specific patient populations. Nonetheless, these therapies are associated with side effects that require careful management. Traditional targeted therapies can lead to hypertension, cardiovascular events, and hand-foot skin reactions, whereas immune checkpoint inhibitors may cause immune-related adverse events affecting the skin, gastrointestinal tract, and endocrine system. Clinicians must be well-versed in these treatments and their potential side effects to provide optimal patient care. The emergence of combination therapies targeting complex biological pathways signifies a new paradigm in HCC treatment, emphasizing the importance of continuous education and vigilant monitoring to optimize patient outcomes.

Introduction

Background

In Korea, cancer remains a major cause of death, with liver cancer being the second most common cause of cancer-related deaths following lung cancer in 2020 (lung cancer: 36.4 deaths, liver cancer: 20.6 deaths per 100,000, according to statistics from the National Statistical Office) [1]. Furthermore, liver cancer represents the most substantial economic burden, particularly

impacting individuals in their most productive years, underscoring its critical importance as a health issue in the country [2]. Thus, this paper aims to examine the latest treatment trends for advanced-stage hepatocellular carcinoma (HCC), referencing the newly revised 2022 HCC guidelines and the 2022 Barcelona Clinical Liver Cancer (BCLC) system [3].

HCC often develops in the context of chronic hepatitis, primarily driven by innate immune activation. However, certain causes are associated with specific immune dysfunctions. Chronic viral hepatitis can lead to liver cancer by initiating inflammatory innate immune responses and fostering an abnormal adaptive immune reaction that fails to eliminate the hepatitis virus [4]. Approximately half of HCC patients receive systemic therapy. Traditionally, sorafenib or lenvatinib were used as first-line treatments, followed by regorafenib, cabozantinib, or ramucirumab as second-line options. However, since 2020, immune checkpoint inhibitors (ICIs) have shown significantly improved overall survival rates compared to sorafenib. Therefore, the combination therapies of atezolizumab with bevacizumab and durvalumab with tremelimumab have become the preferred first-line treatments.

Objectives

This review aims to provide an overview of recent advancements in treating advanced HCC, based on the updated 2022 HCC guidelines and the BCLC system. It specifically updates the following topics: first-line systemic therapy, second-line systemic therapy following the failure of first-line treatment, and the side effects of systemic chemotherapy agents.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

First-line systemic therapy

The first-line treatments for advanced HCC are discussed sequentially, starting with the most preferred medications. Fig. 1 provides a visual overview intended to facilitate a deeper understanding of the comprehensive treatment strategy for advanced HCC.

Atezolizumab and bevacizumab combination therapy

Atezolizumab is an intravenous IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) on the surface of cancer cells, preventing its interaction with the receptor. Bevacizumab, another intravenous IgG monoclonal antibody, binds to vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis and tumor growth.

In the IMbrave150 study, patients with advanced HCC who were treated with a combination of atezolizumab and bevacizumab exhibited a significant increase in median overall survival and progression-free survival (PFS) compared to those treated with sorafenib (6.8 months; 95% CI, 5.7–8.3 vs. 4.3 months; 95% CI, 0.47–0.76, $P < 0.001$). This marked improvement prompted the Food and Drug Administration (FDA) to approve the combination therapy in 2020. The study excluded patients with autoimmune diseases, concurrent HBV and HCV infections, or untreated esophageal or gastric varices. The primary causes of HCC were chronic infections, with HBV and HCV accounting for 49% and 21% of cases, respectively. All participants had preserved liver function (Child-Pugh class A), and 26% had low-risk varices at baseline, with 11% undergoing

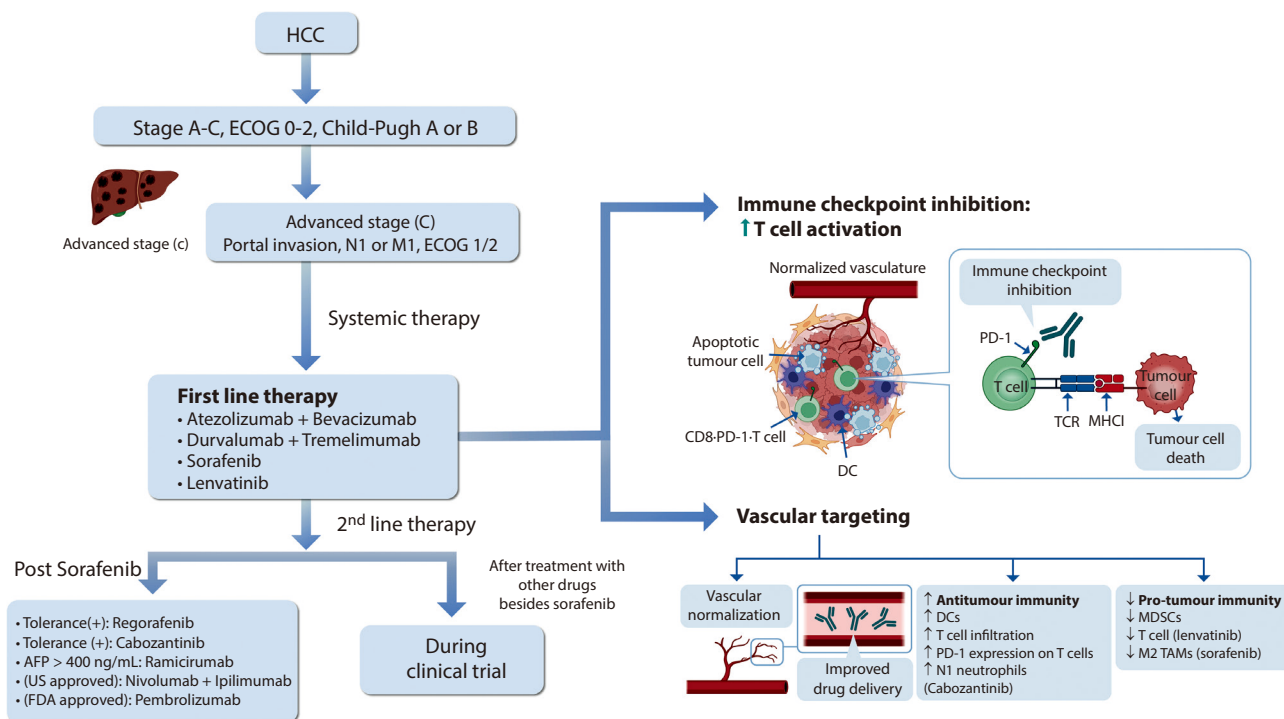


Fig. 1. Systemic therapy approaches for advanced hepatocellular carcinoma (HCC; drawing by the author). ECOG, Eastern Cooperative Oncology Group; N, node; M, metastasis; AFP, alpha-fetoprotein; US, United States; FDA, Food and Drug Administration; PD-1, programmed cell death protein-1; TCR, T cell receptor; MHC 1, major histocompatibility complex class 1; MDSCs, myeloid-derived suppressor cells; M2 TAMs, M2 type tumor-associated macrophages.

treatment. The study was halted at the first interim analysis after demonstrating significant improvements in both overall survival and PFS [5]. Recent updates indicate that after a median follow-up of 15.6 months, the combination of atezolizumab and bevacizumab achieved a median overall survival of 19.2 months, the longest recorded in any phase 3 trial for advanced HCC. Additionally, the overall response rate reached 30%, more than double that of sorafenib [6]. In 2023, a systematic literature review and network meta-analysis were conducted to indirectly compare the combination of atezolizumab and bevacizumab with other treatments for unresectable HCC. The analysis showed that this combination therapy leads to improved overall survival, supporting its use as a first-line treatment for patients with unresectable liver cancer. However, it is important to recognize that this combination may not be suitable for all patients, and careful evaluation is necessary to determine the most appropriate treatment for each individual [7–10].

Durvalumab and tremelimumab combination therapy

Tremelimumab is an intravenous IgG2 monoclonal antibody that targets CTLA-4 on activated T-cells, thereby blocking its interaction with the ligands CD80 and CD86. Durvalumab, a fully human IgG1 antibody, binds to PD-L1, inhibiting its interaction with PD-1 and reversing peripheral tolerance against tumor cells [11,12].

On October 15, 2021, the HIMALAYA study demonstrated that combination therapy significantly improved survival compared to sorafenib, with survival times of 16.43 months versus 13.77 months, respectively (hazard ratio [HR], 0.78; 96.02% CI, 0.65–0.92, $P=0.0035$).

This finding met the primary endpoint of the study. The trial enrolled patients with BCLC stage B or C, Child-Pugh class A, ECOG PS 0 or 1, and at least one measurable lesion according to RECIST 1.1 criteria. Patients requiring non-drug treatment for ascites, those with major portal vein thrombosis, or those co-infected with HBV and HCV were excluded from the study. Patients requiring non-drug treatment for ascites, those with major portal vein thrombosis, or those co-infected with HBV and HCV were excluded. The dosing regimen was determined based on pharmacokinetic studies. The STRIDE regimen, which involves administering 300 mg of tremelimumab once, followed by 1,500 mg of durvalumab in the first cycle and then 1,500 mg of durvalumab alone every 4 weeks, proved effective. It was noted that a high dose of tremelimumab could enhance CD8+ T cell levels in peripheral blood, potentially boosting the efficacy of the combination therapy. This study led to the FDA approval of the combination therapy in October 2022, and it received approval from the European Medicines Agency in January 2023 for the treatment of unresectable HCC. An update in January 2023 from the HIMALAYA study indicated that the median follow-up periods for STRIDE, durvalumab, and sorafenib were 49.12 months (95% CI, 46.95–50.17 months), 48.46 months (95% CI, 46.82–49.81 months), and 47.31 months (95% CI, 45.08–49.15 months), respectively [12–14].

Sorafenib

Sorafenib is an oral multi-tyrosine kinase inhibitor (TKIs) that targets various receptors, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , Raf-1, and c-kit. Its anticancer effects are derived from the dual inhibition of angiogenesis and tumor cell proliferation. Additionally, sorafenib inhibits the phosphorylation of the initiation factor eIF4E and promotes cancer cell death by reducing the levels of the anti-apoptotic protein Mcl-1.

The landmark phase 3 SHARP trial enrolled 602 HCC patients, with 97% classified as Child-Pugh class A. This study involved a comparison between a placebo group of 303 patients and a sorafenib group of 299 patients. Among these, 70% had advanced HCC, with underlying conditions including HBV infection (18%), HCV infection (28%), and alcohol-related diseases (26%). Sorafenib was administered orally at a dosage of 400 mg twice daily and significantly increased the median overall survival to 10.7 months, compared to 7.9 months for the placebo group ($P < 0.001$). Therefore, in 2007, sorafenib was approved by the FDA as the first treatment for HCC [15–18].

Lenvatinib

Lenvatinib, administered orally at a dosage of 12 mg/day for individuals weighing over 60 kg and 8 mg/day for those under 60 kg, is a molecular targeted therapy. It targets multiple receptors, including VEGFR-1/2/3, FGFR-1/2/3/4, PDGFR- α , RET, and c-kit. This therapy inhibits angiogenesis and disrupts fibroblast growth factor signaling in human HCC models [19]. In the multinational phase 3 REFLECT study, lenvatinib demonstrated non-inferiority to sorafenib in terms of survival, with survival times of 13.6 months versus 12.3 months (HR 0.92, 95% CI, 0.79–1.06). Consequently, in 2018, lenvatinib was approved as the first-line systemic treatment for HCC, representing the first such approval in a decade since sorafenib [20,21].

Although immunotherapy is highly effective, its use is limited in patients with recurrent HCC after liver transplantation due to the high risk of allograft rejection. However, retrospective studies have indicated that sorafenib and lenvatinib are safe for these patients. In a retrospective cohort study of 45 patients with recurrent HCC post-liver transplantation treated with lenvatinib, the median overall survival was 14.5 months (95% CI, 0.8–28.2), with a median PFS of 7.6 months

(95% CI, 5.3–9.8) and an objective response rate of 20% [22]. This suggests that lenvatinib is a valuable first-line treatment option for advanced HCC, especially in patients concerned about resistance, those unable to undergo timely upper gastrointestinal endoscopy, or for whom immunotherapy is contraindicated. Lenvatinib was also evaluated in a multinational, multicenter trial assessing the clinical outcomes of multiple kinase inhibitors in cancer patients whose disease had progressed following combination therapy with atezolizumab and bevacizumab. The study included patients classified as Child-Pugh class A and BCLC stage B or C. The results showed that patients treated with lenvatinib experienced a longer median PFS of 6.1 months (95% CI, 1.6–10.5) compared to those treated with sorafenib, which was 2.5 months (95% CI, 1.3–3.8, $P=0.004$). However, overall survival was similar between the two groups (median overall survival, 16.6 months [95% CI, 3.6–29.6] vs. 11.2 months [95% CI, 2.7–19.6]; $P=0.347$). Lenvatinib has shown promising efficacy and tolerable safety as a second-line treatment following atezolizumab-bevacizumab therapy. Therefore, recent guidelines from NCCN, ASCO, ESMO, EASL, and the KLCA-NCC in Korea recommend considering lenvatinib as a second-line option after atezolizumab-bevacizumab treatment. Furthermore, transarterial chemoembolization, the standard treatment for BCLC-B liver cancer, has been shown to be effective in extending PFS and overall survival when used sequentially or in combination with lenvatinib, as demonstrated in studies conducted in China and Japan. However, additional prospective research, including studies with Western populations, is necessary to confirm these benefits. Finally, the combination therapy of lenvatinib with ICIs has been explored across various cancer types and has received FDA approval for use in advanced renal cell carcinoma. The combination of lenvatinib with pembrolizumab is particularly noteworthy, as lenvatinib suppresses angiogenesis and immune inhibition in the tumor microenvironment, enhancing the anti-tumor immune response of pembrolizumab through a synergistic effect. In this context, the phase 3 LEAP-002 study, which evaluates the effectiveness of lenvatinib combined with pembrolizumab versus lenvatinib monotherapy in advanced HCC, has been conducted. Although there were numerical improvements in PFS and overall survival, the combination therapy did not reach statistical significance in enhancing overall survival and PFS compared to placebo. Nonetheless, this study is significant as it suggests that combining lenvatinib with immunotherapy could be a viable strategy for treating advanced HCC [23].

Second-line systemic therapy after failure of first-line systemic therapy

No studies have directly compared the effectiveness of various second-line systemic therapies following the failure of sorafenib. However, regorafenib and cabozantinib have shown improved overall survival compared to placebo in such scenarios. Additionally, ramucirumab has been found to enhance overall survival in patients with serum alpha-fetoprotein (AFP) levels above 400 ng/mL, irrespective of resistance to sorafenib. Table 1 summarizes the survival rates and target agents for each drug, organized according to the sequential treatment strategy for advanced HCC. Currently, there is a significant gap in research concerning the use of approved first-line treatments, such as lenvatinib and the atezolizumab/bevacizumab combination, as second-line options following treatment failure. Furthermore, no research results are available on the efficacy of using durvalumab and tremelimumab combination therapy as a second-line systemic treatment after the failure of first-line treatments [24].

Table 1. Comparison of the clinical outcomes of advanced hepatocellular carcinoma drugs by year and targeted pathways

Year	Drug	ECOG-PS	Overall survival	Median survival (mo)	Line of therapy	Targets
2007	Sorafenib	≤2	0.69 (vs. placebo)	10.7 vs. 7.9	First line	VEGFR 1–3 PDGFR RAF KIT
2018	Lenvatinib	≤1	0.92 (vs. placebo)	13.6 vs. 12.3	First line	VEGFR 1–3 PDGFR RGFR 1–4 RET
2020	Atezolizumab/bevacizumab	≤1	0.58 (vs. placebo)	19.2 vs. 13.4	First line	PD-L1/VEGFA
2022	Durvalumab/tremelimumab	≤1	0.78 (vs. sorafenib)	16.4 vs. 13.7	First line	PD-L1/CTLA-4
2017	Regorafenib	≤1	0.63 (vs. placebo)	10.6 vs. 7.8	Second line	VEGFR 1–3 PDGFR RAF FGFR 1–2
2019	Ramircirumab	≤1	0.71 (vs. placebo)	8.5 vs. 7.3	Second line	VEGFR 2
2019	Cabozantinib	≤1	0.76 (vs. placebo)	10.2 vs. 8.0	Second line	VEGFR 1–3 MET RET
2019	Nivolumab, ipilimumab	≤1	0.78 (vs. sorafenib)	16.4 vs. 13.7	Second line	PD-1/CTLA-4
2022	Pembrolizumab	≤1	0.79 (vs. placebo)	14.6 vs. 13.0	Second line	PD-1

ECOG-PS, Eastern Cooperative Oncology Group – Performance Status.

Regorafenib

Patients who exhibit sorafenib resistance may consider regorafenib as a second-line treatment. Regorafenib operates through three primary mechanisms: angiogenesis inhibition, cell proliferation control, and tumor microenvironment regulation. This oral multi-kinase inhibitor targets a variety of receptors, including VEGFR 1-3, TIE-2, PDGFR- β , c-KIT, RET, RAF-1, and BRAF. The simultaneous blockade of VEGF and TIE-2 receptors is thought to significantly improve the constriction of tumor blood vessels. Studies indicate that regorafenib also possesses immune-modulating properties; it helps prevent immune suppression, regulates macrophages, and enhances the proliferation and activation of CD8⁺ T cells, thereby boosting the anti-tumor immune response.

The RESORCE study demonstrated that patients treated with regorafenib experienced a significantly longer median overall survival compared to the control group (10.6 months vs. 7.8 months; HR 0.63; 95% CI, 0.50–0.79; $P < 0.001$). This finding established regorafenib as the first second-line systemic therapy to show a survival benefit, culminating in its FDA approval in April 2017 for use as a second-line treatment [25–28].

Cabozantinib

This oral molecular targeted therapy simultaneously inhibits MET, VEGFRs, RET, and KIT, making it effective even in cases resistant to sorafenib. It functions by inhibiting the activity of multiple tyrosine kinases and preventing receptor phosphorylation, thereby halting signal transduction. This mechanism results in the death of cancer cells, decreased proliferation, inhibition of metastasis, reduced tumor blood vessel formation, and ultimately, tumor shrinkage.

A similar result was observed in the multinational phase 3 CELESTIAL trial, where cabozantinib significantly extended median overall survival compared to the placebo group (10.2 months vs. 8.0 months; HR, 0.76; 95% CI, 0.63–0.92; $P=0.005$). Therefore, cabozantinib received approval from the EMA and FDA for the treatment of HCC patients who had previously been treated with sorafenib, recommending a daily dose of 60 mg. In November 2021, findings from the COSMIC-132 trial, which investigated the combination of atezolizumab and cabozantinib, were published. The study showed a significant improvement in PFS, with an HR of 0.63. However, interim data did not show a significant improvement in overall survival compared to sorafenib, pending the final analysis [29]. Similarly, the final results of the COSMIC-312 study, reported in 2024, indicated that although the combination of atezolizumab and cabozantinib continued to show a significant benefit in PFS, it did not enhance overall survival compared to sorafenib. In 2020, a matching-adjusted indirect comparison was performed to indirectly compare the outcomes of the CELESTIAL and RESORCE trials in patients who had received sorafenib as first-line therapy. This comparison assessed the efficacy and safety profiles of cabozantinib and regorafenib. The findings demonstrated that cabozantinib, compared to regorafenib, achieved a similar overall survival and a longer PFS in patients with advanced HCC whose disease had progressed following sorafenib treatment [30–32].

Ramucirumab

Ramucirumab is an intravenous monoclonal antibody that specifically targets VEGFR-2. Unlike bevacizumab, ramucirumab exhibits a broader inhibitory profile by blocking all forms of VEGF from binding to VEGFR-2, thereby effectively halting angiogenesis due to its high binding affinity. Elevated AFP levels are typically associated with poor prognosis and increased angiogenesis, as well as heightened VEGFR expression. In the REACH-2 trial, which included patients with serum AFP levels of 400 ng/mL or higher, BCLC-B/C, ECOG PS 0/1, and Child-Pugh class A, participants who received 8 mg/kg of ramucirumab biweekly demonstrated a significant improvement in overall survival compared to those in the placebo group (8.5 months vs. 7.3 months; HR, 0.71; 95% CI, 0.531–0.949; $P=0.0199$) [33–35].

Nivolumab, Ipilimumab

Nivolumab is an intravenous PD-1 inhibitor and a recombinant human IgG4 monoclonal antibody. It functions by binding to the PD-1 receptor on T cells' surfaces, thereby restoring their ability to attack cancer cells. Ipilimumab targets the CTLA-4 receptor on the cell membrane, blocking its interaction with the ligands CD80 and CD86. This combination is conditionally approved by the FDA as a second-line treatment following sorafenib. The CheckMate 040 trial assessed the efficacy and safety of nivolumab and ipilimumab in patients with advanced HCC who had previously received sorafenib treatment. The study demonstrated that the combination therapy led to significant and durable responses, resulting in the approval of the regimen in the United States. This regimen involves administering nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for four doses, followed by nivolumab at 240 mg every two weeks. However, this combination has not yet been incorporated into domestic or BCLC guidelines [36–38]. In 2024, the 5-year results from this cohort were published, confirming the initial findings. The combination therapy in arm A showed clinically meaningful responses and extended survival benefits for patients with advanced HCC previously treated with sorafenib, further endorsing its use as a second-line treatment [39,40].

Pembrolizumab

Pembrolizumab is a human IgG4 monoclonal antibody that targets the PD-1 receptor, inhibiting its interaction with PD-L1 and PD-L2. Although the KEYNOTE-240 study, which compared pembrolizumab with a placebo, did not achieve statistically significant results in its final analysis, the findings still underscore the drug's antitumor activity as a second-line treatment for HCC. These results have also set the stage for further investigations [41]. In November 2018, pembrolizumab was granted accelerated approval by the FDA, following the outcomes of the global phase 2 KEYNOTE-224 study that included patients with advanced HCC who had previously been treated with sorafenib.

In 2022, the phase 3 KEYNOTE-394 study evaluated pembrolizumab as a second-line treatment compared to a placebo in Asian patients. Pembrolizumab was administered at a dose of 200 mg every three weeks, mirroring the placebo group's regimen. The study results indicated a significant improvement in median overall survival (14.6 vs. 13.0 months; HR for death, 0.79; 95% CI, 0.63–0.99, $P=0.0180$) and PFS (2.6 vs. 2.3 months; HR for progression or death, 0.74; 95% CI, 0.60–0.92, $P=0.0032$). Furthermore, the objective response rate was markedly better (12.7% vs. 1.3%, $P<0.0001$), reinforcing the recommendation to use pembrolizumab as a second-line treatment for this patient group [42,43].

Side effects of systemic chemotherapy agents

Adverse effects of traditional targeted therapy

Although sorafenib offers significant benefits to patients, it also has side effects similar to those of other TKIs. Sorafenib targets the VEGF receptor pathway and Raf kinase, both of which are essential for maintaining physiological functions and homeostasis in the body. Inhibiting these signaling pathways can result in therapeutic benefits but also potential side effects. Currently, side effects such as hypertension, thyroid dysfunction, hand-foot syndrome, and fatigue are associated with the inhibition of various tyrosine kinases. Additionally, hypertension, arterial thromboembolism, proteinuria, wound complications, bleeding, and gastrointestinal perforation are closely linked to the VEGF pathway. While most side effects are manageable, severe adverse reactions like cardiac shock or hemorrhage can be life-threatening and may lead to the discontinuation of chemotherapy. Therefore, it is crucial to review these side effects thoroughly [44,45].

Hypertension

Hypertension is one of the most commonly reported side effects of angiogenesis inhibitors such as sorafenib and may manifest within 2 weeks of initiating treatment. This hypertension results from the toxicity inherent in the mechanism of action of sorafenib and is sometimes considered a predictive marker of the drug's antitumor efficacy, suggesting that sorafenib is functioning effectively. Over time, the incidence of hypertension may decrease, indicating that the body might be adapting to the drug, which could potentially reduce the cardiovascular risks observed at the beginning of treatment. Therefore, patients should monitor their blood pressure weekly after starting treatment and can manage hypertension with standard antihypertensive medications without needing to reduce the sorafenib dose. Recent studies suggest that monitoring the steady-state concentration of sorafenib may help in avoiding severe toxicities, including hypertension.

Cardiovascular events

Hypertension induced by TKIs is linked to several complications, including a reduction in left ventricular ejection fraction, heart failure, and coronary artery disease. In a randomized, double-blind clinical study, myocardial ischemia or infarction occurred in 4.9% of patients treated with sorafenib, compared to only 0.4% in the placebo group. This damage is thought to arise from the inhibition of RAF1 and BRAF kinases, which disrupts the ERK kinase cascade and directly suppresses myocardial cell survival. However, cardiac damage caused by sorafenib can generally be managed effectively if the patient's heart function is closely monitored and appropriate treatment is administered.

Arterial thromboembolism

Sorafenib treatment is associated with arterial thromboembolism across various cancer types. However, research on the high-risk factors for sorafenib-induced arterial thromboembolism remains limited, and consensus on prevention and management strategies has not been established. Due to the risk of bleeding, preventive anticoagulant measures such as aspirin are not universally recommended when used concurrently. Consequently, patients who experience such events should discontinue sorafenib, and those with atherosclerosis should use the drug with caution.

Hemorrhage

Patients treated with sorafenib have reported a range of bleeding complications, including nosebleeds, hemoptysis, gastrointestinal bleeding, vaginal bleeding, and even cerebral hemorrhage. A meta-analysis of studies on anti-angiogenic therapy in patients with HCC and renal cell carcinoma showed that sorafenib increased the risk of bleeding events of all grades compared to control groups (OR 1.77, 95% CI, 1.04–3.0). [46] The inhibition of the VEGF pathway may disrupt platelet activation, hinder thrombus formation following trauma, and decrease subendothelial matrix deposition, which in turn raises the risk of bleeding. Given the significant concerns of bleeding and arterial thromboembolism during sorafenib treatment, careful monitoring of patients and tailored treatment approaches are crucial.

Hand-foot skin reaction

Hand-foot skin reactions (HFSR) are the most prevalent dose-limiting toxicity associated with sorafenib, often occurring during treatment and frequently necessitating dose adjustments. This adverse effect significantly impacts the quality of life of patients, making its management a critical component of the treatment plan. HFSR is characterized by symptoms such as erythematous, edematous, and painful blisters on the palms and soles. Typically, these reactions develop within 2 to 4 weeks of starting sorafenib, with a median onset time of 18.4 days. Notably, TKI-induced HFSR often presents with hyperkeratotic lesions surrounded by erythema, primarily affecting areas such as joints, palms, and soles. Meta-analyses have reported an overall incidence of HFSR across all grades ranging from 30% to 40%, with grade 2 or higher lesions occurring in 8% to 9% of cases. This underscores the need for thorough monitoring and appropriate management of this common side effect in patients undergoing sorafenib treatment.

Diarrhea

Gastrointestinal disturbances are commonly observed during sorafenib treatment, manifesting as diarrhea, vomiting, nausea, and loss of appetite. Diarrhea is the most frequently reported

symptom among these. Typically, these gastrointestinal side effects are mild, classified as grade 1 or 2; however, more severe effects, classified as higher grades, can disrupt a patient's daily activities and require proper management. Medications such as loperamide can be employed to manage the symptoms. Dose adjustments are generally unnecessary unless severe grade 3 or 4 side effects occur.

Renal toxicity

Renal toxicity, characterized by proteinuria and acute kidney injury, is a known dose-limiting side effect of sorafenib treatment, although it occurs infrequently. The inhibition of the VEGF pathway and subsequent damage to glomerular capillary endothelial cells are believed to play a role in these complications. Consequently, it is essential to monitor and manage blood pressure during sorafenib treatment to prevent renal complications.

Fatigue

Common side effects typically emerge within the first 4–6 months of treatment and generally resolve after 5–6 months. Effective management during this period is essential, as these effects can significantly affect daily life. Similar side effects have been noted with lenvatinib, another multikinase inhibitor similar to sorafenib. However, the incidence of serious adverse reactions was significantly higher in the lenvatinib group, at 43%, compared to 30% in the sorafenib group [47,48].

Side effects of immune checkpoint inhibitors

Immune checkpoint molecules are pivotal in regulating anti-cancer T-cell responses and are expressed on T-cells, antigen-presenting cells such as dendritic cells and macrophages, and tumor cells. These molecules are essential for naturally suppressing T-cell activity and maintaining self-tolerance. Major inhibitory receptors of immune checkpoints include PD-1, PD-L1, CTLA-4, LAG-3, and TIM-3, while co-stimulatory proteins such as CD25, GITR, and OX40 promote T-cell expansion. Consequently, ICIs that target PD-1, PD-L1, CTLA-4, TIM-3, and LAG-3 have shown significant safety and efficacy in treating HCC. Additionally, immunotherapeutic drugs are not metabolized in the liver, which may lead to predictable pharmacokinetic profiles in patients with cirrhosis [49]. In the treatment of advanced HCC, ICIs have improved survival rates compared to sorafenib, but they are also associated with a spectrum of adverse effects that necessitate careful monitoring. Although the precise mechanisms are not fully understood, these effects are often related to the depletion and exhaustion of regulatory T cells, which play a vital role in maintaining tolerance induced by ICI therapy, especially through CTLA-4 blockade. The depletion of these cells can result in decreased anti-inflammatory cytokines, increased proliferation of CD8+ T cells, and early B-cell alterations, potentially leading to immune-related adverse events. These side effects differ from those associated with traditional chemotherapy, as they can be more unpredictable in their onset and may persist longer. This article will discuss the specific side effects associated with key ICIs, including nivolumab, ipilimumab, atezolizumab, bevacizumab, tremelimumab, and durvalumab, in sequence [50,51].

Nivolumab

A recombinant human IgG4 monoclonal antibody, administered intravenously, functions as a PD-1 inhibitor. It binds to the PD-1 receptors on the surface of T cells, thereby restoring their ability to combat cancer cells.

In a phase 3 multinational randomized controlled trial (CheckMate 459), a comparison between nivolumab and sorafenib revealed an overall incidence of adverse events at 70%, with 22% of patients experiencing grade 3 or higher adverse events. The most common side effects were fatigue (15%), pruritus (13%), rash (11%), AST elevation (11%), diarrhea (8%), decreased appetite (6%), nausea (5%), weight loss (1%), and hypertension (1%). Severe adverse events (grade 3 or higher) included AST elevation (6%), diarrhea (1%), and palmar-plantar erythrodysesthesia. Grade 3 or higher adverse events occurred more frequently in the sorafenib group (47% vs. 18%), although mild side effects were similarly distributed between the two groups (48% vs. 44%).

Nivolumab combined with ipilimumab

Ipilimumab, a CTLA-4 inhibitor, can be used in combination with nivolumab for treatment. The most commonly reported side effects are pruritus (45%), rash (29%), diarrhea (24%), hypothyroidism (20%), fatigue (18%), adrenal insufficiency (14%), and decreased appetite (12%). Additionally, there was a rare instance of a treatment-related death caused by grade 5 pneumonia.

Atezolizumab/bevacizumab

Among patients treated with atezolizumab/bevacizumab, 98% experienced side effects. Of these, 63% reported grade 3 to 4 side effects, and 7% experienced grade 5 side effects. The most common side effects were hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), hepatitis (AST elevation, 19.5%), pruritus (19.5%), diarrhea (18.8%), decreased appetite (17.6%), rash (12.5%), and nausea (12.2%). Severe side effects included upper gastrointestinal bleeding and increased risks of cardiotoxicity, thromboembolic stroke, and gastrointestinal perforation associated with bevacizumab.

A meta-analysis was conducted to assess the risk of bleeding in HCC patients undergoing treatment with atezolizumab/bevacizumab. This analysis, which included 28 studies, indicated an overall bleeding incidence of 8.42% (95% CI, 5.72%–11.54%), with grade 5 bleeding occurring in 2.06% of cases (95% CI, 0.56–4.22). Gastrointestinal bleeding, particularly variceal bleeding, was identified as the most common bleeding site, with an incidence of 5.48% (95% CI, 3.98%–7.17%). The incidence of bleeding was found to be 2.11 times higher (95% CI, 1.21–3.66) when compared to treatment with TKIs. Additionally, high body mass index and high albumin-bilirubin grade were significant predictors of bleeding complications [52].

Tremelimumab/durvalumab

In the HIMALAYA clinical study, 75.8% of the patients experienced side effects, with 25.8% encountering grade 3 to 4 adverse reactions. The most common side effects were diarrhea (26.5%), pruritus (22.9%), rash (22.4%), loss of appetite (17%), fatigue (17%), fever (12.9%), nausea (12.1%), elevated AST (12.4%), and hypothyroidism (10.3%).

There have been reports on the relationship between immune-related adverse events and prognosis. Patients who experienced these immune-related side effects showed an improvement in PFS, although there was no significant difference in overall survival. A meta-analysis revealed that patients who developed skin, gastrointestinal, or endocrine-related side effects following nivolumab treatment exhibited a positive correlation with favorable outcomes. The objective response rate after treatment with nivolumab/ipilimumab was positively correlated with the occurrence of skin or gastrointestinal events, but not with other side effects. However,

in cases involving anti-PD-(L)-1 monotherapy or combination therapy, patients who experienced grade 2 or higher treatment-related adverse effects demonstrated improved overall survival (HR, 0.55; 95% CI, 0.34–0.88).

In 2023, a meta-analysis was conducted to compare the side effects of sorafenib and first-line immunotherapy in treating HCC. The analysis revealed that patients with unresectable HCC who were treated with ICIs exhibited a higher incidence of all-grade pruritus. Conversely, those receiving sorafenib faced increased risks of diarrhea and HFSR. There were no significant differences observed in the rates of fatigue, elevated aspartate transaminase levels, rash, hypertension, or decreased appetite [53].

Conclusion

A new paradigm in HCC treatment is emerging, with a particular emphasis on combination therapies such as atezolizumab with bevacizumab, durvalumab with tremelimumab, and various traditional kinase inhibitors. These therapeutic strategies are designed to target the complex biological pathways of liver cancer, aiming to inhibit tumor growth and metastasis, and thereby improve survival rates in cases of advanced liver cancer. Clinicians must be well-versed in the latest treatments for advanced HCC and understand the specific indications for each to recommend the most appropriate therapy for individual patients. Additionally, since ICIs have been associated with previously unobserved side effects, careful attention and monitoring are required.

ORCID

Hye-Jin Yoo: <https://orcid.org/0009-0004-9636-1237>

Jeong-Ju Yoo: <https://orcid.org/0000-0002-7802-0381>

Sang Gyune Kim: <https://orcid.org/0000-0001-8694-777X>

Young Seok Kim: <https://orcid.org/0000-0002-7113-3623>

Authors' contributions

Project administration: Yoo JJ

Conceptualization: Yoo JJ

Methodology & data curation: Yoo HJ, Kim SG, Kim YS

Funding acquisition: not applicable

Writing – original draft: Yoo HJ

Writing – review & editing: Yoo HJ, Yoo JJ, Kim SG, Kim YS

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Not applicable.

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Not applicable.

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Update on sexually transmitted infections in Korea: a narrative review

Chung-Jong Kim^{1,2}

¹Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea

²Department of Internal Medicine, Ewha Womans University Seoul Hospital, Seoul, Korea

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Corresponding author

Chung-Jong Kim
Department of Internal Medicine, Ewha Womans University College of Medicine,
25, Magokdong-ro 2-gil, Gangseo-gu,
Seoul 07804, Korea
E-mail: cj.kim.id@gmail.com

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Sexually transmitted infections (STIs) continue to pose significant public health challenges in Korea, with syphilis, gonorrhea, chlamydia, *Mycoplasma genitalium*, and herpes simplex virus (HSV) being the most prevalent. This review provides an updated overview of the epidemiology, diagnosis, and treatment of these significant STIs in Korea, highlighting recent trends and concerns. Syphilis incidence rates have fluctuated due to changes in surveillance systems. Starting in 2024, syphilis will be reclassified as a nationally notifiable infectious disease (category 2). Gonorrhea remains a concern due to increasing antibiotic resistance, including the emergence of extensively drug-resistant *Neisseria gonorrhoeae* strains, underscoring the need for vigilant antimicrobial stewardship. Chlamydia continues to be the most commonly reported STI, although its incidence has declined during the COVID-19 pandemic. *M. genitalium* has gained attention as a significant STI with rising antibiotic resistance issues, necessitating updated treatment guidelines and consideration of resistance testing. HSV-2 remains a common cause of genital herpes, with steady incidence rates reported. Updated diagnostic methods, including nucleic acid amplification tests, and revised treatment guidelines are presented to effectively address these infections. The impact of the COVID-19 pandemic on other STIs within Korea remains unclear, necessitating further research. Changes in treatment guidelines, such as the recommendation of doxycycline as first-line therapy for chlamydia, reflect evolving evidence and resistance patterns. The importance of updated diagnostic tools, including resistance testing for *M. genitalium*, is emphasized to improve treatment outcomes. Continued efforts in education, prevention, and research are essential to manage and mitigate the impact of STIs on public health in Korea.

Introduction

Background

Sexually transmitted infections (STIs) are commonly encountered in outpatient clinics. The major STIs primarily addressed in both domestic and international treatment guidelines include syphilis, gonorrhea, chlamydia, and herpes simplex virus (HSV) infection [1–4]. Recently, the incidence and significance of *Mycoplasma genitalium* have been on the rise [5]. The COVID-19 pandemic has significantly affected access to healthcare services, thereby altering the epidemiology of major STIs. It has notably impacted access to HIV services, influencing

transmission rates [6,7]. Additionally, there has been a decline in the incidence of new HIV cases in Korea after COVID-19 [8]. Some studies suggest that this reflects a genuine reduction in incidence rates [8]. The impact on other STIs within the country remains unclear.

Objectives

This review focuses on syphilis, gonorrhea, chlamydia, *M. genitalium*, and HSV. While genital warts or condyloma acuminata are also prevalent STIs [9], they will be addressed separately at a later date.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Syphilis

Syphilis is a disease that has been known for centuries, with documented cases appearing in European and various other countries' records from the 11th to 15th centuries [10]. Historical documents from the Joseon Dynasty in Korea also contain references to syphilis.

In Korea, syphilis is classified under the Infectious Disease Control and Prevention Act as both a Category 4 communicable disease (Article 2, Item 5) and a STI (Item 10). It is monitored alongside six other STIs—gonorrhea, chlamydia infection, chancroid, genital herpes, condyloma acuminatum, and human papillomavirus infection—through designated sentinel surveillance institutions. However, starting in 2024, it has been reclassified as a nationally notifiable infectious disease (category 2 communicable disease), and data on its occurrence will be collected once again [11]. The surveillance system for syphilis has seen several changes over the years. Initially introduced in 2001, the sentinel surveillance system managed syphilis until 2010. It then transitioned to full-scale surveillance following a reorganization of the legal classification system for infectious diseases in 2010, only to revert to sentinel surveillance in 2020.

Epidemiology

The prevalence of syphilis in Korea from 2017 to 2020 is detailed below. In 2019, comprehensive surveillance identified 1,750 syphilis cases, with 1,276 cases (72.9%) occurring in males and 474 cases (27.1%) in females. The age group of 20–40 years had the highest incidence, with 1,281 cases (73.2%), while those aged 60 and older accounted for 192 cases (11.0%). Regarding the stage of the disease, there were 1,176 cases of primary syphilis, 554 cases of secondary syphilis, and 23 cases of congenital syphilis. After shifting to sentinel surveillance in 2020, a total of 330 cases were reported, comprising 228 cases (69.1%) in males and 102 cases (30.9%) in females. The 20–40 age group represented 251 cases (76.1%), and the 60 and older age group had 30 cases (9.1%). The breakdown by stage included 191 cases of primary syphilis, 136 cases of secondary syphilis, and 3 cases of congenital syphilis. These data were sourced from the Weekly Health and Disease Report of the Korea Disease Control and Prevention Agency. Since the transition to sentinel surveillance in 2021, there has been a noticeable change in the number of reported cases. From 2020 to 2023, the reported cases of primary syphilis were 191, 248, 254, and 280, respectively, while secondary syphilis cases were 136, 140, 138, and 131 for the same years (Fig. 1). Starting in 2024, with the resumption of full-

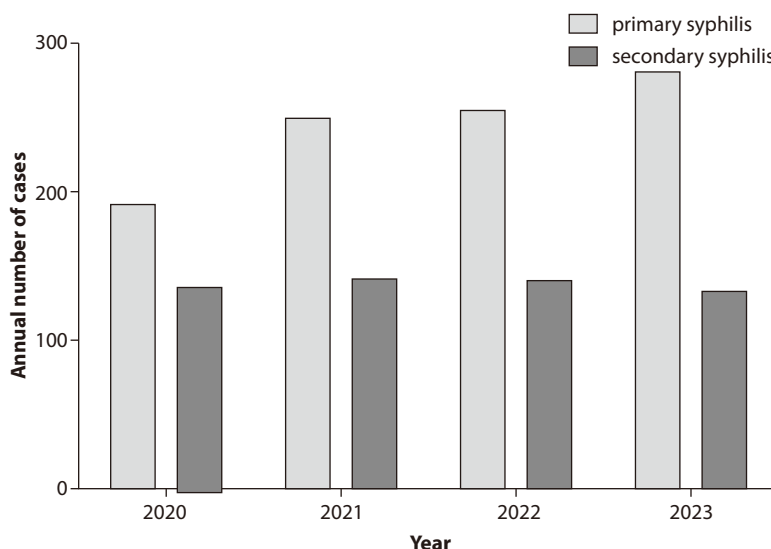


Fig. 1. Annual trends of primary and secondary syphilis from 2020 to 2023 in Korea.

scale surveillance, it will be possible to compare these figures with previous data. Fig. 1 also presents a detailed breakdown of the number of cases for each stage of syphilis.

Microbiology

Syphilis is primarily transmitted through sexual contact or from an infected mother to her child during pregnancy. This disease is caused by the spirochete *Treponema pallidum*. Although less common, transmission can also occur through blood transfusions or organ transplants. Additionally, there is a minimal risk of transmission through needlestick injuries in certain stages of the disease [12].

Clinical manifestations

The clinical presentation of syphilis can be broadly divided into symptomatic periods and asymptomatic latent syphilis periods. The clinical course of syphilis is categorized into symptomatic phases and periods of asymptomatic latent syphilis. The symptomatic stages include primary, secondary, and tertiary syphilis, with periods of latent syphilis occurring between these stages. Primary syphilis, the initial stage of infection, typically presents as a single painless ulcer, known as a chancre, at the site of *T. pallidum* entry. This sore usually appears within 9 to 90 days after exposure and may be accompanied by localized swelling of lymph nodes. While the ulcer is generally painless, it can occasionally be painful. The ulcer characteristic of primary syphilis typically heals spontaneously.

Secondary syphilis typically develops 4–10 weeks after the appearance of the primary lesion and can affect the entire body. The symptoms of secondary syphilis are diverse, with a characteristic rash being a common feature. This rash, frequently involving the palms and soles, is observed in 48%–70% of patients with secondary syphilis. Other manifestations may include abdominal pain, hepatitis, pulmonary nodules, and alopecia. Additionally, condyloma lata, presenting as wart-like lesions, may also occur. Although many patients receive treatment during the secondary stage, the condition might resolve on its own without antibiotics; however, if left untreated, it can progress to latent syphilis. During this stage, the bacteria may

infiltrate the central nervous system, potentially leading to meningitis. Approximately 70% of cases of untreated or latent syphilis remain symptom-free, but some may advance to tertiary syphilis. Tertiary syphilis can involve cardiovascular syphilis, neurosyphilis, and gummatous syphilis. Neurosyphilis is divided into two primary forms: meningeal neurosyphilis, which can present with cranial nerve dysfunction, meningitis, stroke, and changes in hearing or vision, and tabes dorsalis, characterized by demyelination of the dorsal columns and associated with ataxia, diminished reflexes, impaired proprioception, neuropathic pain, and paralysis. Typically, neurosyphilis develops 10–30 years after the initial infection [13].

Diagnosis

Diagnosing syphilis is complex. The most definitive method involves direct evidence of the syphilis bacterium. However, because *Treponema* is difficult to culture, a culture-based diagnosis is not feasible. Although dark-field microscopy can visualize *Treponema* from lesion samples, this method is rarely used today. In cases of primary syphilis, samples from chancres can be tested using PCR or other nucleic acid amplification tests (NAATs) to detect *Treponema*. Additionally, multiplex PCR tests, which diagnose multiple STIs simultaneously, can also detect syphilis from urine samples.

However, in cases of secondary, tertiary, and latent syphilis, it is not feasible to obtain samples that confirm the presence of the pathogen. Therefore, the diagnosis relies on a combination of tests. For initial screening, non-treponemal tests such as the Venereal Disease Research Laboratories test or the rapid plasma reagin test are employed. If these tests yield positive results, confirmation is sought through treponemal tests, including the *T. pallidum* latex agglutination, *T. pallidum* hemagglutination assay, or the fluorescent treponemal antibody absorption immunoglobulin test.

Treatment

Both the Centers for Disease Control and Prevention 2021 treatment guidelines and Korea's 2023 treatment guidelines recommend the same treatment [2]. Penicillin injections are the first-line treatment for syphilis at all stages [14]. Benzathine penicillin G is the drug of choice for all cases except neurosyphilis. Thanks to its depot effect, it can be administered once a week. Benzathine penicillin G must be given intramuscularly, not intravenously. For primary, secondary, and early latent syphilis, a single dose of 2.4 million units of benzathine penicillin G is administered. For late latent syphilis, 2.4 million units are administered weekly for three weeks. Alternatively, doxycycline 100 mg taken twice daily for 14–28 days can be used, but it is contraindicated during pregnancy, where penicillin is the only option.

A characteristic reaction known as the Jarisch-Herxheimer reaction may occur following the treatment of spirochetal infections, including syphilis [15]. This inflammatory response is triggered by the release of cytokines and typically manifests within 24 hours of treatment, presenting symptoms such as myalgia and fever.

Gonorrhea

Gonorrhea, similar to syphilis, is one of the oldest known STIs. The systematic recording and management of gonorrhea in Korea commenced during the Japanese colonial period and persisted through the American military government period following liberation. Since that time, reports on domestic prevalence and antibiotic susceptibility have been published [16].

Epidemiology

The annual incidence of gonorrhea in Korea is shown in Figs. 2, 3. In 2023, sentinel surveillance reported 1,204 cases of gonorrhea, indicating a decreasing trend in its incidence. A particularly concerning issue is the antibiotic resistance of *Neisseria gonorrhoeae*, the bacterium responsible for gonorrhea. There has been a significant global increase in resistance to fluoroquinolones, including ciprofloxacin, and a rising trend in resistance to azithromycin [17]. Additionally, strains resistant to ceftriaxone, considered a last-resort treatment for gonorrhea,

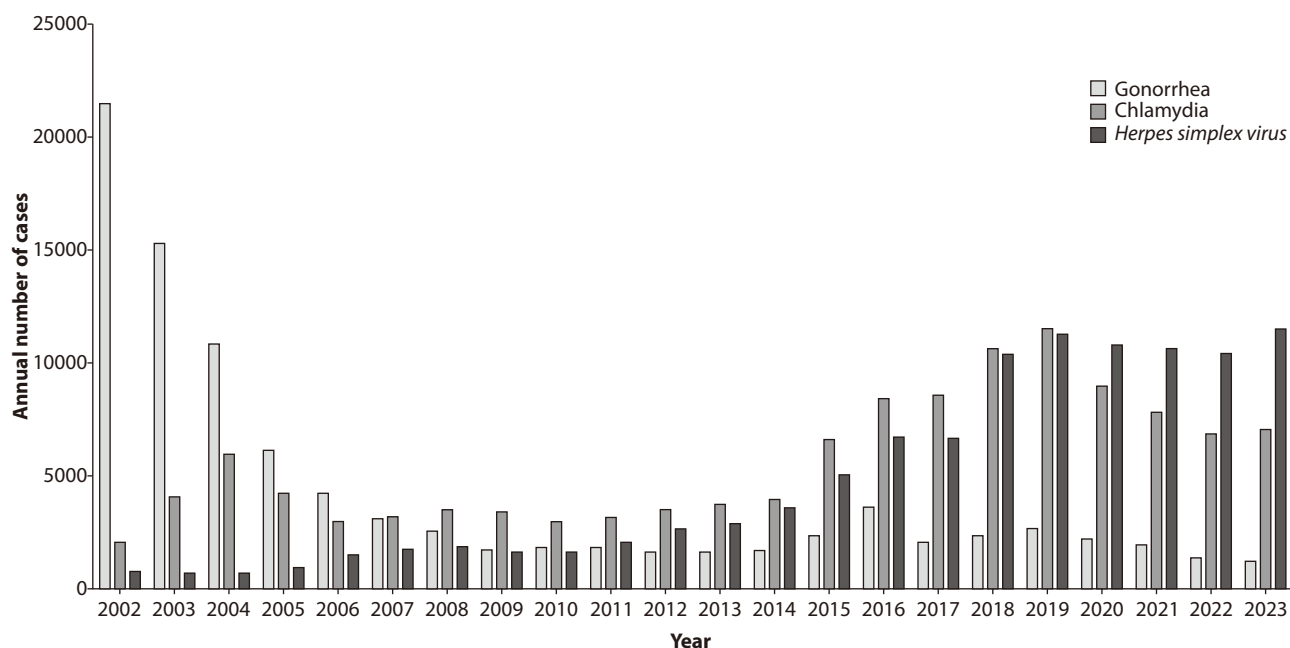


Fig. 2. Annual trends of gonorrhea, chlamydia, and herpes simplex virus infections from 2002 to 2023 in Korea.

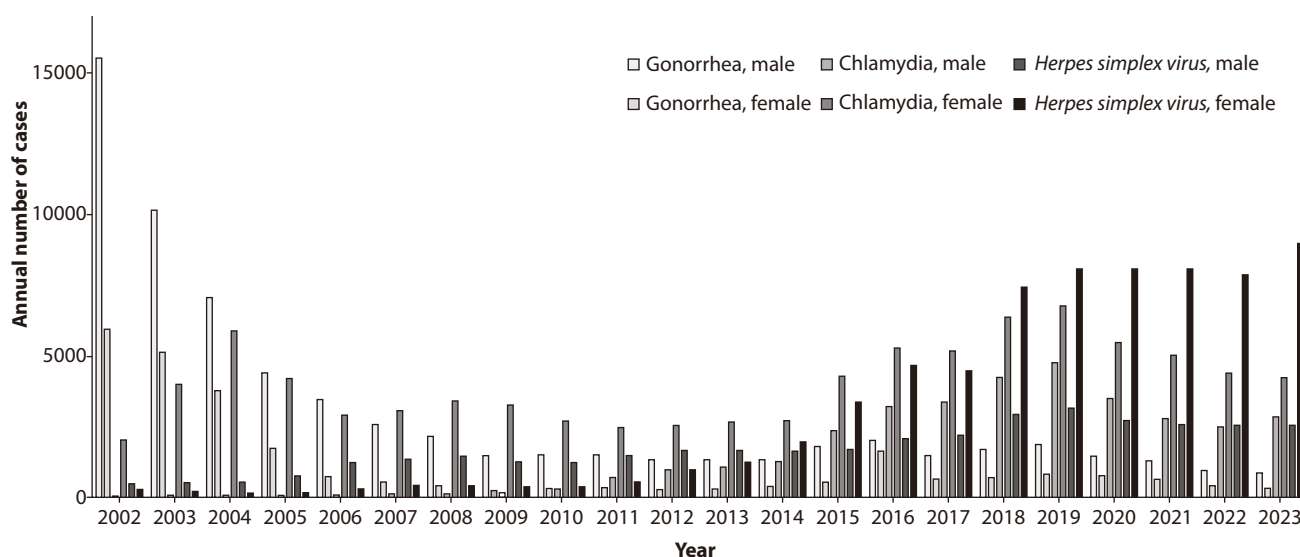


Fig. 3. Annual trends of gonorrhea, chlamydia, and herpes simplex virus infections according to sex from 2002 to 2023 in Korea.

have recently been identified, particularly in countries such as the United Kingdom and Japan. Extensively drug-resistant *N. gonorrhoeae* has also emerged, leading to treatment failures with the combined therapy of ceftriaxone and azithromycin [18–20]. In Korea, the antibiotic resistance rates of *N. gonorrhoeae* have shown concerning trends: resistance to ciprofloxacin increased from 26% in 2000 to 83% in 2006 among strains collected during that period. During the same timeframe, no resistance to ceftriaxone or cefixime was reported. Resistance to tetracycline was noted to be between 93%–100% [21]. From data collected between 2011 and 2013, 3% of the strains were resistant to ceftriaxone, 9% to cefixime, 38% showed intermediate resistance or resistance to azithromycin, and 97% were resistant to ciprofloxacin [22]. Antibiotic resistance testing on *N. gonorrhoeae* conducted by the Korea Centers for Disease Control and Prevention from 2013 to 2015 indicated that almost no strains were susceptible to ciprofloxacin and tetracycline. While susceptibility to ceftriaxone and cefixime was still maintained, resistance to cefixime showed an increasing trend. Furthermore, there was an upward trend in the number of strains exhibiting simultaneous resistance to multiple antibiotics from 2013 to 2015.

Microbiology

Gonorrhea can result in infections in the urogenital tract, oropharynx, and rectum. It can also cause bacteremia, which may manifest with skin lesions or arthritis. In women, between 86.4% and 92.6% of urogenital infections caused by gonorrhea are asymptomatic [23]. Although less precisely determined, a population-based multicenter study with 11,408 participants found that 55.7% to 86.8% of urogenital infections in men were asymptomatic [13,23].

Clinical manifestations

The most common symptom of a gonorrhea infection is gonococcal urethritis, which typically manifests in men as urethral discharge and dysuria following an incubation period of 2 to 8 days. In women who exhibit symptoms, the infection may lead to vaginal discharge, itching, intermenstrual bleeding, or heavy menstrual periods. Pelvic inflammatory disease (PID) associated with gonorrhea can cause symptoms such as abdominal pain or pain during intercourse. Gonococcal pharyngitis may present with a sore throat, pharyngeal exudates, or swollen cervical lymph nodes, whereas gonococcal proctitis can lead to anorectal pain, a sensation of incomplete bowel evacuation, bleeding, or mucoid discharge. In Korea, cases of disseminated gonococcal infection have been reported, presenting as bacteremia and liver abscesses [24]. The typical presentation of disseminated gonococcal infection includes purulent arthritis, polyarthralgia, tenosynovitis, and skin rashes [25].

Diagnosis

The diagnosis of gonorrhea involves identifying *N. gonorrhoeae* from the infected site. Traditionally, bacterial culture was the primary method used; however, NAATs have now become widely employed. Nevertheless, to determine antibiotic resistance, obtaining the pathogen through culture is necessary. Therefore, it is recommended to perform bacterial culture alongside NAATs when diagnosing gonorrhea. In men, first-void urine is commonly tested, and urethral swab tests are also an option. In women, vaginal swab tests are primarily used, although cervical swabs can also be taken. Recently, the use of self-collected samples has been introduced. The sensitivity of culture for detecting gonorrhea ranges from 50% to 85%, with lower sensitivity observed in non-genital sites and among asymptomatic patients [26].

Treatment

The treatment guidelines for gonorrhea are regularly updated. The most recent guidelines from the U.S. Centers for Disease Control and Prevention (CDC), issued in 2021, recommend a single intramuscular dose of 500 mg of ceftriaxone for uncomplicated gonorrhea [2]. Additionally, if a chlamydial infection cannot be ruled out, administering doxycycline (100 mg) twice daily for 7 days is advised. There are notable differences between the U.S. and European guidelines, especially concerning the use of dual therapy [4]. While previous U.S. guidelines favored dual therapy, the current recommendations support monotherapy. The 2023 domestic guidelines also endorse a single intramuscular or intravenous dose of 500 mg ceftriaxone for uncomplicated urogenital, cervical, and rectal gonococcal infections in adults. Alternative treatments include a single intramuscular dose of 2 g of spectinomycin or a combination therapy consisting of 240 mg of intramuscular gentamicin and 2 g of oral azithromycin. For pharyngeal infections, however, both the U.S. and domestic guidelines continue to recommend a single intramuscular dose of 500 mg of ceftriaxone.

Chlamydia

Chlamydia is an infection caused by serovars D through K of *Chlamydia trachomatis*. Previously, it was often categorized with other infections such as non-gonococcal urethritis. However, it is now recognized as one of the most prevalent STIs. In the United States, data from 2019 reported 1,808,703 new cases, making chlamydia the most commonly reported STI [27]. In Korea, surveillance data indicated an increasing incidence of chlamydia infections until 2019, with 11,518 cases reported that year. Following the COVID-19 pandemic in 2020, however, the number of reported cases declined to 7,064 in 2023 (Figs. 2, 3). This decrease may be attributed to factors such as reduced testing and healthcare access during the pandemic, changes in sexual behavior, or the reprioritization of healthcare resources. These factors have been noted in various international studies, although it was challenging to confirm with domestic data. Nonetheless, it is believed that the situation in the country would not have been significantly different.

Clinical manifestations

Chlamydia can lead to urogenital, oropharyngeal, rectal, and ocular infections in both men and women. The majority of these cases are asymptomatic, with over 70% of urogenital infections in women and more than 80% in men presenting no symptoms. Similarly, around 90% of rectal and pharyngeal infections remain asymptomatic [28]. When symptoms do occur, chlamydia infections typically manifest as urethritis, characterized by dysuria and urethral discharge, cervicitis, PID, and proctitis, which includes pain, discharge, and bleeding. In men, the infection may also lead to epididymitis. Additionally, chlamydia can cause Fitz-Hugh-Curtis syndrome, a specific form of PID.

In neonates born vaginally to mothers with chlamydia, there is a risk of developing conjunctivitis or pneumonia. Additionally, a rare manifestation of chlamydia infection, known as lymphogranuloma venereum (LGV), may also occur. LGV progresses through three stages: initially, a small, painless, temporary ulcer appears at the infection site. The second stage, which develops 2 to 6 weeks later, is marked by large, painful inguinal lymph nodes, with approximately 30% of these nodes spontaneously rupturing. If left untreated, the third stage involves chronic lymphadenitis, which leads to scarring, lymphedema, and genital elephantiasis [29].

Diagnosis

Chlamydia is diagnosed by detecting the pathogen with NAATs from the suspected site of infection. The process for collecting samples is similar to that used for gonorrhea; however, since cultures are not conducted, NAATs are the sole diagnostic method employed.

Treatment

The treatment for chlamydia is doxycycline. According to the updated 2021 guidelines from the U.S. CDC, doxycycline is now recommended as the first-line treatment [2], a decision supported by recent studies [30–32]. Domestic guidelines also endorse doxycycline, prescribing 100 mg twice daily for 7 days. Alternative treatments include azithromycin (1 g) or levofloxacin (500 mg), both administered for 7 days. A study conducted in Japan revealed that the antibiotic resistance rates for *C. trachomatis* were 2.0% for azithromycin and 2.4% for clarithromycin [33].

Mycoplasma genitalium

M. genitalium was not widely recognized as an infection in the past, but it has recently gained attention as a STI. In the 2015 guidelines from the U.S. CDC, *M. genitalium* was described as an "emerging pathogen of uncertain significance" [34]. However, with the accumulation of more data, recent guidelines now recommend treatment for it [2].

Epidemiology

Since *M. genitalium* is not a notifiable infection in Korea, nationwide incidence statistics are not compiled. A study conducted in Korea between 2012 and 2015 involving 14,932 soldiers with urological symptoms found that chlamydia was the most prevalent infection at 36.6%, followed by *Ureaplasma urealyticum* at 24.0%, and *M. genitalium* at 21.5%. *N. gonorrhoeae* accounted for 19.0% of the cases [35]. Another study, carried out from 2018 to 2020 on outpatients, identified *M. genitalium* in 3.27% of the cases, with the highest prevalence observed in the 20–29 age group [36].

Clinical manifestations

The urogenital tract is the primary site of *M. genitalium* infection, although it can also occasionally cause proctitis. In cases of recurrent and persistent urethritis, *M. genitalium* is detected in approximately 30%–40% of instances. Although *M. genitalium* often remains asymptomatic, it is present in 30%–40% of men with persistent recurrent urethritis [37]. Symptoms during these episodes typically include dysuria and urethral discomfort. In women, *M. genitalium* is associated with cervicitis, PID, and infertility. The main symptoms in women are those related to cervicitis, such as post-coital bleeding, intermenstrual bleeding, and lower abdominal pain [38].

Treatment

M. genitalium often fails to respond to treatment, primarily due to resistance to the medications used. Therefore, recent major guidelines recommend assessing resistance before selecting a treatment regimen for *M. genitalium* [2]. However, since macrolide resistance testing tools are not yet available domestically, these recommendations cannot be applied in the local context (Fig. 4).

If resistance testing is possible, administer doxycycline (100 mg) twice daily for 7 days initially.

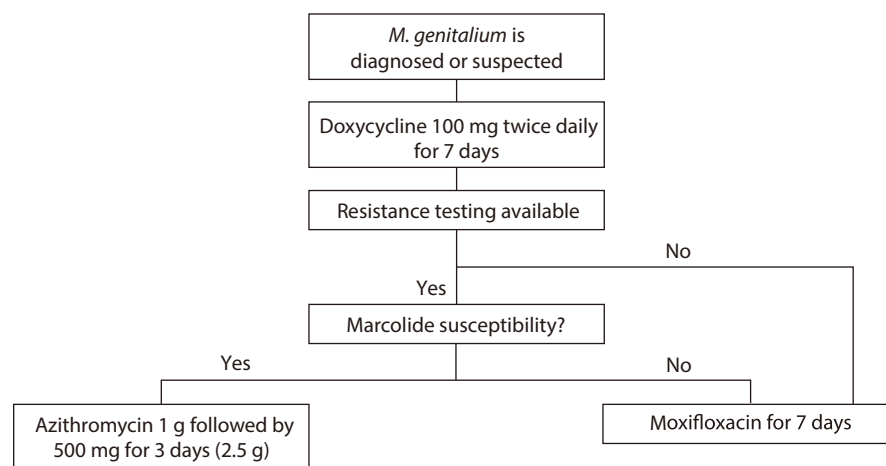


Fig. 4. Treatment flowchart for *Mycoplasma genitalium* infections.

If the organism is susceptible to macrolides, azithromycin can be administered as a single 1 g oral dose followed by three additional 500 mg doses (totaling 2.5 g). In the presence of macrolide resistance, moxifloxacin (400 mg) taken orally for 7 days is recommended. If resistance testing is not available, the recommended approach is to administer doxycycline for one week followed by moxifloxacin for another week. The 2023 domestic guidelines suggest starting treatment with azithromycin (500 mg orally), followed by 250 mg daily for 4 days (total 1.5 g). In cases of treatment failure or recurrence, a 7-day course of doxycycline or minocycline is advised, followed by further treatment decisions based on macrolide susceptibility. If testing is not feasible or if macrolide susceptibility is confirmed, the recommended regimen is 1 g of azithromycin followed by 500 mg daily for 3 days (total 2.5 g), with a follow-up at 21 days to confirm cure. If macrolide resistance is detected, a 7-day course of moxifloxacin 400 mg is recommended.

Herpes simplex virus

Epidemiology

HSV is categorized into type 1 (HSV-1) and type 2 (HSV-2), both of which can cause genital herpes [39]. However, HSV-2 is primarily associated with anogenital herpes, whereas HSV-1 typically leads to cold sores around the lips. In Korea, the incidence of HSV-2 is monitored through a sample surveillance system. Data show that there were 6,657 cases in 2017, 10,347 cases in 2018, 11,229 cases in 2019, 10,759 cases in 2020, 10,637 cases in 2021, 10,403 cases in 2022, and 11,449 cases in 2023. Additionally, the number of cases reported per institution has been steadily increasing (Figs. 2, 3).

Clinical manifestations

Most individuals infected with HSV remain asymptomatic, and the majority are unaware that they are carriers. During the initial infection, which follows an incubation period of approximately 4–7 days post-contact, patients develop multiple painful, bilateral, erythematous lesions. These lesions progress through stages including papules, vesicles, and ulcers, and typically last between 16.5 to 19.7 days [13,40]. Additionally, 39%–68% of patients report experiencing headaches, fever, and lymphadenopathy during this initial phase [13]. Following the initial

outbreak, the virus enters a latent state where it remains asymptomatic. Symptomatic recurrences occur in about 40–50% of cases and are often preceded by prodromal symptoms localized to the affected area. These symptoms, which include itching or burning sensations, help patients recognize the onset of a new outbreak. Recurrences tend to be milder than the initial infection and usually resolve within 5–10 days.

Diagnosis

Testing for HSV can be performed on samples from vesicular lesions using NAATs, such as PCR, which have very high sensitivity. A wet swab is the preferred method, but a dry swab can also be used. While viral culture is an option, it is less sensitive and more time-consuming than NAAT, and thus, it is not recommended as the sole testing method. Viral culture may be utilized in instances where the infection does not respond to treatment or antiviral resistance is suspected. Serological testing is valuable for identifying infections, especially latent infections in the absence of skin lesions, and is frequently employed in demographic studies.

Treatment

Treatment for HSV includes oral or injectable antiviral medications. The primary antiviral drugs used are acyclovir, valacyclovir, and famciclovir. Although these medications do not cure HSV, they help reduce symptoms, shorten the duration of the disease, and decrease the recurrence rate. Despite the availability of various antiviral drugs, most share similar mechanisms of action and efficacy. For suspected initial infections, a 10-day course of antiviral treatment is recommended, which may be extended by an additional week if lesions persist. For recurrent lesions, a shorter course of treatment may be attempted. Topical antiviral treatment alone is not recommended due to its insufficient effectiveness.

Conclusion

This review highlights the evolving landscape of STIs in Korea. The COVID-19 pandemic has significantly impacted the epidemiology of STIs, necessitating adaptations in healthcare delivery and public health strategies. The emergence of antibiotic-resistant strains, particularly in gonorrhea and *M. genitalium*, underscores the importance of antimicrobial stewardship and the development of new therapeutic options. Continuing efforts in education, prevention, and research are essential to manage and mitigate the impact of STIs on public health.

ORCID

Chung-Jong Kim: <https://orcid.org/0000-0002-9987-6533>

Authors' contributions

All work was done by Chung-Jong Kim.

Conflict of interest

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Supplementary materials

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Clinical outcomes and future directions of enhanced recovery after surgery in colorectal surgery: a narrative review

Ji Hyeong Song¹, Minsung Kim²

¹Department of Surgery, Inje University Haeundae Paik Hospital, Busan, Korea

²Department of Surgery, Hallym Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

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Corresponding author

Minsung Kim
Department of Surgery, Hallym Sacred Heart Hospital, Hallym University College of Medicine, 22 Gwanpyeong-ro 170 Beon-gil, Pyeongan-dong, Dongan-gu, Anyang 14068, Korea
E-mail: bongkay4@gmail.com

Keywords

Colorectal neoplasms; Colorectal surgery; Enhanced recovery after surgery; Postoperative complications; Preoperative care

Enhanced recovery after surgery (ERAS) protocols are designed to minimize surgical stress, preserve physiological function, and expedite recovery through standardized perioperative care for primary colorectal surgery patients. This narrative review explores the benefits of current ERAS protocols in improving outcomes for these patients and provides insights into future advancements. Numerous studies have shown that ERAS protocols significantly reduce the length of hospital stays by several days compared to conventional care. Additionally, the implementation of ERAS is linked to a reduction in postoperative complications, including lower incidences of surgical site infections, anastomotic leaks, and postoperative ileus. Patients adhering to ERAS protocols also benefit from quicker gastrointestinal recovery, marked by an earlier return of bowel function. Some research indicates that colorectal cancer patients undergoing surgery with ERAS protocols may experience improved overall survival rates. High compliance with ERAS protocols leads to better outcomes, yet achieving full adherence continues to be a challenge. Despite these advantages, implementation challenges persist, with compliance rates affected by varying clinical practices and resource availability. However, the future of ERAS looks promising with the incorporation of prehabilitation strategies and technologies such as wearable devices and telemedicine. These innovations provide real-time monitoring, enhance patient engagement, and improve postoperative follow-up, potentially transforming perioperative care in colorectal surgery and offering new avenues for enhanced patient outcomes.

