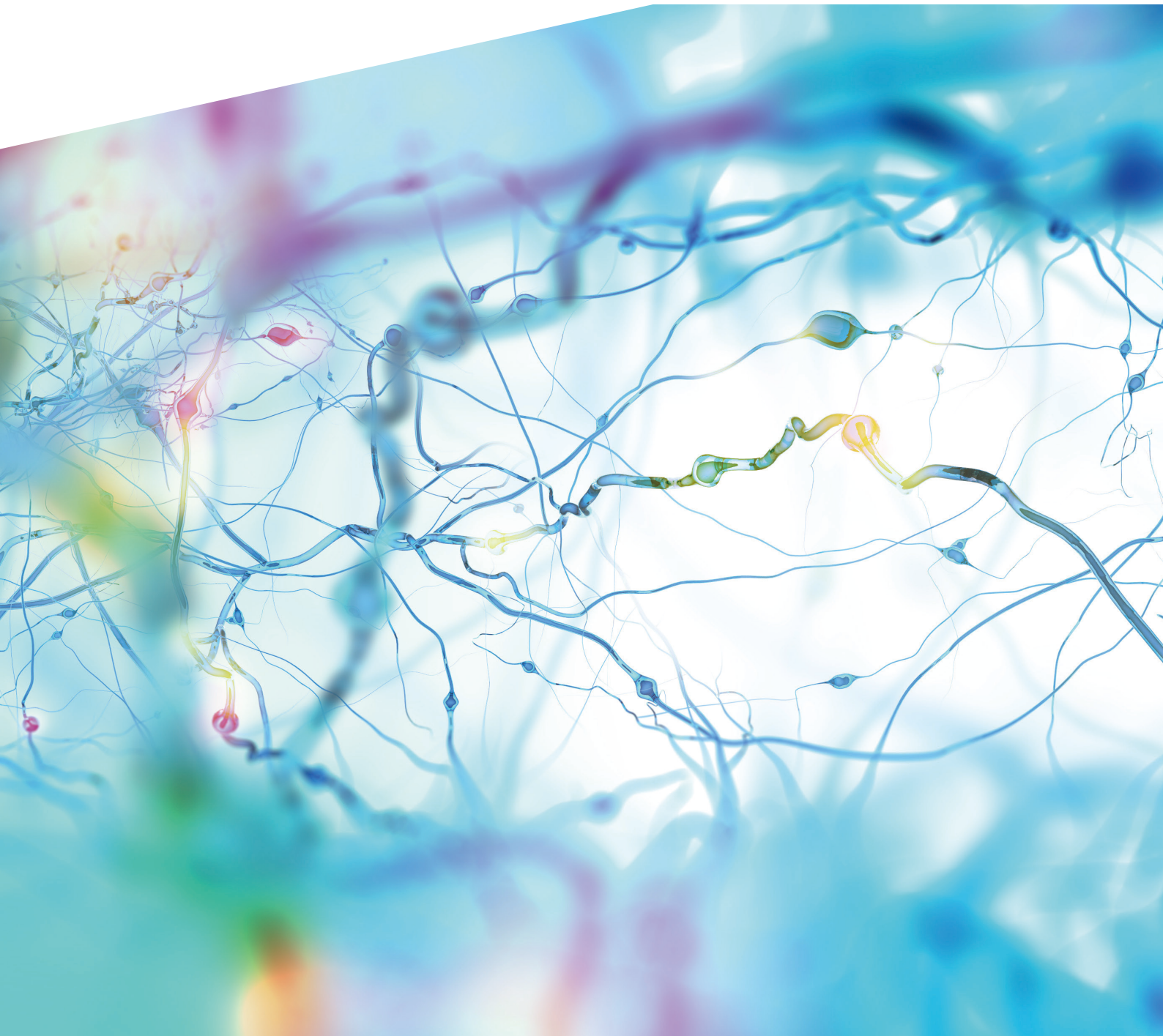
eISSN 2234-2591

Ewha Medical Journal

Vol. 48, No. 2, 2025



Ewha Medical Journal

eISSN 2234-2591

Vol. 48, No. 2, April 2025

Aims & scope

Aims

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.

Copyright & Open access policy

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Publisher Ewha Womans University College of Medicine
Editor-in-Chief Sun Huh

Published by Ewha Womans University College of Medicine and Ewha Medical Research Institute
25, Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea
Tel: +82-2-6986-6305, Fax: +82-2-6986-7026, E-mail: editor@e-emj.org

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Printing correspondence by M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930, Fax: +82-2-6966-4945, E-mail: support@m2-pi.com

· The subscription is free. For inquiry, lease contact the editorial office (Tel: +82-2-6986-6305, E-mail: editor@e-emj.org). All the contents are also available at the EMJ website (https://www.e-emj.org).

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eISSN 2234-2591

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eISSN 2234-2591

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Principles of Best Practice and Transparency in Scholarly Publishing ver. 4: a Korean translation
The Committee on Publication Ethics, DOAJ, the Open Access Scholarly Publishing Association, the World Association of Medical Editors

eISSN: 2234-2591
Open Access

Editorial

Ewha Med J 2025;48(2):e16
https://doi.org/10.12771/emj.2025.00395

Ewha Medical Journal

Recent advances in pulmonary tuberculosis, the application of deep learning to medical topics, and highlights from this issue of *Ewha Medical Journal*

Hae-Sun Chung*

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As the spring semester of 2025 begins, Korea finds itself navigating an unprecedented political crisis following the impeachment and removal of the President. Amid this national upheaval, the conflict between the government and the medical association remains unresolved. Although most medical students have formally registered for classes, academic activities have not fully returned to normal across many institutions. Despite this uncertain environment, *Ewha Medical Journal* remains committed to publishing high-quality, clinically and educationally significant research that advances medical knowledge.

Despite these challenges, we are proud to present the April 2025 issue, featuring 21 carefully selected articles: 6 review articles, 7 original research papers, and a diverse collection of other submissions. A special highlight of this issue is a series of 4 narrative review articles on recent advances in pulmonary tuberculosis (TB), offering updated insights into this crucial and evolving area of infectious disease research. Additionally, 5 original articles focus on the application of deep learning in various medical contexts, reflecting the increasing impact of artificial intelligence on healthcare. We are also pleased to include an article reporting results from a trauma survey among North Korean defectors, which we anticipate will garner international interest due to its relevance to human rights and public health. Furthermore, this issue features a health statistics paper from Statistics Korea analyzing dementia-related death statistics—a resource expected to be widely referenced by researchers, clinicians, and policymakers.

Special topics on pulmonary tuberculosis

This April issue features a special topic section on pulmonary TB, comprising 4 comprehensive narrative reviews addressing both TB and nontuberculous mycobacterial diseases from multiple clinical and policy-oriented perspectives. Drs. Jinsoo Min, Bruno B. Andrade, Ju Sang Kim, and Yoolwon Jeong provide an extensive overview of recent innovations in TB treatment, highlighting precision medicine integration, novel and repurposed drug development, and cohort-based research to enhance therapeutic efficacy and inform policy [1]. They emphasize tailoring treatments to individual patient profiles and stages of disease progression. Dr. Jeong Uk Lim examines how pulmonary TB complicates lung cancer screening in TB-endemic areas, particularly affecting low-dose computed tomography interpretation [2]. His review underscores the necessity of improved diagnostic accuracy through artificial intelligence and biomarkers to minimize false positives and avoid unnecessary procedures. Dr. Joon Young Choi explores the increasing burden of TB-associated chronic obstructive pulmonary disease, detailing its distinct pathophysiology—characterized by persistent inflammation and structural lung damage—and reviewing evidence-based treatment options [3]. Finally, Dr. Chiwook Chung discusses current and emerging treatment strategies for *Mycobacterium avium* complex pulmonary disease, outlining existing regimen limitations, the role of antimicrobial susceptibility testing, and potential adjunctive therapies and surgical interventions [4]. Together, these reviews offer valuable

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Received: March 4, 2025 Revised: April 8, 2025 Accepted: April 8, 2025

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clinical and research insights into the complex landscape of mycobacterial diseases.

Two reviews and 2 original articles

This issue features 2 review articles addressing interdisciplinary healthcare topics. Dr. Dong-Ju Choi reviews telemedicine's potential in heart failure care, highlighting benefits such as improved monitoring, reduced hospitalizations, and enhanced outcomes, while addressing challenges like digital literacy and healthcare system integration [5]. Drs. Min-Young Kim and Eun-Kyoung Pang examine associations between periodontitis and systemic diseases—including diabetes, cardiovascular diseases, and neurodegenerative conditions—emphasizing oral health's role in systemic inflammation and advocating for collaborative care approaches [6].

Two original articles provide unique public health insights. Drs. So Hee Lee, Won Woong Lee, Haewoo Lee, Jin Yong Jun, and Jin-Won Noh analyze trauma and human rights violations among North Korean defectors, reporting high rates of post-traumatic stress disorder and depression and calling for trauma-informed support systems [7]. Drs. Sooji Hong, Bong-Kwang Jung, and Hyun-Jong Yang investigate immunogenic proteins in *Anisakis* larvae molting membranes that may trigger allergic responses in eosinophilic patients, suggesting a novel allergen source requiring further investigation [8].

Deep learning: medical students leading innovation

This issue features 5 original research articles applying deep learning to diverse medical topics, including positron emission tomography-based organ segmentation, SHAP (Shapley Additive Explanations)-enhanced appendix cancer prediction, data imbalance modeling in diabetes, cardiac computed tomography segmentation, and blood glucose prediction using patient-provider interaction modeling. Notably, 4 of these studies were led and authored by undergraduate medical students—an exceptional achievement during widespread disruptions in medical education. These accomplishments were facilitated by the Ewha Green Ribbon Project, initiated under former Dean Eunhee Ha to maintain academic continuity and nurture future scholars. A core component of this project, the artificial intelligence and deep learning education track, was meticulously designed and implemented by Professor So Hyun Ahn. Her dedicated guidance, commitment, and generosity provided students with unique hands-on learning and research experiences in one of the most dynamic fields in medicine today. The publication of these student-led studies is a source of immense pride within our institution, reflecting scholarly achievement and innovation that commands recognition. These results affirm Ewha Womans University College of Medicine's leadership in medical education and its standing as a model of academic excellence nationally and internationally.

Health statistics: national trends in dementia-related mortality

Health statistics articles in *Ewha Medical Journal* primarily focus on presenting and analyzing quantitative data related to health, healthcare, and public health, aiming to deliver meaningful, data-driven insights into public health issues. In this issue, Mr. Seokmin Lee from Statistics Korea presents a comprehensive analysis of dementia-related deaths in Korea between 2013 and 2023 [9]. The study highlights a marked increase in both the number and crude rate of dementia-related deaths, especially among women and the elderly, with Alzheimer's disease identified as the leading cause. Although age-standardized mortality has slightly decreased, the overall dementia burden continues to grow. As noted in the editorial introduction, this paper provides a robust empirical foundation that is expected to be widely cited by healthcare professionals, researchers, and policymakers for both planning and evaluation purposes. Its clarity and depth make it a valuable resource for addressing Korea's dementia care challenges. We greatly value this contribution and look forward to further collaborations with Statistics Korea to ensure vital national health data are disseminated through rigorous academic channels.

Guideline: Korean translation of principles of best practice and transparency

This issue includes the Korean translation of the Principles of Best Practice and Transparency in Scholarly Publishing (ver. 4), a guideline jointly developed by the Committee on Publication Ethics, the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishing Association, and the World Association of Medical Editors [10]. Released on September 15, 2022, this document outlines essential principles for ethical and transparent scholarly publishing, covering topics such as editorial independence, peer review standards, conflicts of interest, and open access policies. The Korean translation, provided by the Korean Council of Science Editors and Infolumi, aims to make these international standards more accessible to Korean editors and publishers. By offering this translation, *Ewha Medical Journal* supports the broader dissemination of global best practices and contributes to enhancing ethical awareness and transparency within the Kore-

an academic publishing community.

Voices and perspectives

This issue marks a significant moment in 2025 with leadership transitions at Ewha Womans University. We congratulate Professor Hyang-Sook Lee on her inauguration as the President of Ewha Womans University, who envisions leading the university into an era of inclusive innovation for a sustainable future. We also welcome Professor Duk-Hee Kang as the 28th Dean of Ewha Womans University College of Medicine, who aims to strengthen global healthcare leadership through innovative research and education. We extend our sincere appreciation to Professor Eunhee Ha, who concluded her term as Dean in January 2025, for her exceptional dedication and service. Their messages are featured in this issue with deep respect.

This issue also includes timely and significant correspondence addressing the sharp decline in Korea's medical research output in 2024 following the mass resignation of resident physicians. The authors analyze publication data across specialties and argue that the prolonged disruption has severely impacted both clinical and academic systems. Given the central role residents play in university hospitals, these findings underscore the structural vulnerability of Korea's research ecosystem. This correspondence offers critical insights into one of the most urgent issues facing the Korean medical community today.

The final article introduced in this editorial was authored by Editor-in-Chief Sun Huh, reporting on *Ewha Medical Journal*'s current status regarding international indexing efforts. The journal passed the scientific evaluation by PubMed Central (PMC) and was successfully included in the DOAJ, but was not accepted by Scopus. These outcomes reflect the dedication of our editorial team, and we reaffirm our commitment to the journal's continued growth.

In these turbulent times, we remain dedicated to publishing articles that uphold scientific rigor and social relevance. Building on the achievements of this April issue, *Ewha Medical Journal* will continue to identify timely and meaningful special topics that resonate with clinicians and researchers. We aim to foster broader collaborations with institutions such as Statistics Korea to transform valuable public data into publishable research. As a medical school-based journal, we will also strengthen educational initiatives that empower students to engage actively in research and scholarly writing. With the journal recently passing the scientific evaluation for PMC, we anticipate formal indexing soon. This milestone is expected to expand our global visibility and attract a more diverse range of submissions from around the world. We sincerely thank all authors, reviewers, and readers for their continued support and look forward to working together to advance academic excellence, global engagement, and meaningful contributions to the medical and scientific communities.

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Authors' contributions

All the work was done by Hae-Sun Chung.

Conflict of interest

Hae-Sun Chung has worked as an Associate Editor of the journal since 2018. However, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. Otherwise, no other potential conflicts of interest relevant to this article were reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Editorial

Ewha Med J 2025;48(2):e18
https://doi.org/10.12771/emj.2025.00108

Ewha Medical Journal

Ewha leading the era of great transformation through inclusive innovation for a sustainable future: a presidential inaugural address

Hyang-Sook Lee*

The 18th President, Ewha Womans University, Seoul, Korea

It is an honor to stand before you today as the 18th president of Ewha Womans University (Fig. 1).

I extend a warm welcome and sincere gratitude to Chairperson Myong-sue Chang and the esteemed members of the Board of Trustees; to former presidents of Ewha—including my immediate predecessor, President Eun Mee Kim; to President Myung Kyung Lee of the Ewha Alumnae Association; and to University Chaplain Reverend Sunhee Ahn; as well as to the many distinguished guests who have honored this occasion with their presence despite their busy schedules. I also express my deepest appreciation to our faculty, staff, students, and alumnae, with whom we are building a vibrant Ewha community.

Ewha's proud history

Today, carrying forward Ewha's proud history and tradition, I stand before you to confront the challenges of a new era, establish a vision for our future, and chart a blueprint for its realization—all inspired by the remarkable achievements of our former presidents and alumnae. Founded in 1886 through the prayers and dedication of missionary Mary F. Scranton, the first principal of Ewha Haktang, our institution was established in the spirit of love and service to the Lord. I am profoundly grateful for God's grace and dedicate all glory to Him for granting me the opportunity to continue this sacred mission as the 18th president of Ewha. I sincerely thank the Ewha family for their steadfast faith and for entrusting me with this vital responsibility. I pledge to be a president who fulfills God's vision and benevolent purpose for Ewha.

Ewha's history is a testament to God's providence, and our journey has been one of faithfully serving His Word. From humble beginnings with a single student to the extraordinary accomplishment of nurturing 260,000 distinguished alumnae, Ewha's story is not merely that of an educational institution but a journey of faith that has empowered women in this country to discover their true selves and dedicate their lives to serving the world. This year is especially significant as it marks both the 100th anniversary of Ewha College's foundation in 1925 and the 90th anniversary of its relocation from Jeong-dong to Sinchon in March 1935—a move that established a new learning environment.

In 1946, sixty years after laying the cornerstone for women's education, Ewha Haktang was officially accredited as Korea's first 4-year university. Another 50 years later, in 1996, Ewha made history again by establishing the world's first engineering college for women, thus opening a new chapter in nurturing engineering talent. Throughout its history, Ewha has achieved numerous "firsts" and "bests," solidifying its reputation as a pioneer ahead of its time. Ewha's journey has always signified the first step toward a new era—a tradition that endures to this day.

Ewha's role in women's education and society innovation

Ewha's endeavors extend well beyond women's education; they have become a driving force behind the transformative changes that have shaped modern Korean society. Throughout the 20th century, Ewha was recognized not only as an institution of higher

*Corresponding email: hsl@ewha.ac.kr
Received: March 7, 2025 Revised: March 17, 2025 Accepted: March 17, 2025

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Fig. 1. Hyang-Sook Lee. The 18th president of Ewha Womans University.

learning but also as a symbol of boldness and innovation that propelled the nation's remarkable development and globalization. There was never any doubt that Ewha's path provided a righteous direction to guide Korean society into the future.

Today, amid a vast current of change driven by cutting-edge technologies, such as artificial intelligence (AI), we face fundamental questions that call for a redefinition of the role and status of universities. Simultaneously, climate-induced environmental changes, a declining school-age population, and growing political and economic instability intensify our concerns about the future direction of higher education. In the face of these internal and external challenges, it falls upon Ewha to respond wisely and proactively, leading the way in addressing current issues and actively shaping the future.

As a member and president of Ewha—an institution that has demonstrated resilience by achieving extraordinary outcomes and significant progress in times of crisis—I am confident that our collective wisdom and capabilities will enable us to overcome the challenges ahead. To this end, I wish to emphasize the spirit of "Ilsinuilsin (日新又日新)," meaning "to renew and improve oneself day by day." This guiding principle, rooted in the historical legacy of Ewha College and its leadership in women's education, is essential for fostering the academic creativity required in this era of technological transformation.

Beginning with education in the humanities, social sciences, and arts—including literature, music, and early childhood education—Ewha has consistently innovated to meet the demands of the times. Even during the challenging period following Korea's liberation, we laid strong academic foundations in diverse fields, including the natural sciences. At the heart of these advancements is Ewha's unique spirit of creating new values and pursuing reinvention, anchored in a Christian ethos of serving the world with righteous influence and discipline. Despite an uncertain future, Ewha has persistently charted a virtuous course and built a forward-looking, sustainable model for universities—a mission that defines our role as a global institution today.

Ewha's 6 visions leading the era of great transformation

Today, at this inauguration ceremony, I am proud to declare a new vision inspired by the zeitgeist: "Ewha Leading the Era of Great Transformation through Inclusive Innovation." Through creative and inclusive innovation, Ewha will establish people-centered values and spearhead change in this era of rapid technological transformation. Moreover, we will continually renew and improve ourselves to benefit society and lead our times by upholding the core values of creativity and challenge, excellence and innovation, cooperation and companionship, sustainability, and sharing and service. To instill pride among all members of our community and to elevate our capabilities and competitiveness, I will implement the following policies:

First, in research, I will create a world-class environment to bolster competitiveness through first-mover research leadership. I will cultivate an optimal setting that supports focused research and enables our faculty to achieve world-class outcomes. Additionally, I will recruit top-tier faculty by introducing flexible contracts, performance-based rewards, and securing special-purpose funds. I will work diligently to establish a virtuous cycle in which Ewha's technological innovations benefit society while further enhancing our research capacity through technology commercialization. I will also promote transdisciplinary convergence research that spans Ewha's diverse academic fields, ensuring balanced development between fundamental and applied disciplines and expanding research opportunities for the next generation of scholars.

Second, in education, I aim to establish Ewha's model for future learning, positioning us to lead the transformation of higher education in the era of AI. Advances in AI represent more than mere technological innovation; they fundamentally alter our lives and thought processes, offering new experiences and possibilities. In this era of change, Ewha is committed to nurturing global women leaders who contribute to national and human advancement, guided by an educational philosophy rooted in our founding Christian values of truth, goodness, and beauty. Building on our outstanding educational system and infrastructure, I will establish an AI-based framework that includes the "AI for All Ewha" initiative and customized AI programs for students across various ma-

jors. I will support our students in developing digital capacities—including problem-setting and problem-solving, creative thinking, innovation, as well as collaboration and communication—while enhancing their AI literacy and expertise. I will provide an educational environment and programs optimized to help our students cultivate unique talents in the AI era.

Third, regarding administrative infrastructure, I will maximize Ewha's growth potential by innovating our administrative systems and advancing campus infrastructure. I will implement an administrative framework grounded in accountability and trust by enhancing staff professionalism and introducing diligent human resources and accountability practices. Additionally, I will establish a foundation for sustainable growth by expanding the systems required for creating an optimal environment for focused research and educational excellence. In particular, I will faithfully execute the campus master plan, including the construction of the EWC, in preparation for Ewha's future.

Fourth, concerning our internal and external environments, I will make bold and strategic efforts to enhance Ewha's brand value and global standing. Drawing on the distinctive values of our time-honored history and tradition, Ewha will further solidify its position as a world-class research and education institution through academic excellence, social responsibility, and global solidarity. In doing so, I will uphold the virtues befitting a prestigious global private university and continue to expand Ewha's positive influence in the international community.

Fifth, a sustainable financial expansion system is essential for university development. For Ewha to continue growing, financial security must be a top priority. I will significantly expand our finances by securing funding through the Ewha University-Industry Collaboration Foundation, boosting fundraising by strengthening external cooperation structures, increasing educational projects, advancing fund management practices, capitalizing on Ewha's brand value, and developing profit-generating businesses.

Sixth, the Ewha University Medical Center (EUMC) is a proud pillar of Korean history alongside Ewha itself. Launched in 1887 as Po Goo Nyo Goan (普救女館), Korea's first exclusive hospital for women, the EUMC has pioneered the education of female medical professionals in Korea by producing the country's first female doctors and nurses, as well as providing medical treatment to the underprivileged. Based on this long history and tradition, Ewha, along with EUMC Mokdong, EUMC Seoul, and its College of Medicine, will create synergy through cooperation for shared growth, strengthen research and treatment capabilities by establishing an Ewha cutting-edge convergence med-healthcare cluster, and enhance the global competitiveness of the EUMC.

Ewha's 6-fold vision is illustrated in Fig. 2.

Humble request for active participation and cooperation

To pursue these goals and policies, the active participation and cooperation of all Ewha members is essential.

Dear Ewha students,

I am keenly aware of your concerns about an uncertain future. However, as you come to recognize that your reverence for the work of the Lord—the true founder of Ewha—is the genuine source of wisdom in embracing challenges, you will soon evolve into creative and enterprising global female leaders, equipped with both Christian values and intellect. I hope that you will nurture your aspirations to become true leaders who contribute to the global community as citizens of the world. I am committed to ensuring that Ewha remains a place where you can freely pursue your dreams and overcome every challenge, fostering a spirit of boundless ambition within our community.

Dear Ewha Womans University staff,

You have devoted yourselves to the growth and development of Ewha, serving as the steadfast pillars of our institution and as the primary agents of change and innovation on campus. The continued progress and advancement of Ewha depend on your effort, passion, and expertise. I kindly ask you to align with Ewha's vision and goals, as you have proudly done in the past, and I trust that you will continue collaborating in support of our mission. Please help create an inspiring and joyful workplace founded on respect, collaboration, and fairness. I, too, will commit my utmost to this shared journey.

Dear esteemed Ewha faculty members,

I express my deepest gratitude and respect for your unwavering dedication to education and research—Ewha's excellence is a direct result of your academic achievements and continuous efforts.

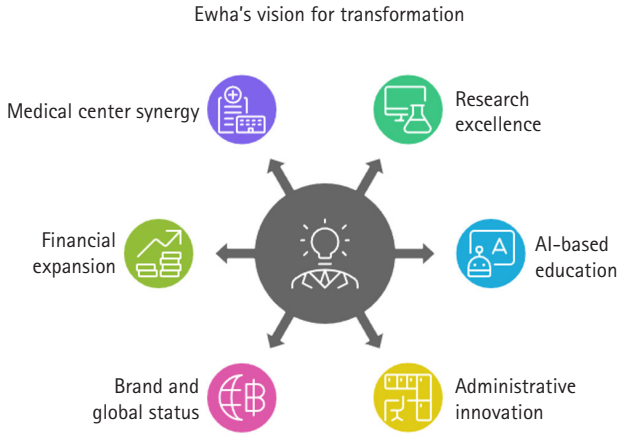

Fig. 2. Diagram of Ewha's 6-fold vision for leading the era of great transformation.

Amid a rapidly changing environment, the university requires a new vision and innovative endeavors. I will spare no effort to support those of you who remain steadfast during these challenging times, both internally and externally, so that together we may achieve the highest possible outcomes. I invite you to join us on this journey as Ewha takes a great leap forward as a prestigious global private university, embracing inclusive innovation in the face of new challenges.

Dear proud Ewha alumnae,

Ewha's reputation and tradition are built on your dedicated efforts and outstanding achievements. Our alumnae, who demonstrate leadership across all fields and embody the spirit of Ewha, are a source of immense pride and a cherished asset to our institution. Your ongoing support and encouragement have always been a strong foundation of our success. As Ewha advances toward a new leap forward, I ask for your unwavering encouragement, continued interest, and steadfast support for the development of your alma mater and the growth of current Ewha students. In return, Ewha will strive to excel—even in times of great transformation—and remain an alma mater of which you can be proud.

Dear distinguished guests and Ewha family members,

Throughout history and across cultures, universities have consistently been at the forefront of driving national competitiveness. Ewha is committed to fulfilling its role as a leading institution in this era of immense challenges and uncertainty. We will meet society's demands by nurturing creative, future-ready talent for the digital age. Through world-class research, development, and innovation—the cornerstones of national competitiveness—Ewha will serve as a powerful engine for growth. Building on 139 years of unwavering dedication to its social responsibilities, Ewha will continue to thrive as a sustainable social asset for future generations.

Character before knowledge and love before technology

Under the vision of "Ewha leading the era of great transformation through inclusive innovation," we strive to advance as a new university worthy of the 21st century. As a prestigious global private university that values individual dignity and character, Ewha is preparing for a new era of science and technology. By aligning research projects with our faculty, financial resources with the institution, and our prestige with the global community—while upholding the core values of creativity and challenge, excellence and innovation, cooperation and companionship, sustainability, and sharing and service—we aim to forge a new Ewha as we embark on a journey toward the future.

Reflecting on the sage words of President Kim Okgill, "Ewha is a house of learning that teaches character before knowledge and love before technology," I will devote my heart and sincerity to guiding Ewha's next leap forward. To this end, I maintain a diary called the "Ewha Notes," in which I document my reflections from meetings with various members of our community and their heartfelt insights about our institution. Cherishing the "Ewha Notes" as a moral compass, I pledge to do my utmost to establish Ewha as a prestigious private university renowned worldwide. From this moment on, I vow to undertake this bold journey together with all members of the Ewha community.

"Trust in the Lord with all your heart, and lean not on your own understanding. In all your ways acknowledge Him, and He will make your paths straight," Proverbs 3:5-6. As we walk with the Lord, guided by His love for Ewha and its members and humbly seeking His wisdom and understanding, He will illuminate the righteous path for our future.

Dear distinguished guests and esteemed Ewha family members, I pray that the Lord's endless grace and blessings be with you, and that His righteousness and love flow abundantly through Ewha.

Thank you.

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Authors' contributions

All work was done by Hyang-Sook Lee.

Conflict of interest

Hyang-Sook Lee has been the president of Ewha Womans University since February 1, 2025. However, she was not involved in the decision-making. No potential conflict of interest relevant to this article was reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

eISSN: 2234-2591
Open Access

Editorial

Ewha Med J 2025;48(2):e19
https://doi.org/10.12771/emj.2025.00129

Ewha Medical Journal

Ewha, where medical education for women began in Korea, is now leading global healthcare through innovative research networks and education: the inaugural address of the 28th Dean of the College of Medicine

Duk-Hee Kang*

Division of Nephrology, Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

Dear beloved students, respected faculty, and esteemed alumnae and staff who uphold Ewha's cherished traditions and values,

I am honored and privileged to greet you as the 28th Dean of Ewha Womans University College of Medicine (Fig. 1). Communicating with you in this message fills me with both joy and a profound sense of responsibility.

Ewha Womans University College of Medicine holds a unique position as Korea's pioneering institution for women's medical education. Reflecting on our history, I recall the selfless devotion of women medical missionaries who, 138 years ago, journeyed to the unfamiliar shores of Joseon, established the Bogu Yeogwan (普救女館), and dedicated themselves to education, healthcare, and missionary work. Although being the "first" is historically significant, the enduring spirit and core values upon which Ewha was founded—spreading God's love, serving those in need, and striving to create a better society through education—are even more valuable.

There are things whose value diminishes over time, such as new buildings, advanced facilities, and premium products. In contrast, cultivating exceptional medical professionals, conducting groundbreaking research that seeds future medicine, and accumulating unparalleled expertise and experience grow ever more valuable with time. These are the essential values that Ewha must continuously uphold.

Our nation's healthcare system now faces significant challenges. The once-envied medical system is now confronted with doubts about its sustainability. Numerous issues await resolution, including disruptions and temporary delays in medical education, ensuring an adequate healthcare workforce, and addressing critical gaps in essential medical care. Even amid unprecedented pressures that keep clinical professors working tirelessly around the clock in clinics and wards, the members of Ewha Womans University College of Medicine have chosen not to merely lament or complain. Instead, we have remained steadfast in our mission by sustaining diverse educational initiatives and research support for our faculty—even during the temporary suspension of formal medical education in 2024.

As the newly appointed Dean, I present the following strategic objectives to propel Ewha Womans University College of Medicine into a new era of advancement (Fig. 2):

First, we aim to build a sustainable Ewha medical education system that is resilient to challenges.

Second, we seek to enhance faculty research capabilities through tailored support and by fostering a collaborative research ecosystem.

Third, we intend to cultivate Ewha's global medical leadership by expanding and solidifying high-level international exchanges.

Fourth, we must recognize that significant progress cannot be achieved solely by the efforts of a few individuals. To nurture a collaborative Ewha medical community founded on open communication, mutual understanding, and cooperation, we aim to establish a culture of respect and appreciation among staff, re-

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Received: March 10, 2025 Revised: March 17, 2025 Accepted: March 17, 2025

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Fig. 1. Duk-Hee Kang. The 28th Dean of the College of Medicine at Ewha Womans University.

searchers, and faculty, empowering everyone to contribute confidently and with pride. Above all, we commit to sincerely listening to and acting on the valuable insights of our alumnae, whose unwavering trust and affection guide us.