Introduction

Background

Enhanced recovery after surgery (ERAS) protocols were developed to reduce perioperative surgical stress, maintain postoperative physiological function, and accelerate recovery through a standardized approach to perioperative care for patients undergoing major colorectal surgery [1–5]. Since the introduction of “fast-track surgery,” the ERAS society has rapidly expanded, influencing changes in surgical and anesthesia protocols across multiple disciplines with a focus on improving the quality of recovery [6,7]. The ERAS concept involves a multidisciplinary and multimodal approach, integrating evidence-based interventions and management changes

through interactive audits [1,2]. The ERAS Society first published guidelines for elective colorectal surgery in 2005, which have been updated to the fourth edition [1,3]. Previous studies have shown that ERAS protocols reduce the length of hospital stay (LOS), decreases postoperative morbidities, and enhance gastrointestinal functional recovery [3,5,8].

Despite the benefits of ERAS, implementing new practices remains challenging. Evidence indicates that changes in clinical practice often take up to 15 years to align with clear evidence [9]. There is a need to support a team-based approach to quickly implement new and improved care [2]. The compliance rate for ERAS protocols is generally reported to be above 60% and can reach over 90%, even in elderly patients who have undergone colorectal surgery [8,10–14]. In addition, ERAS is a continuously evolving framework, built upon the most reliable current evidence in perioperative care [6]. It is important to adopt the latest ERAS protocols and implement further changes based on new, clear evidence [2].

Objectives

The purpose of this review is to present an overview of the available evidence on the advantages of current ERAS protocols in improving outcomes for patients undergoing major colorectal surgery, while also offering guidance for future developments.

Ethics statement

This is a literature-based study; therefore, neither approval by the institutional review board nor obtainment of informed consent was required.

Elements of enhanced recovery after surgery protocols

The ERAS Society guidelines for elective colorectal surgery are shown in Table 1 [1].

ERAS protocols are designed to minimize stress and enhance the response to stress [2,6,15]. By preserving homeostasis, it helps patients avoid catabolism, thereby preventing the loss of protein, muscle strength, and cellular dysfunction [2,3]. The reduction of insulin resistance promotes proper cellular function during tissue injury [16,17]. ERAS protocols include several components to support these objectives: providing preoperative nutritional support to malnourished patients, administering carbohydrates before surgery to minimize postoperative insulin resistance, using epidural or spinal analgesia to reduce the endocrine stress response, employing anti-inflammatory drugs to control inflammation, encouraging early postoperative feeding to ensure adequate energy intake, and optimizing pain control to prevent stress and insulin resistance [1,2,15,17,18]. In addition, ERAS protocols aim to maintain fluid and electrolyte balance. Insufficient fluid can lead to reduced perfusion and organ dysfunction, while excessive intravenous salt and fluid administration is a recognized cause of postoperative ileus and related complications [19]. It is essential to maintain euolemia, cardiac output, and the delivery of oxygen and nutrients to tissues to preserve cellular function, especially during tissue repair. Once euolemia is achieved, vasopressors may be administered as necessary to maintain mean arterial blood pressure. A common recommendation is to target minimal weight change, typically maintaining a net intake of intravenous fluid around 30 mL/kg and limiting weight gain to within 2 kg [2,20–22]. Postoperative intravenous fluids are generally discontinued approximately 24 hours after surgery. A patient on an ERAS pathway should be drinking, eating, mobilizing, and sleeping on the day after surgery. ERAS protocols also avoid several traditional care practices

Table 1. Enhanced recovery after surgery protocol for elective colorectal surgery

Preadmission items
Preadmission information, education and counseling
Preoperative optimization
Smoking cessation
Avoiding alcohol abuse
Prehabilitation
Preoperative nutritional care
Management of anemia
Oral or intravenous iron therapy
Preoperative items
Prevention of nausea and vomiting
Preanesthetic medication
Antimicrobial prophylaxis and skin preparation
Bowel preparation
Preoperative fluid and electrolyte therapy
Preoperative fasting and carbohydrate loading
Intraoperative items
Standard anesthetic protocol
Intraoperative fluid therapy
Avoiding fluid excess and organ hypoperfusion
Preventing intraoperative hypothermia
Minimally invasive surgery
No drainage catheter of the peritoneal cavity and pelvis
Postoperative items
No nasogastric intubation
Postoperative multimodal analgesia
Epidural blockade
Spinal anesthesia/analgesia
Lidocaine infusions
Abdominal wall blocks
Thromboprophylaxis
Postoperative near-zero fluid and electrolyte balance
Early removal of urinary drainage catheter
Prevention of postoperative ileus
Postoperative glycemic control
Postoperative nutritional care
Early oral feeding
Immunonutrition
Early mobilization

that have been proven harmful, such as the routine use of nasogastric tubes, prolonged urinary catheterization, and prolonged or inappropriate use of abdominal drains [1,2,8,13,14].

The implementation of ERAS protocols in clinical settings varies by country and hospital. Adhering to all items of ERAS protocols is essential, yet often challenging to accomplish [10]. A systematic review and meta-analysis reported that several components, including preadmission information, education and counseling, preanesthetic medication, bowel preparation, preoperative fluid and electrolyte therapy, minimally invasive surgery, multimodal analgesia, avoidance of nasogastric intubation, early removal of urinary drainage catheters, and early mobilization, were effectively implemented. However, other elements such as preoperative optimization, anemia management, and postoperative glycemic control were less frequently applied [23].

Analysis of the outcomes of enhanced recovery after surgery protocols

The outcomes of implementing ERAS protocols are summarized in Table 2.

Length of hospital stay

Several studies have reported a reduction in the LOS with the implementation of ERAS protocols. Simpson et al. analyzed 4,363 patients who underwent elective colorectal surgery and found that ERAS protocols significantly reduced LOS [24]. Tamponi et al. reported a significant impact of ERAS protocols on reducing LOS in elective colectomy patients [8]. Toh et al. demonstrated that the reduction in LOS was influenced by the implementation of ERAS protocols and the absence of complications [14]. Liu et al. analyzed 3,768 patients who underwent elective colectomy in 20 medical centers and found that the implementation of ERAS protocols was associated with significant decreases in LOS [25]. Pędziwiatr et al. conducted a prospective cohort study and found that the implementation of ERAS protocols in elective colectomy significantly reduced LOS [26]. These studies also showed that good compliance was associated with a significantly shorter LOS [8,24,26]. Two randomized controlled trials showed that the implementation of ERAS protocols was associated with shorter LOS in elective colectomy. Dag et al. enrolled 199 patients and found that early feeding was associated with a significantly shorter LOS [27]. Lau et al. enrolled 111 patients and reported that the early use of a low-residue diet was associated with a reduction in LOS [28]. Some studies reported that the implementation of ERAS protocols in patients with colorectal cancer undergoing elective surgery was associated with a reduction in LOS [29,30]. Several studies reported that the impact of ERAS protocols on shorter LOS in patients with colorectal cancer undergoing elective minimally invasive surgery. Quiram et al. analyzed 600 patients with rectal cancer who underwent elective minimally invasive surgery, and Vignali et al. analyzed 320 patients, finding that the implementation of ERAS protocols was associated with a significantly shorter LOS [31,32]. Cristóbal et al. prospectively enrolled 300 patients and reported that the implementation of ERAS protocols reduced the LOS in patients with colorectal cancer undergoing robotic surgery [33]. In one study, a multimodal pain management protocol for loop ileostomy reversal was associated with a significantly shorter LOS [15]. Another study showed no differences in LOS despite the implementation of ERAS protocols in elderly patients with colorectal cancer [13].

Complication rate

Several studies have reported a reduction in postoperative complication rates following the

Table 2. Outcomes of ERAS protocols compared with conventional treatment

Author	Study design	Study population	Patients (n)	Outcomes	P-value
Length of stay (days)					
Quiram et al. [31]	Multicenter, Retrospective	Elective RC, MIS	600	3 vs. 5	<0.001
Meillat et al. [29]	Retrospective	Elective CRC	320	5.8 vs. 8.2	<0.001
Wang et al. [30]	Retrospective	Elective CRC	542	7.73 vs. 10.96	<0.001
Vignali et al. [32]	Retrospective	Elective RC, MIS	297	8.9 vs. 12.1	<0.001
Cristóbal et al. [33]	Prospective	Elective RC, MIS	300	5 vs. 7	<0.001
Simpson et al. [24]	Retrospective	Elective colectomy	4,363	6 vs. 7	<0.001
Pędziwiatr et al. [26]	Prospective	Elective colectomy	92	3 vs 5	0.014
Liu et al. [25]	Multicenter, Retrospective	Elective colectomy	3,768	4.2 vs. 5.1	<0.001
Tampo et al. [8]	Retrospective	Elective colectomy	267	5.8 vs. 7.9	<0.001
Toh et al. [14]	Retrospective	Elective colectomy	171	7.0 vs. 10.8	0.024
Kim et al. [15]	Retrospective	Elective stoma reversal	108	2.3 vs. 4.1	<0.001
Dag et al. [27]	RCT	Elective colectomy	199	5.5 vs. 9.0	<0.001
Lau et al. [28]	RCT	Elective colectomy	111	5.0 vs. 7.0	0.01
Complication rate (%)					
Quiram et al. [31]	Multicenter, Retrospective	Elective RC, MIS	600	34.7 vs. 54.3	<0.001
Meillat et al. [29]	Retrospective	Elective CRC	320	21.3 vs. 34.4	0.002
Cristóbal et al. [33]	Prospective	Elective CRC, MIS	300	28.0 vs. 46.0	0.002
Pędziwiatr et al. [26]	Prospective	Elective colectomy	92	9.4 vs. 56.0	0.014
Liu et al. [25]	Multicenter, Retrospective	Elective colectomy	2,406	14.7 vs. 18.1	0.02
Barberan-Garcia et al. [36]	RCT	Elective abdominal surgery	144	31.0 vs. 62.0	0.001
Garfinkle et al. [34]	Retrospective	Elective colectomy	40,446	14.9 vs. 20.3	<0.001
Ripollés-Melchor et al. [35]	Multicenter, Prospective	Elective colectomy	2,084	25.2 vs. 30.3	0.01
Flatus resumption time (days)					
Wang et al. [30]	Retrospective	Elective CRC	542	2.3 vs. 2.9	<0.001
Vignali et al. [32]	Retrospective	Elective RC, MIS	297	2.1 vs. 3.3	<0.001
Lau et al. [28]	RCT	Elective colectomy	111	3.7 vs. 4.8	0.04
Overall survival rate (%)					
Quiram et al. [31]	Multicenter, Retrospective	Elective RC, MIS	600	91.4 vs. 81.7	<0.001
Tidadini et al. [37]	Retrospective	Elective CRC	1,001	76.1 vs. 69.2	0.017
Tidadini et al. [38]	Retrospective	Elective CRC	661	73.1 vs. 64.4	0.016

ERAS, enhanced recovery after surgery ; RC, rectal cancer; MIS, minimally invasive surgery; CRC, colorectal cancer; RCT, randomized controlled trial.

implementation of ERAS protocols. Liu et al. analyzed 2,406 patients who underwent elective colectomy and found that the implementation of ERAS protocols resulted in lower complication rates compared to conventional treatment [25]. Garfinkle et al. studied 40,446 patients undergoing elective colectomy and discovered that oral antibiotic preparation alone significantly reduced surgical site infections, anastomotic leaks, postoperative ileus, and major morbidity [34]. Pędziwiatr et al. conducted a prospective cohort study and determined that ERAS protocols significantly reduced complication rates in elective colectomy surgery [26]. Ripollés-Melchor et al. carried out a

multicenter, prospective study and reported significantly fewer moderate to severe complications after elective colorectal surgery in the ERAS group compared to the conventional treatment group. An increase in ERAS adherence was also associated with a decrease in postoperative complications [35]. Barberan-Garcia et al. conducted a randomized controlled trial with 144 patients undergoing elective major abdominal surgery, including colectomy, and found that personalized prehabilitation reduced complication rates [36]. Several studies have highlighted the impact of ERAS protocols on reducing complication rates in patients with colorectal cancer undergoing elective surgery. Meillat et al. reported that the implementation of an ERAS protocol reduced complication rates after elective colorectal cancer surgery [29]. Quiram et al. analyzed 600 patients with rectal cancer who underwent elective minimally invasive surgery and found that the implementation of ERAS protocols was associated with a significantly lower complication rate [31]. Cristóbal et al. prospectively enrolled 300 patients and reported that the implementation of ERAS protocols reduced the complication rates in patients with colorectal cancer who underwent robotic surgery [33]. However, several other studies found that the implementation of ERAS protocols was not associated with changes in postoperative complication rates [13,15,27,30,32]. Additionally, one study reported higher postoperative complication rates in the ERAS group compared to conventional treatment after elective colectomy [8].

Gastrointestinal functional recovery

Several studies have reported a reduction in gastrointestinal functional recovery time with the implementation of ERAS protocols. Wang et al. analyzed 542 patients with colorectal cancer who underwent elective surgery [30], while Vignali et al. studied 297 patients with rectal cancer who underwent minimally invasive surgery [32]. Both studies found that the implementation of ERAS protocols was associated with a significantly shorter time to first flatus resumption. Lau et al. conducted a randomized controlled trial with 111 patients undergoing elective colectomy and found that the early use of a low residue diet was associated with a faster return of bowel function [28].

Overall survival rates

Multiple studies have reported an association between the implementation of ERAS protocols and improved overall survival rates in patients with colorectal cancer who underwent elective surgery. Quiram et al. analyzed 600 patients with rectal cancer who underwent elective minimally invasive surgery and found that the implementation of ERAS protocols was associated with a significantly higher overall survival rate [31]. Tidadini et al. conducted two retrospective studies and reported that the implementation of ERAS protocols improved overall survival rates in patients with colorectal cancer who underwent elective surgery [37,38].

Future directions of enhanced recovery after surgery protocols

Prehabilitation

Emerging evidence suggests that prehabilitation is beneficial in the treatment of colorectal cancer [39,40]. ERAS protocols should focus on the impact of prehabilitation, especially given the growing interest in its potential to reduce LOS and postoperative complications [6,41]. Prehabilitation, which involves preoperative exercise, nutritional support, and psychological interventions, aims to improve a patient's functional capacity before surgery, thereby reducing the impact of surgical stress [42]. However, the benefits of prehabilitation remain uncertain due to conflicting evidence in the literature. Valkenet et al. reported that preoperative inspiratory

muscle training reduced postoperative pulmonary complications in cardiac and abdominal aortic aneurysm surgeries. Conversely, no significant differences were observed in postoperative complications and LOS in orthopedic surgery [43]. Lemanu et al. reported that poor adherence to prehabilitation was associated with limited improvement in clinical outcomes [44]. These findings may be influenced by the heterogeneity of the studies, including differences in prehabilitation protocols and surgical specialties [45]. Despite these challenges, another review focusing on total body exercise as a prehabilitation intervention reported improvements in postoperative pain, LOS, and physical function [46]. Moreover, a randomized controlled trial involving colorectal surgery patients demonstrated that a multimodal prehabilitation program, including exercise, nutritional counseling, and stress reduction, led to increased functional walking capacity both preoperatively and postoperatively compared to standard rehabilitation [47]. Therefore, prehabilitation may offer significant benefits, particularly when applied in a structured and comprehensive manner. As the evidence for prehabilitation is still in its early stages, further high-quality, randomized controlled trials are needed to better understand its role in ERAS protocols. Future research should aim to establish standardized and structured prehabilitation interventions and identify the specific patient populations that could most benefit from them [41,45].

Use of technology

As ERAS protocols continue to evolve, there is a growing interest in utilizing new technologies to improve patients' outcomes [3]. The integration of wearable devices and telemedicine could enhance existing ERAS protocols [41,45]. Wearable sensors are proving to be valuable for monitoring patients' physical activity and recovery [48]. These devices can track and transmit data on body movement and vital signs, both in-hospital and post-discharge [49,50]. Several studies have demonstrated a correlation between early postoperative physical activity, such as daily step counts, and improved recovery outcomes, including shorter LOS and better functional recovery [51–53]. Real-time monitoring of patient activity provides healthcare providers with essential insights into recovery progress and aids in the early identification of complications [54]. Additionally, providing patients with feedback on their activity levels can motivate them to engage more actively in their recovery process [55,56]. In addition to wearable sensors, telemedicine holds the potential to transform both preoperative and postoperative care [41]. Telemedicine can facilitate remote consultations, monitor postoperative recovery, and reduce the need for unnecessary hospital visits [57]. Some studies have shown that virtual visits and the use of mobile applications for patient self-reporting are promising, with approximately 30% to 70% of patients reporting enhanced care through virtual follow-ups [58–60]. Telemedicine also improves access to healthcare in underserved areas, facilitating better preoperative assessment and preparation [45]. By providing continuous monitoring and feedback, wearable devices and telemedicine can support improved recovery outcomes and enhance overall patient satisfaction. Future research should focus on optimizing these technologies for broader adoption and developing standardized protocols to ensure their effectiveness across various surgical specialties [41,45].

Discussion

ERAS protocols have been established as a highly effective, evidence-based strategy for optimizing surgical recovery, particularly in the field of colorectal surgery. Characterized by its multidisciplinary and multimodal approach, ERAS aims to minimize surgical stress, preserve physiological function, and promote a more rapid recovery. Numerous studies have shown

that implementing ERAS protocols reduces LOS, lowers complication rates, and improves gastrointestinal recovery, especially with high compliance to protocol elements. Despite these successes, challenges remain in the widespread implementation of ERAS protocols in various clinical settings. Future efforts should concentrate on integrating prehabilitation, which emphasizes preoperative exercise, nutrition, and psychological support, and on incorporating emerging technologies such as wearable sensors and telemedicine. These innovations have the potential to further enhance patient outcomes by enabling real-time monitoring and fostering greater patient involvement in their recovery process.

Conclusion

While ERAS protocols have transformed perioperative care, ongoing research, technological advancements, and the integration of prehabilitation remain crucial for optimizing outcomes and enhancing patient care across various surgical disciplines.

ORCID

Ji Hyeong Song: <https://orcid.org/0000-0002-7501-7259>

Minsung Kim: <https://orcid.org/0000-0002-1984-5084>

Authors' contributions

Project administration: Kim M

Conceptualization: Kim M

Methodology & data curation: Kim M

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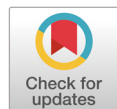
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Gender and healthcare issues related to the Protected Birth Act in Korea

Jiah Jeong

Department of Women-Gender Studies, Chungnam National University, Daejeon, Korea

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Corresponding author

Jiah Jeong
Department of Women-Gender Studies,
Chungnam National University, 99
Daehak-ro, Yuseonggu, Daejeon 34134,
Korea
E-mail: jiah.jeong@gmail.com

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Keywords

Induced abortion; Infanticide; Pregnant women; Vulnerable populations; Republic of Korea

This paper discusses the implications of South Korea's birth notification system and Protected Birth Act, which is set to take effect on July 19, 2024. The legislation aims to prevent infanticide and child abandonment by mandating birth reporting and allowing anonymous births for women in crisis. However, concerns have been raised about the Act's effectiveness in protecting both women and children, particularly regarding issues of disability and migrant families. This paper focuses on gender and healthcare issues, highlighting how the Act perpetuates discrimination against out-of-wedlock pregnancies and upholds normal family ideologies. It notes the absence of critical discussions on women's autonomy, safe pregnancy termination, and paternal responsibility. The importance of healthcare providers understanding and preparing for the Act's implementation is emphasized. The paper calls for strengthening social safety nets to improve healthcare access for vulnerable populations and eliminate discrimination against non-traditional families. Additionally, it addresses the need for comprehensive support systems for crisis pregnancies, including financial assistance, psychological support, parenting education, housing solutions, and expanded healthcare services. This paper acknowledges the Act's significance in providing a systematic state-level approach to protecting pregnant women in crisis, replacing the previous reliance on private organizations. Nonetheless, it also emphasizes the importance of continually reviewing and supplementing the system to address potential rights infringements and ensure its effectiveness. In conclusion, this paper advocates for ongoing discussions on gender and healthcare issues, and for future amendments to the law that reflect real-world circumstances and provide genuine protection for crisis pregnancies and infants.

Introduction: background of the Protected Birth Act in Korea

On March 23, 2023, the Constitutional Court of Korea unanimously declared that Article 46, Paragraph 2 of the "Act on the Registration of Family Relations," which required that "the mother must report the birth of a child born out of wedlock," was unconstitutional (Case 2021 Hon MA975) [1]. This ruling followed a constitutional complaint filed in August 2021 by Mr. A and others who, having fathered children with married women, found themselves unable to register the births of their children born out of wedlock.

The Constitutional Court explained that children born to a married woman and a man who is not

her husband encounter challenges in accessing social insurance and security benefits, engaging in transactions that require identification, and are more susceptible to abuse, abandonment, and criminal targeting. The Court highlighted that this situation infringes upon the plaintiffs' "right to birth registration immediately after birth," a right essential for safeguarding children's protection, facilitating their personal development, and promoting healthy growth under parental care.

Additionally, after extensive societal debate, the National Assembly passed an amendment to the criminal act abolishing the crime of infanticide on July 18, 2023. This amendment, effective from February 9, 2024, replaces the previous maximum sentence of 10 years specifically for infanticide with the application of general homicide and abandonment laws to cases involving infants. This change aims to provide stronger protection for this vulnerable group [2].

These social demands and legal reforms necessitated amendments to the "Act on the Registration of Family Relations," extending the obligation to report births from only parents to include medical institutions where births occur. The urgency for these changes was further highlighted by incidents such as the discovery of two infant corpses in a refrigerator in Suwon, ongoing cases of infant abandonment and murder, and the "Social Parents" project, which revealed that 2,236 children went unregistered between 2015 and 2022.

Consequently, on June 30, 2023, the National Assembly overwhelmingly passed the birth notification system, with 266 votes in favor and one abstention from the 267 members present. There were concerns that this system might prompt an increase in out-of-hospital births among pregnant women who wish to keep their deliveries confidential. This led to discussions about the possibility of implementing a protected birth system, a concept referenced in the minority opinion of the Supreme Court case (2021 Hon Ma975). In response to public interest, the government considered the introduction of a protected birth system to operate concurrently with the medical institution's birth notification system. The primary goal of this system is to safeguard the lives and health of mothers and children by enabling pregnant women facing challenging circumstances to give birth in medical facilities without disclosing their identities [3].

As a result, on October 6, 2023, the National Assembly passed the "Special Act on Support for Crisis Pregnancy and Protected Birth and Child Protection." The act received 133 votes in favor, with 64 abstentions from the 230 members present. The birth notification and protected birth systems are set to be implemented on July 19, 2024.

Key points of the birth notification system and protected birth system

The birth notification system was established based on findings from the National Statistical Office's population trend survey, which indicated that 99.8% of births in 2021 took place in medical institutions. Key details include: [4,5]

- Reporting Process: Heads of medical institutions are required to report birth information to the Health Insurance Review and Assessment Service (HIRA) within 14 days following the birth. Subsequently, local officials verify the parental birth registration and take the necessary actions.
- Reporting Details: The report must include the mother's name, national ID number, infant's gender, number of infants, and date/time of birth.
- Reporting Method: Medical institutions utilize HIRA's computerized system for reporting. HIRA, in turn, informs local officials via a shared administrative information center.
- Peremptory notice: Local officials notify the responsible party if the birth is not registered within 1 month.

- Official Registration: Local officials may officially register a birth following court confirmation if the registration occurs more than 7 days after notification or if the responsible party cannot be identified.

The protected birth system is designed to prevent out-of-hospital births and child abandonment, thereby safeguarding the lives and health of women and children. Key features of the system include: [4,5]

- Counselling: A counseling system has been established to offer comprehensive support and information to pregnant women in crisis. A regional counseling institutions help pregnant women in crisis to receive counseling, information provision, and service linkage at a local network at any time to help them raise children directly after giving birth. It stipulated that not only social security benefits, support for occupation and housing, and support for medical expenses under various laws, but also legal support. And a central counseling agency is responsible for developing counseling contents and procedures.

- Protected Birth Process: When applying for a protected birth, a pseudonym and management number are generated, and pregnant women can use this pseudonym and management number to perform prenatal checkups and childbirth at a medical institution. In this case, the entire medical expenses are supported.

- Child Protection: After the child is born as a protected child, a pregnant woman must have a meditation period to directly raise the child for at least seven days, and can deliver the child to a local government after this period. The head of a local government who has received the child shall take protective measures under the Child Welfare Act without delay and undergo protection procedures such as adoption. A mother who applied for a protected birth may withdraw the protected birth until the child is approved for adoption under the Special Act On Domestic Adoption.

- Record Management: Counseling and birth records are permanently preserved. Specific procedures are in place for disclosing these records to the child or their legal representatives once they reach adulthood.

This system aims to support pregnant women who are experiencing economic, psychological, or physical difficulties. It aims to ensure safe childbirth and secure environments for children while delineating the responsibilities of national and local governments in achieving these objectives.

Protected birth system and gender issues

Many countries acknowledge the importance of social safety nets for crisis pregnancies and are actively working on national initiatives to address this issue. Germany, France, and the United States each offer guarantees for the "right to anonymous birth" through different approaches. Specifically, Germany implemented the Confidential Birth Law (*Vertrauliche Geburt*) in 2013, which has been operational since 2014. This legislation offers legal protection to pregnant women in crisis and establishes "pregnancy conflict counseling centers" (Pro Familia Berlin) to assist them.

In Germany, the government assigns a child's surname anonymously at birth. At the age of 16, the child is granted access to their birth certificate, which includes information about the birth mother, thus upholding the child's right to know their parents. Counseling centers offer detailed information about the confidential birth system and related support policies through anonymous consultations, available on websites and via 24-hour national hotlines. Their primary goal is to

support the pregnant woman's autonomy, including the option of terminating the pregnancy. Adoption or a confidential birth is considered only when parenting is deemed unfeasible.

Germany has a "child's primary care physician system" that allows children to receive regular check-ups and treatment for various illnesses, with most medical expenses covered. Similarly, France's anonymous birth system (*L'accouchement sous X*) and the United States' Safe Haven laws both preserve the anonymity of the birth mother's information, though they are implemented differently [6–10].

The protection of pregnant women in crisis is a topic of global discussion. In response, the Korean government has established a "Task Force for Implementing Birth Notification and Protected Birth Systems." This task force is a collaborative effort involving the government, local authorities, court administration, and relevant agencies (National Health Insurance Service, Health Insurance Review & Assessment Service, Korea Social Security information Service, National Center for the Rights of the Child). They are working together to prepare for the implementation of these systems, which is scheduled for July 19, 2024 [5].

However, several concerns have been raised about the protected birth system in Korea. Critics argue that it inadequately protects both women and children, and they advocate for additional legislation to address issues related to children with disabilities and immigrant women and children [11–14].

Civil society organizations, women's bar associations [13], and parliamentary forums have consistently raised criticisms concerning the rights of women and children [14]. These critiques contend that the law effectively encourages unmarried mothers to give birth in secrecy and does not tackle the underlying issues that result in the abandonment of parental responsibilities. Furthermore, it is argued that the law significantly violates a child's right to know their identity, as the disclosure of birth certificates necessitates consent from both biological parents.

Unlike Korea's protected birth system, Germany's system, which was implemented in 2014, strikes a balance between anonymous birth and a child's right to know their parents. It recommends confidential birth only as a last resort, thereby minimizing potential negative consequences. This approach necessitates a discussion on the "normal family discourse," a critical social agenda in Korea [12].

Germany has completely eliminated legal distinctions between children born inside and outside of marriage, effectively reducing discrimination and prejudice. In contrast, Korea's protected birth system inherently views pregnant women in crisis as belonging to "abnormal" families outside of marriage, and assumes that unmarried mothers are individuals who "want to give birth in secret and abandon child-rearing."

In Korea, where Confucian culture emphasizing chastity is deeply rooted, unmarried mothers frequently face stigmatization as immature, immoral, and lacking in self-control. They become targets of social criticism, associated with the prevailing "normal family ideology," which leads to discrimination and prejudice. The "Framework Act on Healthy Homes" mirrors this cultural stance by assuming that a "normal family"—one formed through legal marriage—is the default, thereby recognizing and protecting only such family structures.

The law fails to address the myriad reasons why individuals might abandon child-rearing, nor does it include protective measures for these issues. This oversight should have been addressed during the legislative process, which is a significant concern. Given that the law was enacted to protect pregnant women in crisis, potentially exposed to the risks associated with out-of-hospital births due to the birth notification system, it should incorporate mechanisms that safeguard women's agency and subjectivity. Although it purports to offer physical, economic,

and psychological support through counseling from pregnancy to childbirth, it does not provide concrete measures that ensure women's rights to make decisions regarding pregnancy termination and reproduction.

Following the Constitutional Court's decision on April 11, 2019, which declared the criminalization of abortion unconstitutional, the abortion law became ineffective starting January 1, 2021, due to the absence of alternative legislation. Currently, without national alternative legislation, there are no safeguards in place for safe pregnancy termination in medical settings. Therefore, illegal drugs such as abortion pills are being distributed online, potentially increasing the number of pregnant women in crisis.

A study by Kim [15] involving 602 women aged 19–44 who had undergone pregnancy termination in the past five years revealed that the majority of those who would be protected by the protected birth system had the following characteristics: 52.7% were in their 20s or younger, 51.3% were unmarried, and 50.7% identified as lower class.

Lastly, the "Crisis Pregnancy and Protected Birth Support and Child Protection Special Act" continues to obscure the role of fathers, assigning the responsibility for post-birth care exclusively to the woman who gave birth. Although women experiencing crisis pregnancies can access support through various laws (National Basic Living Security Act, Single-Parent Family Support Act, National Health Insurance Act, Mother And Child Health Act etc.), this assistance is generic and fails to address their specific needs. Korean society remains entrenched in the practice of faulting women who do not assume responsibility for childcare.

In addition, Article 7 (2) stipulates that it supports the implementation of child support expenses in accordance with the "Act On Enforcing and Supporting Child Support Payment", but it is also obvious that the implementation of child support expenses is not effective. The 2021 Single-Parent Family Survey [16], released by the Ministry of Gender Equality and Family, reveals that 72.1% of respondents reported they had never received legally mandated child support. This finding underscores a significant societal issue: the absence of stringent consequences for failing to pay child support, despite its direct connection to constitutional rights to life and the pursuit of happiness. The lack of paternal responsibility in childbirth must no longer be ignored.

Protected birth system and healthcare issues

Healthcare professionals must accurately understand and prepare for the newly implemented birth notification and protected birth systems. This responsibility entails proper training on procedures and attitudes within medical settings, such as assigning electronic management numbers and pseudonyms to pregnant women in crisis who request protected births, ensuring that birth records remain confidential. Additionally, it involves issuing "Pregnant Woman Certificates" to enable anonymous medical treatment.

The law's target population comprises socially vulnerable individuals whom our society must protect. This system requires an approach that eradicates prejudice and discrimination against single parents and unmarried mothers, promoting diversity instead. Primary care providers, typically the initial contact for pregnant women in crisis, must maintain an impartial attitude and respect for the life of each pregnant woman. This ensures that these women do not feel their rights to self-determination and motherhood are being denied or disrespected.

While medical law focuses on equipping healthcare professionals with an awareness of bioethics and ethical issues in medicine, it is also essential that they develop empathy, understanding, and unbiased thinking, all of which should be grounded in a keen social

awareness.

Benchmarking Germany's "child's primary care physician system" and Seoul's "Seoul Baby Health First Step Parenting Support Project" [17], which was implemented in 2018, could strengthen the medical community's support for women experiencing crisis pregnancies. The Seoul project mandates universal home visits by specialist nurses for all postpartum women and newborns within 4 weeks of childbirth. If health risk factors are identified, these visits can continue up to 25 times until the child reaches the age of 2.

Access to medical institutions is another crucial issue. The government offers financial support through the National Voucher card for prenatal and postnatal care, providing 1 million won (1.4 million for multiple pregnancies) per pregnancy. However, a survey conducted by the Korean Unwed Mothers Families Association [14] revealed that 41 out of 146 single mothers were either unaware of or did not use this card, highlighting the need for a social safety net that ensures pregnant women receive accurate medical information.

According to the 2021 National Health and Nutrition Examination Survey, the rate of Unmet Healthcare Needs Status (excluding dental care) was 6.7% [18]. Unmet medical needs stem from a variety of factors, including physical and economic issues such as accessibility to medical facilities and the cost of healthcare. Emotional factors also play a role, including patient knowledge, attitudes, anxiety or depression, fear of secondary victimization, and a lack of social support.

Although there are no specific data on the proportion of pregnant women in crisis with unmet medical needs, a survey by the Korean Unwed Mothers Families Association [14] suggests that this proportion may be significant. Many single mothers report avoiding medical care due to financial constraints, reluctance, or fear of visiting hospitals.

This result suggests that vulnerable populations, such as women experiencing crisis pregnancies, who are likely to face high rates of unmet medical needs, need a multidimensional approach to analysis and solutions extending beyond mere economic support and including a comprehensive social safety net.

Conclusion: prospects and proposals for the protected birth system

The protected birth system is significant because it represents a governmental initiative to systematically safeguard pregnant women in crisis situations and establish a social safety net that was previously administered by private organizations. This support is particularly vital in a society where unmarried mothers, especially teenagers, encounter instability, discrimination, and stigma associated with pregnancy and childbirth, frequently without support from their families or the broader community.

According to government announcements, non-profit or social welfare corporations with at least three years of experience in counseling unmarried mothers may be designated as crisis pregnancy counseling agencies. Additionally, the government has proposed amendments to the Enforcement Decree and Enforcement Regulations of the Crisis Pregnancy and Protected Birth Support Act. These amendments include the establishment of a 24-hour hotline for women experiencing a crisis pregnancy [5].

Now, we must listen to a range of concerns and voices related to the protected birth system and establish policies that effectively protect pregnant women in crisis, fetuses, and children, which is the fundamental purpose of the legislation. The system must be continually reviewed

and supplemented to address concerns such as potential infringement on women's and children's rights, ensuring that the enacted laws do not become mere academic exercises.

Despite criticisms that the protected birth system seems to be structured to prioritize protected births, it provides a safety mechanism for pregnant women in crisis who choose this as a last resort, ensuring a safe delivery in medical institutions. Additionally, it provides basic legal support for accessing social welfare services to address childcare and economic challenges that may arise during pregnancy, childbirth, and child-rearing.

However, pregnant women in crisis often avoid disclosing their situation publicly, which can result in them not benefiting from various government pregnancy support policies. Therefore, systematic registration and management of pregnant women in crisis should be accompanied by practical support. This support should address challenges in child-rearing, financial issues, psychological support, parenting education, housing, education costs, the expansion of care services, and health check-up services.

As we approach the implementation of the Protected Birth System, our goal is to enhance national accountability and strengthen social safety nets for women facing crisis pregnancies. This system should prevent the burden of childbirth from falling solely on women and should facilitate ongoing discussions on topics such as the ideology of the "normal family," the right to safely terminate a pregnancy, and the roles of both motherhood and fatherhood in caregiving. These discussions must also be reflected in the amendments to the law.

ORCID

Jiah Jeong: <https://orcid.org/0009-0006-8386-9677>

Authors' contributions

All work was done by Jiah Jeong.

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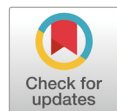
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Exploration of the interaction between remote ischemic preconditioning and anesthetic-induced preconditioning using sevoflurane in isolated perfused rabbit heart

Seung-Hee Yoo¹, Sooyoung Cho^{1,2}, Yoonsun Won¹, Jong Wha Lee^{1,2}

¹Department of Anesthesiology and Pain Medicine, Ewha Womans University Mokdong Hospital, Seoul, Korea

²Department of Anesthesiology and Pain Medicine, Ewha Womans University College of Medicine, Seoul, Korea

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Corresponding author

Jong Wha Lee
Department of Anesthesiology and Pain Medicine, Ewha Womans University Mokdong Hospital, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
E-mail: jhane@ewha.ac.kr

Keywords

Inhalation anesthesia; Myocardial ischemic preconditioning; Myocardial reperfusion injury; Rabbits; Sevoflurane

Objectives: Remote ischemic preconditioning (rIPC) is a novel technique in which brief episodes of ischemia and reperfusion in one organ confer protection against prolonged ischemia in a distant organ. In contrast, anesthetic-induced preconditioning (APC) utilizes volatile anesthetics to protect multiple organs from ischemia-reperfusion injury. Both methods are easily integrated into various clinical scenarios for cardioprotection. However, it remains unclear whether simultaneous application of these techniques could result in complementary, additive, synergistic, or adverse effects.

Methods: An adult rabbit heart Langendorff model of global ischemia/reperfusion injury was used to compare the cardioprotective effect of rIPC and APC alone and in combination relative to untreated (control) hearts. The rIPC group underwent four cycles of 5-minute ischemia on the hind limb, each followed by 5 minutes of reperfusion. The APC group received 2.5 vol% sevoflurane for 20 minutes via a face mask, followed by a 20-minute washout period.

Results: Both *in vivo* rIPC, induced by four 5-minute cycles of ischemia/reperfusion on the hind limb, and APC, administered as 2.5 vol% sevoflurane via a mask, significantly reduced the size of myocardial infarction following 30 minutes of global ischemia by >50% compared to the untreated control group (rIPC, 12.1±1.7%; APC, 13.5±2.1%; P<0.01 compared to control, 31.3±3.0%). However, no additional protective effect was observed when rIPC and APC were combined (rIPC+APC, 14.4±3.3%).

Conclusion: Although combining rIPC and APC did not provide additional protection, there was no inhibitory effect of one intervention on the other.

Introduction

Background

Local ischemic preconditioning (IPC) is a phenomenon where brief, repeated cycles of ischemia and reperfusion protect against a subsequent, prolonged period of potentially lethal ischemia in the same tissue or organ [1,2]. Despite substantial supportive experimental data, its clinical application has been limited due to the challenges of inducing ischemia in the target organ, such as the heart, before a predictable insult. Remote IPC (rIPC) is a newer method where transient

ischemia and reperfusion of one tissue or organ provide protection against a subsequent, prolonged period of ischemia in a distant organ [3]. For instance, we have demonstrated that transient limb ischemia can protect the heart as effectively as IPC in experimental models [4] and can reduce myocardial damage and enhance lung function in children undergoing heart surgery [5]. This method's advantage lies in its simplicity and potential to protect multiple organs without needing to induce ischemia in the target organs, which could lead to dysfunction. Similarly, volatile anesthetics are recognized for their protective effects against ischemia-reperfusion injury across multiple organs, akin to IPC, and are therefore often referred to as "anesthetic-induced preconditioning" (APC) [6]. Although research into the signaling pathways involved in both rIPC and APC is ongoing [7,8], no studies have yet investigated the potential interactions between rIPC induced by transient limb ischemia and APC. As a result, it remains unclear whether using these two clinically viable techniques together might be complementary, additive, synergistic, or adverse.

Objectives

The current study was designed to examine the interaction between rIPC and APC-induced cardioprotection in isolated perfused rabbit hearts.

Methods

Ethics statement

The study protocol was approved by the local committee of the Animal Care and Use of Ewha Womans University College of Medicine (No. SK-2006-6377). The investigation conformed to the *Guide for the Care and Use of Laboratory Animals* published by NIH (NIH publication NO. 85-23, revised 1996).

Preconditioning protocol

Male New Zealand White rabbits weighing 3–4 kg were utilized in this study. During either sham operations or preconditioning, the rabbits were anesthetized with an intravenous injection of Akmezin—a mixture containing 1.18 mg of acepromazine, 0.8 mg of atropine, and 58.81 mg of ketamine per mL of sterile saline—at a dosage of 0.25 mL/kg of body weight initially, followed by intermittent doses of 0.2–0.3 mL depending on the response to painful stimuli. They were allowed to breathe spontaneously, receiving a mixture of oxygen and medical air via a face mask. The animals were randomly assigned to one of four groups: control, rIPC, APC, and rIPC+APC, with six rabbits in each group. The procedures each group underwent are summarized in Fig. 1. The control group experienced the same duration of sedation as the others but did not receive any preconditioning stimulus. The rIPC group underwent four cycles of 5-minute ischemia on a hind limb followed by 5 minutes of reperfusion. The cessation of limb flow following tourniquet application for rIPC was confirmed using pulse oximetry on the affected limb. The APC group was administered 2.5 vol% sevoflurane for 20 minutes via a face mask, followed by a 20-minute washout period. The end-tidal concentration of sevoflurane was monitored using a multi-gas monitor attached to the expiratory limb of the anesthesia circuit. The rIPC+APC group received both rIPC and APC simultaneously, employing the techniques described above.

In vitro perfusion of the heart

Fifteen minutes after either a sham operation or preconditioning, systemic anticoagulation

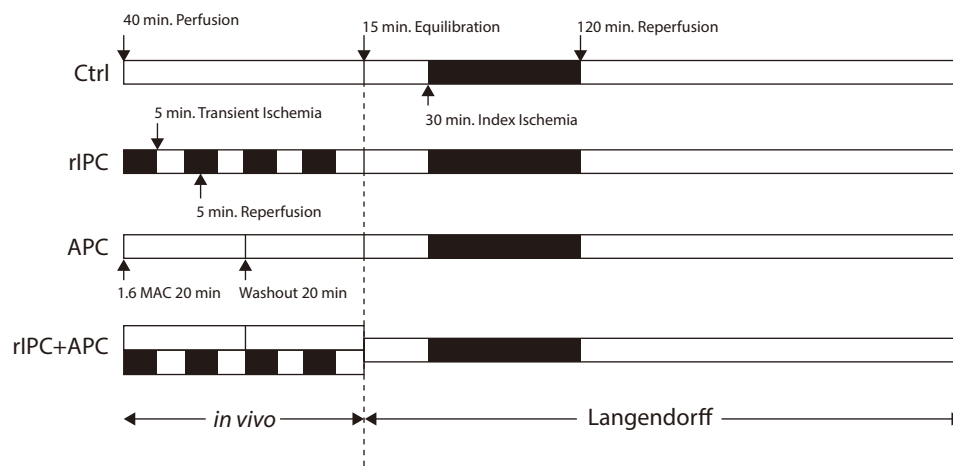


Fig. 1. Summary of procedures received by each treatment group. Before the excision of hearts and assessments using a Langendorff-based model of global ischemia/reperfusion injury, the groups underwent the following *in vivo* treatments (left side of the dashed line): 1. Ctrl: sham operation consisting of 40 min of perfusion (open bar), 2. rIPC: four cycles of 5 min transient limb ischemia (filled bar) alternated with 5 min of reperfusion (open bar), 3. APC group: administered 2.5 vol% sevoflurane (shaded bar) for 20 min via a face mask, followed by a 20-min washout period (open bar), 4. APC+rIPC groups: received both treatments concurrently. The bars to the right of the dashed line illustrate that the excised hearts from each group were equilibrated for 15 min, subjected to 30 min of global ischemia (filled bar), and then 120 min of reperfusion (open bar). Ctrl, control; rIPC, remote ischemic preconditioning; APC, anesthetic-induced preconditioning.

was achieved with an intravenous injection of heparin (1,000 U/kg of body weight). Once adequate anesthesia and analgesia were confirmed, the hearts were excised and immediately mounted on a recirculating Langendorff apparatus. The hearts were perfused retrogradely at a constant flow rate of 25–26 mL/min using a modified Krebs-Henseleit buffer. The buffer's composition per liter was as follows: NaCl 118 mM, KH_2PO_4 1.2 mM, KCl 4.7 mM, MgSO_4 1.2 mM, CaCl_2 1.8 mM, NaHCO_3 25 mM, and glucose 10 mM. The perfusate was continuously bubbled with a gas mixture of 95% O_2 and 5% CO_2 and maintained at a temperature of 37°C using a heat exchanger and warming pump. The heart rate was kept above 180/min, achieved by pacing the right atrium throughout the stabilization period and the 2-hour reperfusion following ischemia. After a 15-minute stabilization period, the hearts underwent 30 minutes of global zero-flow ischemia. During this time, the hearts were immersed in a water-jacketed chamber, also maintained at 37°C, and allowed to beat spontaneously. Following the ischemic period, the hearts were reperfused for 2 hours, and pacing of the right atrium was resumed. The frequency of reperfusion arrhythmias was recorded. While ventricular fibrillation typically reverted to sinus rhythm either spontaneously or in response to physical stimulation, it was incessant in 4 hearts, which were subsequently excluded from the analysis.

Infarction size measurement

At the end of the reperfusion period, hearts were removed from the Langendorff apparatus, and the left ventricle (LV) was carefully dissected from the rest of the heart. The LV was then transversely sectioned into six slices, each 2–3 mm thick, perpendicular to the septum from the apex to the base. Each slice was incubated in 2, 3, 5-triphenyltetrazolium chloride (TTC, 1% in 0.1 M phosphate buffer, pH 7.4, Sigma-Aldrich, St. Louis, MO, USA) at 37°C for 30 minutes

and subsequently fixed in 4% formaldehyde. The slices were then placed on a translucent acrylic holder, and both sides of each slice were photographed using a scanner. The images were analyzed using computerized planimetry (Adobe Photoshop® software, Adobe Systems Incorporated, Mountain View, CA, USA) to determine the area of infarction as a percentage of the total cross-sectional area of the LV. The percentage of infarction for each heart was calculated using the formula: $[(A_1 \times W_1) + (A_2 \times W_2) + (A_3 \times W_3) + (A_4 \times W_4) + (A_5 \times W_5) + (A_6 \times W_6)] \times 100 / \text{Weight of heart}$, where A_i is the mean area of infarct for each slice and W_i is the weight of the respective section.

Statistical analyses

Values are expressed as mean±SEM unless stated otherwise. One-way analysis of variance (ANOVA) followed by a post hoc test was used to compare infarction sizes. Categorical variables were analyzed using Fisher's exact test where appropriate. The null hypothesis was rejected at $P < 0.05$.

Results

The body weight was comparable across all groups (control: 3.9 ± 0.11 kg, rIPC: 3.6 ± 0.08 kg, APC: 3.6 ± 0.14 kg, rIPC+APC: 3.6 ± 0.07 kg, $P > 0.05$). Out of 28 hearts mounted on the Langendorff apparatus, four were excluded due to persistent ventricular fibrillation upon reperfusion (control: 2, rIPC: 1, APC: 1, $P > 0.05$).

Myocardial infarction size

The infarct size, corrected for weight, was assessed in different treatment groups following global ischemia and reperfusion using the Langendorff apparatus (Fig. 2A). This was determined through TTC staining and planimetry, depicted in Fig. 2B. Both rIPC and APC significantly reduced the size of myocardial infarction by more than 50% compared to the control group. However, combining rIPC and APC did not provide any additional protective effect (rIPC, $12.1 \pm 1.7\%$; APC, $13.5 \pm 2.1\%$; rIPC+APC, $14.4 \pm 3.3\%$; $P < 0.01$ compared to control, $31.3 \pm 3.0\%$). There was no significant difference in infarction size among the rIPC, APC, and rIPC+APC groups ($P > 0.05$).

Discussion

Key results

This study demonstrated that sevoflurane and rIPC are equally effective in reducing experimental myocardial damage. Additionally, when administered in combination, these interventions were neither synergistic nor adverse.

Interpretation/comparison with previous studies

It is well known that various inhaled halogenated anesthetic agents can induce a preconditioning-like effect, which has been demonstrated to reduce ischemic myocardial damage in experimental models [9] and in some clinical studies [10,11]. However, the temporal activity of APC varies among different anesthetics, and there are significant uncertainties in the existing literature regarding their activity and potency. In the first study to explore the potential differences among agents known to induce anesthetic preconditioning, halothane, isoflurane, desflurane, and sevoflurane were evaluated using an *in vivo* rabbit coronary ligation model [9].

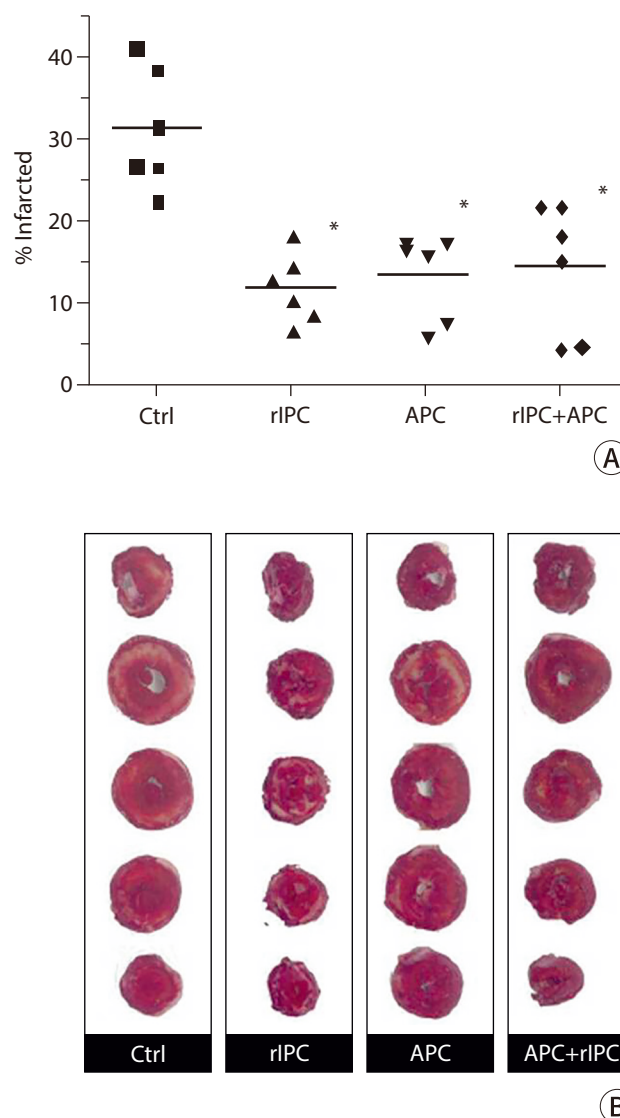


Fig. 2. Cardioprotective effects of rIPC or APC applied singly or in combination. (A) Scattergram displaying the percentage of infarct size (corrected for weight) for the control (filled rectangle), rIPC (filled triangle), APC (filled reversed triangle), and rIPC+APC (filled diamond) treatment groups. The horizontal bar represents the mean value for each group. * $P < 0.01$, indicating statistical significance compared to the control group (all groups, $n = 6$). (B) Representative images of heart slices from each treatment group, stained with TTC to highlight areas of infarction. rIPC, remote ischemic preconditioning; APC, anesthetic-induced preconditioning; TTC, 2, 3, 5-triphenyltetrazolium chloride.

The anesthetic protocol was consistent across all groups, involving a 30-minute administration of 1 minimum alveolar concentration (MAC) of each anesthetic, followed by a 15-minute washout period, and then a 30-minute period of circumflex coronary artery occlusion. Halothane, isoflurane, and desflurane were found to be protective, significantly reducing the size of subsequent infarcts. However, sevoflurane did not confer myocardial protection when administered according to their protocol. It has been proposed that the washout period may be a critical factor in the efficacy of sevoflurane in this model. In a previous study [12], administering 1 MAC of sevoflurane for 30 minutes immediately before ischemia reduced infarct size in dogs.

However, the same dosage followed by a 30-minute washout period did not yield a reduction in infarct size. Interestingly, introducing an additional 2 minutes of local ischemia during the 30-minute washout period led to a decrease in infarct size, with the level of cardioprotection being comparable to that achieved by sevoflurane alone, without a washout period.

The anesthetic protocol used in the current study differed somewhat from those in earlier studies. We administered a slightly higher dose of sevoflurane (2.5 vol% compared to 1 MAC=2.36 vol% in the canine studies mentioned previously) and induced infarction using a Langendorff model. Despite a washout period of 20 minutes, we successfully demonstrated significant myocardial protection, achieving an approximate 50% reduction in myocardial infarction compared to the control group.

The data on the clinical effectiveness of sevoflurane as a cardioprotective agent are somewhat contradictory. In 2007, Piriou et al. [13] investigated the effects of administering sevoflurane for 15 minutes before cardiopulmonary bypass in patients undergoing coronary artery surgery. This two-center study found no effect on postoperative troponin I levels compared to the control group. This contrasts with the findings of De Hert and colleagues, who reported cardioprotective properties of sevoflurane in patients undergoing similar surgeries [14,15]. In their studies, sevoflurane was administered throughout the cardiopulmonary bypass and appeared to provide a protective effect. However, the cardioprotective benefits were less certain when sevoflurane was administered only before the bypass or only after the completion of the coronary anastomosis.

rIPC is an emerging strategy to prevent myocardial damage during cardiac surgery. The effectiveness of local preconditioning of the heart and other organs has been recognized since it was first described by Murry in 1986 [1]. Although highly effective in experimental models, the requirement to induce ischemia in the target tissue or organ before intervention has limited its clinical use. Remote preconditioning, or "preconditioning at a distance," was initially described by Przyklenk in 1983 [3]. In the foundational study, preconditioning the territory of the circumflex coronary artery reduced myocardial infarction following prolonged ligation of the left anterior descending coronary artery. Later studies in rodents demonstrated that similar protection could be achieved by transient ischemia of more distant organs, such as the kidney or mesentery [7]. While remote preconditioning is as effective as local preconditioning, it has not been more clinically applicable than its local counterpart. However, transient limb ischemia as a stimulus for remote preconditioning of the heart shows greater potential. This straightforward technique, which employs a standard blood pressure cuff or tourniquet, has proven highly effective in animal models and, more recently, in clinical studies involving children and adults undergoing cardiovascular surgery [5]. Notably, in most published animal studies and in two of the three positive clinical studies, these effects were observed to be additive to those of inhalational halogenated anesthetics [5,16].

In our own randomized trial focusing on remote preconditioning in children undergoing cardiac surgery with cardiopulmonary bypass, sevoflurane was administered only during the induction of anesthesia. This was followed by a fentanyl infusion and the inhalation of isoflurane throughout the procedure [5]. Despite this regimen, remote preconditioning demonstrated additional benefits compared to the control group. Children who underwent remote preconditioning through transient limb ischemia before cardiopulmonary bypass exhibited decreased troponin release, lower inotrope scores, and enhanced lung function relative to controls. In a separate study involving adults scheduled for elective abdominal aortic aneurysm surgery, participants were randomized to undergo a single 10-minute episode of femoral artery occlusion prior to aortic cross-clamping

[16]. Although all patients received general anesthesia with inhaled desflurane for the duration of the operation, those in the preconditioned group experienced a highly significant reduction in the incidence of postoperative renal dysfunction and myocardial infarction.

Limitations

Our study was not designed to explore mechanistic differences in comparison to other studies; however, the marked variability in the effects of sevoflurane could stem from relatively minor methodological differences in experimental preparations.

Suggestion for further studies

Further studies are needed to determine if there is a dose-response effect for either intervention, whether used alone or in combination. However, we can confirm that there is no inhibitory effect of one intervention on the other when co-administered in this manner. This information will be valuable in designing future clinical studies that involve both techniques. Clearly, a more rigorous assessment of their relative potencies and potential interactions should be addressed in future experimental studies.

Conclusion

The previous clinical studies do not clarify whether the combination of inhaled anesthesia and remote preconditioning has an additive, neutral, or detrimental effect on optimal myocardial protection. Therefore, the current study is timely in assessing this potential interaction. The level of protection provided by sevoflurane was comparable to that achieved through remote preconditioning via transient limb ischemia. Notably, when both were administered together, the degree of protection remained unchanged.

ORCID

Seung-Hee Yoo: <https://orcid.org/0000-0002-6811-7198>

Sooyoung Cho: <https://orcid.org/0000-0002-0232-766X>

Jong Wha Lee: <https://orcid.org/0000-0003-3574-191X>

Authors' contributions

Project administration: Lee JW

Conceptualization: Yoo SH, Cho S, Lee JW

Methodology & data curation: Yoo SH, Cho S, Won Y, Lee JW

Funding acquisition: Not applicable

Writing – original draft: Yoo SH, Cho S, Lee JW

Writing – review & editing: Yoo SH, Cho S, Won Y, Lee JW

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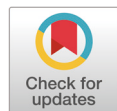
Supplementary materials

Not applicable.

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Early detection of patients with narcotic use disorder using a modified morphine equivalent daily dose score based on an analysis of real-world prescription patterns: a retrospective cohort study

Yi-Jun Kim^{1,2,*}, Kye Hwa Lee^{3,*}

¹Department of Environment Medicine, Ewha Womans University College of Medicine, Seoul, Korea

²Graduate Program in System Health Science and Engineering, Ewha Womans University College of Medicine, Seoul, Korea

³Department of Information Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

*These authors contributed equally to this work.

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Corresponding author

Yi-Jun Kim

Department of Environment Medicine,
Ewha Womans University College of
Medicine, 25, Magokdong-ro 2-gil,
Gangseo-gu, Seoul 07804, Korea
E-mail: yijunkim@ewha.ac.kr

Kye Hwa Lee

Department of Information Medicine,
Asan Medical Center, University of Ulsan
College of Medicine, 88 Olympic-ro 43-
gil, Songpa-gu, Seoul 05505, Korea
E-mail: eva@amc.seoul.kr

Keywords

Narcotic use disorder; Drug abuse
detection method; Overlapping MEDD;
MEDD ratio

Objectives: Addiction to prescription narcotics is a global issue, and detecting individuals with narcotic use disorder (NUD) at an early stage can help prevent narcotics misuse and abuse. We developed a novel index for the early detection of NUD based on an analysis of real-world prescription patterns in a large hospital.

Methods: We analyzed the narcotic prescriptions of 221,887 patients, prescribed by 8,737 doctors from July 2000 to June 2018. To facilitate the early detection of patients at risk of developing NUD after a prolonged period of narcotic use, we developed a weighted morphine equivalent daily dose (wt-MEDD) score. This score was based on the number of prescription dates where the actual MEDD exceeded the intended MEDD. We compared the performance of the wt-MEDD scoring system in identifying patients diagnosed with NUD by doctors against other high-risk NUD indices. These indices included the MEDD scoring system, the number of days on prescribed narcotics, the frequency and duration of prescriptions, narcotics prescriptions from multiple doctors, and the number of early narcotic refills.

Results: A wt-MEDD score cut-off value of 10.5 successfully identified all outliers and diagnosed patients with NUD with 100% sensitivity and 99.6% specificity. This score demonstrated the highest sensitivity and specificity for detecting NUD compared to all other indexes. The predictive performance was further improved by combining the wt-MEDD score with other high-risk NUD indexes.

Conclusion: We developed a novel index, the wt-MEDD score, which showed excellent performance in the early detection of NUD.

Introduction

Background/rationale

According to the 2020 World Drug Report [1], the number of deaths due to opioid overdose has increased by 2.5 times, rising from 18,515 in 2007 to approximately 47,000 in 2018. A significant

aspect of the current overdose crisis is the growing addiction to prescription narcotics [2]. Among patients prescribed narcotics for chronic pain, 21%–29% misuse them, and 8%–12% develop an addiction to these drugs [3]. In recent years, there has been a growing public awareness of the severity of addiction to prescription narcotics [4].

Narcotic abuse can be defined in various ways; for example, MedlinePlus defines prescription narcotic abuse as "taking medicine in a way that is different from what the doctor prescribed" [5]. The primary cause of narcotics abuse is often a strong desire to obtain more narcotics than those prescribed by doctors, driven by a "strong desire or urge to use the substance" [6]. To combat prescription narcotic use disorder (NUD), the Centers for Disease Control and Prevention (CDC) in the United States has issued guidelines for prescribing narcotics [7]. Most states now mandate the registration of narcotic users through prescription drug monitoring programs (PDMPs), which track narcotic prescriptions [8]. According to the CDC guidelines, prescribing a morphine milligram equivalent (MME) per day of ≥ 90 as the morphine equivalent daily dose (MEDD) should be minimized as much as possible [7]. Some studies have indicated that this system has decreased the prevalence of NUD and its sequelae [9,10], but a recent review has reported ambiguous results [11].

A limitation of the CDC guideline and PDMP is that they can only detect the risk of NUD, not NUD itself. Furthermore, the cut-off values for the NUD high-risk indexes are not definitive standards for identifying patients at risk of NUD. For instance, the MEDD restriction cut-off varies significantly between countries: it is 90 MME/day in the USA and 200 MME/day in Canada [12]. Although numerous studies have sought to develop tools to predict NUD, these tools primarily focus on analyzing high-risk factors rather than detecting NUD itself [13,14]. Therefore, there is a need to develop a method that can definitively identify abnormal prescription patterns indicative of NUD.

Hence, in this study, we developed a method to screen for patients with NUD by directly applying the definition of prescription narcotic abuse to analyze extensive real-world clinical data. Patients employing multiple strategies to obtain additional narcotics may have an actual MEDD that exceeds the doctor's intended MEDD due to overlapping prescriptions. To address this, we introduced a weighted (wt)-MEDD score. This score is calculated based on the number of prescription dates where the MEDD ratio ([actual MEDD]/[intended MEDD]) was above a certain level (for example, 1.5), suggesting the presence of NUD, as per the criteria for prescription narcotics abuse.

Objectives

We assessed the effectiveness of the wt-MEDD score in identifying patients diagnosed with NUD by physicians at an early stage of the narcotic prescription pathway, by comparing its performance to that of other narcotic prescription-related indices.

Methods

Ethics statement

This study received approval from the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 1806-182-955) and adhered to the ethical standards established in the 1964 Declaration of Helsinki. The requirement for informed consent was waived because the study was based on database analysis.

Study design

This retrospective cohort study employed real-world data to develop detection methods based on a defined criterion for narcotic abuse. The study adhered to the guidelines outlined in the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement, which can be accessed at: <https://www.strobe-statement.org/>.

Setting

This study evaluated the total narcotics prescriptions from July 2000 to June 2018 at a single large hospital. Prescriptions for patients with cancer and for inpatients were excluded from the analysis. The analysis focused on the following 12 narcotics: fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxycodone/naloxone, tapentadol, alfentanil, meperidine, remifentanyl, buprenorphine, and nalbuphine. Low-dose narcotics such as codeine and tramadol were excluded from the study.

Most patterns of NUD involve taking higher doses than those intended by doctors. The hypothesis was that a patient at risk of developing NUD would employ multiple strategies to achieve a higher MEDD, resulting in a discrepancy between the MEDD intended by the doctors and the overlapping MEDD that the patient achieves through these strategies. Consequently, the MEDD ratio is defined as follows (Fig. 1A):

$$\text{MEDD ratio} = \frac{\text{Overlapping MEDDs owing to multiple prescriptions on the intake date}}{\text{Maximum MEDD prescribed by a single doctor on the intake date}}$$

For example, doctor 1 prescribes 40 MEDD to patient A, deeming it an appropriate dosage. However, patient A subsequently visits Doctor 2 to obtain an additional prescription for narcotics. Unaware of the previous prescription from Doctor 1, Doctor 2 prescribes an additional 15 MEDD, considering it suitable for patient A. Later, patient A returns to doctor 2 before the scheduled follow-up, claiming to have lost the previous prescription, and receives another 15 MEDD. Consequently, patient A ends up receiving a total of 70 MEDD of narcotics, which is 1.75 times the highest intended dose of 40 MEDD prescribed by the doctors. The MEDD ratio, defined as the ratio between the actual MEDD received and the maximum intended MEDD prescribed by the doctors, is thus 1.75 in this scenario (Fig. 1A).

We defined the wt-MEDD score as follows (Fig. 1B):

$$\text{wt-MEDD score} = \text{Number of prescription dates with MEDD ratio} \geq 1.5$$

In Fig. 1, patient A consults doctor 1 on days 1, 6, and 11, and sees doctor 2 on days 1, 5, and 9. This results in a total of five prescription dates for patient A (days 1, 5, 6, 9, and 11). Out of these, the number of dates where the MEDD ratio is ≥ 1.5 amounts to four (day 5, 6, 9, and 11). The wt-MEDD score, which is defined as the number of prescription dates with a MEDD ratio of ≥ 1.5 , is therefore 4, as shown in Fig. 1B. If patient A persists in obtaining narcotics prescriptions from multiple doctors and visiting them earlier than scheduled, the wt-MEDD score will continue increasing.

The choice of a MEDD ratio of 1.5—higher than 1.0 but lower than 2.0—was made to accommodate minor discrepancies between the intended MEDD prescription by doctors and the actual MEDD, such as during initial dose adjustments at the start of narcotic prescriptions. This

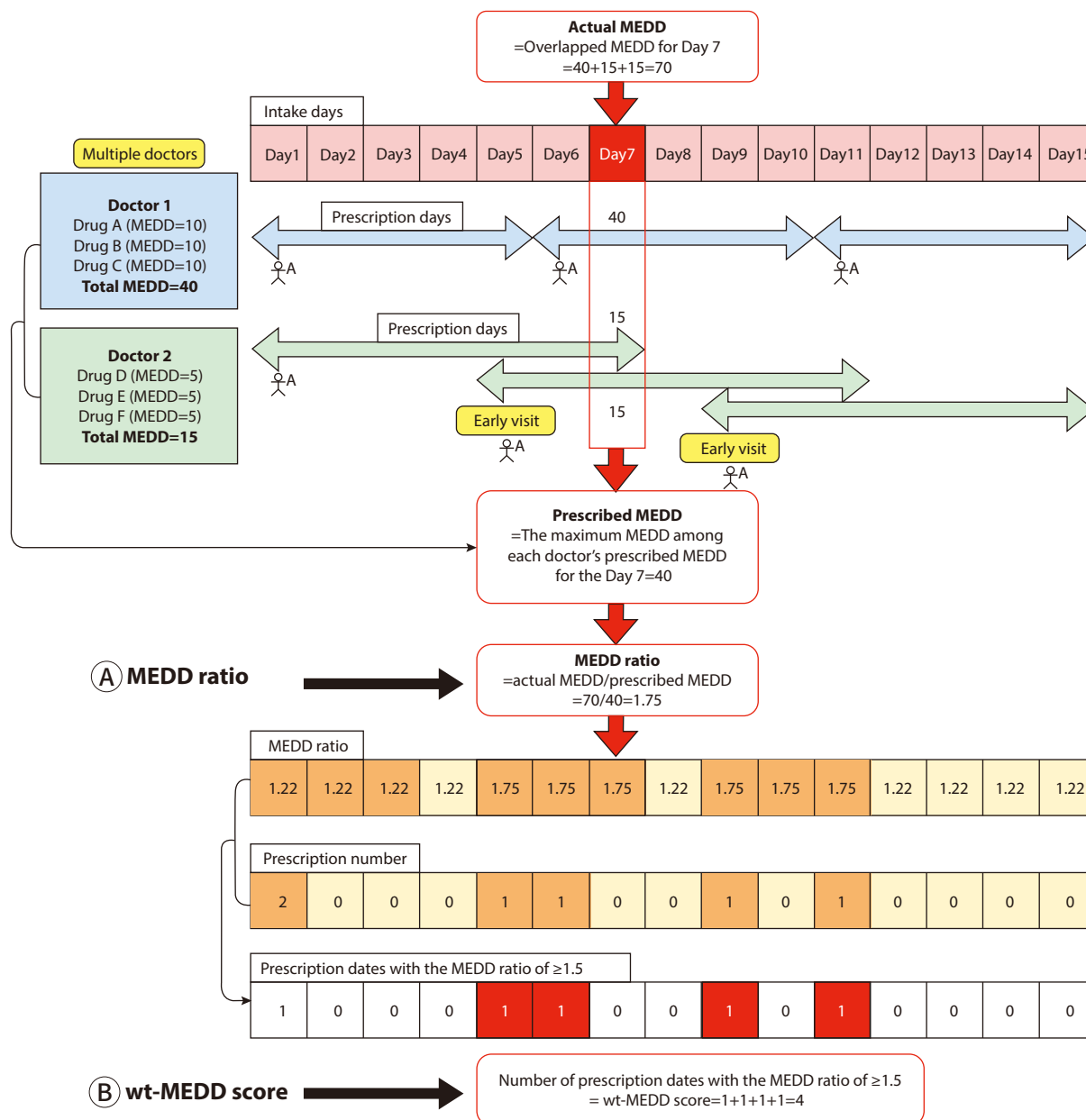


Fig. 1. Schematic diagram of the calculation of the weighted MEDD score. MEDD, morphine equivalent daily dose; wt-MEDD, weighted MEDD.

range also effectively identifies abnormal prescriptions that require further review. Ratios below 1.5 may be overly sensitive, failing to distinguish significant deviations between the actual and intended MEDD. Institutions can adjust the cut-off MEDD ratio based on their preferences, opting for less than 1.5 to increase sensitivity or more than 1.5 to increased specificity. The wt-MEDD score served as a proxy for NUD because repeated prescriptions with a high MEDD rate suggest that the patient is consistently receiving more narcotics than originally prescribed by the physician.

We investigated the clinical applicability of the wt-MEDD score, specifically to monitor abnormal narcotics prescription patterns in a hospital setting. It is necessary to identify both the doctors and patients involved in these practices and to provide them with feedback. To this end,

we utilized the wt-MEDD score to compile lists of doctors and patients associated with abnormal prescription patterns. We identified doctors with outlier wt-MEDD scores and similarly generated a list of patients exhibiting outlier scores to closely monitor their prescription behaviors. These individuals were characterized by a two-tailed P-value of <0.001 , corresponding to a Z score of ≥ 3.29 or ≤ -3.29 . We then extracted the lists of doctors and patients with these outlier wt-MEDD scores and determined the cut-off score for both groups to effectively monitor and address abnormal narcotics prescribing patterns.

Second, we examined whether the wt-MEDD score could be utilized to identify patients with NUD at an earlier stage. Our analysis focused on determining the optimal cut-off value of the wt-MEDD score for detecting patients diagnosed with NUD by physicians, aiming for the highest sensitivity and specificity. If the cut-off value demonstrated high sensitivity and specificity, and if it was reached before the doctors' diagnosis of NUD, it could serve as an early indicator for NUD detection. A list of patients diagnosed with NUD by doctors was extracted from the clinical data warehouse using the codes from the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10) and diagnostic terms in the doctors' medical chart. The accuracy of the NUD diagnoses was verified by ensuring that the chart records met the diagnostic criteria outlined in the DSM-IV-TR or DSM-V. We selected only those patients who had been repeatedly prescribed narcotics at our hospital prior to their NUD diagnosis. Patients diagnosed with NUD at other hospitals, who had little or no history of narcotics prescriptions at our facility, were excluded. Two physicians reviewed the electronic medical record charts to confirm the accuracy of the diagnoses (Fig. 2). Any prescriptions issued to these patients after their NUD diagnosis were omitted from the analysis.

We also analyzed the optimal cut-off values, sensitivity, and specificity of other high-risk NUD indexes (such as the PDMP monitoring categories) and their combinations to confirm the effectiveness of the wt-MEDD score. To determine whether the differences in sensitivity and specificity between the wt-MEDD score and other indexes were statistically significant, the McNemar test was performed.

We observed the time points at which the cut-off values of the wt-MEDD score and other NUD high-risk indexes were reached, as well as the time points at which NUD was diagnosed by a doctor in a patient case. This investigation aimed to determine whether the wt-MEDD score cut-off value could be used to identify NUD earlier. The paired t-test was employed to compare the mean time from the first prescription of narcotics to the point of reaching the wt-MEDD score cut-off value and the subsequent NUD diagnosis by doctors.

Participants

We analyzed the narcotic prescriptions of 221,887 patients, which were prescribed by 8,737 doctors from July 2000 to June 2018.

Variables (study outcomes)

Considering the definition of narcotic abuse and the conditions of PDMP monitoring, the wt-MEDD score and NUD high risk indexes (MEDD, prescription days, prescribing frequency and duration, number of prescribing doctors, and number of early receipt of narcotics before the scheduled visit) were selected for analysis.

Data sources

A clinical data warehouse is a near-real-time database that consolidates data from various

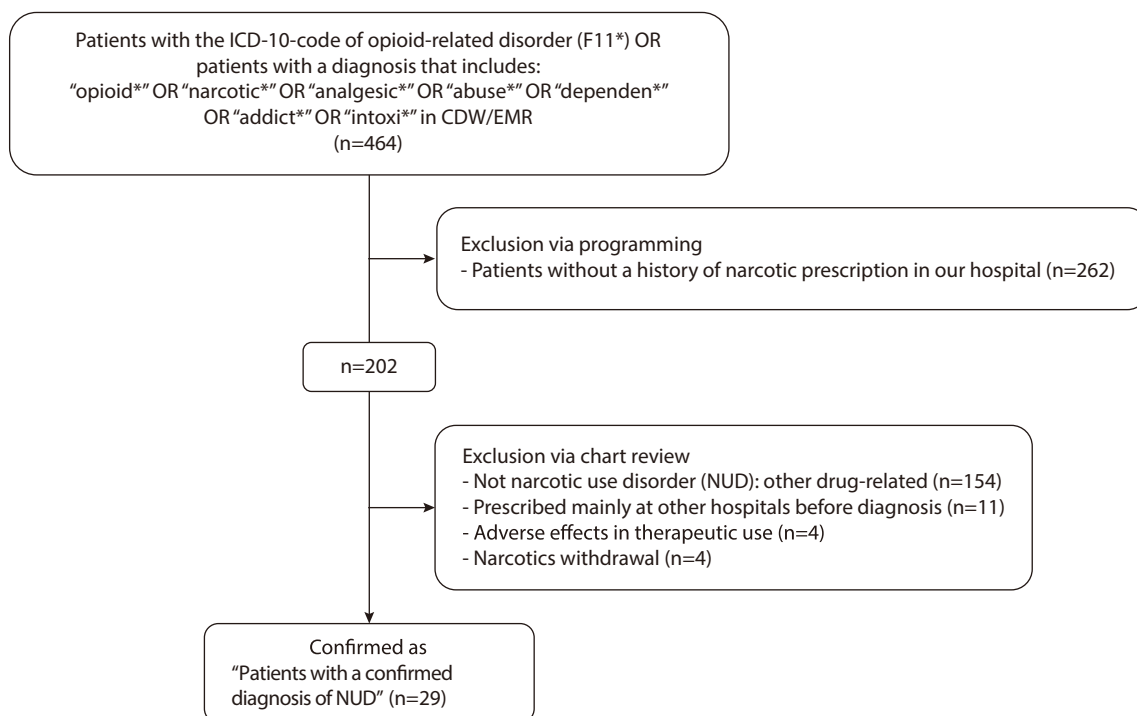


Fig. 2. Flowchart of patient screening and enrollment. ICD, International Classification of Diseases; CDW, clinical data warehouse; EMR, electronic medical records.

clinical sources. A web-based browser facilitated the extraction of a list of patients who met the inclusion criteria, along with their corresponding electronic medical records. Information regarding the prescribed patients was downloaded from the clinical data warehouse into five tables: basic information, narcotic prescription, admission, surgery, and diagnosis records.

Measurements

We calculated the activity of each narcotic based on its mode of administration—tablet, patch, or injection. The table included information on the MME conversion factor, derived from PDMP supplements [15]. The MEDD is calculated by multiplying the MME conversion factor by the daily dose. When MME conversion factor information for a specific drug was not available, we estimated it from the relevant literature [16].

Among the five types of downloaded tables, the narcotic prescription table included information such as the name of the prescribed drug, the date of prescription, the number of days prescribed, and the MEDD (Supplement 1). To calculate the overlapping MEDD for a specific intake date, a new table was created. This table transformed each intake date for a patient into individual rows—not just the prescription dates—by reformatting the data from the prescription table (Supplement 2).

A 3-month interval was established as the measurement period for the time-series analysis, specifically January-March, April-June, July-September, and October-December. The total number of prescriptions issued during each 3-month period was calculated. To analyze temporal changes in MEDD per patient, the highest MEDD recorded in each 3-month interval was identified and compared with the highest MEDDs from the other intervals.

Bias

All target participants were included in this study; therefore, there was no participant bias.

Study size

Sample size estimation was not performed because this study included all target participants.

Statistical methods

R (R Foundation for Statistical Computing, Vienna, Austria; URL: <http://www.R-project.org/>, ver. 3.6.0) and RStudio (RStudio, Boston, MA, USA; URL: <http://www.rstudio.com/>, ver. 1.2.1335) were used for statistical analyses. The ‘dplyr’ package in R was used to analyze data, and the ‘ggplot2’ package was used to generate graphs. Outlier analysis was performed using the ‘outliers’ package. Cut-off value, sensitivity, specificity, and accuracy were calculated using the ‘pROC’ package. A two-tailed P-value of less than 0.05 was considered statistically significant.

Results

Patient and doctor outliers of the weighted morphine equivalent daily dose score

This study included 221,887 patients who received prescriptions for narcotics, written by 8,737 doctors, totaling 555,097 narcotic prescriptions. Upon reviewing the records of 464 patients diagnosed with NUD in the CDM, only 29 were confirmed to have NUD following repeated narcotic prescriptions at our hospital. The majority of patients were diagnosed with NUD at other hospitals before being transferred to our facility (Fig. 2).

The cut-off wt-MEDD score for patient outliers (n=996) was 10.5 (P<0.001). The list of doctor outliers (n=23) for the wt-MEDD score can be found in Supplement 3 and Fig. 3. This list, which included both doctors and patients, was extracted and provided to the hospital committee to monitor prescription abnormalities and offer feedback to the involved doctors.

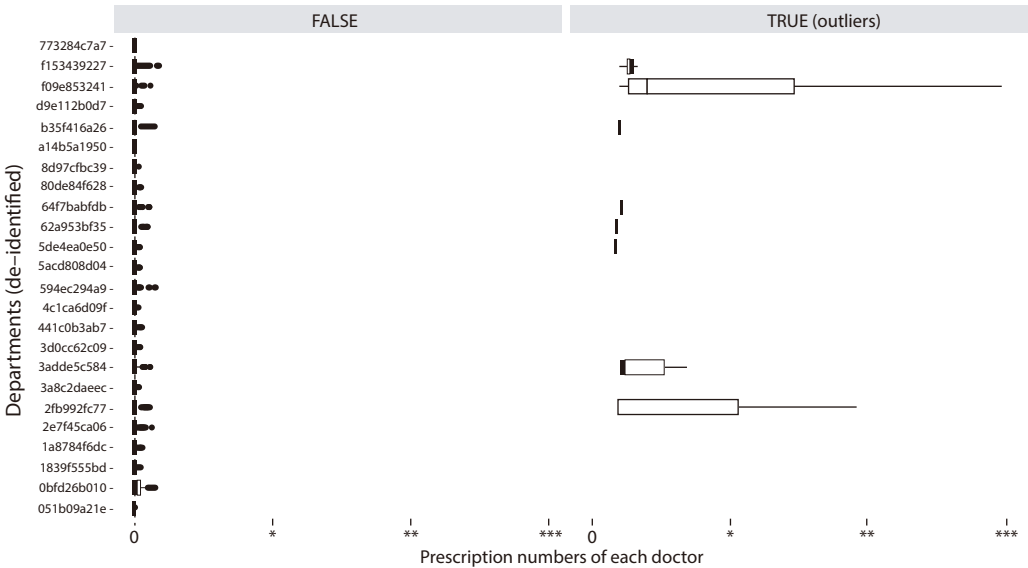


Fig. 3. Outlier doctors for the weighted morphine equivalent daily dose score in various departments.

Comparison of the weighted morphine equivalent daily dose score and narcotic use disorder high risk indexes in detecting diagnosed cases of narcotic use disorder

Table 1 compares the wt-MEDD scoring system with NUD high-risk indexes for detecting diagnosed NUD. The optimal cut-off value for the wt-MEDD score, which demonstrated the highest sensitivity and specificity, was ≥ 10.5 . This value was similar to the cut-off for outlier wt-MEDD scores ($P < 0.001$). The median wt-MEDD score among the 29 patients diagnosed with NUD was 52 (25th–75th quartiles = 25–115), indicating that most patients with NUD had multiple prescriptions with a high MEDD ratio, exceeding the intended prescription level. When compared to other NUD high-risk indexes, the wt-MEDD score exhibited the highest sensitivity and specificity (100.0% and 99.6%, respectively; Table 1). The McNemar test revealed that the sensitivity and specificity of the wt-MEDD score were significantly superior to those of other indexes ($P < 0.001$), with the exception of two indexes: the quarterly number with a doctor number of ≥ 4 and the number of prescriptions ≥ 10 days earlier than the scheduled visit (Table 1).

To improve the ability to detect NUD, we combined the NUD high-risk indexes with the wt-MEDD score and assessed their sensitivity and specificity. A combined model that included the highest overlapping MEDD, total number of prescriptions, and total number of doctors (triple-test) demonstrated excellent sensitivity and specificity, at 96.6% and 99.5% respectively. When the wt-MEDD score was used in conjunction with the triple-test, the sensitivity and specificity further improved to 96.6% and 99.7%, respectively. These results suggest that the wt-MEDD score, when combined with other NUD high-risk indexes, is effective for screening patients with NUD (Table 1).

Comparison of time points of reaching the weighted morphine equivalent daily dose score cut-off value and that of the narcotic use disorder diagnosis

In all 29 patients diagnosed with NUD, the time point at which the wt-MEDD cut-off score was reached occurred earlier than the time point of the doctor's initial diagnosis of NUD. The average time to reach the wt-MEDD cut-off score was 1,024 days (median [quartile 1–quartile 3], 361 [192–2,323]) from the first narcotics prescription. In contrast, the average time until NUD diagnosis was 2,578 days (median [quartile 1–quartile 3], 2,342 [1,396–4,030]). This resulted in an average difference of 1,554 days (95% CI, 1,096–2,010 days, paired t-test, $P < 0.001$).

Patient case report

To provide an example of the clinical application of the new methodology (wt-MEDD score) in identifying cases of NUD, we selected a patient diagnosed with NUD who employed multiple strategies to obtain a higher number of narcotics prescriptions. We retrospectively observed the time-sequential changes in the wt-MEDD score and the NUD high-risk indexes for this patient up until the NUD diagnosis was made (Fig. 4). Fig. 4A demonstrates a gradual increase in the patient's wt-MEDD score over time. Initially, the score was 10 in November 2011, and the patient received a diagnosis of NUD in October 2017. If the wt-MEDD score had been utilized as a screening tool for this patient, it could have potentially led to a diagnosis of NUD 6 years earlier.

The difference between the actual MEDD and the intended MEDD (MEDD ratio) continued to increase until the diagnosis of NUD was made (Fig. 4B). Concurrently, the number of prescription days (mean, minimum, and maximum) showed an increase just prior to the rise in the MEDD ratio (Fig. 4C). Similarly, the patterns of increase in the number of prescriptions (Fig. 4D), the number of prescribing doctors per 3-month period (Fig. 4E), and the instances of early receipt of narcotics for more than 7 days (Fig. 4F) mirrored the trend observed in the MEDD ratio. These

Table 1. Comparison of the performance of various indices for detecting patients diagnosed with NUD

Indexes	Cut-off	Sensitivity (%)	Specificity (%)	Accuracy (%)	McNemar's P-value
MEDD					
wt-MEDD score (*)	10.5	100.0	99.6	99.6	Reference
Highest overlapping MEDD (1)	52.25	100.0	95.6	95.6	<0.001
Number of prescriptions with intended MEDD ≥ 50	10.5	93.1	99.3	99.3	<0.001
Number of prescriptions with intended MEDD ≥ 90	6.5	93.1	99.0	99.0	<0.001
Frequency & duration					
Total prescription number (2)	15.5	100.0	98.8	98.8	<0.001
Total number of quarter	5.5	89.7	98.4	98.4	<0.001
Highest prescription number per quarter ¹⁾ for all prescription periods	4.5	100.0	97.1	97.1	<0.001
Prescription day					
Number of prescriptions with ≥ 14 prescription days at once	11.5	89.7	99.5	99.5	<0.001
≥ 30 days at once (3)	0.5	62.1	98.3	98.3	<0.001
≥ 60 days at once	1.5	27.6	99.7	99.7	<0.001
≥ 90 days at once	3.5	13.8	100.0	99.9	<0.001
Number of doctors					
Total number of doctors (4)	6.5	96.6	98.7	98.7	<0.001
Quarterly number with doctor number of ≥ 4	0.5	93.1	98.3	98.3	0.107
Highest number of doctors per quarter ¹⁾ for all prescription periods	2.5	96.6	96.3	96.3	<0.001
Early prescription					
Number of prescriptions ≥ 1 day earlier than the scheduled visit	1.5	93.1	99.1	99.1	<0.001
≥ 2 days earlier	0.5	89.7	98.6	98.6	<0.001
≥ 3 days earlier	0.5	89.7	98.8	98.8	<0.001
≥ 4 days earlier	1.5	86.2	99.5	99.5	<0.001
≥ 5 days earlier	1.5	86.2	99.5	99.5	<0.001
≥ 6 days earlier	1.5	86.2	99.6	99.6	<0.001
≥ 7 days earlier (5)	0.5	86.2	99.1	99.1	<0.001
≥ 10 days earlier	1.5	82.8	99.7	99.7	0.548
≥ 14 days earlier	0.5	82.8	99.5	99.5	<0.001
Combination of methods					
(1) $\cap$ (2) $\cap$ (4) (triple-test)		96.6	99.5	99.5	<0.001
(1) $\cap$ (2) $\cap$ (3) $\cap$ (4)		58.6	99.8	99.8	<0.001
(1) $\cap$ (2) $\cap$ (3) $\cap$ (5)		82.8	99.8	99.8	<0.001
(1) $\cap$ (2) $\cap$ (3) $\cap$ (4) $\cap$ (5)		58.6	99.9	99.9	<0.001
((1) $\cap$ (2) $\cap$ (3) $\cap$ (4)) $\cup$ ((1) $\cap$ (2) $\cap$ (3) $\cap$ (5))		82.8	99.8	99.8	<0.001
(1) $\cap$ (2) $\cap$ (4) $\cap$ (*)		96.6	99.7	99.7	<0.001
(1) $\cap$ (2) $\cap$ (3) $\cap$ (4) $\cap$ (*)		58.6	99.9	99.9	<0.001
(1) $\cap$ (2) $\cap$ (3) $\cap$ (5) $\cap$ (*)		82.8	99.8	99.8	<0.001
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((1) $\cap$ (2) $\cap$ (3) $\cap$ (4)) $\cup$ ((1) $\cap$ (2) $\cap$ (3) $\cap$ (5))) $\cap$ (*)		82.8	99.8	99.8	<0.001

NUD, narcotic use disorder; MEDD, morphine equivalent daily dose; wt-MEDD, weighted MEDD.

¹⁾ Quarters were defined as Jan-Mar, Apr-Jun, Jul-Sep, and Oct-Dec.

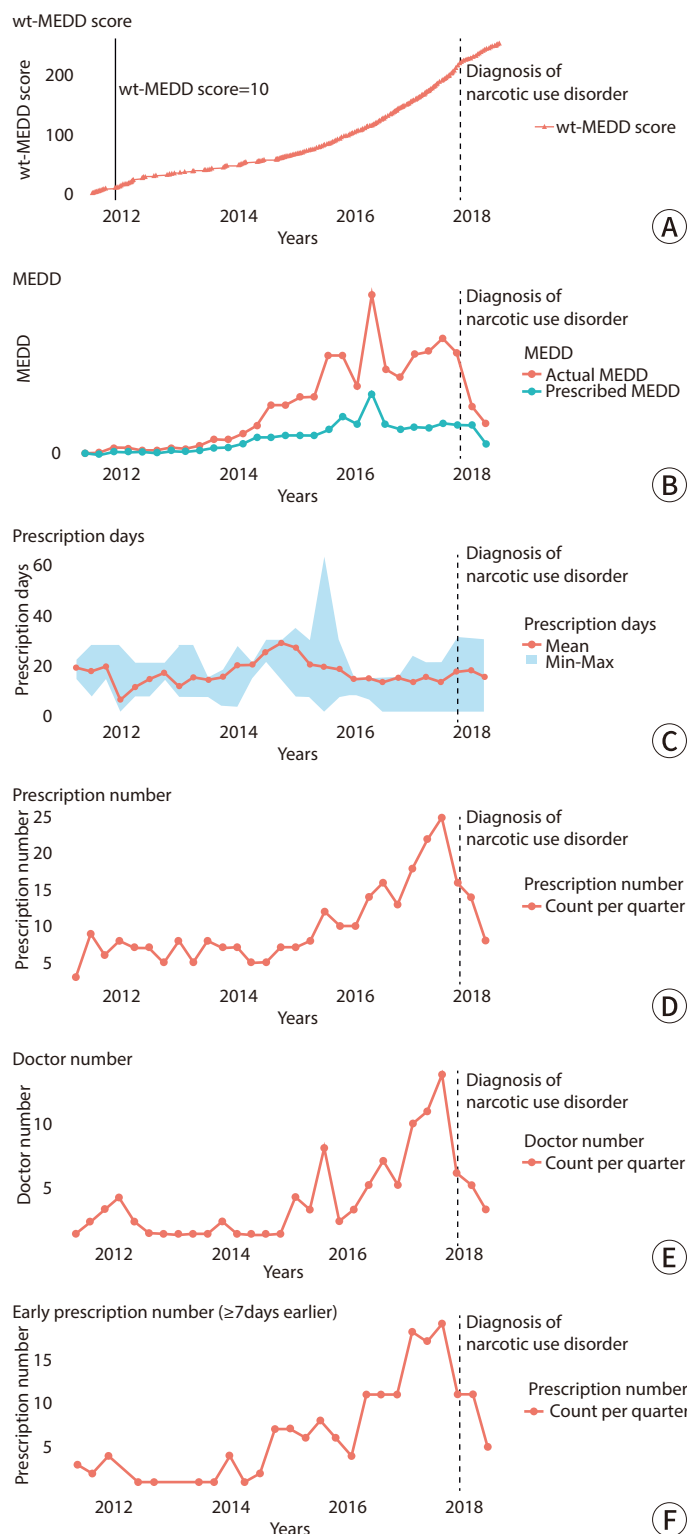


Fig. 4. Temporal changes in various NUD high risk indices for patients diagnosed with NUD. (A) wt-MEDD, (B) highest actual and intended MEDD every 3 months, (C) highest prescription days every 3 months, (D) total number of prescriptions every 3 months, (E) total number of prescribing doctors every 3 months, (F) number of early receipt of narcotics before ≥ 7 days for every 3 months. MEDD, morphine equivalent; wt-MEDD, weighted MEDD; NUD, narcotic use disorder.

findings suggest that employing multiple strategies can elevate the MEDD ratio, potentially leading to a diagnosis of NUD. Despite the use of various strategies to obtain more narcotics, it is possible to effectively screen for NUD at an early prescription stage using only the wt-MEDD score, without the need for multiple indicators.

Discussion

Key results

The wt-MEDD score demonstrated remarkable effectiveness in identifying early patterns of narcotic prescriptions in patients who were later diagnosed with NUD. This score reflects the number of prescription dates with a high MEDD ratio. A wt-MEDD score greater than 10.5 marked patients as significant outliers, aligning with the optimal cut-off value used by physicians to detect NUD. With a sensitivity of 100% and a specificity of 99.6%, a wt-MEDD score of 10.5 proved highly effective in identifying patients diagnosed with NUD. These results indicate that a wt-MEDD score of 10.5 could serve as a screening tool to detect patients with NUD, particularly those engaging in behaviors like "doctor shopping" to obtain excessive amounts of narcotics.

Interpretation

Our hospital undertook an analysis of abnormal patterns in narcotic prescriptions to prevent NUD in patients by providing feedback to prescribing doctors. Initially, we consulted the CDC guideline [7], which proved both reasonable and useful, as evidenced by its alignment with the optimal cut-off values identified in our study for detecting patients with NUD. However, adherence to the CDC guideline alone was insufficient for categorizing a patient with NUD. To provide prescribing doctors with clearer information reflective of NUD, we took into account scenarios that could be problematic without exception. For instance, a patient receiving high doses of narcotics inconsistent with the prescribing doctor's intentions was identified as a problematic situation and thus was considered appropriate for defining NUD.

Comparison with previous studies

In the United States, the PDMP system automatically calculates the MEDD for prescribed narcotics. It provides the total MEDD for multiple prescriptions on the date they are issued; however, it does not calculate the overlapping MEDD that results from multiple prescriptions on a specific intake date [17]. Although the Ohio Automated Rx Reporting System displays daily MME for prescribers, this information is not stored, making it challenging to reconstruct later [17]. Previous studies have examined overlapping prescriptions, focusing either on concurrent benzodiazepine and narcotic prescriptions [18] or on overlapping prescriptions without considering the overlapping MEDD [19]. To our knowledge, this study is the first to evaluate the wt-MEDD score, which is based on the number of days with a high MEDD ratio, as a tool for identifying abnormal prescription patterns.

The wt-MEDD score is effective in identifying abnormal prescriptions, irrespective of the methods patients employ to obtain more narcotics. Additionally, a graph depicting the MEDD ratio over time can be made available for each patient in the outpatient clinic. The capability to quickly observe temporal changes through the graph can significantly reduce the time required to detect unusual prescription patterns.

An opioid-risk tool, previously reported and based on fixed patient characteristics such as a history of alcoholism, has been shown to have a primary prevention effect on NUD [20].

However, it does not contribute to secondary prevention. In contrast, monitoring the wt-MEDD score facilitates screening prior to an increase in the number of abnormal prescriptions.

Limitations

Calculating the wt-MEDD score based on overlapping MEDD could lead to an increase in data volume, as each intake date—rather than just the prescription date—adds an additional row to the table. In our study, the data size for tables based on each intake date was five times larger than those based on each prescription date. However, limiting the analysis to patients who have been prescribed narcotics, rather than including all hospital patients, could alleviate the burden of data analysis. Additionally, our study only included a small number of patients diagnosed with NUD, possibly due to physicians' reluctance to diagnose NUD. This issue is particularly acute for patients who have received narcotics prescriptions from more than one department, where cross-departmental liability issues may complicate the diagnosis of NUD. Consequently, there could be a larger number of undiagnosed NUD cases, especially among those categorized as wt-MEDD outliers. Moreover, our analysis did not include narcotic prescriptions for cancer patients, inpatients, or those receiving relatively low doses of narcotics such as codeine and tramadol. These groups are expected to be analyzed using different criteria. This study was retrospective, suggesting that a prospective trial might be necessary to determine if monitoring the wt-MEDD score can reduce the incidence of NUD. Additionally, since our study population was limited to a single hospital, it did not account for narcotics prescribed to patients at other facilities. Given that patients with NUD are likely to receive narcotics prescriptions from multiple hospitals, an integrated system to monitor narcotic prescriptions nationwide becomes essential. In the United States, for example, the PDMP manages all narcotic prescriptions at the state level [21]. However, the variation in narcotic policies between different hospitals and countries could complicate such analysis [22]. Nonetheless, if the system can effectively detect NUD through hospital prescriptions, a method for confirming the wt-MEDD score might prove universally beneficial.

Conclusion

We defined the wt-MEDD score as the number of prescription days with a high MEDD ratio, based on the definition of narcotic abuse. The wt-MEDD score identified patients diagnosed with NUD with greater sensitivity and specificity than other metrics. Therefore, monitoring the wt-MEDD score could enable early interventions for irregular narcotics prescription patterns by doctors and help prevent the development of NUD in patients.

ORCID

Yi-Jun Kim: <https://orcid.org/0000-0002-1763-4267>

Kye Hwa Lee: <https://orcid.org/0000-0002-7593-7020>

Authors' contributions

Project administration: Kim YJ

Conceptualization: Kim YJ

Methodology & data curation: Kim YJ, Lee KH

Funding acquisition: Kim YJ

Writing – original draft: Kim YJ

Writing – review & editing: Kim YJ, Lee KH

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Research data and R code is available upon request to the corresponding author. Please contact them for collaborative studies.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary materials are available from: <https://doi.org/10.12771/emj.2024.e63>.

Supplement 1. Structure of a part of the narcotic prescription table

Supplement 2. Structure of a part of the modified narcotics prescription table according to each intake date to calculate overlapping MEDD

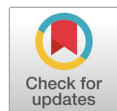
Supplement 3. Partial list of doctor outliers of the wt-MEDD score

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Reduced cardiovascular events through dynamic lifestyle modification in individuals with prediabetes or prehypertension in Korea: a nationwide cohort study

Yeji Kim^{1,*}, Shinjeong Song^{2,*}, Chang Mo Moon³, Hye Ah Lee⁴, Junbeom Park²

¹Department of Cardiology, Korea University Anam Hospital, Seoul, Korea

²Department of Cardiology, Ewha Womans University Medical Center, Seoul, Korea

³Department of Gastroenterology, Ewha Womans University Medical Center, Seoul, Korea

⁴Clinical Trial Center, Ewha Womans University Medical Center, Seoul, Korea

*These authors contributed equally to this work.

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Corresponding author

Hye Ah Lee
Clinical Trial Center, Ewha Womans University Medical Center, 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
E-mail: khyeah@ewha.ac.kr

Junbeom Park
Department of Cardiology, Ewha Womans University Medical Center, 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
E-mail: parkjb@ewha.ac.kr

Keywords

National health programs; Prediabetic state; Prehypertension; Lifestyle; Republic of Korea

Objectives: There is limited knowledge regarding the impact of lifestyle changes on cardiovascular events and mortality among individuals with prehypertension or prediabetes.

Methods: This was a serial retrospective cohort study utilizing data from the Korean National Health Insurance Service Health Screening Cohort. The primary outcome considered in the study was major adverse cardiovascular events (MACE).

Results: A higher risk of MACE was found in men with prehypertension whose unhealthy lifestyle deteriorated (hazard ratio [HR], 1.13; 95% CI, 1.04–1.23; $P=0.004$), those who gained weight (HR, 1.15; 95% CI, 1.03–1.28; $P=0.010$), and those who began smoking (HR, 1.34; 95% CI, 1.17–1.55; $P<0.001$). Conversely, a reduced risk of MACE was observed in men with prehypertension who improved their unhealthy lifestyle, quit smoking, reduced alcohol consumption, or increased the frequency of physical activity. In men with prediabetes, the risk of MACE was higher in those whose unhealthy lifestyle worsened (HR, 1.23; 95% CI, 1.12–1.35; $P<0.001$), those who gained weight (HR, 1.19; 95% CI, 1.06–1.33; $P=0.003$), those who started smoking (HR, 1.41; 95% CI, 1.22–1.64; $P<0.001$), and those who decreased their physical activity frequency (HR, 1.21; 95% CI, 1.09–1.35; $P<0.001$).

Conclusion: Preventive lifestyle changes reduce cardiovascular events and mortality, particularly in men at risk of developing hypertension or type 2 diabetes.

Introduction

Background

Hypertension and type 2 diabetes (T2D) are well-known cardiovascular risk factors. Additionally, obesity, smoking, alcohol consumption, and decreased physical activity are established risk factors associated with hypertension or T2D [1,2]. Previous studies have highlighted that lifestyle modifications can significantly reduce mortality risks in patients with hypertension or T2D [3,4]. However, once patients are diagnosed with hypertension or diabetes, they often begin treatment

with medication, which means that analyses on the effect of lifestyle modifications are very limited. Previous research has primarily focused on how one specific lifestyle change affects hypertension or T2D. Moreover, studies examining whether lifestyle modifications have a similar clinical effect on cardiovascular events or mortality in the prehypertension or prediabetes stages are somewhat scarce. For example, a weight loss of approximately 10 kg may reduce systolic blood pressure by between 5 and 20 mmHg [5]. Alcohol consumption is directly correlated with elevated blood pressure; thus, reducing alcohol intake is associated with lower blood pressure [6]. However, regardless of weight loss, engaging in at least 150 minutes of physical activity per week has been shown to reduce the incidence of T2D by 44% [7]. Furthermore, there are correlations among certain lifestyles, suggesting that individuals who engage in intensive exercise may be more inclined to quit smoking or drinking. Therefore, it is necessary to dynamically analyze the changes in various types of lifestyle modifications rather than focusing on a single type. Furthermore, lifestyle habits such as smoking, drinking, and exercise are influenced by gender. Typically, men are more likely to smoke and drink, leading to the hypothesis that the impact of rigorous management of unhealthy lifestyles on the occurrence of cardiovascular events varies between genders. The frequency and intensity of exercise also differ by gender.

Objectives

Thus, the present study investigated (1) how dynamic changes in lifestyle can affect cardiovascular events; (2) how various lifestyles change organically; (3) whether gender-specific lifestyle changes can affect the occurrence of cardiovascular events, specifically in relation to prehypertension or prediabetes.

Methods

Ethics statement

The Institutional Review Board (IRB) at Ewha Womans Medical College Mokdong Hospital (IRB no. EUMC-2021-11-029) and the NHIS Big Data Steering Department (NHIS-2022-2-197) granted approval for this study. As the NHIS data used were completely anonymous and handled in accordance with the Personal Data Protection Act, obtaining written consent from subjects was not required.

Study design

This is a nationwide, population-based cohort study. It has been described in accordance with the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) statement, which is available at: <https://www.strobe-statement.org/>.

Setting

In December 2022, the authors conducted a search on prediabetes and prehypertension within the National Health Insurance Service–Health Screening Cohort (NHIS-HEALS) database. Prediabetes is defined by the presence of impaired fasting glucose, impaired glucose tolerance, or a hemoglobin A1c level of 5.7%–6.4%, while prehypertension is characterized by a systolic pressure of 120 to 139 mmHg or a diastolic pressure of 80 to 89 mmHg at the initial health screening. The NHIS-HEALS database was established from a cohort of 514,866 Koreans, aged 40 to 79 in 2002, who were randomly selected to represent 10% of the national health screening subjects from 2002 to 2003.

Data source and study cohort

The source of data for this study was the Korean NHIS-HEALS, which is a nationwide population-based cohort. Detailed information on the cohort has already been published elsewhere [8]. Additional details on the study cohort can be found in the Supplement 1.

Participants (study population)

For this study, we constructed a sub-cohort based on the research hypothesis. Initially, we excluded subjects with inconsistent examination dates, resulting in a cohort of 514,795 individuals who had undergone at least one health screening between 2002 and 2003. Of these, 334,937 subjects who also participated in a health screening during the second period (2004–2005) were included. We designated the date of the second health screening as the index date (Fig. 1C). Subsequently, we excluded individuals with a history of specific conditions prior to the index date, as defined by the International Classification of Diseases, Tenth Revision (ICD-10): heart failure (ICD-10: I50, n=668); cerebrovascular accident (I60–I69, n=13,187); cardiovascular

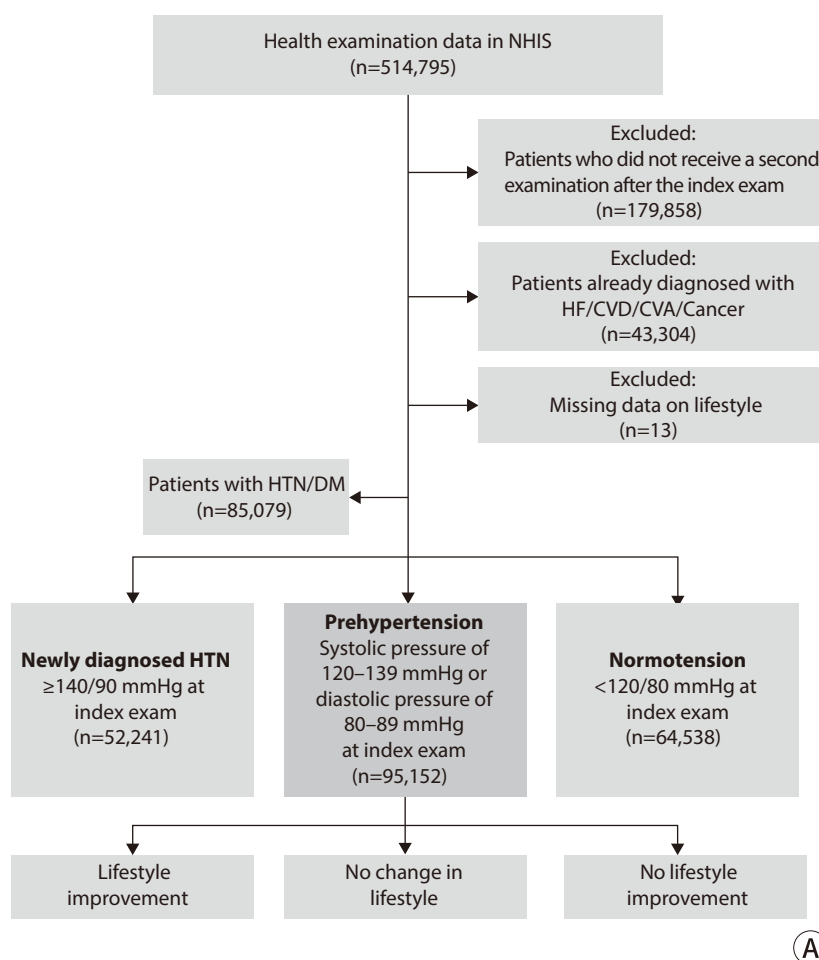
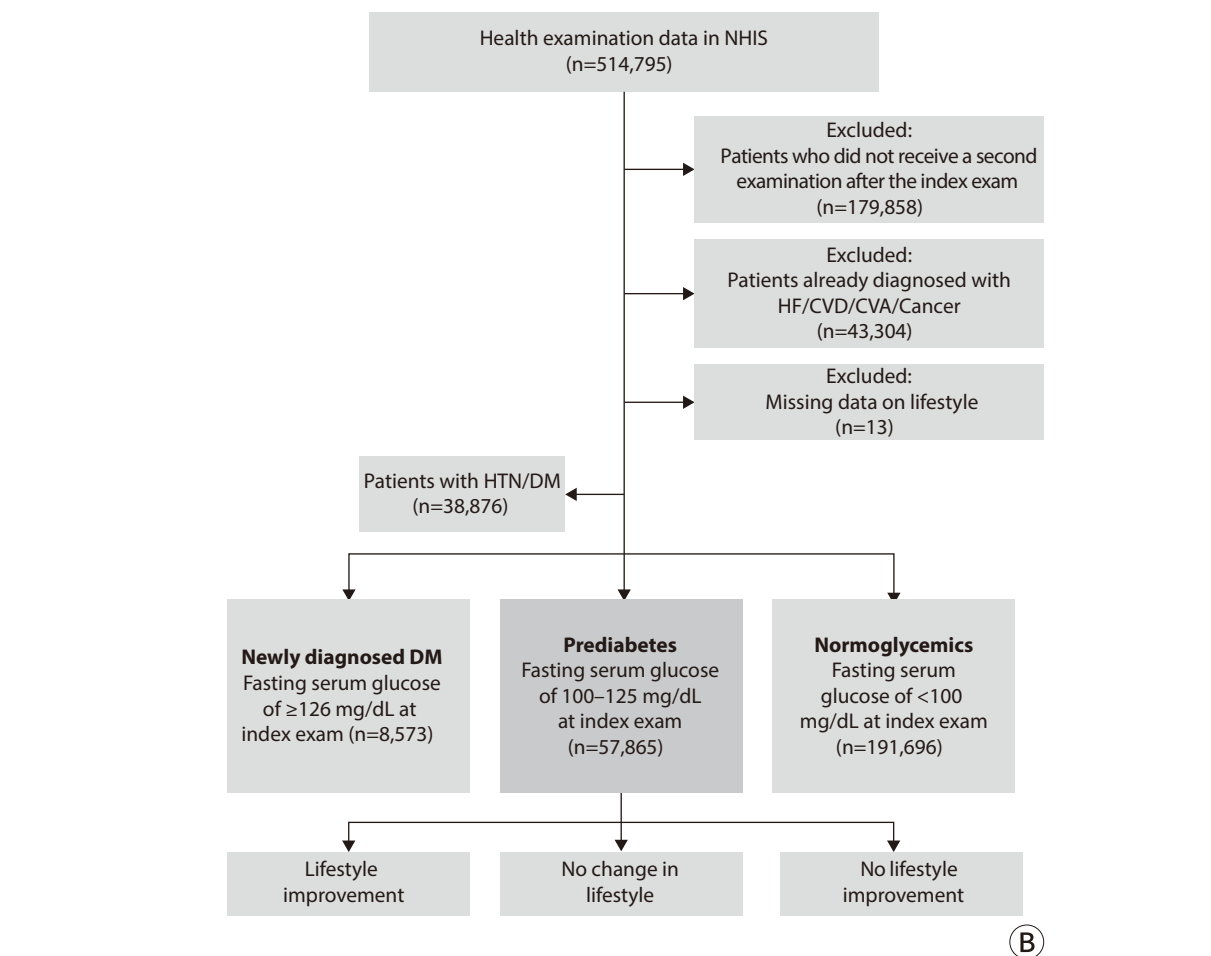


Fig. 1. Flow diagram of selection of the study population from the National Health Insurance Service database. (A) Prehypertension subgroup; (B) prediabetes subgroup; (C) overall schema of the study. NHIS, National Health Insurance Service; HF, heart failure; CVD, cardiovascular disease; CVA, cerebrovascular accident; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index.



Lifestyle (smoking, alcohol, physical activity, and BMI) change over 2 years

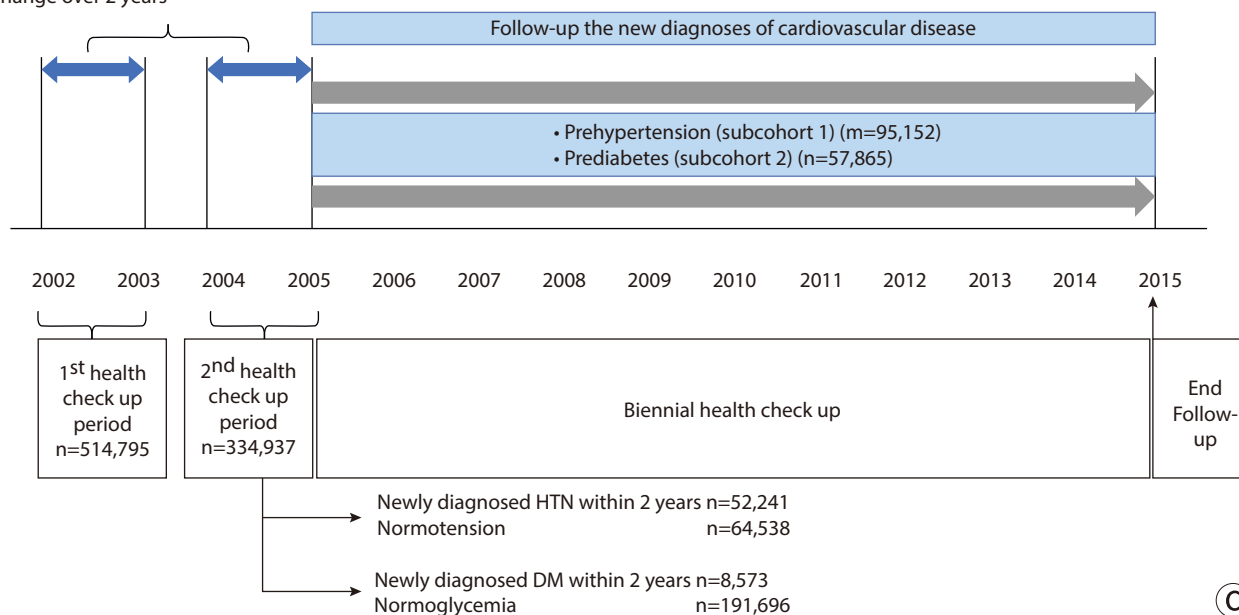


Fig. 1. Continued.

disease (CVD; I20–I25, I71, I72, $n=25,528$); or cancer (C00–C96, $n=3,921$). Additionally, we excluded individuals with missing lifestyle-related data ($n=13$; $n=297,010$).

Next, we defined cohorts for prediabetes and prehypertension. Detailed criteria used to define these cohorts are available in the Supplement 1. The prehypertension cohort included 95,152 subjects (60,084 men and 35,068 women), while the prediabetes cohort comprised 57,865 subjects (37,836 men and 20,029 women). The flow diagram illustrating the selection of the study population is displayed in Fig. 1A, B.

Outcome variables

The primary outcome of the study was major adverse cardiovascular events (MACE), which were defined as death, non-fatal myocardial infarction (MI), or non-fatal stroke resulting from CVD. Hospital admission data were used to identify instances of CVD, including MI (ICD-10: I21), stroke (ICD-10: I60–I69), and cardiovascular death (I20–I25, I71–I72, and I60–I69). The secondary outcome of the study was all-cause mortality. The date of death was obtained from the claims database, and this information was used to determine all-cause mortality. The follow-up period began on the index date and concluded either on the date of the first occurrence of the primary outcome or on the last follow-up date (12/31/2015).

Measurement (assessment of lifestyle changes)

Regarding lifestyle factors, we considered body mass index (BMI), current smoking status, alcohol intake categorized by weekly frequency (never; 2–3 times a month; 1–2 times a week; 3–4 times a week; ≥ 5 times a week), and physical activity also categorized by weekly frequency (never; 1–2 times a week; 3–4 times a week; 5–6 times a week; every day). Changes in these lifestyle factors were assessed using health checkup data from the first observation period (2002–2003) to the second (2004–2005) as shown in Fig. 1C. Detailed methods for evaluating changes in lifestyle factors are available in the Supplement 1.

Study size

A sample size estimation was not performed, as all target subjects were included.

Bias

Since subjects were selected from the cohort database according to the inclusion criteria and disease criteria, selection bias was not a concern.

Statistical analysis

Summary statistics for baseline characteristics were presented as means with SDs for numerical data and as counts with percentages for categorical data. To explore the impact of disease incidence and lifestyle behaviors according to gender, we performed gender-stratified analyses. The incidence rate (per 10,000 person-years) of outcomes was estimated using a Poisson regression model. To evaluate the influence of lifestyle changes on disease incidence, we calculated hazard ratios (HRs) with 95% CIs using the Cox proportional hazards regression model. Detailed descriptions of the covariates used for adjusting the HRs, as well as the methodology for the sensitivity analysis, are available in the Supplement 1.

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set to $P<0.05$.

Results

Males constituted 65.2% of the prehypertension cohort ($n=60,084$). Additionally, women were found to consume less alcohol (32.0% vs. 80.7% for never drinking) and to exercise less frequently (46.4% vs. 65.0% for never exercising) compared to men. Among the men, 44.1% were current smokers ($n=25,201$), whereas only 1.7% of women smoked currently ($n=577$). Similarly, in the prediabetes cohort, men made up 65.4% of the subjects ($n=37,836$). The percentage of women who neither exercised (47.2% vs. 67.7%) nor consumed alcohol (29.8% vs. 80.9%) was lower compared to men. In this cohort, 41.8% of men ($n=15,144$) were current smokers, while only 2.2% of women ($n=432$) were smokers. Furthermore, the prevalence of BMI over 25.0 kg/m² was lower in women than in men in both cohorts (32.3% vs. 28.5% in the prehypertension cohort and 38.1% vs. 36.7% in the prediabetes cohort). The general characteristics of subjects according to group are summarized in Table 1.

Table 2 presents the incidence of diseases during follow-up in subjects with prehypertension and prediabetes, categorized by gender. In the prehypertension cohort, there were 3,979 MACE cases in men and 2,290 in women. The MACE incidence rates were similar between genders (62.6/10,000 PY for men vs. 62.1/10,000 PY for women; $P=0.724$). However, a significant difference was observed in all-cause mortality rates, with men showing a higher rate than women (47.1/10,000 PY vs. 24.3/10,000 PY; $P<0.001$). In the prediabetes cohort, 3,435 MACE cases were recorded in men and 1,904 in women. The incidence rate of MACE in women was slightly higher than in men, but this difference was not statistically significant (88.0/10,000 PY for women vs. 92.8/10,000 PY for men; $P=0.063$). However, there was a significant difference in all-cause mortality between men and women, with men experiencing a higher rate (66.7/10,000 PY vs. 41.4/10,000 PY; $P<0.001$).

As previously mentioned, lifestyle factors were defined as BMI, current smoking, drinking, and physical activity. In the prehypertension and prediabetes cohorts, 26.6% and 26.1% of subjects, respectively, experienced a worsening in one or more lifestyle factors. Conversely, 34.2% and 34.8% of subjects in these cohorts improved in one or more lifestyle factors. Overall, fewer than 10% of subjects experienced a decline or improvement in two or more lifestyle factors (Supplement 2).

By controlling for lifestyle and clinical factors at the initial health screening, we evaluated the effects of lifestyle changes on major outcomes using a multivariate model (Tables 3, 4). In the prehypertension group, 7,376 patients (7.75%) had already been diagnosed with T2D, and 2,601 (2.73%) were taking anti-hyperglycemic medication. Similarly, in the prediabetes group, 11,577 patients (20.01%) had been diagnosed with HTN, and 8,962 (15.49%) were on antihypertensive medication (Table 1). To isolate the effects of medication, the multivariate analysis accounted for the impact of antihypertensive drugs, anti-hyperglycemic drugs, and aspirin. In men with prehypertension, the risk of MACE increased if their lifestyle worsened (HR, 1.13; 95% CI, 1.04–1.23, $P=0.004$), particularly if they gained weight (HR, 1.15; 95% CI, 1.03–1.28, $P=0.010$) or started smoking (HR, 1.34; 95% CI, 1.17–1.55, $P<0.001$). For women with prehypertension, the risk of MACE was higher for those who started smoking (HR, 1.69; 95% CI, 1.15–2.49, $P=0.008$) or reduced their physical activity (HR, 1.25; 95% CI, 1.06–1.47, $P=0.010$). Conversely, in men with prehypertension, improving lifestyle factors reduced the risk of MACE (HR, 0.91; 95% CI, 0.84–0.99, $P=0.025$), particularly through smoking cessation (HR, 0.79; 95% CI, 0.70–0.89, $P<0.001$), drinking less (HR, 1.09; 95% CI, 1.00–1.20, $P=0.048$), or increasing physical activity (HR, 0.91; 95% CI, 0.84–0.99, $P=0.027$). In men with prediabetes, those whose lifestyle factors worsened had a 23% higher risk of MACE compared to those with no lifestyle changes (HR, 1.23; 95% CI, 1.12–1.35, $P<0.001$).

Table 1. Participants' characteristics based on the index examination of National Health Insurance Service National Health Screening

		Prehypertension group			Prediabetes group		
		All	Men	Women	All	Men	Women
Participants (%)		95,152	60,084 (63.15)	35,068 (36.85)	57,865	37,836 (65.39)	20,029 (34.61)
Age (SD)		49.71 (8.08)	49.04 (7.85)	50.85 (8.34)	51.69 (8.90)	50.77 (8.57)	53.42 (9.25)
Income (%)	Quintile 1	13,925 (14.63)	6,069 (10.1)	7,856 (22.4)	8,907 (15.39)	4,382 (11.58)	4,525 (22.59)
	Quintile 2	11,874 (12.48)	5,966 (9.93)	5,908 (16.85)	7,975 (13.78)	4,426 (11.7)	3,549 (17.72)
	Quintile 3	14,207 (14.93)	9,117 (15.17)	5,090 (14.51)	9,080 (15.69)	5,959 (15.75)	3,121 (15.58)
	Quintile 4	19,537 (20.53)	13,603 (22.64)	5,934 (16.92)	11,881 (20.53)	8,271 (21.86)	3,610 (18.02)
	Quintile 5	35,609 (37.42)	25,329 (42.16)	10,280 (29.31)	20,022 (34.6)	14,798 (39.11)	5,224 (26.08)
SBP, mmHg (SD)		123.69 (7.02)	123.78 (7.00)	123.54 (7.07)	128.60 (17.56)	129.80 (16.95)	126.35 (18.45)
DBP, mmHg (SD)		78.06 (5.39)	78.46 (5.14)	77.38 (5.73)	80.86 (11.50)	82.19 (11.25)	78.34 (11.55)
FBS, mg/dL (SD)		95.26 (28.80)	96.56 (30.14)	93.04 (26.20)	107.87 (6.48)	108.11 (6.54)	107.40 (6.34)
Currently smoking (%)		25,778 (28.33)	25,201 (44.05)	577 (1.71)	15,576 (28.07)	15,144 (41.79)	432 (2.24)
Drinking (%)	Never	49,153 (53.27)	26,985 (46.39)	22,168 (65.01)	26,936 (47.36)	11,135 (29.82)	15,801 (80.92)
	2–3 times per month	25,803 (27.96)	19,491 (33.5)	6,312 (18.51)	9,670 (17.00)	7,485 (20.04)	2,185 (11.19)
	1–2 times per week	9,532 (10.33)	6,835 (11.75)	2,697 (7.91)	12,024 (21.14)	10,899 (29.19)	1,125 (5.76)
	3–4 times per week	2,550 (2.76)	1,661 (2.86)	889 (2.61)	5,313 (9.34)	5,076 (13.59)	237 (1.21)
	Everyday	5,235 (5.67)	3,203 (5.51)	2,032 (5.96)	2,927 (5.15)	2,748 (7.36)	179 (0.92)
Exercise (%)	Never	49,153 (53.27)	26,985 (46.39)	22,168 (65.01)	30,678 (54.28)	17,469 (47.2)	13,209 (67.7)
	1–2 times per week	25,803 (27.96)	19,491 (33.50)	6,312 (18.51)	15,407 (27.26)	12,106 (32.71)	3,301 (16.92)
	3–4 times per week	9,532 (10.33)	6,835 (11.75)	2,697 (7.91)	5,405 (9.56)	4,098 (11.07)	1,307 (6.7)
	5–6 times per week	2,550 (2.76)	1,661 (2.86)	889 (2.61)	1,517 (2.68)	1,064 (2.88)	453 (2.32)
	Everyday	5,235 (5.67)	3,203 (5.51)	2,032 (5.96)	3,512 (6.21)	2,271 (6.14)	1,241 (6.36)
BMI, kg/m ² (%)	<23	38,116 (40.08)	22,739 (37.87)	15,377 (43.88)	19,699 (34.06)	12,372 (32.72)	7,327 (36.61)
	23–24.9	27,574 (29.00)	17,901 (29.81)	9,673 (27.60)	16,379 (28.32)	11,041 (29.20)	5,338 (26.67)
	Over 25	29,409 (30.92)	19,412 (32.33)	9,997 (28.52)	21,754 (37.62)	14,403 (38.09)	7,351 (36.73)
CCI score (SD)		0.31 (0.64)	0.27 (0.61)	0.37 (0.68)	0.32 (0.63)	0.57 (0.59)	0.41 (0.70)
Total cholesterol (SD)		199.18 (36.91)	198.46 (36.46)	200.41 (37.65)	203.92 (38.00)	202.14 (37.41)	207.30 (38.87)
Statin (%)		855 (0.9)	410 (0.68)	445 (1.71)	1,026 (1.77)	520 (1.37)	506 (2.53)
HTN (%)					11,577 (20.01)	6,715 (17.75)	4,862 (24.27)
Antihypertensive drug (%)					8,962 (15.49)	5,416 (14.31)	3,546 (17.7)
DM (%)		7,376 (7.75)	4,496 (7.48)	2,880 (8.21)			
Antihyperglycemic drug (%)		2,601 (2.73)	1,708 (2.84)	893 (2.55)			
Aspirin		665 (0.7)	418 (0.7)	247 (0.7)	2,506 (4.33)	1,572 (4.15)	934 (4.66)

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; BMI, body mass index; CCI, Charlson comorbidity index; HTN, hypertension; DM, diabetes mellitus.

Table 2. Disease incidence rate between two biennial health screening periods

Outcome	Prehypertension group			Prediabetes group		
	Men	Women	P for gender difference	Men	Women	P for gender difference
	Incidence rate (per 10,000 PY), [95% CI]	Incidence rate (per 10,000 PY), [95% CI]		Incidence rate (per 10,000 PY), [95% CI]	Incidence rate (per 10,000 PY), [95% CI]	
MACE ¹⁾	62.63 [60.71–64.61]	62.05 [59.56–64.65]	0.724	87.98 [85.09–90.97]	92.78 [88.70–97.04]	0.063
Non-fatal MI	18.52 [17.50–19.60]	12.14 [11.08–13.30]	<0.001	23.13 [21.69–24.67]	19.11 [17.34–21.06]	0.001
Non-fatal stroke	44.21 [42.61–45.87]	50.31 [48.07–52.64]	<0.001	64.04 [61.59–66.58]	74.51 [70.88–78.32]	<0.001
CVD death	3.85 [3.41–4.35]	3.20 [2.69–3.82]	0.093	7.47 [6.68–8.34]	6.55 [5.56–7.71]	0.195
All-cause death	47.13 [45.49–48.82]	24.27 [22.76–25.89]	<0.001	66.73 [64.26–69.29]	41.38 [38.75–44.20]	<0.001

MACE, major adverse cardiovascular events; MI, myocardial infarction; CVD, cardiovascular disease.

¹⁾ MACE was defined as a composite of non-fatal MI, non-fatal stroke, and CVD death.

An increased risk of MACE was also observed in those who gained weight (HR, 1.19; 95% CI, 1.06–1.33, P=0.003), started smoking (HR, 1.41; 95% CI, 1.22–1.64, P<0.001), or decreased their physical activity (HR, 1.21; 95% CI, 1.09–1.35, P<0.001). Additionally, in men with prediabetes, a reduction in alcohol consumption was linked to a higher risk of MACE (HR, 1.17; 95% CI, 1.07–1.29, P=0.001). In women with prediabetes, the risk of MACE was 1.24 times higher for those who gained weight compared to those with no change in BMI levels (HR, 1.24; 95% CI, 1.06–1.45, P=0.006). As weight change can be a consequence of lifestyle changes, the association between unhealthy lifestyles, excluding BMI, and MACE was evaluated. Among pre-hypertensive men, those whose lifestyles worsened had a higher risk of MACE (HR, 1.10; 95% CI, 1.02–1.20, P=0.022). Among pre-hypertensive women, those whose lifestyles improved tended to have a lower MACE risk, although this association was not statistically significant (HR, 0.91; 95% CI, 0.81–1.01, P=0.072) (Table 3, Supplement 3). In the prediabetes group, men whose lifestyles worsened showed a significantly higher risk of MACE (HR, 1.23; 95% CI, 1.12–1.35, P<0.001), while there was no significant difference in MACE risk among comparative female subjects (Table 4, Supplement 4).

To mitigate the risk of reverse causality, a sensitivity analysis was conducted by excluding cardiovascular events that occurred within two years following the observation of lifestyle changes. In the prehypertension male group, the risk of MACE increased among subjects who experienced a decline in lifestyle quality, gained weight, decreased their physical activity frequency, or began smoking between biennial screenings. Conversely, the risk decreased in those who improved their lifestyles or quit smoking. In the prehypertension female group, an increase in MACE risk was observed in subjects who started smoking (Fig. 2A). In the prediabetes group, the MACE risk escalated in men who worsened their lifestyle, gained weight, reduced their physical activity frequency, or started smoking between the biennial screenings. In women, the risk increased among those who gained weight (Fig. 2B).

Discussion

Key results

This study highlights two significant findings: First, the risk of MACE increased in men with prediabetes or prehypertension whose lifestyle factors deteriorated, and this risk escalated even with the worsening of just one parameter. Second, the impact on MACE risk varied slightly

Table 3. Multivariate analysis of total cardiovascular disease events and mortality associated with lifestyle changes between two biennial health screening periods in the prehypertension group

Outcome	Parameter	Change	Men		Women	
			Adjusted hazard ratio	P-value	Adjusted hazard ratio	P-value
			[95% CI]		[95% CI]	
MACE ¹⁾	Unhealthy lifestyle	Worsened	1.13 [1.04–1.23]	0.004	1.10 [0.98–1.23]	0.121
		Improved	0.91 [0.84–0.99]	0.025	0.94 [0.85–1.04]	0.243
	Unhealthy lifestyle (exclude BMI)	Worsened	1.10 [1.02–1.20]	0.022	1.03 [0.90–1.17]	0.718
		Improved	0.92 [0.85–1.00]	0.052	0.91 [0.81–1.01]	0.072
	BMI	Worsened	1.15 [1.03–1.28]	0.010	1.09 [0.95–1.25]	0.220
		Improved	0.98 [0.88–1.09]	0.683	0.97 [0.85–1.11]	0.642
	Currently smoking	Worsened	1.34 [1.17–1.55]	<0.001	1.69 [1.15–2.49]	0.008
		Improved	0.79 [0.70–0.89]	<0.001	0.76 [0.48–1.21]	0.247
	Frequency of drinking	Worsened	1.08 [1.00–1.18]	0.061	0.92 [0.78–1.08]	0.307
		Improved	1.09 [1.00–1.20]	0.048	1.10 [0.88–1.38]	0.413
	Frequency of physical activity	Worsened	1.09 [0.99–1.21]	0.086	1.25 [1.06–1.47]	0.010
		Improved	0.91 [0.84–0.99]	0.027	0.93 [0.83–1.03]	0.166

Adjusted covariates include age, income level (quantiles), current smoking status, alcohol consumption, physical activity, CCI score, BMI, systolic blood pressure, total cholesterol, fasting serum glucose level at the first health screening, and usage of statin medication prior to the index date.

MACE, major adverse cardiovascular events; BMI, body mass index; MI, myocardial infarction; CVD, cardiovascular disease.

¹⁾ MACE was defined as a composite of non-fatal MI, non-fatal stroke, and CVD death.

Table 4. Multivariate analysis of total cardiovascular disease events and mortality associated with lifestyle changes between two biennial health screening periods in the prediabetes group

Outcome	Parameter	Change	Men		Women	
			Adjusted hazard ratio	P-value	Adjusted hazard ratio	P-value
			[95% CI]		[95% CI]	
MACE ¹⁾	Unhealthy lifestyle	Worsened	1.23 [1.12–1.35]	<0.001	1.09 [0.96–1.24]	0.199
		Improved	1.05 [0.96–1.14]	0.304	0.96 [0.85–1.07]	0.425
	Unhealthy lifestyle (exclude BMI)	Worsened	1.23 [1.12–1.35]	<0.001	0.97 [0.83–1.13]	0.671
		Improved	1.08 [0.99–1.17]	0.084	0.97 [0.86–1.09]	0.64
	BMI	Worsened	1.19 [1.06–1.33]	0.003	1.24 [1.06–1.45]	0.006
		Improved	0.93 [0.83–1.04]	0.214	0.93 [0.80–1.07]	0.315
	Currently smoking	Worsened	1.41 [1.22–1.64]	<0.001	0.88 [0.46–1.69]	0.693
		Improved	0.91 [0.80–1.03]	0.138	1.08 [0.69–1.70]	0.741
	Frequency of drinking	Worsened	1.08 [0.99–1.18]	0.102	0.96 [0.81–1.14]	0.65
		Improved	1.17 [1.07–1.29]	0.001	1.06 [0.82–1.38]	0.659
	Frequency of physical activity	Worsened	1.21 [1.09–1.35]	<0.001	1.05 [0.86–1.28]	0.661
		Improved	0.98 [0.90–1.07]	0.632	0.99 [0.88–1.12]	0.912

Adjusted covariates include age, income level (quantiles), current smoking status, alcohol consumption, physical activity, CCI score, BMI, systolic blood pressure, total cholesterol, fasting serum glucose level at the first health screening, and usage of statin medication prior to the index date.

MACE, major adverse cardiovascular events; BMI, body mass index; MI, myocardial infarction; CVD, cardiovascular disease.

¹⁾ MACE was defined as a composite of non-fatal MI, non-fatal stroke, and CVD death.

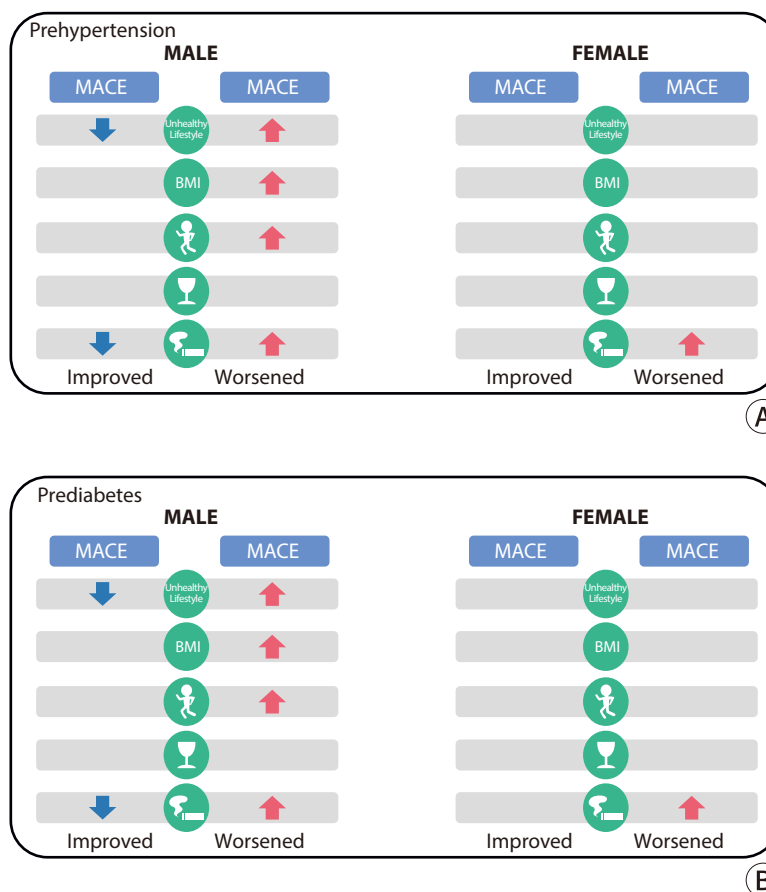


Fig. 2. Risk of cardiovascular disease events and mortality due to lifestyle changes. (A) The prehypertension group; (B) the prediabetes group. For the sensitivity analysis, events occurring 2 years after the observation of the lifestyle changes were excluded and evaluated. MACE, major adverse cardiovascular events; BMI, body mass index.

depending on lifestyle changes, with smoking being strongly linked to an increased risk of MACE in both prediabetes and prehypertension conditions, irrespective of gender.

Interpretation/comparison with previous studies

Smoking is a well-known risk factor for CVD risk. However, the precise level of risk that smoking presents to CVD in the prehypertensive population has not been clearly defined. The incidence of CVD is higher in people with a blood pressure of 120–129/80–84 mmHg and 130–139/85–89 mmHg than in normal blood pressure group in Europe and the United States [9]. Previous studies have demonstrated that smoking significantly influences the progression from prehypertension to hypertension by stiffening the arteries [10]. Furthermore, smoking increases the risk of developing hypertension in a dose-response manner over long-term follow-up [11]. This study confirmed that MACE increased as smoking habits worsened in both women and men. In prehypertensive patients, smoking not only contributes to the progression to hypertension but also independently elevates the risk of CVD. These findings underscore the importance of smoking cessation in patient education for individuals with prehypertension.

In a previous study, smoking was strongly associated with prediabetes in healthy young individuals, showing a linear risk gradient with increased cumulative smoking exposure [12].

Additionally, prior epidemiological studies have indicated that smoking may be an independent risk factor for T2D and is significantly associated with a higher risk of coronary heart disease [13–16]. A meta-analysis of prospective cohort studies revealed a relative risk of 1.55 (95% CI 1.46–1.64) for total mortality and 1.29 (95% CI 1.29–1.71) for cardiovascular mortality, assessing the relationship between smoking and mortality risk in diabetes patients [17]. In this study, men with prediabetes who started smoking showed an increased risk of MACE, while smoking cessation decreased CVD death.