Ewha Womans University College of Medicine owes its current success to each of you. Our continued growth and future achievements depend on your unwavering support. I earnestly hope that Ewha, long renowned for pioneering women's education in medicine, will truly embody the biblical call to "Arise, shine, for your light has come, and the glory of the LORD has risen upon you" (Isaiah 60:1), thereby illuminating our era.

To our beloved students, who may be facing particularly challenging times, I offer these words: our studies and research are not intended to construct ivory towers isolated from society's realities but rather to embark on a journey toward discovering the most effective ways to heal those we encounter daily. Despite temporary setbacks and delays, remain steadfast to the "grand aspirations" with which you entered Ewha and the "excellent habits" you have diligently cultivated. Together, these will serve as an unwavering shield against life's uncertainties.

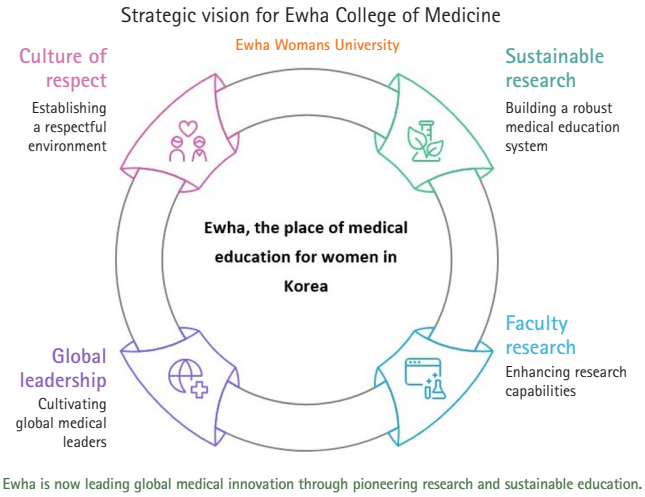

Fig. 2. Four strategic objectives to propel Ewha College of Medicine into a new era of advancement.

The doors of the Dean's office remain open at all times. I invite you to share your thoughts, encouragement, and hopes for Ewha's continued ascent.

Thank you.

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Authors' contributions

All work was done by Duk-Hee Kang.

Conflict of interest

Duk-Hee Kang has been the Dean of the College of Medicine at Ewha Womans University since February 1, 2025. However, she was not involved in the decision-making. No potential conflict of interest relevant to this article was reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

eISSN: 2234-2591
Open Access

Editorial

Ewha Med J 2025;48(2):e20
https://doi.org/10.12771/emj.2025.00045

Ewha Medical Journal

Reflections on 25 hours a day at Ewha Womans University College of Medicine from August 2021 to January 2025: a dean's farewell message

Eunhee Ha*

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Dear esteemed students, staff, alumnae, and faculty members of Ewha Womans University College of Medicine,

On August 1, 2021, when I assumed the significant responsibility as the 26th dean of the College of Medicine [1], I devoted myself as if each day provided 25 hours to advancing both Ewha Womans University College of Medicine and Ewha Medical Center. Over the past 3 years and 6 months, our college has achieved remarkable milestones in various fields amid the sweeping changes of the Fourth Industrial Revolution (Supplement 1). These accomplishments include promoting interdisciplinary research, pioneering advancements in medical education, enhancing school promotion, and expanding partnerships with external organizations as follows:

Advancement of medical education to lead the future of the College of Medicine and communicate with the world

Advancing the medical education system

We improved the quality of medical education by establishing the Ewha Medical Education Center (EMEC) [2]. We also maintained the "6-year accreditation" in medical education, underscoring the excellence of our programs.

Expanding international exchange

We broadened our international collaborations with renowned universities such as the University of Tokyo and Stanford University by hosting joint international academic symposiums, reinforcing our position as a leading global women's medical school.

Strengthening student research capabilities

We introduced the Creative Research Challenge Course to encourage student participation in research through a structured program that begins in the second year of pre-medical studies, thereby contributing to the evolution of future medical education.

Establishing extracurricular programs through the Green Ribbon Project

During students' leaves of absence due to medical school quota issues starting in February 2024 [3], we supported students in planning their futures and nurturing their vision through the Green Ribbon Project. This initiative included self-directed learning programs via the future medical education platform, mentoring by senior students, student research programs, corporate internships, and various open lectures.

Advancement of the College of Medicine through promoting research activity

Strengthening support for graduate students

We established a new scholarship for incoming graduate students to nurture future talents and organized the Future Ready Research Festival to ignite research enthusiasm among both graduate and undergraduate students.

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Received: February 14, 2025 Revised: February 23, 2025 Accepted: February 23, 2025

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Strengthening collaboration with external organizations

We cultivated an enabling research environment through sponsorship agreements with various institutions such as Seoul Clinical Laboratories, Seegene Medical Foundation, and the Cardiovascular Welfare & Research Institute. In addition, we inaugurated the Ewha-SCL Environmental Health Research Center to pioneer new research fields.

Encouraging faculty research and motivation

We instituted the Ewha Womans University College of Medicine Academic Award for professors.

The *Ewha Medical Journal*, a leading global academic journal

Key steps included inviting Dr. Sun Huh—a renowned expert in medical journal editing—as an editor beginning in September 2023; publishing a special issue that highlights current medical trends; and offering students opportunities to participate in the editorial process to secure the journal's long-term growth starting in 2024 (Fig. 1).

Strengthening school promotion and communication with society

Enhancing medical school branding

We announced a school slogan, "Future Ready Ewha Medicine," and launched a medical student ambassador group "EuiRang" to promote the school.

Building various communication channels

We strengthened communication and networking with the alumnae association, students, and faculty to support student activities and increase students' sense of belonging through mentor-mentee programs and various events.

Fostering the Ewha Cutting-Edge Medi.Healthcare Cluster

Through university–industry–hospital collaboration, we established a framework for research planning, performance management, and commercialization with companies in Magok and those affiliated with the Mokdong Hospital's Industry-Academia Cooperation Center [4] (Fig. 2).

Future vision

Ewha Womans University College of Medicine will continue to evolve as the leading institution for educating women physician-scientists and doctors in Korea. We will strive to cultivate future medical professionals equipped with the interdisciplinary thinking and practical skills required in the era of the Fourth Industrial Revolution. Our focus will be on investing in innovative research areas that shape the future of medicine, thereby contributing to the advancement of medical science. We will also fulfill our role as a medical school engaged with society by expanding our medical volunteer activities in collaboration with the local community and by developing educational programs that promote public health. This reflection will serve as a compass, commemorating the dean's efforts in advancing our college and guiding the direction in which we must move forward.

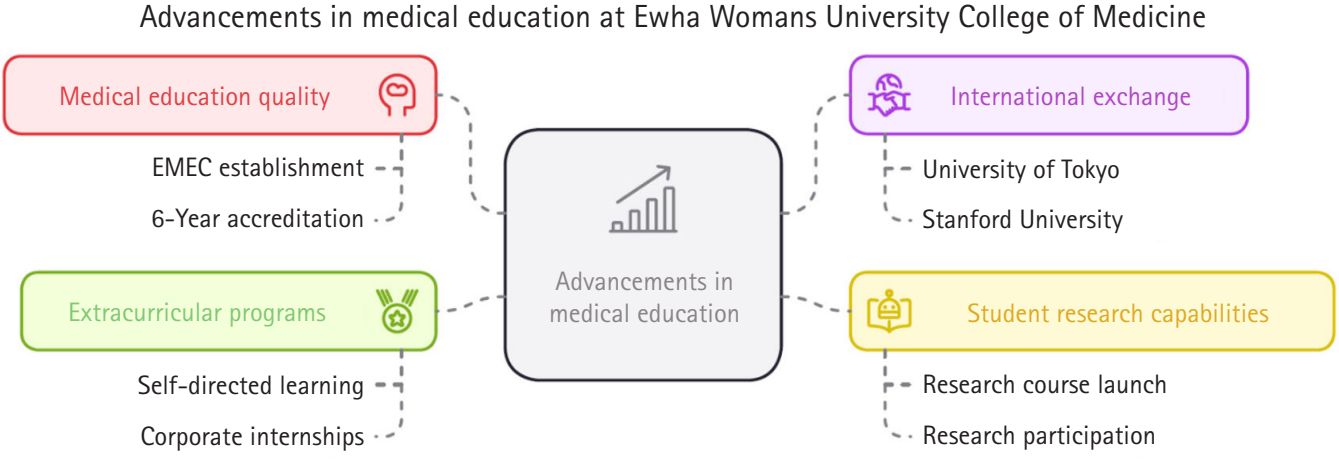

Fig. 1. Diagram of the advancement of medical education to lead the future of the Ewha Womans University College of Medicine and communicate with the world. EMEC, Ewha Medical Education Center.

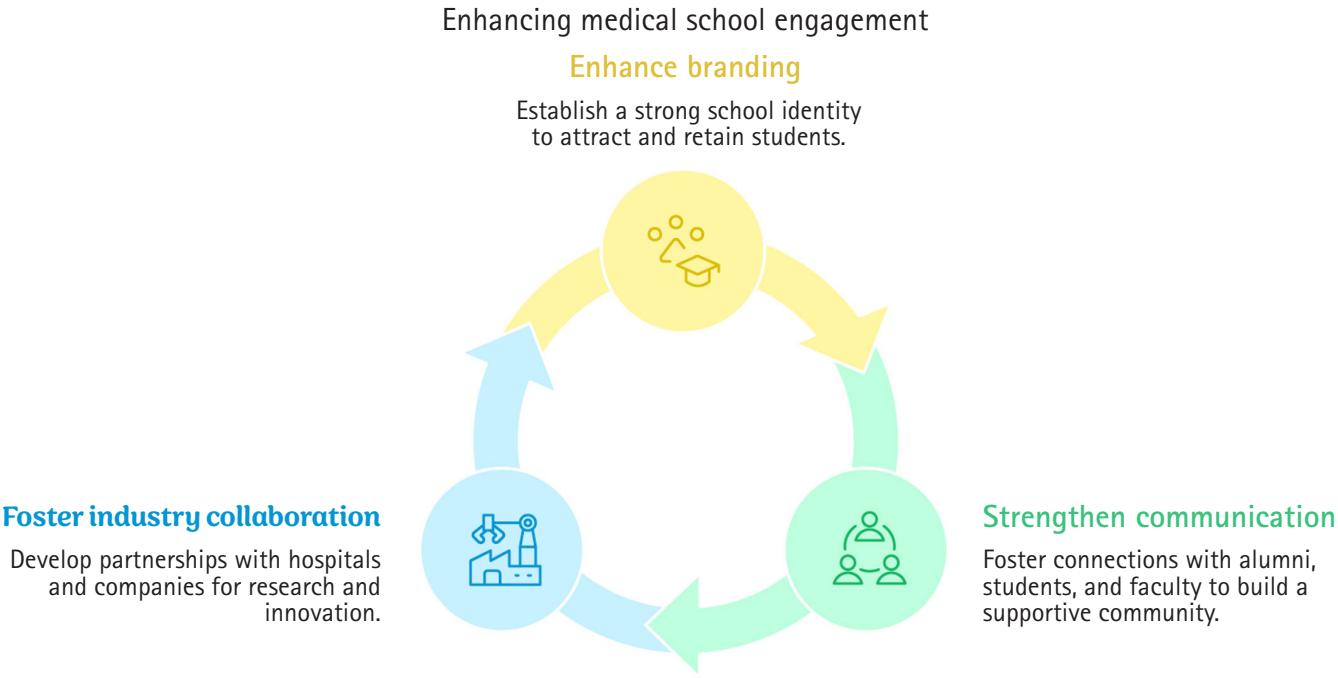

Fig. 2. Diagram of steps taken to strengthen school promotion and enhance communication with society by the Ewha Womans University College of Medicine.

Sincere appreciation to the members and alumnae of Ewha Womans University College of Medicine

During my tenure as dean over the past 3 years and 6 months, our remarkable achievements have been possible solely due to the unwavering support and cooperation of our faculty, students, alumnae, and external partners. I would like to take this opportunity to express my deepest gratitude.

In particular, I am sincerely thankful to the members of the Ewha Womans University College of Medicine Executive Committee, including 4 vice deans, 6 directors, 15 deputy directors, 1 team head, and 27 Self-Evaluation Committee members for Accreditation and Evaluation of Medical Education, who devoted themselves to the significant progress of our institution. Their generous support for research initiatives, the creation of an innovative education system leading the future of medicine, and the enhanced promotional activities that elevated Ewha's prestige have been decisive in propelling our college forward.

During my tenure as dean, I encountered many challenges and difficulties, yet we overcame them through the dedicated efforts and passion of the Ewha faculty, students, and alumnae, along with generous support and collaboration from external organizations. None of this would have been possible without the warm hearts and steadfast determination of the Ewha community. Thank you once again from the bottom of my heart.

Finally, as of February 2025, our students have not yet been able to return to medical school due to ongoing issues regarding the increase in medical school enrollment quotas in Korea [5]. I sincerely hope that there will be a swift return to normalcy in our medical education system.

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Authors' contributions

All work was done by Eunhee Ha.

Conflict of interest

Eunhee Ha served as a dean of the Ewha Womans University College of Medicine from August 2021 to January 2025. However, she was not involved in the peer review process or decision-making. Otherwise, no potential conflict of interest relevant to this article was reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/X057VJ

Supplement 1. Yearly achievements during the author's term as dean from August 2021 to January 26, 2025.

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eISSN: 2234-2591
Open Access

Editorial

Ewha Med J 2025;48(2):e21
https://doi.org/10.12771/emj.2025.00024

Ewha Medical Journal

Ewha Medical Journal passed the scientific evaluation by PubMed Central and succeeded in being included in DOAJ, but failed to be accepted by Scopus

Sun Huh*

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Passing PubMed Central's evaluation for scientific quality

I was thrilled to receive an email on the morning of February 1, 2025 from the PubMed Central (PMC) Applications Team informing me that *Ewha Medical Journal has passed the Scientific Quality Review by NLM for PMC, and PMC will take content back to 2023*. Because the technical evaluation phase remains ongoing, our management team is committed to meeting the technical evaluation criteria for full-text Journal Article Tag Suite (JATS) XML files [1]. This evaluation status is also visible on the PMC Publisher Portal (Fig. 1) [2].

Feedback from PMC reviewers on March 12, 2022, identified 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 [3]. We resubmitted our application to PMC on August 21, 2024. Before submission, the management team meticulously verified the scientific quality of each article. The following efforts were undertaken to address the PMC reviewers' comments:

First, beginning with the October 2023 issue, the study design has been explicitly indicated in each article title.

Second, manuscripts are now structured according to the appropriate reporting guidelines for their respective study designs. For example, we employed the PRISMA statement for systematic reviews, the CONSORT statement for randomized controlled trials, the STROBE statement for observational studies, the COREQ statement for qualitative studies, and the CARE statement for case reports—all available at https://www.equator-network.org/.

Third, the methods sections of all original articles have been revised to align with the corresponding reporting guidelines. Each article now clearly details the study design, setting, participants, data sources and measurement, variables, potential biases, sample size, and statistical analysis.

Fourth, all manuscripts have been proofread by professional native English speakers to eliminate unfamiliar or ambiguous expressions.

Fifth, a conflict of interest statement has been included in every article.

Sixth, our editorial board now represents three continents—Asia (Korea), Oceania (Australia), and North America (United States). In addition, since 2022 we have attracted contributions from an internationally diverse group of authors, including those from China, Indonesia, Thailand, Turkey, Iran, Australia, the United States, Bulgaria, Denmark, Germany, the Netherlands, Switzerland, and the United Kingdom, even though our primary regional focus remains Korea.

We hope that the reviewers will recognize these efforts. We are pleased to have passed the scientific evaluation on our second application. This achievement was made possible with the full financial support and encouragement of Dr. Eun Hee Ha, Dean of the Ewha Womans University College of Medicine (August 2021–January 2025). Many medical journals in Korea have been included in PMC since 2008 [4]. As of February 1, 2025, 165 journals from Korea were found with the search term "journalspmc AND

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Received: February 1, 2025 Revised: February 5, 2025 Accepted: February 5, 2025

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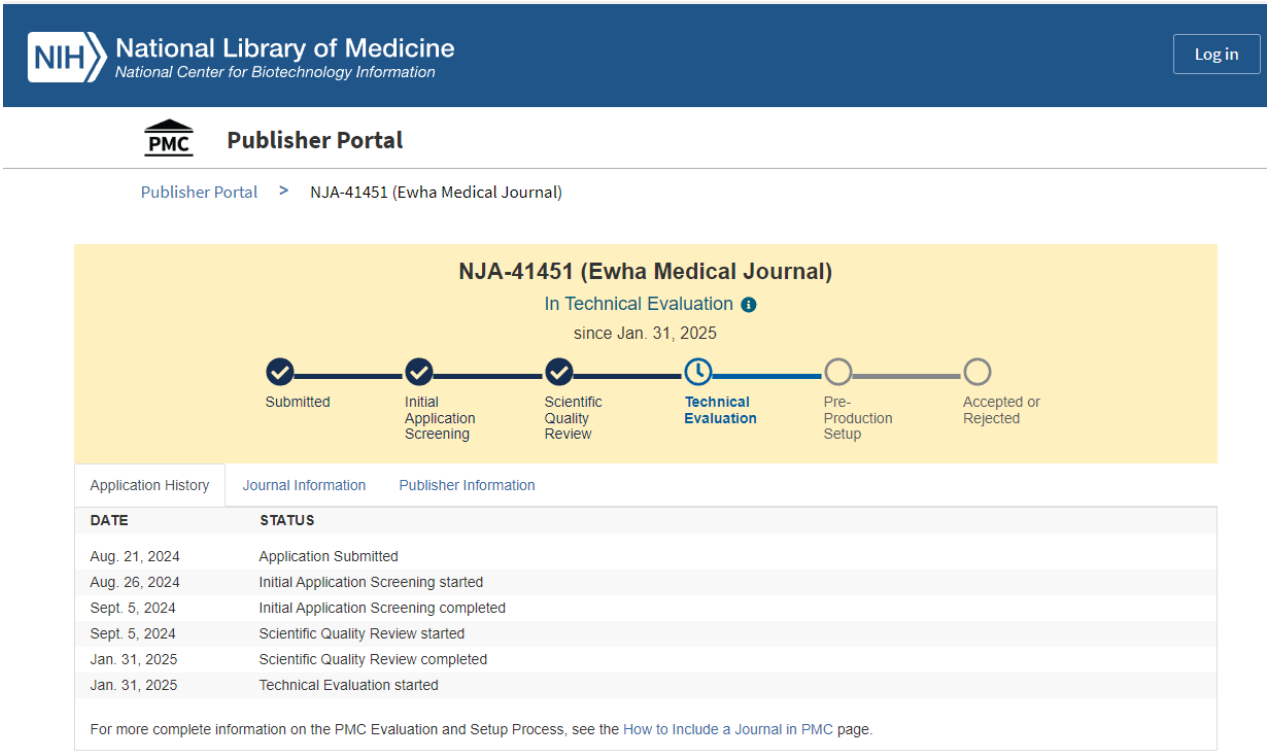

Fig. 1. Evaluation phase status found in the PMC Publisher Portal [cited 2025 Feb 1].

Korea [country]" in the NLM Catalogue at https://www.ncbi.nlm.nih.gov/nlmcatalog (Supplement 1). Of these, 21 journals appeared as duplicates due to title changes, leaving 144 unique journals included in PMC. Additionally, some journals are published by organizations located outside Korea, so the total number of Korean journals in PMC is even higher. Both Korean and English journals—such as the *Ewha Medical Journal, the Journal of the Korean Society of Radiology, Women's Health Nursing, and Ŭi sahak (Korean Journal of Medical History)*—have been indexed in PMC [5]. Being a PMC journal and searchable in PubMed is expected to attract manuscript submissions from researchers worldwide, even though our journal's primary focus remains on Korea [6].

Being accepted in DOAJ

Another piece of good news is that the *Ewha Medical Journal* has been included in the Directory of Open Access Journals (DOAJ). I received a message from DOAJ stating that *the application submitted for the Ewha Medical Journal on August 24, 2024, has been accepted for inclusion in DOAJ* on November 24, 2024. The journal's dashboard is found at https://doaj.org/toc/2234-2591 (Fig. 2). Being listed in DOAJ signifies international recognition as a high-quality open-access journal that meets strict evaluation criteria [7].

Failure to be listed in Scopus

Unfortunately, on January 6, 2025, we received disappointing news from the Scopus Title Evaluation Team—namely, *the Content Selection and Advisory Board (CSAB) has advised not to accept the title for Scopus inclusion at present* (Supplement 2). The main reasons cited were the low annual publication volume, the presence of multiple subject areas without clear cohesion, contributions from outside Korea, and a perceived lack of focus in the editorial strategy. We may reapply on January 6, 2027, or later. Although these comments are disheartening, our editorial team remains committed to enhancing the journal in response to the CSAB's feedback.

Role of the editor-publisher of society journals

Typically, journal editors at commercial publishing companies focus solely on peer review, while all other editing and publishing tasks are handled by the publisher. These tasks are supported by professional management teams—including managing editors, manuscript editors, copy editors, ethics editors, legal consultants, statistical editors, language editors, layout editors, graphic designers, and information technology engineers who produce full-text

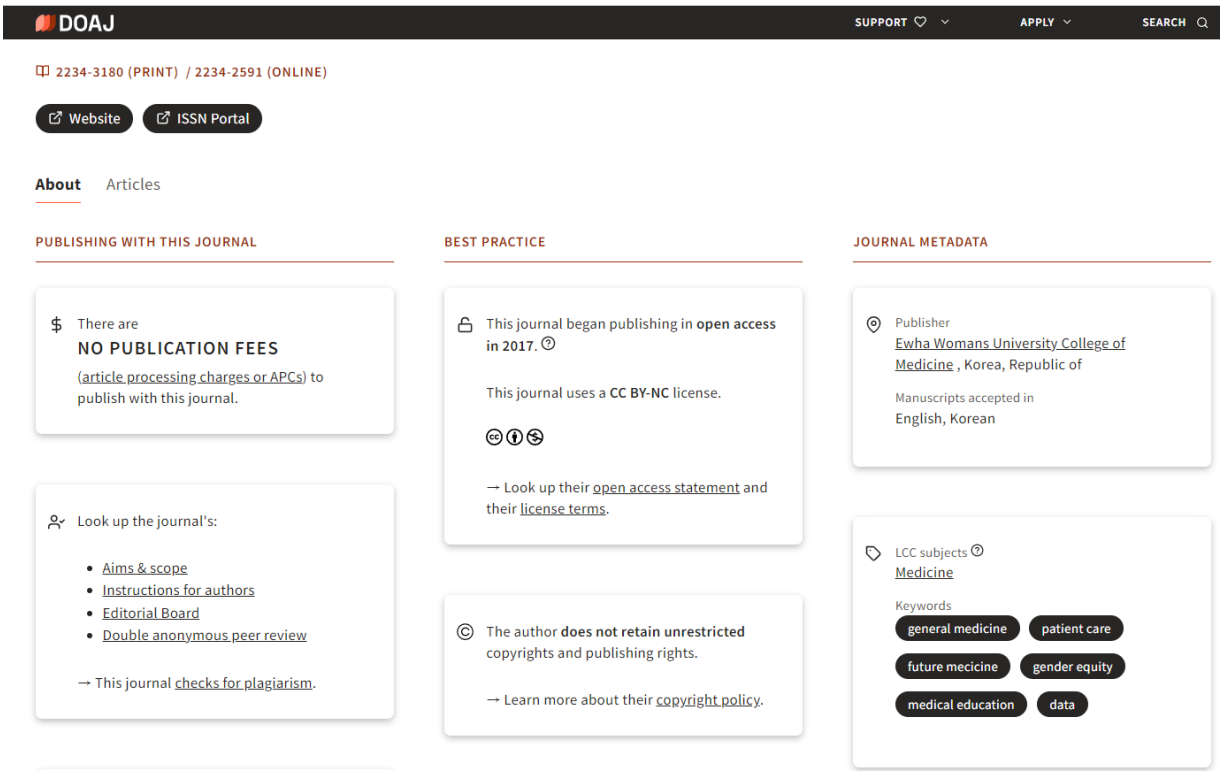

Fig. 2. Dashboard of the *Ewha Medical Journal* found at https://doaj.org/toc/2234-2591.

XML files, manage websites, and maintain submission systems. In contrast, the editor-publisher of a society journal must be familiar with the entire editing and publishing process. Overseeing applications to international literature databases is also a crucial responsibility for the editor-publisher. Fully understanding and meeting all evaluation criteria for editing and publishing is challenging, and there are no shortcuts. Our editors and management team at the *Ewha Medical Journal* are committed to upholding international standards of scientific rigor in both style and format.

Change of publishing company

Starting in February 2025, M2PI (https://www.m2-pi.com/), a top-tier publishing company that has produced 210 scientific, technological, engineering, and medical journals in Korea, will take over publishing for the *Ewha Medical Journal*. Since 2020, GuhMok (https://www.guhmok.com/) has provided excellent editing and publishing support. I appreciate the sincere and high-quality work of Mr. Yeon-Wook Kim and his team. The change in publishing company is intended to introduce more sophisticated journal metrics, enhanced search technologies, and unique presentation features.

Provision of templates for reporting guidelines of common study design

Starting in February 2024, we will provide templates for reporting guidelines to assist authors. Using these templates will simplify manuscript preparation and enable reviewers to quickly assess the scientific quality of submissions. Templates will be available for systematic reviews/meta-analyses, randomized controlled trials, non-randomized controlled trials, before-and-after studies, observational studies, diagnostic studies, qualitative studies, and case reports. For other study designs, authors may refer to the Equator Network (https://www.equator-network.org/) and consult with an editor before submission. Most clinical articles from Korea are observational studies—such as cohort, case-control, or cross-sectional studies—and the Korean translation of the STROBE statement was provided in the October 2024 issue of the journal [8].

I am pleased to share the successful applications to three databases [3]. However, the challenge of gaining inclusion in Scopus remains. I hope that the change in our publishing partner and the implementation of reporting guideline templates will serve as a turning point in elevating the journal to a top-tier level.

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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. Otherwise, no potential conflict of interest relevant to this article was reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/JSBQ32

Supplement 1. 165 journals in NLM Catalog (https://www.ncbi.nlm.nih.gov/nlmcatalog) found with the search term, "journalspmc AND Korea [country]".

Supplement 2. Letter from Scopus Title Evaluation team.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e22
https://doi.org/10.12771/emj.2025.00115

Ewha Medical Journal

Bridging science and policy in tuberculosis treatment through innovations in precision medicine, drug development, and cohort research: a narrative review

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Recent advancements in tuberculosis treatment research emphasize innovative strategies that enhance treatment efficacy, reduce adverse effects, and adhere to patient-centered care principles. As tuberculosis remains a significant global health challenge, integrating new and repurposed drugs presents promising avenues for more effective management, particularly against drug-resistant strains. Recently, the spectrum concept in tuberculosis infection and disease has emerged, underscoring the need for research aimed at developing treatment plans specific to each stage of the disease. The application of precision medicine to tailor treatments to individual patient profiles is crucial for addressing the diverse and complex nature of tuberculosis infections. Such personalized approaches are essential for optimizing therapeutic outcomes and improving patient adherence—both of which are vital for global tuberculosis eradication efforts. The role of tuberculosis cohort studies is also emphasized, as they provide critical data to support the development of these tailored treatment plans and deepen our understanding of disease progression and treatment response. To advance these innovations, a robust tuberculosis policy framework is required to foster the integration of research findings into practice, ensuring that treatment innovations are effectively translated into improved health outcomes worldwide.

Keywords: Drug-related side effects and adverse reactions; Iatrogenic disease; Precision medicine; Treatment outcome; Tuberculosis

Introduction

Background

Tuberculosis (TB) continues to pose an immense global health challenge. The World Health Organization (WHO) Global TB Report offers a sobering snapshot of the current epidemic: in 2023, an estimated 10.8 million people worldwide developed TB, corresponding to an incidence rate of approximately 134 cases per 100,000 population [1]. Although TB-related deaths declined modestly from 1.32 million in 2022 to 1.25 million in 2023, TB has re-emerged as the world's leading infectious disease killer, surpassing coronavirus disease 2019. A particularly alarming finding is the diagnostic gap: only about 8.2 million of the estimated 10.8 million cases were detected, leaving roughly 2.7 million "missing" cases that fuel ongoing transmission. The situation is further complicated by the rising prevalence of drug-resistant TB; an estimated 400,000 cases of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) were reported in 2023, yet only around 44% of these patients received appropriate treatment [1]. Parallel to these trends, current TB treatment strategies face several significant

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Jinsoo Min and Yoolwon Jeong jointly supervised this work.
Received: March 9, 2025 Revised: March 20, 2025 Accepted: March 25, 2025

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challenges. The discovery of effective medications such as streptomycin and para-aminosalicylic acid in 1944 marked the beginning of chemotherapeutic TB treatment. A pivotal advancement occurred in 1952 with the introduction of "triple therapy," which combined streptomycin, para-aminosalicylic acid, and isoniazid; however, this regimen required up to 24 months of continuous treatment. Further progress emerged in the 1970s when combining isoniazid and rifampicin reduced treatment duration from 18 to 9 months, followed by the 1980s discovery that adding pyrazinamide allowed for cures in only 6 months. For the past 40 years, the global standard for TB treatment has been a 6-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol, achieving success rates as high as 88%. Nevertheless, its prolonged duration, substantial pill burden, and side effects pose significant challenges for patient adherence [2], potentially leading to acquired drug resistance, treatment failure, and even death.

Objectives

This review aims to critically assess recent advancements in TB treatment research and innovation, focusing on developing therapies that mitigate the limitations of current recommended treatments while aligning more closely with patient-centered care. By addressing persistent treatment challenges, we explore how recent research is paving the way for more effective and accessible interventions in the global fight against TB. This evaluation highlights the shift toward treatments that not only improve therapeutic outcomes but also enhance patient adherence and satisfaction.