In this study, we also analyzed changes in the risk of MACE, specifically excluding BMI to assess whether its inclusion as a factor influenced the outcomes. Males in the prehypertension and prediabetes groups who experienced a deterioration in their lifestyle had an increased risk of MACE, a trend that persisted even when BMI was excluded. However, among women in both groups, the risk of MACE did not show significant differences when unhealthy lifestyle parameters were considered, with or without BMI (Tables 3, 4). Previous research has demonstrated a U-shaped relationship between obesity and all-cause mortality and a linear association between BMI and cardiovascular events [18–20]. In this context, changes in an individual's BMI category do not directly correlate with an increase or decrease in CVD risk. For instance, overweight patients with stable coronary heart disease exhibited lower mortality compared to those of normal weight, and overweight patients with acute coronary syndrome showed significantly lower in-hospital and 12-month mortality [21–23]. Furthermore, BMI does not accurately reflect body composition, such as muscle mass or fat distribution. This phenomenon, known as 'reverse causality,' suggests that BMI is often considered a result influenced by other confounding factors rather than a standalone factor in previous studies [24]. In particular, the BMI values in this dataset do not indicate any intention to lose weight. Additionally, a decrease in BMI could also result in a reduction in muscle mass. Given these considerations, although the primary outcome based on lifestyle changes, excluding BMI, revealed significant differences in MACE risk among male groups, an analysis of the impact of BMI parameters on the detailed elements of MACE yielded conflicting results (Supplementals 5, 6).

Previous studies have shown that women generally have lower rates of smoking and obesity than men, while men are more likely to engage in regular and sustained physical activity [25,26]. When comparing men and women, the increase in MACE among men whose unhealthy lifestyles worsened could be linked to differences in lifestyle patterns between the genders. Indeed, data from the NHIS indicate gender-specific lifestyle patterns; men are more likely to smoke, be obese, and consume more alcohol. A previous study demonstrated that moderate to high physical activity during leisure time was associated with a lower risk of MACE [27]. Specifically, Fig. 2 illustrates that a decreased frequency of physical activity was associated with an increased risk of MACE in both the prehypertension and prediabetes male groups.

Limitations

This study may have several limitations. First, there is a potential for misclassification bias, as the diagnoses of prediabetes and prehypertension were based on the recorded history in the NHIS and single measurements of blood pressure or serum glucose levels. Second, the data on lifestyle patterns were derived from self-reported questionnaires, which may have introduced some misclassification. Third, further research is necessary to determine if similar trends are observable in multi-racial populations beyond Asians. Fourth, the study assessed changes in lifestyle by analyzing data collected at two distinct time points, specifically between the index examination and the second examination. However, it is possible that any lifestyle changes

occurring after the second examination were not captured.

Conclusion

In this retrospective cohort study, a worsening smoking habit was associated with an increased incidence of MACE in populations with prehypertension and men with prediabetes. This finding remained consistent after sensitivity analysis. Specifically, a decline in healthy lifestyle habits among men significantly increased the risk of MACE. Therefore, lifestyle modifications are crucial even before the diagnosis of hypertension or T2D, as they can significantly reduce cardiovascular events and mortality, particularly in men.

ORCID

Yeji Kim: <https://orcid.org/0009-0005-4185-9342>

Shinjeong Song: <https://orcid.org/0000-0002-5789-854X>

Chang Mo Moon: <https://orcid.org/0000-0003-2550-913X>

Hye Ah Lee: <https://orcid.org/0000-0002-4051-0350>

Junbeom Park: <https://orcid.org/0000-0003-2192-9401>

Authors' contributions

Project administration: Moon CM, Park J

Conceptualization: Kim Y, Song S, Moon CM, Lee HA, Park J

Methodology & data curation: Moon CM, Lee H, Park J

Funding acquisition: Lee HA, Park J

Writing – original draft: Kim Y, Song S

Writing – review & editing: Kim Y, Song S, Moon CM, Lee HA, Park J

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

The datasets generated and/or analyzed during the current study are available in online repositories. The names of the repositories and accession numbers can be found below: <https://nhiss.nhis.or.kr>.

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Not applicable.

Supplementary materials

Supplementary materials are available from: <https://doi.org/10.12771/emj.2024.e60>.

Supplement 1. Supplemental methods

Supplement 2. Distribution pattern according to the changes in lifestyle pattern

Supplement 3. Univariate analysis of total cardiovascular disease events and mortality associated with lifestyle changes between two biennial health screening periods in the prehypertension group

Supplement 4. Univariate analysis of total cardiovascular disease events and mortality associated with lifestyle changes between two biennial health screening periods in the prediabetes group

Supplement 5. Multivariate analysis of all-cause death, non-fatal MI, and non-fatal stroke associated with lifestyle changes between two biennial health screening periods in the prehypertension group

Supplement 6. Multivariate analysis of all-cause death, non-fatal MI, and non-fatal stroke associated with lifestyle changes between two biennial health screening periods in the prediabetes group

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Comparison of the long-term outcomes of cast immobilization methods in distal radius fractures: a systematic review of randomized controlled trials

Maria Florencia Deslivia^{1,2}, Claudia Santosa^{1,2}, Sherly Desnita Savio¹, Erica Kholinne^{2,3},
Made Bramantya Karna¹, Anak Agung Gde Yuda Asmara¹

¹Orthopaedics and Traumatology Department, Prof. Dr. IGNG Ngoerah General Hospital, Faculty of Medicine Udayana University, Bali, Indonesia

²Department of Orthopedic Surgery, St. Carolus Hospital, Jakarta, Indonesia

³Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

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Corresponding author

Sherly Desnita Savio
Orthopaedics and Traumatology
Department, Prof. Dr. IGNG Ngoerah
General Hospital, Faculty of Medicine
Udayana University, Jl. Diponegoro,
Dauh Puri Klod, Denpasar, Bali 80113,
Indonesia
E-mail: sherlydsavio@gmail.com

Keywords

Consensus; Conservative treatment;
Surgical casts; Visual analog scale; Wrist
fractures

Objectives: Conservative treatment for distal radius fractures typically involves closed reduction and immobilization with a plaster cast. However, no consensus exists regarding the best method and duration for immobilization. This study investigated the functional outcomes associated with different plaster cast application techniques in the treatment of stable distal radius fractures.

Methods: A systematic search was performed in accordance with PRISMA guidelines for studies in the last 5 years. The inclusion criteria were randomized controlled trials that investigated non-operative treatments for distal radius fractures. We excluded studies with short-term follow-up (less than 3 months), ongoing trials, those that did not directly address fractures, and studies involving the use of sugar-tong splints or non-circular immobilization. The outcomes evaluated included subjective measures (Disabilities of the Arm, Shoulder and Hand score; Patient-Rated Wrist Evaluation score; Mayo Wrist Score; and visual analog scale) and objective outcomes (complication rate and radiological parameters).

Results: We included seven articles from 2017 to 2022. These studies reported a total of 542 fractures, predominantly in women, with a mean age of over 50 years. Both short and long arm casts demonstrated similar functional and radiological outcomes. A longer immobilization period (>3 weeks) should be considered to prevent re-displacement.

Conclusion: In stable fractures treated conservatively, the use of both short and long arm casts resulted in comparable functional outcomes in older patients. Immobilization for at least 3 weeks is recommended, as it provided similar clinical and radiological outcomes compared to longer periods of immobilization (level of evidence: 2A).

Introduction

Background

Distal radius fractures are among the most common fractures encountered in the emergency room [1]. In the younger population, these fractures typically result from high-energy trauma, whereas in older adults, weakened, porous bones make them susceptible to fractures from minor trauma. For stable distal radius fractures in both groups, the conservative treatment approach is

closed reduction followed by immobilization using a plaster cast [2]. However, there is still no clear guideline on the best method and immobilization period to apply plaster cast.

One of the most debated aspects of plaster cast application involves the length of the cast (above or below the elbow) and the duration of immobilization. Even when an acceptable reduction is unattainable, previous studies have demonstrated that well-established radiological parameters do not necessarily correlate with a favorable functional outcome in older patients. Conversely, functional outcome reflects the patient's satisfaction with the treatment and should be the primary consideration [3].

Objectives

The aim of this study is to investigate the clinical and radiological outcomes of various non-operative treatments for distal radius fractures, focusing on the length of the cast and the duration of immobilization. We hypothesize that using a short arm cast with a shorter period of immobilization will yield clinical and radiological outcomes comparable to those achieved with a long arm cast and a longer immobilization period (>4 weeks).

Methods

Ethics statement

This was a literature-based study; thus, neither institutional review board approval nor informed consent was required.

Study design

This systematic review was performed in accordance with the PRISMA guidelines [4]. A review protocol was registered on PROSPERO (registration number: CRD42020212627).

Eligibility criteria

All types of randomized controlled trials (RCTs) published as full articles were included in this study. The selection of articles was based on the stated inclusion and exclusion criteria, following the PICO (population, intervention, comparison, outcome) method as outlined in Supplement 1.

Information sources

We performed a systematic search of English-language literature from the past five years on PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

Search strategy

The search terms included, but were not limited to, "distal radius fracture," "Colles fracture," "management," "treatment," "casting," "immobilization," and "nonoperative."

Selection and data collection process

The quality of the included RCTs was assessed by two independent reviewers using the 13-item 2015 Updated Method Guideline for Systematic Reviews from Cochrane [5].

Data items

The data were extracted using a standardized data collection form by a research team, with each selected article being independently screened by two reviewers. Disagreements between

reviewers about whether to include or exclude a study will be resolved through consensus, and if necessary, by consulting a third reviewer.

Study risk of bias assessment

A critical appraisal of all potential studies was conducted to assess their eligibility, utilizing a scoring system adapted from the Joanna Briggs Institute. The evaluation criteria included study population, exposures, confounding factors, outcomes, follow-up duration, and statistical analysis.

Effect measures

Data were extracted from study reports and under appropriate conditions for each test to compare and identify associations.

Synthesis methods

The variables collected included patient age, sex, fracture classification, interventions used, follow-up, Disabilities of the Arm, Shoulder, and Hand (DASH) score, Patient-Rated Wrist Evaluation (PRWE) score, the Mayo Wrist Score, the visual analog scale score, the complication rate, and radiological parameters (volar tilt, radial inclination, radial length, ulnar variance). The results were then tabulated into specific tables for drawing conclusions.

Reporting bias assessment

The quality and reliability of potential studies were evaluated by four authors (MFD, CS, SDS, EK), as well as the published protocols and registrations.

Certainty assessment

No certainty assessment was done.

Results

Study selection

The identification of studies in the primary literature search and the flow diagram of the selection process, according to PRISMA guidelines, are presented in Fig. 1.

Study characteristics

The initial electronic search across all databases yielded 156 records. Following a selection process, seven articles were included in the analysis.

Risk of bias in studies

All seven studies were confirmed to be of high quality, each receiving a "yes" response for more than seven parameters, as shown in Supplement 2.

Results of syntheses

Baseline characteristics

A total of 542 distal radius fractures were analyzed. All studies reported a higher proportion of female participants over the age of 50. Most of these fractures were stable, extra-articular fractures with minimal displacement; however, unstable fractures were also observed. The follow-up period ranged from 3 to 18 months (Table 1).

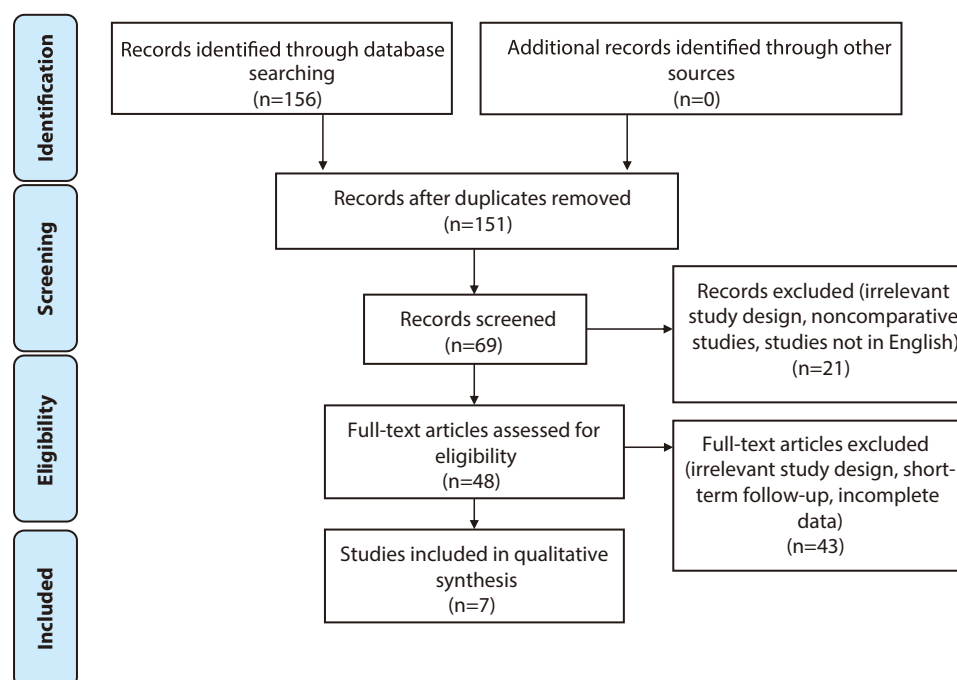


Fig. 1. Identification of studies in the primary literature search and the flow diagram of selection process according to the PRISMA guideline.

Table 1. Basic characteristics of studies

No	Author	Intervention	Control	Sample size (n)	Gender (male/female)	Mean age (yr)	Fracture classification	Follow-up (mo)
Immobilization methods								
1	Park et al. [6]	PC SAC	PC LAC	I: 36 C: 33	I: 2/34 C: 4/29	I: 66.1 C: 67.5	Stable fracture	6
2	Caruso [7]	PC SAC	PC LAC	I: 37 C: 37	I: 3/33 C: 4/32	I: 72.3 C: 69.5	Extra-articular and dorsal displacement (type 2R3A2.2)	3
3	Okamura et al. [8]	PC SAC	PC LAC	I: 64 C: 64	I: 23/41 C: 17/47	I: 60.52±14.74 C: 62.97±13.03	2R3A2/2R3A3/2R3C1 /2R3C2/2R3C3	6
Immobilization periods								
1	Christersson et al. [9]	PC 10 d	PC 10 d+3 wk	I: 54 C: 55	I: 7/47 C: 4/51	I: 67 C: 64.7	2R3A3/2R3C2/2R3C3	12
2	Bentohami et al. [10]	PC 3 wk	PC 5 wk	I: 36 C: 36	I: 10/26 C: 13/23	I: >60 yr in 41.67% of patients C: >60 yr in 50% of patients	Stable fractures	12
3	Boersma et al. [11]	PC 1 wk	PC 4–5 wk	I: 26 C: 14	I: 7/19 C: 4/10	I: 52.3±16.2 C: 56.5±9.6	2R3A/2R3B/2R3C	12
4	Olech et al. [12]	PC 4 wk	PC 6 wk	I: 26 C: 24	33 women+17 men	I: 71.34±4.99 C: 72.2±5.46	Stable fractures	12–18

PC, plaster cast; SAC, short-arm cast; LAC, long-arm cast; I, intervention; C, control.

Outcomes of plaster casting

The seven RCTs discussed plaster casts in terms of the cast length (short versus long arm cast; $n=3$) and the length of the immobilization period ($n=4$). Three RCTs concluded that the clinical outcomes were comparable between short arm casts and long arm casts (Table 2). Long arm casts and short arm casts demonstrated comparable radiological outcomes, as measured by volar tilt, radial inclination, radial height, and ulnar variance (Table 3).

Ten days of immobilization has not been proven effective radiologically, as it has been associated with redisplacement in terms of radial inclination and radial height compared

Table 2. Comparison of clinical outcomes

No	Author	Conclusion	DASH	PRWE	Mayo Wrist Score	VAS	Complication
Immobilization methods							
1	Park et al. [6]	SACs were as effective as LACs for stable distal radius fractures in older patients. Furthermore, they were more comfortable and introduced fewer restrictions on daily activities.	SAC: 30 ± 15 LAC: 26.8 ± 14.3	NA	NA	SAC: 2.5 ± 1.2 LAC: 2.1 ± 0.84	NA
2	Caruso et al. [7]	Patients treated with SACs had comparable radiological and functional scores to those treated with LACs, with fewer complications secondary to immobilization of the elbow joint.	SAC: 0.8 (0–2.1) LAC: 1.7 (0–2.5)	NA	NA	NA	NA
3	Okamura et al. [8]	SACs demonstrated no difference in DASH outcomes, comparable reduction maintenance, and fewer adverse effects than LACs.	6 mo: SAC: 9.88 LAC: 9.44	NA	NA	6 mo (wrist): SAC: 4.89 LAC: 7.03 6 mo (shoulder): SAC: 2.69 LAC: 3.52	SAC: 9 LAC: 19 Most common: shoulder pain, malunion
Immobilization periods							
1	Christersson et al. [9]	PC removal 10 d after reduction in moderately displaced DRFs is not recommended.	NA	NA	NA	Insignificant pain difference at 12 mo ($P=0.92$)	NA
2	Bentohami et al. [10]	Equal patient-reported outcomes between 3 wk and 5 wk of plaster cast immobilization.	I: 0 C: 12.5	I: 5.0 C: 8.8	NA	I: 3.1 C: 2.6	No complication in fracture healing, no non-union or CRPS
3	Boersma et al. [11]	1 wk of PC treatment for nonreduced DRFs resulted in comparable functional outcomes, pain scores, complication rates, and secondary displacement.	I: 4.6 ± 9.5 C: 3.5 ± 4.1	I: 2.9 ± 6.6 C: 2.1 ± 3.3	NA	4 wk: I: 2.2 ± 1.7 C: 1.9 ± 2.0	I: 1 C: 4 Most common: ulnar sided wrist pain, DRUJ pain, CRPS
4	Olech et al. [12]	Similar VAS and Mayo Wrist Scores between the two groups. The greatest volar tilt angle occurred after 6 wk of PC. No significant differences in other radiological parameters between the two groups.	NA	NA	I: 58.46 ± 21.24 C: 61.87 ± 22.97	VAS pain: I: 2.53 ± 3.06 C: 3.58 ± 2.56 VAS activity: I: 7.61 ± 1.83 C: 7.58 ± 2.3	NA

DASH, Disabilities of the Arm, Shoulder, and Hand; PRWE, Patient-Rated Wrist Evaluation; VAS, visual analog scale; SAC, short arm cast; LAC, long arm cast; NA, not available; PC, plaster cast; I, intervention; C, control; DRF, distal radius fracture; DRUJ, distal radioulnar joint; CRPS, complex regional pain syndrome.

Table 3. Comparison of radiological outcomes

No	Author	Volar tilt (°)	Radial inclination (°)	Radial length (mm)	Ulnar variance (mm)
Immobilization methods					
1	Park et al. [6]	3 mo: - SAC: -0.2 ± 6.0 - LAC: 3.9 ± 6.2 6 mo: - SAC: -3.6 ± 5.6 - LAC: 2.3 ± 6.2	3 mo: - SAC: 13.4 ± 6.5 - LAC: 15.4 ± 6.1 6 mo: - SAC: 10.1 ± 7.1 - LAC: 12.4 ± 6.9	3 mo: - SAC: 5.0 ± 3.7 - LAC: 6.2 ± 2.6 6 mo: - SAC: 3.1 ± 3.9 - LAC: 4.5 ± 2.9	NA
2	Caruso et al. [7]	3 mo: SAC: 0 ($[-4.5]-8$) LAC: 0 ($[-4]-7.5$)	3 mo: SAC: 22 (19–24.5) LAC: 21 (17.5–23)	3 mo: SAC: 9 (7–10) LAC: 8 (6–10)	3 mo: SAC: 0 (0–1) LAC: 0 ($[0.5]-2.25$)
3	Okamura et al. [8]	SAC: -1.04 LAC: -1.27	SAC: 18 LAC: 16.31	SAC: 7.89 LAC: 7.49	SAC: 1.41 LAC: 1.93
Immobilization periods					
1	Christersson et al. [9]	12 mo: the 10-d group exhibited 1.1° more redisplacement ($P=0.48$) than the 1-mo group	12 mo: the 10-d group exhibited 3.2° more redisplacement ($P=0.002$) than the 1-mo group	12 mo: The 10-d group demonstrated 0.7 mm more axial compression ($P=0.02$) than the 1-mo group	NA
2	Bentohami et al. [10]	1 Patient in each group showed secondary displacement			
3	Boersma et al. [11]	NA	NA	NA	NA
4	Olech et al. [12]	I: 9.13 ± 7.12 C: 3.29 ± 5.11	I: 1.9 ± 1.62 C: 2.45 ± 2.47	I: 0.55 ± 2.84 C: 0.25 ± 1.03	NA

SAC, short arm cast; LAC, long arm cast; NA, not available.

to 1 month of immobilization. However, these findings remain controversial, as one study demonstrated similar outcomes between 1 week and 4–5 weeks of plaster cast immobilization. Generally, a minimum of 3 weeks of immobilization in a plaster cast is sufficient to provide satisfactory clinical and radiological outcomes for up to 18 months of follow-up.

Reporting biases

All the studies reviewed were sourced from peer-reviewed journals. However, it was uncertain whether the reports fully disclosed all study outcomes.

Discussion

Interpretation

This study aimed to objectively compare conservative treatment methods for distal radius fractures. The findings indicated that both long and short arm casts were equally effective in preventing displacement and achieving satisfactory functional outcomes. However, an immobilization period of less than three weeks was associated with poorer radiological outcomes, which could potentially lead to inferior final functional results.

Comparison with previous studies

Immobilization with casting is the common initial treatment for a distal radius fracture.

Although the final radiographic alignment may not be optimal, long-term motion and patient-reported outcomes from casting are similar to those of surgical treatments [1,13,14]. To optimize the effectiveness of casting, the brachioradialis was identified as a major deforming force, necessitating the use of a long-arm brace in supination to neutralize its action [15]. However, based on three RCTs analyzed in this systematic review, there is no significant difference in DASH scores between long-arm and short-arm casts. We also discuss the results of studies on various periods of immobilization.

Patient-reported outcome measures for the upper extremity

Patient-reported outcome measures are crucial in short-term follow-up because recent evidence suggests they do not correlate with radiological measures [3,16,17]. However, it is important to use a consistently reliable measurement tool to ensure valid comparisons between different treatments. Previous studies have shown that the DASH and PRWE scales are reliable, valid, and responsive tools for assessing upper limb injuries, making them superior to other outcome measures [18,19].

When to place a long arm cast and how long to immobilize the patient in a plaster cast?

The main disadvantage of a long arm cast is that it restricts forearm rotation and elbow flexion-extension. It is also heavy and cumbersome, which can increase the incidence of shoulder pain [6] and limit daily activities [20]. Conversely, a short arm cast may offer the advantage of causing less temporary disability and inconvenience, as it allows for elbow motion. However, a long arm cast is known to better maintain reduction because it prevents the long wrist flexors and extensors from deforming the fracture [20]. Some surgeons recommend using a long arm cast for unstable fractures, generally defined by the Lafontaine criteria, which include at least three of the following: dorsal angulation of more than 20 degrees, dorsal comminution, intra-articular radiocarpal fracture, associated ulnar fracture, and age over 60 years [21]. In these cases, it is believed that the long arm cast prevents elbow motion and forearm rotation, minimizing the risk of fracture displacement. However, this approach remains a matter of debate, as some surgeons still prefer short arm casts regardless of fracture stability [6].

The current systematic review revealed no significant differences in functional scores between short arm casts and long arm casts for stable or extra-articular distal radius fractures. Tolerance for functional loss appears to be influenced by age and activity level, with younger individuals demonstrating better DASH scores after short-term follow-up. Additionally, many authors have noted that older populations are more accepting of functional deficits or imperfect outcomes due to their lower functional demands [22].

The immobilization period is a significant factor in the non-operative treatment of distal radius fractures. Removing the plaster cast early is aimed at facilitating quicker functional recovery and enhancing clinical outcomes. However, our literature review indicates that removing the plaster cast before 1 month leads to poorer functional [9] and radiological outcomes [23]. It was also recommended to immobilize the arm in a functional position [23].

Strengths and limitations of the study

In previous systematic reviews, van Delft et al. [24] and de Bruijn et al. [25] explored the duration of cast immobilization for distal radius fractures. However, these reviews did not set a time restriction for the inclusion of studies, which could introduce bias. Additionally, their focus was limited to the duration of casting, without considering other relevant parameters. Saka et al. [26] compared the effectiveness of below-elbow and above-elbow casts for treating this

condition, yet the evidence provided was of low certainty. Similarly, Raj et al. [27] investigated various immobilization techniques, but the significant variation in mean follow-up periods raised concerns about potential bias in their findings.

This study aims to objectively compare clinical and radiological parameters concerning conservative treatment methods for distal radius fractures, focusing on the technique of application and the duration of immobilization. All included studies are recently published RCTs with a minimum follow-up period of three months, which should provide a high-quality overall analysis. However, our study has several limitations. The number of RCTs investigating non-operative treatment methods for distal radius fractures remains limited. Among the available studies, the strength of evidence is insufficient, with notable heterogeneity, particularly in terms of fracture types. Future studies should consider pooling outcomes from RCTs that involve similar fracture types. Despite these limitations, this study provides evidence supporting conservative treatment for distal radius fractures.

Conclusion

In patients with distal radius fractures, both short arm casts and long arm casts provide similar functional and radiological outcomes. To prevent re-displacement, an immobilization period of at least 3 weeks should be considered.

ORCID

Maria Florencia Deslivia: <https://orcid.org/0000-0001-8726-3425>

Claudia Santosa: <https://orcid.org/0009-0007-6823-4857>

Sherly Desnita Savio: <https://orcid.org/0000-0003-4269-1156>

Erica Kholinne: <https://orcid.org/0000-0002-4326-8205>

Made Bramantya Karna: <https://orcid.org/0009-0001-0650-3974>

Anak Agung Gde Yuda Asmara: <https://orcid.org/0009-0005-9295-9167>

Authors' contributions

Project administration: Deslivia MF, Savio SD

Conceptualization: Deslivia MF, Savio SD, Karna MB, Asmara AAGY

Methodology & data curation: Deslivia MF, Savio SD

Funding acquisition: Deslivia MF, Santosa C, Asmara AAGY

Writing – original draft: Deslivia MF, Santosa C, Savio SD, Kholinne E

Writing – review & editing: Deslivia MF, Santosa C, Savio SD, Kholinne E, Karna MB, Asmara AAGY

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Not applicable.

Supplementary materials

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Supplement 1. Inclusion and exclusion criteria based on the PICO

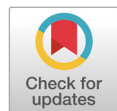
Supplement 2. Quality assessment of the included studies

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Prevalence and associated factors of ADHD-like symptoms among pharmacy students at Prince of Songkla University, Thailand in 2024: a cross-sectional study

Krittiya Rakchat[✉], Saranan Eadcharoen[✉], Amarawan Pentrakan[✉]

Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand

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Corresponding author

Amarawan Pentrakan
Department of Social and Administrative
Pharmacy, Faculty of Pharmaceutical
Sciences, Prince of Songkla University,
15 Kanchanavanit Road, Hat Yai,
Songkhla 90110, Thailand
E-mail: amarawan.p@psu.ac.th

Keywords

Attention deficit disorder with hyperactivity;
Pharmacy students; Prevalence;
Socioeconomic factors; Thailand

Objectives: This study investigated the prevalence of attention-deficit hyperactivity disorder (ADHD) and its associated factors among pharmacy students at Prince of Songkla University in 2024. It was hypothesized that the prevalence of ADHD would be associated with various demographic, socioeconomic, historical, and behavioral factors.

Methods: This cross-sectional descriptive study involved pharmacy students from years 1–5 at Prince of Songkla University in Thailand. Data were gathered from 761 students using a self-administered questionnaire that included the Adult ADHD Self-Report Scale (ASRS Screener V1.1). Descriptive statistics, the chi-square test, the Fisher exact test, and multiple logistic regression were employed for data analysis.

Results: In total, 526 students participated in the study (participation rate: 69%), with an average age of 21 ± 1.57 years. The risk of ADHD was prevalent in 14.4% of the respondents (76 students; 95% CI: 11.4%–17.5%). Significant factors associated with an increased risk of ADHD included identifying as not disclosed or preferring not to report gender (adjusted OR [OR_{adj}], 3.32; 95% CI, 1.04–10.57), having insufficient monthly income (OR_{adj}, 2.02; 95% CI, 1.13–3.61), and recent traffic violations (OR_{adj}, 2.02; 95% CI, 1.09–3.76). It was also found that difficulties with executive functioning, such as organization and procrastination, were highly prevalent among pharmacy students.

Conclusion: The study identified a substantial prevalence of ADHD risk among pharmacy students, with factors including gender, financial challenges, and behavioral patterns such as traffic violations significantly associated with this risk. These findings underscore the necessity for targeted mental health interventions in university settings.

Introduction

Background/rationale

Attention-deficit hyperactivity disorder (ADHD) is a neurological condition primarily characterized by difficulties with inattention, hyperactivity, and impulsivity. Although ADHD is most commonly associated with children and adolescents, it can affect individuals of any age, making it a significant global issue [1]. The COVID-19 pandemic has exacerbated symptoms

of ADHD, such as impulsivity, restlessness, and concentration challenges, especially among students who are under increased academic pressure. A study conducted in Japan [2] reported a notable increase in the prevalence of ADHD among university students during the pandemic, reaching approximately 12%. This rise was accompanied by worsened symptoms, including reduced focus, impaired multitasking, emotional instability, and increased impulsivity and hyperactivity, which negatively impacted social interactions and overall functioning.

Similar trends have been observed in Thailand, where growing evidence suggests that the COVID-19 pandemic has increased risk behaviors related to violence and mental health issues among adolescents [3]. These impacts have led to physical inactivity, sedentary lifestyles, and subsequent physical changes with long-term implications. Moreover, the pandemic has contributed to the development of psychological conditions such as emotional distress, conduct problems, hyperactivity, and inattention, particularly among adolescents with chronic illnesses [4]. These negative effects may have lasting consequences, including emerging ADHD symptoms, which could lead to further adverse physical health outcomes over time.

Research has identified several factors that contribute to the risk of ADHD and other mental health issues among students. These factors are typically categorized into personal demographics, familial influences, and social dimensions [5]. Notably, the COVID-19 pandemic has intensified certain behavioral changes, such as an increased reliance on excessive digital technology, which have been linked to symptoms of ADHD [6]. Furthermore, evidence suggests that medical students exhibit a higher prevalence of ADHD-like symptoms compared to their peers in other academic fields [7]. The shift to online classes due to COVID-19 has resulted in an overall decline in academic performance [8]. Individuals experiencing significant academic stress are particularly prone to displaying symptoms of ADHD.

Despite heightened awareness of ADHD, there is limited research on its prevalence and associated factors among students in the post-COVID-19 era, particularly within the pharmacy student population. The rigorous demands of pharmacy programs, combined with the challenges of adapting to new learning environments, may lead to an increase in ADHD-like symptoms in these students.

Objectives

This study aimed to investigate the prevalence of ADHD-like symptoms and their associated factors among pharmacy students, focusing on first- to fifth-year students in 2024 at Prince of Songkla University, Thailand.

Methods

Ethics statement

This study received approval from the Human Research Ethics Committee of the Faculty of Pharmaceutical Sciences at Prince of Songkla University (Approval No. 68108/36). Additionally, participants were given an invitation letter to review prior to deciding whether to participate in the research project.

Study design

A cross-sectional descriptive survey was conducted to explore the prevalence of ADHD-like symptoms and their associated factors among pharmacy students at Prince of Songkla University, Thailand.

Settings

The online questionnaire survey was conducted among pharmacy students at Prince of Songkla University, Thailand, from January 15 to February 14, 2024.

Participants

This research involved all students from years 1 to 5 at the Faculty of Pharmaceutical Sciences, Prince of Songkla University, who are currently enrolled in both the Industrial Pharmacy and Pharmaceutical Care programs and have consented to provide information.

Variables

Drawing from the literature review, we have categorized factors potentially associated with ADHD-like symptoms into four domains. The first domain, demographic factors, includes variables such as age and gender. The second domain, socioeconomic status, covers elements like current education level, field of study, living situation, and adequacy of monthly income. The third domain, history, encompasses both personal and familial aspects, specifically past behavioral issues and diagnoses of ADHD. The fourth domain, personal behavior, examines factors such as history of traffic violations, alcohol consumption, and smoking habits. Additionally, the category of online activities explores patterns of internet usage, including duration and extent. The framework outlining the relationship between these factors and ADHD is presented in Fig. 1.

Data sources/measurement

The research employed an online questionnaire structured into three sections: (1) Personal demographics, socioeconomic status, and past ADHD diagnosis: This section collected data on various variables such as age, gender, academic year, field of study, residence, adequacy of monthly income, and both personal and familial history of ADHD. It provided a comprehensive demographic and socioeconomic profile. (2) Personal behavior and online activities: This section explored participants' behavior and online engagement through eight questions covering topics such as traffic violations, alcohol consumption, smoking, online learning hours, and media usage patterns. It aimed to examine correlations between personal behaviors and online activities. (3) The Adult ADHD Self-Report Scale (ASRS) V1.1: This reliable screener, with a sensitivity of 0.93 and specificity of 0.71, was employed to assess potential ADHD symptoms in adults [9]. The scale

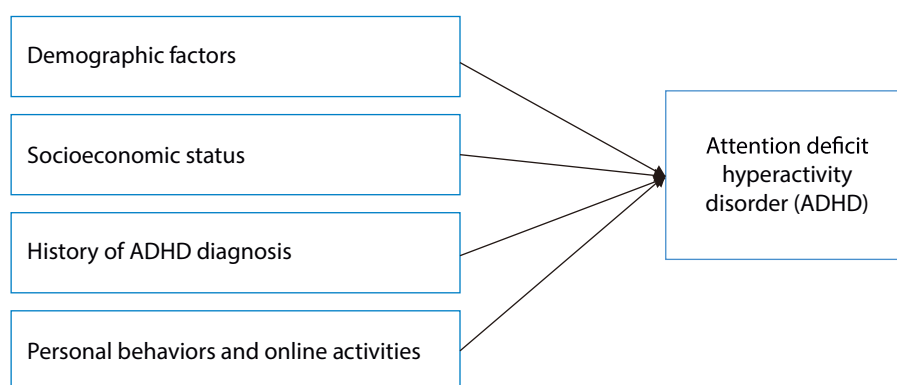


Fig. 1. Conceptual framework for studying the relationship between various factors and ADHD-like symptoms.

includes six questions, each rated on a 5-point scale ranging from “never” to “very often.” The questions are designed to measure the frequency of symptoms, aiding in the initial screening for ADHD. To assess ADHD symptoms, scores are assigned as follows: for items one through three, a score of 1 is given if responses range from “sometimes” to “very often”; otherwise, the score is 0. For items four through six, a score of 1 is assigned if responses are “often” or “very often”; otherwise, the score is 0. A total score of 4 or higher indicates potential ADHD symptoms.

The research data are available in Dataset 1.

Bias

This research took measures to prevent bias by anonymizing the identities of the respondents. Participants have the freedom to choose whether or not they wish to partake in this study.

Study size

The sample size was not estimated, as this study included the entire population that consented to provide information.

Statistical methods

This study utilized descriptive statistics to analyze personal data, including frequency distributions, percentages, means, and SDs. To investigate the relationships among variables, inferential statistics are employed, focusing on the analysis of single-variable relationships. Depending on the data, either the chi-square test or the Fisher exact test was used, with the latter being applied when expected values were fewer than 5 in more than 20% of cases. For the analysis of multiple variables, multiple logistic regression was conducted, and the results are presented as adjusted OR (OR_{adj}) and 95% CIs. All statistical analyses were performed using SPSS software, with the significance threshold set at 0.05. For data visualization, Tableau software was used.

Results

Participants

ADHD was evaluated in 761 pharmacy students across years 1 to 5 at Prince of Songkla University using the ASRS screener. Out of these students, 526 (69%) voluntarily participated, with an average age of 21 ± 1.57 years. The majority of the participants were female (73%), enrolled in the industrial pharmacy program (59.9%), did not drink alcohol (66.2%), did not smoke (98.1%), and had no previous ADHD diagnosis (95.3%). The screening identified 76 students (14.4%; 95% CI, 11.4%–17.5%) as meeting the criteria for ADHD.

Table 1 presents the frequency distributions of subgroup variables and analytical factors associated with ADHD. The study employed the chi-square or Fisher exact test to identify significant associations between the occurrence of ADHD and various variables. These variables included gender, adequacy of monthly income, history of prior ADHD diagnosis, frequency of traffic rule violations in the past 3 months, daily internet or smartphone use, and duration of online study sessions.

The results revealed a statistically significant difference in ADHD rates based on gender ($P=0.017$). Furthermore, individuals with insufficient income were more likely to have ADHD compared to those with sufficient income ($P=0.021$). Additionally, there was a significant association concerning individuals with a prior ADHD diagnosis, who were much more likely to

Table 1. Preliminary test results for the relationship between screening factors and ADHD assessment results

Factors	n (%)	ADHD assessment results (n=526)		P-value ¹⁾
		No ADHD n (%)	ADHD n (%)	
Age (yr)				0.793
≤20	116 (22.1)	100 (86.2)	16 (13.8)	
21–23	322 (61.2)	273 (84.8)	49 (15.2)	
≥23	88 (16.7)	77 (87.5)	11 (12.5)	
Gender				0.017
Male	122 (23.2)	102 (83.6)	20 (16.4)	
Female	384 (73.0)	335 (87.2)	49 (12.8)	
Undisclosed gender	20 (3.8)	13 (65.0)	7 (35.0)	
Year of study				0.137
1	126 (24.0)	106 (84.1)	20 (15.9)	
2	137 (26.0)	122 (89.1)	15 (10.9)	
3	99 (18.8)	78 (78.8)	21 (21.2)	
4	96 (18.3)	82 (85.4)	14 (14.6)	
5	68 (12.9)	62 (91.2)	6 (8.8)	
Program of study				0.897
Industrial pharmacy	315 (59.9)	270 (85.7)	45 (14.3)	
Clinical pharmacy	211 (40.1)	180 (85.3)	31 (14.7)	
Residence				0.307
Home	86 (16.3)	69 (80.2)	17 (19.8)	
Off-campus dormitory	214 (40.7)	185 (86.4)	29 (13.6)	
On-campus dormitory	226 (43.0)	196 (86.7)	30 (13.3)	
Living arrangement				0.226
With family	90 (17.1)	73 (81.1)	17 (18.9)	
With friends	215 (40.9)	190 (88.4)	25 (11.6)	
Living alone	221 (42.0)	187 (84.6)	34 (15.4)	
Adequacy of monthly income				0.021
Sufficient	350 (66.5)	310 (88.6)	40 (11.4)	
Insufficient	176 (33.5)	140 (79.5)	36 (20.5)	
Personal history of ADHD diagnosis				0.005
Yes	4 (0.8)	2 (50.0)	2 (50.0)	
No	502 (95.4)	433 (86.3)	69 (13.7)	
Unsure	20 (3.8)	15 (75.0)	5 (25.0)	
Family history of ADHD diagnosis				0.189
Yes	6 (1.1)	4 (66.7)	2 (33.3)	
No	498 (94.7)	429 (86.1)	69 (13.9)	
Unsure	22 (4.2)	17 (77.3)	5 (22.7)	
Traffic violation behavior (in the past 3 months)				0.013
Ever violated traffic rules	166 (31.6)	133 (80.1)	33 (19.9)	

Table 1. Continued

Factors	n (%)	ADHD assessment results (n=526)		P-value ¹⁾
		No ADHD n (%)	ADHD n (%)	
Never violated traffic rules	303 (57.6)	271 (89.4)	32 (10.6)	0.318
Unsure	57 (10.8)	46 (80.7)	11 (1.3)	
Frequency of drinking (in the past 3 months)				0.318
Do not drink	349 (66.3)	304 (87.1)	45 (12.9)	
Drink less than or equal to 3 times per week	43 (8.2)	38 (88.4)	5 (11.6)	
Drink more than 3 times per week	115 (21.9)	94 (81.7)	21 (18.3)	
Smoking				0.625
Non-smoker	517 (98.3)	443 (85.7)	74 (14.3)	
Smoker	9 (1.7)	7 (77.8)	2 (22.2)	
Time spent on the internet/smartphone per day (hr)				0.040
Less than 4	70 (13.3)	65 (92.4)	5 (7.1)	
4–6	134 (25.5)	119 (88.8)	15 (11.2)	
More than 6	322 (61.2)	266 (82.6)	56 (17.4)	
Length of online study/learning session (hr)				0.027
Less than or equal to 1	40 (7.6)	34 (85.0)	6 (15.0)	
More than 1 up to 2	288 (54.8)	246 (85.4)	42 (14.6)	
More than 2 up to 3	140 (26.6)	127 (90.7)	13 (9.3)	
More than 3	58 (11.0)	43 (74.1)	15 (25.9)	
Most frequent time of using online media				0.053
Daytime	33 (6.3)	32 (97.0)	1 (3.0)	
Nighttime	486 (92.4)	413 (85.0)	73 (15.0)	
Both	7 (1.3)	5 (71.4)	2 (28.6)	

ADHD, attention-deficit hyperactivity disorder.

¹⁾ Chi-square test or Fisher exact test (for expected values below 5 in more than 20% of cases).

be deemed at risk for ADHD in this assessment ($P=0.005$). Furthermore, a statistically significant association was observed between ADHD assessment results and behavioral factors, including traffic violations ($P=0.013$), internet usage ($P=0.040$), and the duration of study sessions ($P=0.027$).

Main results

Fig. 2 presents a bar chart that displays responses to the ASRS screener for six key questions. Each bar represents the frequency of ADHD-related symptoms as rated by different groups of students. The x-axis indicates the number of students, and the colored segments within each bar show varying frequency responses, from "never" to "very often". Key observations reveal that many individuals often struggle to complete tasks after finishing the challenging parts, suggesting issues with task follow-through. Similarly, numerous respondents frequently encounter difficulties in organizing tasks that require careful planning, indicating problems with executive functioning.

Memory issues were prevalent, with a significant number of respondents reporting that they sometimes or often forgot appointments or obligations. Tasks requiring substantial mental effort

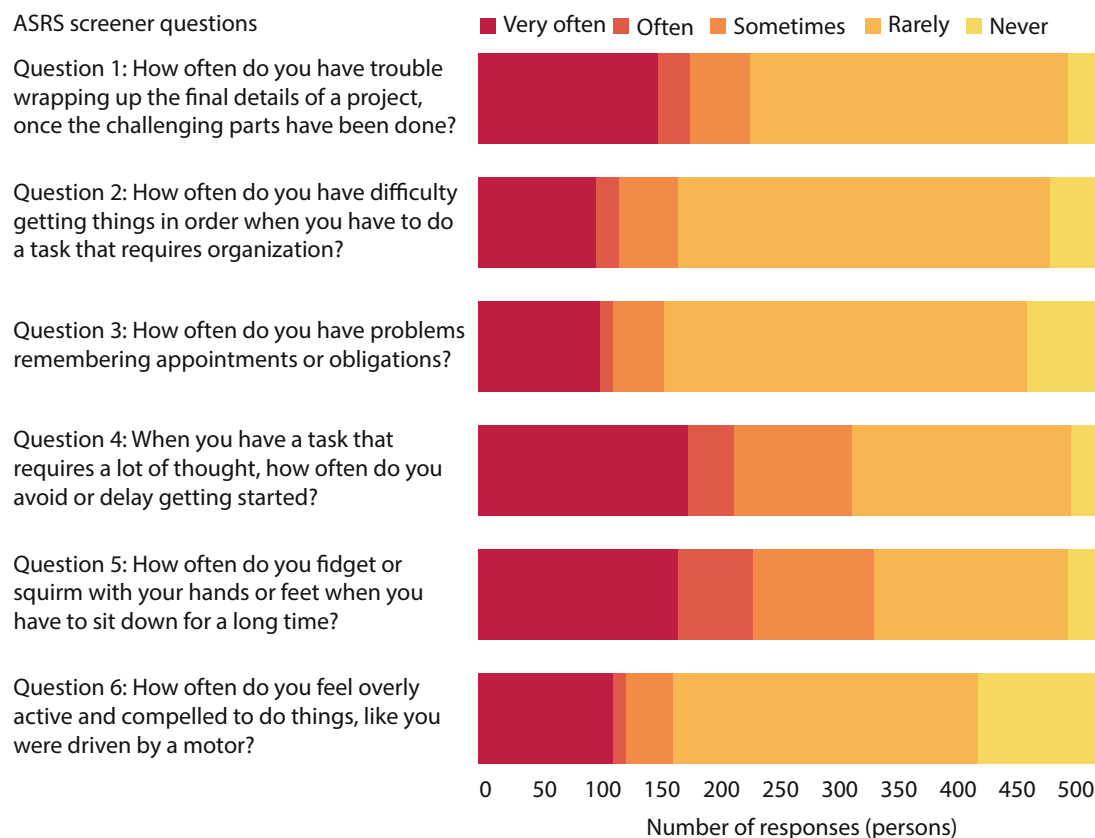


Fig. 2. The distribution of responses to the ASRS screener questions among pharmacy students. ASRS, Adult ADHD Self-Report Scale; ADHD, attention-deficit hyperactivity disorder.

frequently led to avoidance and procrastination, with many respondents admitting they delayed starting such tasks “very often” or “often.” Restlessness was another common issue, with numerous respondents experiencing fidgeting or squirming when required to sit for extended periods. Although responses varied, fidgeting was frequently reported by a significant portion of respondents. Additionally, feelings of hyperactivity and the urge to stay in motion were apparent, with many respondents experiencing this “sometimes.”

Multiple logistic regression analysis of factors related to the prevalence of ADHD identified significant associations after adjusting for the influence of a past ADHD diagnosis. The factors found to be statistically significant included not disclosed or unspecified gender (OR_{adj} , 3.32; 95% CI, 1.04–10.57), insufficient monthly income relative to expenses (OR_{adj} , 2.02; 95% CI, 1.13–3.61), and a history of traffic violations within the past 3 months (OR_{adj} , 2.02; 95% CI, 1.09–3.76), as detailed in Table 2.

Discussion

Key results

This research investigated the prevalence of ADHD and its associated factors among pharmacy students in 2024. The study involved 526 pharmacy students from first to fifth years at Prince of Songkla University, who participated voluntarily. The findings indicate that

Table 2. Factors related to the prevalence of ADHD

Factor	OR _{adj}	95% CI	P-value ¹⁾
Gender (reference: female)			
Male	1.264	(0.627–2.546)	0.512
Unspecified gender	3.317	(1.041–10.574)	0.043
Adequacy of monthly income (reference: sufficient)			
Insufficient	2.019	(1.129–3.611)	0.018
Traffic violation behavior (reference: never violated traffic rules in the past 3 months)			
Ever violated traffic rules in the past 3 months	2.021	(1.086–3.759)	0.026
Unsure	1.189	(0.470–3.007)	0.714

ADHD, attention-deficit hyperactivity disorder.
¹⁾ Multiple logistic regression, with a significance level at 0.05.

14.4% of the students showed signs of ADHD. The initial analysis examined the relationship between ADHD and various factors, including gender, monthly income sufficiency, previous ADHD diagnoses, recent traffic violations, daily internet and smartphone usage, and the length of online study sessions. Further analysis on the impact of previous ADHD diagnoses revealed several risk factors that increase the likelihood of an ADHD diagnosis. Individuals of unspecified gender were found to have higher odds of ADHD than female students, although no significant difference was found between male and female students. Additionally, students with insufficient income were more than twice as likely to have ADHD than those with adequate income. Moreover, students who had committed traffic violations in the past 3 months were approximately twice as likely to have ADHD compared to those who had not.

Interpretation

Current pharmacy students appear to have a higher risk of developing ADHD-like symptoms, with a prevalence exceeding the 8% reported before the COVID-19 pandemic by the Mental Health Institute in Thailand [10]. Fig. 2 visualizes the prevalence of these behaviors among students. The cognitive symptoms reported in pharmacy students include impaired attention, difficulty in task management, forgetfulness, and reduced executive functioning—consistent with common ADHD challenges. Difficulties in executive functioning, such as organization and procrastination, were highly prevalent. While hyperactivity and impulsive symptoms were also present, they were less pronounced compared to the challenges associated with inattention. The findings suggest that several factors may contribute to this increased ADHD risk among pharmacy students, including mental health struggles related to gender identity, financial stress, and environmental influences. Notably, students with insufficient income were twice as likely to exhibit ADHD-like behaviors compared to those with sufficient income. Furthermore, students who violated traffic rules show a doubled risk of ADHD, with even those unsure about their traffic behavior showing an increased likelihood. This may be linked to traits such as impulsivity, inattention, and difficulties with executive functioning, which can contribute to higher rates of risky or rule-breaking behaviors, particularly in risky driving.

Comparison with previous studies

Our findings are consistent with increased rates of ADHD observed in other countries since

the onset of the COVID-19 pandemic. For example, a study in Europe noted an increase in the consumption of ADHD medications following the pandemic [11]. Additionally, our results align with studies indicating that not disclosed and transgender individuals experience significantly higher rates of mental health challenges than their cisgender counterparts [12]. There is also substantial evidence suggesting that chronic financial stress can contribute to cognitive and behavioral issues typically associated with ADHD [13]. Moreover, our findings corroborate the connection between traffic violations and unmedicated ADHD drivers, especially in situations that require low levels of attention [14]. However, our study identifies a correlation between the duration of online learning and the manifestation of ADHD symptoms, which contradicts previous research suggesting no link between learning styles and mental health issues [15].

Limitations/generalizability

While our study offers valuable insights, its scope was limited to a single university in Southern Thailand, potentially affecting its generalizability. The cross-sectional design provided only a snapshot in time and lacked the depth of a longitudinal study. Furthermore, the reliance on self-reported data could introduce biases, and the sample size for certain subgroups, such as male students, was relatively small. Future research should aim to include larger sample sizes to address these limitations.

Suggestions

To advance research on ADHD prevalence among pharmacy students, further studies are essential to fully comprehend their behavioral patterns and coping strategies. This understanding is crucial for developing effective support mechanisms tailored to their specific needs. Additionally, it is important to explore targeted interventions that address specific risk factors identified in the study, including insufficient income, gender identity, and recent traffic violations. Addressing these factors will improve our understanding of ADHD in this group and inform the development of more precise and effective intervention strategies.

Conclusion

Several factors increase the likelihood of experiencing ADHD-like symptoms. Individuals of unspecified gender, those with insufficient monthly income, and those with recent traffic rule violations were more prone to exhibit ADHD-like symptoms. Notably, symptoms such as difficulties in executive functioning, including organization and procrastination, were highly prevalent among pharmacy students.

ORCID

Krittiya Rakchat: <https://orcid.org/0009-0007-0621-3452>

Saranan Eadcharoen: <https://orcid.org/0009-0007-3683-7573>

Amarawan Pentrakan: <https://orcid.org/0000-0003-1442-3605>

Authors' contributions

Project administration: Pentrakan A

Conceptualization: Rakchat K, Eadcharoen S, Pentrakan A

Methodology & data curation: Rakchat K, Eadcharoen S, Pentrakan A

Funding acquisition: not applicable

Writing – original draft: Rakchat K, Eadcharoen S, Pentrakan A
Writing – review & editing: Rakchat K, Eadcharoen S, Pentrakan A

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Data files are available from Harvard Dataverse: <https://doi.org/10.7910/DVN/BRQQDV>

Dataset 1 . Raw response data from 526 participants in Thailand

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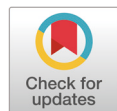
Supplementary materials

Not applicable.

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Adequacy of the physician workforce for preparing for future society in Korea: an English translation

Yun-Chul Hong

Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Korea

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Corresponding author

Yun-Chul Hong
Department of Preventive Medicine,
College of Medicine, Seoul National
University, 103 Daehak-ro, Jongno-gu,
Seoul 03080, Korea
E-mail: ychong1@snu.ac.kr

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Keywords

Medically underserved area; Patient acceptance of health care; Population forecast; Physicians; Workforce

Objectives: This study aimed to assess whether the current physician workforce in Korea is sufficient to meet future healthcare demands, considering demographic changes and increasing medical needs. The objective was to project the future supply and demand for physicians and identify potential regional disparities.

Methods: Data on outpatient and inpatient utilization rates were obtained from the 2018 Health Insurance Statistical Yearbook, and population projections were sourced from Statistics Korea (2017–2067). Medical demand was estimated by multiplying these utilization rates by the population projections. The supply of physicians was projected using a cohort-component model that incorporated medical school quotas and age-specific attrition rates. Two scenarios were developed to account for changes in productivity: Scenario 1 assumed a 50% decrease in productivity for physicians aged 65–75, and Scenario 2 assumed a 75% decrease. Additionally, regional projections were analyzed using data from provincial and secondary medical service areas.

Results: National-level projections suggest a looming shortage of physicians, despite an increase in medical school admissions. Both scenarios predict a physician shortage, particularly in regions such as North Gyeongsang, South Chungcheong, and Jeju Island, by 2047. In contrast, Seoul is likely to see a surplus of physicians. The regional analysis underscores substantial disparities in physician distribution, with underserved areas experiencing increasingly severe shortages.

Conclusion: The study concludes that without flexible adjustments to medical school admission quotas and healthcare delivery systems, Korea will face significant physician shortages in the coming decades. To address this, it is necessary to increase the number of physicians in underserved regions and improve the efficiency of healthcare utilization.

Introduction

Background

Estimating the demand for and supply of an appropriate number of physicians, and planning for their adequate provision, is crucial for the proper functioning of healthcare services.

Objectives

This study was conducted to determine whether the current number of physicians is adequate

to meet the needs of a future society, considering that social changes, such as demographic shifts, are expected to increase medical demand. Thus, instead of evaluating whether the current physician workforce is excessive or insufficient, this study projects the future physician workforce based on the assumption that the number of physicians in 2018 was appropriate.

Methods

Ethics statement

This study does not involve human subjects. Therefore, approval by the institutional review board and the acquisition of informed consent were not required.

Study design

This study is a simulation based on various data sources, including the Health Insurance Statistical Yearbook, the Report of Statistics Korea, and the number of physicians in Korea.

Data sources and analyses

Since medical demand reflects the population's use of medical services, we utilized data from the 2018 Health Insurance Statistical Yearbook to calculate per capita outpatient and inpatient utilization by age and gender. We then used population projection data from Statistics Korea (2017–2067) to estimate medical demand. Assuming a workload ratio of 1:3 between outpatient and inpatient services, we multiplied the outpatient demand by 3 to estimate the total demand.

For the supply side, we estimated the number of physicians based on medical school quotas using a cohort-component algorithm. We assumed a 95% pass rate for students taking the national medical licensing examination, allowing for those who were unsuccessful to retake the exam in subsequent years. We made projections by age groups (20s, 30s, 40s, 50s, 60s, 65s, 70s), using the mortality rates for each age group from 2018 Statistics Korea data to calculate attrition rates. The retirement age was set at 75 years.

To calculate the balance between supply and demand, we first needed to quantify medical demand in terms of the number of physicians required to meet it. We estimated the daily workload for each physician, based on the assumption that they work 265 days per year, using data from 2018. For physicians aged 65 to 75, we adjusted their expected daily productivity to 50% of that of their younger colleagues in Scenario 1, and to 75% in Scenario 2. Additionally, we factored in an annual increase of 0.5% in the daily work capacity of a physician, attributing this improvement to technological advancements. With these calculations, we determined the required number of physicians each year and compared it to the projected physician supply for that year.

Regional data were categorized into two groups: by province and by secondary medical service area. Physician supply projections utilized age-specific physician data from either the province or the secondary medical service area, as specified in the 2016 data from the Ministry of Health and Welfare. Medical demand for each province was estimated using population projections from Statistics Korea for the years 2017 to 2047. As there were no distinct projections available for secondary medical service areas, the 2018 population ratios were applied to the national projections.

Results

National-level physician workforce supply and demand projections

National-level projections scenario 1

Assuming that the supply and demand of physicians were appropriately balanced in 2018, even with an increase in the admission quota for medical schools and graduate medical schools to 1,500 students starting in 2021, a shortage of physicians is still predicted. However, since an excess in the physician workforce may emerge after a certain period, it is necessary to implement flexible adjustments by appropriately increasing or decreasing quotas (Fig. 1 and Table 1).

National-level projections scenario 2

Even assuming that the productivity of physicians aged 65 and over decreases not by 50% but by 75%, a shortage of physicians is still predicted, even with an increase in the admission

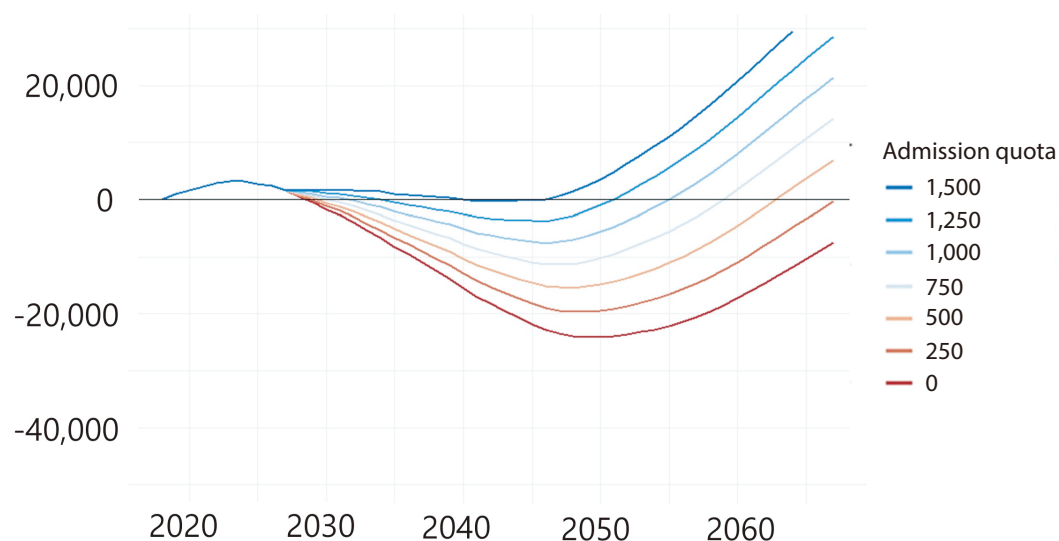


Fig. 1. Scenario 1 of the national supply and demand of physicians in Korea.

Table 1. Timing and magnitude of physician shortages based on assumed increases in medical school admission quotas

Admission quota (assumption)	Year of greatest physician shortage	Magnitude of shortage (number of physicians)
Maintain current quota	2050	26,570
250	2048	22,237
500	2048	18,059
750	2046	14,018
1,000	2046	10,231
1,250	2046	6,445
1,500	2043	3,035

quota to 1,500 students starting in 2021. However, this scenario could also lead to an excess of the physician workforce after a certain period. Therefore, measures to appropriately adjust the quotas are deemed necessary (Table 2).

Table 2. Surplus or shortage of physicians per 1,000 population in 2018 and 2047

Region	Year	Surplus/shortage of physicians per 1,000 population	
		Scenario 1	Scenario 2
Seoul	2018	1.14	1.16
	2047	1.79	1.97
Busan	2018	0.26	0.28
	2047	0.68	0.8
Daegu	2018	0.39	0.4
	2047	0.71	0.83
Incheon	2018	-0.25	-0.26
	2047	-0.83	-0.79
Gwangju	2018	0.49	0.5
	2047	0.75	0.87
Daejeon	2018	0.54	0.55
	2047	0.67	0.79
Ulsan	2018	-0.23	-0.23
	2047	-0.48	-0.42
Sejong	2018	-1.12	-1.14
	2047	-1.91	-1.94
Gyeonggi	2018	-0.3	-0.31
	2047	-0.91	-0.87
Gangwon	2018	-0.49	-0.49
	2047	-1.02	-0.97
Chungcheongbuk-do	2018	-0.55	-0.56
	2047	-1.13	-1.1
Chungcheongnam-do	2018	-0.71	-0.73
	2047	-1.34	-1.32
Jeollabuk-do	2018	-0.31	-0.31
	2047	-0.46	-0.39
Jeollanam-do	2018	-0.74	-0.75
	2047	-1.08	-1.04
Gyeongsangbuk-do	2018	-0.93	-0.94
	2047	-1.48	-1.46
Gyeongsangnam-do	2018	-0.44	-0.44
	2047	-0.84	-0.79
Jeju	2018	-0.32	-0.33
	2047	-1.06	-1.03

Regional physician workforce supply and demand projections

The projection of physician workforce supply and demand by region revealed that Seoul had the highest concentration of physicians, with a ratio exceeding 1.14–1.16 physicians per 1,000 population as of 2018. In contrast, regions such as Chungcheong, Jeolla, Gyeongsang Provinces, and Jeju Island had fewer than 1 physician per 1,000 population. Given the current trends, by 2047, these regions are expected to face a more severe shortage of physicians.

Projections for secondary medical service areas

In an analysis of 56 secondary medical service areas, Hongseong was identified as having the most significant physician shortage in 2018, with approximately 1.58 fewer physicians per 1,000 people than the national average. This shortage was closely followed by Mungyeong and Sokcho, each with a deficit of 1.45 physicians per 1,000 population, Sacheon with 1.42, and both Jincheon and Andong with 1.40. On the other hand, Seoul had the highest surplus of physicians in 2018, with about 1.02 more physicians per 1,000 population than the national average. Following Seoul were Yangsan with 0.64 additional physicians per 1,000 population, Bucheon with 0.21, Gwangju with 0.18, and Busan with 0.16.

In 2018, most secondary medical service areas in metropolitan cities had an excess of physicians, whereas areas experiencing a shortage of physicians were predominantly found in the Chungcheong, Jeolla, and Gangwon regions.

Assuming no increase in medical school quotas, projections for the physician supply and demand in 2035 suggest a deepening shortage in Hongseong, which already had the most significant shortage in 2018. By 2035, the shortage is expected to reach approximately 2.29 physicians per 1,000 population. Following closely are Mungyeong, with a projected shortage of 2.19 physicians per 1,000 population, Andong with 2.12, Sacheon with 2.10, and Sokcho with 2.04, all of which are anticipated to experience worsening shortages compared to 2018. Conversely, areas like Seoul, Yangsan, Bucheon, Suwon, and Cheonan are expected to have an excess of physicians. The surplus is particularly notable in Seoul and Yangsan, where the excess is predicted to exceed 1.41 and 1.12 physicians per 1,000 population, respectively, relative to 2018.

Discussion

According to the regional supply and demand projection scenarios from a study on the adequacy of the physician workforce, the areas anticipated to experience the most significant shortages of physicians by 2047—excluding the Gyeonggi area in the metropolitan region—are North Gyeongsang Province, South Chungcheong Province, North Chungcheong Province, South Jeolla Province, and Jeju Island.

Therefore, it will be necessary to increase the number of physicians providing medical services in regions experiencing shortages. Meanwhile, according to 2018 OECD data, South Korea has fewer clinical physicians than the OECD average, yet it records the highest number of outpatient visits per capita, at 16.9 times per year. This indicates a significant imbalance in physician supply and demand, underscoring an urgent need to enhance healthcare utilization behaviors and the overall healthcare delivery system.

ORCID

Yun-Chul Hong: <https://orcid.org/0000-0001-9010-7271>

Authors' contributions

All work was done by Yun-Chul Hong.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Please contact the corresponding author for research data.

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Supplementary materials

Not applicable.

Editor's note

This is an essential article on the estimated number of physicians needed to prepare for the future of society in Korea. Therefore, it will be helpful to cite the author's work. The article was supplemented according to the journal's style and format. An abstract was also included.



맥커스커 주관적 인지 장애 검사(McSCI): 지각된 인지 저하의 새 측정 도구

The McCusker Subjective Cognitive Impairment Inventory (McSCI): a novel measure of perceived cognitive decline – a Korean translation

Hamid R. Sohrabi^{1,2,3,4}, Brandon E. Gavett^{5,6}, Michael Weinborn^{3,5}, Craig P. Speelman⁷,
 Romola S. Bucks⁵, Ralph N. Martins^{1,3,4}

¹Centre for Healthy Ageing, Health Futures Institute, Murdoch University, Murdoch, WA, Australia

²School of Psychology, Murdoch University, Murdoch, WA, Australia

³School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia

⁴Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Macquarie Park, NSW, Australia

⁵School of Psychological Science, University of Western Australia, Crawley, WA, Australia

⁶Department of Neurology, University of California, Sacramento, CA, USA

⁷Experimental Psychology Unit, School of Arts and Humanities, Edith Cowan University, Joondalup, WA, Australia

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Corresponding author

Hamid R. Sohrabi
 Centre for Healthy Ageing, Health
 Futures Institute, Murdoch University,
 Murdoch, WA, Australia
 E-mail: hamid.sohrabi@murdoch.edu.au

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Keywords

주관적 인지 저하; 치매; 맥커스커 주관적 인지 장애 검사; 인지; McSCI-S; 지각된 인지 저하; 노인

Objectives: 주관적 인지 저하(subjective cognitive decline, SCD)는 객관적인 중대한 저하의 증거 없이 자신의 인지 기능에 대한 자기 또는 타인의 우려를 의미하며, 이는 치매 위험의 지표이다. 현재 사용 가능한 SCD 측정 도구의 신뢰도와 타당성에 대한 합의가 부족하다. 따라서 새로운 심리측정학적으로 타당한 SCD 측정 도구를 도입하는 것이 시급하다. 새로운 SCD 측정 도구인 맥커스커 주관적 인지 장애 자가보고서(McCusker Subjective Cognitive Impairment Inventory, McSCI-S)의 심리측정학적 특성을 보고한다.

Methods: 기존에 출판된 측정 도구의 검토와 SCD를 가진 사람들에 대한 임상 및 연구 데이터를 바탕으로, 기억력, 언어능력, 지남력, 주의력 및 집중력, 시간간 구성 능력 및 실행 기능의 6가지 인지 영역에 대한 우려를 평가하기 위한 46문항 자가보고 설문지를 개발했다. McSCI-S를 526명의 참가자를 대상으로 요인 분석, 문항 반응 이론(item response theory) 분석 및 의사결정 기준점(receiver operating characteristic) 곡선을 통해 검증하였다.

Results: 단일차원 모델(unidimensional model)이 적합한 것으로 나타났다(comparative fit index=0.94, Tucker–Lewis index=0.94, root mean square error of approximation[90% CI]=0.052[0.049, 0.055], weighted root mean square residual=1.45). McSCI-S의 내적 일관성은 우수했다($\alpha=0.96$). SCD를 가진 참가자를 식별하기 위해 ≥ 24 의 기준 점수(cut-off value)를 제안한다. McSCI-S 점수가 높을수록 연령, 성별 및 교육 수준을 통제 한 후에도 전반적인 인지 기능, 일화적 언어 기억력, 실행 기능의 저하 및 더 큰 기억력 불만 및 우울 점수와 관련이 있었다($P<0.001$).

Conclusion: 우수한 신뢰도와 구성 타당성은 McSCI-S가 다양한 인지 영역에 대한 자가보고 우려(self-reported concerns)를 포착하면서 SCD를 정확하게 추정함을 시사한다. 심리측정학적 분석은 이 측정 도구가 코호트 연구뿐만 아니라 개인별 임상 환경에서도 SCD를 평가하는 데 사용할 수 있음을 나타낸다.

주요 사항(Key Points)

- 심리측정학적으로 타당한 주관적 인지 저하(subjective cognitive decline, SCD) 측정 도구의 긴급한 필요성을 해결하기 위해 새로운 측정 도구를 제안한다.
- 맥커스커 주관적 인지 장애 자가보고서(McCusker Subjective Cognitive Impairment Inventory, McSCI-S)는 우수한 신뢰도와 타당성으로 인지적 우려(cognitive concerns)를 측정한다.
- McSCI-S는 99.9%의 정확도로 평균 이상의 SCD 수준을 가진 개인을 식별할 수 있다.
- 이 SCD 측정 도구는 연구 및 임상 환경에서 개인 및 그룹 수준의 임상 의사 결정에 신뢰성 있게 사용할 수 있다.