Ethics statement

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

Treatment strategy across the disease spectrum

Recent research has significantly expanded our understanding of TB, moving beyond a simple classification of the infection as either latent or active. Instead, TB is now recognized as a disease spectrum encompassing several distinct stages, each with unique clinical and biological characteristics (Fig. 1) [3]. At one end of this spectrum is latent TB infection, a condition in which individuals harbor *Mycobacterium tuberculosis* without exhibiting any symptoms or other evidence of active TB. Although these individuals appear healthy, they remain at risk of progressing to more severe forms of the disease later in life. Moving along the continuum, the concept of incipient TB has emerged to describe an early stage of infection. In this phase, subtle changes—often detectable

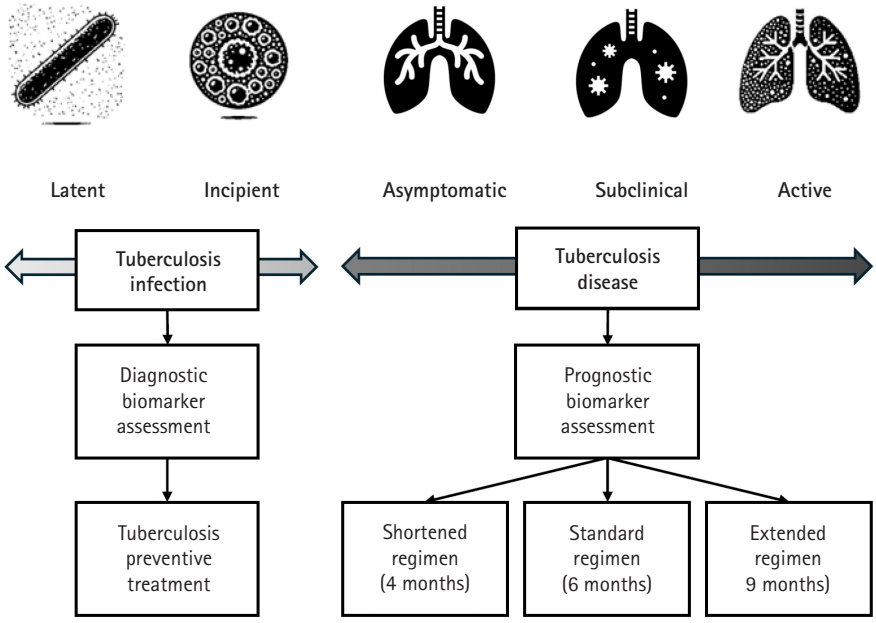

Fig. 1. Continuum from tuberculosis infection to active tuberculosis disease. Starting with latent tuberculosis infection—where individuals harbor *Mycobacterium tuberculosis* without symptoms—the continuum progresses to incipient stages marked by metabolic and immunological changes that signal the early evolution of infection. It then enters an asymptomatic or subclinical phase, during which the disease is microbiologically active but exhibits minimal or no overt symptoms. Finally, the continuum culminates in active tuberculosis, characterized by symptomatic disease that necessitates comprehensive treatment. (Drawn by the authors.)

through sensitive immunological or radiographic methods—suggest that the infection is beginning to evolve toward a more active state, even though clinical symptoms are not yet apparent. Further along the spectrum lies subclinical TB [4], a stage in which the disease is microbiologically active and identifiable with advanced diagnostic tools, yet the affected individual may still exhibit minimal or no overt symptoms (Fig. 2).

Finally, at the most advanced end of the spectrum is active TB, where the infection manifests with clear clinical symptoms and necessitates prompt, often intensive, treatment. Comprehensive reviews emphasize that this continuum—or disease spectrum—provides a more accurate framework for understanding TB pathogenesis than the traditional binary model [5-7]. They highlight the benefits of adopting a stage-specific approach to treatment [5,6]. For example, individuals with latent or incipient TB might be managed with shorter, less aggressive regimens aimed at preventing disease progression, thereby reducing drug exposure and associated side effects. In contrast, patients with subclinical or active TB typically require the standard, comprehensive multidrug therapy to ensure both cure and transmission prevention. It is even possible that patients with limited subclinical TB could be treated with fewer drugs and shorter regimens. This nuanced perspective on TB not only improves diagnostic precision but also supports the development of tailored therapeutic strategies that address the specific needs of patients at different disease stages.

Strategies to shorten tuberculosis treatment duration

The foremost objective of TB treatment research is to develop rapid and effective therapies that can reduce the global spread of TB and lower TB-related mortality, ultimately contributing to disease eradication. To achieve this goal, researchers are focusing on shortening treatment duration while enhancing overall efficacy [8]. In practice, this involves developing short-course treatment regimens that improve patient adherence, minimize side effects, and ensure complete pathogen elimination. Three key strategies have been proposed to shorten TB treatment duration, each supported by extensive background research and clinical experience (Fig. 3).

The first strategy involves optimizing combinations of currently available anti-TB drugs [9]. By re-evaluating existing drug combinations, adjusting dosages and schedules, and exploring synergistic interactions, it is possible to enhance collective effectiveness, reduce treatment duration, and improve outcomes without increasing toxicity. The second strategy is to develop new drugs with novel mechanisms of action while repurposing existing drugs for TB treatment [10]. Most current anti-TB drugs target similar bacterial pathways, and over time, the bacteria have developed resistance to these mechanisms. Researchers are therefore focused on discovering compounds that act on previously untargeted

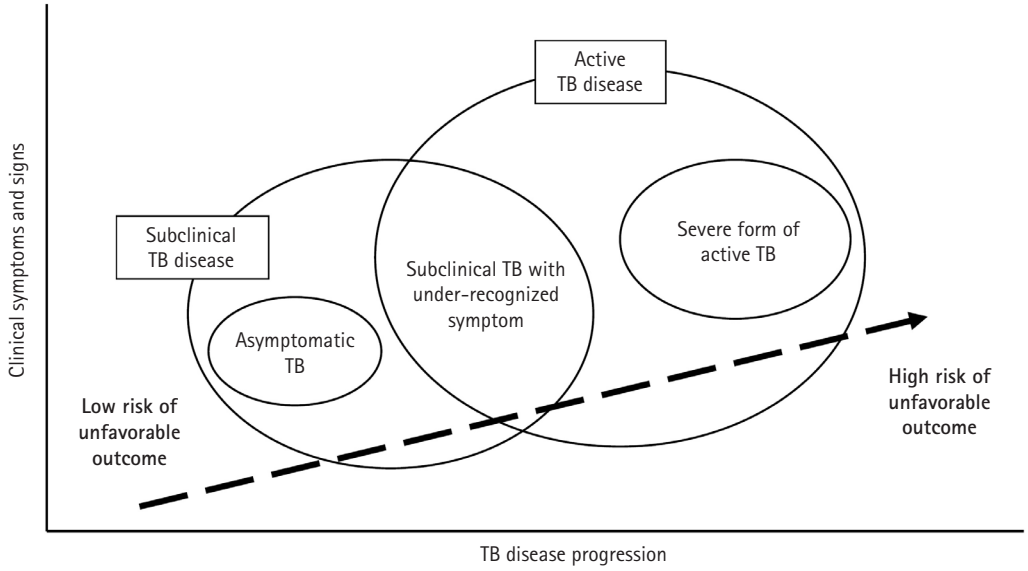

Fig. 2. Progression of tuberculosis (TB) disease from a subclinical to an active state. This figure highlights the transition phase in which individuals may not show obvious symptoms despite ongoing microbiological activity (subclinical tuberculosis), progressing to active tuberculosis disease where symptoms become clinically evident and require immediate, intensive treatment. The upward movement in the diagram signifies a deterioration in the condition, emphasizing the critical need for early detection and intervention during the subclinical stage to prevent the full development of active tuberculosis and its complications. (Drawn by the authors.)

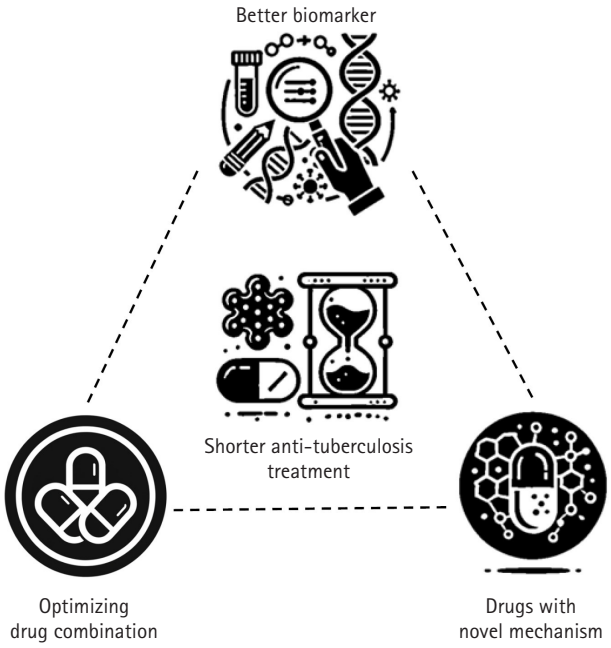

Fig. 3. Strategies to shorten tuberculosis treatment. This diagram illustrates 3 key strategies aimed at reducing tuberculosis treatment duration while enhancing efficacy and patient outcomes. The "better biomarker" strategy focuses on developing and utilizing advanced biomarkers to tailor treatment duration and intensity to individual patient needs, thereby optimizing therapeutic outcomes. The "optimizing current drugs" strategy emphasizes enhancing the effectiveness of existing anti-tuberculosis medications through dose optimization and the exploration of synergistic drug combinations. Finally, the "novel mechanism drugs" strategy represents the exploration of new drugs and the repurposing of existing medications to target previously unexploited bacterial pathways, with the goal of overcoming drug resistance and further improving treatment efficacy. (Drawn by the authors.)

pathways—such as unique components of the mycobacterial cell wall or other critical functions—while also repurposing drugs originally designed for other diseases that have proven effective against TB. These novel and repurposed drugs may offer greater potency, help overcome existing resistance, and contribute to a faster, more efficient treatment course. The third strategy is to identify and validate reliable prognostic biomarkers that can predict treatment outcomes [11].

A major challenge in TB treatment is the wide variation in patient responses; while some patients clear the infection rapidly, others experience relapse or treatment failure. By developing biomarkers—such as specific molecular signatures or immune profiles—that accurately reflect disease activity and predict prognosis, clinicians can tailor treatment duration and intensity to individual needs. This personalized approach not only minimizes unnecessary drug exposure and side effects but also ensures that high-risk patients receive the full benefit of extended therapy.

Recent advances in drug discovery and development

The landscape of TB treatment has been enriched by the development and repurposing of several drugs, each with distinct mechanisms and clinical applications (Table 1). Bedaquiline disrupts the TB bacterium's energy production by targeting adenosine diphosphate (ATP) synthase. Delamanid and pretomanid, both members of the nitroimidazoles class, exhibit antimycobacterial activity through a dual mechanism: they interfere with mycolic acid synthesis and induce respiratory poisoning [12].

Linezolid, an antibiotic that inhibits bacterial protein synthesis, was originally approved for drug-resistant Gram-positive infections and has proven effective against MDR/RR-TB.

Clofazimine, initially used for leprosy, has demonstrated potential in TB treatment by interfering with DNA replication. Research on high-dose rifampicin is currently underway to determine whether increasing the dosage from the traditional 10 mg/kg can increase efficacy and shorten treatment duration without raising adverse effects [13]. The global TB drug pipeline reveals numerous new therapeutic compounds at various stages of development [14]

Sudapyridine (WX-081) is a promising new anti-TB drug developed as an analog of bedaquiline [15]. It has demonstrated superior efficacy and safety in preclinical trials, showing excellent antimycobacterial activity and improved pharmacokinetic parameters with fewer side effects—such as reduced QTc prolongation—compared to its predecessor.

Currently, sudapyridine is undergoing Phase III clinical trials (NCT05824871). Telacebec (Q203) is a groundbreaking oral antibiotic that targets drug-resistant TB by selectively inhibiting the cytochrome bc1 complex of *M. tuberculosis*, which is crucial for the bacterium's energy production. Initially developed by Qurient Co. Ltd., Telacebec showed promising results in a Phase 2a early bactericidal activity clinical trial (NCT03563599) that evaluated its safety, pharmacokinetics, and efficacy in adult, treatment-naïve, sputum smear-positive patients with drug-susceptible pulmonary TB [16]. The trial, completed in September 2019, confirmed Telacebec's ability to significantly reduce the time to sputum positivity over the first 14 days of treatment, indicating potent bactericidal activity.

Delpazolid (LCB01-0371), a novel oxazolidinone developed by LegoChem BioSciences, has shown promise in early bactericidal activity trials, comparing favorably with the standard

Table 1. Overview of current and developmental tuberculosis treatment drugs and their mechanisms of action

Types	Examples	Class	Mechanism of action
New drugs	Bedaquiline	Diarylquinolines	Inhibits ATP synthesis by targeting mycobacterial ATP synthase
	Delamanid, pretomanid	Nitroimidazoles	Inhibits mycolic acid synthesis
	Telacebec	Imidazopyridines	Inhibits cytochrome bc1 complex, disrupting energy production
Repurposed drugs	Linezolid, depazolid	Oxazolidinones	Inhibits protein synthesis, binds to the 23S RNA peptidyl transferase center of the prokaryotic ribosomal 50S subunit
Revived drugs	Clofazimine	Riminophenazines	Interferes with DNA and cellular functions, anti-inflammatory effects
Optimized drugs	Rifampicin, rifapentine	Rifamycines	Inhibits DNA-dependent RNA polymerase, blocking RNA transcription

ATP, adenosine diphosphate.

HRZE regimen and linezolid in reducing bacterial load in TB patients [17]. An ongoing Phase IIb clinical trial is assessing the safety, efficacy, tolerability, and pharmacokinetics of various doses of delpazolid in combination with bedaquiline, delamanid, and moxifloxacin over a 16-week treatment period in adult patients with newly diagnosed, smear-positive, drug-sensitive pulmonary TB (NCT04550832).

Another important strategy focuses on optimizing combination therapies to enhance efficacy and reduce treatment duration (Table 2). Researchers are re-assessing how current and novel drugs can be combined more effectively, exploring synergistic interactions that boost bactericidal activity while minimizing toxicity. The recommended regimen for drug-susceptible pulmonary and extrapulmonary TB, developed over 4 decades ago, consists of 6 months of isoniazid; rifampicin; pyrazinamide; ethambutol [18]. Numerous studies [19-21] that attempted to shorten treatment durations with fluoroquinolones failed to demonstrate non-inferiority until a successful 4-month regimen [22]—which included rifapentine, isoniazid, pyrazinamide, and moxifloxacin (4HPZM)—was developed. This regimen has received WHO endorsement for treating drug-susceptible TB in individuals aged 12 and older. Despite its success, challenges remain, including the need for ongoing support to ensure patient adherence and resistance testing for rifampicin and moxifloxacin, factors that may hinder its cost-effectiveness and broader implementation. Additionally, the availability of rifapentine remains restricted.

In Korea, concerns over the use of rifapentine complicate the adoption of the 4HPZM regimen. Rifapentine—a rifamycin antibiotic similar to rifampin but with a longer half-life that permits weekly dosing—was introduced in a pilot study in 2016 as a TB preventive treatment [23]. However, the study was prematurely terminated due to reports of anaphylaxis associated with rifapentine. Currently, rifapentine is not approved in Korea, and unresolved safety concerns make it difficult to adopt the WHO-recommended 4-month regimen. Further research and review are needed before this shorter regimen can be considered for use in Korea.

The Nix-TB trial demonstrated the efficacy of the BPaL regimen [24], which consists of bedaquiline, pretomanid, and linezolid, in curing patients with extensively drug-resistant TB or other difficult-to-treat DR-TB within 6 months, albeit in an uncontrolled study setting. Subsequently, the TB-PRACTECAL trial showed that adding moxifloxacin to BPaL (forming the BPaLM regimen) for 24 weeks was as effective as the WHO's standard care for treating pulmonary MDR/RR-TB [25,26], while offering a better safety profile. In 2022, WHO endorsed BPaLM for 6 months as the new standard for MDR/RR-TB treatment in patients aged 14 and older who have not previously been treated with bedaquiline, pretomanid, or linezolid [27].

The BEAT India study, a prospective open-label, single-group cohort study, evaluated the effectiveness of a 24- to 36-week entirely oral regimen combining bedaquiline, delamanid, linezolid, and clofazimine (BDLC) in treating patients with pulmonary MDR-TB, including those resistant to fluoroquinolones or second-line injectables [28]. The study concluded that 91% of patients achieved a favorable outcome with minimal cardiotoxicity, although myelosuppression and peripheral neuropathy were common yet manageable side effects. WHO recently supported a 6-month regimen of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine (BDLLfxC) in the BEAT-TB study, which proved effective and safe for children, adolescents, and pregnant and breastfeeding women with MDR/RR-TB [29]. This trial employed an approach in which either levofloxacin or clofazimine was omitted from the regimen based on fluoroquinolone drug susceptibility testing results. The endTB study further explored combinations of these drugs, resulting in WHO guidance on 3 alternative 9-month, injectable-free regimens (BLMZ, BLLfxCZ, BDLLfxZ) that are contingent on fluoroquinolone susceptibility [30]. These regimens, tailored for both adults and children, demonstrate a continued commitment to refining TB treatment to enhance accessibility and effectiveness.

Alongside these approaches, the MDR-END regimen has been

Table 2. Currently available treatment regimens for drug-susceptible tuberculosis and multidrug-resistant/rifampicin-resistant tuberculosis

Target	Treatment regimen	Duration (mo)	Evidence
DS-TB	INH, RIF, PZA, EMB	6	BMRC [18]
	RFP, INH, PZA, Mfx	4	Study 31/A5349 [22]
Fluoroquinolone-susceptible MDR/RR-TB	Bdq, Pa, Lzd, Mfx	6	TB-PRACTECAL trial [25,26]
	Bdq, Dlm, Lzd, Lfx, Cfz	6	BEAT-TB study [29]
	Dlm, Lfx, Lzd, Pza	9	MDR-END study [31]
	Bdq, Lzd, Mfx, Pza	9	EndTB study [30]
	Bdq, Cfz, Lzd, Lfx, Pza	9	EndTB study [30]
	Bdq, Dlm, Lzd, Lfx, Pza	9	EndTB study [30]
Fluoroquinolone-resistant MDR/RR-TB	Bdq, Pa, Lzd	6	Nix-TB trial [24]
	Bdq, Pa, Lzd, Cfz	6	BEAT-India study [28]

DS-TB, drug-susceptible tuberculosis; MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis; INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; RFP, rifapentine; Mfx, moxifloxacin; Bdq, bedaquiline; Pa, pretomanid; Lzd, linezolid; Dlm, delamanid; Cfz, clofazimine.

formulated as a 9-month all-oral combination of delamanid, levofloxacin, linezolid, and pyrazinamide, specifically designed for MDR/RR-TB [31]. Offering a robust therapeutic option for patients with drug-resistant TB, this regimen is now recommended as one of the first-line therapies for MDR/RR-TB according to the recently updated Korean TB treatment guidelines. Additionally, a non-interventional, prospective observational registry is currently underway in Korea to assess the real-world efficacy and safety of the MDR-END regimen.

The TRUNCATE trial demonstrated that shorter treatment regimens for rifampicin-susceptible TB are feasible when a risk-stratified approach is applied [32]. In this trial, patients with mild TB who had no risk factors for treatment failure or recurrence were successfully treated with an 8-week regimen. This regimen, which included both first-line and second-line drugs such as bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol, proved to be as effective as the standard longer treatments. This finding suggests that the majority of TB patients might be cured in significantly less time than the conventional 24 weeks if similar approaches are implemented. Identifying the smaller group of patients who require longer treatment due to more complex cases remains a focus of current research.

Host-directed therapies

Host-directed therapies (HDTs) can significantly optimize TB treatment by addressing several critical challenges encountered with current regimens. By modulating the host's immune response to better control and eliminate *M. tuberculosis*, HDTs have the potential to shorten treatment duration—a key advantage for patients with drug-resistant TB strains who often require prolonged therapy [33]. This reduction in treatment time minimizes exposure to toxic drugs and decreases the likelihood of further resistance development. Moreover, HDTs can enhance the efficacy of existing TB medications by boosting the host's immune capacity to fight the infection more effectively [34]. This improvement is particularly important for patients with compromised immune systems, such as those co-infected with human immunodeficiency virus (HIV), where conventional TB treatments may be less effective. By strengthening the immune response, HDTs help these patients better manage and overcome TB. Additionally, HDTs focus on reducing inflammation and preventing tissue damage caused by both the disease and its treatment. Excessive inflammation, a hallmark of severe TB, can lead to extensive lung damage that worsens patient outcomes and hinders recovery. By controlling inflammatory responses, HDTs not only protect lung tissue and preserve lung function but also improve overall treatment outcomes. This approach holds promise as a potential option for managing post-TB lung disease [35], offering a way to mitigate long-term respiratory complications and enhance recovery.

Development of biomarkers

The current treatment guidelines for drug-susceptible TB advocate a uniform 6 month short-course regimen for all patients—a "one size fits all" approach (Fig. 4). However, clinical observations reveal that TB is a heterogeneous disease; some patients display a favorable prognosis and might safely undergo treatment shortening to as little as 4 months, while others, such as those who remain culture-positive at 2 months or who exhibit cavitary lesions on initial chest X rays, face a higher risk of relapse and may benefit from extending therapy to 9 months [36]. Unfortunately, the scientific evidence supporting these adjustments is still limited.

In recent years, interest in measuring the host response to TB

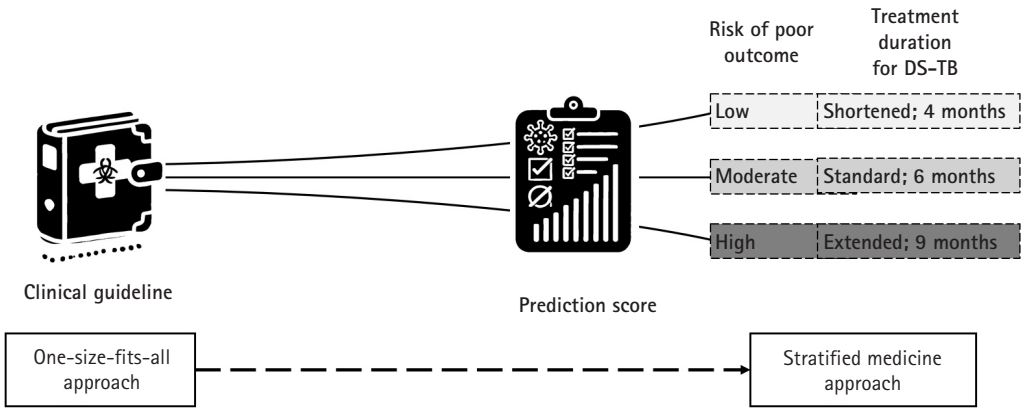

Fig. 4. Treatment approaches in tuberculosis management. This diagram contrasts 2 distinct approaches to tuberculosis treatment. The traditional one-size-fits-all approach involves administering the same treatment regimen to all patients regardless of individual differences. In contrast, the stratified medicine approach uses a clinical scoring system to determine treatment duration based on a patient's risk level—low, moderate, or high—thereby tailoring therapy to individual needs. This strategy aims to optimize outcomes by adjusting treatment length according to disease severity and prognosis, ultimately enhancing both efficacy and patient adherence. DS-TB, drug-susceptible tuberculosis. (Drawn by the authors.)

has grown. Biomarker tests that detect blood RNA signatures and other analytes have demonstrated the capacity to distinguish between different TB disease states [3]. The development of robust prognostic biomarkers would enable a biomarker-guided therapy strategy, allowing clinicians to predict a patient's likely treatment outcome from the outset. For example, prediction scores that combine clinical information—such as body mass index and time to sputum culture positivity—with markers of host response have shown promise, particularly since a high baseline mycobacterial load is an important predictor of relapse. One innovative example is the Xpert MTB Host Response (MTB-HR) prototype (Cepheid). This new fingerstick blood test generates a "TB score" based on the mRNA expression of 3 genes, providing a rapid, non-sputum-based, point-of-care test. In trials conducted across multiple countries, the MTB-HR prototype demonstrated high sensitivity and specificity in distinguishing TB from other respiratory diseases and showed potential for monitoring TB treatment response [37-39].

With validated biomarkers, patients expected to have a good prognosis could receive a shortened regimen (for example, 4 months), whereas those predicted to have a poorer prognosis could be assigned an extended regimen (up to 9 months) [40]. This "stratified medicine" approach would not only individualize therapy—optimizing treatment efficacy and minimizing unnecessary drug exposure and side effects—but also improve patient adherence. Furthermore, integrating these biomarkers into TB clinical research can enhance trial design by enabling more precise patient stratification. This refinement would lead to better interpretation of treatment responses, more efficient clinical trials, and ultimately, more personalized and effective TB treatment strategies on a global scale. An accessible, point-of-care relapse prediction score would accelerate the development and implementation of shorter, individualized TB treatment regimens.

Advancing TB treatment research through cohort studies: a global perspective

TB treatment research is undergoing a transformative shift, driven by an expanding arsenal of new and repurposed compounds and increasingly sophisticated clinical trial methodologies [41]. While randomized controlled trials (RCTs) remain the gold standard for establishing treatment efficacy and informing public health guidelines, cohort studies provide an indispensable complementary approach. By capturing real-world, longitudinal data from diverse populations, cohort studies illuminate the complexities of TB pathogenesis, treatment responses, and long-term patient outcomes that controlled trials often cannot fully capture [42,43]. Cohort studies offer a critical advantage by investigating TB in naturalistic settings, encompassing a broad spectrum of patients who might otherwise be excluded from RCTs due to stringent eligibility criteria. This inclusivity ensures that TB treatment strategies reflect the heterogeneous nature of affected populations, including pregnant and lactating women, children, the elderly [44], and individuals with comorbid conditions such as diabetes [45] and HIV/acquired immunodeficiency syndrome.

Additionally, cohort studies facilitate the evaluation of treat-

ment effectiveness and safety across varied demographic and geographic settings, generating data that more accurately reflect routine clinical practice. Beyond clinical outcomes, cohort studies serve as a powerful tool for deciphering TB disease progression, tracking the entire spectrum from latent TB infection and asymptomatic TB to active disease and post-treatment relapse [46]. The ability to monitor patients over extended periods enables researchers to assess host–pathogen interactions, immune responses, and environmental or genetic factors that influence TB trajectory [47]. This longitudinal framework is instrumental in identifying biomarkers that can predict treatment response, disease recurrence, and even progression from infection to active disease—key areas where existing diagnostic and prognostic tools remain insufficient. One of the most pressing challenges in TB research is the need for reliable biomarkers that can expedite drug development and optimize treatment regimens [48]. Current clinical trials rely on treatment success and relapse rates as primary endpoints, requiring prolonged follow-up periods that significantly delay the translation of new therapies into practice. The 2-month sputum culture conversion, commonly used as an early marker of treatment response, has limited predictive value, necessitating large sample sizes and extended study durations [49]. This inefficiency underscores the urgency of developing more precise host-derived and pathogen-based biomarkers to serve as early surrogates for treatment outcomes [50].

Cohort studies provide an ideal framework for identifying and validating such biomarkers. By systematically collecting longitudinal data on clinical, microbiological, immunological, and molecular markers, cohort studies enable researchers to correlate specific biomarkers with disease progression and treatment response [51]. This approach facilitates the development of personalized TB treatment strategies, allowing for tailored regimens that minimize toxicity, reduce treatment duration, and improve adherence. The integration of advanced omics technologies, including transcriptomics, proteomics, and metabolomics, into cohort research holds immense potential for uncovering novel predictors of treatment success and relapse, paving the way for adaptive clinical trial designs that can accelerate drug evaluation and enhance patient stratification [52]. The push toward precision medicine in TB hinges on understanding individual variations in treatment response and disease susceptibility [53]. Unlike conventional clinical trials that focus on population-level outcomes, cohort studies allow for deep phenotyping of TB patients by integrating host genetics, microbiological characteristics, immune responses, and environmental exposures into predictive models. This approach has the potential to revolutionize TB treatment by shifting from one-size-fits-all regimens to more targeted, individualized therapies [54].

Furthermore, cohort studies provide a dynamic platform for evaluating new therapeutic strategies outside the constraints of traditional RCTs. The use of real-world evidence derived from these studies is increasingly recognized as a critical component in regulatory decision-making, bridging the gap between experimental treatments and their practical implementation in endemic settings [55]. Given the diversity of TB manifestations across different populations, leveraging cohort study data ensures that treatment recommendations are both context-specific and globally applicable [56].

The Regional Prospective Observational Research in Tuberculosis (RePORT) International consortium exemplifies the power of global collaboration in cohort-based TB research. Operating across Brazil, India, South Africa, China, Indonesia, the Philippines, Uganda, and the Republic of Korea, RePORT International fosters the development of harmonized, prospective cohort studies that generate high-quality, standardized data for cross-regional analyses. By unifying research efforts across diverse epidemiological landscapes, the consortium facilitates comparative studies on TB transmission, treatment response, and biomarker discovery, thereby amplifying the impact of cohort research on a global scale.

With the recent integration of RePORT Korea, in collaboration with the Korea National Institute of Health and the National Institute of Infectious Diseases, the RePORT framework continues to expand its global reach. This integration strengthens data-sharing initiatives, harmonized protocols, and collaborative research networks, enabling Korean researchers to both contribute to and benefit from international TB research efforts. Moreover, RePORT Korea's engagement with the Cohort Study of Pulmonary Tuberculosis (COSMOTB) [57]—a prospective observational study encompassing nearly 3,000 patients across 20 hospitals—underscores the growing momentum of global TB cohort studies in advancing treatment research and biomarker discovery.

By aligning with RePORT International's commitment to standardized methodologies and open data-sharing, RePORT Korea is poised to make significant contributions to biomarker-driven TB research, potentially accelerating the development of novel diagnostic and prognostic tools. This level of global integration is necessary for overcoming the persistent challenges in TB treatment research, driving innovation in drug development, clinical trial efficiency, and personalized medicine approaches.

The next frontier in TB treatment research lies at the intersection of cohort studies, precision medicine, and biomarker-driven clinical trials. While randomized trials remain fundamental for evaluating treatment efficacy, cohort studies provide the essential context, diversity, and longitudinal data required to refine thera-

peutic strategies, predict treatment success, and improve patient outcomes. By leveraging global research consortia such as REPORT International and initiatives like COSMOTB, the TB research community can accelerate the discovery of biomarkers, optimize treatment regimens, and ultimately redefine the paradigm of TB management. These efforts will enhance clinical decision-making, improve patient care, and propel TB eradication efforts forward, bridging the persistent gaps in our understanding of this complex disease.

Connecting TB treatment research to TB policy

To effectively combat TB, it is crucial to connect TB treatment research with policy-making. This connection enables the formulation of strategies that directly address the evolving challenge of drug resistance and improve treatment outcomes globally. Successful TB research hinges on effective collaboration among various stakeholders—including government bodies, private industries, and academic institutions—which is vital for pooling resources, sharing knowledge, and driving innovation in support of large-scale, complex research projects.