서론(Introduction)

연구 배경(Background)

주관적 인지 저하(SCD)는 이전의 정상적인 능력에 비해 자신 또는 제보자가 지각하는 인지 저하를 의미한다[1]. 보다 구체적인 구성 요소인 주관적 기억 불만(subjective memory complaint, SMC)은 자신의 기억 능력에 대한 자신 또는 타인의 우려를 포함한다. 현재 인지 장애가 없는 상태에서의 SCD/SMC는 향후 인지 저하[1-3] 및 알츠하이머병(Alzheimer's disease, AD)과 관련이 있다[4]. 현재 사용 가능한 SCD/SMC 측정 도구는 검증 단계에서 사용된 표본 크기가 작고, 최적 이하의 심리측정학적 특성을 가지며, 연구에 기반한 기준 점수(cut-off score)의 부족, 그리고 가장 중요한 것으로 표집된 인지 영역의 수로 대표되는 내용 타당성이 제한적이라는 주요 한계가 있다. 기존의 SCD 측정 도구는 cohort 수준과 비교하여 개인 수준에서 미묘한 주관적 변화를 감지하는 데 민감도가 낮아[5], 임상 환경에서의 적용이 제한된다. 예를 들어, 환자에 대한 개별 수준의 의사 결정에서 검사 신뢰도는 0.95 이상이어야 한다[6]; 그러나 많은 기존의 SCD 측정 도구는 이 조건을 충족하지 못한다[7-10]. 또한 19종 연구에서 사용된 34개 문항 SCD 측정 도구를 검토한 결과, 이들 중 61.8%(n=21)의 측정 도구가 특정 인지 기능과 개념적으로 관련이 없는 문항(예: 감정적 및 심리적 상태 또는 신체 및 운동 기능을 평가하는 문항)을 포함하고 있음을 알 수 있었다[11].

연구 목적(Purpose)

맥커스커 주관적 인지 장애 검사(McSCI; 발음: 맥씨)는 임상적으로 정보에 기반하고 심리측정학적으로 타당한 SCD 측정 도구를 제공하기 위해 개발되었다. 이 논문에서 McSCI-자가보고서(McSCI-S)의 요인 구조, 신뢰도 및 구성 타당성을 포함한 심리측정학적 특성을 보고하려고 한다.

방법(Methods)

윤리 선언(Ethics Statement)

관심 있는 참가자에게는 McSCI 연구에 등록하기 전에 서명할 통합된 연구별 정보 및 동의서 팩이 제공되었다. 이 연구는 Ramsay Health Care WA/SA(서호주 및 남호주) 인간 연구 윤리 위원회(Human Research Ethics Committee)의 승인을 받았다.

참가자(Participants)

호주 서부(WA)와 뉴사우스웨일스(NSW)에서 진행 중인 여러 연구에서 모집되었다. 이 연구에는 다음이 포함된다: (i) 서호주 기억 연구(WAMS), 30세 이상의 지역사회 거주자 중 정신과 또는 신경과 병력이 없는 개인의 신경심리학적 및 생물학적 노화 지표에 대한 종단 연구[12,13]; (ii) Kerr Anglican Retirement Village Initiative in Ageing Health(KARVIAH) 연구(NSW), 65-90세의 은퇴 마을 거주자를 대상으로 치매의 미래 위험을 예방하기 위한 커큐민의 효능을 조사한 완료된 임상 시험[14]; (iii) 호주 영상, 바이오 마커 및 라이프스타일(AIBL) 노화 연구, 60세 이상의 전임상, 전구 증상 및 임상 단계의 AD 참가자를 모집하는 진행 중인 종단 관찰 연구[15]; (iv) 주관적 기억 불만을 가진 뇌 아밀로이드-PET 양성 남성에서 테스

토스테론의 효능을 평가하기 위한 56주간의 이중 맹검 무작위 연구(DHA 보충 유무와 함께) [TotAL 연구; (ACTRN12618000761268)]; (v) 우성 유전 알츠하이머 네트워크(DIAN), AD에 대한 알려진 돌연변이를 가진 가족의 18세 이상 개인에 대한 관찰 연구[16].

모든 연구에서 참가자는 부모 연구의 포함/제외 기준에 따라 인지 능력에 영향을 미치는 주요 의학적, 정신과적 또는 신경과적 상태(예: 치매)가 없고; 교정 여부에 관계없이 정상적인 청력과 시력을 가지며; 독립적으로 생활하고; 읽고 쓸 수 있으며; 동의할 수 있고; 모집 당시 30세 이상인 경우 McSCI 연구에 포함될 수 있었다.

측정 도구(Measures)

이 연구에서 사용된 측정 도구는 다음과 같다.

맥커스커 주관적 인지 장애 자가보고서(The McCusker Subjective Cognitive Impairment Inventory-Self-Report)

2013년 1월에 '주관적 인지 불만', '주관적 인지 장애', '주관적 기억 불만', '자가보고 인지 문제', '자가보고 기억 문제', 그리고 '치매', '경도 인지 장애' 또는 'MCI', '알츠하이머병' 또는 'AD'('subjective cognitive complaints', 'subjective cognitive impairment', 'subjective memory complaints', 'self-reported cognitive problems', 'self-reported memory problems', and 'dementia', 'mild cognitive impairment' or 'MCI' and 'Alzheimer's disease' or 'AD')등의 키워드로 PubMed 검색을 수행했다. 우리는 약 30개의 출판된 설문지를 사용한 논문을 포함하여 SMC/SCD에 대한 205개의 논문을 확인했다(미발표 데이터). 또한 SCD에 포함되어야 할 인지 영역/기능을 결정하기 위해 전임상 AD, MCI 및 치매의 인지 저하를 보고하는 문헌을 조사했다[17].

초기 96개의 문항 은행(item bank)이 개발되었다. 저자 중 두 명은 박사과정 학생 및 연구 조교와 세 명의 독립 심리학자(감사의 글 참조)의 도움을 받아 이러한 문항을 특정 인지 영역 평가, 문항 명확성, 적합성 및 외관 타당성에 대해 평가했다. 언어 능력(language skills, LS; 6개 문항), 지남력(orientation, O; 6개 문항), 주의력 및 집중력(attention and concentration, AC; 6개 문항), 시공간 구성 능력(visuoconstruction abilities, VC; 6개 문항), 실행 기능(executive function, EF; 9개 문항), 기억력(memory, MA; 13개 문항)의 6가지 인지 영역을 대표하는 46개의 문항이 선택되었다(표 1의 McSCI-S 설문지 및 부록의 인지 영역, 각 인지 영역에 할당된 문항 및 기술적 세부사항 참조)[18]. 이 46개의 문항은 참가자들에게 단어에 대한 의견을 묻기 위해 제공되었으며, 적절한 경우 이해도를 향상시키기 위해 문항을 수정했다. McSCI-S 문항은 5점 Likert 척도(0-4)로 점수가 매겨지며, 응답은 '거의 항상 그렇다'(점수: 4)에서 '거의 결코 그렇지 않다'(점수: 0)까지이다. 가능한 McSCI 총점은 0에서 184까지이며, 점수가 높을수록 더 많은 우려를 나타낸다.

기타 측정 도구(Other Measures)

McSCI-S와 기존의 인지 측정 도구 간의 타당성과 관계를 조사하기 위해 동일한 연구 방문에서 수집된 WAMS 데이터를 분석했다. 전반적인 인지 기능은 몬트리올 인지 평가(Montreal Cognitive Assessment, MoCA)를 사용하여 평가되었다[19]. 언어적 일화 기억력은 캘리포니아 언어 학습 검사-II(California Verbal Learning Test-II, CVLT-II)를 사용하여 평가되었으며, 학습 총점, 단기 및 장기 지연 자유 회상 및 인식 히트를 포함한다[20]. Trail Making Test B(시간: 초)[21]는 주의력/처리 속도 및 실행 기능을 평가하는 데 사용되었다[22]. SMC는 기억력 평가 클리닉-설문지(Memory Assessment Clinic-Questionnaire, MAC-Q)를 사용하여 평가되었으며, 이는 6개의 문항으로 구성된 기억력 저하에 대한 지각된 평가 도구이며 총점은 7에서 35까지이다. ≥ 25 의 기준 점수는 SMC를 나타낸다[8]. 우울-불안-스트레스 척도-21(Depression Anxiety Stress Scale-21, DASS-21)은 21개의 자가보고식 문항으로 구성되며, 각 문항은 0-3 척도로 평가되며 총점은 2를 곱하여 0-126의 점수 범위를 만든다[23].

데이터 분석(Data Analysis)

McSCI-S의 심리측정학적 특성은 문항 반응 이론(item response theory, IRT) 방법을 사용하여 평가

표 1. 맥커스커 주관적 인지 장애 자가보고서(McCusker Subjective Cognitive Impairment Inventory, McSCI-S)

이 설문지는 지난 5년 전과 비교하여 지난 2년 동안 경험하거나 인지한 기억력, 언어, 집중력 및 기타 정신 능력의 점진적인 변화를 묻는다. 각 문항을 주의 깊게 읽고 신체 건강(예: 관절염, 청력 또는 시력 문제)과 관계없이 현재의 정신 능력을 설명하는 답변을 선택해 주세요(✓ 또는 ×로 표시). 선택할 답변이 없는 문항은 주어진 상황에서 본인이 어떻게 수행할지에 대해 최선을 다해 추측해 주세요.

지난 2년 동안	거의 항상 그렇다	대체로 그렇다	가끔 그렇다	대체로 그렇지 않다	거의 그렇지 않다
1. 언어와 말하기 능력에 더 많은 어려움을 느낀다.					
2. 기억력에 심각한 문제가 있다.					
3. 여러 가지 일을 집중하는 데 어려움을 겪는다.					
4. 집안의 일상적인 문제를 해결하는 데 더 많은 어려움을 느낀다.					
5. 물건을 어디에 두었는지 기억하지 못한다.					
6. 낱파를 자주 헛갈린다.					
7. 잘 아는 사람과 대화 중 이름을 잊을 때가 있다					
8. 방금 들은 것을 반복하는 것이 어렵다(예: 전화번호, 주소 등).					
9. 몇 주 전에 있었던 일의 세부 사항을 잊어버린다.					
10. 예전만큼 체계적이지 못하다.					
11. 쉽게 산만해지고 대화나 영화 줄거리를 따라가지 못한다.					
12. 글을 쓰거나 타이핑하는 속도가 느려졌다.					
13. 가까운 미래에 하려던 일을 잊어버린다.					
14. 일을 해야 할 시간보다 더 일찍 또는 늦게 하는 경우가 있다.					
15. 주차장에서 차를 어디에 주차했는지 자주 잊는다.					
16. 미리 계획을 세우고 제시간에 이 계획을 실행하는 데 어려움을 겪는다.					
17. 어렸을 때 학교에서 배운 기본적인 것들을 자주 잊는다.					
18. 청력과 상관없이, 가끔 다른 사람들이 하는 말을 이해하지 못할 때가 있다.					
19. 물체나 사람과 부딪힐 가능성이 더 높아졌다.					
20. 일상적인 문제(예: 입을 옷 선택하기, 구매할 물건 선택하기 등)에 대한 결정을 내리는 데 어려움을 겪는다.					
21. 다른 사람들이 나에게 같은 이야기를 반복한다고 말한 적이 있다(예: 같은 이야기나 질문을 반복함).					
22. 운전하거나 걸어서 집으로 돌아갈 때, 집을 지나쳐버릴 때가 있다.					
23. 알고 있던 유명한 사람들(예: 배우, 가수, TV 캐릭터)을 알아보지 못할 때가 있다.					
24. 가장 내 응급 상황(예: 물이 새는 수도꼭지, 거미나 작은 무독성 도마뱀 등)을 관리하는 것이 어렵다.					
25. 일상 용품의 이름을 잊어버린다(예: 부엌 도구, 친숙한 가정 용품).					
26. 들은 것, 읽은 것, 본 것을 기억하기 위해 더 노력해야 한다.					
27. 좋아했던 일이라도 정신을 집중하지 못한다.					
28. 동시에 두 가지 일을 할 수 없다(예: 설거지하면서 누군가와 이야기하기, 운전하면서 라디오 듣기).					
29. 요일을 자주 잊는다.					
30. 최근에 배운 기기/도구의 사용법을 자주 잊는다(예: 컴퓨터, 휴대폰/스마트폰).					
31. 친구나 친척의 주소를 지도에서 찾지 못한다.					
32. 잘하던 기술을 활용한 게임(예: 브리지, 체스, 카드, 골프)이나 활동을 더 이상 잘하지 못한다.					
33. 말을 할 때 적절한 단어를 찾는 데 어려움을 느낀다.					
34. 내 필체가 크게 변했다.					

표 1. 계속

지난 2년 동안	거의 항상 그렇다	대체로 그렇다	가끔 그렇다	대체로 그렇지 않다	거의 그렇지 않다
35. 오래된 사진을 볼 때, 예전에 알았던 사람들을 알아보지 못할 때가 있다.					
36. 요즘에는 어떤 것을 이해하기 위해 몇 번씩 읽어야 한다.					
37. 주변에서 일어나고 있는 일에 주의를 기울이지 못한다.					
38. 그림을 정확히 따라 그리지 못할 때가 있다(예: 나무, 집 등).					
39. 간단한 산수를 머릿속으로 더 이상 계산하지 못한다.					
40. 집 안에서 특정 방(예: 욕실, 침실, 거실)으로 가는 길을 헛갈릴 때가 있다.					
41. 대화가 중단되면, 그 대화를 이어가기 어렵다.					
42. 유명한 장소나 건물을 보아도 알아보지 못할 때가 있다.					
43. 누군가에게 길을 알려주는 데 어려움을 겪는다. 길을 혼동하기 때문이다.					
44. 방금 시작한 일을 중단하는 것이 어렵다.					
45. 가까운 친척의 이름이나 생일을 잊어버린다(예: 손자, 조카 등).					
46. 자신 있게 사용하던 것들을 사용하는 데 어려움을 겪는다(예: 전동 칫솔, 전자레인지, 계산기).					

되었다. 이를 통해 문항 난이도 매개변수와 개인의 특성 수준 추정치를 동일한 척도에서 배치할 수 있다. McSCI-S 문항의 다분 문항(polytomous item) 특성으로 인해 Samejima[24]가 소개한 등급 반응 모델(graded response model, GRM)이 모델 적합과 문항 매개변수 추정을 위해 사용되었다.

요인 구조(Factor Structure)

McSCI-S가 6개의 다른 인지 영역에 걸친 우려를 묻기 때문에, 점수가 단일차원 또는 다차원 요인 구조로 더 잘 설명되는지 결정하고자 했다. Mplus 버전 8[25]을 사용하여 두 가지 경쟁 모델을 지정했다: 단일 요인 확인적 요인 분석(confirmatory factor analysis, CFA) 모델과 6요인 CFA 모델. 모델 적합성은 비교 적합 지수(comparative fit index, CFI), Tucker-Lewis 지수(Tucker-Lewis index, TLI), 근사 오차 제곱 평균(root mean square error of approximation, RMSEA), 가중 근사 제곱 평균 잔차(weighted root mean square residual, WRMR) 등 표준 적합 기준을 사용하여 판단했다. 다차원 모델의 우수성은 추정 문제의 부재, 우수한 모델 적합 통계, 충분히 구분되는 요인(즉, 요인 상관관계 <0.9), 충분한 크기(즉, >0.40)의 표준화된 요인 부하량 및 부호(즉, 양수)로 표시된다. 최상의 모델은 psych 패키지(버전 1.8.12)를 사용하여 McDonald's omega를 계산하여 추가로 평가되었다(R 버전 3.5.2)[26].

등급 반응 모델(Graded Response Model)

단일차원성 가정을 확인한 후, Samejima의 GRM을 사용하여 문항 및 척도 매개변수를 추정했다. 문항 변별도모수(a)와 각 문항에 대해 최대 4개의 난이도모수(b)를 추정했다. 이러한 매개변수 추정치는 총 시험 정보, 표준 오차 및 기본 특성(θ)의 범위에 따른 신뢰도를 포함한 McSCI-S의 척도 수준 심리측정학적 특성을 평가하는 데 사용되었다.

기준 점수 계산(Cut-off Score Calculation)

상대적으로 신뢰할 수 있는 기준 점수를 식별하기 위해 Youden 지수[27]를 사용했다. Youden 지수는 0에서 1까지의 점수 범위를 가지며, 점수가 높은 기준점수가 선별 또는 진단 목적으로 더 나은 성능을 나타낸다고 간주된다. Youden 지수는 다음 공식으로 계산되었다: Youden의 $J = (\text{민감도} + \text{특이도}) - 1$ [28,29].

결과(Results)

CFA 결과와 McSCI-S와 다른 측정 도구 간의 연관성이 제공된다. 필요한 경우 추가 정보나 결과는 부록에 제공된다.

인구 통계(Demographics)

표 2는 CFA 코호트(n=526)의 인구 통계 데이터를 제공한다. 참가자의 연령은 39세에서 97세(M=71.47; SD=7.28)까지 분포했으며, 35.4%가 여성이다. 교육 연수는 6년에서 24년(M=13.06; SD=3.08)까지 분포했다. IRT 표본(n=385)에서는 269명(69.8%)이, 전체 데이터가 있는 더 큰 표본(n=503)에서는 347명(68.9%)이 MAC-Q 절단값 ≥ 25 를 사용하여 기억 불만자였다.

요인 분석, 타당성 및 신뢰도(Factor Analysis, Validity and Reliability)

McSCI-S 요인 구조(McCusker Subjective Cognitive Impairment Inventory–Self-Report Factor Structure)

첫 번째 CFA 모델은 McSCI-S 문항 점수가 각기 다른 인지 영역(즉, 언어, 기억, 주의력 및 집중력, 실행 기능, 지남력 및 시공간 구성)에 해당하는 각 상관 요인으로 설명될 수 있다는 가설을 테스트했다. 이는 적합한 것으로 나타났지만(CFI=0.94, TLI=0.94, RMSEA[90% CI]=0.051[0.048, 0.054], WRMR=1.41), 요인 간의 구별이 충분하지 않았다. 모든 요인의 추정 상관관계가 0.87을 초과했으며, 15개의 요인 상관 중 13개는 $g > 0.90$ (95% CI[0.99, 1.04])였다. 이러한 결과는 요인 간의 중복성을 강하게 시사하며, 보다 간결한 모델이 필요함을 나타낸다.

단일차원 모델도 데이터에 잘 맞았으며, CFI=0.94, TLI=0.94, RMSEA[90% CI]=0.052[0.049, 0.055], WRMR=1.45로, 6요인 모델에 비해 모델 적합도에 거의 감소가 없었다. 또한 단일차원 모델의 McDonald's omega는 0.96으로, 단일 요인 모델을 강력히 지지했다.

등급 반응 모델(Graded Response Model)

단일차원성 가정을 확인한 후, Samejima의 GRM을 사용하여 문항 및 척도(scale) 모수(parameter)를 추정했다. 분별도모수(discrimination parameter)와 경계모수(threshold parameter=boundary parameter) 추정치는 표 3에 나타나 있다. 모든 분별도모수는 최소 1.04에서 최대 2.68까지 우수한 성능을 보였다. 첫 번째(가장 낮은) 경계모수는 -1.97(Item 5)에서 2.00(Item 40)까지 분포하여, 매우 낮은 특성 수준($q < -2$)의 SCD는 McSCI-S 문항으로 신뢰성 있게 측정되지 않을 수 있음을 시사한다. 반면, 마지막(가장 높은) 경계모수는 1.92(Item 25)에서 4.77(Item 44)까지 분포하여, 높은 및 매우 높은 특성 수준($q > 2$)의 SCD는 McSCI-S로 정확하게 추정될 수 있음을 나타낸다. 그림 1은 SCD의 기본 특성 수준과 McSCI-S의 예상 점수 간의 관계를 보여준다. 척도 정보와 표준 오차는 부록의 그림-Supp File-A에 나타나 있다. 그림 1에서 볼 수 있듯이, McSCI-S는 기본 특성의 넓은 범위에서 높은 정보를 제공한다(약 -2 SD에서 +4 SD까지). 따라서 이 간격 내에서 추정된 SCD의 표준 오차는 낮으며($SE < 0.31$), 이는 McSCI-S가 대부분의 특성

표 2. CFA(confirmatory factor analysis) 코호트(n=526)의 인구 통계 데이터

변수	전체	범위
연령, M(SD)	71.47(7.28)	39–97
여성 성별, N(%)	186(35.4)	-
교육 연수, M(SD)	13.06(3.08)	6–24
McSCI-S 총점, M(SD)	36.96(22.53)	0–122

McSCI-S, 맥커스커 주관적 인지 장애 자가보고서.

표 3. 등급 반응 모델의 매개변수 추정치

Item	a	b1	b2	b3	b4
1	1.27	-0.59	0.53	2.44	3.92
2	1.28	-1.96	-0.37	1.68	3.14
3	1.91	-0.77	0.5	1.7	3.02
4	1.96	-0.20	1.24	2.46	-
5	1.24	-1.97	-0.45	2.11	3.91
6	1.46	-0.89	0.58	2.09	3.49
7	1.22	-0.91	0.34	2.65	3.94
8	1.58	-1.45	0.08	1.63	2.94
9	1.51	-1.20	0.36	2.09	3.7
10	1.85	-0.46	1.01	2.22	3.17
11	1.99	-0.45	0.92	2.25	-
12	1.83	-0.30	0.95	1.86	3.06
13	1.72	-0.88	0.76	2.37	-
14	2.02	-0.03	1.51	2.78	-
15	1.48	0.07	1.83	3.77	-
16	1.9	0.29	1.73	3.05	-
17	1.54	-0.37	1.02	2.37	-
18	2.13	-0.16	1.04	2.5	-
19	1.4	0.48	1.73	3.61	-
20	1.93	0.27	1.46	2.66	-
21	1.15	-0.36	1.06	3.52	-
22	1.92	1.69	3.12	-	-
23	1.04	-0.35	1.39	3.96	-
24	1.41	1.24	2.67	3.26	-
25	1.31	0.6	1.92	-	-
26	1.92	-0.69	0.56	1.96	3.06
27	2.68	0.23	1.25	2.19	-
28	1.41	0.45	1.57	2.75	3.67
29	1.42	0.41	1.92	3.2	-
30	1.48	-0.59	0.52	1.98	3.26
31	2	0.95	2.22	-	-
32	1.56	0.19	1.61	2.81	-
33	1.51	-0.94	0.52	2.59	-
34	1.3	0.08	1.35	2.37	3.65
35	1.68	0.48	1.76	3.25	-
36	1.8	-0.75	0.5	1.97	3.36
37	1.74	-0.13	1.2	2.82	-
38	1.19	0.79	2.5	3.35	-
39	1.5	0.55	1.64	2.88	-
40	2	2	-	-	-

표 3. 계속

Item	a	b1	b2	b3	b4
41	1.3	-0.43	1.17	3.21	-
42	1.57	0.5	2.04	-	-
43	1.97	0.36	1.61	2.67	-
44	1.09	-0.16	1.39	2.85	4.77
45	1.26	0.06	1.23	2.47	3.88
46	1.33	1.28	2.8	-	-

a, 분별도모수; b, 경계모수.

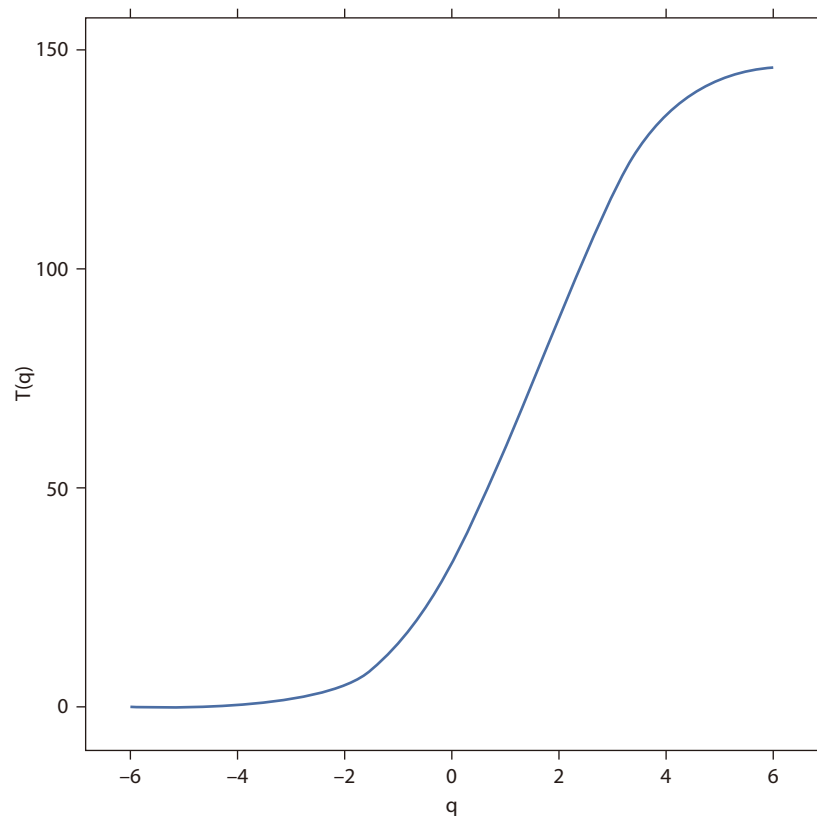


그림 1. SCD(subjective cognitive decline) 특성 수준과 McSCI-S(McCusker Subjective Cognitive Impairment Inventory) 예상 점수 간의 관계. x축은 잠재적 특성 수준(SCCs)을 나타내며, 점수가 높을수록 더 많은 불만을 나타낸다. y축은 예상되는 McSCI-S 총점을 보여준다. S자형 곡선은 잠재적 특성과 총점 간의 관계를 나타낸다.

수준에서 SCD를 정확하게 추정할 수 있음을 의미한다. 또한 높은 정보의 결과로 특성 연속체의 대부분에서 높은 신뢰도가 나타났으며, 이는 부록의 그림 Supp-File에 나타나 있다. 특히, 우수한 신뢰도의 지표인 0.90 이상의 신뢰도 추정치는 능력 수준이 -1.73에서 4.54 사이에서 발견되었다. 0.95 이상의 신뢰도 추정치, 즉 매우 바람직한 측정 속성은 -0.89에서 3.72의 능력 수준 범위에서 가능하다. 즉, 평균 이상($q > 0$)의 SCD를 가진 인구의 99.99%에 대해, McSCI-S의 정밀도는 우수하며($SEs < 0.23$), 신뢰도는 개인 수준의 SCD 선별 의사 결정에 가장 바람직한 범위에 있다[6]. 반대로, SCD 특성 연속체의 하위 절반에서 McSCI-S의 심리측정학적 속성은 덜 바람직하지만 불충분하지는 않으며, 이는 개인이 이 특성에서 매우 낮을 때(즉, 높은 수준의

인지 저하를 보고하지 않을 때) SCD 추정치가 덜 정확하고 신뢰도가 낮음을 의미한다. McSCI-S의 문항 수준에 대한 추가 세부사항은 표 Supp-2에 나와 있으며, 관찰된 점수에 해당하는 잠재적 특성 z-점수를 제공한다. 그림 Supp-2는 각 McSCI 문항의 문항 반응 범주 특성 곡선을 보여주며, 측정되는 기본 특성의 함수로 각 문항의 응답 옵션이 어떻게 작동하는지에 대한 시각적 묘사를 제공한다.

다른 측정 도구와의 연관성(Association with Other Measures)

WAMS의 노화 종단 연구에서 39–97세의 383명으로 구성된 코호트에서 예비 연구를 수행했다[18]. 이 하위 코호트의 인구 통계 데이터는 표 Supp-3에 제시되어 있다. 연령은 McSCI-S 총점 또는 IRT 요인 점수와 유의한 연관성이 없었다($P > 0.05$). McSCI-S 총점은 전반적인 인지 기능 및 특정 인지 기능과 부적 연관성이 있었으며, MoCA, CVLT-II 학습 시도 1–5 총점 및 CVLT-II 단기 및 장기 지연 자유 회상($r = -0.14, -0.21, -0.13, -0.13$; $P < 0.05$)이 이에 해당한다. McSCI-S 총점은 또한 TMT-B 및 DASS 우울 점수와 관련이 있었다($P < 0.05$; 표 4).

MAC-Q 기준점수 ≥ 25 를 사용하여 참가자를 SMC와 비불만자로 분류했다. 두 그룹은 McSCI-S 총점에서 유의한 차이를 보였다($t(df=376) = -7.29, P < 0.001$, (그림 Supp-3)). McSCI-S 요인 점수를 사용하여도 MAC-Q에서 유래한 SMC와 비불만자 간의 유의한 차이가 확인되었다($t(df=197.6) = 6.11, P < 0.01$). MAC-Q와 McSCI-S 총점 또는 요인 점수 간의 연관성은 유의했다($r = 0.53$ 및 0.55 ; $P < 0.001$); 그러나 73%의 분산은 공유되지 않았으며, MAC-Q와 McSCI-S는 SCD의 다른 측면을 포착하는 것으로 보인다.

기준 점수(Cut-off Score)

McSCI-S의 최적의 기준 점수를 식별하기 위해 ROC 곡선 분석을 수행했다. 참가자($n=503$)는 MAC-Q 기준 점수를 사용하여 SMC의 부재 또는 존재를 기준으로 두 그룹으로 분류되었다. 이 모델은 곡선 아래 영역(AUC)=0.70; 95% CI=0.65–0.75를 나타냈다. Youden 지수를 사용하여 24점 이상의 기준 점수는 민감도=0.79 및 특이도=0.50을 나타냈다(ROC 그래프, 민감도, 특이도 및 Youden's J에 대한 데이터는 부록의 그림 Supp-4 및 표 Supp-4에 제시됨). 이 기준 점수는 더 높은 민감도를 위해 선택되었다.

고찰(Discussion)

결과는 McSCI-S가 신뢰할 수 있는 SCD 측정 도구임을 명확히 나타낸다. 또한 McSCI-S 총점(총점과 IRT 기반 요인 점수 모두)은 인지 기능의 객관적 측정 도구와 유의하게 관련되어 있어 우수한 동시 타당성의 증거를 제공한다.

McSCI-S 문항은 기억력, 주의력 및 작업 기억, 언어, 실행 기능, 지남력 및 시공간 기술을 포함하여 SCD 이니셔티브(SCD-I) 작업 그룹에서 이전에 중요하다고 확인한 대부분의 인지 영역에 대한 우려를 포착하도록 개발되었다[11]. 그러나 McSCI-S에 대한 CFA 결과는 6요인 모델이 아닌 단일 요인 모델이 데이터에 가장 적합하다는 것을 보여주었다. 이러한 결과는 주어진 응답자의 SCD를 단일 총점으로 가장 잘 나타낼 수 있음을

표 4. McSCI(McCusker Subjective Cognitive Impairment Inventory)와 다른 측정 도구 간의 연관성($n=382$)

	연령	교육	MoCA	MAC-Q	DASS-D($n=69$)	CVLT-L1-5	CVLT-SD-FR	CVLT-LD-FR	CVLT-Recog.	TMT-B
McSCI-S 총점	0.033	-0.14 ^a	-0.18 ^b	0.53 ^b	0.45 ^b	-0.21 ^b	-0.13 ^a	-0.13 ^a	-0.041	0.24 ^b
McSCI-S IRT 요인 점수	0.06	-0.14 ^a	-0.10	0.55 ^b	0.25 ^b	-0.15 ^a	-0.10	-0.09	-0.01	0.19 ^a

Pearson 상관 계수(양측 검정)를 사용했다.

MoCA, 몬트리올 인지 평가; MAC-Q, 기억 불만 설문지; DASS-D, 우울-불안-스트레스 척도/교육, 교육 연수; CVLT, 캘리포니아 언어 학습 검사-II; CVLT-L1-5, CVLT-II 학습 시도 1–5 총점; CVLT-SD-FR, CVLT-II 단기 지연 자유 회상 점수; CVLT-LD-FR, CVLT-II 장기 지연 자유 회상; CVLT-Recog., CVLT-II 인식 히트; McSCI, 맥커스커 주관적 인지 장애 검사(McSCI-S); McSCI-T, McSCI-S 총점; TMT-B, Trail Making Test-B; IRT, item response theory.

^a $P < 0.05$.

^b $P < 0.01$.

나타내지만, 이는 바이오마커를 통해 확인된 전구증상 및 임상 단계의 치매 또는 기타 신경과/정신과적 상태를 가진 위험이 높은 개인에 대해 McSCI-S의 영역별 점수를 미래 연구에서 사용해서는 안 된다는 것을 의미하지는 않는다. 즉, 임상 코호트에서는 응답 패턴이 다차원 모델과 더 명확하게 일치할 수 있다. 주목할 점은 최근 연구에서 나이가 들면서 인지 저하가 특정 영역별 방식이 아니라 대부분의 인지 영역에 걸쳐 비교적 균일하게 진행된다는 더욱 설득력 있는 증거를 제공했다는 것이다[30]. 이러한 발견은 간접적으로 McSCI-S의 단일차원 요인 구조를 지지한다.

기준에 출판된 SCD 측정 도구(예: [7-10])와 비교하여 McSCI-S는 훨씬 높은 신뢰도와 더 나은 타당도 통계를 보였다. 예를 들어, McSCI의 오메가 계수는 유사한 측정 도구보다 훨씬 높았으며, 이전에 우리는 더 작은 표본에서 McSCI의 강한 신뢰도 결과를 보고했다(Cronbach's $\alpha=0.96$; $n=367$)[18]. 또한 IRT 분석은 전체 검사에 단일 신뢰도 값을 가정하지 않기 때문에 신뢰도 추정치에 미묘함을 추가했다. McSCI-S의 IRT 결과는 평균 및 이상의 SCD 수준에서 신뢰도가 가장 높았으며, 낮은 수준의 SCD에서는 신뢰도가 낮았다. 이는 중요한 발견이며, 이는 McSCI-S가 전임상 AD 단계에서와 같이 SCD가 높을 때 추정할 수 있음을 나타낸다. 반면에 치매의 임상 단계에서는 통찰력 감소로 인해 낮은 수준의 SCD를 나타낼 수 있다[31]. 따라서 McSCI-S는 치매 환자보다 위험에 처한 사람들을 감지하는 데 더 잘 활용될 수 있다. 이러한 심리측정학적 속성은 McSCI가 다른 측정 도구와 비교하여 신경퇴행성 과정과 관련된 SCD를 감지하는 데 더 나은 성능을 보인다는 것을 시사하지만, 이는 우리가 평가한 것이 아니며 추가 연구를 통해 지지가 필요하다.

내용 타당성(content validity)은 McSCI-S가 다른 SCD 측정 도구(MAC-Q)와 유의하게 관련되어 있고, 불만이 있는 사람과 없는 사람 간에 유의한 차이가 있음을 발견함으로써 지지되었다. 동시 타당성(concurrent validity)에 대한 증거는 McSCI-S 점수가 낮은 객관적 인지 기능 측정 도구(MoCA 및 CVLT-II 등)와 관련이 있다는 발견에서 나왔다. 이는 예상된 바였다. SCD와 객관적 인지 측정 도구 간의 관계에 대한 이전 연구는 대부분 두 가지 간의 설득력 있는 연관성을 확립하는 데 성공하지 못하거나 SCD 측정 도구에 대한 충분한 타당성의 증거를 제공하지 못했다[32-35].

ROC 분석 후 제안된 McSCI-S의 기준 점수 ≥ 24 이다. 이 기준 점수는 특이도의 희생을 감수하고 더 나은 민감도를 위해 선택되었다. 주목할 점은 Youden 지수가 ROC 결과에 기반하며, 이는 진성 양성 사례와 진성 음성 사례를 식별하는 데 금 표준의 정확성에 의존한다는 것이다. 여기에서는 MAC-Q를 사용했는데, 이는 우리가 참가자를 모집한 여러 코호트 연구에서 사용할 수 있는 주요 SMC 측정 도구였기 때문이다. MAC-Q에 대한 이상적인 신뢰도 데이터(Cronbach's $\alpha=0.57$)가 부족하기 때문에[36], 더 견고한 SCD 측정 도구를 사용한 향후 연구에서는 McSCI-S의 절단값이 약간 다를 수 있다.

McSCI-S 점수가 높을수록 우울 점수가 높았다. 우울증의 중증도와 SCD 간의 관계에 대한 풍부한 증거가 있다[37,38]. 또한 우울 증상은 인지 저하 및 치매의 위험 인자로 제안되었으며, 치매 위험이 높은 사람들을 나타낼 수 있다[12]. 그러나 우울증과 SCD 간의 강한 관계는 중복되거나 명확하지 않은 문항에서 비롯될 수도 있다. 예를 들어, 우울증 측정 도구는 종종 기억력 및 기타 인지적 우려에 대한 문항을 포함하거나[39], 완료하기에 혼란스러운 문항을 포함한다. 이를 염두에 두고 McSCI를 개발하는 동안 우리는 기분 문항(mood items)을 제외하고, 참가자들로부터 문항의 단어에 대한 피드백을 받아 이러한 편향의 원천을 최소화하고자 했다[39]. 향후 연구에서는 우울증의 영향을 통제 후 McSCI-S가 인지 저하율과 MCI 및 치매로의 전환을 얼마나 잘 예측하는지 결정할 수 있다.

결론(Conclusions)

이 같은 결과는 SCD가 광범위한 상태와 관련이 있으며 다양한 근본적인 병인을 나타낸다는 것을 시사한다. 따라서 치매를 예측하는 패턴과 우울증, 성격 또는 기타 요인을 나타내는 패턴을 구별하기 위해 인지에 대한 자가보고 우려를 정확하게 포착하는 것이 중요하다. McSCI-S는 다른 측정 도구와 비교하여 매우 높은 신뢰도와 타당성을 포함한 강력한 심리측정학적 특성을 보였으며, 따라서 개인 및 그룹 수준에서 SCD를 평가하는 데 적합한 측정 도구이다.

McCusker Subjective Cognitive Impairment Inventory 사용에 대한 각주(End Note for Using McSC-S)

McSCI-S 사용은 저작권 및 지적 재산권 계약을 따른다. McSCI-S는 형식, 지침, 단어 및 문항 번호를 변경하지 않고 그대로 사용될 수 있으며, 연구자 및 대학 강사가 학술 목적으로 또는 임상이가 단일 환자 평가에 사용할 수 있다. 그러나 이러한 적용에서는 이 출판물을 참고해야 한다. 제약회사 또는 기타 비학술 연구 기관(예: 단일 또는 대량 평가, 종이와 연필, 전자 또는 온라인 형식 등)에 의한 이 측정 도구의 모든 적용은 교신 저자의 허가를 받아야 한다. 또한 McSCI-S는 다른 언어로 번역되지 않았다. 이러한 노력이 환영되지만, 교신 저자와의 협의 하에 적절한 허가를 받은 후에 이루어져야 한다. 다른 형태의 번역 또는 적용(예: 컴퓨터화, 웹 기반 앱 및 온라인, 종이와 연필 또는 오디오)은 측정 도구의 일관성과 심리측정학적 특성을 유지하기 위해 교신 저자의 허가가 필요하다.

ORCID

Hamid R. Sohrabi: <https://orcid.org/0000-0001-8017-8682>

Brandon E. Gavett: <https://orcid.org/0000-0003-1938-1854>

Michael Weinborn: <https://orcid.org/0000-0001-7094-9930>

Craig P. Speelman: <https://orcid.org/0000-0001-8629-174X>

Romola S. Bucks: <https://orcid.org/0000-0002-4207-4724>

Ralph N. Martins: <https://orcid.org/0000-0002-4828-9363>

Authors' contributions

Project administration: Sohrabi HR, Gavett BE, Weinborn M, Speelman CP, Bucks RS, Martins RN

Conceptualization: Sohrabi HR, Gavett BE, Weinborn M, Speelman CP, Bucks RS, Martins RN

Methodology & data curation: Sohrabi HR, Gavett BE, Weinborn M, Speelman CP, Bucks RS, Martins RN

Funding acquisition: Sohrabi HR, Martins RN

Writing – original draft: Sohrabi HR, Gavett BE, Weinborn M, Speelman CP, Bucks RS, Martins RN

Writing – review & editing: Sohrabi HR, Gavett BE, Weinborn M, Speelman CP, Bucks RS, Martins RN

Conflict of interest

Gavett BE, Weinborn M, Speelman CP, and Bucks RS report no conflict of interest directly or indirectly associated to this manuscript. Sohrabi HR and Martins RN report being Directors of SMarT Minds WA, Australia. Sohrabi HR and Martins RN have had or are receiving personal reimbursements or research support from the Pharmaceutical and Nutraceutical companies including Alektor, Alnylam Pharmaceuticals, CWEK PTY LTD, WA, Australia, and Biogen pharmaceuticals.

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Data availability

The data presented in this study are available from corresponding authors upon written, formal request. The data are held in a password protected, secure cloud environment, based at our universities.

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Supplementary materials

Supplementary materials are available from: <https://doi.org/10.12771/emj.2024.e74>.

Supplement 1. The McCusker Subjective Cognitive Impairment Inventory (McSCI): A novel measure of perceived cognitive decline. GUID: F3464114-B9EF-4BC4-84DB-41C0A96CD3F1

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Septic cerebral embolism following lumbar spine surgery in a 69-year-old man with a lumbar epidural abscess in Korea: a case report

Yo Seob Lee 

Department of Anesthesiology and Pain Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea

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Corresponding author

Yo Seob Lee
Department of Anesthesiology and Pain Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
E-mail: lystruth@naver.com

Keywords

Embolism; Epidural abscess; Intracranial embolism; Multiple organ failure; Sepsis

Septic embolism and stroke are serious complications in patients with sepsis and often necessitate urgent surgical intervention to control the source of infection. A 69-year-old man presented with severe pain in his back and left thigh. MRI revealed extensive posterior epidural or subdural abscesses extending from the cervical to the lumbar level, as well as an abscess in the iliopsoas muscle. The patient underwent urgent drainage of the abscesses and decompression of the lumbar spine. Postoperatively, he developed sudden-onset atrial fibrillation and altered mental status. Brain CT showed multiple embolic infarctions. His condition deteriorated due to persistent infection, leading to disseminated intravascular coagulation, acute kidney injury, and septic shock. This case highlights the risk of cerebral embolism and hemorrhagic complications in patients with sepsis who undergo surgery. Early recognition of individuals at high risk and comprehensive perioperative management are critical to reducing the likelihood of such complications.

Introduction

Patients with sepsis or septic shock may require preoperative optimization. These individuals often need urgent surgical intervention to control the source of infection. The preoperative assessment should prioritize the identification and management of organ dysfunction [1]. Septic cerebral emboli can also lead to vessel wall infection and potentially result in stroke, particularly in patients with severe sepsis [2].

Septic embolism occurs when a blood clot containing bacteria, known as a septic embolus, obstructs a blood vessel [3]. This embolus originates from an infectious site within the body, detaches, and travels through the bloodstream, eventually blocking small vessels. The origin of septic emboli depends on the anatomic location of the infection and the associated vascular structures. Infective endocarditis, for instance, is a well-known and frequent source of septic emboli. Risk factors for these emboli include intravenous drug use and the presence of an indwelling vascular catheter [4].

In the present case, the primary objective was to provide safe, optimal care for a critically ill patient with sepsis, ensuring that source control surgery could be performed with minimal risk and maximal benefit. This situation presents substantial challenges regarding perioperative

management, especially in cases of septic shock. The patient in this report had spinal abscesses extending from the cervical to the lumbar level, which led to the development of cerebral embolism following lumbar spine surgery.

Case presentation

Ethics statement

The patient provided informed consent for publication of the images.

Patient information

A 69-year-old man, measuring 176 cm and weighing 72 kg, presented with severe back pain and radiating pain in his left thigh. His medical history included hypertension, dyslipidemia, and previous lumbar injection.

Clinical findings

Upon physical examination, the patient's vital signs were unstable, with a blood pressure (BP) of 95/55 mmHg, a heart rate (HR) of 110–115 beats per minute, and a body temperature (BT) of 38.0°C. An ECG revealed sinus tachycardia. Chest radiography appeared normal, with no active lesions evident.

Diagnostic assessment

MRI of the spine revealed a posterior epidural or subdural abscess extending from the cervical to the lumbar level, a fluid collection or abscess in the left iliopsoas muscle approximately 7.6 cm in height (Fig. 1), and intradural disc herniations at the L3–L4 and L4–L5 levels.

Laboratory findings indicated an elevated C-reactive protein level of 41.5 mg/dL, a white blood cell count of over 12,000/ μ L, and a decreased platelet count of 128,000/ μ L. Given the suspicion of infection, the patient was promptly started on empiric antibiotic therapy with vancomycin and



Fig. 1. Spine MRI revealed a posterior epidural or subdural abscess extending from the cervical to the lumbar level. Additionally, an abscess approximately 7.6 cm in height was identified in the left iliopsoas muscle.

ceftriaxone, and preparations were made for abscess drainage and L3–L5 posterior decompression.

Upon arrival in the operating room, the patient's BP was 117/80 mmHg, an ECG indicated sinus tachycardia with an HR of 135 beats per minute, and the measured BT was 38.4°C. For the induction of general anesthesia, 50 mg of rocuronium was administered. Anesthesia was maintained with total intravenous anesthesia using a target-controlled infusion of propofol (2.3–3.0 ng/mL) and remifentanyl. The patient was ventilated with a mixture of oxygen and air.

Therapeutic intervention and timeline

Intraoperatively, the patient's HR remained high (133–145 beats/min), and his BT gradually increased to 38.8°C. These changes are attributed to exacerbation of the patient's septic condition. Acetaminophen and intravenous fluids were administered to manage the elevated BT. Additionally, the use of heating circuits and body warmers was discontinued to avoid further increases in temperature. Following intravenous hydration, the patient's HR decreased to 110–120 beats per minute, and his BT stabilized at 37.0°C–37.5°C. Intraoperatively, BP was maintained between 90–105 systolic and 60–70 diastolic mmHg. The fraction of inspired oxygen was set at 0.5, and the patient's arterial partial pressure of oxygen was approximately 105 mmHg. One hour into surgery, the estimated blood loss exceeded 500 mL while the hemoglobin level fell below 8 g/dL, prompting the transfusion of 2 units of packed red blood cells. Subsequently, the patient's HR increased to 130–140 beats per minute, and his mean arterial pressure (MAP) dropped to 60–70 mmHg. In response, intravenous fluids and norepinephrine were administered at a rate of 0.05 µg/kg/min to maintain a MAP of at least 70 mmHg. The total duration of anesthesia was 170 minutes, after which the patient was transferred to the post-anesthetic care unit.

In the post-anesthetic care unit, ECG and arterial line monitoring were performed. The patient's HR was 115–120 beats per minute, and he was mentally alert. However, after 10 minutes, atrial fibrillation was abruptly detected on the ECG, and the patient began to show signs of drowsiness. Subsequently, he became unresponsive and exhibited a pinpoint pupil reflex, necessitating an immediate neurology consultation. To manage the atrial fibrillation, diltiazem was administered for rate control, and norepinephrine was given continuously as the MAP dropped to 65–75 mmHg. Considering the clinical situation, brain CT was deemed necessary and was performed in the CT room. The patient was then transferred to the intensive care unit.

The brain CT scan revealed multiple embolic infarctions (Fig. 2). However, neurology consultation determined that these infarctions were not the primary cause of the patient's altered mental status. Consequently, aspirin therapy was initiated. To further evaluate the persistent atrial fibrillation and the possibility of infective endocarditis, transthoracic echocardiography and coronary angiography were performed. These tests indicated stress-induced cardiomyopathy, but no cardiac vegetation was detected.

Follow-up and outcomes

On postoperative day (POD) 8, the patient developed acute intraventricular hemorrhage in the right lateral ventricle and intracerebral hemorrhage, measuring 4.5 cm in diameter, in the right occipital lobe. This was likely due to septic thrombosis related to aspirin use or coagulopathy associated with septic shock. Consequently, the patient's mental status deteriorated to stupor. His condition continued to decline due to ongoing infection, ultimately leading to disseminated intravascular coagulation, acute kidney injury, and septic shock. Given this worsening general condition, further surgical intervention was considered unfeasible. Unfortunately, the patient died on POD 33.

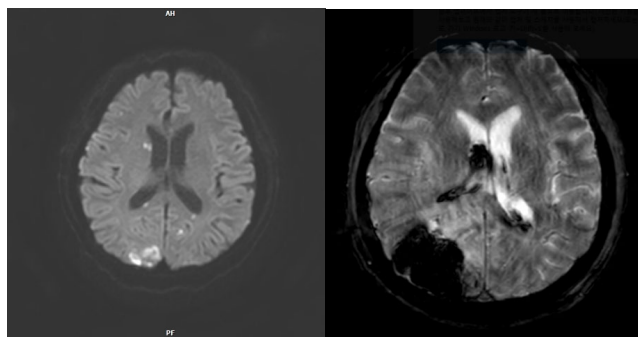


Fig. 2. Brain CT revealed multiple bilateral infarctions. On postoperative day 8, the patient developed acute intraventricular hemorrhage in the right lateral ventricle, along with a 4.5-cm intracerebral hemorrhage in the right occipital lobe.

Discussion

Recent evidence suggests that infections, particularly sepsis, may act as acute triggers for stroke, significantly increasing its risk within a short period [5]. Potential mechanisms linking sepsis to stroke include atrial fibrillation, hemodynamic instability, coagulopathy, systemic inflammatory response syndrome, and prolonged inflammation [6]. Thus, effective risk management requires identifying patients at the highest risk for stroke following sepsis and bloodstream infections. In the present case, the patient exhibited altered mental status postoperatively, and cerebral embolism was confirmed by brain CT. Among the most common high-risk cardiac conditions that can lead to embolic ischemic stroke is infective endocarditis [7]. To investigate the presence of vegetation on the mitral valve and to determine if a thrombus was associated with atrial fibrillation, transthoracic echocardiography and coronary angiography were conducted. These tests revealed only stress-induced cardiomyopathy. Considering the patient's condition, it is regrettable that transesophageal echocardiography was not performed to reassess for vegetation, which was not detected on transthoracic echocardiography. Additionally, given the patient's overall state and vital signs, utilizing brain oximetry during anesthetic management may have provided valuable insights.

The use of low-dose aspirin is a common practice for the primary and secondary prevention of stroke [8]. The present patient developed intraventricular hemorrhage in the right lateral ventricle and intracerebral hemorrhage in the right occipital lobe on POD 8, following the initiation of aspirin therapy. Although the need for antiplatelet therapy due to cerebral embolic infarction could have played a role, the patient exhibited persistently low platelet counts of 80,000–90,000/ μ L; instead, prolonged coagulopathy secondary to sepsis may have been the primary cause. Furthermore, hemorrhagic transformation of ischemic brain infarcts can result in intracerebral hemorrhage, especially in patients receiving anticoagulant therapy.

Sepsis requires the presence of infection, which may not be immediately evident in the perioperative setting. Patients with conditions such as perforated viscera or undrained abscesses require prompt surgical intervention to prevent exacerbation of the infection and severe systemic reactions [9]. In the present case, MRI revealed an epidural or subdural abscess extending from the cervical to the lumbar level, necessitating immediate surgical intervention given the patient's unstable vital signs. In cases of suspected sepsis, early recognition and focused management are critical. This includes the timely administration of antibiotics,

intravenous fluids, and vasopressors (if hypotension is evident) to ensure adequate organ perfusion. Supportive measures such as monitoring urine output, providing high-flow oxygen, and tracking lactate levels are also important to prevent organ failure. In this case, empiric antibiotics were initiated preoperatively upon confirmation of infection, and vasopressors and intravenous fluids were administered intraoperatively, along with an increase in fraction of inspired oxygen. However, the patient's HR remained persistently elevated at 110–140 beats per minute. Given the continued instability of his vital signs postoperatively, intraoperative administration of the class III antiarrhythmic medication amiodarone may have been beneficial. Amiodarone is particularly useful for hemodynamically unstable patients, as it effectively controls ventricular rate and promotes successful conversion to and maintenance of sinus rhythm in those with atrial fibrillation [10].

Overall, the patient's condition deteriorated due to ongoing infection and complications such as hemorrhagic events. This case underscores the importance of vigilant perioperative management, the early identification of patients at high risk, and the use of tailored therapeutic strategies. Comprehensive postoperative monitoring is essential to mitigate potential complications following surgery in patients with sepsis.

ORCID

Yo Seob Lee: <https://orcid.org/0000-0001-6829-5536>

Authors' contributions

All work was done by Yo Seob Lee.

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How should medical students and young physicians prepare to be National Assembly members in Korea?

Hyun-Yung Shin[✉]

Department of Family Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Corresponding author

Hyun-Yung Shin
Department of Family Medicine, Seoul
St. Mary's Hospital, College of Medicine,
The Catholic University of Korea, 222,
Banpo-daero, Seocho-gu, Seoul 06591,
Korea
E-mail: shydeborah@gmail.com

Introduction

I have personally experienced the direct impact that politics can have on our lives. After I entered medical school in 2000, the pharmaceutical separation crisis emerged, disrupting my ability to maintain a normal academic schedule [1]. Rather than attending classes, I found myself participating in rallies, facing the risk of failing my courses. This experience taught me firsthand how healthcare policies can bring educational institutions and hospitals to a standstill. As the medical community's protest against the implementation of the pharmaceutical separation system ultimately failed, I also learned that the world is not easily swayed and that the arguments of the medical community do not always gain widespread acceptance.

In this article, I will share my thoughts on the recent upheaval in healthcare settings triggered by the resignations of medical residents in response to government policies. I will also reflect on my four years of legislative activities as a physician in the 21st National Assembly, from June 5, 2020, to May 29, 2024. Additionally, I will share a message for medical students and young doctors who aspire to serve in the National Assembly.

Medical residents' resignations in response to the government's policy of increasing the quota of medical schools

In February 2024, the Korean government took steps to expand medical school admissions in response to a projected shortage of 10,000 doctors within the next decade [2]. The government successfully finalized an increase of 1,509 medical school admissions for 2025, which could be seen as a partial victory in overcoming opposition from the medical community. However, the policy to expand medical school enrollment ultimately led to indefinite leaves of absence for medical students and the resignation of residents, thereby disrupting the medical ecosystem [3]. The government now faces the significant challenge of assuming responsibility and restoring the system over an extended period [4].

The most serious consequence of this crisis has been the erosion of trust between doctors and patients. As the medical community became socially demonized, the shift toward a society where distrust between doctors and the public prevails accelerated. Even more unfortunate is that as distrust and suspicion toward doctors increase, the field of critical care medicine becomes increasingly avoided from young doctors and medical students. Ultimately, it is the patients who

suffer the most from this damage.

However, the medical community also has areas to reflect upon. Social acceptance for the medical community is achieved when it demonstrates its expertise as a professional group and fulfills its social responsibilities. It is time to reflect on the efforts made so far by the medical community and consider how these efforts can be expanded to ensure that the majority of citizens can empathize with and support the arguments presented by doctors.

Efforts to strengthen the medical community's policy capabilities do not occur automatically.

First, medical professionals need to become more sensitive to societal changes. This can be challenging since they spend the majority of their time in examination rooms. Nevertheless, by strengthening their understanding of social structures and actively engaging with various occupations and professions, they can contribute to societal transformation.

Second, communication skills must be developed. Communicating as an expert with patients is fundamentally different from everyday social interactions. It is essential to cultivate social skills and engage in debates and dialogues. These efforts help acknowledge other groups within healthcare organizations and strengthen policy alliances. Through mutual understanding, we must foster open discussions and build consensus with patients, healthcare consumers, and various healthcare professional organizations on the direction of future healthcare.

Third, we must acknowledge that the executive and legislative branches fundamentally strive to hear and incorporate the perspectives of the general public, vulnerable groups, and minorities into their policies. By understanding the government's decision-making process in healthcare, we can better anticipate future policy shifts. At the crossroads of leading or being led, has the medical community not typically adopted a more passive role, allowing itself to be guided by others?

If the medical community can foster a culture of dialogue and compromise, working collaboratively with citizens to develop the Korean healthcare system, there remains a glimmer of hope that we can find solutions even in the midst of a medical crisis, however tricky it may be.

Bills Proposed in the 21st National Assembly

During my term, I proposed several bills aimed at improving the medical field. Some passed, while others were discarded due to the expiration of the term. These bills were introduced to achieve institutional results for the healthcare sector.

Partial Amendment to the Health and Medical Personnel Support Act

This bill addressed the need for more specific methodologies evidence based estimation planning of supply and demand of the health care personnel. It proposed the establishment of a committee within the government's healthcare workforce support agency to enhance the rationality of projections and provide long-term evidence for sustainable forecasting. This proposal aimed to prevent recurring political confrontations over physician quotas and establish a financially sustainable system. However, the government adopted a reserved stance, suggesting further discussion before proceeding with legislation [5].

Partial Amendment to the Act on Remedies for Harm from Medical Accidents and Mediation of Medical Disputes

This bill sought to extend full support from government (or nation) for no-fault obstetric accidents to encompass pediatric care, thereby establishing a basic safety net for unavoidable

medical accidents. It would have substantially alleviated the burden of pediatric care and addressed the responsibilities associated with a low birth rate. However, the bill lost momentum during deliberation due to a lack of support from medical societies and associations [6].

Bill on Fostering and Supporting Essential Medicine

This bill sought to overcome the crisis in essential medicine and to safeguard the right to life and health for all citizens. It advocated for enhanced government support in areas characterized by high severity, urgency, and labor intensity. The bill also sought to create a legal foundation for national responsibility in maintaining stable management of medical institutions and preventing the exodus of healthcare professionals working in essential medicine. However, it was discarded at the end of the Assembly term due to unresolved definitions and insufficient active discussions regarding state support [7].

Partial Amendment to the Act on the Improvement of Training Conditions and Status of Medical Residents

This bill aimed to protect the health and rights of medical residents by restricting the duration of continuous training and setting maximum limits on overall training hours, particularly in intensive care units. It also required state support for residents working in critical departments. Although the bill was passed with some amendments, it compromised on reducing the working hours from 36 to 24 by permitting the government to determine the reduced hours through an enforcement decree following pilot projects [8].

These bills represent efforts to address critical issues in the Korean healthcare system, from workforce planning to resident welfare. They demonstrate the complex interplay between medical needs and political realities.

How should medical students or young physicians prepare to participate in policy-making?

In our highly advanced world, various media outlets have evolved repeatedly to provide knowledge and information equitably to all. As the disparity in medical information progressively diminishes, we find ourselves in an era that requires increasingly specialized expertise in healthcare policy. The active roles from expertise in the medical field are needed for the national assembly and government during the policy making and decision process. However, the level of medical expertise and understanding of medical real field among policymakers still leaves much to be desired.

Young doctors and medical students who recognize the importance of politics must now speak out and take action. While skilled clinicians who provide excellent patient care are invaluable, the contributions of experts who work to change global regulations to enhance the healthcare system are even more beneficial to patients and the public.

Believe in yourself and keep moving forward, regardless of the environment you find yourself in or the challenges you face. Before you realize it, you will reach the intersection of medicine and politics. Remember, the National Assembly, politicians, and various organizations and individuals are not fundamentally different from you. To effectively engage in the political arena as a medical professional, it's essential to cultivate an interest in politics early on and contemplate the true meaning of effective governance. Opportunities to influence the world through political action are abundant and accessible: supporting causes, immersing yourself in political news, studying

medical laws and policies, joining political parties, participating on petition boards, engaging in civic activities, and volunteering. These pursuits are what ultimately have the power to change the world.

ORCID

Hyun-Yung Shin: <https://orcid.org/0000-0001-7261-3365>

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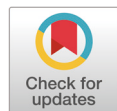
Supplementary materials

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Could I become a physician in the pharmaceutical industry?: practical insights from a 12-year veteran in pharma

Yoenjung Lee

Medical Affairs, Takeda Pharmaceuticals Korea Co., Ltd., Seoul, Korea



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Corresponding author

Yoenjung Lee
Medical Affairs, Takeda Pharmaceuticals
Korea Co., Ltd., 37F 300 Olympic-ro,
Songpa-gu, Seoul 05551, Korea
E-mail: ppattuu@gmail.com



Fig. 1. Author's photo.

It was 10 a.m. on a Monday this September, and I was preparing a training session aimed at boosting my team's confidence in publishing academic papers. By a happy coincidence, the guest lecturer for our session was the Editor-in-Chief of the *Ewha Medical Journal*, representing my beloved alma mater, Ewha. Following a wonderful session and a lively discussion, the lecturer assigned me a small task: as a physician working at a pharmaceutical company rather than in a hospital, could I write an essay to assist those considering various career paths in medicine? Twelve years earlier, I had left a position in the Department of Family Medicine at a university hospital to embark on a career in the pharmaceutical industry. The experiences shared by senior colleagues at that time gave me courage, and now I hope that sharing my own story will help guide those who follow (Fig. 1).

Medical affairs and the role of physicians in pharma

In Korea, the role of medical affairs in a pharmaceutical company and the responsibilities of a pharmaceutical physician are defined in the *Pharmaceutical Medicine* [1]. The Korean Society of Pharmaceutical Medicine characterizes pharmaceutical medicine as a discipline focused on the medical facets of drug research, development, evaluation, registration, post-marketing surveillance, and medico-marketing. Professionals in this field are referred to as pharmaceutical physicians. The book provides an overview of the history and framework of medical affairs through the lens of pharmaceutical physicians. Chapter 2, "Pharmaceutical Physicians," features Dr. Byung-Hoon Jeon, a specialist in obstetrics and gynecology, who held the position of Medical Director at Pfizer Korea in 1961 and later at GSK Korea until 2001. The text indicates that a medical affairs structure similar to that of U.S. companies has been present in global pharmaceutical companies in Korea since the 1960s.

The medical affairs department typically operates under the leadership of a Medical Director or Head of Medical Affairs. This department generally comprises physicians, pharmacists, nurses,

and life sciences experts who hold graduate-level degrees. The structure of the department may vary based on the size of the company, its key products, and the stages of its product life cycles. Standard components of the department include a medical information team and a medical franchise team. In some instances, the team may also encompass clinical operations, pharmacovigilance, regulatory affairs, or patient support functions.

The medical franchise team is tasked with medico-marketing responsibilities. This team comprises roles such as Medical Advisors, Medical Managers, and Medical Scientific Liaisons (MSLs), each specializing in a particular product and disease area. Typically, the team includes physicians, with positions generally available within this group. Their duties involve developing late-phase (Phase 3 and 4) clinical trials, engaging with healthcare professionals, and relaying insights from these professionals to internal stakeholders, including regulatory affairs, market access, and marketing. Additionally, they provide medical advice concerning drug reimbursement and marketing activities and are actively involved in communications with health authorities.

What have I done at pharmaceutical companies?

I was part of the 1997 cohort at Ewha Medical School. After completing my residency in the Family Medicine Department at Ewha Mokdong Hospital, I served as an assistant professor at CHA Bundang Medical Center. In 2012, I joined my first global pharmaceutical company. Since then, I have worked at four other global company, making this my fifth.

My initial position was as Senior Medical Manager, a role typically reserved for more senior employees; however, my hospital experience was deemed valuable. In this capacity, I served as a medical consultant, focusing on the therapeutic indications of a botulinum toxin product. I was solely responsible for managing this product area. My duties included devising medical strategies to secure regulatory approval for new indications and reimbursement, organizing advisory board meetings with key experts, and training first-time injectors. This role provided me with significant insights into medical affairs and the nuances of functioning effectively within a corporate environment.

I served as a Medical Advisor at my second company, leading the medical team for ophthalmology product. During my tenure, I had the valuable opportunity to be involved in the launch of a new product, working closely with the marketing, regulatory affairs, and market access teams. Thanks to our successful collaborations, the product achieved strong market performance. This role strengthened my skills in conducting advisory board meetings, supporting investigator-initiated trials, and organizing impactful symposia featuring renowned international speakers. As the team expanded from one to three members, I was promoted to Senior Medical Advisor, I worked at this company 5 years and had the valuable experience of growing my role, responsibilities, and maturity alongside the new product launch.

From my third company onward, I transitioned into managerial roles, overseeing multiple teams as a middle manager and a medical director. It was a period of two and a half years, during which I learned the role of a manager, leading multiple teams, mediating conflicts between them, and achieving the organization's goals.

I currently hold an executive position since my fourth company, where I contribute to the overall scientific strategic direction of company. This career progression, often referred to as the 'managerial track,' is a typical path for pharmaceutical physicians who aim to combine their expertise with leadership skills. Such skills are essential for managing specialized departments like medical affairs.

Career paths in the pharmaceutical industry are notably diverse. Similar to how a first-year resident progresses to a second-year, career advancement is not always linear or obligatory. Many professionals find fulfillment working in smaller teams or as individual contributors, without pursuing traditional management roles. Others choose to deepen their expertise in a specific therapeutic area, serving as advisors and strategists for global clinical trials. For instance, some may specialize as medical advisors in anti-cancer drugs, launching new products and conducting local research in this niche. These individuals pursue an 'expert track,' focusing on developing profound knowledge and experience in a particular area. Ultimately, there is no universally correct path; pharmaceutical physicians evolve through diverse experiences and opportunities.

What competencies do pharmaceutical physicians need?

Much has been discussed about the essential skills required for working in medical affairs, with numerous studies and surveys emphasizing these competencies [2–5]. The most crucial skills include medical expertise, the ability to rapidly absorb new information, and strong communication abilities. The latter is particularly important for translating complex medical content into practical insights that can be understood by both internal teams and external customers, primarily healthcare professionals. Additionally, a patient centered approach and high ethical standards are fundamental to medical affairs.

Most physicians inherently possess basic competencies such as medical expertise and patient-centered mindset. Additionally, if you have consistently shown the ability to listen carefully to patients and communicate effectively with various hospital staff, patients, and students, you will have ample examples to highlight these competencies. However, two additional skills that are particularly vital for physicians in pharmaceutical roles, yet less frequently discussed, are flexibility of thought and leadership.

Unlike hospitals, where a physician's role is central and supported by other professionals, the corporate environment necessitates collaboration among individuals from diverse backgrounds, working as equals to achieve business goals. A flexible mindset is crucial for adapting to a company setting, as it fosters understanding and respect for different viewpoints and approaches. Moreover, leveraging expertise to develop mutually satisfying solutions significantly enhances one's value within a corporate context.

Leadership is crucial, even without formal authority. It forms the bedrock of company culture through successful collaboration and teamwork. Leadership involves not only guiding a team but also motivating others, setting goals, and solving problems. For physicians, this often entails a balance between their extensive medical knowledge and the soft skills necessary to influence and inspire others. Consider a past project where you collaborated with a diverse group of stakeholders—senior professors, younger residents, nurses, and administrators. How did you lead, and what feedback did you receive from your collaborators? Reflecting on these experiences can help identify emerging leadership qualities that could be beneficial in a corporate setting.

Why did I choose a pharmaceutical career?

One day, I asked myself why I chose a professional career. My conclusion was that I sought to challenge myself in a broader context. As a physician, I was committed to caring for patients and contributing to a healthier society, but I also wanted to broaden my horizons. To any junior

colleagues contemplating a career shift, whether for reasons similar to mine or different, I hope my journey encourages you to seize the vast opportunities that lie ahead.

ORCID

Yoenjung Lee: <https://orcid.org/0009-0005-5400-9726>

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Conflict of interest

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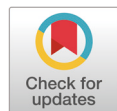
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The leitmotifs we shared

Minyoung Kim¹

Ewha Womans University College of Medicine, Seoul, Korea



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Corresponding author

Minyoung Kim
Ewha Womans University College
of Medicine, 260 Gonghang-daero,
Gangseo-gu, Seoul 07804, Korea
E-mail: kmin0@ewhain.net

*Minyoung Kim is a senior student at Ewha Womans University College of Medicine in 2024. This is an English translation of the Korean essay. This essay was awarded the highest honor—the grand prize—in the 2024 Korean Medical Student Essay Competition on September 28, 2024, hosted by the Korean Medical Association and organized by the Korean Physician Essayists Association.

A vacation began, one with no clear end in sight due to a leave of absence from medical school that began in March 2024. It was my first time on a vacation with no specific plans to return, carrying only what I truly needed. As I packed up four years' worth of belongings, I prepared to move to my great-aunt's house in Bucheon. Always having struggled with letting go, I spent a significant amount of time deciding what to discard, eventually deciding to pack only the things I would never part with.