Furthermore, adherence to a global strategy that promotes sustained investment in TB research is indispensable. Such a strategy fosters innovation, ensures data transparency, and improves access to new discoveries, thereby facilitating the creation of evidence-based TB policies. These policies are essential because they rely on scientific data to inform decisions that enhance the effectiveness, efficiency, and reach of TB treatment programs.

Implementing clear and robust regulatory and ethical frameworks ensures that research activities align with the needs and priorities of those most at risk. This alignment helps build trust, enhances the recruitment and retention of study participants, and ensures that research outcomes are both relevant and accepted. Active community engagement is also pivotal, as it ensures that TB treatment research addresses the real-world conditions of affected populations, making the research not only ethical but also practical and applicable.

By integrating these elements, TB research can significantly enhance the potential for developing effective new treatments, thereby improving patient outcomes and contributing to the global eradication of TB. This comprehensive approach ensures that advancements in TB treatment are scientifically robust and appropriately tailored to meet the diverse needs of populations affected by this devastating disease, all underpinned by evidence-based policymaking that ensures the sustainability and relevance of TB control efforts.

Korea, despite being a high-income country, continues to face significant challenges with TB [58]. In response, the third national strategic plan for TB control was introduced in 2023, focusing on the full spectrum of TB management—including prevention, diagnosis, and treatment. This plan emphasizes the development of innovative therapeutic agents and treatment strategies using cutting-edge technologies such as artificial intelligence and omics data. Additionally, it supports creating an optimized evaluation system for preclinical and nonclinical stages, as well as a nationally led infrastructure for standardizing and sharing research resources. These efforts are intended to bolster scientific advancements in TB treatment and ensure effective, patient-centered therapies grounded in robust scientific evidence in Korea.

Challenges in TB treatment development and deployment

To effectively address the multifaceted challenges of TB treatment development, a holistic approach is required that spans from the laboratory to local communities. First, the process of drug development for TB faces significant hurdles. High attrition rates in TB drug development often stem from difficulties in translating preclinical results into safe, effective, and regulatory-approved therapies. Financial limitations further restrict the advancement of promising treatments due to the high costs associated with extensive clinical testing. Additionally, stringent regulatory requirements frequently cause significant delays. Strategic partnerships and policy reforms are essential to bridge these gaps and reduce the time from discovery to clinical application.

Second, the implementation of TB treatment guidelines varies significantly across different healthcare environments. These guidelines, primarily based on data from controlled clinical trials, may not always align with the diverse realities of various regions—especially in areas with unique epidemiological profiles, healthcare infrastructures, and cultural practices. To ensure global efficacy, it is crucial to assess the adaptability of these guidelines to local conditions. This might involve customizing treatment protocols to better suit regional healthcare settings, thereby making the guidelines more relevant and effective worldwide.

Lastly, the real-world deployment of new TB treatments is often hindered by several obstacles, particularly in regions with limited resources where TB is most prevalent. Key challenges include limited access to the latest medications—especially in low-resource settings where the TB burden is highest—and healthcare infrastructures that may lack the capacity to implement new protocols effectively. Additionally, socioeconomic barriers such as poverty, lack of education, and inadequate healthcare cover-

age can restrict patient access to treatment and follow-up care, severely affecting adherence rates and overall treatment success. Enhanced efforts to improve medication accessibility, strengthen healthcare capacities, and implement supportive policies are required to overcome these barriers, ensuring that advancements in TB treatment are effectively realized and benefit those in need.

By addressing these interconnected aspects, from drug development and guideline adaptability to practical rollout challenges, this comprehensive strategy aims to optimize TB treatment at all levels and significantly advance global TB eradication efforts.

Conclusion

Integrating cutting-edge TB treatment research into TB policies is crucial for effectively addressing the global TB epidemic. Innovations in drug development and strategic treatment optimization are necessary to tackle the challenges of drug resistance and improve treatment outcomes. Implementing a comprehensive approach that improves the accessibility and effectiveness of TB treatments requires strong collaboration among governments, private sectors, and academic institutions, along with a steadfast commitment to evidence-based policymaking.

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Conflict of interest

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

Funding

This work was supported by the Research Program funded by the Korea National Institute of Health (grant number: 2022 E200100).

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e23
https://doi.org/10.12771/emj.2025.00052

Ewha Medical Journal

Impact of pulmonary tuberculosis on lung cancer screening: a narrative review

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Lung cancer remains a leading cause of cancer-related mortality worldwide. Low-dose computed tomography (LDCT) screening has demonstrated efficacy in reducing lung cancer mortality by enabling early detection. In several countries, including Korea, LDCT-based screening for high-risk populations has been incorporated into national healthcare policies. However, in regions with a high tuberculosis (TB) burden, the effectiveness of LDCT screening for lung cancer may be influenced by TB-related pulmonary changes. Studies indicate that the screen-positive rate in TB-endemic areas differs from that in low-TB prevalence regions. A critical challenge is the differentiation between lung cancer lesions and TB-related abnormalities, which can contribute to false-positive findings and increase the likelihood of unnecessary invasive procedures. Additionally, structural lung damage from prior TB infections can alter LDCT interpretation, potentially reducing diagnostic accuracy. Nontuberculous mycobacterial infections further complicate this issue, as their radiologic features frequently overlap with those of TB and lung cancer, necessitating additional microbiologic confirmation. Future research incorporating artificial intelligence and biomarkers may enhance diagnostic precision and facilitate a more personalized approach to lung cancer screening in TB-endemic settings.

Keywords: Artificial intelligence; Biomarkers; Early detection of cancer; Lung neoplasms; Pulmonary tuberculosis

Introduction

Background

Lung cancer is a leading cause of cancer-related deaths globally [1]. In the United States, its 5-year age-adjusted incidence and mortality rates are recorded at 49.0 and 32.4 per 100,000, respectively [2]. One of the primary reasons for lung cancer's high mortality rate is that it is often diagnosed at an advanced stage when curative treatment option is limited [3]. The introduction of lung cancer screening (LCS) using low-dose computed tomography (LDCT) has been associated with a measurable decrease in lung cancer-related mortality [4,5].

LDCT plays a pivotal role in detecting lung lesions suspected of malignancy while maintaining low radiation exposure [6]. Individuals presenting with abnormal lung findings may require continued monitoring or definitive diagnostic procedures such as percutaneous needle aspiration, bronchoscopy, or surgical resection [7,8]. LDCT enables the early detection of lung cancer, which is often not detectable on routine chest X-rays [9]. In countries with a high tuberculosis (TB) burden, LCS with LDCT is especially crucial, as conventional chest X-rays often fail to clearly differentiate TB-related sequelae from malignant lesions. Among the various forms of TB sequelae, cavitary lesions and aspergillomas pose a significant challenge in distinguishing them from lung cancer [10]. This, in turn, contributes to improved patient survival by facilitating the diagnosis of lung cancer at an earlier stage [11]. Consequently, several global health organizations endorse LCS, leading to its integration into many national healthcare policies [12-14]. However, conditions such as TB and histoplasmosis can produce LDCT findings resembling malignancies, potentially resulting in unnecessary imaging and invasive testing, which may subject patients to procedural risks and psychological distress [15,16].

Pulmonary TB remains a critical public health concern [17], and presents a diagnostic challenge in differentiating it from malignancy, especially in patients with a past history of mycobacterial

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Received: February 16, 2025 Revised: March 14, 2025 Accepted: March 17, 2025

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infection, a positive tuberculin skin test or interferon-gamma release assay [18,19], and concurrent radiographic pulmonary abnormalities. The diagnosis of lung cancer may be delayed when malignant lesions are mistaken for active TB [20,21].

Objectives

This review aims to examine how TB affects LCS and further explores what clinicians should know to distinguish between the 2 diseases.

Ethics statement

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

Low-dose computed tomography screening for lung cancer

LDCT screening is linked to a substantial reduction in both lung cancer-related and overall mortality [22]. The National Lung Screening Trial, a randomized clinical study, demonstrated that LDCT reduced lung cancer-specific mortality by 20% and overall mortality by 6.7% compared to chest radiography [4,23]. A subsequent 10-year follow-up from the Dutch-Belgian lung cancer screening trial (NELSON) reaffirmed these findings, further supporting the expansion of LDCT-based screening programs [5]. Currently, the U.S. Preventive Services Task Force advises LCS for asymptomatic individuals aged 50 to 80 years who are either current smokers or former smokers who quit within the last 15 years, with a smoking history of at least 20 pack-years [12,24].

In 2015, a Korean multi-society collaborative committee issued LCS guidelines, advocating annual LDCT screening for individuals aged 55–74 years who are either current or former smokers (having quit within the past 15 years) with a history of at least 30 pack-years of smoking [25]. To implement a standardized screening protocol, a multidisciplinary expert committee developed the Korean Lung Cancer Screening Project (K-LUCAS), a population-based, single-arm trial focusing on high-risk individuals who meet these criteria. LDCT results within this initiative follow Lung Imaging Reporting and Data System (Lung-RADS) classification as recommended by the American Radiology Society [26].

Does tuberculosis affects lung cancer screening?

TB is a widespread infectious disease [27], affecting around 25% of the global population with *Mycobacterium tuberculosis* infection. Since 2000, an estimated 58 million individuals have survived the disease [28,29].

For risk-based LCS, age and tobacco use are key determinants; moreover, several lung cancer risk prediction models also consider chronic obstructive pulmonary disease (COPD) and a history of prior cancer [8,30,31], but other comorbidities, along with pulmonary TB is not included [32,33]. Furthermore, most trials on LCS were from regions with low TB prevalence [5,13,34]. In contrast, studies from TB-endemic areas have reported varying screen-positive rates, creating challenges for developing countries in implementing LCS programs [35-37]. It is important to understand key studies on the differences between low TB burden countries and those with a more significant burden.

Studies indicate that individuals with TB face an elevated risk of lung cancer compared to those without TB. A population-based cohort study conducted in Taiwan found that a history of TB was associated with a 1.76-fold increase in lung cancer risk. Multivariate analysis confirmed pulmonary TB as an independent risk factor for lung cancer [38]. A prospective cohort study in Korea found a significant link between pre-existing TB and a higher likelihood of developing lung cancer, with hazard ratios of 1.37 in men and 1.49 in women [39]. A meta-analysis including approximately 477,000 individuals from 44 studies showed that the lung cancer detection rate by LDCT for LCS was 0.94% in high TB-burden countries [40].

Korea is considered a TB-endemic region while providing a unique clinical environment for the advanced detection of 2 major lung diseases: pulmonary TB and lung cancer [41,42]. In 2022, Korea reported a total of 20,383 TB cases, corresponding to an incidence rate of 39.8 per 100,000 people [43]. A multicenter prospective study in Korea (K-LUCAS) involving 11,394 participants, of whom TB sequelae were identified in 13%, reported a 0.6% lung cancer diagnosis rate; the specificity of Lung-RADS was higher in participants without TB sequelae (85%) compared to those with sequelae (80%) ($P < 0.001$), while sensitivity remained unchanged between groups [36].

TB can influence lung cancer risk, particularly among populations eligible for LCS. Moon et al. [29] not only demonstrated an increased lung cancer risk in TB patients but also identified age over 60, smoking, and comorbid COPD or asthma as risk factors among TB survivors. In the COPD subgroup, a well-established risk factor for lung cancer [44], patients with a history of TB had a significantly higher risk of developing lung cancer compared to those without (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.03–1.50) [45].

Beyond its impact on lung cancer prevalence, concurrent pulmonary TB also influences lung cancer-related mortality. A retro-

spective study in China found that individuals with TB had significantly higher lung cancer mortality (25 vs. 3.1 per 1,000 person-years), with the highest risk observed within the first 5 years post-diagnosis (HR, 6.7–13). The increased risk remained at 5–9.9 years (HR, 3.4; 95% CI, 1.3–9.1) and persisted beyond 10 years (HR, 3.0; 95% CI, 1.3–7.3). This association remained significant even after adjusting for confounding factors [46] (Table 1).

Differentiation between pulmonary tuberculosis and lung cancer

In China, 45 out of 6,683 patients (0.7%) initially diagnosed with TB were later confirmed to have lung cancer, primarily due to radiologic suspicion and 27% having a positive sputum acid-fast stain [47].

Radiologic evaluation plays a important role in diagnosing TB, with early bronchogenic spread typically appearing as 2–4 mm centrilobular nodules and branching linear opacities on computed tomography (CT), corresponding to intrabronchiolar and peribronchiolar necrosis. As the disease advances, these nodules may coalesce into larger 5–8 mm lesions or form consolidated lobular opacities [48]. Following anti-TB treatment, residual structural changes, including bronchovascular distortion, bronchiectasis, fibrosis, and emphysema, may persist [49]. Miliary TB on CT often presents initially as ground-glass opacities with indistinct nodules, progressing to discrete miliary nodules measuring less than 3 cm [50]. The variability in pulmonary nodule size frequently complicates diagnosis, particularly when clinical symptoms are non-specific. In some cases, TB manifests as multiple well-defined nodules with partial fusion, further increasing the likelihood of misinterpretation [51]. Additionally, in patients with a history of TB or malignancy, imaging similarities between these diseases increase the risk of misdiagnosis [52].

Positron emission tomography (PET)/CT is an essential tool for lung mass characterization and offers higher accuracy than CT alone for mediastinal lymph node staging in malignancies [53]. However, false positives remain a concern due to increased fluo-

Table 1. Key studies on the influence of pulmonary tuberculosis on lung cancer screening

Study references	Design	Country	Patients	Key findings
[40]	Meta-analysis	Multinational	44 studies with 477,424 individuals	Screen-positive and lung cancer detection rates in high TB-burden countries compared to regions with lower TB incidence
[36]	Multicenter prospective study	Korea (K-LUCAS)	11,394 participants	Lung cancer diagnosis 0.6%; TB sequelae identified in 13%. Specificity of Lung-RADS was higher for participants without TB sequelae (85%) than for those with TB sequelae (80%) ($P<0.001$). Sensitivity was not different between groups.
[38]	Retrospective nationwide population-based cohort study	Taiwan	5657 pulmonary TB patients and 23,984 age- and sex-matched controls	Lung cancer incidence was higher in pulmonary TB patients (269 vs. 153 per 100,000 person-years; IRR, 1.76; 95% CI, 1.33–2.32; $P<0.001$). The risk remained elevated at 2–4 years (IRR, 1.98), 5–7 years (IRR, 1.42), and 8–12 years (IRR, 1.59) post-infection.
[46]	Retrospective study	China	42,422 participants from Xuanwei County	Lung cancer mortality was significantly higher in individuals with TB (25 vs. 3.1 per 1,000 person-years), especially within the first 5 years post-diagnosis (HR, 6.7–13). The risk remained elevated at 5–9.9 years (HR, 3.4; 95% CI, 1.3–9.1) and beyond 10 years (HR, 3.0; 95% CI, 1.3–7.3). The association was significant in the adjusted model.
[45]	Retrospective nationwide population study	Korea	13,165 Korean men and women with COPD	Compared to participants without a history of TB, the fully adjusted subdistribution HR (95% CI) for lung cancer in those with a pulmonary TB history was 1.24 (1.03–1.50).
[29]	Retrospective population study	Korea	75,467 TB survivors	The risk of developing lung cancer was 1.72 times higher in TB survivors compared to controls. Among them, current smokers with at least 20 pack-years had the greatest risk (adjusted HR, 6.78) relative to never-smokers without TB.

TB, tuberculosis; K-LUCAS, Korean Lung Cancer Screening Project; Lung-RADS, Lung Imaging Reporting and Data System; IRR, incidence rate ratio; CI, confidence interval; HR, hazard ratio; COPD, chronic obstructive pulmonary disease.

rodeoxyglucose (FDG) uptake in inflammatory and infectious conditions [54]. Lymph node TB, for example, often exhibits significant FDG uptake, which can be confused with malignancy in patients with multiple hypermetabolic lesions [55]. Therefore, when PET/CT shows increased FDG uptake in patients suspected of having metastases, tuberculous lymphadenopathy should be considered in the differential diagnosis. As the next step in differential diagnosis, pathological evaluation using endobronchial ultrasound-guided transbronchial needle aspiration can provide a more confirmative diagnosis.

When performing a pathologic diagnosis, granulomatous inflammation often occurs in infectious diseases such as TB, as well as in local inflammatory reactions in malignant tumors [56,57]. Hence, although biopsy pathology is important for distinguishing cancer from TB, it cannot be performed routinely due to procedure-related risks [58]. Microbiological confirmation is essential for the definitive diagnosis of pulmonary TB, with a positive sputum culture being a key diagnostic indicator [59]. Tumor markers cannot be specific indicators for differentiating between TB and metastasis [52].

Do nontuberculous mycobacteria affect lung cancer screening?

Nontuberculous mycobacteria (NTM) are widely present in the human environment and are closely associated with chronic pulmonary infections [60-62]. Among the various species, *Mycobacterium avium-intracellulare* complex is the leading cause of NTM-pulmonary disease (NTM-PD) worldwide [63,64]. Although the incidence and prevalence of NTM disease vary among different populations, both have been increasing over time [65-67]. Pulmonary TB and NTM-PD share a similarity in that both diseases often yield positive sputum AFB smears [68,69]. Furthermore, radiologic findings such as lung cavitary lesions, tree-in-bud patterns, and bronchogenic spread are observed in both diseases [68,70].

There are limited studies on the impact of NTM on LCS. However, given its radiologic similarity to pulmonary TB and its high incidence in certain countries, including Korea, the presence of pulmonary NTM is likely to influence LCS outcomes. In Korea, the annual prevalence of NTM diseases rose from 11.4 to 56.7 cases per 100,000 people between 2010 and 2021 [71]. This increasing trend suggests a growing health burden associated with NTM [72], potentially affecting LCS practices and outcomes.

A key distinction between NTM and TB is that, in most cases, pulmonary NTM is not airborne and therefore person-to-person transmission is not proven [73]. However, since LDCT findings alone cannot definitely differentiate between NTM and TB, microbiologic studies are essential along with routine imaging follow-up. However, even when microbiologic evidence confirms NTM, if serial imaging shows changes in lesion size or shape that raise suspicion of malignancy, more aggressive diagnostic measures, such as pathological confirmation, should be pursued.

In a retrospective study of 388 patients with NTM-PD, 14 suspected of having lung cancer were analyzed, with 3.6% presenting as solitary nodules or mass-like consolidations, often incidentally detected, showing poor contrast enhancement, internal calcifications, and strong PET/CT FDG uptake in those who underwent PET/CT [74].

TB is not the only lung infection linked to an increased risk of lung cancer [75-78], suggesting that NTM could also be a potential risk factor. Like TB, NTM infections may contribute to an increased risk of lung cancer by inducing chronic inflammation [79]. Chronic lung inflammation or scar tissue formation following respiratory infections may contribute to lung cancer development [80]. Although current evidence directly connecting NTM to lung cancer is limited, further research is necessary given the growing prevalence of NTM in many populations. For future studies, it will be necessary to analyze the lung cancer detection rate among NTM populations.

Future perspectives

A major challenge in detecting lung cancer in TB-endemic regions is distinguishing TB-related lesions from true malignancies to reduce unnecessary invasive procedures. Recent advancements in artificial intelligence are expected to play a crucial role by supporting clinicians in making informed decisions regarding the need for pathological diagnosis [81,82]. Furthermore, there is a significant need for biomarkers that can reliably differentiate benign lesions from early-stage cancers during imaging, whether in low-dose CT screening or incidentally detected nodules [83,84]. As imaging alone may not be adequate to distinguish between TB and lung cancer, future studies should investigate the potential of liquid biopsy techniques, such as circulating tumor cells, circulating tumor DNA, extracellular vesicles, and tumor-educated platelets, in cancer screening [85].

Conclusion

Pulmonary TB significantly complicates LCS by mimicking malignant lesions LDCT, potentially leading to misdiagnosis, delayed treatment, and unnecessary procedures. In TB-endemic regions, distinguishing TB sequelae from lung cancer remains a di-

agnostic challenge, increasing patient risks and psychological distress. While LDCT enhances early detection and reduces mortality, TB's presence elevates lung cancer risk and mortality, necessitating improved differentiation strategies. Future advancements in AI and biomarkers could refine LCS accuracy, optimizing outcomes in high-TB-burden areas.

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Authors' contributions

All work was done by Jeong Uk Lim.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e24
https://doi.org/10.12771/emj.2025.00059

Ewha Medical Journal

Pathophysiology, clinical manifestation, and treatment of tuberculosis-associated chronic obstructive pulmonary disease: a narrative review

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Chronic obstructive pulmonary disease (COPD) is a leading cause of respiratory morbidity and mortality, most often linked to smoking. However, growing evidence indicates that previous tuberculosis (TB) infection is also a critical risk factor for COPD. This review aimed at providing a comprehensive perspective on TB-COPD, covering its epidemiologic significance, pathogenesis, clinical characteristics, and current management approaches. Tuberculosis-associated chronic obstructive pulmonary disease (TB-COPD) is characterized by persistent inflammatory responses, altered immune pathways, and extensive structural lung damage—manifested as cavitation, fibrosis, and airway remodeling. Multiple epidemiologic studies have shown that individuals with a history of TB have a significantly higher likelihood of developing COPD and experiencing worse outcomes, such as increased breathlessness and frequent exacerbations. Key pathogenic mechanisms include elevated matrix metalloproteinase activity and excessive neutrophil-driven inflammation, which lead to alveolar destruction, fibrotic scarring, and the development of bronchiectasis. Treatment generally follows current COPD guidelines, advocating the use of long-acting bronchodilators and the selective application of inhaled corticosteroids. Studies have demonstrated that indacaterol significantly improves lung function and respiratory symptoms, while long-acting muscarinic antagonists have shown survival benefits.

Keywords: Bronchodilator agents; Chronic obstructive pulmonary disease; Muscarinic antagonist; Smoking; Tuberculosis

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a major global health concern characterized by persistent respiratory symptoms and irreversible airflow limitation, resulting in a substantial socioeconomic burden [1,2]. COPD has long been attributed to prolonged exposure to harmful particles and gases, most notably from cigarette smoke [3]. However, studies indicate that additional risk factors—including genetic predispositions, early life disadvantages, infections, air pollution, and occupational hazards—may also contribute to its development [4,5]. An analysis of the Korean COPD Subgroup Study cohort found that 39% of COPD patients had a history of pulmonary infection (referred to as COPD-I) [6].

Tuberculosis (TB) remains one of the world's deadliest infectious diseases, affecting approximately 10 million people annually despite significant advances in diagnosis and treatment [7]. Although improvements in TB treatment have markedly reduced mortality, the long-term pulmonary sequelae of TB are increasingly recognized as a major cause of chronic respiratory impairment, including airflow limitation, bronchiectasis, and fibrosis [8]. These changes may lead to persistent respiratory symptoms and a reduced quality of life [8]. Previous studies have demonstrated that individuals with a history of TB face a higher risk of developing COPD compared to the general population [9-14]. The overlap between post-TB lung disease and COPD may complicate diagnosis and give rise to unique clinical manifestations [15].

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Received: February 17, 2025 Revised: March 10, 2025 Accepted: March 10, 2025

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Objectives

This article aims to review current knowledge on the epidemiology, pathogenesis, clinical presentations, and therapeutic strategies related to TB-associated COPD (TB-COPD).

Ethics statement

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

Epidemiology and global burden

The global impact of both TB and COPD is profound, significantly contributing to morbidity and mortality [3]. Despite remarkable advances in TB diagnosis and treatment, TB remains a leading infectious disease, with the World Health Organization reporting approximately 10 million new cases annually [7]. High-burden regions such as Southeast Asia, Africa, and the Western Pacific continue to experience a high prevalence of TB [16]. Moreover, individuals with low socioeconomic status and older adults are at higher risk for TB [17-19]. Importantly, a substantial number of TB survivors develop long-term pulmonary sequelae, which are increasingly recognized as a major contributor to the burden of chronic respiratory diseases [8].

COPD, traditionally regarded as a disease associated with cigarette smoking, is now understood to have a multifactorial etiology [20]. Previous studies have demonstrated that a prior TB infection is a significant risk factor for developing COPD. In an analysis of the Burden of Obstructive Lung Disease (BOLD) study, patients with a TB history had a 2.5-fold higher risk of airflow obstruction and a 2.1-fold higher risk of spirometric restriction [10]. A pooled analysis of 6 cohorts across 13 low- and middle-income countries (LMICs) found that individuals with a history of TB had lower lung function and a 4-fold increased risk of developing COPD compared to those without a TB history [14]. Furthermore, a meta-analysis revealed that a history of TB was associated with a 2.6-fold increased risk of future chronic airflow obstruction, with a pooled COPD prevalence of 21% among TB survivors [11].

Conversely, COPD itself has been identified as a risk factor for pulmonary TB, with a reported hazard ratio (HR) of 2.47 (95% confidence interval [CI], 2.21–2.76) [21]. Moreover, the use of inhaled corticosteroids (ICS) in COPD patients may further increase the risk of developing TB [22,23].

The dual burden of TB and COPD is particularly pronounced in LMICs, where TB incidence remains high and access to advanced respiratory care is limited [24]. In these settings, the long-term consequences of TB are more likely to manifest, contributing to persistent respiratory symptoms and airflow obstruction that accelerate COPD progression. This intersection not only complicates clinical management but also demands substantial healthcare resources [25]. Notably, the BOLD study demonstrated that the prevalence of airflow obstruction was 19.5% in Cape Town (TB prevalence: 15.4%), 15.2% in Nampicuan and Talugtug, Philippines (TB prevalence: 10.8%), and 7.0% in Pune, India (TB prevalence: 7.0%), underscoring the significant COPD burden in TB-endemic regions [10]. These epidemiological findings underscore the critical need for integrated public health strategies, including enhanced surveillance, improved diagnostic modalities, and targeted interventions, particularly in resource-limited regions [25]. Recognizing the epidemiological associations between TB and COPD is essential for reducing the global burden of chronic respiratory diseases.

Pathogenesis of TB-COPD

Molecular mechanisms

TB-COPD is driven by persistent immune activation that leads to progressive lung damage [26-28]. TB infection stimulates alveolar macrophage activation and neutrophil infiltration, which in turn release high levels of proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 [26]. These cytokines promote granuloma formation and sustain inflammation even after TB treatment, ultimately causing structural lung damage and airway remodeling [27]. The chronic inflammatory response is further intensified by oxidative stress and excessive immune cell recruitment, contributing to long-term pulmonary dysfunction [29]. Notably, the inflammatory profile in TB-COPD differs from that observed in smoking-related COPD [30].

Matrix metalloproteinases (MMPs) play a pivotal role in the tissue destruction observed in TB-COPD [27-29,31]. MMP-1, MMP-8, and MMP-9 are highly expressed in TB-infected lungs, where they degrade extracellular matrix components, resulting in alveolar destruction and emphysema formation [29,31,32]. TB infection upregulates MMP expression in response to hypoxia and chronic inflammation, further exacerbating lung tissue damage. Studies have demonstrated that TB patients with elevated MMP levels exhibit more severe lung function impairment, along with increased fibrosis and remodeling [33]. Persistent dysregulation of MMPs even after TB treatment suggests a mechanistic link between post-TB disease and COPD [27,31].

Neutrophilic inflammation significantly contributes to airway remodeling and irreversible airflow obstruction in TB-COPD

[26]. In TB patients, neutrophils are excessively recruited to the lungs, where they undergo necrotic cell death and release neutrophil extracellular traps (NETs), which consist of DNA, histones, and proteolytic enzymes [29,34,35]. Although NETs help contain bacteria, their excessive formation results in tissue necrosis, fibrosis, and airway remodeling. Additionally, oxidative stress and excessive neutrophil degranulation contribute to the progression of emphysema and persistent lung inflammation in TB-COPD [36,37].

Structural lung damage, fibrosis, and airway remodeling

Structural lung damage and fibrosis in TB-COPD stem from chronic inflammation, excessive immune activation, and dysregulated tissue repair mechanisms following TB infection [26]. In severe cases, TB-COPD may present as extensive structural lung damage—often termed TB-destroyed lung—characterized by parenchymal destruction, traction bronchiectasis, and persistent airflow obstruction [38,39]. Granuloma formation—a hallmark of TB—leads to necrosis and cavitation, resulting in fibrotic scarring and architectural distortion of the lung parenchyma [40]. Fibrotic changes following TB infection are typically asymmetrical and heterogeneous, primarily affecting the upper lobes, which distinguishes TB-COPD from smoking-related COPD [41]. These fibrotic alterations cause traction bronchiectasis, pleural thickening, and permanent alveolar damage, contributing to restrictive lung function abnormalities and airflow obstruction [42].

Furthermore, post-TB scarring frequently results in bronchial stenosis and large airway obstruction, particularly in patients with a history of endobronchial TB [42]. Moreover, a previous study demonstrated that post-TB patients exhibit significantly lower maximal mid-expiratory flow, forced expiratory flow at 50% (FEF50), and FEF75, suggesting early small airway impairment [41].

Histological analysis of post-TB lungs revealed residual healed and fibrotic granulomas predominantly located along bronchovascular bundles [43]. These granulomas were encircled by fibrosis, resulting in bronchiolar narrowing, distortion, and occasional dilation. Additionally, adjacent pulmonary arterioles were partially incorporated into the fibrotic process, with multinucleated giant cells present, although no detectable organisms were found on special stains.

Clinical manifestations

TB survivors frequently experience significant post-TB lung damage, which has been linked to poor outcomes such as accelerated lung function decline, persistent respiratory symptoms, and frequent healthcare visits within 1 year after completing treatment [44,45]. This persistent lung damage elevates the risk of developing TB-COPD, as structural and functional airway impairments can lead to chronic airflow obstruction and long-term respiratory complications.

TB-COPD exhibits clinical manifestations distinct from those of COPD caused by tobacco smoking. TB-COPD primarily affects younger individuals following TB infection, presenting with fixed airflow obstruction, cavitation, and fibrosis (Fig. 1A). In contrast, non-TB-COPD predominantly affects older adults with a history of smoking or environmental exposure and is characterized by fixed or partially reversible airflow obstruction, airway wall thickening, and emphysema (Fig. 1B) [22]. Hemoptysis may occur in TB-COPD patients, particularly in those with secondary infections, bronchiectasis, or chronic pulmonary aspergillosis [22]. TB-COPD may be static or progressive with recurrent exacerbations, whereas non-TB-COPD typically follows a progressive course with recurrent acute exacerbations [22].