The first item was the blue waterproof bag. Two years ago, around this time, I arrived at Vienna Central Station in Austria, about midway through a trip to Europe. I was headed to my accommodations, carrying a massive 29-inch suitcase that was half the size of my body. Perched precariously on top was a large hemp bag I had bought in Giverny, France. As I crossed the street, the inevitable happened—the bag fell. A beer bottle I had impulsively bought to drink on the train shattered inside, staining the black asphalt of the crosswalk. I hastily grabbed the Giverny bag with one hand while fumbling to drag my suitcase with the other, but it was futile. The traffic light started blinking. Just then, a stout, blue-eyed man approached, lifted my suitcase, and set it on the sidewalk. Then, he handed me a blue waterproof bag. "From South Korea? A student? I use this bag for groceries, but it seems like you need it more. Don't hesitate to use it. Welcome to Vienna, good luck, and enjoy your youth."

This act of kindness came at my most desperate moment. The bag's waterproof feature was so effective that not a single drop of beer leaked while I made my way to the hostel. After washing and drying it thoroughly, I carefully folded it and brought it back to Korea. Every time I moved my dormitory belongings, I used that bag, as it felt like the luck the man had wished upon me followed wherever it went. I started to believe that this waterproof bag would never allow my "good luck" to spill or drain, and that every semester would end well. So, with a fervent hope that I would get through this next hurdle, I packed my things into the lucky blue bag.

After luck, I packed happiness. The second item was a pink clipboard, once indispensable for hospital rounds and patient interviews during my medical school days. Although it no longer served its original purpose, I kept it tucked deep in my bag because of a single piece of paper pinned at the back—a lyric sheet for an unreleased song titled "Happiness." It was a gift from a patient during my psychiatry rotation the previous year. He had been hospitalized for alcoholism and struggled with withdrawal symptoms every morning, but by 10 a.m., he would shyly relax, listening to songs he requested on a Bluetooth speaker. One day, I struck up a conversation with him, asking, "How do you know so many great songs? Thanks to you, I look forward to this time every day."

He shared his story—how he had once dreamed of becoming a composer, enrolled in a

university music program, but eventually gave up on his dream to work for his father's company, leading him to his current situation. As he spoke about composing, this calm man in his mid-thirties, clad in hospital garb, transformed into a ten-year-old boy, his voice bright and his eyes sparkling. That light was truly beautiful, and I found myself desperately hoping that it wouldn't fade. I begged him daily to show me his first composition. A few days later, he gave me a sheet of lyrics, written in neat sections with colored pencils in purple, blue, and green.

"Your gentle breath comes to me like a light, reflecting happy tears in this moment. I will never forget how the deep sorrow within me disappears with a single smile."

He explained that the song was about his first love at the age of twenty. The moment he said that, he transformed back to being a bright-eyed young man studying music.

A nurse told me later, "I saw him sitting on the bed, writing something. When I asked, he said it was lyrics for a song he was giving to the medical student, and it was the first time I saw him smile."

I was profoundly grateful that the light in his eyes hadn't disappeared. With his permission, I kept the lyrics pinned to the back of my clipboard. During tough rotations, whenever I felt drained, I would flip the clipboard over and read those lyrics. I could vividly imagine the moments when he had carefully pressed each word onto the paper, returning to be the dreamy, delicate young man he once was. I could see his radiant first love and pictured him somewhere playing his favorite minor chords on a synthesizer. While the blue waterproof bag was a talisman of luck from a benevolent adult who extended his gentleness when I was young, these lyrics were another kind of talisman, evoking the thrill and melancholy of being twenty. In tough times, I thought of that young man's eyes, and for his sake, I prayed to every god I knew to grant him a smoother life.

While packing happiness, I remembered something I had given my heart to. Near the end of my psychiatry rotation, a woman was admitted. She was the mother of a nine-year-old and loved roses. She often spoke fondly about visiting a rose festival in May and drew her child, her home, and the colorful roses surrounding it during art therapy sessions. This woman reminded me of a rose herself, standing tall and blossoming even as her thorns pricked and blood flowed, her petals tinted by that very blood for the sake of her child. I wanted to support her in some way. I found a rose that resembled her during a study break. The "Emma Wood" rose, with its soft pink blush, like a single drop of watercolor on white paper, was small yet full of delicately curled petals. Its meaning? "Confession of first love." Since personal items were not allowed in the ward, I committed to memory its name, shape, and significance before my next visit with her.

"There's a rose that looks like you. It's called 'Emma Wood,' a soft pink rose, and it means 'confession of first love.' When you leave here, you must find it."

Her face, always drowsy from medication, brightened like a blooming flower bud.

"There's a rose that looks like me? My goodness! I'll write it down. When I leave, I'll look for it. I'll write down your name, too, to remember that you told me about it. Thank you."

In his novel *Essays in Love*, Alain de Botton likens the act of constantly recalling shared experiences with a partner to the musical term "leitmotif." In the novel, a man approaches the narrator's lover and hands her a crumpled note that says, "I love you." This becomes a leitmotif in the couple's relationship, and they continually recreate this moment by passing silly notes like, "Pass the salt," forging a private bond that draws them closer. A leitmotif, which is unique to the shared experience of two individuals, serves as a powerful glue, even when it appears trivial. As they repeatedly bring it up, they become willingly isolated from the world and fall deeper in love.

Just as the blue waterproof bag had become a leitmotif of good fortune in my own narrative, I

hoped that the man's first song and the "Emma Wood" rose would become leitmotifs for them. I continued to remind her until my final day on the ward, hoping she would hold on firmly to life even after her discharge. "Don't forget to find the 'Emma Wood' rose when you get out. Promise me."

I think I've found the reason I struggle so much with throwing things away. As in Kim Chun-Soo's poem "Flower," when an object enters my life, it transforms into something more—a flower, a leitmotif. Every time I pack my belongings, I reflect on the meanings attached to each item and the stories behind them. Inevitably, the people with whom I've shared these leitmotifs come to mind, and I find myself praying that their lives continue to play out in beautiful harmony. That's why I can never throw anything away.

ORCID

Minyoung Kim: <https://orcid.org/0009-0004-6429-0198>

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Supplement 1. Korean version of this essay in PDF format

Editor's note

This essay by Ms. Minyoung Kim, an undergraduate at Ewha Womans University College of Medicine, won the grand prize in the 2024 14th Korean Medical Student Essay Competition, hosted by the Korean Medical Association and organized by the Korean Physician Essayists Association (Fig. 1). Engaging in essay writing—such as crafting personal narratives—is highly beneficial for medical students, as it helps them organize their thoughts through writing, cultivate logical reasoning, and enhance their empathy and communication skills with others.

Ms. Kim's essay might catch the judges' attention through its nuanced depiction of episodes intertwined with cherished personal items, written when her study time was reduced due to a leave of absence from medical school that began last March. Particularly noteworthy is how she interpreted empathy with others as a leitmotif and structured her essay around this theme. We hope this beautiful work will be shared in Korean and English with medical students worldwide, allowing them to connect with Ms. Kim's leitmotifs.



Fig. 1. Grand Prize recipient, medical student Ms. Min-young Kim (left) and award presenter, Dr. Hyung Joon Yoo (right) at CM Hospital, the president of the Korean Physician Essayists Association.



Clinical practice guidelines for the diagnosis and treatment of scabies in Korea: Part 1. Epidemiology, clinical manifestations, and diagnosis — a secondary publication

Jin Park¹, Soon-Hyo Kwon², Young Bok Lee³, Hei Sung Kim⁴, Jie Hyun Jeon⁵,
Gwang Seong Choi⁶;

on behalf of the Scabies Study Group of Korean Dermatological Association

¹Department of Dermatology, Jeonbuk National University Medical School, Jeonju, Korea

²Department of Dermatology, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea

³Department of Dermatology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

⁴Department of Dermatology, Incheon St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

⁵Department of Dermatology, Korea University Guro Hospital, Seoul, Korea

⁶Department of Dermatology, Inha University Hospital, Incheon, Korea

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Corresponding author

Gwang Seong Choi
Department of Dermatology, Inha
University Hospital, 27 Inhangro, Jung-
gu, Incheon 22332, Korea
E-mail: garden@inha.ac.kr

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Keywords

Diagnosis; Epidemiology; Practice guideline; *Sarcoptes scabiei*; Scabies

Scabies is a skin disease caused by the parasite *Sarcoptes scabiei* var. *hominis*, which is primarily transmitted via direct skin or sexual contact or, less commonly, via contact with infested fomites. In Korea, the incidence of scabies has decreased from approximately 50,000 cases per year in 2010 to about 30,000 cases per year in 2021. However, outbreaks are consistently observed in residential facilities, such as nursing homes, especially among older adults. The clinical manifestations of scabies vary based on the patient's age, health status, the number of mites, and the route of transmission. Typical symptoms of classic scabies include intense nocturnal itching and characteristic skin rashes (burrows and erythematous papules), with a predilection for the interdigital web spaces, inner wrists, periumbilical areas, axillae, and genital areas. In contrast, older adults with immunodeficiency or neurological disorders may exhibit hyperkeratotic scaly lesions or an atypical distribution with mild to no itching (crusted scabies). The diagnosis of scabies is based on clinical symptoms and the results of diagnostic tests aimed at identifying the presence of the parasite. While a history of close contact and characteristic clinical findings suggest scabies, confirmation of the diagnosis requires detecting scabies mites, eggs, or scybala. This can be achieved through light microscopy of skin samples, non-invasive dermoscopy, and other high-resolution *in vivo* imaging techniques.

Introduction

Background

Scabies is a highly contagious skin disease marked by severe itching, resulting from the infestation of mites within the skin. As of 2017, over 200 million people globally were affected, with a notably high prevalence in tropical and low-income areas [1]. In Korea, scabies was once

prevalent, representing about 10% of outpatient visits in some general hospitals until the early 1980s. However, the incidence declined to less than 1% by the 1990s, likely due to strengthened public health measures. Recent years have seen a resurgence of scabies, which is thought to be linked to the increase in long-term care facilities associated with an aging population. In 2010, data from the Health Insurance Review and Assessment Service reported over 50,000 cases, but this number decreased to around 30,000 cases by 2021. Despite this decline, there remains a risk of scabies re-emerging.

To reduce scabies outbreaks, especially in communal living settings like nursing homes, it is crucial to implement preventive measures, ensure early detection, and adopt effective management practices. These steps help mitigate risk factors and curb the spread of the disease. Several countries, including the U.S. and various European nations, have established guidelines for the diagnosis, treatment, and prevention of scabies [2–4]. In Korea, the Korea Disease Control and Prevention Agency (KDCA) has been issuing guidance on scabies prevention and management since 2018 [5,6]. Nevertheless, clinical guidelines developed by dermatology experts with experience in treating scabies are vital to broadly support healthcare providers.

Objectives

In 2023, the Korean Dermatological Association (KDA) prioritized the eradication of scabies, launching clinical services, educational programs in communal facilities, and public awareness campaigns. To bolster these initiatives, the authors formed a committee within the KDA tasked with developing standardized clinical guidelines for managing scabies. We believe this guideline will serve as a valuable resource for everyone engaged in the treatment and prevention of scabies.

Ethics statement

As this was a literature review study, it did not require approval from an institutional review board. Informed consent was obtained from the patients depicted in the figures for the use of their photographs.

Definition, transmission, and epidemiology

- Scabies is a skin infection caused by the scabies mite. It is transmitted primarily through direct skin contact or sexual contact with an infected individual. Transmission can also occur, though less commonly, through indirect contact with contaminated objects.
- The number of scabies cases in Korea has steadily declined, from approximately 50,000 in the early 2010s to around 30,000 in 2021. While scabies is more prevalent among older adults and its incidence increases with an aging population, about 17% of cases also occur in individuals under the age of 20.
- Factors contributing to the ongoing occurrence of scabies cases include the expansion of elderly care facilities, increasing drug resistance, diagnostic difficulties due to atypical clinical presentations in clean environments or cases of scabies incognito, and a rise in travel from regions where the disease is endemic.

Definition

Scabies is a skin infection caused by the mite *Sarcoptes scabiei*, which belongs to the phylum Arthropoda, subclass Arachnida, order Astigmata, and family Sarcoptidae [7]. This mite

parasitizes more than 40 animal species, burrowing into the skin and causing infections in both humans and animals. There are different varieties of scabies mites that infect humans and other animals. In Korea, three types have been identified: *S. scabiei* var. *hominis* (human scabies mite), *S. scabiei* var. *canis* (dog scabies mite), and *S. scabiei* var. *suis* (pig scabies mite). Of these, only *S. scabiei* var. *hominis* is transmitted between humans and causes clinical disease, and is commonly referred to as the "scabies mite" in medical practice. Mature female mites measure 0.30–0.45 mm in length and 0.25–0.35 mm in width, while mature male mites are approximately half that size [5]. They are oval and grayish-white, with brown legs and a gnathosoma (mouth parts) that is distinct from the idiosoma (body), which is short, blunt, and round with eight legs. These mites lack eyes and respiratory organs, and feature a distinctive long bristle on the third pair of legs.

The lifecycle of *S. scabiei* comprises four stages: egg, larva, nymph, and adult [5]. After mating on the skin surface, female mites burrow 1–2 mm into the stratum corneum. Here, they lay an average of 35–50 eggs throughout their 4–6-week lifespan. In contrast, male mites typically die within two days of mating. The eggs hatch into larvae within 4–5 days, develop into nymphs, and reach adulthood within 10–14 days. Scabies mites move at a rate of approximately 2.5 cm per minute on the skin and can survive for 24–36 hours, and up to one week, off the host. They are most active at temperatures above 20°C.

Transmission

Scabies primarily spreads through direct skin-to-skin or sexual contact with an infected person. It can also spread less commonly through indirect contact with contaminated items such as fabrics, doorknobs, bedding, or furniture. Individuals infected with scabies can transmit the disease during the asymptomatic incubation period and remain contagious until the mites and eggs are eliminated through treatment. Crusted scabies, which is highly contagious, often occurs in communal settings such as nursing homes, long-term care facilities, prisons, and daycare centers. High-risk groups for scabies infection include household members and sexual partners of individuals with scabies. Crusted scabies is more likely to affect those who are immunocompromised, older adults, individuals with physical or mental disabilities, and those in poor conditions or with severe underlying diseases [6].

Epidemiology

In Korea, the prevalence of scabies among outpatients at eight general hospitals across six regions, including Seoul, was approximately 2% in the 1960s, rising to 3%–7% in the 1970s, and reaching 10% in the early 1980s. However, by the 1990s, it had declined to below 1% [8]. Data from the Korean Health Insurance Review and Assessment Service show that the number of scabies cases in Korea decreased from 51,331 in 2010 to 29,693 in 2021 (Fig. 1) [9]. During the same period, the age-standardized incidence rate per 100,000 people fell from 97.6 to 43.4. Factors contributing to this decline include improved personal hygiene, heightened awareness of scabies in institutional settings such as nursing facilities, and the social isolation measures and movement restrictions associated with the COVID-19 pandemic.

Scabies was most prevalent among individuals in their 40s, accounting for 16% of cases in 2010–2011. However, from 2012 to 2020, the highest incidence shifted to those in their 50s, with a steady increase in this age group. The higher incidence among older adults can be attributed to factors such as population aging, an increase in long-term care facilities, and relative poverty among older adults [9]. In contrast, among individuals under 20, the rate of scabies declined

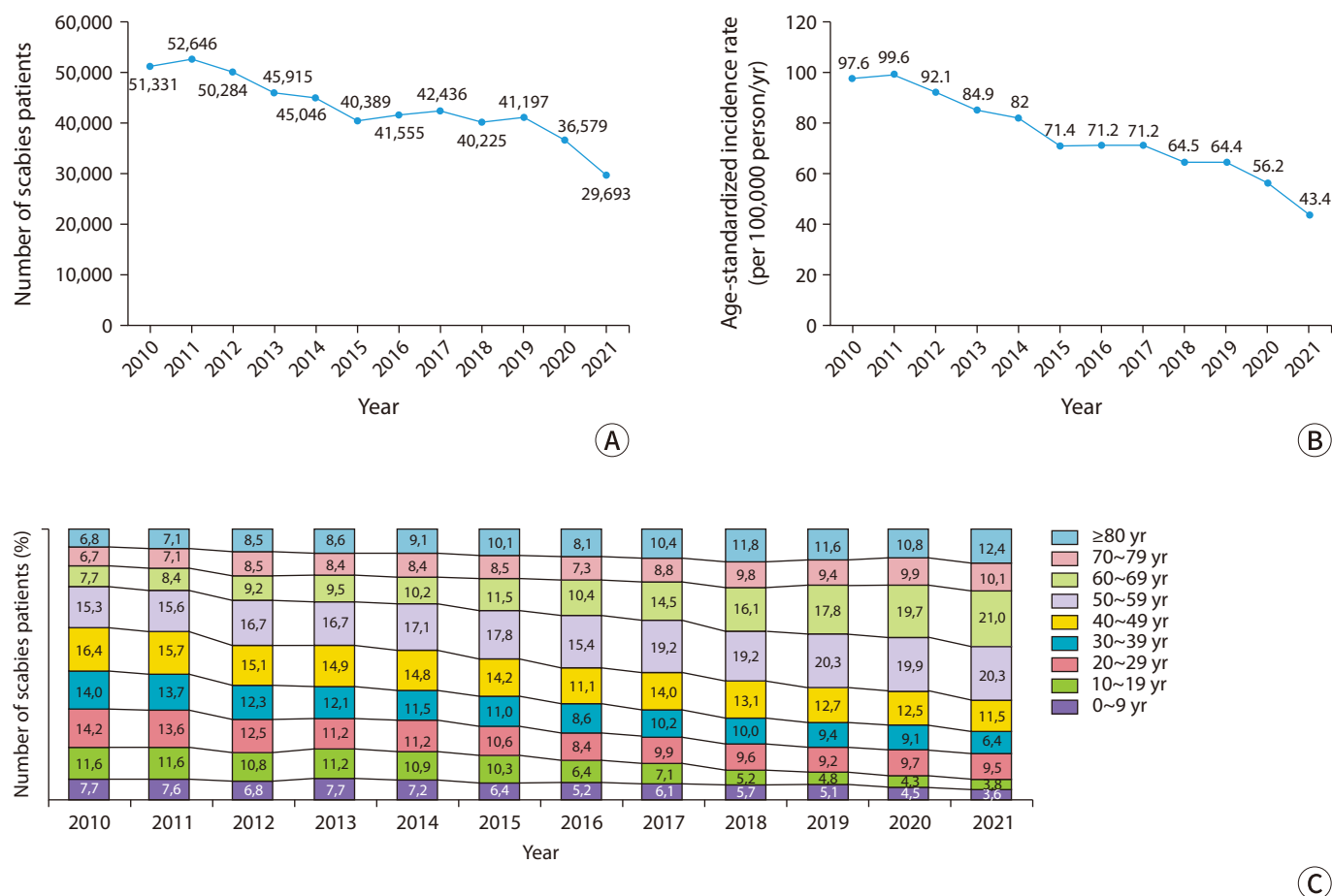


Fig. 1. Epidemiology of scabies in Korea, 2010–2021. (A) Incidence rate. (B) Age-standardized incidence rate. (C) Age distribution of patients.

from 33.5% of all cases in 2010 to 16.9% in 2021. The rise in scabies cases among older adults suggests that infections in younger individuals are likely due to secondary transmission from caregivers, healthcare workers, or family members.

The persistent incidence of scabies can be attributed to several factors, including the expansion of elderly care facilities, increasing drug resistance, challenges in diagnosing atypical or cryptic scabies in clean environments, and increased travel to endemic regions [5,10]. Additionally, the rising trend of group infections in facilities, driven by an aging population and prolonged stays, has emerged as a significant social concern.

Clinical manifestations

- The clinical presentation of scabies varies depending on the patient's age, health status, mite load, and route of transmission.
- Characteristic skin symptoms of the condition include intense itching that worsens at night, along with the presence of burrows and red bumps in typical areas. These areas often include the interdigital web spaces of the fingers, the inner wrists, and around the navel.
- In older adults, immunocompromised persons, or infants, scabies may manifest differently, exhibiting less itching and atypical skin features. These can include involvement of the scalp,

face, palms, and soles, as well as hyperkeratotic scaling or nodules.

The clinical manifestations of scabies vary based on factors such as the patient's age, health status, underlying diseases, the number of mites present, the route of transmission, and the time elapsed before diagnosis. While nocturnal itching and the appearance of burrows are common symptoms, infants and older patients with underlying conditions may present with unique and varied symptoms. Many patients experience severe itching that disrupts sleep and diminishes their quality of life [11]. Additionally, they may develop skin complications such as bacterial infections, eczema, or bullous pemphigoid [12]. In rare cases, systemic complications such as glomerulonephritis, vasculitis, lymphadenopathy, and sepsis may arise [13]. Scabies is typically categorized into three types based on its clinical features: classic, crusted, and nodular (Table 1).

Classic scabies

The primary symptom of classic scabies is intense itching that worsens at night. An analysis of Korean scabies patients revealed that 76.4% experienced nocturnal itching, 23.6% reported severe itching, and 13.8% had sleep disturbances due to the intense itching. This itching is caused by the direct activity of the mites as well as an immunological reaction, primarily Type IV delayed hypersensitivity, to their digestive secretions, excretions, and eggs [14,15]. The worsening of symptoms at night is linked to increased mite activity, elevated secretion levels, and heightened nerve sensitivity, which occurs due to a decrease in sympathetic nervous activity [14].

The incubation period before the onset of itching typically ranges from 4 to 6 weeks. However,

Table 1. Clinical characteristics of scabies

	Classic scabies	Crusted scabies	Nodular scabies
Prevalence	Common	Rare	Uncommon (10%–30%)
Infectivity	Small number of mature mites per patient (five or fewer in mature female mites in half of the cases)	Large numbers of mature mites per patient (1–2 million; infectivity: very high)	Similar to classic scabies
Route of transmission	Direct skin contact	Direct skin contact	Direct skin contact
High-risk groups	Immunocompetent individuals (more common in older adults)	Immunocompromised individuals (e.g., AIDS, malignant tumor, autoimmune disease, immunosuppressant or steroid use, Down syndrome, neurologic or psychological disorders)	Sexually active individuals Infants and younger children
Pruritus	Intense (worse at night)	Mild or absent	Intense
Typical skin rash presentation	Multiple burrows, or erythematous macules and papules (2–3 mm) (often excoriated)	Hyperkeratotic, fissured, scaly erythematous patch or plaque (reminiscent of psoriasis or seborrheic dermatitis)	Multiple red-brown nodules (5–20 mm) Burrows
Typical skin rash distribution	Common: fingers (interdigital web spaces), inner wrists, extensor aspects of the extremities (elbows and knees), periumbilical area, axillary folds, waist, buttocks, and genital area Head, palms, and soles in infants and young children	Bony prominences (fingers, elbows, and iliac crest), palms and soles, head (face and scalp), auricular region	Genital area (penis and scrotum in men), buttock, inguinal, and axillary regions
Complications	Secondary eczema or bacterial infection, glomerulonephritis	Erythroderma, lymphadenopathy, sepsis	

AIDS, acquired immune deficiency syndrome.

it can be shorter (i.e., less than 4 weeks) when a large number of scabies mites are present [16]. In cases of reinfection, symptoms can manifest within 1 to 3 days [17]. Itching may continue for several weeks even after the mites have been eradicated. The severity of the itching often correlates with the number of scabies lesions.

The burrows created by female mites as they tunnel through the stratum corneum are distinctive dermatological manifestations. These burrows typically measure 2–10 mm in length and appear as grayish-white or light brown linear tracks, either thread-like or wavy. Upon close examination, one might notice fine scales on their surface, accompanied by slightly darker or raised edges and ends (Fig. 2A, B) [3]. Commonly, these burrows are located between the interdigital web spaces of the fingers, on the inner wrists, around the navel, buttocks, male genitalia, female breasts, and armpits [2,4]. This distribution pattern indicates the mites' preference for warmer, thinner, and less hairy skin [18]. In approximately 80% of patients, 1 to 4 burrows are found within the same area of skin. Small, erythematous macules and papules, typically 2–3 mm in size and often accompanied by severe itching, are common skin lesions resulting from hypersensitivity to mites (Fig. 2C, D). These lesions are usually observed around the lower abdomen, inner thighs, axillae, and inner arms, although they do not always correspond with the distribution of the burrows [2,17]. In most healthy adults, the scalp, face, palms, and soles are typically unaffected. However, in infants and older adults, one may observe burrows, papules, vesicles, and pustules on the palms and soles [19]. In cases of prolonged infestation, repeated scratching and infection can result in atypical presentations, including excoriations, oozing, and crusted lesions (Fig. 2E, F).

Crusted scabies

Previously known as Norwegian scabies, crusted scabies primarily affects immunocompromised

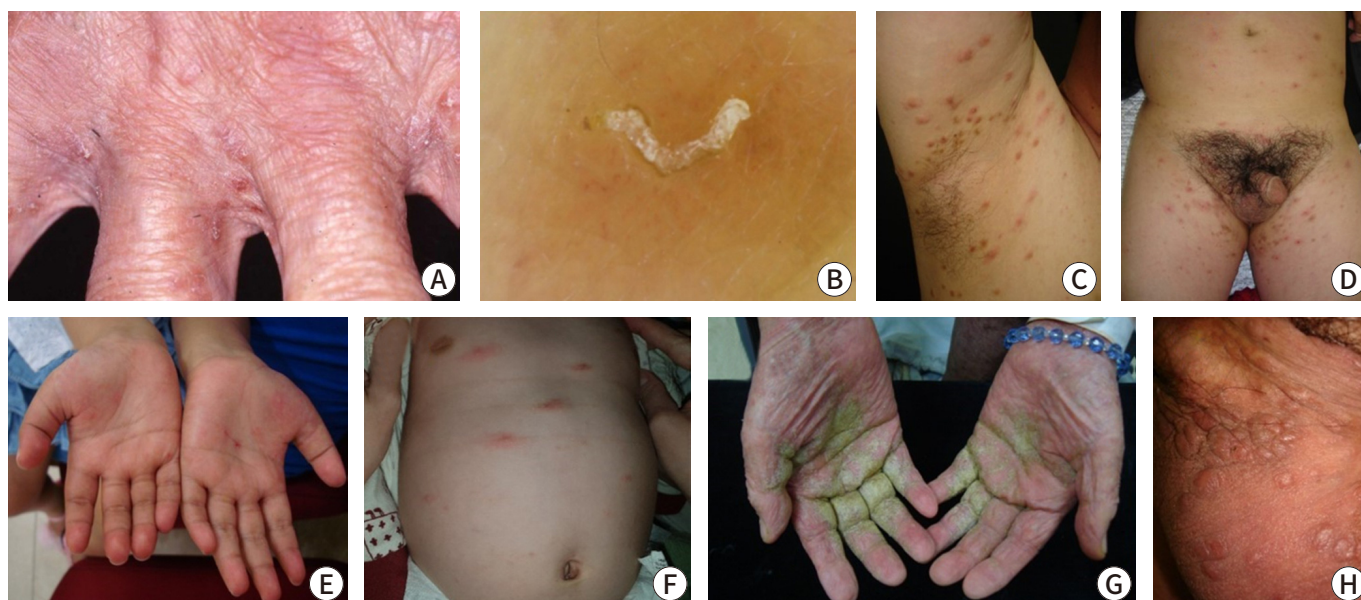


Fig. 2. Clinical photographs of scabies. (A,B) Characteristic classic scabies showing burrows in the interdigital web space. (C,D) Typical erythematous macules, papules, and excoriated crusts in the typical distribution (axilla, groin) of classic scabies. (E,F) Atypical clinical features of scabies in infants showing palmoplantar involvement or atypical skin lesions, such as wheals or vesicles. (G) Crusted scabies revealing diffuse hyperkeratotic scaly lesions in immunocompromised individuals. (H) Nodular scabies revealing multiple nodules in the scrotum.

individuals due to physical or mental disabilities, chronic systemic illnesses, or prolonged steroid use [20]. However, approximately 40% of cases do not have identifiable risk factors [21]. This form of scabies is highly contagious because of the large number of mites present, yet patients typically experience minimal or no itching due to a diminished cellular immune response. It is characterized by extensive, thick hyperkeratotic scales and fissures, which resemble psoriasis or chronic eczema (Fig. 2G). Skin lesions commonly appear on the palms, soles, head, neck, buttocks, elbows, and knees, particularly in areas subjected to friction. Burrows may also be present in non-hyperkeratotic areas. In some instances, the infection can extend to the nails, causing nail deformities, or progress to erythroderma [22–24]. Secondary bacterial infections and lymphadenopathy are common, and patients who are immunocompromised are at an increased risk of developing sepsis [25].

Nodular scabies

Nodular scabies is a variant of classic scabies, affecting approximately 10%–30% of all cases. It is characterized by intensely itchy, red-brown papules and nodules ranging from 5–20 mm in size. These lesions are typically located on the male genitalia, buttocks, groin, and axillae (Fig. 2H). In infants, nodules can also be found on the trunk, limbs, or even across the entire body. Early in the disease, burrows may occasionally be visible on the surface of these nodules. Even after the mites have been eradicated, the nodules often persist for some time, with 80% resolving within three months, though some may last up to a year [26].

Uncommon variants of scabies include canine scabies and scabies incognito. Canine scabies is caused by *S. scabiei* var. *canis* and is transmitted from dogs or other animals. Due to host specificity, it typically resolves spontaneously in humans within a few days and does not spread between humans [27,28]. Scabies incognito occurs when the prolonged use of steroids or other treatments suppresses the immune and inflammatory responses, leading to atypical clinical features [29,30]. Instead of the usual symptoms of itching or burrows, scabies incognito presents with widespread eczema-like lesions, which can result in a delayed diagnosis and the potential for ongoing transmission to others.

Diagnosis

- Scabies is diagnosed clinically through a patient's history of contact with others who have scabies and the presence of characteristic skin symptoms. Confirmation of the diagnosis is achieved by identifying mites using microscopy or dermoscopy.
- A clinical diagnosis of scabies is possible when burrows are visible or when there is a history of contact with a scabies patient, accompanied by nodules in the genital area or characteristic small papules in typical locations.
- Microscopic examination of skin samples provides high specificity. In contrast, dermoscopy is a quick and convenient method that achieves accuracy comparable to microscopy when conducted by experienced clinicians. This technique is particularly advantageous for older patients or infants who may have difficulty cooperating during testing.

The diagnosis of scabies primarily relies on a clinical evaluation, which includes assessing contact history and identifying characteristic skin lesions. Confirmation is achieved through microscopy, dermoscopy, or high-magnification imaging techniques that detect mites [2–4,31]. In many medical institutions in Korea, there is limited access to these mite detection tests; thus, treatment for scabies often begins based solely on the clinical diagnosis [32]. According to a

Korean multicenter study, approximately half of the scabies cases were diagnosed clinically without confirmatory testing. While a patient's history and typical skin findings are invaluable for raising suspicion and aiding in the diagnosis when confirmatory tests are unavailable, they cannot fully replace diagnostic tests. Special consideration should also be given to immunocompromised patients, infants, and older adults, who may not exhibit typical clinical symptoms.

Recently, a consensus was reached by 34 global scabies experts on standardized diagnostic criteria for scabies [2,33]. These criteria categorize the diagnosis into three levels based on diagnostic certainty: suspected, clinical, and confirmed. This stratification provides a valuable tool for diagnosing classic scabies in various clinical settings [34]. The sensitivity and specificity of these standardized criteria range from 69% to 83% and 70% to 96%, respectively [33,34]. However, these criteria may be less appropriate for atypical cases, such as crusted scabies. A simplified version of the criteria, presented in Table 2, is also in use, although its accuracy still requires further validation.

Clinical diagnosis

Contact history is a crucial factor in diagnosing scabies, as it is observed in most cases. When a patient presents with pruritic skin lesions and has a history of contact with someone diagnosed with scabies, scabies should be suspected. This contact history can include direct interactions with the infected individual, such as those involving cohabitants, family members, sexual partners, roommates, healthcare providers, or caregivers. Additionally, individuals who have had close skin contact or direct exposure to contaminated clothing or bedding are considered to be at high risk (Table 3) [2,5]. Therefore, it is essential to thoroughly investigate contact

Table 2. Criteria for the diagnosis of scabies¹⁾

Stage	Criteria ²⁾
Suspected scabies	- Close contact with scabies patients and pruritus - Close contact with scabies patients and skin rash (any type)
Clinical scabies	- Scabies burrows - Close contact with scabies patients, pruritus, and typical skin lesions (one of the following): - Typical erythematous papules or vesicles in a typical distribution (including the periumbilical area, inner thigh, buttock, axilla, and inner forearm) - Multiple nodules in the genital area or axilla - Multiple papules, vesicles, or pustules in the palmoplantar distribution of an infant
Confirmed scabies	- Detection of scabies mites, eggs, or scybala in skin samples using light microscopy - Visualization of scabies mites, eggs, or scybala using high-resolution imaging techniques, including dermoscopy <i>in vivo</i>

¹⁾ These criteria were modified from the 2020 International Alliance for the Control of Scabies.

²⁾ At least one item for each stage.

Table 3. Definition of close contact and high-risk groups for transmission of scabies

Close contact	- Skin contact¹⁾ with an individual diagnosed with scabies - Sexual contact with an individual diagnosed with scabies (especially, nodular scabies) - Brief direct contact with linens (such as towels, clothing, and bedding) used by an individual diagnosed with scabies (especially, crusted scabies)
High-risk groups	- Family members, housemates, and sex partners living with an individual diagnosed with scabies - Healthcare workers, caregivers, and inpatients who share the living environment of an individual diagnosed with scabies (occupational exposures) - A person who has handled linens (towels, clothing, and bedding) of an individual diagnosed with scabies

¹⁾ At least 5–10 minutes of close and continuous contact for acquiring classic scabies (a simple touch, handshake, and hugs are not generally included, except in crusted scabies).

history, family history, sexual relationships, and any visits or stays in long-term care facilities during the history-taking process. However, not all patients with scabies will have an identifiable contact history, and in some cases, the contact may not yet have been diagnosed with scabies. Furthermore, even with a known contact history, itching and skin lesions may not manifest until the end of the incubation period.

Itching is a common symptom among patients with scabies, though it is nonspecific and alone is not sufficient for diagnosis. This is especially pertinent in older adults, who may experience intense itching as a result of dry skin, medications, or psychological factors. Similarly, immunocompromised individuals or young children might exhibit mild or no itching at all; therefore, the absence of itching should not rule out the possibility of scabies.

Clinically, scabies is often diagnosed through the observation of burrows during a physical examination or when a patient with a history of contact presents with distinctive skin findings, such as nodular lesions on the male genitalia or pruritic papules in typical locations. Burrows, a hallmark of scabies, are commonly located between the interdigital web spaces of the fingers or on the inner wrists. Although these thread-like lesions might be visible to the naked eye of an experienced physician, early stages of the disease, secondary eczema, or bacterial infections can obscure the burrows. Therefore, it is advisable to thoroughly examine typical sites. In infants, it is also important to check the palms, soles, and scalp. The "burrow ink test" can be helpful in identifying burrows. This test involves rubbing the suspected burrow area with a surgical marker and then removing the excess ink with an alcohol swab (Fig. 3) [35,36]. Erythematous papules with intense itching on the lower abdomen, inner thighs, or nodules on the male genitalia can also support the diagnosis, although these findings are not specific.

Confirmed diagnosis (scabies mite detection)

Scabies can be confirmed by visually detecting live mites through a microscopic examination of skin samples, dermoscopy, or other high-magnification imaging methods [2]. For microscopy, skin samples are collected from suspected burrows using a scalpel or adhesive tape, placed on a slide, and observed under a light microscope (Fig. 4). Applying mineral oil to the lesion before sampling helps to capture live mites, eggs, and feces (scybala) [37]. Alternatively, potassium hydroxide can be used to dissolve the keratin or debris in skin samples, which offers a clearer view of mites and eggs but dissolves mite feces. Although microscopy has high specificity, it can be cumbersome and has low sensitivity, with positive detection rates varying from 10% to 70%,



Fig. 3. Burrow ink test (staining of the linear burrow with washable blue ink). (A) Naked eye examination, (B) hand-held polarized dermoscope ($\times 10$), and (C) high-resolution videodermoscope ($\times 100$; circle: burrow, arrowhead: scabies mite).

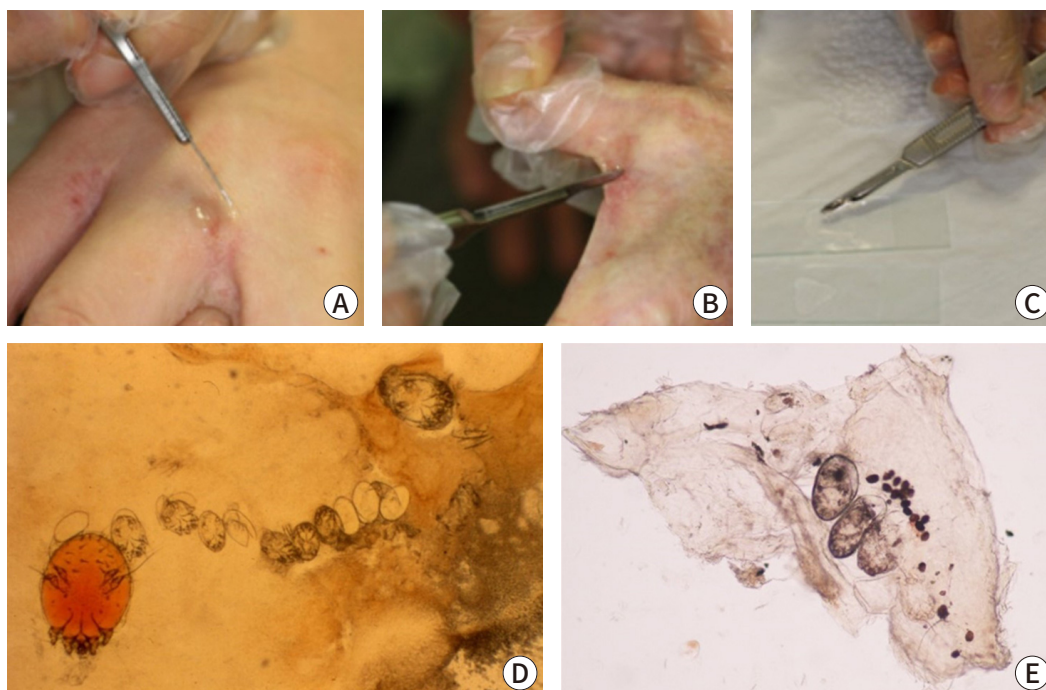


Fig. 4. Skin scraping method findings of scabies. (A–C) Skin scraping method. Adapted from Cho [7] with CC-BY-NC. (D,E) Microscopic findings from a skin scraping sample showing scabies mites, eggs, and scybala *in vitro* ($\times 100$).

depending on the examiner's skill and sampling site [38]. Sampling from typical burrows without abrasion of eczema on areas such as the finger webs and inner wrists can improve detection rates. A negative result does not exclude scabies if clinical suspicion remains high. In a Korean study, the scabies mite detection rate from a single burrow is around 36%, and only 66.7% of scabies cases have detectable mites [39].

Dermoscopy is becoming increasingly popular as a quick, non-invasive, and convenient diagnostic method. While high magnification ($\times 50$ or greater) provides the best accuracy, skilled clinicians are able to detect mites using handheld devices at magnifications of $\times 10$ – 20 [40]. Typically, dermoscopy reveals a distinctive brown triangular mite head, known as the "delta sign" or "hang glider sign," along with a jet-like burrow filled with bubbles and secretions, which gives a "jet with condensation trail" appearance (Fig. 5) [41,42]. These features are recognized for their high sensitivity and specificity [43–45]. Additional indicators include the wake sign, which shows the trail of mite movement, and the gray-edge line or bluish-white structures that represent mite feces [46]. Dermoscopy is particularly advantageous for patients who might find sample collection distressing, such as older adults, immunocompromised individuals, and infants, as it spares them from unnecessary skin sample collection. However, the detection rate can vary significantly depending on the examiner's expertise and the specific area being observed. Other high-magnification imaging techniques, such as reflectance confocal microscopy and optical coherence tomography, are also capable of identifying mites within the stratum corneum, though these methods are rarely used in clinical practice [47–50].

Skin biopsies are generally not performed for diagnosing scabies; however, they can reveal mites, eggs, and feces in the stratum corneum, as well as inflammatory infiltrates, including eosinophils, in the dermis (Fig. 6) [51]. Blood tests do not aid in the diagnosis of scabies. While



Fig. 5. Dermoscopic findings of scabies *in vivo*. (A) A triangular mite (hang glider sign) and curvilinear burrow (jet with condensation trail; ×10). (B) Multiple scabies mites and feces within burrows in crusted scabies (×10). (C) Scabies mite using a high-resolution imaging device (×300).

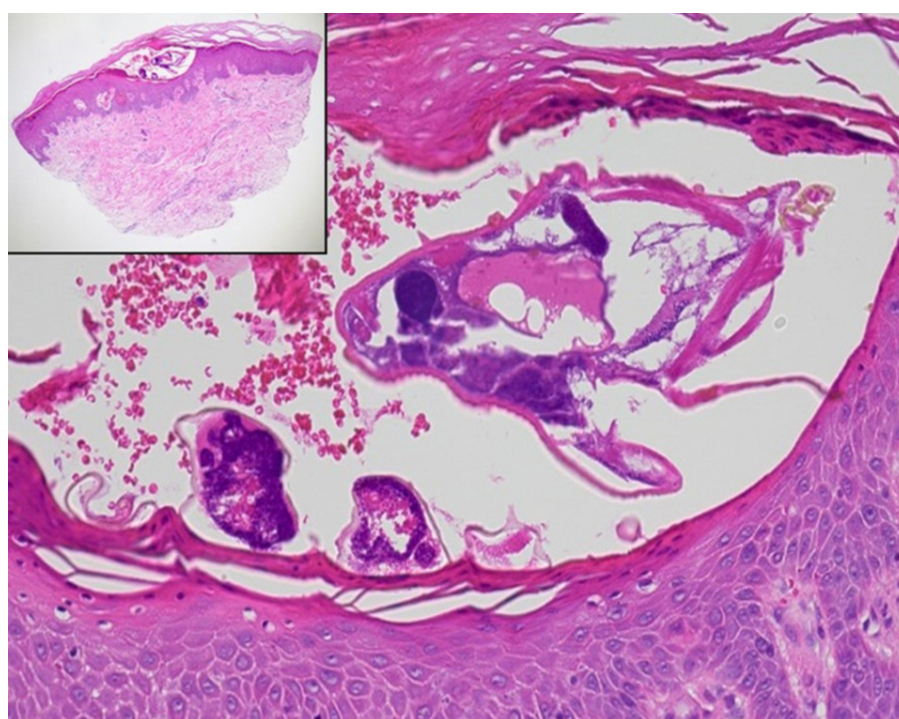


Fig. 6. Histopathological findings of scabies showing a burrow in the stratum corneum with *Sarcoptes scabiei* mites (hematoxylin and eosin stain; ×400 [inset: ×40]).

eosinophils and immunoglobulin E levels may be elevated in patients experiencing itchiness, these elevations are nonspecific. Tests for specific mite antibodies are not commonly used due to their lack of sensitivity and low specificity, which results from cross-reactivity with dust mites [52]. In cases where sexual transmission is suspected or nodules are present in the genital area, testing for sexually transmitted infections, such as syphilis, is advised [53].

Advanced molecular methods are being developed to detect mites. These include nested PCR, reverse transcription-PCR targeting the *cox-1* gene, matrix-assisted laser desorption/ionization-time of flight mass spectrometry, and loop-mediated isothermal amplification. However, further research is required to validate these methods for routine clinical use [47,54–56].

Table 4. Differential diagnosis of various types of scabies

Type	Main differential diagnosis
Classic scabies	Arthropod bites, atopic dermatitis, chickenpox, contact dermatitis, delusion of parasitosis, dermatitis herpetiformis, folliculitis, impetigo, Langerhans cell histiocytosis, lichen planus, papular urticaria, pityriasis rosea
Crusted scabies	Atopic dermatitis, Darier disease, mycosis fungoides, erythroderma, pityriasis rubra pilaris, psoriasis, seborrheic dermatitis, Sezary syndrome, xerotic eczema
Nodular scabies	Prurigo nodularis, pseudolymphoma, secondary syphilis (condyloma lata)
Infantile scabies	Infantile acropustulosis, dyshidrotic eczema (pompholyx), urticaria pigmentosa

Differential diagnosis

Given the nonspecific itching and varied clinical presentations of scabies, it is essential to differentiate it from several other skin conditions (Table 4) [2]. The primary differential diagnoses for classic scabies include insect bites, papular urticaria, atopic dermatitis, contact dermatitis, folliculitis, impetigo, and pityriasis rosea. Delusional parasitosis should be considered in patients who believe in a mite invasion on or inside the skin and repeatedly request diagnostic testing for mite detection without a history of contact. These patients may present objects such as hair, lint, or skin flakes, known as "the matchbox sign," as "proof" of the infestation, despite normal findings on examination. Crusted scabies, characterized by its hyperkeratotic scaling, can closely resemble xerotic eczema, psoriasis, or cutaneous T-cell lymphoma. It may also be mistaken for seborrheic dermatitis when it appears on the head and neck. Nodular scabies may be confused with pseudolymphoma or secondary syphilis, while common lesions on the palms and soles in infants should be differentiated from conditions such as infantile acropustulosis or pompholyx (dyshidrotic eczema).

ORCID

Jin Park: <https://orcid.org/0000-0002-8830-5479>
Soon-Hyo Kwon: <https://orcid.org/0000-0002-7295-5725>
Young Bok Lee: <https://orcid.org/0000-0002-8642-2479>
Hei Sung Kim: <https://orcid.org/0000-0003-0576-0474>
Jie Hyun Jeon: <https://orcid.org/0000-0003-2456-7573>
Gwang Seong Choi: <https://orcid.org/0000-0002-5766-0179>

Authors' contributions

Project administration: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS
Conceptualization: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS
Methodology & data curation: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS
Funding acquisition: not applicable
Writing – original draft: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS
Writing – review & editing: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Conflict of interest

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Supplementary materials

Not applicable.

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Clinical practice guidelines for the diagnosis and treatment of scabies in Korea: Part 2. Treatment and prevention — a secondary publication

Jin Park¹, Soon-Hyo Kwon², Young Bok Lee³, Hei Sung Kim⁴, Jie Hyun Jeon⁵,
Gwang Seong Choi⁶;

on behalf of the Scabies Study Group of Korean Dermatological Association

¹Department of Dermatology, Jeonbuk National University Medical School, Jeonju, Korea

²Department of Dermatology, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea

³Department of Dermatology, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

⁴Department of Dermatology, Incheon St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

⁵Department of Dermatology, Korea University Guro Hospital, Seoul, Korea

⁶Department of Dermatology, Inha University Hospital, Incheon, Korea

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Corresponding author

Gwang Seong Choi
Department of Dermatology, Inha
University Hospital, 27 Inhangro, Jung-
gu, Incheon 22332, Korea
E-mail: garden@inha.ac.kr

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Treatment should be initiated for all suspected, clinical, or confirmed cases of scabies. Patients affected should be adequately isolated, and high-risk groups with close contact histories should be treated regardless of their symptoms. Optimal treatment strategies can be selected based on age, clinical subtype, and the patient's health status. In Korea, commercially available preparations for scabies treatment include topical 5% permethrin, topical 10% crotamiton, and oral ivermectin. Topical 5% permethrin is the first-line selective treatment for both classic and crusted scabies. Alternative treatments include topical 10% crotamiton and oral ivermectin. After completing treatment, follow-up visits at 2 and 4 weeks are recommended to monitor the therapeutic response. Treatment is considered to have failed if scabies mites or burrows are detected, new clinical characteristics develop, or there is an aggravation of pruritus. Scabies itch should be adequately managed with emollients, oral antihistamines, and topical corticosteroids. Preventive measures, including personal hygiene, patient education, and environmental control, should be implemented to reduce the transmission of scabies.

Treatment

- Treatment for scabies should be chosen based on factors such as age, clinical form, and overall health status. Additionally, close contacts should be treated simultaneously with the patient, irrespective of symptom presence.
- Topical 5% permethrin is the first-line treatment for both classic and crusted scabies. When the use of topical 5% permethrin is not feasible, alternative treatments include topical 10% crotamiton or oral ivermectin.
- Treatment is deemed unsuccessful if there is an exacerbation of pruritus, the emergence of new characteristic skin lesions such as burrows, or if mites continue to be detected after the treatment.

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When selecting an appropriate treatment for scabies infestation, it is important to consider factors such as the patient's age, the clinical form of the disease, and overall health status. Treatment should be administered simultaneously to both the patient and any close contacts, including family members living in the same household and facility staff, regardless of whether they show symptoms. In Korea, the available scabicial treatments include topical 5% permethrin cream, 10% crotamiton ointment, and oral ivermectin (Table 1, Supplement 1). Although 5%–10% sulfur ointments are not commercially available within the country, they can be specially prepared or imported as needed. Topical 5% permethrin is the first-line treatment for both classic and crusted scabies. If the use of topical 5% permethrin is not feasible, alternative options include 10% crotamiton ointment or oral ivermectin.

Treatment of classic scabies

Topical 5% permethrin

Permethrin, approved by the U.S. Food and Drug Administration (FDA) for use in individuals aged two months and older (approved for ages two years and older in Korea), is typically the first-line treatment for scabies. It effectively targets all life stages of the scabies mite, including eggs, and has been shown to be more efficacious than oral ivermectin [1]. Although a single application might theoretically be sufficient to reduce the risk of treatment failure, it is recommended to apply permethrin twice, one week apart, and to schedule a follow-up visit two weeks after the initial treatment to confirm eradication. Generally, the application should remain on the skin for at least 8–12 hours; however, an *in vitro* study suggested that maintaining 5% permethrin on the skin for only 8 hours may not fully eradicate the mites [2]. Therefore, it is advisable to wait approximately 12 hours post-application before washing. Studies in the early 2000s reported an approximate 95% efficacy of 5% permethrin, while a 2020 survey in Germany indicated an efficacy rate ranging from 80% to 100% [3]. However, more recent studies in Austria and other regions have reported lower treatment efficacy than previously observed [4,5]. Although permethrin-resistant scabies mites have not been definitively identified, an increase in cases suspected to involve treatment resistance highlights the need for caution.

Table 1. Drugs available in Korea for the treatment of scabies

Drug (product)	FDA approval for scabies treatment	Domestic approval (class)	Usage (dosing)
Topical 5% permethrin (Omecclean, 30 g cream/tube)	Yes	Yes (prescription drug)	- Adult: 25–30 g (1 tube) - 6–12 years: 15 g (1/2 tube) - 2 months–5 years: up to 7.5 g (1/4 tube)
Topical 10% crotamiton (Uracin, 50 g ointment/tube)	Yes (only for adults)	Yes (over-the counter drug)	Adult: 25–30 g (1/2 tube)
Oral ivermectin (Stromectol, 3 mg/tablet)	No	No (orphan drug) Indication in KOEDC - Failure or nonadherent to topical treatment - Widespread institutional outbreaks	- 15–24 kg: 1 tablet - 25–35 kg: 2 tablets - 36–50 kg: 3 tablets - 51–65 kg: 4 tablets - 66–79 kg: 5 tablets - ≥80 kg: 200 µg/kg - Adult dose: 9–15 mg/d

FDA, Food and Drug Administration; KOEDC, Korea Orphan & Essential Drug Center.

Topical 10% crotamiton

Crotamiton has received approval from the U.S. FDA for the treatment of scabies infections in adults, boasting an efficacy rate of about 60%. The typical regimen involves daily application for 3 to 5 days (e.g., on days 1, 2, 3, and 8), with each application left on the skin for 8 hours. Due to its relatively lower efficacy and instances of treatment failure, crotamiton is generally used as a secondary option when first-line treatments, such as topical permethrin or oral ivermectin, are not suitable. Crotamiton is favored in clinical practice for pediatric patients due to its minimal skin irritation and anti-itch properties. In Korea, its use is also sanctioned for children, though it is advised to limit extensive application in infants and young children.

Topical 5%–10% sulfur

Sulfur is considered safe for use in infants under two months of age and in pregnant women. It is typically applied nightly over three consecutive days, with the final application being washed off the next day. However, its unpleasant odor and propensity to stain may deter its use. While sulfur-based formulations are not commercially available in Korea, they can be self-prepared or imported for use.

Topical 1% lindane

Lindane was previously approved by the U.S. FDA; however, it is no longer produced or used due to concerns over neurotoxicity.

Oral ivermectin

Ivermectin, introduced in 1981, remains the sole oral medication for treating scabies, with a half-life of 12–56 hours. Although the FDA has approved it for treating other parasitic infections such as strongyloidiasis and onchocerciasis in the U.S., clinical experience has also established its safety and efficacy for scabies. In 2001, France authorized the use of ivermectin for managing scabies outbreaks in institutional settings. It is typically employed when the first-line topical treatment, permethrin, is unsuitable or ineffective. In Korea, ivermectin is imported under the brand name Stromectol and is classified as an orphan drug, necessitating specific administrative procedures for its prescription in hospitals (Supplement 2).

Ivermectin does not eliminate scabies eggs. Therefore, for classic scabies, a dosage of 200 µg/kg is administered twice, 1–2 weeks apart, to coincide with the mite's life cycle. This is followed by an evaluation of the treatment's efficacy. Taking ivermectin with food increases its absorption [6]. Its safety in children under 15 kg and pregnant women has not been confirmed, although serious side effects are rare in infants and pregnant women who have taken it [7,8]. Consequently, it may be considered when other treatments are either unavailable or have failed. While some practices combine oral ivermectin with topical agents, the effectiveness and evidence supporting this combined approach in the treatment of classic scabies have not yet been conclusively established.

Treatment of crusted scabies

- The medications used to treat crusted scabies are similar to those for classic scabies; however, the frequency of application and dosage may differ.
- Due to its high transmissibility, isolation is recommended to prevent the risk of spreading the infection.
- While some cases of scabies are treated solely with topical permethrin, in countries where oral ivermectin is accessible and approved, it is often used concurrently. For crusted scabies that is resistant to topical permethrin alone, a combination of oral ivermectin and topical

treatments may be considered. However, there are currently no standardized guidelines regarding the frequency and intervals of topical applications or their combination with oral medications for treating crusted scabies. Typically, permethrin ointment is applied daily for one week and then twice weekly until no mites or eggs are detected [9]. Ivermectin is administered on days 0, 1, 7, 8, and 14, with optional additional doses on days 21 and 28 [7]. The treatment regimens for ivermectin are categorized into three phases based on the severity of the symptoms of crusted scabies: Phase 1 includes days 0, 1, and 7; Phase 2 includes days 0, 1, 7, 8, and 14; Phase 3 includes days 0, 1, 7, 8, 14, 21, and 28 [8].

- The removal of the thick crust associated with crusted scabies aids in treatment. Consequently, keratolytic agents such as 5%–10% salicylic acid, 10% urea, and 5% lactic acid, which are not typically used in treating classic scabies, can be employed to enhance drug penetration and improve treatment efficacy.
- If secondary bacterial infections with organisms such as *Streptococcus pyogenes* or *Staphylococcus aureus* are present, appropriate antibiotics should be administered [9].

Precautions in scabies treatment

- Simultaneously treat individuals who have been in contact with or are cohabitating with a scabies patient.
- For classic scabies, thoroughly apply the medication from the neck down to the feet, covering all skin areas. This includes under the nails and in skin folds, such as the groin. After applying the medication, it should remain on the skin for an adequate period (at least 8 hours) before it is washed off.
- For infants, young children, and certain older adults with scalp or facial involvement, the treatment should be applied over the entire body, including the face and scalp.
- Wearing plastic gloves during application is recommended, as excessive absorption of the medication through the palms can cause numbness, tingling, or a stinging sensation.

Treatment failure

Typically, itching from scabies subsides about three days after the application of scabies treatment. However, if itching persists or worsens without improvement, initially improves but then intensifies again, or if new burrows or skin lesions emerge, or mites are still detected within 7–14 days post-treatment, treatment failure should be considered. It is important to note, however, that persistent itching alone should not be immediately considered a sign of treatment failure. Itching may continue for several weeks due to hypersensitivity reactions to the mites or their waste products, even after all mites have been eliminated.

Common causes of treatment failure include improper treatment, continued close contact with untreated infected individuals, inadequate disinfection of clothing and bedding, and the use of topical steroids during treatment. Drug resistance is also suspected as a potential factor. Treatment failure can occur even with highly effective ointments if the treatment is not applied thoroughly or if instructions are not followed carefully. However, if instructions are followed diligently and the medication is applied thoroughly, most cases of recurrence are due to reinfection from untreated carriers of scabies [10].

Treatment for children, pregnant women, and institutional outbreaks

Children

Permethrin is approved by the FDA as a first-line treatment for children over 2 months old and

has well-established safety data. However, in Korea, it is only approved for use in children aged 2 years and older [6,11]. For children, unlike adults, the application should cover all areas of the body except around the eyes and mouth, including the face [12]. Crotamiton may be considered a second-line treatment, although it is less effective and requires a longer treatment duration than permethrin [13]. Sulfur ointment is safe for use in very young infants under 2 months old; however, it is not commercially available in Korea. Lindane is contraindicated in children [5]. The safety of ivermectin has not been established for children weighing less than 15 kg [6].

Pregnant and breastfeeding women

Permethrin is considered safe for use in pregnant and breastfeeding women and is recommended as a first-line treatment by the Centers for Disease Control and Prevention (CDC) [6]. However, it is not approved for use in pregnant and breastfeeding women in Korea. Therefore, it is important to adhere strictly to the recommended dosage and application guidelines to avoid any potential risks. When applied, less than 2% of the permethrin dose is absorbed systemically [14]. While it is unclear whether permethrin is excreted into breast milk, it is advisable to pause breastfeeding for five days after its application. Sulfur ointment is also considered safe for pregnant and breastfeeding women, but it is not commercially available in Korea. Lindane, on the other hand, is contraindicated for use in pregnant and breastfeeding women [15]. The safety of ivermectin during pregnancy has not yet been established [6].

Treatment in institutional outbreaks

Mass treatment for scabies is recommended in areas where it is endemic or for managing outbreaks in closed community settings [7]. In situations involving suspected transmission within a community or institution, such as healthcare facilities or nursing homes, it is advisable to treat all individuals at risk, regardless of whether they exhibit symptoms. Oral ivermectin is the preferred option for mass treatments due to its ease of administration compared to topical treatments. Typically, a single dose of oral ivermectin is administered at 200 µg/kg [16], and evidence suggests that a second dose one week later may improve treatment efficacy (Table 2) [17].

Scabies-related itching

- The itching associated with scabies can significantly affect quality of life and may continue for some time even after all mites have been eradicated. This necessitates proactive management from the onset.
- Moisturizers, oral antihistamines, and topical steroids can help alleviate itching associated with scabies.

Table 2. Summary of drugs for scabies treatment in children, pregnant and breastfeeding women

Drugs	Use in children	Use in pregnancy	Use in breastfeeding
Topical 5% permethrin	Safe in children ≥2 months (FDA)	Approved	Not recommended
Topical 10% crotamiton	Safe in children	Not recommended	Not recommended
Oral ivermectin	Not approved in children <15 kg or 5 years of age	Only recommended in France	Only recommended in France

FDA, Food and Drug Administration.

Mechanism of itching in scabies patients

The itching associated with scabies infection is thought to involve multiple immunological mechanisms, including hypersensitivity reactions to the mites and their secretions [18]. The innate immune response, primarily driven by the complement system, plays a significant role, with substantial involvement of mast cells. The T-cell-mediated response varies between classic scabies and crusted scabies: a Th1 response is predominant in classic scabies, while a Th2 response prevails in crusted scabies. Notably, in crusted scabies, there is an observed infiltration of CD8+ T-cells within the dermis and increased apoptosis of keratinocytes, which can exacerbate the itching [19].

Additionally, the increased expression of Toll-like receptors-3, -4, and -7 in peripheral nerves due to scabies mites, along with the activation of protease-activated receptor-2 by proteases secreted by the mites, and certain IgE-mediated allergic reactions are considered direct causes of scabies-related itching. Immune responses involving macrophages, prostaglandins, and leukotrienes also contribute to the itching. Furthermore, secondary bacterial infections may exacerbate the itching through interleukin-31 expression and Toll-like receptors activation [20].

Treatment of itching in scabies patients

Many scabies patients experience severe itching, which disrupts their sleep and diminishes their quality of life, necessitating proactive itch relief treatment. For patients with concurrent skin or systemic conditions that induce itching, such as atopic dermatitis or chronic kidney disease, intensive treatment from the start is advised. These conditions may foster an environment conducive to mite survival due to compromised barriers or immune abnormalities, potentially exacerbating the itching associated with scabies [21].

Standard approaches typically include moisturizers, topical corticosteroids, and oral antihistamines as the first line of treatment. Moisturizers help restore the skin barrier and prevent dryness, which aids in relieving itching [7,18,22]. Antihistamines are commonly chosen for initial treatment, with first-generation antihistamines also aiding in improving sleep for scabies patients [23]. Topical steroids can help manage inflammatory itching; however, their use should be limited to areas of intense itch. Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are effective, particularly for nodular scabies lesions [24]. While systemic steroids are generally avoided due to potential side effects like immunosuppression or increased blood glucose, short-term use may be considered when severe itching persists after mite eradication [25]. Narrow-band UVB phototherapy is considered a safe option, even for pregnant women and children [26].

In some cases, contact dermatitis may occur after applying topical scabicides. Should this happen, treatment with oral antihistamines and topical steroid ointments is recommended [18,27]. If traditional treatments do not alleviate the itching associated with scabies, alternative therapies, including protease-activated receptor-2 inhibitors, Th2 cytokine inhibitors, transient receptor potential channel modulators, and gabapentin-class antidepressants, might be considered [20]. While these medications are not typically used in everyday practice, research has demonstrated their efficacy in relieving itching.

Prevention and infection control

- Scabies patients require contact precautions or isolation until 24 hours after the final application of treatment.
- Close contacts should receive a single preventive treatment, even if they are asymptomatic,

- and should then be monitored for the development of symptoms over a 6-week period.
- The patient's clothing, bedding, and linens must be laundered and dried using heat. Additionally, medical equipment and items, as well as the surrounding environment that the patient has touched, should be disinfected with alcohol or other standard methods.
 - When a case of scabies is identified, it is essential to isolate the patient, manage contacts, and control the environment to prevent transmission (Table 3).

Patient contact precautions and isolation

Effective management of scabies patients is essential to prevent transmission and ensure optimal treatment outcomes. For classic scabies, it is important to adhere to contact precautions throughout the treatment period. Patients should avoid close contact with others until 24 hours after the final treatment application or until a physician confirms that the risk of transmission has decreased. At home, physical contact between the scabies patient and other household members should be minimized, and sharing personal items should be avoided. In healthcare settings, patients may be isolated in a single room or placed in cohort isolation, depending on the resources available at the institution. For crusted scabies, which is highly contagious, more stringent precautions are necessary. Contact tracing and disinfection measures should be expanded. Patients should remain in single-room or cohort isolation until a physician confirms that the risk of transmission has decreased. Healthcare providers, caregivers, and family members should continue to observe contact precautions.

Table 3. Recommended measures for scabies prevention

	Classic scabies	Crusted scabies
Isolation	- Maintain contact precautions for up to 24 hours after the last treatment or until the doctor determines that the infectiousness has subsided.	- Isolate in single rooms or cohorts until the doctor determines that the infectiousness has subsided.
Contact management	- Administer preventive treatment once. - Medical staff, employees, caregivers, and family members should wear disposable gloves and gowns and perform hand washing before and after contacting the patient. - Observe for symptoms for 6 weeks, considering the incubation period.	
Room management	- For rooms used by scabies patients, clean daily using a dedicated vacuum cleaner or disposable absorbent cloth during the isolation or treatment period. - For rooms that have been vacated or after a patient has been discharged, clean and disinfect using standard methods. - Empty the vacuum cleaner bag daily, clean the dust collection tube, and dispose of the absorbent cloth as infectious medical waste.	
Item management	- Disinfect diagnostic equipment such as dermoscopes, blood pressure cuffs, stethoscopes, and wheelchairs using standard methods before they are used by another patient. - Clean beds, sofas, etc. with a vacuum cleaner. - Put items that cannot be laundered in a plastic bag and store them for at least 7 days before reuse. - Discard any remaining medication used by scabies patients.	
Laundry management	- Machine wash in hot water at 50°C for 10–20 minutes and dry at a high temperature. - Laundry handlers should wear disposable gloves and gowns. - For items that cannot be laundered, store them in a plastic bag for at least 7 days and dry them at 50°C or higher. - Manage all laundry the patient uses for at least 3 days before treatment and change the patient's clothing, bedding, and towels daily.	
Patient's home management	- Clean the entire house with a vacuum cleaner daily during the isolation or treatment period. - Machine wash and dry contaminated clothing, bedding, towels, etc. in hot water at 50°C for 10–20 minutes. - For items that cannot be laundered, store in a plastic bag for at least 7 days and dry at 50°C or higher.	

Contact management

Given the potential for asymptomatic latency lasting several weeks, it is essential to manage contacts of scabies patients effectively. When a case occurs within a family, all close contacts, including cohabitants and family members, should undergo simultaneous treatment, regardless of whether they exhibit symptoms [7,27,28]. Generally, both children and adults can return to daycare, school, or work the day after treatment. However, in some instances, their return may be postponed until the completion of treatment is confirmed.

Close contacts should receive a single preventive treatment and be monitored for symptoms over a 6-week period. For hospitalized scabies patients, healthcare staff, caregivers, and family members must wear personal protective equipment, including disposable gloves and gowns, during contact with the patient and adhere to hand hygiene practices. Healthcare personnel who have been in contact with scabies patients may return to work the day after receiving preventive treatment. Any staff member who develops symptoms should immediately stop working, undergo diagnostic testing, and receive treatment if diagnosed [21,23,27–32].

Environmental management

Scabies mites can survive off a human host for 48–72 hours, but they generally cannot live longer than 3 days in the environment. They are killed by exposure to temperatures above 50°C for 10 minutes. In households where a scabies case has occurred, any clothing, bedding, or towels used by the patient within the past three days should be machine-washed in hot water (above 50°C) for 10–20 minutes and dried on high heat. Items that cannot be washed should be sealed in plastic bags for at least seven days, then tumble-dried at high heat for 10–20 minutes at temperatures of 50°C or higher.

In healthcare facilities and nursing homes, patient rooms must be cleaned daily during isolation periods. This cleaning should be performed using either a dedicated vacuum cleaner or disposable absorbent cloths. The bags or containers of the vacuum cleaner should be emptied and cleaned daily, with disposable bags being replaced as needed. Additionally, the interior of the vacuum should be sanitized. Absorbent cloths used in the cleaning process must be disposed of as medical waste. Shared medical equipment, including dermoscopes, blood pressure cuffs, stethoscopes, and wheelchairs, must be disinfected with either alcohol or diluted bleach after each patient use.

Laundry from scabies patients requires careful handling on treatment days. It should be sealed in a plastic bag and placed in a designated contaminated laundry bin. Subsequently, it should be machine-washed at a temperature of 50°C or higher for 10–20 minutes and then heat-dried. Staff responsible for handling this laundry must wear personal protective equipment, which includes disposable gloves and gowns, and ensure that the patient's laundry is kept separate from other items. Additionally, medical waste from scabies patients should be disposed of in dedicated containers.

Conclusion

The Scabies Eradication Public Health Project Committee of the Korean Dermatological Association has developed clinical practice guidelines specifically designed for Korean patients. These guidelines are based on medical evidence, consensus among domestic scabies specialists, and external validation. They provide a comprehensive overview of the epidemiology, clinical symptoms, diagnosis, treatment, follow-up, prevention, and management of scabies in Korea. Additionally, a clear and concise diagnostic and treatment algorithm is included to aid

healthcare professionals in making quick decisions during scabies consultations (Fig. 1). We hope these guidelines will serve as a reliable and practical resource for the treatment and prevention of scabies, ultimately contributing to improved public health.