Studies indicate that TB-COPD may lead to poorer outcomes compared to smoking-related COPD. An analysis of the Korean National Health Insurance Service database (2010–2017) revealed that TB survivors had a significantly higher risk of developing COPD (adjusted HR [aHR], 1.63; 95% CI, 1.54–1.73) and of COPD-related hospitalization (aHR, 2.03; 95% CI, 1.81–2.27) [46]. Furthermore, TB-COPD patients were more likely to require COPD-related hospitalization compared to non-TB COPD patients (aHR, 1.84; 95% CI, 1.17–2.92). Additionally, an analysis of a multicenter COPD cohort in South Korea found that COPD patients with a history of TB experienced worse outcomes, including more severe symptoms (COPD assessment test: 16.1 vs. 14.8, $P = 0.002$), poorer quality of life (St. George's Respiratory Questionnaire for COPD: 36.6 vs. 32.6, $P < 0.001$), and a higher prevalence of exacerbations (28.8% vs. 23.5%, $P = 0.031$) as well as severe exacerbations requiring hospitalization (3.9% vs. 1.5%, $P = 0.002$) [47]. Moreover, a single-center study conducted in China reported that TB-COPD patients were more likely to have bronchiectasis and emphysema and experienced more significant breathlessness and frequent exacerbations compared to non-TB-COPD patients [48]. Elevated IL-6 levels and the presence of bronchiectasis have been identified as risk factors for future exacerbations in TB-COPD [39,49]. Further investigations involving larger populations and longer follow-up periods are needed to enhance the generalizability of these findings.

Management strategies

The treatment of TB-COPD is primarily guided by current

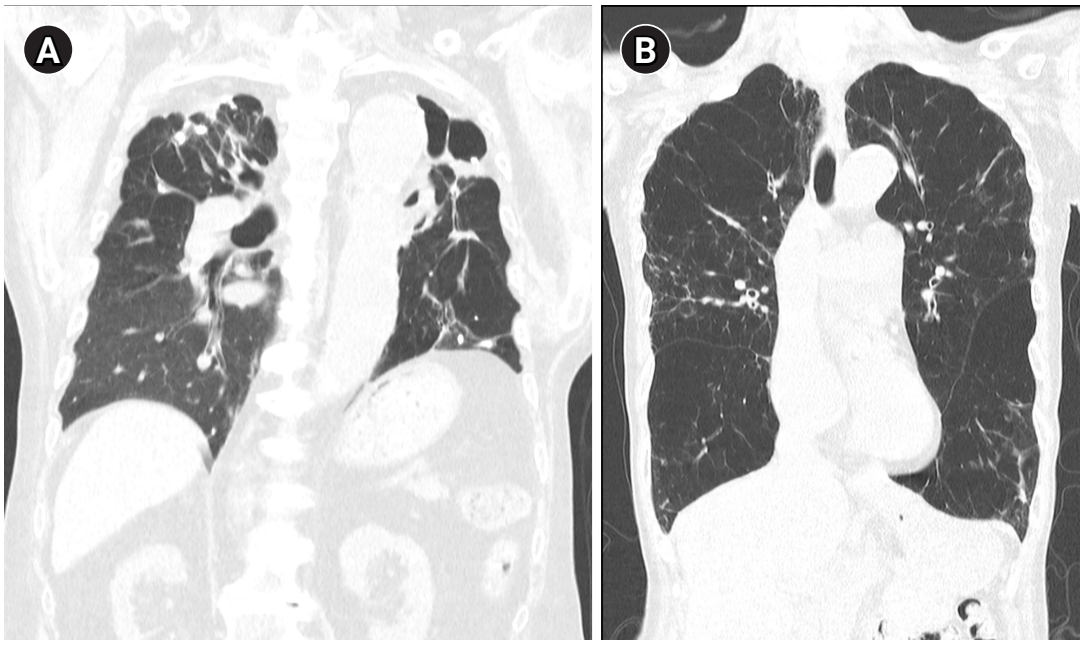

Fig. 1. Representative computed tomography images illustrating typical radiologic features of tuberculosis-associated chronic obstructive pulmonary disease and smoking-related chronic obstructive pulmonary disease. (A) A patient with tuberculosis-associated chronic obstructive pulmonary disease shows fibrotic changes, cavitation, and traction bronchiectasis predominantly in the upper lobes. (B) A patient with smoking-related chronic obstructive pulmonary disease exhibits emphysematous lesions and airway wall thickening typical of smoking-related chronic obstructive pulmonary disease.

COPD management guidelines [22]. Long-acting bronchodilators constitute the cornerstone of therapy, and ICS should be reserved for patients with high blood eosinophil levels and frequent exacerbations [3]. However, the use of ICS may contribute to TB relapse in COPD patients with radiologic sequelae of prior TB [50]. In patients with central airway obstruction, inhaled medications may have limited efficacy; in such cases, interventional bronchoscopic procedures—including bronchoscopic dilation, airway stenting, argon plasma coagulation, and electrocautery—can be beneficial [22]. For patients with recurrent hemoptysis due to bronchiectasis, bronchial artery embolization or surgical resection of the affected area may be necessary [22].

Few studies have addressed the treatment of TB-COPD. The indacaterol effectiveness in COPD patients with tuberculosis history (INFINITY) study, a randomized double-blind placebo-controlled trial, evaluated the efficacy and safety of indacaterol in patients with TB-COPD [51]. After 8 weeks, indacaterol significantly improved forced expiratory volume in 1 second (+140 mL, $P < 0.001$), dyspnea scores, and health status compared to placebo, while maintaining a comparable safety profile.

Notably, a large proportion of patients enrolled in this study were never-smokers, which enhances the relevance of the findings. These results suggest that indacaterol is a beneficial treatment option for TB-COPD. A post-hoc analysis of the INFINITY study identified factors associated with improved lung function in response to indacaterol, revealing that a shorter smoking history and a high bronchodilator response were linked to better outcomes [52]. Moreover, the use of long-acting muscarinic antagonists (LAMAs) has also shown benefits in TB-COPD patients. A retrospective, single-center study analyzing the mortality benefits of LAMA therapy in TB-COPD found that the LAMA group had a significantly lower 5-year mortality rate compared to the non-LAMA group (3.1% vs. 14.1%, $P = 0.039$) [53]. Additionally, an analysis of the Korean National Health Insurance claims database found that tiotropium use was associated with reduced mortality in patients with TB-destroyed lungs, although the study included both COPD and non-COPD patients (HR, 0.560; 95% CI, 0.38–0.82) [54].

Conclusion

TB-COPD is a distinct clinical entity characterized by unique structural and inflammatory features compared to smoking-related COPD. Numerous studies have demonstrated a heightened likelihood of chronic lung impairment following TB infection, resulting in persistent airflow limitation and increased healthcare needs. The underlying mechanisms include sustained immune activity, elevated production of MMPs, and pronounced neutro-

phil-driven inflammation, ultimately leading to fibrotic scarring and airway remodeling. Clinically, individuals with TB-COPD often present at a younger age, exhibit marked fibrotic changes in the lung, and may experience hemoptysis due to coexisting bronchiectasis. Management generally follows standard COPD recommendations, emphasizing long-acting bronchodilators and cautious use of inhaled corticosteroids based on individual risk profiles. Both indacaterol and tiotropium have demonstrated benefits in improving pulmonary function, reducing exacerbations, and lowering mortality in these patients. In certain cases, interventional or surgical procedures may be necessary to address severe airway obstructions or persistent hemoptysis.

In addition, early TB detection, prompt and effective TB treatment (including latent TB management), and the development of host-directed therapies can help limit the progression of post-TB lung disease [55]. By combining these approaches, clinicians may improve patient outcomes, reduce the global burden of TB-COPD, and enhance the quality of life for affected individuals.

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Authors' contributions

All work was done by Joon Young Choi.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e25
https://doi.org/10.12771/emj.2025.00080

Ewha Medical Journal

Current and emerging treatment strategies for *Mycobacterium avium* complex pulmonary disease: a narrative review

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The *Mycobacterium avium* complex (MAC), comprising *M. avium* and *M. intracellulare*, constitutes the predominant cause of nontuberculous mycobacterial pulmonary disease (NTM-PD) in Korea, followed by the *M. abscessus* complex. Its global prevalence is increasing, as shown by a marked rise in Korea from 11.4 to 56.7 per 100,000 individuals between 2010 and 2021, surpassing the incidence of tuberculosis. Among the older adult population (aged ≥65 years), the prevalence escalated from 41.9 to 163.1 per 100,000, accounting for 47.6% of cases by 2021. Treatment should be individualized based on prognostic indicators, including cavitary disease, low body mass index, and positive sputum smears for acid-fast bacilli. Current therapeutic guidelines recommend a 3-drug regimen—consisting of a macrolide, rifampin, and ethambutol—administered for a minimum of 12 months following culture conversion. Nevertheless, treatment success rates are only roughly 60%, and over 30% of patients experience recurrence. This is often attributable to reinfection rather than relapse. Antimicrobial susceptibility testing for clarithromycin and amikacin is essential, as resistance significantly worsens prognosis. Ethambutol plays a crucial role in preventing the development of macrolide resistance, whereas the inclusion of rifampin remains a subject of ongoing debate. Emerging therapeutic strategies suggest daily dosing for milder cases, increased azithromycin dosing, and the substitution of rifampin with clofazimine in severe presentations. Surgical resection achieves a notable sputum conversion rate of approximately 93% in eligible candidates. For refractory MAC-PD, adjunctive therapy with amikacin is advised, coupled with strategies to reduce environmental exposure. Despite advancements in therapeutic approaches, patient outcomes remain suboptimal, highlighting the urgent need for novel interventions.

Keywords: Bacterial drug resistance; Ethambutol; Lung diseases; *Mycobacterium avium* complex; Tuberculosis

Introduction

Background

Nontuberculous mycobacteria (NTM) are ubiquitous organisms found in various environments, including soil and water [1]. Although NTM infections can affect both pulmonary and extrapulmonary systems, pulmonary disease (PD) is the most common clinical manifestation worldwide [2]. The global prevalence and incidence of NTM-PD have steadily increased, with *Mycobacterium avium* complex (MAC) being the leading cause, followed by the *M. abscessus* complex [3,4].

In Korea, the annual prevalence of NTM-PD increased from 11.4 per 100,000 in 2010 to 56.7 per 100,000 in 2021, surpassing the tuberculosis (TB) rate of 52.1 per 100,000 in 2021 [5]. Notably, among older adults (aged ≥65 years), the prevalence rose dramatically from 41.9 to 163.1 per 100,000, with this age group accounting for 47.6% of total cases in 2021 [5]. Given the rapidly aging demographic structure in Korea, the proportion of older adults with NTM-PD is expected to increase, which will impose a substantial socioeconomic burden on the national healthcare system [5].

The most significant human pathogens in MAC are *M. avium*, *M. intracellulare*, and *M. chimaera*. Although MAC includes several other species, such as *M. arosiense*, *M. colombiense*, *M. bouchedurhonense*, *M. marseillense*, *M. vulneris*, *M. timonense*, and *M. yongonense*, most laboratories are unable to identify these species and subspecies due to the lack of capacity to conduct the molecular methods necessary for their detection [3]. In Korea, the most

*Corresponding email: sawadax@naver.com
Received: February 23, 2025 Revised: March 11, 2025 Accepted: March 14, 2025

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common causative species of NTM-PD are MAC (79.8%), comprising *M. avium* (41.4%) and *M. intracellulare* (38.4%), followed by the *M. abscessus* complex (16.4%) [4]. Although the number of reported NTM-PD cases has risen over the past decades, the proportions of causative species have remained largely unchanged [4].

Treating NTM-PD is challenging. Even with more than 12 months of treatment using at least 3 antibiotics, overall success rates for MAC-PD hover around 60% [6-10]. Furthermore, even after successful treatment, more than one-third of patients experience recurrence of MAC-PD [11]. Thus, current treatment strategies for MAC-PD must be reassessed to improve clinical outcomes.

Objectives

This review comprehensively summarizes existing guidelines and recent updates in treatment approaches for MAC-PD.

Ethics statement

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

Clinical presentations of MAC-PD

The diagnostic criteria for NTM-PD were established in the 2007 American Thoracic Society, and Infectious Diseases Society of America (ATS/IDSA) guidelines and have remained unchanged in the 2020 American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America (ATS/ERS/ESCMID/IDSA) guidelines. To diagnose NTM-PD, all clinical, radiologic, and microbiologic criteria should be met [2,12] (Table 1).

The natural course of NTM-PD is influenced by its clinical presentation, which can be categorized into 2 types: fibrocavitary and nodular bronchiectatic [2,3]. Traditionally, the fibrocavitary type is the most common. It is characterized by cavitary lesions in the upper lobes and is often associated with other pulmonary conditions, such as a history of TB or chronic obstructive pulmonary disease. This form typically develops in older males with a history of cigarette smoking and/or alcohol abuse. If left untreated, it rapidly progresses within 1–2 years, potentially leading to extensive lung destruction and respiratory failure [2,3].

In contrast, the nodular bronchiectatic type typically presents as bilateral bronchiectasis with nodular opacities and/or centrilobular infiltrates, frequently affecting the right middle lobe and/or lingula segment. This type predominantly develops in postmenopausal nonsmoking females and usually progresses more slowly than the fibrocavitary form [2,3]. In advanced stages, even this type may develop cavitary lesions [13,14].

A significant proportion of patients with NTM-PD have underlying lung diseases, such as bronchiectasis or TB-destroyed lungs, which raises concerns about bacterial coinfections [15]. Recent studies have reported the clinical features of patients with NTM-PD and bacterial coinfections. Among 180 patients who underwent bronchoscopy, 169 (93.9%) had bronchiectasis and 22 (12.2%) had TB-destroyed lungs. MAC was identified in 153 patients (85.0%), and bacterial coinfections were present in 80 individuals (44.4%). The most commonly identified bacteria were *Klebsiella pneumoniae* (25/80, 31.3%), followed by *Pseudomonas aeruginosa* (20/80, 25.0%) and *Staphylococcus aureus* (20/80, 25.0%). Compared with those without *P. aeruginosa*, patients with this bacterium were older, had a higher prevalence of smoking, exhibited more respiratory symptoms such as cough, and showed more extensive lung involvement [15].

Table 1. Diagnostic criteria for nontuberculous mycobacterial pulmonary disease

	Diagnostic criteria
Clinical	(1) Pulmonary or systemic symptoms and (2) appropriate exclusion of other diagnoses
Radiologic	(1) Nodular or cavitary opacities on chest radiograph or (2) bronchiectasis with multiple small nodules on high-resolution computed tomography scan
Microbiologic	(1) Positive culture results from at least 2 separate expectorated sputum samples (over an interval of a week or more) or (2) positive culture results from at least one bronchial wash or lavage or (3) transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM
	When 2 positive cultures are obtained, the isolates should be the same NTM species (or subspecies in the case of *Mycobacterium abscessus*) in order to meet disease criteria.

AFB, acid-fast bacilli; NTM, nontuberculous mycobacteria.

Natural courses and treatment decision of MAC-PD

The diagnosis of MAC-PD does not always require immediate treatment. Approximately 40%–60% of patients remain stable for several years after diagnosis without intervention [14,16]. Furthermore, around 40%–50% of patients achieve spontaneous negative culture conversion without therapy [16,17]. Therefore, physicians should closely monitor disease progression and make timely decisions about initiating treatment, weighing the potential risks and benefits.

Observational studies have identified several prognostic factors linked to the progression and mortality of MAC-PD. These include: (1) cavitary lesions [14,16,18], (2) low body mass index (BMI) [16-18], (3) extensive disease [16,19], and (4) positive sputum acid-fast bacilli (AFB) smear [16,17]. Treatment should be considered when patients exhibit these risk factors.

A scoring system, known as the BACES (BMI, age, cavity, erythrocyte sedimentation rate, and sex) score, was recently developed to predict mortality in patients with NTM-PD [20]. The BACES score comprises 5 items: (1) BMI < 18.5 kg/m^2, (2) age ≥ 65 years, (3) presence of a cavity, (4) elevated erythrocyte sedimentation rate, and (5) male sex (each item is assigned one point). The estimated risk of 5-year mortality increases with higher BACES scores, ranging from 1.2% at a score of 0 to 82.9% at a score of 5, demonstrating excellent discrimination performance (Harrell's C index = 0.812) [20]. A higher BACES score is associated with greater disease severity (e.g., positive sputum AFB smear and cavity presence), an increased risk of disease progression, persistent sputum AFB smear positivity, and higher all-cause and disease-specific mortality [21]. Although the BACES score was not designed to predict treatment response in MAC-PD, it may help guide decisions on whether patients should be monitored or require immediate treatment (scores 0–1: observation; scores 2–3: treatment if symptomatic; scores 4–5: immediate treatment) [20] (Table 2).

Current guidelines for antibiotics treatment

Although some randomized controlled trials have investigated 3-drug regimens that include a macrolide, no well-designed landmark study has definitively established this combination therapy for MAC-PD [22-24]. Recent systematic reviews have reported improved sputum culture conversion rates (54% vs. 38%) and overall treatment success (65.7%) with macrolide-containing regimens [8,9]. Moreover, in cases of macrolide-resistant disease, sputum culture conversion rates drop to approximately 20% [25]. Thus, macrolides remain a crucial component of MAC-PD treatment because outcomes are poor without them. Regarding companion drugs, only regimens that combine rifampin with ethambutol or clofazimine with ethambutol have been shown to prevent macrolide resistance during treatment [22,26,27]. Ethambutol is the most effective companion drug in this regard. Although the role of rifampin is not entirely clear, current guidelines favor its use until further evidence shows that macrolide resistance develops similarly in both 3-drug and 2-drug regimens [12].

The 2020 ATS/ERS/ESCMID/IDSA guidelines recommend a 3-drug macrolide-based regimen for patients with macrolide-susceptible MAC-PD. This regimen includes a macrolide (azithromycin or clarithromycin), rifampin, and ethambutol [12]. Since the 1997 ATS guidelines, this 3-drug regimen has been a cornerstone of MAC-PD treatment and has served as the basis for many subsequent studies [28]. For patients with advanced or severe bronchiectatic, cavitary, or macrolide-resistant MAC-PD, parenteral amikacin (or streptomycin) should be added to the initial treatment for at least 2–3 months [12]. Dosing frequency varies among disease types [12]; an intermittent regimen (3 times

Table 2. The BACES score system

Variable	Detail	Point
Body mass index (kg/m^2)	< 18.5	1
Age (yr)	≥ 65	1
Cavity	Visible on chest computed tomography	1
Elevated erythrocyte sedimentation rate	> 15 mm/hr for male, > 20 mm/hr for female	1
Sex	Male	1
Treatment recommendation		
Scores 0–1	Observation	
Scores 2–3	Treatment if symptomatic	
Scores 4–5	Immediate treatment	

BACES, body mass index, age, cavity, erythrocyte sedimentation rate, and sex.

per week) is recommended for patients with the nodular bronchiectatic type, whereas a daily regimen is advised for those with cavitary or severe bronchiectatic disease. Treatment should continue for at least 12 months after sputum culture conversion. If culture conversion is not achieved after 6 months of guideline-based treatment, indicating refractory disease, amikacin liposome inhalational suspension (ALIS) is recommended [12,29].

The 2017 British Thoracic Society (BTS) guidelines recommend a similar regimen consisting of a macrolide, rifampin, and ethambutol [30]. Although both guidelines propose intermittent and daily regimens, their indications differ slightly. The BTS guidelines recommend a daily regimen with parenteral or nebulized amikacin for patients with severe MAC-PD, defined by a positive sputum AFB smear, lung cavitation or severe disease, marked systemic symptoms, or a history of treatment failure [30]. Thus, a daily regimen is not limited solely to cavitary disease.

Several discrepancies exist between the 2 guidelines regarding drug regimens. First, the BTS guidelines recommend azithromycin 250 mg daily for a daily regimen, while the ATS/ERS/ESCMID/IDSA guidelines suggest 250–500 mg daily. Second, the BTS guidelines propose parenteral aminoglycosides for up to 3 months for severe MAC-PD, whereas the ATS/ERS/ESCMID/IDSA guidelines recommend aminoglycosides for at least 2–3 months for cavitary or advanced/severe bronchiectatic MAC-PD. Third, although both guidelines advocate the use of parenteral aminoglycosides for advanced/severe bronchiectatic MAC-PD, the ATS/ERS/ESCMID/IDSA guidelines do not clarify whether a daily or intermittent regimen should be used, while the BTS guidelines favor a daily regimen. Fourth, the BTS guidelines recommend using a parenteral formulation of amikacin for nebulization, whereas the ATS/ERS/ESCMID/IDSA guidelines recommend ALIS (Table 3).

Treatment outcomes of MAC-PD

Over the past decade, several systematic reviews and meta-analyses have examined the treatment outcomes of MAC-PD [6-10]. Success rates varied across studies due to differences in study design, drug regimens, treatment outcomes, and disease severity. Pooled success rates ranged from 39% to 68%, which remains relatively lower than those for TB [6-10]. Subgroup analyses consistently showed that macrolide-containing regimens yielded better outcomes than those without macrolides [6-8,10]. Furthermore, the ATS-recommended 3-drug regimen (macrolide, rifampin, and ethambutol) demonstrated superior outcomes (61.4% success compared to 52.3% for other macrolide-containing regimens), with even more favorable results when maintained for at least 1 year (65.7%) [9] (Table 4).

Antimicrobial susceptibility testing

Before initiating treatment, it is essential to perform antimicrobial susceptibility testing for clarithromycin (a representative macrolide) and amikacin, as *in vitro* susceptibility for these drugs correlates with treatment outcomes [12]. The resistance breakpoints are defined as ≥ 32 μg/mL for clarithromycin, > 64 μg/mL for parenteral amikacin, and ≥ 128 μg/mL for ALIS [12,31]. Although susceptibility testing can be conducted for other drugs, their clinical utility remains uncertain. For example, Luo et al. [32] proposed tentative epidemiological cutoff values for clofazimine in *M. avium* and *M. intracellulare* as 1 μg/mL and 2 μg/mL, respectively; however, further studies are needed to confirm these breakpoints.

A recent report from a referral hospital in Korea (2016–2020) detailed antimicrobial susceptibility patterns among NTM isolates [31]. Among 308 strains of MAC, nearly all were susceptible to clarithromycin (*M. avium*: 90/91, 99%; *M. intracellulare*: 217/217, 100%). However, susceptibility to amikacin was slightly lower in *M. avium* (69/91, 76%) than in *M. intracellulare* (191/217, 88%; P = 0.01) [31]. Disappointingly, most MAC strains were not susceptible to moxifloxacin (*M. avium*: 20/91, 22%; *M. intracellulare*: 18/217, 8%). and linezolid (*M. avium*: 27/91, 30%; *M. intracellulare*: 16/217, 7%) [31]. These data underscore the crucial role of macrolide in MAC treatment.

Constructing treatment regimen

Macrolides

Among macrolides, azithromycin is generally preferred over clarithromycin in most clinical settings. This preference is due to its once-daily dosing (compared to clarithromycin's twice-daily schedule), fewer side effects and drug interactions, and a serum concentration that is less affected by coadministration with rifampin [12,33]. Gastrointestinal disturbances are common with long-term macrolide use and occur more frequently with clarithromycin than with azithromycin.

For mild disease, an intermittent regimen is often preferred over a daily regimen because it is associated with fewer gastrointestinal disturbances and yields comparable treatment outcomes, as previous studies have demonstrated [12,34]. A meta-analysis reported similar treatment success rates between intermittent and daily regimens (61%; 95% confidence interval [CI], 55%–67% vs. 60%; 95% CI, 53%–66%) [7]. However, one landmark study found that overall treatment outcomes were not entirely satisfac-

Table 3. Treatment of *Mycobacterium avium* complex pulmonary disease according to current guidelines

Disease types	No. of drugs	Drug regimen	Treatment duration
2020 American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America guidelines [12]			
Nodular-bronchiectatic MAC-PD	3	• Azithromycin 500 mg TIW (clarithromycin 1 g in 2 divided doses TIW) • Rifampin 600 mg TIW (rifabutin 300 mg TIW) • Ethambutol 25 mg/kg TIW	At least 12 months after culture conversion
Cavitary MAC-PD	≥ 3	• Azithromycin 250–500 mg daily (clarithromycin 500 mg twice daily) • Rifampin 450 mg or 600 mg daily (rifabutin 150–300 mg daily, 150 mg daily with clarithromycin) • Ethambutol 15 mg/kg daily • Intravenous amikacin 10–15 mg/kg daily or 15–25 mg/kg TIW (streptomycin 10–15 mg/kg daily or 15–25 mg/kg TIW) for at least 2–3 months	At least 12 months after culture conversion
Refractory MAC-PD (sputum culture positive after 6 months of guideline-based therapy)	≥ 4	• Azithromycin 250–500 mg daily (clarithromycin 500 mg twice daily) • Rifampin 450 mg or 600 mg daily (rifabutin 150–300 mg daily, 150 mg daily with clarithromycin) • Ethambutol 15 mg/kg daily • Amikacin liposome inhalational suspension or 590 mg per day • Intravenous amikacin 10–15 mg/kg daily or 15–25 mg/kg TIW (streptomycin 10–15 mg/kg daily or 15–25 mg/kg TIW) for at least 2–3 months	At least 12 months after culture conversion
Macrolide-resistant MAC-PD		• Expert consultation	
2017 British Thoracic Society guidelines [30]			
Non-severe MAC-PD (i.e., negative sputum AFB smear, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	3	• Azithromycin 500 mg TIW or clarithromycin 1 g in 2 divided doses TIW • Rifampin 600 mg TIW • Ethambutol 25 mg/kg TIW	A minimum of 12 months after culture conversion
Severe MAC-PD (i.e., positive sputum AFB smear, radiological evidence of lung cavitation/severe infection, severe symptoms/signs of systemic illness, or a history of treatment failure)	≥ 4	• Azithromycin 250 mg daily or clarithromycin 500 mg twice daily • Rifampin 600 mg daily • Ethambutol 15 mg/kg daily • Intravenous amikacin 15 mg/kg once daily or 7.5 mg/kg twice daily or 15–25 mg/kg TIW for up to 3 months or intravenous streptomycin 15 mg/kg daily for initial 1 month, followed by 15 mg/kg TIW for up to 3 months or nebulized amikacin 500 mg twice daily (dose reduction: 250–500 mg once or twice daily)	A minimum of 12 months after culture conversion
Clarithromycin-resistant MAC-PD	≥ 4	• Rifampin 600 mg daily • Ethambutol 15 mg/kg daily • Isoniazid 300 mg (+pyridoxine 10 mg) daily or moxifloxacin 400 mg daily • Intravenous amikacin 15 mg/kg once daily or 7.5 mg/kg twice daily or 15–25 mg/kg TIW for up to 3 months or intravenous streptomycin 15 mg/kg daily for initial 1 month, followed by 15 mg/kg TIW for up to 3 months or nebulized amikacin 500 mg twice daily (dose reduction: 250–500 mg once or twice daily)	A minimum of 12 months after culture conversion

MAC-PD, *Mycobacterium avium* complex pulmonary disease; TIW, 3 times per week; AFB, acid-fast bacilli.

Table 4. Summary of meta-analyses of treatment outcomes of *Mycobacterium avium* complex pulmonary disease

Author	Year	No. of studies	No. of participants	Study designs	Definition of treatment success	Estimated pooled rates of study outcomes, % (95% CI)
Xu et al. [6]	2014	28	2,422	Prospective and retrospective study	Variable (specified by mycobacterial culture endpoints)	• Treatment success: 39% (38%–41%) • Macrolide-containing regimens: 42% (40%–44%) • Macrolide-free regimens: 28% (24%–32%)
Kwak et al. [7]	2017	16	1,462	Randomized controlled trials, observational studies	12 months of sustained culture negativity	• Treatment success: 60.0% (55.1%–64.8%) • Macrolide-free regimens: 53.6% (38.0%–69.3%)
Pasipanodya et al. [8]	2017	21	2,534	Prospective studies, clinical trials, reports from established disease registries	Sputum culture conversion	• Sustained sputum culture conversion • Macrolide-containing regimens: 54% (45%–63%) • Macrolide-free regimens: 38% (25%–52%)
Diel et al. [9]	2018	42	2,748	Randomized study, prospective study, retrospective study	Sputum culture conversion	• Sputum culture conversion • Macrolide-containing regimen: 52.3% (44.7%–59.9%) • ATS recommended 3-drug regimen: 61.4% (49.7%–72.5%) • ATS recommended 3-drug regimen for at least 1 year: 65.7% (53.3%–77.4%)
Nasiri et al. [10]	2020	45	3,862	Randomized trial, retrospective study	Sputum culture conversion and completion of the planned treatment without relapse	• Treatment success: 68.1% (64.7%–71.4%) • Macrolide-containing regimens: 69.0% (65.7%–72.3%) • Macrolide-free regimens: 58.5% (38.8%–78.2%)

CI, confidence interval; ATS, American Thoracic Society.

tory: symptom improvement occurred in 75% of patients on daily treatment compared to 82% on intermittent treatment (P = 0.181), radiologic improvement was observed in 68% vs. 73% (P = 0.402), and sputum culture conversion rates were 76% vs. 67% (P = 0.154) [34].

A recent report evaluated daily regimen outcomes in non-cavitary nodular bronchiectatic MAC-PD [35]. Among 110 patients, 53 (48.2%) received daily treatment. The culture conversion rate was significantly higher in the daily group than in the intermittent group (90.6% [48/53] vs. 70.2% [40/57], P = 0.008). This difference was particularly notable in 36 patients with a positive AFB smear, where conversion rates were 85.0% (17/20) for daily treatment vs. 50.0% (8/16) for intermittent treatment (P = 0.034). Even among patients with a negative AFB smear, the daily group achieved a higher conversion rate (93.9% [31/33] vs. 78.0% [32/41], P = 0.098) [35]. These findings suggest that a daily regimen for non-cavitary nodular bronchiectatic MAC-PD may improve outcomes—a recommendation also supported by the 2017 BTS guidelines [30].

Current guidelines recommend an azithromycin dose of 250 mg daily or 500 mg 3 times weekly [12,30]. However, the peak serum concentration (C_{max}) of azithromycin was found to be lower with a daily regimen than with an intermittent regimen (median: 0.24 μg/mL vs. 0.65 μg/mL, P < 0.001), as rifampin may significantly reduce the C_{max} of azithromycin in the daily regimen [36]. In the daily regimen, a lower azithromycin C_{max} was common, whereas a higher azithromycin C_{max} was linked to favorable microbiologic responses [36]. For severe MAC-PD, such as cavitary or smear-positive disease, the currently recommended azithromycin dose might be suboptimal, and at least 500 mg daily should be used.

Macrolide monotherapy should be avoided in MAC-PD because it can lead to macrolide resistance [12,30,37]. Treatment outcomes in patients with macrolide-resistant MAC-PD are poor; sputum culture conversion following antibiotic treatment and surgical resection reaches only 21% (95% CI, 14%–30%), with

1-year all-cause mortality at 10% (95% CI, 5%–20%) [25]. Thus, long-term macrolide maintenance therapy should be selected cautiously to prevent exacerbations of bronchiectasis or cystic fibrosis [37]. Given the poor treatment outcomes in cases of macrolide-resistant MAC, preserving macrolide susceptibility is a critical aspect of MAC treatment strategies.

Ethambutol

Ethambutol is the second most important antibiotic in the treatment of MAC-PD, as it is the most effective agent identified to date for preventing macrolide resistance [12,30]. It is generally well tolerated; however, its major side effect is optic neuritis, which is typically reversible upon discontinuation [38]. All patients should undergo a baseline ophthalmologic evaluation before treatment initiation and be monitored for symptoms during therapy [12,38]. Dyschromatopsia—an early sign of optic neuritis—can be detected using the Ishihara pseudo-isochromatic plate examination [12,38]. In Korea, the Han pseudo-isochromatic plate is also commonly used. If new visual symptoms develop, ethambutol should be discontinued until an ophthalmologist can rule out ethambutol-related optic toxicity. If an ophthalmologic evaluation is delayed for more than one month, it is reasonable to halt the entire treatment rather than stopping ethambutol alone, to avoid the development of macrolide resistance.

Rifampin

Rifampin is the third agent in the standard 3-drug regimen [12,30]. Although current guidelines favor a 3-drug regimen over a 2-drug combination (macrolide and ethambutol), this recommendation is conditional and based on very low certainty [12]. The precise role of rifampin in MAC treatment remains uncertain; a more significant concern is its drug interactions, particularly with macrolides [33]. Rifampin induces cytochrome P450 enzymes, thereby lowering the serum concentrations of both macrolides and ethambutol. Concurrent administration of rifampin has been shown to reduce the C_{max} of clarithromycin by 68% and that of azithromycin by 23%, resulting in C_{max} levels falling below the target range in 56% of patients for clarithromycin, 35% for azithromycin, and 48% for ethambutol [33]. Additionally, an *in vitro* hollow fiber experiment comparing the pharmacokinetic profiles of a 3-drug regimen (azithromycin, ethambutol, and rifampin) with those of a 2-drug regimen (azithromycin and ethambutol) found that rifampin neither enhanced the antimycobacterial effect nor prevented macrolide resistance [39].

The minimal inhibitory concentration (MIC) of rifampin against *M. avium* (median 4 mg/L) is higher than the current clinical breakpoints for M. tuberculosis (0.5 mg/L). A target area under the time–concentration curve (AUC)/MIC ratio of > 197.3 was reported as driving the efficacy of rifampin against MAC. Given the previously reported rifampin mean AUC of 68.42 mg·hr/L in patients with MAC-PD, the median MIC of 4 mg/L requires AUCs as high as 789.2 (197.3 × 4) mg·hr/L for rifampin to be effective. Even in patients with TB receiving rifampin at 50 mg/kg, the mean AUC only reaches 571 mg·hr/L [40]. These findings cast doubt on the effectiveness of rifampin in NTM treatment and may help explain the unsatisfactory outcomes associated with current treatment guidelines.

Several studies have suggested that a 2-drug regimen consisting of a macrolide and ethambutol may be as effective as a 3-drug regimen that includes rifampin. For instance, a randomized controlled trial in Japan compared a 3-drug regimen (clarithromycin, ethambutol, and rifampicin) with a 2-drug regimen (clarithromycin and ethambutol) in patients with MAC-PD [22]. Among 119 patients, culture conversion was achieved in 40.6% (24/59) of those receiving the 3-drug regimen and in 55.0% (33/60) of those receiving the 2-drug regimen. Even in patients with cavitary disease, culture conversion rates were similar between the 2 groups, with 73.3% (11/15) for the 3-drug regimen and 68.7% (11/16) for the 2-drug regimen [22].

A retrospective study in Korea examined the efficacy of an intermittent regimen of azithromycin and ethambutol for non-cavitary MAC-PD [41]. In this study of 38 patients, 29 (76%) achieved culture conversion after 12 months of treatment, and notably, none of the 9 patients who did not convert developed macrolide resistance. A positive AFB smear was significantly associated with treatment failure (adjusted odds ratio [aOR], 26.7; 95% CI, 2.1–339.9) [41].

A third retrospective study from Korea compared the individual contributions of rifampin and ethambutol in MAC-PD [42]. In this study of 237 patients, 122 (51.5%) received a regimen of macrolide, ethambutol, and rifampin; 58 (24.5%) received macrolide and ethambutol; 32 (13.5%) received macrolide and rifampin; and 25 (10.6%) received macrolide alone. Overall, 190 of 237 patients (80.2%) achieved culture conversion after a median treatment duration of 1.7 months (interquartile range [IQR], 0.5–4.7), and a microbiological cure was observed in 129 of 177 patients (72.9%) who completed treatment. Compared to macrolide monotherapy, combining a macrolide with both ethambutol and rifampin (aOR, 5.12; 95% CI, 1.72–15.24) or with ethambutol alone (aOR, 5.74; 95% CI, 1.54–21.42) was significantly associated with microbiological cure, whereas combining macrolide with rifampin was not (aOR, 2.43; 95% CI, 0.69–8.58) [42]. These results call into question the additional benefit of including rifampin in a regimen that already contains macrolide and etham-

butol.

For MAC-PD cases with a low mycobacterial burden—such as non-cavitary, smear-negative disease—a 2-drug regimen of azithromycin and ethambutol may be sufficient. Conversely, for MAC-PD with a high mycobacterial burden, such as cavitary or smear-positive disease, a 3-drug regimen might be necessary; however, the third agent should likely not be rifampin.

Clofazimine

Recently, clofazimine, which was originally used to treat leprosy, has been repurposed for the treatment of NTM-PD [12,30]. Although several studies have demonstrated its efficacy in MAC-PD, clofazimine has not yet been fully incorporated into current guidelines because these studies were published after the guidelines were issued. For example, a retrospective study conducted in Canada evaluated treatment outcomes of a clofazimine-containing regimen [26]. Among 107 patients, 90 (84%) received a regimen of clofazimine, macrolide, and ethambutol, while 14 (13%) received a regimen of rifampin, macrolide, and ethambutol. All 90 patients (100%) treated with clofazimine achieved sputum culture conversion, compared to 71% (10/14, P = 0.0002) in the rifampin group. Microbiological relapse occurred in 52 of 107 patients (49%), with no significant difference between the 2 groups [26].

Another retrospective study from Korea assessed the outcomes of a clofazimine-containing regimen in severe MAC-PD [43]. Among 170 patients, 121 (71.2%) had cavitary disease. All patients received a macrolide, and 150 (88.2%) received ethambutol (excluding 20 patients with prior ophthalmic complications); only 15 (8.8%) received rifampicin. Within 6 months, 77 patients (45.3%) achieved culture conversion, and microbiological cures were observed in 84 of 154 patients (54.6%). Notably, the microbiological cure rate increased to 71.0% (22/31) among patients who received clofazimine for 6–12 months, compared to 23.1% (6/26) in those treated for less than 6 months [43].

Finally, a randomized controlled trial conducted in the Netherlands compared regimens in which 21 patients received clofazimine and 19 received rifampin, both in addition to macrolide and ethambutol [44]. Sputum culture conversion rates were similar in both groups, with 62% (13/21) in the clofazimine group and 58% (11/19) in the rifampin group. Moreover, pharmacokinetic data revealed that the maximum serum concentration ($C_{highest}$) of azithromycin was significantly higher in the clofazimine group compared to the rifampin group (0.64 mg/L vs. 0.35 mg/L at 1 month, P = 0.005; 0.75 mg/L vs. 0.31 mg/L after 4 months, P < 0.001) [44]. These findings support the inclusion of clofazimine in MAC-PD treatment regimens.

Currently, clofazimine is administered at a daily dose of 100 mg; however, its pharmacokinetics are complex due to its high protein-binding, lipophilicity, and accumulation in adipose tissue, which results in an extremely long elimination half-life of 30–70 days [45]. Consequently, it takes several months for plasma concentrations to reach steady state. In an *in vivo* experiment involving 12 individuals, the C_{max} of clofazimine was 0.87 mg/L after a loading dose of 300 mg daily for 4 weeks, with adverse events remaining tolerable. In a virtual simulation of 1,000 individuals, the median time to reach the target concentration (defined as 80% of steady state) was 5.3 months with a 100 mg daily regimen without a loading dose. However, when a loading dose of 300 mg daily was administered for 4 weeks followed by maintenance at 100 mg daily, the median time to target concentration decreased to 3.8 months. Extending the loading phase to 6 weeks further reduced the median time to 1.4 months [45]. These results suggest that incorporating a loading phase of clofazimine should be considered to accelerate the attainment of steady-state concentrations.

Amikacin

Parenteral aminoglycosides, such as amikacin and streptomycin, are recommended for patients with cavitary or severe MAC-PD [12,30]. A retrospective study in Korea compared treatment outcomes in cavitary MAC-PD between patients who received streptomycin and those who received amikacin [46]. Among 168 patients treated with a guideline-based 3-drug regimen plus a parenteral aminoglycoside, 127 (75.6%) received streptomycin and 41 (24.4%) received amikacin for a median duration of 17.1 weeks (IQR, 14.0–17.6 weeks). The overall culture conversion rate was 75.6% (127/168), with similar rates observed in the streptomycin group (74.8%, 95/127) and the amikacin group (78.0%, 32/41; P = 0.674). Adverse event rates were comparable between the 2 groups [46]. These findings indicate that either amikacin or streptomycin can be effectively used in the treatment of MAC-PD.

Systemic administration of aminoglycosides is associated with serious adverse effects, including ototoxicity and renal toxicity, which limit their long-term use. Consequently, inhaled amikacin has emerged as an alternative that maintains efficacy while reducing systemic toxicity. The 2020 ATS/ERS/ESCMID/IDSA guidelines recommend ALIS for patients with cavitary or refractory MAC-PD, a recommendation supported by a phase 3 randomized controlled trial [12]. However, ALIS carries a high economic burden (approximately US$16,000 per 4 weeks) and is not covered by the national health insurance program in Korea, limiting its widespread adoption [29]. Moreover, treatment outcomes

with ALIS in Korea have been unsatisfactory; among 6 patients with refractory MAC-PD treated with ALIS, one was already culture-negative before its initiation, and only one of the remaining 5 patients with positive cultures achieved culture conversion [29].

Although the 2017 BTS guidelines recommended the inhalation of a parenteral formulation of amikacin, the supporting evidence is limited. A recent retrospective study investigated the efficacy of inhaled amikacin in combination with clofazimine in refractory MAC-PD [47]. In this study of 52 patients, 17 (33%) achieved culture conversion, and only 12 (23%) attained microbiological cure [47]. These findings suggest that while inhaled amikacin with clofazimine may offer favorable outcomes in some cases of refractory MAC-PD, more effective treatment strategies are still needed.

Reevaluating treatment strategies beyond guidelines

Recent research suggests several novel treatment strategies that warrant consideration: (1) employing a daily treatment regimen for non-severe MAC-PD; (2) using a daily dose of 500 mg of azithromycin in such regimens; (3) omitting rifampin in non-severe MAC-PD; (4) replacing rifampin with clofazimine in severe MAC-PD; and (5) incorporating a loading phase for clofazimine. These strategies are summarized in Table 5.

Refractory and recurrent MAC-PD

Despite long-term antibiotic treatment, overall success rates for MAC-PD remain unsatisfactory, with a significant proportion of patients remaining culture-positive, indicating refractory disease [6-10]. Interestingly, macrolide resistance is uncommon among patients with refractory MAC-PD who are on long-term macrolide-containing regimens [34]. One study demonstrated that refractory MAC-PD is usually due to reinfection with new strains rather than persistent infection [48]. In a cohort of 481 treatment-naive MAC-PD patients, 72 (15.0%) remained sputum culture-positive after at least 12 months of treatment and were classified as having refractory disease. Among the 49 patients with both pre- and post-treatment isolates, mycobacterial genotyping revealed that 36 (73%) had been reinfected with new strains, while only 13 (27%) had persistent infection with their original strains [48]. These findings may explain why macrolide resistance is rare in refractory MAC-PD.

Recurrences of MAC-PD are also common following the completion of long-term antibiotic therapy. However, evidence suggests that most recurrences represent reinfections rather than treatment failures or relapses [13,49]. For example, one study reported that an intermittent regimen (3 times weekly) in patients with recurrent non-cavitary nodular bronchiectatic MAC-PD achieved similar sputum culture conversion rates compared to a daily regimen (82% [22/27] vs. 81% [21/26]) [49]. Additionally, in 15 of 53 patients (28%), different MAC species were identified compared to the previous treatment, and among 38 patients with the same species, genotype analysis revealed that 86% (12/14) of cases were reinfections with new strains [49].

Current guidelines recommend the adjunctive use of parenteral or nebulized amikacin alongside a 3-drug oral regimen to reinforce treatment in refractory or recurrent MAC-PD [12,30]. However, given that a substantial proportion of these cases are due to reinfection, adjunctive amikacin may be unnecessary and could cause undesirable adverse effects, particularly in non-severe

Table 5. Treatment strategies of *Mycobacterium avium* complex pulmonary disease reflecting recent research

Disease types	No. of drugs	Drug regimen	Treatment duration
Non-severe MAC-PD (i.e., negative sputum AFB smear, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	2	• Azithromycin 500 mg daily (250 mg, if intolerable to 500 mg) • Ethambutol 15 mg/kg daily	A minimum of 12 months after culture conversion
Severe MAC-PD (i.e., positive sputum AFB smear, radiological evidence of lung cavitation/severe infection, severe symptoms/signs of systemic illness, or a history of treatment failure)	≥ 4	• Azithromycin 500 mg daily (250 mg, if intolerable to 500 mg)	A minimum of 12 months after culture conversion
Refractory MAC-PD (sputum culture positive after 6 months of guideline-based therapy)		• Ethambutol 15 mg/kg daily • Clofazimine 100 mg daily (consider 200–300 mg for initial 4–6 weeks for loading phase) • Intravenous amikacin 15 mg/kg daily or 15–25 mg/kg TIW for at least initial 2–3 months, followed by nebulized amikacin 250–500 mg once or twice daily	

MAC-PD, *Mycobacterium avium* complex pulmonary disease; AFB, acid-fast bacilli; TIW, 3 times per week.

cases (e.g., negative sputum AFB smear, bronchiectatic disease without cavitation, or mild-to-moderate symptoms) [30]. In such cases, oral regimens might be feasible for selected patients, depending on disease severity and microbiologic evidence. Moreover, to reduce the risk of reinfection from environmental exposures, lifestyle and environmental modifications should be recommended for these patients [50].

There is currently no proven treatment strategy for macrolide-resistant MAC-PD. While maintenance of macrolide therapy is common after the detection of macrolide resistance, surgical resection and prolonged parenteral aminoglycoside administration remain crucial treatment strategies [25]. The 2017 BTS guidelines suggest adding other drugs, such as isoniazid, moxifloxacin, or nebulized amikacin, although the efficacy of these regimens remains inconclusive [30]. Recently, bedaquiline and ALIS have been investigated for the treatment of macrolide-resistant MAC-PD; however, treatment outcomes have been unsatisfactory [51,52].

Surgical treatment

The success rate of medical treatment for MAC-PD has been unsatisfactory, with many patients experiencing treatment failure due to macrolide resistance. Consequently, adjuvant surgical lung resection has been employed to improve outcomes in selected patients [3,12,30,53]. Typically, patients with focal parenchymal disease and sufficient predicted pulmonary reserve following surgery are considered candidates for resection; unfortunately, only a minority of NTM-PD patients meet these criteria [53].

There are 3 main indications for surgery [53]. First, surgical treatment is usually considered after the failure of medical therapy, particularly when the disease is confined to a focal parenchymal region while the remainder of the lung is relatively unaffected. Surgical resection may also be indicated in cases of recurrent treatment failures, antimicrobial resistance, or intolerance to antimicrobial agents. Second, surgery may be performed to alleviate or eliminate potentially life-threatening symptoms, such as hemoptysis; resection can control these symptoms even if some residual disease remains. Third, in a small subset of cases, debulking surgery (i.e., removal of the most severely damaged lung parenchyma) may slow disease progression by limiting the spread of infection to less affected areas [53].

A recent meta-analysis synthesized results from 15 studies involving 1,071 patients with NTM-PD who underwent adjunctive surgical treatment [54]. After surgical resection, sputum culture conversion was achieved in 93% (95% CI, 87%–97%), and recurrence was identified in 9% (95% CI, 6%–14%) of patients during a median 34 months of follow-up. Additionally, 17% (95% CI, 13%–23%) experienced postoperative complications, and in-hospital mortality occurred in 0% (95% CI, 0%–2%) [54]. These findings suggest that adjunctive surgical treatment is an effective therapeutic alternative with acceptable complication rates.

Nonpharmacological treatment

NTM are ubiquitous environmental pathogens commonly found in natural water, soil, and household environments [1,50]. Water distribution systems, such as plumbing, are key transmission routes into households. NTM have been isolated from drinking water tanks and pipelines, where they adhere to surfaces and form biofilms due to their lipid-rich, hydrophobic outer membrane. This membrane also confers natural resistance to disinfectants like chlorine, making water chlorination a more favorable environment for NTM survival compared to other microorganisms [1].

Several strategies are recommended to reduce exposure to environmental water: (1) heat water to temperatures exceeding 55–65°C before use; (2) use bacteriologic filters (with pore sizes <0.45 μm) on showerheads and taps; (3) regularly clean showerheads with vinegar to remove biofilms; (4) choose showerheads with larger holes to reduce aerosol formation; (5) shorten the duration of showers; (6) avoid spas or hot tubs; and (7) boil drinking water for 10 minutes (noting that bottled water is not free from NTM contamination) [1,50].

Household dust and soil also serve as significant sources of NTM exposure. Soil particles can become aerosolized during activities like farming or gardening, increasing the risk of inhalation. To reduce exposure, it is recommended to moisten soil before handling it or to wear masks during these activities [1,50].

In addition to minimizing environmental exposure, it is important to address host factors that increase vulnerability to NTM-PD [50]. First, impaired mucus clearance from the airways is a significant risk factor; therefore, hydration and airway clearance techniques, such as using mechanical oscillation devices (e.g., oscillating positive expiratory pressure devices), are recommended. Second, a lower BMI is associated with a higher incidence of NTM-PD and a poorer prognosis, so increasing caloric intake and protein supplementation may be beneficial. Third, gastroesophageal reflux disease is linked to an increased risk of NTM-PD (subdistribution hazard ratio, 3.36; 95% CI, 2.10–5.37) [55]. It is hypothesized that NTM may enter the stomach via drinking water and then be aspirated into the lungs along with gastric acid reflux [50]. The inherent acid resistance of NTM, due to their lipid-rich outer membrane, further contributes to this mechanism [1]. To

Table 6. Nonpharmacological treatment strategies of *Mycobacterium avium* complex pulmonary disease

Strategy	Method
Avoid environmental exposures	
Reduce exposure to environmental water	• Heat water at temperatures exceeding 55–65°C before use • Use bacteriologic filters on showerheads and taps • Regularly clean showerheads with vinegar to remove biofilm • Use showerheads with large holes to reduce aerosol formation • Shorten the duration of showers • Avoid spas or hot tubs • Boil drinking water for 10 minutes
Reduce exposure to environmental soil	• Moisten soil with water • Wear masks during activities
Lifestyle modifications	
Improve airway clearance	• Airway hydration • Airway clearance techniques using mechanical oscillation devices
Nutritional support	• Increase caloric intake • Protein supplementation
Management of gastroesophageal reflux disease	• Dietary modifications (e.g., avoiding coffee, alcohol, and carbonated beverages) • Postural modifications (e.g., elevating head during sleep, and maintaining upright position after meals) • Smoking cessation

manage gastroesophageal reflux disease, dietary modifications (such as avoiding coffee, alcohol, and carbonated beverages), postural adjustments (such as elevating the head during sleep and remaining upright after meals), and smoking cessation are recommended (Table 6) [50].

Conclusion

Although the prevalence of MAC-PD has been rapidly increasing, the treatment outcomes of current guideline-based regimens remain unsatisfactory. To improve these outcomes, treatment strategies must be updated in light of recent research findings. Since 2020, a multicenter prospective observational cohort study (NTM-KOREA) has been launched to optimize treatment modalities for NTM-PD in Korea [56]. We hope that further investigation under this program will lead to more effective treatment strategies for MAC-PD.

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Authors' contributions

All work was done by Chiwook Chung.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e26
https://doi.org/10.12771/emj.2025.00360

Ewha Medical Journal

The role and prospects of telemedicine in the treatment of heart failure patients: a narrative review

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Heart failure (HF) represents a significant global health burden characterized by high morbidity, mortality, and healthcare utilization. Traditional in-person care models face considerable limitations in providing continuous monitoring and timely interventions for HF patients. Telemedicine—defined as the remote delivery of healthcare via information and communication technologies—has emerged as a promising solution to these challenges. This review examines the evolution, current applications, clinical evidence, limitations, and future directions of telemedicine in HF management. Evidence from randomized controlled trials and meta-analyses indicates that telemedicine interventions can improve guideline-directed medical therapy implementation, reduce hospitalization rates, improve patient engagement, and potentially decrease mortality among HF patients. Remote monitoring systems that track vital signs, symptoms, and medication adherence allow for the early detection of clinical deterioration, enabling timely interventions before decompensation occurs. Despite these benefits, telemedicine implementation faces several barriers, including technological limitations, reimbursement issues, digital literacy gaps, and challenges in integrating workflows. Future directions include developing standardized guidelines, designing patient-centered technologies, and establishing hybrid care models that combine virtual and in-person approaches. As healthcare systems worldwide seek more efficient and effective strategies for managing the growing population of individuals with HF, telemedicine offers a solution that may significantly improve patient outcomes and quality of life.

Keywords: Digital technology; Heart failure; Medication adherence; Patient-centered care; Telemedicine

Introduction

Background

Heart failure (HF) is a significant global health burden characterized by the heart's inability to pump sufficient blood to meet the body's metabolic demands. It affects approximately 26 million people worldwide and is associated with substantial morbidity, mortality, and healthcare costs [1]. Despite advances in pharmacological and device therapies, HF continues to pose major challenges, with high readmission rates and a 5-year mortality approaching 50% in some populations [2]. Traditional in-person care models for HF management have inherent limitations, including inadequate monitoring between scheduled visits, delayed recognition of early decompensation signs, geographic barriers to specialist access, difficulties in optimizing medication regimens, and challenges in promoting patient self-management [3]. Telemedicine, broadly defined as the delivery of healthcare services using information and communication technologies (ICT) over a distance, has emerged as a promising approach to address these gaps. The World Health Organization first formalized the concept of telemedicine in 2007, emphasizing distance as a critical factor in its application; however, contemporary definitions now encompass any healthcare delivery that uses ICT for remote patient care, regardless of geographic proximity [4]. The coronavirus disease 2019 (COVID-19) pandemic significantly accelerated telemedicine adoption across all medical specialties, including cardiology, by necessitating alternative care delivery models [5]. For example, one large health system reported a 683% increase in virtual urgent-care visits over just 6 weeks in 2020 [6]. This rapid implementation demonstrated both the feasibility and potential benefits of virtual care approaches for managing cardiovascular disease, particularly chronic conditions such as HF.

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Received: Marach 1, 2025 Revised: April 2, 2025 Accepted: April 2, 2025

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Objectives

This review examines the role and prospects of telemedicine in HF care, focusing on its historical development and definition, current clinical applications and supporting evidence, implementation challenges, and future directions.

Ethics statement

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

Historical development of telemedicine

The evolution of telemedicine has paralleled advances in communication technology. Early forms of remote healthcare communication began in the 1840s with the invention of the telegraph, which enabled rudimentary long-distance medical consultations. The subsequent invention of the telephone expanded these capabilities; reports dating back to the early 1900s describe telephone-based diagnoses of croup and remote auscultation techniques [7]. The systematic development of telemedicine as a formal healthcare delivery approach gained momentum in the mid-20th century with several key milestones. In the 1960s, the National Aeronautics and Space Administration significantly advanced telemedicine by developing physiological monitoring systems for astronauts. These systems enabled the transmission of vital signs, including electrocardiograms (ECGs), from space to medical teams on Earth [8]. The emergence of the World Wide Web in the 1990s transformed telemedicine by broadening access beyond specialized fields such as aerospace medicine [9]. In 2003, the US Veterans Affairs healthcare system pioneered large-scale telemedicine implementation with its Home Telehealth program, targeting rural veterans with limited access to medical facilities [10]. By 2010, the Veterans Affairs had established a national telehealth center, initially focusing on mental healthcare for veterans affected by conflicts like the Iraq War and later expanding to comprehensive care models that included cardiovascular disease management [11]. The telemedicine market has experienced substantial growth, valued at approximately $21.2 billion in the United States alone and $49.8 billion globally in 2018, with projections suggesting a fivefold increase in the global market by 2026. Notably, the market encompasses both telemedicine products (hardware and software) and services (consultations and monitoring), with roughly equal distribution between these segments [12].

Taxonomy and components of telemedicine

Types of telemedicine interactions

The terms "telemedicine" and "telehealth" are often used interchangeably, but subtle distinctions exist. Telemedicine typically refers to remote clinical services, such as video consultations, telephone consultations, chat-based consultations, and remote diagnosis or data analysis. In contrast, telehealth covers a broader range of remote healthcare services, including not only telemedicine but also remote patient monitoring, remote surgery, remote diagnostics, electronic intensive care units, and remote clinical trials [13]. Telemedicine can be categorized based on synchronicity and the entities involved. Synchronous telemedicine refers to real-time interactions, where communication occurs instantly without delays. In a physician-to-patient setting, this includes live video or phone consultations during which a doctor provides immediate diagnosis and treatment recommendations. In a physician-to-physician context, it involves real-time discussions between medical providers who consult a specialist via video or phone call regarding a patient's case [14].

Asynchronous telemedicine follows a store-and-forward approach, where medical data is recorded and reviewed later rather than in real time. In a physician-to-patient setting, this includes cases in which a patient uploads medical images or symptoms for later analysis by a doctor, who then provides medical advice. In a physician-to-physician context, a general practitioner may send a patient's ECG or chest X-ray to a specialist, such as a radiologist or cardiologist, who reviews the data and offers expert opinion when available [15].

Hybrid telemedicine combines both synchronous and asynchronous approaches, leveraging real-time monitoring alongside delayed data analysis to provide more efficient and comprehensive care. In a physician-to-patient setting, a patient continuously records vital signs using wearable devices that automatically transmit and store data for later review. Physicians can then analyze trends over time and provide feedback asynchronously. In a physician-to-physician context, a doctor might consult an artificial intelligence (AI)–driven system to analyze stored medical data before discussing findings with a specialist in real time [16].

In HF management, various modalities have been applied that often combine remote monitoring of patient data with either synchronous or asynchronous provider feedback. This hybrid model shows promise in HF care by enabling continuous data collection with prompt intervention when necessary. For example, an HF patient can use a wearable device to continuously track vital signs such as heart rate, blood pressure, and oxygen levels. The data are recorded and transmitted, allowing physicians to analyze trends

over time and detect early signs of HF. If a concerning pattern emerges, such as a gradual weight increase due to fluid retention, the physician can intervene before symptoms worsen, either through a video consultation or messaging. This approach is especially valuable in HF management, where rapid and proactive responses are critical to preventing acute decompensation and hospitalizations [17].

Technical components of telemedicine systems

Effective telemedicine implementation for HF management requires a well-integrated technological infrastructure. Essential components include digital platforms, communication devices, and remote monitoring technologies. Digital platforms form the foundation of telemedicine services, ranging from basic data management systems to advanced platforms that incorporate AI for predictive analytics. These platforms facilitate secure data collection and storage, seamless integration with clinical workflows, communication between patients and providers, and the provision of analytics to support clinical decision-making [18]. Communication devices are vital for patient engagement in telemedicine, as they provide the primary means for remote interaction [19]. For example, the smartphone—one of the most well-known devices—is versatile, widely accessible, and serves as a key interface for telemedicine applications [20]. Remote monitoring devices enable health monitoring outside traditional clinical settings. These devices include connected blood pressure monitors, wireless weight scales, pulse oximeters, activity trackers, multi-parameter monitoring systems, and implantable hemodynamic sensors such as CardioMEMS [21].

For effective HF management, remote monitoring typically focuses on 3 key domains: risk factor monitoring, which tracks changes in blood pressure, glucose levels, and weight; medication adherence monitoring, which uses digital reminders and smart pillboxes to ensure patients follow their prescribed regimens; and symptom monitoring, which assesses clinical indicators such as dyspnea, fatigue, and edema [22,23]. The integration of these technological components creates a comprehensive telemedicine ecosystem that addresses the complex needs of HF patients throughout their care journey. By leveraging digital platforms, communication devices, and remote monitoring tools, telemedicine can enhance HF management, improve patient outcomes, and expand access to care (Tables 1, 2).

Clinical evidence for telemedicine in HF management

Reduced hospital readmissions and mortality rates

Remote monitoring systems have been shown to reduce hospital readmissions for HF patients. The TIM-HF2 trial, published in *The Lancet* in 2018, is one of the largest randomized studies of telemedicine in HF to date, involving approximately 1,500 participants [24]. This study implemented a structured telemedicine program that monitored body weight, blood pressure, heart rate, ECG, oxygen saturation, and self-reported health status. The results demonstrated a significant reduction in both all-cause mortality and HF-related hospitalizations in the intervention group

Table 1. Telemedicine components

Components	Telehealth ⊃ Telemedicine
Digital platform	- Secure data collection and storage
	- Clinical workflow integration
	- Provider-patient communication support
	- Analytics for decision-making
	- AI for predictive capabilities
Communication device	- Smartphones for application interface
	- Primary remote interaction tools
	- Patient engagement enablers
	- Secure messaging capabilities
	- Virtual visit technology
Remote monitoring technology	- Risk factor monitoring
	- Medicine adherence
	- Symptom monitoring

AI, artificial intelligence.

Table 2. Telemedicine types

Types	Synchronous+	Asynchronous=	Hybrid
Visits	Virtual visits: Direct physician-patient interaction with immediate assessment and treatment recommendations	eVisits: Patient-submitted health data and symptoms reviewed by physicians with delayed response and treatment plans	Remote monitoring: Continuous tracking of vital signs and symptoms synchronously through wearable devices with asynchronous physician review
Consult	Virtual consults: Live video consultations between physicians for immediate specialist input on patient cases	eConsults & second opinions: Medical data and images forwarded to specialists for expert review and recommendations when available	Predictive analytics: AI-driven analysis of patient data to identify deterioration patterns and risk factors, enabling proactive interventions

AI, artificial intelligence.

compared to standard care (hazard ratio, 0.70; 95% confidence interval [CI], 0.50–0.96; P = 0.0281). Subgroup analyses from this trial suggested particularly pronounced benefits among patients with diabetes mellitus as a comorbidity, underscoring the potential value of telemedicine for HF patients with multiple chronic conditions.