These guidelines should be applied based on the healthcare provider's knowledge and clinical experience, taking into account each patient's specific circumstances, clinical subtypes, and

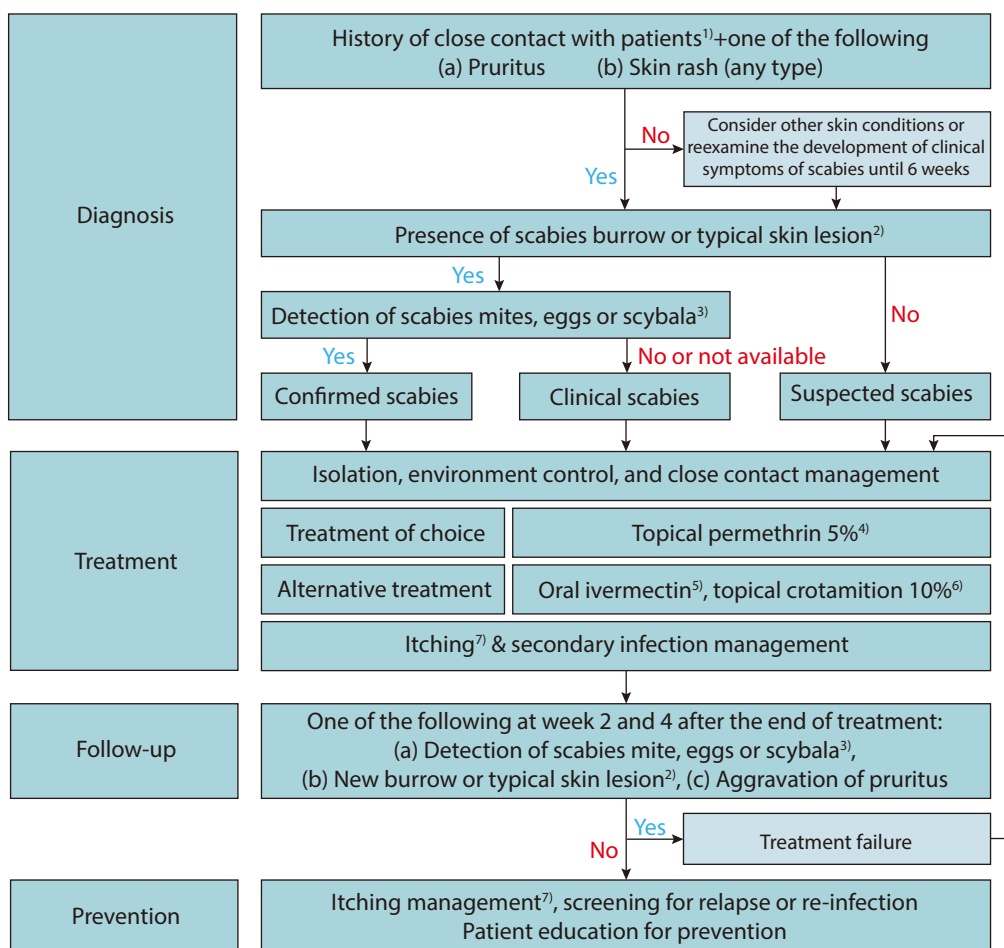


Fig. 1. Proposed algorithm for the diagnosis and treatment of scabies in Korea. ¹⁾ One of the following: (a) Skin contact with an individual diagnosed with scabies, (b) sexual contact with an individual diagnosed with scabies (especially nodular scabies), (c) brief direct contact with linens (such as towels, clothing, and bedding) used by an individual diagnosed with scabies (especially crusted scabies); ²⁾ One of the following: (a) Typical erythematous papules or vesicles in a typical distribution including the periumbilical area, inner thigh, buttock, axilla, inner forearm, (b) multiple nodules in genital area or axilla, (c) multiple papules, vesicles, or pustules in the palmoplantar distribution of an infant; ³⁾ Light microscopy, dermoscopy, or other high-resolution imaging techniques including could be used; ⁴⁾ In general, apply on the whole body, except the face and scalp, at least 30 minutes after taking a shower. For treatment of infants and older adults, it should be applied to the lesion on the scalp and face; the recommended doses are as follows: 25–30 g (1 tube) for adults, 15 g (1/2 tube) for ages 6–12 years, and up to 7.5 g (1/4 tube) for ages 2–5 years; cleansed out after at least 8–12 hours of application. Application is repeated after 7–10 days. For crusted scabies, 5% permethrin cream should be applied daily for a week, then twice weekly until any mite or egg is not identified. However, 5% permethrin cream is not permitted for use in patients aged <2 years and pregnant or lactating women in Korea; therefore, Centers for Disease Control and Prevention guidelines recommend using 5% permethrin cream in patients older than 2 months and pregnant or lactating women; ⁵⁾ For classic scabies, the recommended dose is 200 µg/kg twice weekly; For crusted scabies, ivermectin is administered on days 0, 1, 7, 8, 14, 21, and 28. Safety in patients who are pregnant or weigh <15 kg is not established; ⁶⁾ Apply repeatedly for 3–5 days (i.e., days 1, 2, 3, and 8), and leave on for at least 8 hours; it can be used for children and pregnant or lactating women cautiously; ⁷⁾ Emollients, H1 antihistamines, topical or systemic steroids (in selected cases), topical calcineurin inhibitors, and narrow-band ultraviolet B could be used.

the available healthcare environment. Additionally, we anticipate further research on scabies involving Korean patients, which will facilitate the development of systematic clinical guidelines supported by new clinical evidence.

ORCID

Jin Park: <https://orcid.org/0000-0002-8830-5479>

Soon-Hyo Kwon: <https://orcid.org/0000-0002-7295-5725>

Young Bok Lee: <https://orcid.org/0000-0002-8642-2479>

Hei Sung Kim: <https://orcid.org/0000-0003-0576-0474>

Jie Hyun Jeon: <https://orcid.org/0000-0003-2456-7573>

Gwang Seong Choi: <https://orcid.org/0000-0002-5766-0179>

Authors' contributions

Project administration: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Conceptualization: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Methodology & data curation: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Funding acquisition: not applicable

Writing – original draft: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Writing – review & editing: Park J, Kwon SH, Lee YB, Kim HS, Jeon JH, Choi GS

Conflict of interest

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Data availability

Not applicable.

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Supplementary materials

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Supplement 1. Methods of administering drugs to treat scabies

Supplement 2. Ivermectin supply flow chart

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국제의학학술지편집인위원회

Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals (revised in January 2024): a Korean translation

International Committee of Medical Journal Editors



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Translator

Jin-Hong Yoo
 Division of Infectious Diseases,
 Department of Internal Medicine,
 Bucheon St. Mary's Hospital, College
 of Medicine, The Catholic University of
 Korea, Seoul, Korea
 E-mail: jhyoo@catholic.ac.kr

Scientific reviewer

Committee for Publication Ethics, Korean
 Association of Medical Journal Editors
 E-mail: office@kamje.kr

ORCID

Jin-Hong Yoo
<https://orcid.org/0000-0003-2611-3399>

목차

I. 권고안에 관하여

- A. 권고안의 목적
- B. 권고안의 사용자
- C. 권고안의 역사

II. 저자, 기여자, 전문가 심사자, 편집인, 발행인, 학술지 소유주의 역할과 책임

- A. 저자와 기여자의 역할
 1. 저자됨(Authorship)의 중요성
 2. 저자의 정의
 3. 저자가 아닌 기여자(Non-author Contributors)
 4. 인공지능(Artificial Intelligence, AI) 지원 기술
- B. 재정적, 비재정적 이해관계와 활동의 공시 및 이해충돌(Disclosure of Financial and Non-Financial Relationships and Activities and Conflicts of Interest)
 1. 대상자(Participants)
 - a. 저자
 - b. 전문가 심사자(Peer Reviewers)
 - c. 편집인 및 학술지 편집진(Journal Staff)
 2. 이해관계와 활동의 보고
- C. 투고와 심사 과정에서의 책임
 1. 저자
 - a. 약탈적(Predatory) 또는 가짜 학술지(Pseudo-Journals)

2. 학술지
 - a. 보안(Confidentiality)
 - b. 적시성(Timeliness)
 - c. 전문가심사(Peer Review)
 - d. 진실성(Integrity)
 - e. 다양성과 포용(Diversity and Inclusion)
 - f. 학술지 계량지표(Journal Metrics)
3. 전문가 심사자

D. 학술지 소유주와 편집권의 독립

1. 학술지 소유주
2. 편집권의 독립

E. 연구 대상자(Research Participants)의 보호

III. 논문 출판과 관련된 편집 및 출판 상의 문제들

- A. 정정기사(Corrections), 논문 취소(Retractions), 재출판, 판본 관리(Version Control)
- B. 학술적 부정행위, 우려 표명(Expression of Concern), 논문 취소(Retraction)
- C. 저작권
- D. 중복출판(Overlapping Publications)
 1. 이중투고(Duplicate Submission)
 2. 이중출판(Duplicate Publication)과 사전출판(Prior Publication)
 3. 프리프린트(Preprints)
 - a. 프리프린트 문서 보관소 선택하기
 - b. 프리프린트 문서 보관소에 있는 원고를 전문가심사 학술지에 투고하기
 - c. 투고 원고에 프리프린트 인용하기
 4. 허용되는 이차출판(Secondary Publication)
 5. 동일 자료에 기반한 원고
- E. 독자통신(Correspondence)
- F. 비용(Fees)
- G. 별호(Supplements), 주제별 간행물(Theme Issues), 특별 연재물(Special Series)
- H. 후원자(Sponsorship) 또는 동반자 관계(Partnerships)
- I. 온라인 출판(Electronic Publishing)
- J. 광고
- K. 학술지와 대중매체

- L. 임상시험(Clinical Trials)
 - 1. 등록
 - 2. 자료 공유(Data Sharing)

IV. 원고 준비와 투고

- A. 의학학술지에 투고하기 위한 원고의 준비
 - 1. 일반 원칙
 - 2. 특정한 연구계획을 위한 보고 지침(Reporting Guidelines)
 - 3. 원고의 구성(Manuscript Sections)
 - a. 표지(Title Page)
 - b. 초록(Abstract)
 - c. 서론(Introduction)
 - d. 방법(Methods)
 - i. 연구 대상의 선택 및 서술
 - ii. 기술 정보(Technical Information)
 - iii. 통계
 - e. 결과(Results)
 - f. 고찰(Discussion)
 - g. 참고문헌(References)
 - i. 일반적인 고려사항
 - ii. 형태와 형식(Style and Format)
 - h. 표(Tables)
 - i. 그림(Illustrations/Figures)
 - j. 측정 단위
 - k. 약어와 부호
- B. 투고

I. 권고안에 관하여

A. 권고안의 목적

국제의학학술지편집인위원회(International Committee of Medical Journal Editors, 이하 ICMJE로 약함)는 의학학술지에 게재되는 연구의 수행과 보고 과정, 그리고 기타 게재물과 관련하여 잘 정리된 관례와 윤리 표준을 검토하고, 저자, 편집인, 그리고 전문가심사(peer review)와 생의학 관련 출판 관계자들이 명확하고 균형 잡힌(unbiased) 의학학술지 논문을 작성하고 배포하는 데 도움을 주고자 이 권고안을 개발하였다. 또한 이 권고안은 매체, 환자와 가족, 일반 독자들이 의학 학술지의 편집과 출판 과정을 이해하는 데 매우 유용할 것이다.

B. 권고안의 사용자

이 권고안의 일차적인 목적은 ICMJE 회원 학술지에 투고하려는 저자들이 사용하도록 하는 데 있다. 그러나 ICMJE 회원이 아닌 많은 학술지들도 자발적으로 이 권고안(<https://www.icmje.org/journals-following-the-icmje-recommendations>)을 사용하고 있다. ICMJE는 이 권고안의 사용을 장려하지만, 사용을 강권하거나 감독하려는 의사는 없다. 모든 경우에 저자들은 투고하려는 학술지의 투고규정과 함께 이 권고안을 참조해야 한다. 또한 저자들은 특정한 형태의 연구인 경우 그 기술 방식을 규정한 가이드라인을 참조해야 한다. 예를 들어 무작위 임상시험은 CONSORT 가이드라인을 참조할 수 있으며, 각종 특정한 연구의 기술 방식은 <http://www.equator-network.org>에 정리되어 있다. ICMJE는 이 권고안을 지지하는 학술지에게 투고규정의 내용에 이 권고안을 포함시키고, 이 권고안을 준용하고 있음을 투고규정에 명확히 밝힐 것을 권장한다. 이 권고안을

지지한다는 점을 ICMJE 웹사이트에 게시하고자 하는 학술지는 웹페이지(<https://www.icmje.org/journals-following-the-icmje-recommendations/journal-listing-request-form/>) 상에서 ICMJE 사무국에 요청하면 된다. 이 권고안을 지지한다는 점을 ICMJE 웹사이트에 게시하고 있는 학술지들 가운데 더 이상 이같은 게시를 원치 않을 경우에는 같은 방법으로 게시를 철회할 수 있다.

ICMJE는 교육적, 비영리적인 목적으로 사용하는 경우 저작권의 제약 없이 이 권고안 전체의 광범위한 보급을 권장한다. 그러나 ICMJE는 새로운 사안이 발생할 때마다 주기적으로 권고안을 갱신하므로 이 권고안과 부속 문서를 사용할 때는 ICMJE 웹사이트에서 공식적인 최신 권고안을 열람하는 것이 좋다.

C. 권고안의 역사

ICMJE는 종전에 생의학 학술지 투고 원고의 통일양식(Uniform Requirements for Manuscripts Submitted to Biomedical Journals, 이하 통일양식으로 약함)이라는 명칭으로 여러 편의 가이드라인을 개발해 왔다. 통일양식은 학술지들 간에 원고의 준비와 형식을 표준화하려는 시도로 1978년에 처음 출판되었다. 그러나 해를 거듭하면서 이러한 가이드라인으로 해결하기 힘든 문제들이 발생하기 시작하여 별도의 문건(separate statements)으로 발간하여 기존 문서를 갱신하였으며, 그 명칭을 '의학학술지에 게재되는 학술 저작물의 생산, 보고, 편집 및 출판에 대한 권고안'(Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals)으로 개칭하였다. 이 권고안의 이전 판은 <https://www.icmje.org> 내 기록보관소(archives section)에서 열람할 수 있다.

II. 저자, 기여자, 전문가 심사자, 편집인, 발행인, 학술지 소유주의 역할과 책임

A. 저자와 기여자의 역할

1. 저자됨(Authorship)의 중요성

저자됨이란 저자로서의 자격을 인정하는 것으로 학술적, 사회적, 재정적으로 중요한 영향력을 갖는다. 또한 저자됨은 출판된 저작물에 대한 책임과 의무를 의미한다. 이 권고안은 논문 작성에 실질적인 학술적 기여를 한 연구자는 저자로서 인정을 받고, 동시에 저자로 인정받은 연구자는 출판된 저작물에 대한 책임과 의무에 관한 역할을 잘 이해하고 있다는 점을 확실히 하기 위해 기획되었다. 편집인은 자료가 저소득 및 중간 소득 국가들(low-income and middle-income countries, LMICs)에서 나온 경우 저자 명단에서 LMICs의 현지 연구자들이 빠진 채 투고되었는지 여부를 놓치지 말아야 한다. 현지 연구자가 저자에 포함됨으로써 연구의 공정성, 맥락 및 그 연구가 주는 시사점이 추가된다. 현지 연구자들이 저자 명단에 포함되지 않았다면 즉각 의문을 제기하여 하고 게재 불가로 이어질 수도 있다.

저자명의 기술만으로는 어떤 기여로 저자의 자격을 획득했는지 알 수 없기 때문에 일부 학술지들은 제출된 연구에 참여한 것으로 기술된 저자들의 구체적인 역할에 대한 정보를 요구하고(최소한 원저자만이라도) 게재하기도 한다. 편집인들은 기여자의 자격(contributorship)에 대한 정책의 개발과 수행에도 노력해야 한다. 이와 같은 정책들로 기여도를 둘러싼 모호성을 어느 정도 해소시킬 수 있지만, 저자 자격에 합당한 기여도의 양과 질에 대한 의문은 여전히 남는다. 이에 따라 ICMJE는 모든 학술지들이 수용할 만한 저자와 기여자의 구분을 포함한 저자됨의 기준을 개발하였다.

2. 저자의 정의

ICMJE는 다음 네 가지 기준을 모두 충족할 경우를 저자됨으로 정의할 것을 권고한다:

- 1) 연구의 구상이나 설계에 실질적인 기여; 또는 자료의 획득, 분석, 해석
- 2) 연구 결과에 대한 논문 작성 또는 중요한 학술적 부분에 대한 비평적 검토
- 3) 출판되기 전 최종본에 대한 승인
- 4) 연구의 정확성 또는 진실성에 관련된 문제를 적절히 조사하고 해결하는 것을 보증하고, 연구의 모든 부분

에 책임을 진다는 점에 동의

저자는 수행한 연구의 모든 부분에 대해 책임이 있다는 점에 더하여, 저자는 어느 공저자가 연구의 어느 부분에 대해 책임이 있는지 파악하고 있어야 한다. 아울러 저자는 공저자들이 기여한 부분에 대한 연구 진실성을 담보할 수 있어야 한다.

저자로 기록된 모든 연구자는 이상 네 가지 기준을 충족하여야 하고, 네 가지 기준을 충족한 모든 연구자는 저자로 기록한다. 네 가지 기준을 모두 충족하지 못한 연구자는 기여자로 기록한다(II.A.3 항 참조). 이 저자됨의 기준은 저자로 인정받을 만한 자격이 있고, 연구에 대한 책임을 질 수 있는 연구자들에게만 저자됨을 한정하기 위한 것이며, 연구에 참여하면서도 두 번째나 세 번째 기준을 충족할 기회를 갖지 못한 연구자들의 저자 자격을 제한하기 위해 기획된 것은 아니다. 그러므로 첫 번째 기준에 부합하는 모든 연구자들은 원고의 작성, 검토, 최종 승인에 참여할 기회를 가져야 한다.

연구를 수행하는 사람들은 이들 저자됨의 기준에 부합하는 연구자들을 식별할 책임이 있으며, 이상적으로 말하자면 연구를 처음 기획할 때부터, 또는 연구 진행과정 중에, 수정하는 단계에서 이 기준에 따라 저자됨을 설정해야 한다. ICMJE는 공동연구를 수행하는 연구자들의 협업과 공저자됨(co-authorship)을 장려한다. 저자로 기록된 모든 연구자들이 네 가지 저자됨의 기준을 충족하는지를 판별하는 것은 저자들의 공동책임이며, 투고 받은 학술지의 책임이 아니다. 저자로서 자격이 있는지 판별하거나 저자됨을 둘러싼 갈등을 중재할 책임은 학술지 편집인의 역할이 아니다. 만약 저자됨을 둘러싼 합의점을 찾지 못할 경우, 학술지 편집인이 아니라 연구가 수행된 기관에 조사를 요청해야 한다. 저자란에 저자를 기술하는 순서를 결정하는 기준은 다양할 수 있는데 이는 편집인이 아니라 저자들이 결정하는 것이다. 만약 저자들이 논문이 투고되었거나 출판된 이후에 특정 저자의 철회 또는 추가를 요청한 경우 학술지 편집인은 그 사유를 제시할 것과 논문에 기록된 모든 저자들과 철회 또는 추가 대상 저자가 서명한 문서를 요청해야 한다.

책임저자는 원고가 투고, 심사, 출판 과정 중에 있는 동안 학술지와 교신하는 데 일차적인 책임을 진다. 책임저자는 학술지 업무의 필수 요건, 즉 저자됨과 관련한 상세 정보의 제공, 연구윤리심의 승인 획득, 임상시험등록 관련문건 작업, 연구와 관련한 이해관계 및 활동의 공시 등을 적절하게 수행하고 보고하는 데 철저를 기해야 한다. 단, 이들 업무를 한 두 명의 공저자와 분담할 수도 있다. 책임저자는 논문 투고에서 심사 과정에 걸친 전 과정에서 편집진과 적시에 교신이 가능해야 하고, 출판 후에도 저작물에 대한 비평이 있을 경우 이에 회신할 수 있어야 하며, 저작물에 대한 의문이 제기되어 학술지가 추가적인 자료나 정보를 요청하면 이에 협조해야 한다. 비록 학술지와 교신하는 데 일차적인 책임은 책임저자에게 있지만, ICMJE는 편집인이 모든 저자들에게도 연락이나 통지할 것을 권고한다.

많은 연구자들로 이루어진 대규모 연구집단이 연구를 수행할 때는 연구를 시작하기 전에 저자를 정하고 투고 전에 저자 명단을 다시 확인하는 것이 이상적이다. 저자로 기록된 모든 연구자들은 원고의 최종 승인을 포함하여 네 가지 저자됨의 기준을 충족해야 하고, 저작물에 대해 공적인 책임을 져야 하며, 같은 연구를 수행한 다른 연구자들의 연구의 정확성과 진실성에 대해 완전한 신뢰를 가져야 한다. 또한 이들은 공시 양식(disclosure form)을 완성하는 데 참여한 연구자로 간주될 것이다.

일부 대규모 연구집단은 저자명에 개별 저자와 함께 연구집단 자체를 함께 기재하거나 연구집단만 저자로 기재하기도 한다. 대규모 연구집단에 의해 진행된 연구를 투고할 때는 책임저자는 연구집단명을 명기해야 하고, 저자로서 연구에 책임이 있는 연구자들을 명확히 적시해야 한다. 논문의 저자 기재란은 논문에 대한 책임소재가 누구에게 있는지 확인시켜 주는 것으로 MEDLINE은 저자 기재란에 기재된 모든 이름을 저자명단에 포함시킨다. 저자란에 연구집단명이 포함되어 있는 경우, 논문 내에 해당 연구집단에 속한 연구 참여자들이 저자 또는 공동 연구자로 기재되어 있으면 MEDLINE은 이들 연구 참여자들도 저자 또는 공동 연구자로 저자명단에 포함시킨다.

3. 저자가 아닌 기여자(Non-author Contributors)

저자됨의 네 가지 조건을 모두 충족하지 못하는 연구참여자는 저자가 아니라 기여자로 기록한다. 다른 기여 없이 단독으로 저자됨의 요건을 충족할 수 없는 연구 활동의 예로서 연구비 획득, 연구집단에 대한 일반적인 감독, 일반적인 행정지원, 원고작성 지원, 기술적인 편집, 언어 교정, 최종 원고 교정 등을 들 수 있다. 저자됨의 요

건이 충족되지 않는 연구자들은 개별적으로 기여자로 기록되거나, 임상 조사자(clinical investigators) 또는 참여 조사자(participating investigators)와 같은 명목으로 다른 연구자들과 함께 기록될 수 있으며, 그들이 기여한 바는 과학 자문(scientific advisors), 연구 계획의 정밀 검토(critically reviewed the study proposal), 자료 수집(collected data), 대상 환자의 치료 및 자료 제공(provided and cared for study patients) 등과 같이 상세히 기술해야 한다.

감사의 글(Acknowledgement)은 연구의 자료와 결론에 기여한 것으로 인정한다는 보증을 의미하므로 편집인은 책임자에게 기여자로 인정된 모든 사람에게 기여자로 인정 받았다는 서면 승인을 받을 것을 요청하여야 한다. 글쓰기에 인공지능의 도움을 받았다면 이를 감사의 글에 보고하여야 한다.

4. 인공지능(Artificial Intelligence, AI) 지원 기술

투고 시, 학술지는 저자가 제출된 원고의 작성과정에서 인공지능(AI) 지원 기술(예를 들어 Large Language Models[LLM], 챗봇 또는 이미지 크리에이터)을 사용했는지 여부를 공개하도록 요구해야 한다. 그러한 기술을 사용한 저자는 어떤 식으로 사용했는지를 커버 레터와 투고한 원고 내의 적절한 섹션 모두에 기술해야 한다. 예를 들어, AI가 글쓰기 보조에 사용되었다면, 감사의 글 섹션(II.A.3 참조)에 이것을 기술하도록 한다. AI가 데이터 수집, 분석, 또는 그림 생성에 사용되었다면, 저자는 방법 부분에 그 사용에 대해 기술해야 한다(IV.A.3.d 섹션 참조). 챗봇(ChatGPT 등)은 논문 저작물의 정확성, 무결성, 독창성을 책임질 수 없고, 이러한 책임들은 저자됨에 요구되는 사항이기 때문에 저자 명단에 들어가면 안 된다(II.A.1 섹션 참조). 따라서 AI 지원 기술의 사용을 포함한 제출된 모든 자료에 대해 책임은 인간에게 있다. 저자들은 신중하게 결과를 검토하고 편집해야 하는데, 이는 AI가 부정확하거나 불완전하거나 편향됨에도 불구하고 권위 있어 보이는 척하는 결과물을 생성할 수 있기 때문이다. 저자들은 AI와 AI 지원 기술을 저자 또는 공동 저자로 나열하거나 AI를 저자로서 인용해서는 안 된다. 저자는 AI에 의해 생성된 텍스트와 이미지를 포함하여 논문에 표절 소지가 없다고 확고하게 주장할 수 있어야 한다. 전체 인용을 포함하여 모든 인용된 자료가 적절하게 되었는지에 대한 책임은 인간에게 있다.

B. 재정적, 비재정적 이해관계와 활동의 공시와 이해충돌(Disclosure of Financial and Non-Financial Relationships and Activities and Conflicts of Interest)

과학적 과정과 출판된 논문의 연구 진실성에 대한 대중의 신뢰는 부분적으로 연구의 기획, 실행, 논문 작성, 논문 심사, 편집, 출판 과정에서 저자의 이해관계와 활동이 연구에 직접적이든 원론적이든 얼마나 투명하게 처리되었는가에 달려 있다.

이해충돌과 편향(bias)의 가능성은 환자의 권익 또는 연구의 타당성과 같이 일차적인 이해와 관련한 전문적인 판단이 재정적 이득과 같은 이차적인 이해에 의해 영향을 받을 가능성이 있을 때 존재한다. 이해충돌에 대한 인식은 이해충돌 자체만큼 중요하다.

저자의 관계나 활동이 이해충돌을 일으키는지에 대해서는 의견이 다를 수 있다. 이해관계나 활동이 항상 논문 내용에 문제가 되는 영향을 끼치는 것은 아니지만, 이해충돌 가능성의 존재는 실제 이해충돌만큼이나 과학에 대한 신뢰를 잠식할 수 있다. 궁극적으로 독자들은 저자의 관계와 활동이 논문 내용과 관련이 있는지를 스스로 판단할 수 있어야 하며, 이러한 판단을 위해 연구 과정의 투명한 공시가 필요하다. 연구과정의 완전한 공시는 연구 투명성에 대한 저자의 노력을 보여주고 연구수행 과정에 대한 신뢰를 유지하는 데 도움을 준다.

고용 관계, 자문역, 주식 소유권 또는 매입 우선권, 사례금, 특허권, 전문가 증언과 같은 재정적인 부분은 가장 쉽게 인지할 수 있는, 가장 흔한 잠재적인 이해충돌로 간주되며 학술지와 저자, 나아가 과학 자체의 신뢰도를 훼손할 가능성이 가장 높은 부분이다. 그 밖에 사적인 개인관계나 경쟁관계, 학문적 경쟁, 지적 신념 등도 이해충돌을 일으키거나 이해충돌로 보여질 수 있다.

저자는 모든 연구 데이터에 대한 저자의 접근을 방해하거나 데이터를 분석 및 해석하고 자신이 선택한 시기와 장소에서 독립적으로 원고를 작성하고 출판하는 것을 방해하는 모든 영리 및 비영리 연구후원자와 타협하는 것을 피해야 한다. 저자들이 그들의 연구를 출판할 수 있는 장소를 통제하는 정책은 이러한 학문적 자유 원칙에 위배된다. 저자와 연구후원자 간에 은밀한 합의가 의심되는 경우 이에 대한 소명 요구를 받을 수도 있다.

학술지의 공시 문서에 저자의 이해관계와 활동을 의도적으로 밝히지 않는 것은 부정행위의 한 형태로서 III.B 항에서 논의될 것이다.

잠재적인 이해충돌에 대한 공시는 뚜렷이 구별되어야 하며, 해당 연구 작업에 대한 직접적인 지원 외의 더 넓은 범위를 포함한다. 원고에 연구비 지원에 대한 명기는 연구 논문에 대한 직접적인 지원만을 언급해야 한다. 연구 작업에 대한 개개인의 기여에 대한 지원도 이런 방식으로 보고되어야 한다. 저자의 연구 작업 시간에 대해 기관이 지원해 준 전반적인 사항에 대해서는 이 연구에 직접 지원된 전반적 재정적 지원과는 구별하여 기술하여야 한다. 연구비 지원에 대한 적절하게 기술된 예시는 다음과 같다: "이 연구는 A로부터 연구비를 지원받았다; F 박사의 연구에 쏟은 시간은 B에 의해 지원받았다."

1. 대상자(Participants)

저자뿐만 아니라 전문가 심사자, 편집인, 편집위원 등을 포함하는 논문 심사 및 출판에 관여하는 모든 관계자들은 논문 심사 및 출판 과정에서 자신의 역할을 수행하면서 자신과 관련된 이해관계와 활동을 고려하고 공개하여야 한다.

a. 저자

어떤 형태의 원고든지 투고할 때는 저자들은 연구에 영향을 미치거나 영향을 주었을 것으로 비춰질 수 있는 모든 이해관계와 활동을 밝힐 의무가 있다. ICMJE는 저자의 공시를 용이하게 하고 표준화하기 위해 공시 양식(disclosure form)을 개발해 왔다. ICMJE 회원 학술지들은 저자들에게 이 형식을 사용할 것을 요청하고 있으며, ICMJE는 다른 학술지들도 이 형식을 채택할 것을 권장한다.

b. 전문가 심사자(Peer Reviewers)

논문 심사를 의뢰할 때 전문가 심사자에게 해당 논문의 심사에 영향을 줄 수 있는 이해관계와 활동이 있는지 확인해야 한다. 전문가 심사자는 편집인에게 이해관계와 활동에 대해 밝혀야 하며, 편향 가능성이 있으면 해당 논문 심사를 거절해야 한다. 전문가 심사자는 심사한 논문이 출판되기 전에 해당 논문으로부터 얻은 정보를 자신의 이득을 위해 사용해서는 안 된다.

c. 편집인 및 학술지 편집진(Journal Staff)

투고된 논문에 대한 최종결정권을 갖고 있는 편집인이 해당 논문과 관련하여 이해충돌을 일으킬 만한 이해관계와 활동이 있는 경우에는 편집관련 결정에서 배제되어야 한다. 편집관련 결정에 관여하는 편집진은 편집판단에 영향을 줄 수 있는 재정적 또는 기타 이해관계와 활동에 대해 보고해야 하며, 이해충돌의 가능성이 있을 경우 편집결정 과정에서 배제되어야 한다. 편집진은 편집 과정에서 얻은 정보를 개인적인 이득을 위해 사용해서는 안 된다. 편집인은 자신과 편집진들의 이해충돌 가능성과 관련한 공시문을 정기적으로 출판해야 한다. 객원 편집인 역시 이 원칙을 동일하게 준수해야 한다.

학술지는 편집관련 결정에 참여하는 인사가 투고한 원고의 평가를 위한 추가적인 예방조치와 명시적으로 규정된 정책을 갖고 있어야 한다. 이에 대한 더 상세한 지침은 COPE(Committee on Publication Ethics; https://publicationethics.org/files/A_Short_Guide_to_Ethical_Editing.pdf)와 WAME(World Association of Medical Editors; <http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals>)에서 볼 수 있다.

2. 이해관계와 활동의 보고

논문은 ICMJE의 이해관계 공시 양식과 같은 부속 문서와 함께 출판되어야 하며, 다음과 같은 내용이 모두 포함되어야 한다: 1) 저자의 이해관계와 활동, 2) 연구 지원자에 관한 내용, 즉 연구지원자를 밝히고 어떤 역할을 하였는지; 자료의 수집, 분석 및 해석, 논문 작성; 연구결과의 투고와 관련하여 어떤 간섭이나 제약이 있었는지 여부, 3) 저자가 연구 자료에 접근할 수 있었는지, 접근할 수 있었다면 어느 정도, 어떤 성격의 접근이 가능했는지, 연구 종료 후에도 계속 접근이 가능했는지 등이다.

위 내용의 공표를 돕기 위해 편집인은 연구 결과에 소유권이나 재정적 이해관계가 있는 연구지원자의 지원을 받은 저자들에게 "나는 이 연구의 모든 자료에 모두 접근할 수 있고, 자료의 진실성과 자료 분석의 정확성에 모든 책임을 진다"와 같은 서명된 문서를 요구할 수 있다.

C. 투고와 심사 과정에서의 책임

1. 저자

저자는 저자됨과 이해관계와 활동의 공시에 대한 원칙을 준수해야 한다. 이는 본 권고안 IIA 및 IIB 항에 상세히 기술되어 있다.

a. 약탈적(Predatory) 또는 가짜 학술지(Pseudo-Journals)

스스로를 "전문 의학 학술지(scholarly medical journal)"라고 광고하지만 제대로 기능하지 않는 학술지가 점차 증가하고 있다. 이들 약탈적 또는 가짜 학술지는 투고된 원고의 거의 대부분을 게재 승인하고 출판하며, 흔히 게재 승인 후에 원고 처리(또는 출판) 비용을 투고자에게 고지한다. 그들은 전문가심사 과정을 거친다고 주장하지만 확인되지 않으며, 의도적으로 널리 알려진 학술지와 유사한 학술지명을 사용하기도 한다. 그들은 자신이 ICMJE 회원 학술지이며(회원 여부는 ICMJE 웹사이트에서 확인할 수 있음), ICMJE, WAME, COPE와 같은 단체의 편집 가이드라인을 준수한다고 주장하기도 한다. 연구자들은 이러한 학술지들의 실체를 알고 있어야 하며, 자기 연구의 출판을 위해 이들 학술지에 투고하는 것을 삼가야 한다. 저자들은 자신이 투고하고자 하는 학술지의 진실성, 역사, 업무 관행, 평판 등을 평가할 책임이 있다. WAME와 같은 여러 기관에서 나온 지침(<https://www.wame.org/identifying-predatory-or-pseudo-journals>, <https://www.wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing>)은 평판이 좋은 학술지를 식별하는 데 도움이 된다. 과학 멘토, 선임 동료 또는 다년간의 학술 출판 경험을 가진 인사들에게 조언을 구하는 것도 도움이 될 수 있다. 저자들은 약탈적 또는 가짜 학술지에 게재된 논문을 인용해서는 안 된다.

2. 학술지

a. 보안(Confidentiality)

학술지에 투고된 원고는 비공개 교신(privileged communication)으로 저자의 개인적인 기밀에 속하는 자산이며, 원고의 전부 또는 일부가 적정한 시기보다 먼저 공개될 경우 피해를 입을 수 있다.

그러므로 편집인은 원고와 관련한 정보, 즉 원고가 접수되어 심사 중에 있는지, 원고의 내용, 심사진행 상태, 심사평, 원고가 채택될 가능성 등을 저자와 전문가 심사자 외에는 공개해서는 안 된다. 편집자는 원고 처리 과정에서 AI 기술을 사용하는 것이 기밀을 침해할 수 있음을 알아야 한다. 제3자가 소송 등을 위해 원고와 심사평을 요청하는 경우 편집인은 정중히 이를 거절해야 하며, 법률적인 문제로 소환되는 경우에도 이 같은 기밀에 속하는 문건이 제공되지 않도록 최선을 다해야 한다.

또한 편집인은 전문가 심사자들에게 그들이 갖고 있는 원고, 관련 자료 및 정보가 노출되지 않도록 엄격히 관리할 것을 요청해야 한다. 심사자들에게 제공하는 지침에는 AI 사용에 관한 지침이 포함되어야 한다. 전문가 심사자와 학술지 편집진은 투고된 원고를 공개적으로 논의해서는 안 되며, 논문이 출판되기 전에는 원고의 내용을 전용해서는 안 된다. 전문가 심사자는 개인적인 용도로 원고를 계속 가지고 있으면 안 되며, 심사가 끝나면 해당 원고와 관련한 모든 인쇄물과 디지털 자료를 폐기해야 한다.

심사 결과 채택되지 않은 원고는 자체 규정 등에 의해 보류 요청이 있는 경우가 아니면 학술지 측은 편집 시스템 내의 모든 관련자료를 삭제하는 것이 최상의 정책이다. 채택되지 않은 원고를 계속 보유하는 학술지는 투고규정을 통해 이 사실을 고지해야 한다.

논문이 출판된 후에는 논문과 관련하여 문제가 발생할 가능성에 대비하여 논문 원고, 심사평, 교정본, 기타 교신 문서 등을 최소한 3년 이상 보관해야 하며, 자체 규정에 따라 가능하면 영구 보존하는 것이 좋다.

편집인은 전문가 심사자와 저자의 동의 없이 심사평을 출판하거나 공표해서는 안 된다. 만약 학술지의 운영 정책이 저자와 전문가 심사자의 신원을 모르게 하고 심사평에도 서명을 남기지 않는 것이라면 전문가 심사자의 서면동의 없이 전문가 심사자의 신원을 저자를 비롯한 누구에게도 노출시켜서는 안 된다.

부정 또는 허위가 의심되는 경우 보안 문제는 파기될 수 있다. 이 경우 편집인은 저자나 전문가 심사자에게 보안 원칙을 파기할 수 있다는 점을 통보해야 하며, 그 외에는 보안 원칙을 지켜야 한다.

b. 적시성(Timeliness)

편집인은 원고와 관련 자료의 처리가 적시에 진행되도록 최선을 다해야 한다. 편집인은 어떤 원고를 출판하기로 결정하였으면 정시에 출판될 수 있도록 하고, 의도적인 지연 출판이 필요한 경우에는 저자와 긴밀히 상의해야 한다. 출판할 의사가 없는 원고에 대해서는 가능한 신속히 저자에게 통보하여 다른 학술지에 투고할 수 있도록 해 주어야 한다.

c. 전문가심사(Peer Review)

전문가심사는 학술지에 투고된 원고에 대한 전문가(반드시 편집위원회 일원일 필요는 없다)의 비판적 평가이다. 편향되지 않고, 독립적인 비판적 평가는 과학 연구를 포함한 모든 학술 활동의 본질적인 부분이며, 전문가심사는 이러한 과학 활동의 연장선 상에 있다.

전문가심사의 실제적인 가치에 대해서는 많은 논란이 있으나, 이 과정은 과학 학술단체 내 구성원들의 원고에 대한 공정한 평가를 용이하게 만든다. 더 현실적인 관점에서 보면 편집인이 어떤 원고가 해당 학술지에 적합한지를 판단하는 데 도움을 준다. 전문가심사는 흔히 논문의 질을 향상시키는 데 도움이 된다.

학술지는 적절한 전문가 심사자를 선정할 수 있는 시스템을 갖출 책임이 있다. 편집인은 전문가 심사자가 온라인 출판만을 위한 보충 자료를 포함하여 전문가심사에 필요한 모든 자료에 접근할 수 있도록 하고, 공표된 이해관계의 맥락에서 심사평이 적절히 평가되고 해석될 수 있도록 해야 한다.

전문가심사를 거치는 학술지(peer-reviewed journal)는 투고된 모든 논문을 심사 의뢰할 의무는 없으며, 심사평(긍정적이든, 부정적이든)을 반드시 따라야 하는 것도 아니다. 편집인은 학술지에 게재할 모든 콘텐츠의 선택에 대한 궁극적인 책임을 지며, 편집관련 결정은 원고 내용이 학술지에 적합하지 등과 같은 원고의 질과 무관한 요소에 의해서도 영향을 받는다. 편집인은 출판 전에는 언제든지 원고를 반려할 수 있으며, 출판 결정이 난 후라도 논문의 진실성에 대한 우려가 발생한 경우에는 출판을 취소할 수 있다.

학술지에 따라 원고의 수와 종류, 전문가 심사자의 수와 특성, 전문가 심사자 정보의 공개 여부, 기타 심사 과정 상의 문제 등이 다를 수 있다. 이러한 연유와 저자에 대한 배려 차원에서 학술지는 모든 유형의 원고에 대해 그들의 심사 과정을 상세히 공표해야 한다. 학술지는 전문가 심사자에게 심사를 의뢰한 원고의 채택 또는 반려 여부를 통지해야 하며, 학술지에 대한 전문가 심사자의 기여에 공식적인 감사를 표해야 한다. 편집인은 동일한 원고의 심사에 참여했던 전문가 심사자들의 심사평을 서로 공유할 수 있도록 하여 전문가 심사자들이 심사 과정을 통해 서로 정보를 얻을 수 있도록 해 주는 것이 좋다.

연구 계획서와 분리되어 있는 경우 심사 과정의 일부로 편집인은 연구 계획서, 통계분석 방법 및/또는 연구와 관련한 계약 등을 검토하고, 게재 결정을 하기 전에 저자로 하여금 출판 시 또는 출판 후에 이와 같은 문서들을 공개하도록 권장하여야 한다. 일부 학술지는 논문 게재의 조건으로 이들 문서를 공개적으로 게시할 것을 요구하기도 한다.

이 개정본을 준비 중일 때는 논문 출판 전후로 연구에 대한 검증을 위한 자료 이용의 중요성이 대두됨에 따라 독립적인 자료 분석과 자료의 공개적인 이용에 대한 학술지의 요구가 넘쳐 났다. 현재 일부 학술지 편집인은 게재 결정 전에 독립적인 통계 전문가에게 자료의 통계 분석을 의뢰하기도 한다. 어떤 학술지들은 저자에게 제3자가 연구 자료를 검토 및/또는 재분석 할 수 있도록 요청만 하기도 하지만, 또 어떤 학술지들은 검토 또는 재분석을 위해 연구 자료의 공개를 권장 또는 요구하기도 한다. 학술지는 연구 자료를 분석하고, 미래의 저자들이 쉽게 접근할 수 있는 곳에 자료를 게시하기 위한 학술지 고유의 필요조건을 수립하고 공표해야 한다.

일부에서는 진정한 전문가심사는 오직 논문이 출판된 이후부터 시작된다고 주장한다. 이런 관점에서 보면 의학 학술지는 독자들이 출판된 논문에 대해 논평, 질의, 비평을 가할 수 있는 체계를 가지고 있어야 하며, 출판된 논문에 대한 의문이 제기되었을 때 저자들은 이에 적극적으로 응해야 하고, 학술지 측의 연구 자료 또는 추가 정보에 대한 요청에 협조해야 한다(III항 참조).

ICMJE는 연구자들이 발표된 결과를 뒷받침하는 1차 데이터와 분석 절차를 10년 이상 보관할 의무가 있다고 생각하며, 적절한 데이터 저장소에 이러한 데이터를 보존하여 장기간 사용이 가능케 할 것을 권장한다.

d. 진실성(Integrity)

편집관련 결정은 원고의 학술지에 대한 적합성, 독창성, 전체적인 질, 주요 현안에 대한 근거 제시 등에 기반하여야 한다. 이러한 결정은 상업적인 이해, 개인적인 관계 또는 의제, 부정적인 연구 결과(negative finding)

또는 인정받고 있는 이론에 대한 도전적인 연구 결과 등에 영향을 받아서는 안 된다. 더구나 저자들은 학술지에 논문을 출판하거나 공개적인 이용이 가능하도록 하기 위해 투고하는 것이기 때문에 편집인은 통계학적인 의의가 증명되지 않았거나 결론이 결정적이지 않은 연구 결과를 출판 고려 대상에서 배제해서는 안 된다. 이러한 연구들은 메타분석(meta-analysis)을 통해 여타 연구 결과들과 결합하면 여전히 중요한 연구주제에 필요한 자료로서 활용이 가능하며, 이러한 연구들을 출판함으로써 불필요하게 같은 연구가 반복되는 것을 방지할 수 있고, 유사한 연구를 계획 중인 다른 연구자들에게 유익한 정보를 제공할 수 있다 학술지는 이의제기 절차를 명확히 공개해야 하고, 이의제기와 불만의 처리를 위한 체계를 갖추고 있어야 한다.

e. 다양성과 포용(Diversity and Inclusion)

학문적 문화를 향상시키기 위해 편집인들은 광범위하고 다양한 저자, 전문가 심사자, 편집진, 편집위원, 독자들의 참여를 모색해야 한다.

f. 학술지 계량지표(Journal Metrics)

연구와 학술지의 질을 평가하기 위한 간접적인 도구(proxy)로서, 특정 연구 계획의 중요도 또는 개별 연구자의 학문적 성취도(채용, 승진, 종신직, 시상 또는 연구비 지원을 위한 적합성 판정)를 측정하는 데 있어서 학술지의 영향력 지수(impact factor)가 광범위하게 오용되고 있다. ICMJE는 단일 척도로서 영향력 지수에 대한 의존도를 줄이고, 대신 독자와 저자에게 적합한 다양한 학술지 계량지표를 제공할 것을 권장한다.

3. 전문가 심사자(Peer Reviewers)

학술지에 투고된 원고는 비공개 교신으로 저자의 개인 기밀에 속하는 자산이며, 원고 내용의 전부 또는 일부가 적절한 시기보다 먼저 공개되면 저자가 피해를 입는다.

그러므로 전문가 심사자는 원고 정보가 노출되지 않도록 관리를 철저히 해야 하며, 논문이 출판되기 전에 원고에 대해 공개적으로 논의하거나 원고 내용을 도용 또는 전용해서는 안 된다. 전문가 심사자는 개인적인 목적으로 원고를 보관해서는 안 되며, 심사를 완료한 후에는 원고를 폐기해야 한다. 논문심사 과정에서 동료나 교육 중인 제자의 도움을 받은 심사자는 편집인에게 제출하는 심사평 서류에 이들의 기여를 고지하여야 한다. 논문심사에 기여한 이들은 위에서 설명한 대로 원고의 기밀성을 유지해야 하며, 이러한 이유로 기밀성이 보장될 수 없는 소프트웨어 또는 기타 AI 기술 사이트에 원고를 업로드하는 것이 금지될 수 있다. 심사자가 심사를 용이하게 수행하기 위해 AI 기술을 사용하려면 사전에 학술지에 허가를 요청해야 한다. 심사자는 AI가 잘못되거나 불완전하거나 편향될 수 있음에도 권위있어 보이는 척하는 결과물을 생성할 수 있음을 알고 있어야 한다.

전문가 심사자는 심사 의뢰를 받으면 수락 여부를 즉시 통보하고, 주어진 시한 내에 심사평을 제출하는 것이 바람직하다. 심사평은 건설적이고, 정직하고 정중해야 한다.

전문가 심사자는 투고논문의 평가에 편향을 일으킬 수 있는 이해관계와 활동이 있으면 이를 공표해야 하며 해당 원고의 심사를 반려해야 한다.

D. 학술지 소유주와 편집권의 독립

1. 학술지 소유주

학술지 소유주와 편집인은 공동 목표를 갖고 있지만, 책임과 권한이 다르고 이러한 차이는 상호 간에 갈등을 불러 일으키기도 한다. 의학학술지는 소유주와의 관계와 지배구조를 명확하게 공표해야 한다. 의학 출판은 기후 변화를 악화시키는 탄소 배출의 원인이 되며, 이는 인류의 안녕과 지구의 건강에 긴급한 위협이 된다. 편집인, 발행인, 학술지 소유자 및 다른 이해 관계자들은 탄소 순배출 제로를 달성하기 위한 목표로 탄소 배출을 줄이기 위한 즉각적인 전략을 개발하도록 함께 노력해야 한다. 편집인의 임명권은 소유주에게 있으며, 소유주는 편집인을 임명할 때 계약서에 편집인의 권리, 의무, 권한, 임용과 관련한 일반적인 사항, 갈등 발생 시의 조정 방법 등을 명확히 적시한다. 편집인으로서의 직무 수행은 상호 동의한 방법에 의해 평가할 수 있으며, 평가 항목에는 독자층의 확보에만 국한되는 것이 아니라, 원고 처리 시간, 학술지 관련 각종 지표, 기타 여러 가지 항목이 포함될 수 있다.

편집인의 면직은 학술적인 부정행위를 범했거나, 학술지의 장기 목표에 부합하지 않거나, 상호 동의한 평가 방법에 의해 직무 수행에 부적합하다고 판단되거나, 책임 있는 지위에 걸맞지 않는 부적절한 행동을 한 경우 등, 상당한 사유가 있을 때만 가능하다.

임명과 면직은 소수의 학술지 경영진보다는 독립된 전문가 패널의 평가에 기초해야 한다. 이는 특히 면직의 경우에 필요하다. 과학계에서 언론의 자유가 중요한 가치로 평가되고, 학술지 소유주와 갈등이 있는 상황이 발생했을 때 이를 극복해야 하는 것이 편집인의 의무라고 흔히 일컬어지기 때문이다.

2. 편집권의 독립

ICJME는 세계의학편집인협회(WAME)의 편집권 독립에 대한 정의(<http://wame.org/editorial-independence>)를 그대로 수용한다. 이 정의에서 말하는 편집권 독립이란 편집위원장이 학술지의 내용과 출판 시기 등 편집과 관련한 모든 권한을 가지는 개념을 뜻한다. 학술지 소유주는 개별 논문의 심사, 선정, 출판 계획 및 편집 등에 직접적으로 간섭하거나 간접적으로 영향을 미칠 수 있는 환경을 조성해서는 안 된다. 편집인은 학술지의 상업적 측면이 아니라 연구의 타당성과 독자들 관점에서의 중요성에 맞추어 편집 관련 결정을 내려야 한다. 편집인은 의학과 관련한 모든 부분에 대해(소유주의 상업적 목적과 상충하더라도) 불이익을 당할 우려 없이 자유롭게 책임 있는 비판을 할 수 있어야 한다.

또한 편집위원장은 광고 또는 별호 발행과 같은 후원자와 관련된 기사의 게재 여부, 학술지 제호 사용, 학술지 게재물에 대한 상업적 사용에 관한 일반적인 정책 등에 관한 최종결정권을 가져야 한다.

편집인이 편집 정책을 수립하고 관리하는 데 도움을 줄 수 있는 독립적이고 다양한 구성으로 이루어진 편집자문위원회를 설립할 것이 권장된다. 편집 관련 결정과 잠재적인 논란의 소지가 있는 의견의 표현을 지원하기 위해 학술지 소유주는 편집인과 관련하여 법적 문제가 발생할 경우를 대비한 보험에 가입하고, 필요할 때는 언제나 편집인에게 법적 자문을 제공해야 한다. 법적 문제가 발생한 경우, 편집인은 즉시 법무 자문과 학술지 소유주 또는 발행인에게 통지해야 한다. 편집인은 ICMJE 정책에 따라 저자와 전문가 심사자(심사자 명명과 심사평)를 보호해야 한다(II C.2.a 항 참조). 편집인은 뉴스 섹션과 소셜 미디어를 포함한 각종 매체에 실리는 소식을 점검하는 모든 조치를 취하고, 편집사무국 직원들로 하여금 상시적인 사건기록과 학술지 출판 전에 모든 이해 당사자들의 반응을 살피는 등의 저널리스트로서의 자세를 견지하도록 해야 한다. 진실과 공익을 뒷받침하는 이 같은 작업은 특히 명예훼손 같은 법적 혐의에 대비하는 데 적합하다.

실제적인 편집권의 독립을 위해서는 편집인은 위임경영자나 행정담당자가 아닌 소유 구조의 최고위층과 접촉할 수 있어야 한다. 편집인과 편집 조직은 편집권 독립주의를 견지해야 하고, 편집권이 침해되면 국제적인 의료, 학술 및 일반 단체의 이목을 집중시켜야 한다.

E. 연구 대상자(Research Participants)의 보호

모든 연구자는 2013년 개정된 헬싱키 선언(<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>)에 따라 인간대상 연구의 계획, 수행, 보고가 이루어지는지 확인해야 한다. 저자들은 지역, 지방 또는 국가 규모의 독립적인 심의 기구(윤리위원회, 기관심의위원회 등)로부터 연구 수행에 대한 승인을 받아야 하며 편집자가 요청할 경우 이에 관한 문서를 제공할 수 있도록 준비해야 한다. 연구가 헬싱키 선언을 준수하면서 진행되었는지 의문이 들 경우, 저자는 연구 방법의 합리적 근거를 설명하고, 지방, 지역 또는 국가 규모의 심의 기구가 연구의 의심스런 부분에 대해 명시적으로 승인했음을 제시해야 한다. 책임 있는 심의 기구에 의한 승인이 편집자들이 연구의 수행이 적절했는지 여부를 스스로 판단하는 것을 무의미하게 만드는 것은 아니다.

환자는 사생활을 보호 받을 권리가 있으며, 이 권리는 고지에 입각한 동의서(informed consent, 이하 동의서로 약함)에 의하지 않고서는 침해될 수 없다. 이름, 이름의 머리 글자, 병록번호 등과 같은 개인정보는 논문의 서술 부분, 사진, 가계도 등, 어떤 형태로도 출판할 수 없다. 단, 환자의 개인정보가 과학정보로서 필수불가결한 경우에는 출판하기 전에 환자, 환자의 부모 또는 보호자에게 설명하고 서면으로 동의서를 받아야 한다. 출판 예정인 원고를 환자에게 보여주면서 설명하고 동의를 받아야 하며, 저자는 환자에게 개인정보가 출판물뿐만 아니라 인터넷 등을 통해 공개될 가능성이 있다는 사실을 밝혀야 한다. 환자의 동의는 문서로 남겨야 하며 관련 법령에 따라 학술지나 저자 별로, 또는 양자 별로 각각 보관하여야 한다. 여기에 적용되는 법령은 지역에 따라 다르

고, 학술지는 법령의 취지를 따라서 개별적인 관련 규정을 두어야 한다.

환자의 세부적인 신상은 꼭 필요한 경우가 아니면 공개해서는 안 된다. 환자의 익명성을 담보하기 어려운 가능성이 조금이라도 있으면 동의서를 받아야 한다. 예를 들어 사진에서 눈 주위를 가리는 정도로는 익명성을 보장할 수 없다. 환자의 정보를 익명으로 처리하는 경우, 저자는 이 같은 수정으로 인해 객관적 사실이 왜곡되지 않는다는 것을 보증해야 하고, 편집인은 원자료가 수정되었음을 밝혀야 한다.

학술지는 동의서와 관련한 규정을 투고규정에 반드시 포함시켜야 하며, 동의서를 받은 경우에는 게재하는 논문에 그 사실을 적시하여야 한다.

III. 논문 출판과 관련된 편집 및 출판 상의 문제들

A. 정정기사(Corrections), 논문 취소(Retractions), 재출판, 판본 관리(Version Control)

의도하지 않은 오류(honest error)는 과학과 출판의 한 부분이며, 오류가 발견되었을 때는 정정 기사를 게재해야 한다. 정정기사는 사실 관계의 오류를 바로잡기 위해 필요하다. 논쟁이 있는 사안은 학술지의 인쇄본이나 온라인 판의 편집인에게 보내는 편지(letters to editor) 또는 독자통신(correspondence)을 통해, 또는 학술지 웹사이트에 의견을 게시함으로써 가장 적절하게 처리될 수 있다. 체계적 문헌고찰(systematic review)이나 임상진료지침(clinical guideline)에서 볼 수 있는 전작의 갱신본은 전작의 연작물로 보지 않고 하나의 새로운 출판물로 취급된다.

정정기사가 필요한 경우, 학술지는 다음과 같은 최소한의 규범을 따라야 한다.

- 학술지는 수정된 내용을 가능한 신속히 전작을 인용하여 상세하게 게재해야 한다. 정정기사는 적절한 색인을 위해 온라인 또는 인쇄본 상에 페이지 번호가 매겨진 문건(numbered print page)으로 목차에 포함되어야 한다.
- 학술지는 새로운 논문 판본을 수정된 부분의 상세한 설명과 수정 일자와 함께 게재해야 한다.
- 학술지는 전작을 포함한 모든 논문 판본을 보관해야 한다. 보관 자료(archive)는 독자가 직접 접근하거나, 요청을 하면 열람이 가능해야 한다.
- 전작의 온라인 판에는 갱신된 최신 판본이 있다는 사실을 눈에 잘 띄게 게재해야 한다.
- 인용은 가장 최신 판본으로 해야 한다.

코딩 문제 또는 계산 착오로 인해 발생한 오류는 논문 전체에 널리 퍼질 수 있으며(pervasive error), 논문 전체에 광범위한 부정확한 결과를 초래할 수 있다. 이와 같은 오류가 논문의 결과, 해석 및 결론의 방향이나 중요성에 변화를 줄 정도가 아닌 경우에는 위에서 언급한 최소 규범에 따라 정정 기사를 게재해야 한다. 논문의 연구 결과와 결론을 무효화 할 정도로 심각한 오류가 발생하면 논문을 취소해야 할 수도 있다. 그러나 분류 오류나 계산 착오 등과 같은 의도하지 않은 오류가 논문의 결과, 해석 및 결론의 방향 또는 중요성에 큰 변화를 초래한 경우에는 논문 취소 후 재발행('교체'라고도 지칭)을 고려할 수 있다. 오류가 의도된 것이 아닌 것으로 판명되고, 기본적인 과학성이 유효하며, 수정된 논문이 추가 심의와 엄격한 편집 과정을 거쳐 승인되면 기존 논문은 취소하고, 설명과 함께 수정된 논문을 재발행 함으로써 과학적 논문으로서의 완전한 수정이 완성된다. 이와 같은 경우 변경된 내용과 정도를 보충 자료나 부록 등에 고시하면 완전한 투명성을 담보하는 데 도움이 된다.

B. 학술적 부정행위, 우려 표명(Expression of Concern), 논문 취소(Retracton)

학술 연구논문과 비학술 연구논문에서 학술적 부정행위는 자료 위조, 영상물의 기만적인 조작을 포함한 자료 변조, 표절 등에만 국한되지 않는다. 일부에선 임상시험과 기타 인간 대상 연구의 결과를 출판하지 않는 것도 과학적 부정행위로 간주한다. 이들 행위는 각각의 문제가 있지만, 서로 같은 성질의 것은 아니다. 각각의 상황은 관련이 있는 이해 당사자들의 개별적인 평가가 필요하다. 학술적 부정행위의 혐의가 있거나, 제출된 원고에 기술된 내용의 실행 여부나 진실성에 우려가 제기되는 경우, 편집인은 출판윤리위원회(COPE)와 같은 조직이 권고하는 조사 절차(<http://publicationethics.org/resources/flowcharts>)를 개시해야 하고, 이 절차가 끝날 때까지 해당 연구의 평가를 유보한다는 우려 표명을 게재할 수 있다. 만약 저자의 소속기관을 조사해야 하는 상황

이면 편집인은 반드시 조사 결과를 찾아 독자들에게 그것이 적절했는지 알리고, 만약 부정행위로 판명이 나면 논문 취소를 게재해야 한다. 부정행위를 입증하지 못하는 경우가 있을 수 있지만, 이런 경우 독자에게 논쟁점을 부각시키기 위해 편집인에게 보내는 편지를 연속적으로 게재할 수 있다.

우려 표명이나 논문 취소는 단순히 편집인에게 보내는 편지가 아니다. 이들 기사에는 적절한 색인을 위해 명확한 표식을 붙이고, 온라인 또는 인쇄본 상에 페이지 번호가 매겨진 문건(numbered print page)으로 목차에 포함되어야 하며, 기사 제목에는 원전 논문의 제목을 포함시켜야 한다. 온라인 판에서는 논문 취소와 원전 논문이 양방향으로 링크되어야 하고, 취소된 논문에는 초록, 논문 전문 및 PDF 파일 등 모두가 취소되었음을 알리는 명확한 표식을 붙여야 한다. 이상적으로는 논문 취소의 저자는 원전 논문의 저자와 동일해야 하지만, 그것이 불가능할 때는 어떤 조건 하에서 책임 있는 다른 인사에게 논문 취소를 받아낼 수도 있고, 편집인이 우려 표명이나 논문 취소의 단독 저자가 될 수도 있다. 논문 취소에는 해당 논문을 취소하게 된 사유가 기술되어야 하고, 해당 논문을 인용한 문헌이 모두 포함하여야 한다. 취소된 논문은 독자들이 판단할 영역으로 남겨두어야 하며, 해당 논문에는 취소된 논문이라고 명확히 표시해야 한다.

부정 논문이라고 밝혀지면 해당 저자의 전작 논문들도 그 타당성을 담보할 수 없다. 편집인은 해당 저자의 소속기관에 저자가 이전에 편집인의 학술지에 게재한 논문의 타당성을 검토해 달라고 요청하거나, 전작 논문까지 취소할 수도 있다. 이것이 불가능할 경우, 편집인은 해당 저자의 전작 논문의 타당성이 불명확하다는 우려 표명의 게재를 고려해야 한다.

연구진실성은 부적절한 연구 방법론에 의해서도 훼손될 수 있고, 이로 인해 논문 취소에 이르기기도 한다. 논문 취소와 우려 표명에 대한 상세한 지침은 COPE의 업무 흐름도(<http://publicationethics.org/resources/flowcharts>)를 참조하면 된다. 취소된 논문의 인용을 방지하는 지침은 이 권고안 IV.A.1.g.i 항에 정리되어 있다.

C. 저작권

학술지는 출판할 논문의 저작권 형태를 명확히 하고, 학술지가 저작권을 보유하는 경우 음향 또는 영상 자료, 연구계획서, 원자료를 포함한 모든 형태의 내용물의 저작권 양도에 대한 학술지의 입장을 구체적으로 밝혀야 한다. 학술지는 저자에게 저작권 양도를 요구할 수 있다. 일부 학술지는 출판권의 양도를 요구하기도 한다. 일부 학술지는 저작권의 양도를 요구하지 않고 저작물 이용 약관(Creative Commons License)을 활용하기도 한다. 논문의 저작권 상태는 학술지에 따라 다르다. 공공기관의 직원이 업무의 일부로 작성한 문서와 같은 일부 저작물은 저작권 설정이 불가능하다. 편집인은 어떤 것에 대해서는 저작권을 포기할 수도 있고, 또 어떤 것에 대해서는 특정한 협정에 의해 보호받을 수도 있다.

D. 중복출판(Overlapping Publications)

1. 이중투고(Duplicate Submission)

저자는 둘 이상의 학술지에 동일 언어든, 다른 언어든 같은 원고를 이중으로 투고해서는 안 된다. 이러한 원칙의 근거는 하나 이상의 학술지에 이중으로 투고된 원고를 출판할 권리를 두고 학술지 간에 합의를 이루지 못할 수 있고, 학술지들이 이중으로 투고된 줄 모르고 동일한 원고에 대해 불필요하게 심사, 편집 및 게재할 가능성이 있기 때문이다.

2. 이중출판(Duplicate Publication)과 사전출판(Prior Publication)

이중출판은 이미 출판된 논문과 상당한 부분이 중복되는 논문을 전작에 대한 명백하고 가시적인 인용을 하지 않고 출판한 경우이다. 사전출판에는 공공 영역(public domain)에 정보를 공개하는 것도 포함될 수 있다.

저자와 학술지 편집인이 명백한 의도를 갖고 그 논문을 다시 출판하는 것이라는 설명이 없는 한(예: 역사적 의미가 있거나 과학사에 남을 획기적인 연구), 학술지 독자는 그들이 읽는 논문이 원저라고 믿을 권리가 있다. 이러한 입장은 국제저작권법, 윤리적 규범, 정보 자원의 효과적인 이용 등에 입각한 것이다. 특히 연구논문의 이중출판이 문제가 되는데, 하나의 연구 업적이 부당하게 중복 인정되거나 결과의 중요성이 부적절하게 부각되어 학술적 근거를 왜곡시키기 때문이다.

투고하는 원고가 이미 출판된 논문의 많은 부분을 포함하고 있거나 다른 학술지에 투고되었거나 게재 예정인

논문과 매우 밀접하게 연관된 내용을 포함하고 있는 경우, 저자는 투고 편지에 이 같은 사실을 밝히고, 편집인이 이 같은 원고를 처리하는 데 도움이 되도록 관련 문헌을 제공해야 한다(IV.B 항 참조).

이 권고안은 편집인에게 보내는 편지, 프리프린트(preprint), 또는 학술 대회에서 게시된 초록이나 포스터와 같은 예비 보고(preliminary report)를 완성시켜 보고하는 논문은 이중출판으로 간주하지 않는다. ICMJE는 의료기술 평가기관, 의료 규제기관, 의료기기 규제기관 또는 기타 규제기관이 출판한 평가 보고서에 포함된 결과 또는 자료를 중복 출판으로 간주하지 않는다. 또한 학술대회에서 발표되었지만 아직 최종본으로 게재되지 않은 논문, 또는 학술대회 자료집이나 그 유사한 형태로 게재를 고려 중인 논문 등도 이중출판으로 간주하지 않는다. 학술 대회의 내용이 언론 보도를 통해 발표된 경우도 이중출판으로 보지 않지만, 추가적인 자료가 포함된 도표나 그림이 풍부한 보도인 경우에는 이중출판으로 간주될 수 있다. 그러나 저자는 학술대회에서 발표한 내용이 학술적 분야 밖으로 전파되는 것이 연구 결과물의 출판에 부정적인 영향을 미칠 수 있는 요인이 될 수도 있다는 것을 고려해야 한다.

자신의 연구물을 프리프린트 서버(preprint server)에 게시하려는 저자는 그것이 아직 전문가심사를 거치지 않은 것임을 나타내 주는 서버를 선택해야 하고, 저자의 이해관계와 활동에 관한 공시를 포함시켜야 한다. 저자는 연구물이 이전에 프리프린트 서버에 게시된 적이 있다면 학술지에 이를 알려야 할 책임이 있다. 또한 독자들의 관심이 후속 버전(최종 인쇄본도 포함)을 향하도록 프리프린트를 개정하는 책임은 학술지 편집인이 아닌 저자에게 있다(섹션 III.D.3 참조). 공중보건 당국에 의해 정의된 공중보건 비상사태가 발생할 경우 공중보건에 즉각적인 영향을 미치는 정보는 사전 공개로 인하여 추후 학술지 게재에 불이익을 받을 것이라는 우려 없이 전파되어야 한다. ICMJE는 편집인들이 저자들에게 유전자은행 정보와 같은 공개적 이용이 가능한 핵심 자료를 지체 없이 이용할 수 있는 우선권을 부여할 것을 권장한다.

게재가 결정되었으나 아직 출판되지 않은 논문이나 편집인에게 보내는 편지 등에 포함된 정보를 대중매체, 정부기관 또는 제조업체와 공유하는 것은 대부분의 학술지의 정책에 위배된다. 그러나 이와 같은 사전 공개는 새로운 중요한 치료법이 개발되었거나, 대중에게 시급히 알려야 할 중대 질환이 발생했을 때, 또는 약물, 백신, 기타 생물학적 제품, 의료기구 등의 심각한 부작용이 발생했을 때와 같이 공중보건에 심각한 위해를 초래할 수 있는 경우에는 정당화될 수 있다. 이러한 사전 공개는 인쇄물이든 온라인이든 논문 출판에 해가 되지 않지만, 가능하면 사전에 편집인과 상의하고 동의를 구해야 한다.

ICMJE는 연구 결과(연구 대상자, 핵심 결과 및 부작용)를 간략한(500단어) 구조화된 초록 또는 표로 제한하여 III.L항에 명시된 기준을 충족하는 등록기관에 게시한 경우는 사전출판으로 간주하지 않는다. ICMJE는 저자에게 게시된 연구 결과가 아직 전문가심사 학술지에 게재되지 않았으며, 논문이 게재될 때에는 충분한 참고문헌 인용과 함께 연구 결과가 갱신될 수 있다는 점을 고지할 것을 권장한다.

여러 학술지의 편집인이 한 논문을 동시에 합동으로 게재하는 것이 공중보건에 있어서 최선의 이익이 될 것이라고 판단한 경우에는 동시 발행도 가능하다. 그러나 이런 경우 미국 국립의학도서관은 동시에 게재된 모든 출판물을 별도로 색인하므로 편집인은 동시출판이라는 점을 독자들에게 명확히 고지해야 한다.