A comprehensive systematic review and meta-analysis examined the effectiveness of telemedicine, including home telemonitoring systems (hTMS), in HF management. This review analyzed 27 studies selected from an initial pool of 4,947 articles and demonstrated significant reductions in all-cause mortality (pooled odds ratio [OR], 0.65), cardiovascular mortality (OR, 0.68), and HF-related hospitalizations (OR, 0.77), particularly among patients with heart failure with reduced ejection fraction (HFrEF) [25]. Similarly, research on hTMS, which analyzed 65 non-invasive and 27 invasive studies involving 36,549 HF patients, revealed a 16% reduction in all-cause mortality, a 19% reduction in first HF hospitalization, and a 15% reduction in total HF hospitalizations [26]. These findings underscore that telemedicine plays a crucial role in improving outcomes by enhancing disease management, reducing hospital admissions, and lowering mortality rates in HF patients.

Utilizing advancements in communication technology, social networking service (SNS)-based emergency coordination has demonstrated potential for improving care efficiency. By enabling real-time communication among emergency cardiac care teams, this approach facilitates targeted resource allocation and optimized medication management. One study reported that implementing an SNS (BAND) for emergency cardiac teams significantly improved door-to-intervention times for patients with ST-elevation myocardial infarction. This was achieved by allowing emergency medical services to rapidly assess hospital availability, determine percutaneous coronary intervention capability, and coordinate patient transport in real time. The BAND enabled rapid pre-hospital communication, early diagnostic sharing, and streamlined preparation before patient arrival, ultimately reducing treatment delays and improving outcomes [27] (Fig. 1).

The door-to-device time was significantly shorter in the SNS

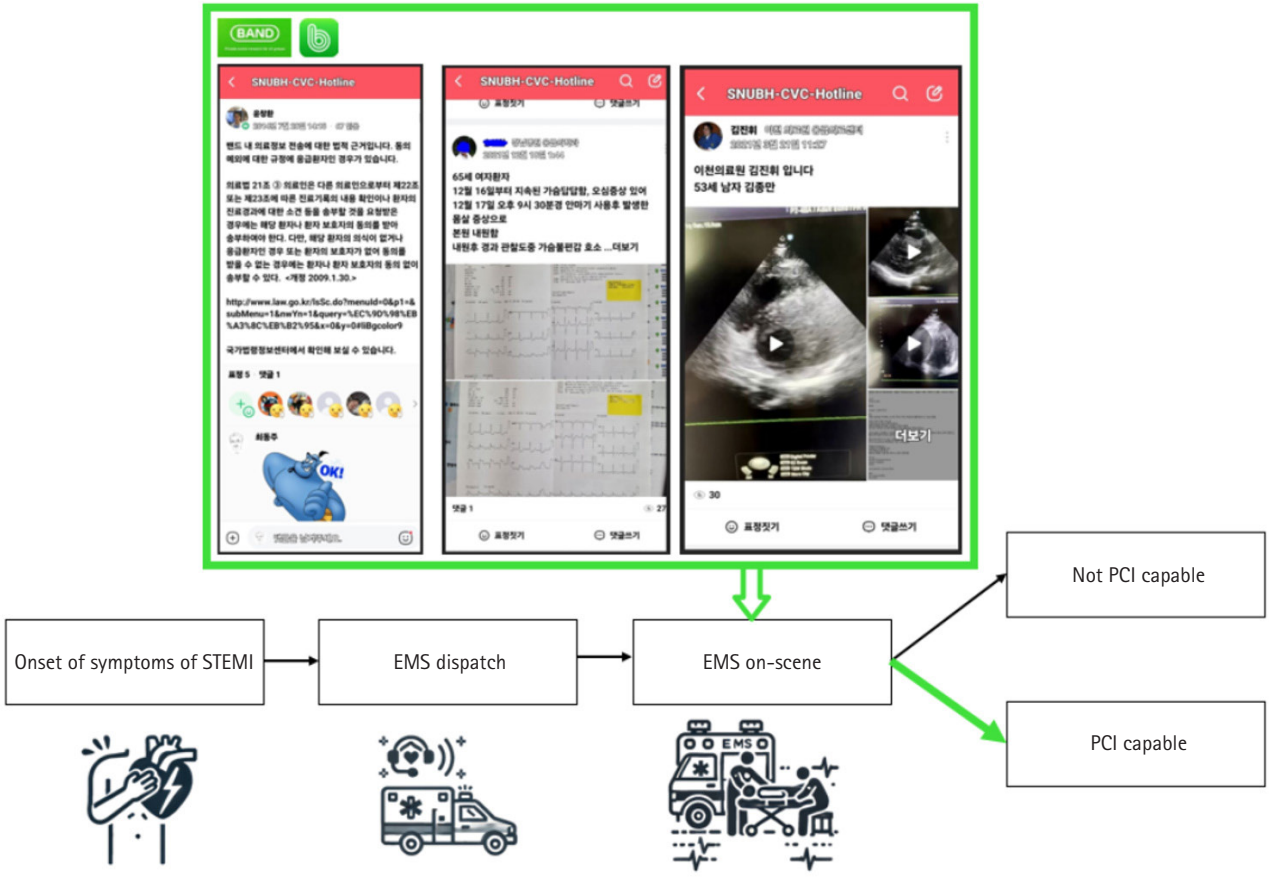

Fig. 1. Telehealth in ST-elevation myocardial infarction using a social networking service (SNS) band to reduce the time for transfer. Adapted from Park et al. [27] under the CC-BY-NC license. STEMI, ST-segment elevation myocardial infarction; EMS, emergency medical service; PCI, percutaneous coronary intervention.

(+) group compared to the SNS (–) group across all cases (P < 0.001) and during off-hours (P < 0.001), while no significant difference was observed on weekdays (P = 0.184) (Fig. 2A). Furthermore, the first medical contact-to-device time was significantly shorter in the SNS (+) group (P = 0.031), indicating that SNS utilization contributes to a more rapid treatment process (Fig. 2B).

In addition to non-invasive telemonitoring, implantable devices such as the CardioMEMS HF system enable direct measurement of pulmonary artery pressure. This approach facilitates earlier detection of worsening HF compared to conventional monitoring methods. By identifying clinical deterioration before the onset of severe symptoms, these devices support timely intervention, optimization of medical therapy, and more informed clinical decision-making. Collectively, these early responses can reduce hospital admissions and lead to significant cost savings in HF management through telemedicine [28,29].

Improved medication adherence

Telemedicine significantly enhances medication adherence through integrated features designed specifically for HF patients. One key benefit is the optimization of guideline-directed medical therapy (GDMT), which comprises evidence-based pharmacological treatments—such as angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors—recommended by clinical practice guidelines for HF management. Despite their proven benefits, GDMT is frequently underprescribed or administered at suboptimal doses due to barriers such as physician inertia, concerns about side effects, and inadequate follow-up [30,31]. Research indicates that telemedicine can overcome these challenges. In a randomized controlled trial involving 66 HF patients, those in the remote monitoring intervention group showed significant improvements in GDMT adherence compared to the standard care group. At the 6-month follow-up, the intervention group achieved a higher 4-GDMT score (64.6%) compared to 56.5% in the standard care group, demonstrating a significant enhancement in GDMT implementation. Although improvements in left ventricular ejection fraction and B-type natriuretic peptide levels did not reach statistical significance—likely due to the limited sample size—these findings support the potential of remote monitoring to improve GDMT quality and clinical outcomes in patients with HFrEF [32].

Improved patient engagement

Telemedicine promotes patient engagement in HF management through multiple mechanisms. Virtual consultations offer opportunities for patient education and self-management support, allowing physicians to guide patients on symptom recognition, lifestyle modifications, and self-care strategies [33]. Structured symptom tracking using patient-reported outcome measures also helps patients become more aware of their condition and actively participate in monitoring their health [34]. Virtual cardiac rehabilitation programs further enhance engagement by

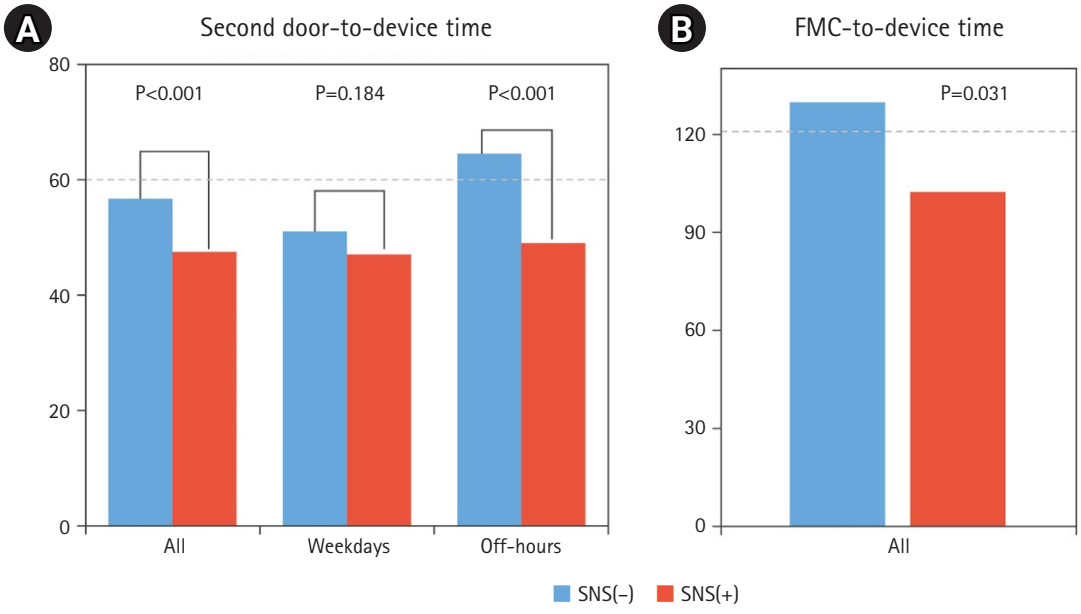

Fig. 2. Impact of social networking service (SNS) on time to revascularization. Reproduced from Park et al. [27] under the CC-BY-NC license. FMC, first medical contact.

providing home-based exercise sessions with remote monitoring, virtual classes on nutrition and lifestyle modification, online support groups, and telehealth coaching sessions [35,36].

A multi-center study conducted across 7 South Korean hospitals developed and tested an advanced telemedicine system incorporating AI-enhanced predictive algorithms [37]. This comprehensive platform included a patient smartphone application, connected weight and blood pressure monitoring devices, and a provider dashboard with automated alerts. The smartphone application allowed patients to track symptoms—including dyspnea, fatigue, edema, and palpitations—using a structured scale, while also logging vital signs such as blood pressure, heart rate, weight, and body water. The system integrated Bluetooth-connected monitoring devices to ensure automated, real-time data collection (Fig. 3).

Additionally, AI-assisted dietary analysis enabled sodium intake estimation via image recognition to support better dietary management. Beyond self-monitoring, the app provided personalized feedback on medication adherence and symptom trends (Fig. 4A). A clinical decision support system continuously analyzed patient data to detect significant health changes, generating alerts that prompted patients to assess their condition and seek medical attention when necessary. Furthermore, educational resources on HF management were available to improve patient knowledge and self-care practices (Fig. 4B).

In a randomized evaluation involving approximately 130 patients followed for 4 weeks, the intervention group demonstrated significant improvements in dyspnea symptom scores compared to the control group. This evidence shows that technology-enabled care can yield measurable clinical improvements while simultaneously increasing patient engagement and empowering individuals to take a more active role in managing their condition.

Challenges and barriers to telemedicine implementation

Technological barriers and infrastructure

A fundamental challenge is the availability and reliability of technology. Telemedicine depends on stable internet connections and sufficient bandwidth, which may be lacking in rural areas or low-resource settings. Patients in regions with poor connectivity or those who cannot afford broadband may be unable to effectively participate in video visits or continuous data transmission. Even when connectivity is available, ensuring interoperability between various devices and platforms is difficult [38]. In HF telemonitoring programs, patients might use different brands of blood pressure cuffs, weight scales, and wearables; integrating these diverse data streams into a coherent platform for physicians is technically complex [39]. Lack of standardization can result in systems that

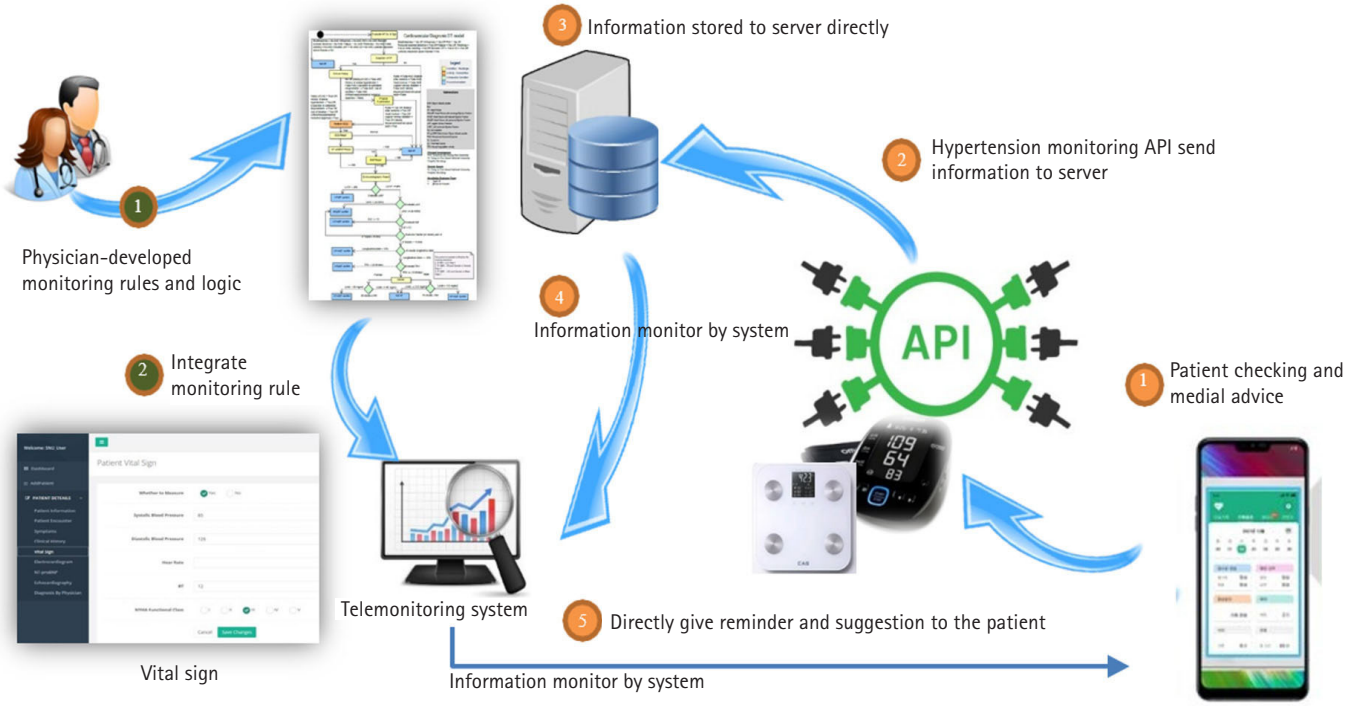

Fig. 3. An advanced telemedicine system incorporating artificial intelligence (AI) for heart failure patients' home care. Reproduced from Yoon et al. [37] under the CC-BY license. API, Application Programming Interface.

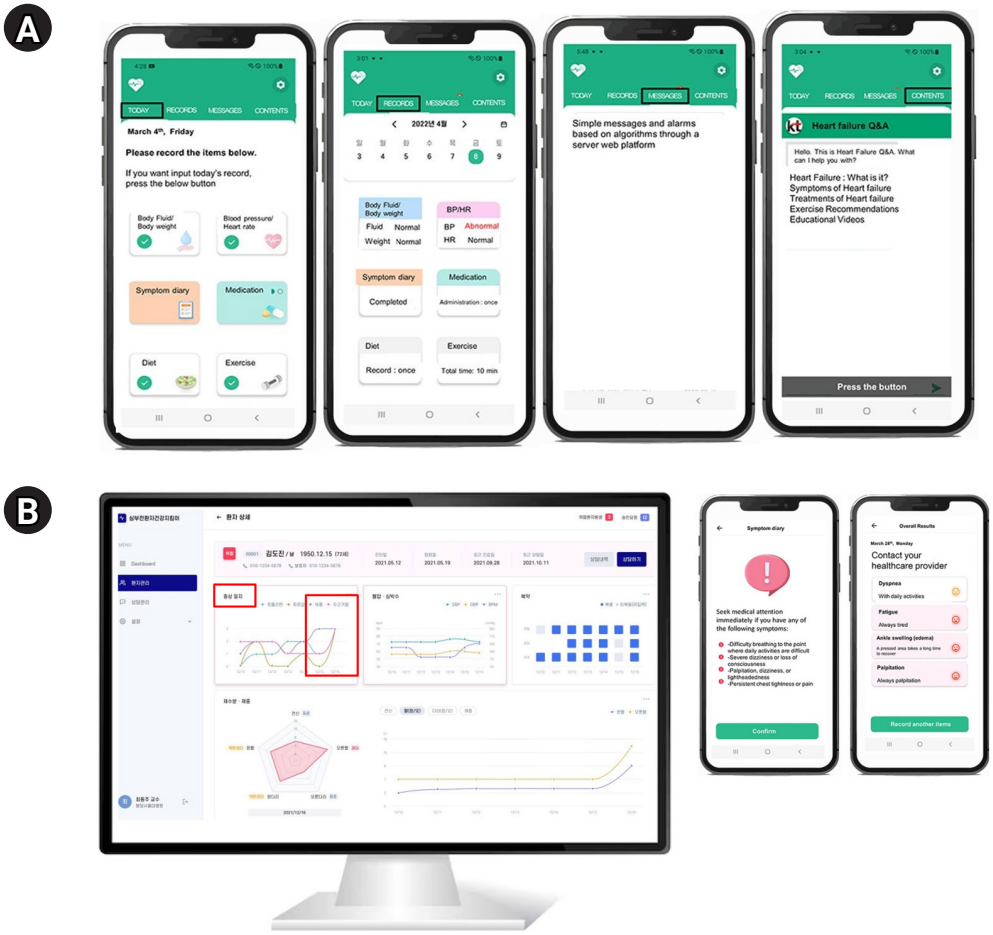

Fig. 4. Telehealth in heart failure using an artificial intelligence (AI) platform. (A) How the AI platform appears on the smartphone screen and (B) the provider dashboard and patient alert system. Reproduced from Yoon et al. [37] under the CC-BY license.

do not communicate effectively, leading to fragmented information. Moreover, data security and privacy are major concerns. Transmitting personal health information over networks raises the risk of data breaches or unauthorized access, and both physicians and patients may worry about the confidentiality of sensitive medical information. While strict adherence to security protocols (such as encryption, secure servers, and Health Insurance Portability and Accountability Act-compliant software) is essential, not all telemedicine solutions meet these standards [40].

Regulatory and reimbursement issues

Health policy and reimbursement frameworks have not always kept pace with telemedicine technology. Historically, many insurance systems provided limited or no reimbursement for telemedicine services, discouraging investment in virtual care. For example, before 2020, Medicare in the United States only reimbursed telehealth for patients in certain rural areas or specific circumstances, often at lower rates than in-person visits. Licensing requirements also posed challenges; a physician must typically be licensed in the state where the patient is located, complicating cross-state telemedicine even over short distances [41]. This fragmentation meant that a patient seeking consultation from a renowned HF specialist in another state via telemedicine could face legal barriers unless the physician obtained multiple state licenses. Malpractice coverage for telehealth was another uncertain area. Although many of these regulatory constraints were relaxed during the COVID-19 pandemic—leading to a significant uptick in telemedicine use—it remains uncertain whether these favorable policies will persist long-term. If reimbursement reverts to pre-pandemic models or cross-state licensing flexibility is withdrawn, providers may scale back telehealth offerings. Uncertainty in payment models is a barrier, and healthcare organizations may hesitate to invest in telemedicine programs if financial sustainability is unclear [42]. Additionally, telemedicine raises questions regarding interstate practice, liability laws across jurisdictions, and even issues like the remote prescribing of controlled substances

[43]. Policymakers and regulatory bodies are actively addressing these issues, yet the absence of universally adopted telemedicine guidelines and inconsistent policies across regions continues to hinder widespread adoption. Continued advocacy is required to ensure that providers are adequately compensated for telemedicine services and that patients receive insurance coverage comparable to in-person care.

Patient factors: digital literacy and trust

Telemedicine inherently requires patients to engage with digital technology, introducing challenges related to patient capability and access. Digital literacy—the ability to use devices and navigate digital interfaces—varies widely among patient populations [44]. Older patients, who comprise a large proportion of those with HF, may be less familiar with smartphones, computers, or even basic cell phone functions. Additionally, some patients may experience cognitive impairments or visual/hearing deficits that complicate the use of telehealth apps. Socioeconomic factors also play a role; patients with lower incomes or education levels may lack access to appropriate devices or struggle with the usability of health-related applications. Consequently, vulnerable populations risk being excluded from the benefits of telemedicine, potentially exacerbating existing health disparities—a phenomenon often referred to as the digital divide. Another barrier is trust and personal preference. Some patients are skeptical of remote care, feeling that virtual visits are not as thorough as in-person consultations [45]. Concerns may include discomfort discussing sensitive issues via video or fears that clinical details may be overlooked. Establishing trust in telemedicine requires assuring patients that their needs will be fully addressed and emphasizing that remote care complements, rather than replaces, face-to-face interactions when clinically appropriate.

Physician factors: workflow challenges

Integrating telemedicine into HF management presents significant workflow challenges for physicians. They must adapt to video visit platforms, manage electronic patient communications, and interpret continuous remote monitoring data—often leading to "alert fatigue" when numerous patients transmit daily readings. In addition, many physicians require training in virtual examination techniques and must overcome initial resistance to this modality, which some feel lacks the personal connection of traditional care. These challenges are often mitigated through the use of smart alert algorithms and, in some cases, by deploying dedicated telemonitoring personnel—resources that may not be readily available in all clinical settings [46]. Various factors impede access to healthcare, each contributing to the complex landscape of healthcare accessibility [47] (Fig. 5).

Future perspectives and recommendations

Standardization of telemedicine protocols and guidelines

A key recommendation is the development of standardized guidelines and policies for telemedicine in HF. Professional societies and public health authorities are already working toward this goal. The American Heart Association recently published a scientific statement outlining best practices for telehealth in cardiovascular and stroke care [48]. Such guidelines provide a structured framework for determining when and how to use telemedicine, along with clearly defined standards for quality, safety, privacy, and data security, as well as metrics for evaluating outcomes. Regulators are encouraged to harmonize policies across regions—for example, by simplifying licensure for telemedicine across state or national borders—to facilitate access to expert care regardless of patient location. Furthermore, integrating telemedicine documentation and data into existing health information systems is crucial for continuity of care. Initiatives such as creating standardized telehealth visit codes and telemonitoring data fields in electronic health records can help make telemedicine a seamless part of clinical workflows. In addition, reimbursement models should be formalized to ensure permanent coverage of telehealth services at

Fig. 5. Various factors impeding access to healthcare, each contributing to the complex landscape of healthcare accessibility. Adapted from Anawade et al. [47] under the CC-BY license.

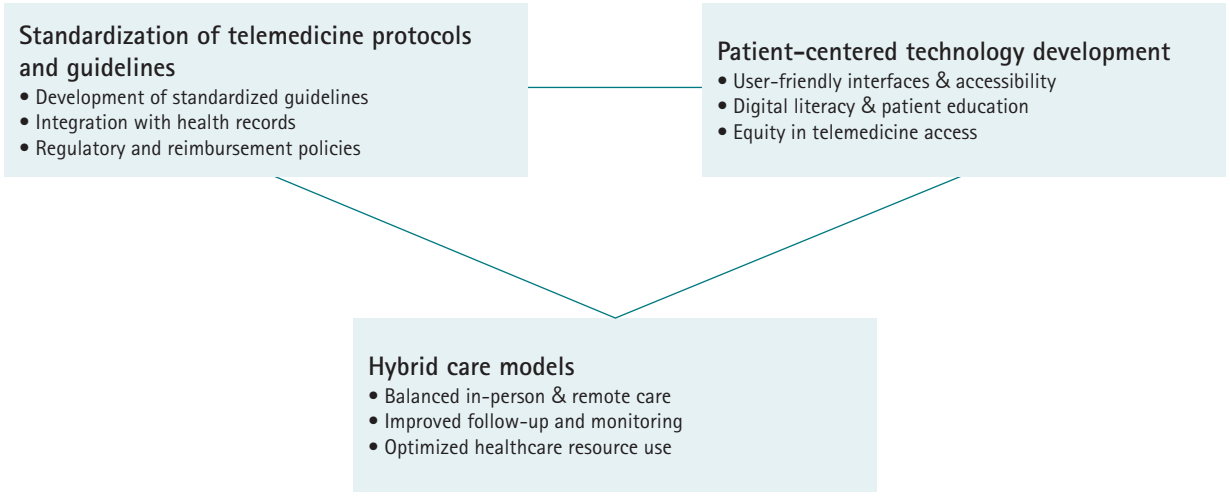

Fig. 6. Future perspectives and recommendations for telemedicine in heart failure (Drawn by the author).

parity with in-person care, particularly given their demonstrated clinical efficacy.

Patient-centered technology development

A critical future focus for telemedicine is to improve accessibility and acceptability across diverse patient populations. This effort requires involving patients in telehealth system design, developing user-friendly interfaces, and providing educational resources such as tutorial videos, helplines, and peer mentoring to improve digital literacy. To address equity concerns, healthcare systems should consider device lending programs and internet access support for underserved communities, while also implementing culturally sensitive adaptations in language and health education. Rather than adopting a one-size-fits-all approach, providers should assess individual circumstances and preferences—offering high-tech monitoring for tech-savvy patients while maintaining low-tech options like phone calls for others. Continuous collection of patient experience data will help refine these services, ensuring that telemedicine's benefits extend to all populations, including those in remote or historically underserved communities, and ultimately preventing digital disparities in HF care outcomes [49].

Hybrid care models

Experts recommend adopting hybrid models that blend in-person and remote care rather than treating telemedicine as a complete replacement for traditional approaches. For HF patients, this means scheduling in-person visits for critical moments, such as initial diagnosis or when detailed physical examinations are necessary, while using telemedicine for routine monitoring and follow-ups. This balanced approach can increase healthcare capacity by allowing physicians to manage larger patient panels while providing more frequent touchpoints without overwhelming clinic schedules. Telemedicine can also enhance after-hours support, potentially preventing emergency department visits through remote assessment and medication adjustments, thereby reducing acute care burdens on healthcare providers (Fig. 6).

Conclusion

HF requires continuous management and is associated with high mortality, making telehealth an essential tool for effective care. This review has examined substantial evidence supporting telemedicine's effectiveness in improving clinical outcomes, optimizing medication therapy, and providing personalized care. Despite its effectiveness and growing implementation, significant challenges remain and must be addressed to realize telemedicine's full potential. When thoughtfully implemented with attention to evidence and integrated with existing care systems, telemedicine has the potential to significantly improve the quality of HF management.

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Authors' contributions

All work was done by Dong-Ju Choi.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Review

Ewha Med J 2025;48(2):e27
https://doi.org/10.12771/emj.2025.00101

Ewha Medical Journal

Relationship between periodontitis and systemic health conditions: a narrative review

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This review examines the bidirectional relationship between periodontitis and systemic health conditions, offering an integrated perspective based on current evidence. It synthesizes epidemiological data, biological mechanisms, and clinical implications to support collaborative care strategies recognizing oral health as a key component of overall wellness. Periodontitis affects 7.4% to 11.2% of adults worldwide, and its prevalence increases with age. Beyond its local effects, including gingival inflammation, periodontal pocket formation, and alveolar bone loss, periodontitis is associated with various systemic conditions. Emerging evidence has established links with obesity, diabetes mellitus, cardiovascular disease, chronic kidney disease, inflammatory bowel disease, rheumatoid arthritis, respiratory diseases, adverse pregnancy outcomes, certain malignancies, neurodegenerative diseases, psychological disorders, and autoimmune conditions. These associations are mediated by 3 primary mechanisms: dysbiotic oral biofilms, chronic low-grade systemic inflammation, and the dissemination of periodontal pathogens throughout the body. The pathophysiology involves elevated levels of pro-inflammatory cytokines (including interleukin 6, tumor necrosis factor alpha, and C-reactive protein), impaired immune function, oxidative stress, and molecular mimicry. Periodontal pathogens, particularly *Porphyromonas gingivalis*, are crucial in initiating and sustaining systemic inflammatory responses. Treatment of periodontitis has demonstrated measurable improvements in numerous systemic conditions, emphasizing the clinical significance of these interconnections. Periodontitis should be understood as more than just a localized oral disease; it significantly contributes to the overall systemic inflammatory burden, with implications for general health. An integrated, multidisciplinary approach to prevention, early detection, and comprehensive treatment is vital for optimal patient outcomes. Healthcare providers should acknowledge oral health as an essential element of systemic well-being.

Keywords: Cardiovascular diseases; Diabetes mellitus; Obesity; Oral health; Periodontitis

Introduction

Background

Periodontitis is a chronic inflammatory disease known to affect the supportive structures of the teeth [1-3]. In addition to its local impacts, such as gingival inflammation, periodontal pocket formation, and alveolar bone loss, periodontitis is strongly associated with systemic inflammation, which leads to various systemic conditions. These include obesity, diabetes mellitus, cardiovascular disease, pregnancy, chronic kidney disease (CKD), respiratory diseases, rheumatoid arthritis, neurodegenerative diseases, malignancy, stress, depression, and autoimmunity [1-7].

The global prevalence of periodontitis underscores its status as a public health issue. Overall, 7.4% [2] to 11.2% [3] of the adult population exhibit severe periodontitis, with a higher prevalence among older generations. The rising prevalence of this condition in tandem with increasing life expectancy, as well as reductions in root caries-related tooth loss, make periodontitis a primary concern given its adverse economic, social, and health system impacts [2]. In 2015, severe periodontitis accounted for an estimated 3.5 million disability-adjusted life years, exceeding the burden of untreated dental caries [8]. Nevertheless, its indirect consequences, such as reduced chewing efficiency, aesthetic compromise, and diminished quality of life, remain underemphasized [8].