저자가 사전고지 없이 이중출판을 시도한다면 투고된 원고는 즉각적으로 반려될 것이다. 편집인이 이중출판인 사실을 모르는 상태에서 원고가 이미 출판되었다면 해당 논문은 저자의 해명이나 동의와 상관 없이 취소될 수 있다.

COPE의 업무 흐름도(<http://publicationethics.org/resources/flowcharts>)는 중복출판의 처리에 관한 상세한 지침을 보여 준다.

3. 프리프린트(Preprints)

프리프린트로서 저작물을 게시하면 전문가심사 및 그 저작물의 출판에 대한 학술지의 관심 또는 우선순위에 영향을 미칠 수 있다. 학술지는 프리프린트의 게시 및 인용과 관련된 그들의 정책을 '저자를 위한 안내 정보'에 명확하게 설명해 놓아야 한다. 저자는 프리프린트 서버에 저작물을 게시하기 전에 자신의 저작물을 제출하고자 하는 학술지의 정책에 익숙해져야 한다.

a. 프리프린트 문서 보관소 선택하기

프리프린트 문서 보관소는 생물 의학 분야에서 계속 증가해오고 있다. 전문가심사에 앞서 과학적 발견을 배포

하는 것에는 유익함과 유해함이 동시에 존재한다. 잠재적인 유익함을 극대화 함과 동시에 잠재적 유해함을 최소화 하기 위해서, 전문가심사를 받지 않은 저작물의 프리프린트들이 널리 공개되길 원하는 저자들은 다음과 같은 특징을 가진 프리프린트 문서 보관소를 선택해야 한다:

- 프리프린트란 전문가심사를 받지 않은 저작물임을 명확히 밝힌다.
- 저자로 하여금 이해 관계의 공개를 문서화 하도록 요구한다.
- 저자에게 연구비 출처를 표시하도록 요구한다.
- 프리프린트 문서 보관서 사용자가 게시된 프리프린트와 관련된 우려 사항을 관리자에게 알릴 수 있는 명확한 프로세스를 마련한다. 이를 위해서는 조회인들이 공개적으로 주석을 다는 기능을 갖추는 것이 바람직하다.
- 게시 철회된 프리프린트의 메타자료(metadata)를 유지관리하고 프리프린트의 철회 시기와 이유를 명시하는 철회 안내문을 게시한다.
- 저자로 하여금 프리프린트가 이후 논문으로서 전문가심사 학술지에 게재될 때를 표시할 수 있는 기전을 가진다.

b. 프리프린트 문서 보관소에 있는 원고를 전문가심사 학술지에 투고하기

저자는 학술지에 투고된 저작물이 프리프린트 서버에 게시되어 있는 경우 그 학술지에 알리고 게시가 투고 전에 발생했건 전문가심사 과정 중에 발생했건 프리프린트에 대한 링크를 제공해야 한다. 또한 원고 본문, 아마도 서론에서 프리프린트가 열람 가능하고 심사자가 해당 프리프린트에 접근할 수 있는 방법을 표시하는 것도 도움이 된다. 또한 프리프린트가 수정되어 정식 출판된 논문까지 포함하여 후속 버전이 있음을 안내하는 것은 저자의 책임이다(학술지 편집자의 책임이 아님). 저자는 프리프린트 문서 자료실에 출판된 버전의 논문이나 전문가심사 과정에서 학술지 피드백에 기반을 둔 수정 사항을 포함한 중간 과도기 버전을 올려놓아서는 안 된다.

c. 투고 원고에 프리프린트 인용하기

투고된 원고나 출판된 논문에서 프리프린트가 인용된다면, 그 인용은 프리프린트임을 분명히 나타내야 한다. 프리프린트가 전문가심사 학술지에 결국 출판된 경우, 저자는 가능한 프리프린트보다는 정식 출판된 논문을 인용하여야 한다. 학술지는 인용 정보 다음에 이어서 "프리프린트"라는 단어를 참고 문헌 목록에 포함하고, 본문에도 인용된 그 자료가 프리프린트임을 표시하도록 고려해야 한다. 프리프린트 문서 보관소가 DOI를 발행하는 경우, 인용은 프리프린트 및 DOI에 대한 링크를 포함해야 한다. 저자는 프리프린트로 게시되었지만 전문가심사 학술지에 전혀 출판되지 않고 있는 프리프린트를 참고 문헌에 등재하는 것에 각별히 유의해야 한다. 그러나 그에 관한 우려가 발행하는 시차는 논문의 주제와 인용의 구체적인 이유에 따라 다를 것이다.

4. 허용되는 이차출판(Secondary Publication)

이미 다른 학술지나 온라인 판에 게재된 출판물의 이차출판은 정부기관과 전문 단체에 의해 만들어진 지침서(동일 언어뿐만 아니라 여러 언어를 포함하여)와 같이 중요한 정보를 가능한 광범위하게 전파하려 할 때 정당화될 수 있고, 어떤 면에서는 유익할 수도 있다. 특정한 이유로 이차출판이 필요한 경우에 다음 조건을 모두 충족하면 가능하다.

- 1) 저자는 원전을 출판한 학술지 편집인과 이차출판을 하려는 학술지 편집인 양쪽의 승인을 받아야 한다. 이차출판과 관련이 있는 학술지 편집인은 원전에 접근할 수 있어야 한다. 원전 출판의 우선권은 편집인들과 저자 간에 출판 간격을 조정함으로써 존중되어야 한다.
- 2) 이차출판은 원전 논문과 다른 독자층을 대상으로 기획되어야 한다. 이 경우 축약본(abbreviated version)으로 충분할 수도 있다.
- 3) 이차출판 된 논문은 원전의 저자, 자료와 해석을 성실하게 그대로 반영하여야 한다.
- 4) 이차출판 된 논문은 독자, 전문가 심사자 및 여러 문헌관리 주체에게 해당 논문이 다른 곳에서 전부 또는 일부 출판되었음을 고지해야 한다. 예를 들어, 각주 등에 "이 논문은 처음 게재된 논문[논문 제목, 서지사항]의 연구에 기초하고 있다"와 같이 기술할 수 있으며 이차출판 된 논문에는 원전 논문이 인용되어야 한다.

5) 이차출판된 논문의 제목에 원전 논문의 이차출판(원본 또는 요약본의 재출판, 또는 번역본의 출판)이라는 것을 명기해야 한다. 미국 국립의학도서관은 번역본을 이차출판으로 간주하지 않으며, 원전 논문이 게재된 학술지가 MEDLINE에 색인되어 있으면 번역본을 다시 인용하거나 색인하지 않는다. 같은 학술지가 한 논문을 동시에 여러 언어로 출판했을 때 MEDLINE은 인용문헌의 서지사항에 존재하는 여타 언어본을 기록한다(예: Angelo M. Journal networking in nursing: a challenge to be shared. Rev Esc Enferm USP. 2011 Dec 45[6]:1281-2, 1279-80, 1283-4. Article in English, Portuguese, and Spanish. No abstract available. PMID 22241182).

5. 동일 자료에 기반한 원고

만약 서로 다른 저자 또는 같은 저자가 공공 자료(public database) 또는 같은 자료를 이용한 체계적 문헌고찰이나 메타분석과 같이 동일한 자료를 분석한 원고를 투고한 경우, 분석 방법이나 결론 또는 분석 방법과 결론 모두 다를 수 있기 때문에 각각은 독립된 원고로 간주되어야 한다. 만약 자료 해석과 결론이 유사하면 편집인은 먼저 투고된 원고에 우선권을 주는 것이 합리적이지만 반드시 그럴 필요는 없다. 편집인은 이런 방식으로 중복되는 하나 이상의 원고를 게재할 수도 있다. 다른 방식의 분석 방법이 상호 보완적일 수 있고 모두 동일한 가치가 있을 수 있기 때문이다. 그러나 동일한 자료에 근거한 원고들은 투명성을 확보하기 위하여 동일한 자료로 이미 출판된 논문을 적절히 인용함으로써 별개의 논문으로 정당하게 인정되도록 서로를 충분히 고려하여야 한다. 임상시험 자료의 이차 분석에는 원전 출판을 인용하고, 그것이 이차 분석과 그 결과라는 점을 분명히 밝혀야 하며, 원전 출판에 사용된 것과 같은 임상시험 등록번호를 사용해야 한다. 간혹 대규모 임상시험의 경우 동일한 시험대상 표본을 사용하면서도 연구설계 시에 여러 가지 세부연구목표를 개별적으로 출판할 목적으로 기획되기도 한다. 이 경우 모든 연구결과 지표가 등록된 연구계획에 정의된 것이라면 저자는 등록된 한 가지 임상시험 번호를 사용할 수 있다. 저자가 몇 가지 세부연구를 ClinicalTrials.gov 같은 등록기관에 별도로 등록한 경우에는 각각의 연구에 고유한 임상시험 번호를 부여 받아야 한다. 연구에서 가장 중요한 문제는 투명성이며, 어떤 실험 모델이 사용되더라도 독자가 명확하게 알 수 있어야 한다.

E. 독자통신(Correspondence)

의학학술지는 독자들이 학술지에 실린 논문에 대한 논평, 질의, 비평 등을 개진할 수 있도록 독자통신란이나 온라인을 포함한 여러 가지 가능한 방법을 제공해야 한다. 독자통신란이나 온라인 포럼 등에서 논의가 된 논문의 저자는 같은 방법으로 비평 받은 사안에 대해 회신해야 할 의무가 있으며, 편집인은 해당 저자에게 비평에 대한 회신을 요청해야 한다. 비평을 제기한 저자에게는 해당 논문과 관련한 경쟁관계나 이해관계 여부에 대해 밝힐 것을 요청해야 한다.

독자통신은 원고 길이, 문법 교정, 서술 방식 등에 대한 편집이 필요할 수 있다. 그렇지 않으면, 편집인은 온라인 논평 시스템과 같은 방법으로 편집되지 않은 독자통신을 열람할 수 있도록 해 주어야 한다. 이와 같은 논평은 추후에 페이지 번호가 부여되는 인쇄본 또는 온라인 판에 게재되지 않는 한 MEDLINE에 색인되지 않는다. 그러나 학술지는 투고된 독자통신을 관리하는 시스템을 운영하고, 그러한 사실을 독자들에게 알려야 한다. 편집인은 무례하거나, 부정확하고, 중상적인 논평을 걸러내기 위한 노력을 항상 기울여야 한다.

책임 있는 논쟁, 비평 및 의견 불일치는 과학에서 또 하나의 중요한 모습이며, 편집인은 자신이 발행한 출판물에 대해 자신의 학술지 내에서 이와 같은 담론이 오가는 것을 장려해야 한다. 편집인은 부적절하고, 흥미롭지 못하고, 타당성이 결여된 논평은 거절할 권리를 가지고 있지만, 다양한 의견의 개진을 허용하고 건전한 논쟁을 증진시킬 의무 또한 가지고 있다. 독자통신을 가능한 범위 내에서 관리하고 공정성을 유지하기 위해서는 게재된 논문에 대한 의견을 개진하고 그에 대한 토론을 할 수 있는 시한을 설정할 수도 있다.

F. 비용(Fees)

학술지는 재정 운영 방식에 대해 투명해야 한다. 투고 원고의 처리와 학술지 출판에 소요되는 제반 비용이나 수수료에 대해 잠재적 저자들이 원고를 투고하기 전에 쉽게 찾아볼 수 있도록 명확하게 게시하거나, 저자들이 투고할 원고를 준비하기 전에 저자들에게 설명하여야 한다(<https://publicationethics.org/sites/default/files/principles-transparency-best-practice-scholarly-publishing.pdf> 참조).

G. 별호(Supplements), 주제별 간행물(Theme issues), 특별 연재물(Special Series)

별호는 서로 관련이 있는 쟁점(issue)이나 주제(topic)를 다룬 논문을 묶어 발행하는 것으로 학술지와 별개로 독립적인 간행물로 발간하기도 하고, 정규 학술지의 일부로 발간되기도 한다. 일반적으로 출판 비용은 발행인이 아닌 다른 후원자로부터 지원받는다. 별호는 외부의 재정지원을 받기 때문에 주제와 선택과 관점 등에서 내용의 편향이 발생할 수 있다. 따라서 편집인은 다음과 같은 원칙을 채택해야 하며, 이는 재정지원자나 외부 편집인이 있는 주제별 간행물과 특별 연재물에서도 마찬가지로 적용된다.

- 1) 학술지 편집인은 저자와 전문가 심사자의 선정, 별호 내용의 결정을 포함하는 별호 발간에 대한 정책과 발간 실무에 대하여 전적인 책임을 지며, 재정지원을 한 기관이나 단체가 편집에 관여하게 해서는 안 된다.
- 2) 학술지 편집인은 별호 발간을 위해 한 명 이상의 외부 편집인을 임명할 권한을 가지며, 그들의 업무에 대해 책임을 진다.
- 3) 학술지 편집인은 별호 원고에 대해 외부에 심사 의뢰를 할 수 있고, 외부 심사에 관계 없이 원고를 반려할 수 있는 권한을 가져야 한다. 이러한 조건은 별호 원고의 심사 전에 저자와 외부 편집인에게 고지되어야 한다. 별호의 주제를 발의한 주체, 별호 출판의 재정지원자 및 별호에서 다루고 있는 재정지원자의 제품 등을 서문(introductory material)에 명확히 밝혀야 한다.
- 4) 별호의 광고는 정규 학술지와 같은 정책으로 관리하여야 한다.
- 5) 편집인은 독자가 별호의 페이지를 정규 학술지의 페이지와 쉽게 구별할 수 있도록 편집하여야 한다.
- 6) 학술지 편집인과 별호 편집인은 별호의 재정지원자로부터 개인적으로 지원이나 보수를 받아서는 안 된다.
- 7) 별호에서 이차출판 되는 논문은 원전 논문을 인용함으로써 쉽게 구별할 수 있어야 한다.
- 8) 이 권고안에서 기술하고 있는 저자됨과 이해관계의 고지와 관련한 원칙이 별호에도 적용되어야 한다.

H. 후원자(Sponsorship) 또는 동반자 관계(Partnership)

다양한 단체나 기관들이 후원자 또는 동반자 관계, 연석 회의, 그 밖의 여러 형태로 학술지 또는 편집인과 교류를 모색할 수 있다. 편집의 독립성을 담보하기 위해서는 “별호, 주제별 간행물, 특별 연재물”(III.G 항)은 위에서 기술한 대로 동일한 원칙에 의해 관리되어야 한다.

I. 온라인 출판(Electronic Publishing)

대부분의 의학학술지는 현재 인쇄본뿐만 아니라 온라인 상으로도 출판되며, 일부는 온라인 판으로만 출판되기도 한다. 인쇄본이든 온라인 출판이든 적용되는 원칙은 동일하며, 이 권고안은 양자에 동일하게 적용된다. 그러나 온라인 출판은 판본의 갱신이 가능할 뿐 아니라, 다음에 기술하는 것과 같은 링크 안정성과 서버에 저장된 내용물의 보관이 문제점으로 대두된다. 수정과 판본 관리에 대해서는 이 권고안 III.A 항에 상세히 기술되어 있다. 온라인 출판은 다른 웹사이트와 링크가 가능해서 학술지 외부 자료의 출처로 이동할 수 있는데 이 부분은 학술지 편집인이 관리할 수 없는 영역이다. 이러한 이유와 함께 다른 웹사이트에 링크된 것이 해당 사이트를 보증하는 것처럼 인식되기 때문에 학술지 웹사이트에서 다른 웹사이트로 링크를 설정할 때는 주의를 기울여야 한다. 학술지가 다른 웹사이트에 링크를 설정할 때 해당 웹사이트의 내용, 광고, 제품, 기타 대상에 대해 보증이나 책임이 없다는 것을 고지하여야 하고, 해당 웹사이트의 유용성에 대한 책임을 질 필요는 없다.

학술지 웹사이트, 독립적인 기록보관소 또는 기타 안전한 저장소에 게재 논문을 영구적으로 보존하는 것은 역사의 기록을 위해 필수적이다. 비록 개별 논문이 학술지 웹사이트에 게시되는 기간이 짧더라도 언제든지 해당 논문을 내려 받을 수 있어야 하므로 학술지 웹사이트에서 한 논문을 전체로 삭제하는 것은 정당화될 수 없다. 이러한 기록보관소는 무료로 개방하든지 기록보관소 회원들에게 접근이 가능해야 하며, 다중으로 기록보관소를 만들어 두는 것이 좋다. 그러나 명예훼손 소송과 같은 법적인 사유로 삭제된 경우, 논문이 있던 인터넷 웹페이지 주소(Uniform Resource Locator, URL)에 구체적인 삭제 사유를 게시해야 하고, 학술지의 내부 기록보관소에는 해당 논문을 보관하고 있어야 한다.

학술지의 모든 내용물을 영구적으로 보존하는 것은 학술지 발행인의 의무이며, 학술지가 폐간됐을 때는 그 내용물의 이용을 제공할 수 있는 제 3자에게 모든 학술지 파일을 확실하게 이관시켜야 한다.

학술지 웹사이트는 학술지 사무국, 편집위원 명단, 투고규정과 같은 비논문 웹페이지(nonarticle webpage)

에 마지막으로 갱신된 일자를 게시해야 한다.

J. 광고

대부분의 의학학술지들은 광고를 게재하여 수입을 창출한다. 그러나 학술지가 광고에 지배되어서는 안 되며, 광고가 편집 결정에 영향을 미치는 것을 허용해서도 안 된다. 학술지는 광고에 대한 공식적이고 명백한 명문규정을 인쇄본과 디지털 파일(electronic version)로 가지고 있어야 한다. 최상의 정책은 광고가 동일한 제품을 포함하는 학술지 콘텐츠(editorial contents)와 함께 게재되는 것을 금지하는 것이다. 광고는 일반 기사와 쉽게 감별되어야 한다. 편집인은 인쇄본과 온라인 판의 광고 게재를 승인하고 광고 정책을 실행하는 데 있어 완전하고 최종적인 권한을 가져야 한다.

학술지는 건강을 침해한다고 증명된 제품의 광고를 게재하면 안 된다. 편집인은 각 나라마다 시행하고 있는 광고에 관한 기존 산업적 기준을 지키거나 학술지 자체 기준을 만들어야 한다. 법률로 규제할 필요가 있는 경우가 아니면 특정 조직이나 기관의 이해로 인하여 안내 광고(classified advertising)와 기타 간이 광고(nondisplay advertising)까지 통제해서는 안 된다. 편집인은 학술지 광고에 대한 모든 비판을 수용해야 한다.

K. 학술지와 대중매체

학술지는 대중매체와 상호작용을 통해 우선순위를 두고 경쟁하는 데 있어서 균형을 이루어야 한다. 일반 대중은 모든 학술지 콘텐츠에 정당한 관심을 가지며, 적절한 시간 내에 중요한 정보를 얻을 권리가 있고, 편집인은 이를 용이하게 할 의무가 있다. 그러나 충분한 전문가심사와 검증이 이루어지기 전에 대중매체가 연구 결과를 보도하면 부정확하고 성급한 결론을 확산시킬 우려가 있으며, 환자 진료에 임하는 임상 의사는 연구의 결론만 가지고 환자에게 조언하기에 앞서 연구의 상세한 내용을 알고 있어야 한다.

이러한 정보 공개의 우선순위를 조정하고, 연구 결과가 학술지에 게재되기 전에 대중매체를 통하여 공개되는 것을 제한하기 위해 일부 국가와 일부 학술지들은 보도유예 제도(embargo system)를 도입하고 있다. 보도유예 제도는 신중하게 기사를 작성할 수 있는 시간이 부족한 상태에서 경쟁자들보다 먼저 기사를 송출해야 하는 부담을 줄여 주기 때문에 대부분 기자들이 환영하는 공평한 경쟁의 기회를 만들어 준다. 일반에 의학 정보를 공개하는 시기를 일관성 있게 관리하는 것도 경제적인 혼란을 막는 데 긴요할 수 있다. 일부 논문들은 금융시장에 큰 영향을 미칠 수 있는 정보를 담고 있기 때문이다. ICMJE는 보도유예 제도가 학술지의 이해에 치중되어 과학 정보의 신속한 전파를 저해한다는 사실을 인정하지만, 이 제도가 단점보다 장점이 더 많다고 믿는다.

다음과 같은 원칙을 인쇄본과 온라인 판에 동일하게 적용하면 편집인들은 대중매체와의 관계 설정에 도움이 될 것이다.

- 편집인은 연구자가 생산한 의학 정보를 전문가심사 학술지를 통하여 대중에게 질서 있게 전파할 수 있다. 이를 위해서는 심사 또는 게재 대기 중에 있는 원고는 일반에 공개하지 않겠다는 저자의 합의와 학술지가 출판될 때까지 연구 내용을 보도하지 않겠다는 대중매체의 협조를 얻어 내고, 이와 동시에 학술지는 보도 자료(press release)와 같은 방법으로 대중매체에 정확한 정보를 제공하는 데 협조하여야 한다.
- 편집인은 보도유예 제도가 상호 존중을 바탕으로 한다는 사실에 유념해야 한다. 즉, 법적인 강제나 공권력은 전혀 개입되지 않는다. 언론매체나 생의학 학술지 상당수가 보도유예 제도를 존중하지 않는다면 보도유예 제도는 바로 와해될 것이다.
- 연구자들이 자신의 연구 성과에 대한 믿음에도 불구하고, 명백하고 시급한 공중보건 상의 중요성으로 인하여 학술지에 완전한 논문으로 게재되기 전에 긴급히 보도해야 하는 의학 연구란 실제로 거의 없다. 만약 이러한 예외적인 상황이 발생하면 공중보건에 책임이 있는 적합한 기관이 이러한 정보를 임상 의사와 대중매체에 전파할 것인지를 결정해야 하고, 그 결정에 책임을 져야 한다. 사안에 관련된 원고가 특정 학술지에 투고된 상태라면 저자와 관계기관은 해당 학술지 편집인과 상의한 다음 대중매체에 공개하여야 한다. 학술지 편집인이 즉각적인 공개의 필요성을 인정하는 경우에는 출판 전 공개를 금하는 정책을 유보하고 예외로 취급한다.
- 출판 전 공개를 제한하는 정책은 학술대회에서 발표한 내용이나 논문 초록에는 적용되지 않는다(이중출판 허용 참조). 학술대회에서 논문을 발표하는 연구자들은 기자들과 논문에 대해서 자유롭게 토론할 수 있지만,

공개적으로 발표된 것보다 더 상세한 정보를 제공하는 것은 자제해야 하고, 이와 같은 상세한 정보의 제공이 학술지 편집인이 저자의 연구 성과에 할당하는 우선순위에 미치는 부정적인 영향을 고려해야 한다(이중 출판 항 참조).

- 논문 출판이 임박한 경우, 편집인과 편집사무국은 대중 매체가 정보를 정확하게 전달하도록 보도자료를 제공하고, 질문에 답하며, 학술지를 미리 나누어 주고, 기자에게 적당한 전문가를 소개하는 등으로 협조하여야 한다. 이러한 협조의 제공은 대중매체가 보도 시기를 학술지의 발행 시기에 맞추는 데 얼마나 협조하느냐에 달려 있다.

L. 임상시험(Clinical Trials)

1. 등록

ICMJE의 임상시험 등록 정책은 ICMJE 웹사이트에 게시된 Updates and Editorials(<https://www.icmje.org/news-and-editorials/>)와 FAQs(<https://www.icmje.org/about-icmje/faqs/>)에 상세하게 기술되어 있다.

간단히 설명하면, ICMJE는 모든 의학학술지 편집인들이 임상시험이 논문 게재를 전제로 할 때에는 임상시험에 환자를 참여시키기 전에 또는 시작할 때 공공 임상시험 등록기관에 임상시험을 등록할 것을 요청할 것을 권장한다. 자신의 학술지를 ICMJE 웹사이트의 ICMJE 지침을 준수하는 학술지 명단에 포함시켜 줄 것을 요청한 학술지 편집인은 이러한 명단에 포함되는 것이 ICMJE의 임상시험 등록 정책을 따라야 한다는 것을 의미한다는 점을 인식해야 한다.

ICMJE는 임상시험 등록 자료가 처음으로 등록기관에 제출된 일자리를 임상시험 등록일로 사용한다. 등록 자료의 제출과 등록기관에 게시된 것 사이에 상당한 지연이 있을 때 편집인은 지연이 초래된 상황에 대해 질의할 수 있다.

ICMJE는 임상시험 대상자를 전향적으로 중재군(intervention) – 동시비교군(concurrent comparison)이 동반될 수도 있음 – 과 대조군(control)으로 배정하여 의학적 중재를 시행하고 그로 인한 건강관련 결과와 인과 관계를 연구하는 것을 임상시험이라고 정의한다. 의학적 중재에는 생의학 또는 건강관련 결과를 개선시키는 데 사용되는 방법들, 즉 약제, 외과 수술, 의료용 기구, 행동치료, 환자교육 프로그램, 영양요법, 삶의 질 개선, 개호(process-of-care) 등이 포함된다. 건강 결과(health outcomes)란 환자와 임상시험 참여자에서 약물동태학적 지표나 부작용 같은 생의학 또는 건강과 관련한 지표를 말한다. ICMJE는 첫 번째 임상시험 대상자 등록시점을 정의하지는 않지만, 첫 참여자의 동의서를 받은 때로 하는 것이 가장 합리적이다.

ICMJE는 최소 24개 항목의 허용 가능한 임상시험 등록정보를 포함하는 WHO International Clinical Trials Registry Platform(ICTRP; <https://www.who.int/clinical-trials-registry-platform/network/who-data-set>) 또는 WHO ICTRP에 자료를 제공하는 ClinicalTrials.gov의 기본 명부에 등재된 등록기관에 공개적인 접근이 가능하도록 등록한 임상시험을 인정한다. 이들은 등록기관으로서 여러 가지 기준에 합당하기 때문이다. 이들은 일반 대중이 무료로 이용할 수 있고, 전향적 임상시험을 계획하는 모든 연구자들에게 개방되어 있으며, 비영리 단체에 의해 관리되고 있고, 등록된 자료의 신뢰성을 담보할 수 있으며, 온라인으로 열람이 가능하다. 인정되는 등록기관은 임상시험 등록 시에, 그리고 첫 대상자 등록 전(<https://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf> 또는 <https://www.who.int/clinical-trials-registry-platform>)에 게시된 24개의 필수 임상시험 입력자료 항목을 갖추고 있어야 한다. ICMJE는 24개 입력 항목 중 하나라도 빠졌거나, 정보가 불충분하게 기술되어 있는 경우, 또는 EU-CTR에 제출되는 1상 시험이나 기술 정보가 "lock box"에 위치하는 기기의 임상시험과 같이 임상시험 정보에 공개적으로 접근할 수 없을 경우 해당 임상시험은 부적절한 것으로 간주한다. ICMJE 정책을 준수하기 위해 ClinicalTrials.gov에 기기 시험을 등록하는 연구자는 기기 승인 전에 공개 게시를 선택하여 "lock box"에서 정보를 개방해야 한다. 지역, 지방 또는 국가 규모의 독립적인 심의 기구(예: 윤리위원회, 기관심의위원회)에서 받은 연구수행 승인은 ICMJE의 전향적 임상시험 등록 요건을 충족하지 못한다. 비록 필수적인 것은 아니지만, ICMJE는 저자들에게 연구 결과가 아직 전문가심사 학술지에 게재되지 않았으며, 연구 결과가 게재될 때에는 완전한 참고문헌의 인용과 함께 등록이 갱신될 수 있다는 고지문을 포함할 것을 권장한다. 임상시험 등록의 목적은 연구 성과의 선택적 게재와 선택적 보고 및 연구 역량의 불필요한 중복을 방지하며, 환자와 일반 대중이 흥미를 갖고 참여할 만한 임상시

험이 계획되고 진행 중이라는 사실을 알리는 데 도움을 주고, 새로 제안된 연구에 대해 연구윤리위원회 구성원들이 고려 중인 연구에 적합한 유사 연구와 자료의 관점에서 해당 연구의 승인을 판단하는 데 도움을 주고자 하는 데 있다. 원고 제출 시에 임상시험을 등록하는 경우와 같은 후향적 등록은 이런 목적과 부합하지 않는다. 이 부분은 관찰연구(observational study)와 같은 다른 형태의 연구에도 적용할 수 있다. 따라서 ICMJE는 임상시험이 아닌 연구의 등록도 권장한다. 그러나 임상시험이 아닌 연구에서는 노출(exposure) 또는 중재가 개입되지 않으므로 ICMJE는 이를 강제하지 않는다.

모태가 되는 1차 임상시험(primary clinical trial)의 이차적인 자료 분석은 독립된 임상시험으로 등록되어서는 안 되며, 1차 임상시험의 등록번호를 사용해야 한다.

ICMJE는 저자들이 임상시험 등록기관에 보고된 종합 임상시험 결과와 관련한 연구비 및 관리 기관이 정하는 요건을 확실하게 충족시킬 것을 권장한다. 학술지에 게재된 연구 결과와 등록기관에 보고되어 있는 내용 간에 불일치가 있을 경우, 이를 소명할 책임은 학술지 편집인이 아닌 저자에게 있다. ICMJE는 연구 결과(임상시험 대상자와 기본 특성, 1, 2차 결과, 부작용)를 간단한(500단어) 초록 또는 표로 제한하여 앞서 기술한 기준을 충족하는 등록기관에 게시한 경우는 사전출판으로 간주하지 않는다.

ICMJE는 학술지가 논문을 출판할 때 임상시험 등록번호를 초록의 말미에 기술할 것을 권장하며, 등록번호가 있는 임상시험에 대해서는 보고하고 있는 임상시험이나 원고에서 언급하고 있는 다른 임상시험의 약어(acronym)를 처음으로 사용할 때 등록번호를 기술할 것을 권장한다. 편집인은 임상시험을 적절하게 등록하지 못한 것과 연관된 상황이 편향된 보고로 이어진 것인지 아니면 편향된 보고를 의도한 것이었는지 고려할 필요가 있다. 임상시험 사전 등록의 중요성 때문에 이러한 정책에 예외가 발생하는 경우, 반드시 임상시험을 등록하고 저자는 임상시험 등록이 완성된 시점과 지연된 사유를 출판 시에 밝혀야 하며, 편집인은 예외가 허용된 사유를 고지해야 한다. ICMJE는 이러한 예외는 드물어야 하며, 임상시험을 사전에 등록하지 않은 저자는 논문 투고 거부당할 위험을 감수해야 한다는 점을 강조한다.

2. 자료 공유(Data Sharing)

ICMJE의 자료 공유 선언 정책은 ICMJE 웹사이트의 Updates and Editorials(<https://www.icmje.org/update.html>)에 자세히 기술되어 있다.

- 1) 2018년 7월 1일부로 임상시험 결과를 보고하는 ICMJE 회원 학술지에 투고할 때는 아래 기술하는 자료 공유 선언문(Data Sharing Statement)을 포함해야 한다.
- 2) 2019년 1월 1일 이후 대상자 등록을 시작하는 임상시험은 임상시험 등록 시에 반드시 자료 공유 계획을 함께 제출하여야 한다. 임상시험 등록과 관련한 ICMJE의 정책은 <https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>에 설명되어 있다. 임상시험 등록 후 자료 공유 계획에 변동사항이 발생하였을 경우, 이를 논문 투고 시에 자료 공유 선언문에 반영하여 출판하여야 하며, 임상시험 등록 기록을 갱신해야 한다.

자료 공유 선언문에는 반드시 다음과 같은 내용이 포함되어야 한다: 개별적인 익명화된 대상자(deidentified participant) 자료(자료 사전 포함)를 공유할 것인가(“결정되지 않음”은 수용 불가); 어떤 자료를 공유할 것인가; 어떤 추가, 관련 자료(연구 계획, 통계 처리 계획)를 제공할 것인가; 자료 공유는 언제부터 시작하고 얼마 동안 지속할 것인가; 어떤 기준-대상자, 분석 방법, 접근 방식(mechanism)-으로 자료에 접근하게 할 것인가? 이상의 필수 요건을 충족하는 자료 공유 선언문의 실례가 되는 보기를 다음 표에 제시하였다. 공유 자료를 이용하여 2차 분석을 하는 연구자는 제안한 이용 목적에 맞게 이용하고 있음을 입증해야 하며, 자료를 생산하고 그것을 지원했던 연구를 검색할 수 있도록 허용한 연구자에게 적절한 신뢰를 제공하기 위해 항구적이고 고유한 식별자를 이용하여 자료의 출처를 참조할 수 있게 하여야 한다. 또한 2차 분석이 이전 분석과 어떻게 다른지 완전하게 설명해야 한다. 임상시험 자료를 생산하고 공유를 허용하는 연구자는 그들의 노력으로 인해 상당한 인정을 받을 자격이 있다. 다른 연구자가 수집한 자료를 이용하는 연구자는 자료를 수집한 연구자와 협동 연구를 모색해야 한다. 협동 연구가 항상 가능하거나, 실용적인 것은 아니며, 원하지 않을 수도 있으므로 연구 자료를 생산한 연구자의 노력은 반드시 인정되어야 한다.

표. ICMJE의 필수 요건을 충족하는 자료 공유 선언문 예시*

구성요소	예 1	예 2	예 3	예 4
익명화된 대상자의 개별 자료(자료 사전 포함)를 공유할 것인가?	그렇다	그렇다	그렇다	아니다
어떤 자료를 공유할 것인가?	임상시험 동안 수집된 모든 익명화된 대상자의 개별 자료	논문에 보고된 결과에 기초가 되는 익명화된 개별 자료(본문, 표, 그림, 부록)	논문에 보고된 결과에 기초가 되는 익명화된 개별 자료(본문, 표, 그림, 부록)	해당 사항 없음
어떤 문서를 추가적으로 제공할 것인가?	연구 계획, 통계 분석 계획, 동의서 양식, 임상연구 보고서, 분석 코드	연구 계획, 통계 분석 계획, 분석 코드	연구 계획	해당 사항 없음
자료 공유는 언제 가능한가?(개시, 종료일)	출판 즉시. 종료일 없음	출판 후 3개월 후부터 가능. 5년 후 종료	출판 후 9개월 후부터 가능. 35년 후 종료	해당 사항 없음
누구와 공유할 것인가?	자료 접근을 원하는 모든 사람	방법론적으로 건전한 제안을 하는 연구자	자료 사용을 제한한 연구자가 이러한 목적으로 확인된 독립적인 심의 기구(learned intermediary)의 승인을 받은 연구자	해당 사항 없음
분석 유형의 목적은 무엇인가?	모든 목적을 위하여	승인된 연구 계획서의 목적을 달성하기 위하여	연구 대상자의 개별 데이터를 이용한 메타분석을 위하여	해당 사항 없음
어떤 방식으로 의해 데이터를 이용하게 할 것인가?	(링크 주소)에서 무제한 이용이 가능하다.	데이터 접근을 승인 받기 위해서는 제안서를 특정 사이트(예, xxx@yyy)에 보내어 데이터 접근 동의를 얻어야 한다. 데이터는 제3자의 웹사이트(링크 주소)에서 5년간 사용할 수 있다.	제안서는 출판 후 36개월까지만 접수할 수 있다. 36개월 후에는 우리 대학의 데이터 웨어하우스에서 이용할 수 있지만, 축적된 메타데이터 외에 다른 연구자의 지원을 받을 수 없다. 제안서 제출과 데이터 접근에 관한 정보는 (링크 주소)에서 볼 수 있다.	해당 사항 없음

* 이들 예시는 자료 공유에 필요한 요건의 범위를 보여주는 것으로 모든 요건을 포함하는 것은 아니다.

IV. 원고 준비와 투고

A. 의학학술지에 투고하기 위한 원고의 준비

1. 일반 원칙

원저 연구논문의 본문은 대체로 서론(Introduction), 방법(Methods), 결과(Results) 그리고 고찰(Discussion)이라는 부분으로 구성된다. 이를 소위 "IMRAD" 구조라고 하며, 임의로 만든 출판 형식이 아니라 과학적인 연구 과정을 반영하여 구성된 것이다. 논문 내용을 조금 더 조직적으로 정리하기 위해 각각의 장 내에서 부제목으로 다시 구분할 필요가 흔히 발생한다. 메타분석과 같이 특정 유형의 논문은 원저 논문과 다른 구성 형식을 필요로 할 수 있으며, 증례보고, 종설(review article), 사설(editorial) 등은 덜 구조화되거나 비구조화된 형식을 취할 수 있다.

온라인 출판의 형태에서는 세부적인 부분 또는 하나의 장 전체를 추가할 수 있고, 정보를 누적해 나아갈 수 있으며, 여러 논문의 교차연결이나 추출도 가능하게 하는 등, 온라인 판만이 갖는 장점이 있다. 온라인 판에서만 볼 수 있는 보충 자료도 심사를 위해 일차 원고의 투고 시 함께 제출되어야 한다.

2. 특정한 연구계획을 위한 보고 지침(Reporting Guidelines)

보고 양식 지침은 여러 가지 연구설계(study design)를 위하여 개발되었다. 예를 들어 무작위 임상시험을 위한 CONSORT(<http://www.consort-statement.org>), 관찰연구를 위한 STROBE(<http://strobe-statement.org/>), 메타분석을 위한 PRISMA(<http://prisma-statement.org>), 진단법의 정확성(diagnostic accuracy)을 위한 STARD(<http://www.equator-network.org/reporting-guidelines/stard/>) 등이다. 이러

한 보고 지침은 저자들이 수행한 연구를 상세하게 기술하고, 편집인, 전문가 심사자, 독자 및 다른 연구자들이 해당 연구를 평가하는 데 도움을 주기 때문에 학술지 편집인은 저자들에게 이러한 보고 지침을 따를 것을 요청해야 한다. 저자는 연구 설계, 자료 분석, 결과 및 결과 해석에서 성별 정보를 혹은 생물학적, 사회적 성별 정보를 보고하기 위한 SAGER(Sex and Gender Equity in Research) 지침을 참조하는 것이 좋다. 종설을 투고하는 저자는 문헌을 수집, 선택하고, 자료를 추출하고, 결과를 도출한 방법을 기술해야 하며, 이는 체계적 문헌고찰에서 필수적이다. 여러 가지 보고 지침을 찾아볼 수 있는 가장 좋은 웹사이트는 EQUATOR Network(<http://www.equator-network.org/home>)와 미국 국립의학도서관의 Research Reporting Guidelines and Initiatives(http://nlm.nih.gov/services/research_report_guide.html)이다.

3. 원고의 구성(Manuscript Sections)

다음은 모든 종류의 연구 형태와 원고 형식의 각 장에서 기술되어야 할 일반적인 요건들이다.

a. 표지(Title Page)

논문과 저자에 관련된 일반적인 정보를 원고 표지에 기술한다. 일반적으로 논문 제목, 저자 정보, 면책 선언, 연구지원자 정보, 글자수 등이 포함되며, 가끔 표와 그림의 개수를 기술하기도 한다.

논문 제목: 제목은 전체 논문을 압축적으로 표현한 것으로 초록과 함께 논문 검색에 용이하도록 특징적이고 고유한 정보를 담아야 한다. 일부 학술지는 특정 형태의 연구인 경우 제목에 해당 연구 형태에 대한 정보를 포함할 것을 요구하고 있으며, 이는 보고 지침에서도 권장하는 사항으로 특히 무작위 임상시험과 체계적 문헌고찰이나 메타분석에서 중요하다. 일부 학술지는 글자와 공백을 합해 40자 이내의 축약 제목을 원고의 표지에 기술하거나 온라인 상에서 별도의 항목으로 입력할 것으로 요청하기도 한다. 온라인 투고 시스템은 제목의 글자수를 제한하기도 한다.

저자 정보: 각 저자의 최종 학력과 연구가 수행된 기관과 부서명이 정확히 기술되어야 한다. 그러나 일부 학술지는 저자의 최종 학력은 기술하지 않기도 한다. 대부분의 온라인 투고 시스템은 저자 주소와 전자메일을 포함한 전체 연락처를 입력할 것을 요구하지만 원고 표지에는 책임저자의 주소, 전화 번호, 팩스 번호 및 전자메일 주소 등을 기술한다. 또한 ICMJE는 저자의 ORCID(Open Researcher and Contributor Identification) 명단을 기재할 것을 권장한다.

면책 선언(Disclaimers): 예로써 투고된 원고에 표현된 견해는 저자 자신의 주장이지 연구가 수행된 기관 또는 연구 지원자의 공식 견해가 아니라는 것을 선언하는 것을 들 수 있다.

연구 지원 정보(Source of Support): 연구비, 실험 설비, 약제, 기타 연구 수행 또는 논문 작성에 필요한 지원 등에 대하여 기술한다. 연구비 출처 및 소속의 부적절한 귀속은 피해야 한다.

글자수: 초록, 감사의 글, 표, 그림 설명문, 참고문헌 등을 제외한 본문의 글자수는 편집인과 전문가 심사자에게 해당 논문에 담긴 정보가 논문의 길이에 합당한지, 원고가 학술지의 형식과 글자수 제한에 적당한지를 판별할 수 있도록 해 준다. 본문의 글자수와 별도로 초록의 글자수도 같은 이유로 유용하다.

표와 그림의 개수: 일부 학술지는 해당 파일을 업로드 하기 전에 제출하는 표와 그림의 숫자를 기술할 것을 요구한다. 이는 편집인과 전문가 심사자들이 모든 그림과 표가 실제로 원고에 포함되었는지 쉽게 알 수 있도록 하고, 표와 그림은 상당한 공간을 차지하기 때문에 그림과 표에 제시된 정보가 원고의 길이에 합당한지, 전체 원고가 학술지의 글자수 제한에 적당한지를 판별하는 데 도움을 준다.

이해충돌 선언: 각각의 저자들의 이해충돌에 관련된 정보는 원고의 한 부분으로 구성되어야 한다. 학술지들은 관련 정보를 제출 받고 이를 어디에 게시할 것인지에 대한 기준을 만들어야 한다. ICMJE는 ICMJE 회원 학

술지들이 사용할 수 있도록 통일된 공시 양식(http://www.icmje.org/coi_disclosure.pdf)을 개발하였으며, 다른 학술지들에게도 이 양식을 채용할 것을 권장한다. 이러한 양식이 이용 가능함에도 불구하고 편집인은 편집 관련 결정을 내리기 전에 각 저자들로부터 공시 양식을 수집하는 작업을 줄이고, 전문가 심사자와 독자들이 각 저자들의 양식을 읽어야 하는 수고를 덜기 위해 원고의 표지나 기타 공시란(disclosure section)에 저자의 이해관계와 활동을 기술할 것을 요구할 수도 있다.

b. 초록(Abstract)

원저, 체계적 문헌고찰, 메타분석 등은 구조화된 초록이 요구된다. 초록에는 연구의 배경, 목적, 기본적인 방법(연구 대상의 선정, 연구 설정[setting], 측정 방법, 분석 도구), 주요 결과(가능하면 구체적인 효과의 크기, 통계학적 및 임상적 의의 포함) 및 주요 결론 등이 포함된다. 새롭고 중요한 연구 성과와 소견을 강조하고, 중요한 제한점을 기술하되 결과를 과장해서는 안 된다. 임상시험의 초록은 CONSORT 그룹이 필수사항으로 요구하는 항목을 포함해야 한다(<https://www.equator-network.org/reporting-guidelines/consort/>). 연구비 출처는 초록의 말미에 본문과 분리해서 기술하여 눈에 잘 띄게 하고 MEDLINE 검색에 색인되도록 해야 한다. 연구비를 받았다는 기술에는 연구작업에 대한 직접적인 지원만 포함되어야 한다. 연구작업에 저자가 들인 시간에 대한 기관의 일반적인 지원은 작업에 대한 직접적인 전반적 연구비 지원과 구별되어야 한다. 연구비를 받았다는 기술의 적절한 예는 다음과 같다: "이 연구는 ABC에 의해 연구비 지원을 받았고, XYZ의 지원에 의해 F 박사는 연구 작업에 자신의 시간을 쏟을 수 있었다."

초록은 많은 디지털 데이터베이스에서 색인되어 있는 논문에서 유일한 핵심 요소이고,

초록만 읽는 독자들도 많은 만큼 저자는 초록이 논문을 정확하게 반영하도록 작성하는 데 주의를 기울여야 한다. 그러나 유감스럽게도 많은 초록이 본문을 충실하게 반영하지 못하는 것이 사실이다. 저자와 편집인은 심사 과정과 수정 과정에서 초록과 본문 간에 내용이 서로 일치하는지 주의를 기울여야 한다. 구조화된 초록 형식은 학술지에 따라 다르고, 일부 학술지는 하나 이상의 형식을 요구하기도 하므로 저자는 투고하는 학술지의 양식을 따라서 충실하게 초록을 작성하여야 한다. ICMJE는 초록 말미에 임상시험 등록번호를 기재할 것을 권장한다. 또한 ICMJE는 등록번호가 있는 임상시험에 대해서는 보고하고 있는 임상시험이나 원고에서 언급하고 있는 다른 임상시험의 약어를 처음으로 사용할 때 등록번호를 기술할 것을 권장한다. 자료가 공공 저장소에 저장되어 있고 이차 분석에 사용될 수 있는 경우에는 저자는 초록 말미에 항구적이고 고유한 자료 식별자, 번호 및 저장소 이름을 기술해야 한다.

c. 서론(Introduction)

연구의 배경(논문에서 제기하는 학술적인 문제의 성격과 중요성)을 기술한다. 특정한 연구 목적이나 목표, 또는 실험이나 관찰에 의해 검증하고자 하는 가설을 기술한다. 서론에는 꼭 필요한 참고문헌만 인용하고, 연구에서 나온 결과 또는 결론은 기술하지 않는다.

d. 방법(Methods)

방법 부분을 기술하는 원칙은 연구에서 사용된 특정한 방법을 선택한 이유와 과정을 명확하게 기술해야 한다는 것이다. 방법 부분은 자료에 접근할 있는 다른 연구자가 동일한 결과를 재현할 수 있을 정도로 상세하게 기술하는 것을 목표로 해야 한다. 일반적으로 연구 계획이나 연구계획서가 작성될 시점에서의 정보만을 기술하고, 연구를 진행하면서 얻어진 모든 정보는 결과 부분에 기술한다. 연구 수행을 보조하기 위한 계약(예: 자료수집과 관리 등)을 맺거나 보수를 지불한 기관이 있으면 상세하게 기술하여야 한다.

방법 부분에는 연구가 독립적인 지방, 지역 또는 국가 규모의 심의 기구(예: 윤리위원회, 기관심의위원회)에 의해 승인되었음을 기술해야 한다. 연구가 헬싱키 선언을 준수하면서 진행되었는지 의심스러우면 저자는 연구 방법의 합리적 근거를 설명하고, 지방, 지역 또는 국가 규모의 심의 기구가 연구의 의심스런 부분에 대해 명시적으로 승인했음을 제시해야 한다(II.E 항 참조). 연구를 수행하기 위해 AI 기술을 사용한 경우, 저자는 '방법'에서 사용한 상세 내역을 자세히 기술해야 하는데 이는 저자가 사용한 접근법을 재현할 수 있게 하기 위함이다. 그 내역에는 어떤 AI 도구를 사용했는지, 그 버전 및 할 수 있으면 어떤 프롬프트로 질문을 했는지 등을 포함한다.

i. 연구 대상의 선택 및 서술

관찰이나 연구 대상(대조군을 포함한 건강한 개체 또는 환자)의 선택 또는 배제기준을 포함한 선정방법과 대상군의 특성을 명확히 기술한다. 연구 설계 단계에선 나이, 성별, 인종 등의 변수가 적절한지가 항상 불분명하기 때문에 저자들은 대표성을 가진 대상이 연구에 포함될 수 있도록 노력해야 하고, 최소한 연구 대상에 대한 정보 및 기타 적절한 인구통계학적 변수를 제시해야 한다. 저자는 연구 샘플이 더 큰 규모의 관심 모집단에 대해 얼마나 대표성이 있는지에 대해 의견을 달아 놓도록 한다.

성별을 기술할 때에 생물학적 요인을 나타내는 sex와 정체성, 정신사회학적 또는 문화적 요인을 나타내는 gender라는 용어를 정확히 구분하여 사용한다. 부적절한 경우가 아니라면 연구 대상자의 sex 및/또는 gender와 동물 또는 세포의 sex를 기술하고, sex와 gender를 구분하는 방법을 정의한다. 만약 연구 대상이 배타적인 집단(예: 한 가지 성으로만 구성된 경우)만 포함하고 있을 때는 전립선암처럼 명백한 경우가 아니면 그 사유에 대한 근거를 밝혀야 한다. 민족 또는 인종을 구분한 방법을 정의하고 그 타당성을 밝혀야 한다. 인종 또는 민족 정보가 수집되지 않은 경우, 왜 수집되지 않았는지 설명한다. 인종 및 민족성은 생물학적 구성 요소가 아닌 사회적이며, 저자는 그 맥락에서 인종 및 민족성과 관련된 결과를 해석해야 한다. 저자는 독립적이고 정확하고 정중한 언어를 사용하여 연구 대상자의 특성을 서술하고, 연구 대상자에게 피해를 줄 수 있는 용어의 사용을 삼가야 한다.

ii. 기술 정보(Technical Information)

연구의 주요 목적과 이차 목적을 특정한다. 이들은 대개 일차 및 이차 결과로 확인된다. 다른 연구자들도 재현할 수 있을 정도로 방법, 기자재(괄호 안에 제조사 및 주소를 기술) 및 과정을 상세하게 기술한다. 통계검정 방법을 포함하여 기존에 확립된 방법에 대해선 참고문헌을 제시한다. 통계검정 방법은 이전에 발표된 방법이라도 잘 알려져 있지 않은 경우에는 간단한 설명과 함께 참고문헌을 제시하고, 새롭게나 실질적으로 변형된 방법인 경우 그 방법을 사용한 근거를 제시하고 제한점을 고찰한다. 사용된 약제와 화학물질은 일반명(generic name), 용량, 투여방법을 포함하여 정확하게 기술한다. 적절한 학명과 유전체명을 사용한다.

iii. 통계

연구 내용을 이해할 만한 독자가 연구 자료를 접했을 때 연구의 적절성을 판별하고 논문에 나타난 결과를 확인할 수 있을 정도로 통계검정 방법을 자세하게 기술하여야 한다. 가능하면 연구 소견을 정량화하고, 측정 오차 또는 불확실성의 정도(예: 신뢰구간 등)를 표시하는 지표를 같이 제시한다. 연구 결과의 효과와 추정치의 정밀성과 관련한 중요한 정보는 제시하지 않고 단순히 통계학적 가설검정만을 위한 P 값에만 의존하는 일은 피해야 한다. 연구계획과 통계검정에 대한 참고문헌은 가능하면 표준적인 방법인 것이어야 한다. 통계용어, 약어, 기호를 설명하고, 통계검정에 사용한 프로그램명과 판본을 기술한다.

e. 결과(Results)

연구 결과는 본문, 표, 그림에 중요한 주요 결과를 먼저 기술한 다음, 논리적인 순서에 따라 기술한다. 표나 그림의 내용을 전부 본문에 반복하여 기술하지 말고, 중요한 관찰 소견만을 강조하거나 요약한다. '방법' 부분에서 서술한 모든 일차 및 이차 결과를 기술한다. 보충 자료나 상세한 기술 정보는 부록(appendix)에 기술하거나, 학술지 온라인 판에만 게재함으로써 본문의 흐름을 방해하지 않고 쉽게 읽을 수 있도록 한다.

측정된 자료는 절대치로부터 도출된 값(예: 퍼센트)뿐만 아니라 절대치를 같이 기술한다. 표와 그림은 논문에서 쟁점이 되는 부분을 설명하고 뒷받침할 자료를 제시하는 데 필요한 것으로 한정한다. 항목(entry)이 많은 경우에는 표 대신 그래프로 작성하고, 같은 자료를 표와 그래프로 중복하여 제시하지 않는다. "무작위(random)", "정상(normal)", "유의한(significant)", "상관성(correlations)", "표본(sample)" 등과 같은 전문 통계용어를 비전문적으로 부적절하게 사용하지 않는다.

나이와 성별 같은 인구통계학적 변수는 계층 별로 자료가 축적되어 여러 연구 간에 좋은 자료로 활용되기 때문에 변수 별로 제시하는 것이 일반적이며, 만약 변수 별로 층화시켜 제시할 필요가 없는 경우에는 그 사유를 설명해야 한다.

f. 고찰(Discussion)

고찰은 주요 연구 결과를 간략히 요약하고, 이들 결과에 대한 해석 또는 가능한 기제를 논의하는 것으로 시작하는 것이 좋다. 연구의 참신성과 중요성, 그리고 그로부터 얻은 결론 등을 가장 유용한 근거에 입각하여 강조한다. 연구의 한계를 설명하고, 연구 결과가 향후 연구와 임상 진료 또는 정책에 미치는 의의를 고찰한다. 적절한 문맥에서 sex와 gender와 같은 변수가 연구 결과에 미치는 영향 또는 관련성과 자료의 제한점을 고찰한다. 서론이나 결과 부분 등 원고의 다른 부분에 기술한 상세한 자료나 기타 정보를 반복하여 서술하지 않는다.

결론을 연구 목표와 연관시키되 검증되지 않은 가설을 기초로 서술하지 말아야 하고, 뒷받침할 자료가 없는 결론은 피한다. 특히 임상적 의의와 통계학적 의의를 구분하여 기술하고, 연구 내용이 경제적인 문제와 관련한 자료와 분석을 다루고 있지 않는 한, 경제적으로 또는 비용 면에서 유리하다는 등의 서술은 피해야 한다. 선취권을 주장하는 문장을 피하고, 완료되지 않은 연구를 암시하는 듯한 서술은 하지 말아야 한다. 근거가 있으면 새로운 가설이나 이론을 주장하되 가설임을 분명히 밝혀야 한다.

g. 참고문헌(References)

i. 일반적인 고려사항

저자들은 가능한 한 원저 연구의 출처가 되는 참고문헌을 제시해야 한다. 가능한 한 초록보다는 출판된 논문들에 대한 참조가 이루어져야 한다. 참고문헌은 저자, 편집인, 전문가 심사자들의 사익 추구를 위해 이용되어서는 안 된다. 저자들은 약탈적 또는 가짜 학술지에 게재된 논문을 인용해서는 안 된다. 프리프린트가 인용될 때는 그 참고 문헌이 프리프린트임을 분명히 표시해야 한다(섹션 III.D.3 참조). 종설이 항상 원저의 내용을 정확하게 전달하는 것은 아니기 때문에 종설에 인용된 참고문헌은 독자에게 원저 문헌으로 안내하는 효과적인 수단이 될 수 있다. 한편 해당 주제에 대하여 너무 많은 문헌을 열거하면 인쇄본의 공간을 과다하게 차지하게 된다. 핵심이 되는 최소한의 문헌으로도 방대한 양의 문헌만큼 참고문헌으로서 역할을 할 수 있다. 더 필요한 참고문헌이 있으면 출판된 논문의 온라인 판에 추가할 수 있고, 온라인 상에서 효과적으로 문헌검색을 할 수 있기 때문이다.

게재가 승인되었으나 아직 출판되지 않은 논문을 인용하는 경우 “인쇄 중(in press)” 또는 “근간(近刊, forthcoming)”으로 기술한다. 투고하였으나 아직 게재 여부가 결정되지 않은 원고를 인용할 경우에는 서면동의를 얻어 본문에 “미발표 자료(unpublished observations)”로 기술한다. 출판된 논문은 사용된 데이터 세트의 고유하고 영구적인 식별자를 인용해야 한다. 필수적인 핵심정보가 아니면 공개된 출처에서 얻을 수 없는 자료를 개인 통신(personal communication)으로 인용하는 것을 삼가야 한다. 꼭 필요한 경우에는 본문에서 정보 제공자의 이름과 제공 일자를 괄호 안에 기재하여 인용한다. 과학논문의 형식으로 작성된 자료인 경우는 저자의 서면동의를 받고 자료의 정확성 또는 정보원의 신뢰성을 확인하여야 한다. 이미 생성물을 주요 소스로서 참고 문헌에 넣는 것은 허용되지 않는다.

모든 학술지는 아니지만 일부 학술지는 인용된 참고문헌이 정확하게 기재되었는지 점검한다. 가끔 출판된 논문에서 참고문헌 서지사항의 오류가 발견되기도 하는데 이러한 오류를 줄이기 위하여 저자는 인용된 학술지의 인쇄본이나 PubMed 같은 전자 서지정보 자료를 이용하여 인용된 참고문헌의 정보를 반드시 확인하여야 한다. 특히 저자는 취소된 논문이 인용되지 않았는지 확인할 책임이 있으며, 문맥 속에서 언급하는 것 외에는 취소된 논문을 정식으로 인용하면 안 된다. MEDLINE에 색인되는 학술지에 발표된 논문의 취소에 대하여 ICMJE는 PubMed가 취소된 논문에 대한 권위 있는 정보를 갖고 있다고 생각한다. MEDLINE에서 취소된 논문은 PubMed에서 “Retracted publication [pt]”로 찾을 수 있는데([www.ncbi.nlm.nih.gov/pubmed/?term=retracted+publication+\[pt\]](http://www.ncbi.nlm.nih.gov/pubmed/?term=retracted+publication+[pt])) 각괄호 안의 “pt”는 출판 형태를 의미하며, PubMed의 취소된 출판물 명단으로 이동시켜 준다.

참고문헌은 본문에서 처음 인용된 순서대로 번호를 붙인다. 본문, 표 및 그림에서 인용된 참고문헌은 괄호 안에 아라비아 숫자로 기술한다.

표와 그림에서만 인용된 참고문헌은 특정한 표 또는 그림이 본문에서 인용된 순서에 따라 번호를 붙인다. 인용된 문헌의 학술지명은 MEDLINE에서 사용하는 학술지명 형식(<http://www.ncbi.nlm.nih.gov/nlmcatalog/journals>)에 따라 학술지 약어명으로 기술한다. 그러나 본문 내 참고문헌의 인용방식은 학술지에 따라 괄호 안에 참고문헌의 인터넷 링크(electronic reference)를 기술하기도 하고, 본문 뒤에 참고문헌 번호를 기술하기도

하기 때문에 저자들은 투고하고자 하는 학술지의 투고규정을 참조해야 한다.

ii. 형태와 형식(Style and format)

참고문헌의 기재양식은 미국 국립의학도서관의 International Committee of Medical Journal Editors(ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References(http://www.nlm.nih.gov/bsd/uniform_requirements.html)를 따르며, 미국 국립의학도서관의 Citing Medicine 2판(<http://www.ncbi.nlm.nih.gov/books/NBK7256/>)에 상세하게 설명되어 있다. 이들 자료는 새로 개발되는 매체를 통해 정기적으로 갱신되고 있으며, 현재 인쇄물뿐만 아니라 시청각 매체, CD-ROM, DVD, 디스크, 인터넷 자료 등이 포함된다.

h. 표(Tables)

표는 본문의 내용을 집약적으로 발췌하여 효과적으로 보여주는 것으로 필요한 정보를 더 상세하고 정확하게 나타내기도 하며, 본문보다 표에 자료를 정리함으로써 본문의 길이를 줄이는 효과가 있다. 표는 특정 학술지의 투고규정에 따라 작성하되 오류를 피하기 위하여 학술지 투고 사이트에서 제공하는 편집기에 표 작성 프로그램이 있다면 그것을 이용하는 것이 가장 좋다.

본문에서 인용되는 순서대로 표에 번호를 붙이고 각각에 제목을 붙인다. 표의 제목은 짧게 작성하되 제목만 보고도 본문을 참조할 필요 없이 표의 내용을 이해할 수 있을 정도의 정보를 담고 있어야 한다. 제출된 모든 표는 본문에서 인용되어야 한다.

행(column)마다 짧거나 약어로 된 표제(heading)를 만든다. 표제에서 제시하기 힘든 설명문은 표 밑에 각주를 만들어 기술한다. 표에서 사용된 모든 비공식 약어는 모두 각주에서 약어해설을 해야 하며, 표 내용에 대한 설명이 더 필요한 경우 부호를 사용하여 각주에 설명을 추가한다. 부호는 학술지에 따라 알파벳 또는 *, †, ‡, § 같은 기호를 사용할 수 있기 때문에 저자들은 학술지 투고규정을 참조하여야 한다. 평균의 표준편차와 표준오차와 같은 통계학적 척도를 구체적으로 밝힌다.

다른 저자의 출판 또는 미출판 저작물의 자료를 이용할 때에는 저작권자로부터 사용 허가를 받아 원전의 출처를 명시해야 한다.

인쇄본으로 출판하기에 용량이 너무 큰 백업 자료를 담은 추가적인 표는 학술지의 온라인 판으로 출판하는 것이 적합하며, 기록보관소에 자료의 보관을 위탁하거나, 요청하는 독자에게 저자가 직접 제공할 수도 있다. 가용한 추가 자료가 있다는 사실과 자료를 얻을 수 있는 방법을 본문에 적절하게 기술하여야 한다. 저자는 원고를 투고할 때 이러한 추가 자료를 함께 제출하여 전문가 심사자가 열람할 수 있게 해 주어야 한다.

i. 그림(Illustrations/Figures)

원고에 포함된 그림의 디지털 영상은 인쇄본에 적합한 형태로 제출되어야 한다. 대부분의 논문 투고 시스템은 영상의 질에 관한 자세한 안내를 하고 있으며, 원고가 투고되면 영상 자료를 점검한다. 인쇄물로 투고하는 경우 전문적으로 작도 또는 촬영한 것이거나 사진 품질의 디지털 인쇄물이어야 한다.

병리조직 표본이나 현미경 사진뿐만 아니라 영상의학 영상이나 기타 임상 및 진단 영상자료 등은 고해상도의 영상 파일로 제출해야 한다. 전후 비교(before-and-after) 영상은 동일한 강도, 방향 및 빛의 색깔로 촬영되어야 한다. 블로팅 사진은 많은 과학 논문에서 일차적인 증거로 이용되기 때문에 편집인들은 학술지 웹사이트에 블로팅 원본 파일을 별도로 제출하도록 요구하기도 한다.

일부 학술지는 제출된 그림을 새로 그리기도 하지만 대부분의 학술지는 원본 그대로 인쇄한다. 그림에 추가되는 글자, 숫자, 기호는 선명하고 일정해야 하며, 출판 과정에서 그림을 축소하더라도 글자를 읽을 수 있을 만큼 충분한 크기가 되어야 한다. 그림은 슬라이드 발표에 그대로 이용되는 경우가 많아서 가능하면 그 자체로 독해가 가능한 수준으로 제작되어야 한다. 그림의 제목과 설명문은 그림 자체와 구별되는 레전드(legend)에 속하는 부분이다.

현미경사진은 사진 안에 축척을 표시한다. 사진 안에 기호, 화살표, 또는 글자 등이 사용되었을 때는 식별이 쉽도록 사진의 배경과 대조를 이루어야 한다. 그림에 삽입된 축척을 설명하고, 사용된 염색법을 명확히 밝힌다.

그림은 본문에서 인용된 순서대로 번호를 붙인다. 이전에 출판된 그림인 경우에는 저작권자로부터 그림 사용

에 대한 서면 허가를 받고 원전의 출처를 밝혀야 한다. 사용 허가는 공공문서를 제외한 저자나 발행인과 무관하게 요구되는 부분이다.

원고에서 그림의 레전드(제목과 설명문)는 본문과 별도의 페이지에 각 그림에 상응하는 번호를 기술한다. 그림에서 특정 부위를 표시하기 위해 부호, 화살표, 숫자 또는 글자가 사용된 경우에는 각각을 레전드에 명확히 밝혀야 한다.

j. 측정단위

길이, 높이, 무게 및 부피의 측정치는 미터법 단위(meter, kilogram, liter) 또는 그의 십배수 단위로 기록한다.

학술지가 별도로 규정하지 않는 한, 온도는 섭씨로, 혈압은 mm Hg로 기록한다. 혈액학, 임상화학 또는 기타 측정치의 단위는 학술지에 따라 다를 수 있다. 저자는 투고하고자 하는 학술지의 단위에 대한 투고규정을 참조하여야 하고, 필요하면 지역별 특정 단위체계와 국제단위체계(International System of Units, 이하 SI로 약함)의 두 가지 방식으로 모두 기술한다.

그러나 아직 SI 단위가 전세계적으로 통용되는 것은 아니기 때문에 일부 학술지들은 저자에게 SI 단위 이외의 단위나 기타 다른 단위를 추가로 기술할 것을 요구하기도 한다. 약물농도는 SI 단위나 질량 단위로 기술하지만 다른 적절한 단위가 필요할 때는 괄호 안에 단위를 병기해야 한다.

k. 약어와 부호

약어는 표준약어만 사용하여야 한다. 표준화되지 않은 약어를 사용하면 독자가 혼동하기 쉽다. 논문 제목에는 약어를 사용하지 않는다. 표준 측정단위의 약자를 제외하고 약어는 처음에 나타날 때 먼저 약어의 철자를 풀어 쓰고, 괄호 안에 약어를 기술해야 한다.

B. 투고

원고는 투고편지(cover letter)와 함께 또는 완전한 학술지 투고 형식에 맞추어 투고되어야 하며, 다음과 같은 정보가 포함되어야 한다. 중복출판으로 간주될 소지가 있는 동일하거나 매우 유사한 연구의 논문 투고 또는 출판 여부에 관한 내용. 해당사항이 있으면 새로 투고하는 논문 원고에 이들 문헌을 특정하여 인용하여야 하고, 문헌 사본을 함께 제출하여 편집인이 판단하는 데 협조하여야 한다(III.D.2 항 참조).

논문 원고나 저자의 공시 양식에 이해충돌을 야기할 수 있는 재정적 또는 여타 관계와 활동에 관한 정보가 들어있지 않은 경우에는 별도의 고지문을 추가한다(II.B항 참조).

저자됨과 관련한 내용. 공저자 모두에게 기여 내용을 요구하지 않는 학술지의 경우에는 투고편지에 다음과 같은 내용이 포함될 것을 요구하기도 한다: 모든 공저자가 원고를 검토하고 승인했다는 점, 이 권고안의 앞 부분에서 서술한 저자됨의 요건을 충족한다는 점, 연구진실성을 담보하는 별도의 양식을 제출하지 않는 경우에는 모든 공저자들이 투고하는 원고의 연구진실성에 동의한다는 점 등이 포함된다(II.A항 참조).

책임저자 연락처. 원고 내에 저자의 연락처가 기술되지 않은 경우 원고의 수정 및 최종 승인을 위해 저자들과 연락을 취할 수 있는 책임저자 정보가 필요하다.

연구 수행과 관련한 우려가 제기되거나(예를 들어 연구기관이나 심의기구 등을 통하여), 시정 조치가 권고된 경우에는 편지나 정해진 양식을 통해 편집인에 이 사실을 알려야 한다. 편지 또는 양식에는 원고가 목적하는 특정 학술지의 논문 형식이나 형태와 같은 편집인에게 유용한 추가적인 정보가 담겨야 한다. 만약 투고하는 원고가 이전에 다른 학술지에 투고된 적이 있는 경우에는 해당 학술지의 편집인, 전문가 심사자의 심사평과 저자의 답변을 함께 제출하면 도움이 된다. 편집인은 저자에게 이런 자료 제출을 요청함으로써 심사과정을 신속히 진행할 수 있고, 투명성과 정보의 공유를 제고할 수 있다.

많은 학술지들은 저자들이 학술지가 요구하는 모든 구성요건을 충족시키는 데 도움이 되도록 투고 전 원고점검표를 제공한다. 일부 학술지는 CONSORT와 같은 특정한 연구인 경우에는 해당 연구에 특정한 원고점검표를 요구하기도 한다. 저자들은 학술지가 이러한 원고점검표를 요구하는지 확인해야 하고, 원고를 투고할 때 함께 제출해야 한다.

그림을 포함하여 이미 출판된 저작물을 이용하거나, 신원이 드러날 수 있는 보고를 해야 하거나, 연구에 기여한 인물을 언급해야 하는 경우에는 상응하는 사용 허가를 얻어 원고와 함께 제출해야 한다.

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