The biological mechanisms underpinning these systemic links are multifactorial, including dysbiotic oral biofilms, chronic low-

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Received: March 4, 2025 Revised: April 8, 2025 Accepted: April 8, 2025

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grade inflammation, and the dissemination of periodontal pathogens and their bioproducts throughout the body [1]. These mechanisms trigger an immune reaction that causes additional local tissue damage while mediating systemic inflammatory states, thereby altering the pathophysiology of diseases beyond the oral cavity [6].

However, findings regarding periodontitis and systemic conditions have sometimes been misinterpreted due to a lack of uniformity in study design, inconsistent disease definitions, and small sample sizes [1-8]. With improved definitions of periodontal diseases and global research guidelines, these issues are now being addressed, paving the way for more robust and reproducible studies [4,5,7].

Objectives

The purpose of this review is to provide an integrative perspective, based on contemporary evidence, on the relationship between periodontitis and systemic diseases. Grounded in epidemiologic data, biological plausibility, and clinical implications, the review underscores the ongoing need for collaborative care strategies that recognize oral health as an integral component of general health and wellness.

Ethics statement

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

Periodontitis and obesity

Obesity is known to be strongly associated with periodontitis [9-13]. Individuals with a body mass index of 30 kg/m^2 or greater face a significantly elevated risk of periodontal disease [9,11,14-16]. Many studies have found that obesity contributes to periodontitis through systemic inflammation, altered immune function, and dysbiosis of the oral microbiota [9,10,12,13,17-19]. Studies report that central obesity, particularly when defined using the waist-to-hip ratio, significantly increases the likelihood of developing periodontitis [10-12,18]. Various meta-analyses have demonstrated a linear dose-response correlation of adiposity with the risk and severity of periodontal tissue damage [10,18,20,21]. Prospective studies have revealed that individuals with overweight and obesity experience more rapid progression of periodontitis compared to their normal-weight counterparts [14,16,20].

Obesity drives chronic low-grade systemic inflammation, characterized by elevated levels of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and C-reactive protein (CRP) [11]. These cytokines exacerbate the destruction of periodontal tissues by disturbing the balance between bone resorption and regeneration [22-24]. Dysbiotic changes in the oral microbiome, such as an increase in gram-negative anaerobic bacteria, create an ideal environment for the development of periodontal disease [17,19]. Other factors, such as adipokines, also link obesity to periodontitis [20,23,25]. For example, increased leptin levels mediate inflammation, while low adiponectin levels impair tissue repair and regeneration [26,27]. Insulin resistance associated with obesity further compromises immune cell function, reducing the capacity of the immune system to defend against bacterial infections of the periodontal tissues [25].

Clinical guidelines

A comprehensive, multidisciplinary approach is necessary to manage periodontal disease in patients with obesity. Effective periodontal treatment, such as scaling and root planing, helps reduce microbial load and inflammation [28]; however, adjunctive anti-inflammatory medications may also be required. Dentists should emphasize the importance of weight management and lifestyle changes—particularly regarding diet and exercise—in decreasing systemic inflammation. Active collaboration with primary physicians and nutritionists is essential for addressing comorbidities. Regular follow-up appointments should ideally occur every 3 to 4 months to evaluate periodontal disease progression and the effectiveness of treatment strategies [29]. Patient education should focus on fostering intrinsic motivation to maintain good oral health and on understanding the interactive relationship between obesity and periodontal health [28,29].

Periodontitis and diabetes mellitus

Diabetes mellitus and periodontitis have a well-established reciprocal association. Periodontitis is termed the sixth complication of diabetes, and patients with diabetes are about 3 times more likely to develop severe periodontitis as their nondiabetic counterparts [28,30-33]. Hyperglycemia exacerbates periodontal disease by promoting oxidative stress and the formation of advanced glycation end products [34-37]. Conversely, periodontitis worsens glycemic control by increasing the systemic inflammatory load. Longitudinal research indicates that patients with poorly managed diabetes experience more severe periodontal tissue loss and recover more slowly after therapy compared to those without diabetes.

Diabetes accelerates the deterioration of periodontal tissue through several mechanisms [34]. Oxidative stress induced by

chronic hyperglycemia results in an overabundance of advanced glycation end products, which attach to receptors on various cells [35]. This interaction triggers the release of pro-inflammatory cytokines, including TNF-α and IL-6, thereby exacerbating both local and systemic inflammation [38]. Furthermore, reduced neutrophil function in patients with diabetes impairs pathogen removal, while elevated CRP levels contribute to delayed wound healing [39,40]. Pathogens such as *Porphyromonas gingivalis* worsen systemic insulin resistance by triggering inflammatory cytokine cascades [41].

Clinical guidelines

Effective management of periodontal disease in patients with diabetes requires cooperation between dentists and endocrinologists. Individuals with poorly controlled diabetes should undergo periodontal evaluation every 3 months. Non-surgical therapy, including scaling and root planing, improves glycemic control, with reductions in hemoglobin A1c levels of up to 0.4% [28]. During invasive procedures for patients with uncontrolled diabetes, the dentist should monitor blood glucose levels and administer prophylactic antibiotics. A focused educational program can inform patients about the role of oral health in glycemic control. Individualized oral hygiene measures, including antiseptic mouthwashes and interdental cleaning, should be encouraged for all patients. Nutritional counseling and smoking cessation programs also contribute to improved treatment outcomes [42].

Periodontitis and cardiovascular disease

Epidemiological evidence supports a robust association between periodontitis and cardiovascular disease [43-45]. Severe periodontitis increases the risk of major adverse cardiovascular events, such as myocardial infarction or stroke, by a factor of 1.4 [44]. The primary mechanisms linking these conditions include chronic inflammation, endothelial dysfunction, and microbial dissemination [46,47]. Periodontal pathogens such as *P. gingivalis* have been detected in atherosclerotic plaques, demonstrating the systemic impact of periodontitis [48]. Longitudinal studies indicate that periodontitis accelerates the progression of cardiovascular disease by elevating levels of certain systemic inflammatory markers, such as CRP [49].

Periodontal inflammation provokes a systemic acute-phase response, increasing levels of CRP, IL-6, and TNF-α [49-52]. These inflammatory mediators can act on the endothelium, causing dysfunction and promoting atherogenesis. Lipopolysaccharides from periodontal pathogens, particularly *P. gingivalis*, circulate into the bloodstream, triggering macrophage foam cell formation and rapid plaque development [53-55]. Periodontal infections also promote platelet aggregation, thereby increasing the risk of thrombosis. Dysbiotic changes in the oral microbiota further induce systemic inflammation, creating a feedback loop that aggravates both periodontal and cardiovascular conditions [56].

Clinical guidelines

The management of patients with cardiovascular disease complicated by periodontal disease may require additional medications and follow-up visits with a cardiologist. The dentist should assess the risk of bleeding for patients on antiplatelet or anticoagulant therapy before performing invasive procedures [57,58]. Non-surgical periodontal therapy, in conjunction with adjunctive anti-inflammatory medication to reduce systemic inflammation, is a promising approach [59]. Regular dental check-ups, typically every 3 to 4 months, are recommended to monitor oral health and mitigate systemic risk factors, avoiding delayed diagnosis of any issues. Patients should be informed of the potential cardiovascular benefits of maintaining good periodontal health. Preventive lifestyle changes, such as smoking cessation and dietary modifications, are crucial for improving treatment outcomes [60].

Periodontitis and chronic kidney disease

Periodontitis and CKD share a bidirectional relationship. Patients with CKD are predisposed to eburnation due to immune dysfunction; as such, they may experience persistent periodontal inflammation that, in turn, accelerates CKD progression [61-63]. Observational studies have also shown that patients with advanced periodontal disease are at an increased risk of developing further renal impairment [62,64]. Furthermore, periodontal therapy has been linked to improvements in renal parameters, such as serum creatinine and estimated glomerular filtration rate [65].

Chronic systemic inflammation driven by periodontal pathogens, such as *P. gingivalis*, may contribute to the onset of CKD [66]. Elevated concentrations of pro-inflammatory cytokines—including IL-6, TNF-α, and CRP—further amplify endothelial dysfunction and oxidative stress in renal tissues [67,68]. Bacterial pathogens and their endotoxins can enter the bloodstream, creating a pro-inflammatory state that provokes renal damage. Furthermore, uremia in CKD impairs immune responses, exacerbating the adverse effects on both periodontal and kidney health [69].

Clinical guidelines

Managing periodontal disease in patients with CKD necessitates close collaboration with nephrologists. Periodontal examinations are recommended every 3 months to control microbial load

and, consequently, systemic inflammation. Non-surgical periodontal therapies, such as scaling and root planing, have been shown to be effective in reducing systemic inflammatory markers among those with CKD [70-72]. Dentists should avoid prescribing medications that may compromise renal function and must carefully manage bleeding tendencies in patients taking anticoagulants [65,70]. Patient education should emphasize proper oral hygiene and the interrelationship between periodontal and kidney health. Nutritional counseling for these patients may also include recommendations to reduce sodium and phosphate intake.

Periodontitis and inflammatory bowel disease

Epidemiological evidence suggests a strong association between inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, and periodontitis [73]. Patients with IBD exhibit a significantly increased frequency and severity of periodontitis, characterized by greater clinical attachment loss and deeper periodontal pockets [74,75]. Both conditions share common inflammatory pathways, with elevated levels of pro-inflammatory cytokines—namely IL-6, IL-1β, and TNF-α—contributing significantly to tissue destruction at both systemic and local levels [76,77]. Microbiota dysbiosis also plays a major role; periodontitis is marked by an overgrowth of pathogenic bacteria, such as *P. gingivalis* and *Fusobacterium nucleatum*, which may translocate to the gut and exacerbate IBD symptoms [78]. In addition, shared genetic predispositions, including polymorphisms in *IL23R* and *NOD2*, support a common immunological basis for these conditions [79].

Clinical guidelines

Given this bidirectional interaction, the dental regimen for patients with IBD should include routine periodontal examinations, oral hygiene instruction, and non-invasive periodontal therapy to reduce bacterial load [73,80]. During active IBD flares, extreme caution is advised when scheduling dental treatments. Non-steroidal anti-inflammatory drugs, which may aggravate gut inflammation, should be avoided. Due to the immunosuppressive state, prophylactic antibiotics may be considered [81-83]. Close collaboration between dentists and gastroenterologists is essential to enhance periodontal health and, when possible, reduce systemic inflammation to improve IBD management [84].

Periodontitis and rheumatoid arthritis

Periodontitis and rheumatoid arthritis share common inflammatory pathways and genetic predispositions, which underpin the relationship between these conditions. Studies have shown that individuals with rheumatoid arthritis are nearly twice as likely to develop periodontitis compared to the general population [85]. This is a reciprocal association, as periodontitis exacerbates systemic inflammation in rheumatoid arthritis, potentially worsening joint symptoms [86,87]. Moreover, observational studies have demonstrated that untreated periodontitis is associated with higher disease activity scores in patients with rheumatoid arthritis, highlighting the impact of local and systemic oral inflammation [86].

The pathogenic link between periodontitis and rheumatoid arthritis primarily involves immune dysregulation driven by *P. gingivalis*, a major periodontal pathogen. This organism produces peptidylarginine deiminase, an enzyme that catalyzes the citrullination of proteins—a hallmark of the pathogenesis of rheumatoid arthritis [88,89]. The citrullination process results in the generation of anti-citrullinated protein antibodies, which promote joint inflammation [90]. Elevated levels of inflammatory cytokines, such as TNF-α, IL-6, and IL-17, are common to both periodontitis and rheumatoid arthritis, contributing to systemic and local tissue destruction [91,92]. Additionally, dysbiosis of the oral microbiome perpetuates inflammatory cycles, creating a vicious feedback loop that increases the severity of both diseases [93].

Clinical guidelines

Effective management of periodontitis in patients with rheumatoid arthritis requires a multidisciplinary approach. Collaboration between periodontal and rheumatology teams is essential to concurrently address systemic and oral inflammation. Follow-up periodontal examinations should be performed every 3 months. Evidence indicates that non-surgical periodontal therapy, including scaling and root planing, reduces systemic inflammatory markers and improves rheumatoid arthritis symptoms. In severe cases, adjunctive therapies—such as anti-inflammatory or antibiotic treatments—may be considered [94,95]. Patients should receive oral hygiene instructions, including proper techniques for brushing, flossing, the use of interdental brushes, and chlorhexidine rinses. Given that smoking is a known aggravating factor for both rheumatoid arthritis and periodontitis, smoking cessation should be strongly encouraged [96]. Nutritional counseling aimed at avoiding inflammatory food triggers may further improve overall health outcomes for these patients.

Periodontitis and respiratory diseases

Evidence suggests that periodontitis may play a role in the evo-

lution and exacerbation of respiratory diseases such as pneumonia, chronic obstructive pulmonary disease (COPD), and asthma [97]. Strong evidence indicates that aspiration of oral contents into the respiratory tract can initiate or worsen respiratory tract infections [98,99]. Severe periodontitis is associated with an increased prevalence of pneumonia, particularly among hospitalized and ventilated patients. Studies have also reported a higher tendency for the development of COPD in individuals with periodontitis, with inflammatory markers and microbial load serving as significant mediators [98,100].

The translocation of oral pathogens, including bacteria such as *P. gingivalis* and *F. nucleatum*, into the respiratory tract is a key factor in the pathogenesis of periodontitis-related respiratory diseases [101,102]. These pathogens stimulate local and systemic inflammation, triggering the release of pro-inflammatory cytokines such as IL-1β and TNF-α and thereby aggravating airway inflammation and tissue damage. The dysbiosis observed in the oral cavity and respiratory tract is driven by the uncomplicated colonization of these bacteria. Toxins associated with the periodontium serve as markers of systemic inflammation, weakening the respiratory system's immune defense against pathogens and increasing the risk of infection [101,102].

Clinical guidelines

Managing periodontal health in patients with respiratory diseases requires a preventive approach. Regular dental checkups, professional cleanings, and improved oral hygiene practices are essential to minimize the risk of aspiration-related infections. The use of antimicrobial mouthwashes and effective plaque control techniques can significantly reduce the bacterial load in the oral cavity [103]. Collaboration with pulmonologists is recommended for patients with severe respiratory conditions, particularly those who are immunocompromised or on ventilatory support [103]. Patient education should emphasize the importance of maintaining oral health, including smoking cessation, to improve respiratory outcomes and overall quality of life [104].

Periodontitis and adverse pregnancy outcomes

Periodontitis has been shown to be significantly correlated with adverse pregnancy outcomes, including preterm birth, low birth weight, and preeclampsia [105,106]. In pregnant women with untreated periodontal disease, the risk of such outcomes is about 1.5 times greater than in those without periodontal disease [107]. Periodontal infection is thought to alter fetal intrauterine development through systemic inflammation and the dissemination of microflora from periodontal pockets. Meta-analyses have confirmed the correlation between maternal periodontal disease and preterm birth, particularly among women with severe periodontitis [107]. In addition, elevated levels of inflammatory biomarkers such as IL-6 and CRP in mothers with periodontitis are linked to impaired placental function [108].

The underlying pathophysiology involves both local and systemic inflammatory mechanisms. Oral pathogens, such as *F. nucleatum*, can migrate from the periodontal tissues to the placenta, triggering an immune response that ultimately destabilizes placental integrity [109]. Elevated levels of cytokines, including IL-1β, TNF-α, and prostaglandins, can provoke uterine contractions, leading to preterm birth [110]. Chronic periodontal inflammation potentiates oxidative stress and endothelial dysfunction, jeopardizing fetal nutritional supply and growth [111,112]. Dysbiosis of the maternal oral microbiota further increases systemic inflammation, initiating a cascade of adverse pregnancy events [113].

Clinical guidelines

Managing periodontal disease in pregnant women requires adherence to specific strategies, as improper management may lead to systemic inflammation. Non-surgical periodontal therapies such as scaling and root planing can be safely performed during the second trimester [114,115]. Regular oral examinations, along the use of antimicrobial mouthwashes and other oral hygiene methods, are consistently recommended for high-risk pregnancies [115-117]. Pregnant women should be informed of the maternal and fetal complications associated with untreated periodontal disease. Obstetricians should collaborate closely for high-risk pregnancies to ensure coordinated healthcare. Moreover, prenatal care may be optimized by incorporating targeted nutritional guidance and smoking cessation support, promoting both maternal and fetal health.

Periodontitis and malignancy

Periodontitis has been implicated as a precipitating factor for various malignancies, especially oral, pancreatic, and colorectal cancers [118-120]. Chronic inflammation, induced by persistent infection and immune dysregulation, is the primary factor linking periodontitis to tumor development and progression [121]. Certain pathogens, such as *F. nucleatum*, have been shown to play a role in the etiology of colorectal cancer, modulating the tumor microenvironment and stimulating metastasis [122,123].

The connection between periodontitis and malignancy occurs through both direct and indirect mechanisms. The sustained in-

flammation in periodontal tissues leads to the systemic release of pro-inflammatory cytokines, such as IL-6 and TNF-α, which, in turn, promote angiogenesis and enable immune evasion during tumor growth [124,125]. Oncogenic signaling pathways are activated when oral pathogens, including *F. nucleatum*, adhere to epithelial cells, thereby encouraging cell proliferation and survival [123]. Furthermore, dysbiosis of the oral microbiome fosters additional systemic inflammation that supports carcinogenesis. Increased oxidative stress associated with chronic gingival infections also contributes to DNA damage, potentially heightening the risk of malignant transformation [126,127].

Clinical guidelines

For patients with cancer or at risk of cancer, intervention aimed at chemoprevention should incorporate maintenance of periodontal health [128]. Periodontal examinations and cleanings should be performed regularly to reduce systemic inflammation and microbial load [129]. Collaboration with oncologists is necessary to develop an effective dental care protocol, especially for patients undergoing chemotherapy and radiation therapy, whose side effects impact oral health [119]. Specifically, dentists should educate patients on the benefits of maintaining proper oral hygiene—such as regular brushing—and the use of topical measures, including fluoride applications and antimicrobial rinses [130,131]. Nutritional counseling may also help bolster immune support and manage systemic inflammation.

Periodontitis and neurodegenerative diseases

The mechanisms linking periodontitis with neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, include both systemic inflammation and direct microbial invasion [132-135]. Periodontal pathogens, particularly *P. gingivalis*, produce virulent factors—specifically, gingipains—that compromise the integrity of the blood-brain barrier, allowing bacteria and inflammatory mediators to enter the central nervous system [136]. This process triggers microglial activation and the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, which further contribute to neuronal damage [137,138]. Additionally, *P. gingivalis* has been shown to induce the deposition of amyloid-β plaques and the phosphorylation of tau proteins, both hallmarks of Alzheimer's disease [139]. Systemic inflammation caused by chronic periodontitis may further augment oxidative stress and neuroinflammation, thereby accelerating neurodegeneration [140].

Clinical guidelines

For patients at risk of developing neurodegenerative diseases, as well as those already diagnosed, an ongoing, preventive approach to managing periodontitis is recommended. Regular dental appointments and periodic cleanings should be instituted to minimize the microbial burden and reduce systemic inflammation [141]. Caregivers should be involved to help ensure adherence to proper oral health practices, such as brushing with fluoride toothpaste and using an antimicrobial mouthwash. Collaboration with neurologists is recommended to monitor the interplay between oral and cognitive health. Dentists should educate patients on the importance of maintaining oral health for overall neurological function. For individuals in the advanced stages of neurodegenerative disease, care plans should be personalized to account for physical and cognitive limitations [142].

Periodontitis, stress, and depression

Stress and depression are strongly correlated with periodontitis through both behavioral and physiological mechanisms. Studies indicate that individuals experiencing chronic stress or depression may require more extensive periodontal treatment, with odds ratios reaching approximately 1.5 compared to those without these conditions [143-145]. Lifestyle factors common among stressed or depressed individuals, such as poor oral hygiene, smoking, and unfavorable dietary practices, can exacerbate the progression of periodontal disease [144,146]. Additionally, depression heightens systemic inflammation, contributing to periodontal tissue breakdown [147]. Stress-related hormones, particularly cortisol, interfere with the immune response by suppressing the activity of immune cells that target periodontal pathogens, which can lead to increased bacterial proliferation and inflammation in periodontal tissues [148]. In conjunction with depression, stress elevates the release of pro-inflammatory cytokines such as IL-6 and TNF-α, further worsening tissue destruction and bone resorption [148].

Clinical guidelines

Managing periodontal disease in patients experiencing stress or depression requires a holistic approach that addresses both psychological and oral health [149,150]. Dentists should collaborate with mental health professionals to provide integrated care. Regular periodontal evaluations and cleanings are recommended to control bacterial load and reduce inflammation. To improve overall health outcomes, stress relief options such as mindfulness, counseling, or cognitive-behavioral therapy should be suggested. Dentists should educate patients about the importance of maintaining good oral hygiene and the bidirectional relationship of

stress and depression with periodontal health. In addition, treatments may include the use of antimicrobial mouthwashes and anti-inflammatory medications to help control inflammation. Furthermore, smoking cessation and nutritional counseling to support immune function should be key components of the treatment regimen [151,152].

Periodontitis and autoimmunity

Autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus type 1, and rheumatoid arthritis share inflammatory pathways and dysregulated immune responses with periodontitis. In these conditions, periodontal attachment loss is often particularly severe. Meta-analyses have revealed that systemic lupus erythematosus significantly increases the risk of periodontitis compared to the general population [153,154]. These conditions are characterized by elevated inflammatory markers, such as CRP, which link systemic inflammation with the progression of oral disease. However, apart from studies on rheumatoid arthritis, there is a marked deficiency of well-designed studies investigating the correlation between periodontitis and other autoimmune diseases, largely due to methodological weaknesses—particularly the inconsistent use of clinical indices. Thus, the conclusions that can be drawn at this time are limited and should be interpreted with discretion [155-158]. *P. gingivalis*-induced molecular mimicry and immune dysregulation exacerbate the autoimmune response by elevating IL-17 levels, which in turn causes further destruction of periodontal tissues [159]. In the production of autoantibodies, a process known as citrullination, *P. gingivalis* has been shown to contribute to several autoimmune diseases, especially rheumatoid arthritis. Dysbiosis of the oral microbiome enhances systemic immune activation and further impairs tissue repair mechanisms. Moreover, periodontal pathogens stimulate dendritic cell maturation and the release of pro-inflammatory cytokines, thereby intensifying autoimmune activity and tissue destruction [160].

Clinical guidelines

Patients with autoimmune diseases require multidisciplinary care to effectively manage both systemic and periodontal inflammation. Coordination between dental professionals and rheumatologists can facilitate favorable treatment outcomes. Periodontal debridement should ideally be performed at least every 3 months, depending on the severity of the condition, to reduce bacterial load and inflammation. In addition, anti-inflammatory and immunomodulatory therapies tailored to the patient's systemic condition may positively impact periodontal outcomes [161]. Dentists must carefully evaluate and consider the potential oral side effects of systemic treatments, such as dry mouth caused by immunosuppressive therapies; in such cases, adjunctive therapies like topical fluorides and artificial saliva support may be necessary [161-163]. For patients receiving biologic or high-dose immunosuppressive therapies, medical clearance may be required prior to dental treatment [162].

Conclusion

Periodontitis is a chronic inflammatory condition with significant implications for systemic health. It is more than simply a localized oral disease, as evidenced by its established associations with systemic conditions such as diabetes, cardiovascular disease, adverse pregnancy outcomes, respiratory disorders, autoimmune diseases, and neurodegenerative diseases. These links are mediated by dysbiotic biofilms, systemic inflammation, and the dissemination of bacterial components and inflammatory mediators into the circulation—mechanisms implicated in the pathogenesis of numerous systemic diseases.

Despite extensive research on periodontitis, historical impediments such as varying definitions of the disease, differences in study design, and small sample sizes have limited the comparability of findings. However, recent advances in classification systems and evidence-based research guidelines have substantially improved the quality and interpretability of periodontal studies, enabling researchers to better understand the systemic implications.

This review underlines the need for an integrated approach to the management of periodontitis. Collaborative care across dental and medical disciplines can address the systemic effects of periodontitis and oral diseases, improving both oral and general health outcomes. Given the rising prevalence of periodontitis due to aging populations, increased life expectancy, and lifestyle issues, such an effort is especially timely.

In addressing periodontitis and systemic disease, priority should be given to prevention, early detection, and comprehensive treatment within an integrated model of care. Interdisciplinary networks should be established and strengthened to emphasize evidence-based interventions for individuals with periodontitis and those at risk, ultimately enhancing intervention options. By considering oral health as an integral component of systemic well-being, healthcare providers can be better positioned to improve quality of life and mitigate the overall impact of this widespread disease.

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Authors' contributions

Conceptualization: EKP. Data curation: EKP. Methodology/formal analysis/validation: EKP. Project administration: EKP. Funding acquisition: not applicable. Writing–original draft: MYK. Writing–review & editing: MYK, EKP.

Conflict of interest

Min-Young Kim has been a student editor since January 2025; however, she was not involved in peer review process.

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e28
https://doi.org/10.12771/emj.2025.00367

Ewha Medical Journal

Status of human rights violations and trauma among North Korean defectors: a cross-sectional study

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Purpose: This study aimed to identify the types of human rights violations and the associated psychological trauma experienced by North Korean defectors. It also examined the impact of trauma on the defectors' interpersonal relationships, employment, and overall quality of life, while evaluating existing psychological support policies to suggest potential improvements.

Methods: A multidisciplinary research team conducted an observational survey and in-depth interviews with approximately 300 North Korean defectors residing in South Korea from June to September 2017. Standardized measurement tools, including the Post-Traumatic Stress Disorder (PTSD) Checklist (PCL-5), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder Scale-7 (GAD-7), and Short Form-8 Health Survey (SF-8), were employed. Statistical analyses consisted of frequency analysis, cross-tabulation, factor analysis, and logistic regression.

Results: The findings revealed a high prevalence of human rights violations, such as public executions (82%), forced self-criticism (82.3%), and severe starvation or illness (62.7%). Additionally, there were elevated rates of PTSD (56%), severe depression (28.3%), anxiety (25%), and insomnia (23.3%). Defectors who resided in China before entering South Korea reported significantly worse mental health outcomes and a lower quality of life. Moreover, trauma was strongly and negatively correlated with social adjustment, interpersonal relationships, employment stability, and overall well-being.

Conclusion: An urgent revision of existing policies is needed to incorporate specialized, trauma-informed care infrastructures within medical institutions. Furthermore, broad societal education to reduce stigma and enhance integration efforts is essential to effectively support the psychological well-being and social integration of North Korean defectors.

Keywords: Democratic People's Republic of Korea; Health policy; Human rights; Post-traumatic stress disorders; Social integration

Introduction

Background

North Korean defectors are known to experience trauma-related disorders, such as post-traumatic stress disorder (PTSD), following their harrowing experiences [1-4]. Previous research has documented various forms of discrimination and human rights violations, notably among North Korean women, during the defection and resettlement processes in North Korea, third countries, and South Korea. It has also been suggested that the psychological and physical trauma encountered during defection and stays in third countries plays a major role in the social adjustment difficulties faced by North Korean defectors in South Korea [5,6].

Objectives

This study aimed to identify the specific human rights violations experienced by North Korean defectors at different stages—while in North Korea, during the defection process, and after resettlement in South Korea—and to examine the associated psychological trauma. It also analyzes how trauma affects the defectors' interpersonal relationships, workplace experiences, and daily

*Corresponding email: sohee.lee@nmc.or.kr
This paper is an abridged, secondary publication of the 2017 Human Rights Situation Survey Research Report after English translation.
Received: March 1, 2025 Revised: April 3, 2025 Accepted: April 3, 2025

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lives, exploring its influence on social adaptation in South Korea. Furthermore, the study evaluates current psychological support policies for North Korean defectors, identifies deficiencies, and proposes targeted improvements.

Methods

Ethics statement

This study was conducted in accordance with ethical guidelines for research involving human participants. The study protocol was approved by the Institutional Review Board (IRB) of the National Medical Center, Seoul, Korea (IRB no., H-1704-077-002) and all procedures were performed in compliance with the Declaration of Helsinki.

The original Korean report is available at Supplement 1.

Study design

This cross-sectional observational survey was designed to investigate the human rights violations and trauma experiences of North Korean defectors. The study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement available at: https://www.strobe-statement.org/.

Setting

A multidisciplinary research team was established, consisting of psychiatrists experienced in treating North Korean defectors and conducting related research, experts in North Korean human rights, and public health PhD holders, was assembled. The team operated as a collaborative, multi-institutional unit to ensure a comprehensive and specialized approach to the study.

Participants

Survey data were collected from approximately 300 North Korean defectors who had entered South Korea from June to September 2017. The gender distribution was structured at approximately a 7:3 ratio between women and men, reflecting the demographic profile of North Korean defectors in South Korea. Sampling was aimed to match the population distribution in terms of age, gender, and residential area (metropolitan cities and provinces). Recruitment was carried out using snowball sampling and through Hana Centers, organizations related to North Korean defectors, and counseling centers to ensure a representative sample.

Variables

Outcome variables comprised the survey questions measuring human rights violations, trauma experiences, mental health, psychological state, and quality of life.

Data sources/measurement

Establishment of survey tools for the study

A human rights violation assessment form was developed and combined with standardized tools to construct survey questions that measured diverse aspects including trauma experiences, mental health, psychological state, quality of life, and demographic factors (Table 1).

Development of an in-depth interview tool

Approximately 10 key questions were selected for in-depth interviews with North Korean defectors. The domains and corresponding items were systematically determined, and specific questions were finalized during researcher meetings and through

Table 1. Survey tools

Evaluation items	Tools
Socio-demographic domain	Motivation for defection, year of defection, defection route, year of entry into South Korea, marital status, medical history, etc.
Human rights violations and PTSD	
Human rights violation questionnaire	Human rights violation questionnaire developed specifically for North Korean defectors
Traumatic event list	Life Events Checklist (LEC-5)
Post-traumatic symptoms	PTSD Checklist-5 (PCL-5)
Depression	Patient Health Questionnaire-9 (PHQ-9)
Anxiety	7-item Anxiety Scale (Generalized Anxiety Disorder Scale, GAD-7)
Suicide risk	Korean version of the Suicidal Tendency Scale (K-MINI)
Insomnia	Insomnia Severity Index (ISI)
Quality of life	Short Form-8 Health Survey (SF-8)
Alcohol and smoking habits	Alcohol Use Disorders Identification Test (AUDIT-C); smoking assessment questions

PTSD, post-traumatic stress disorder.

expert consultations.

Implementation of the survey and in-depth interviews

A trauma expert with extensive experience in treating North Korean defectors administered the survey to approximately 300 North Korean defectors upon their entry to South Korea, and conducted in-depth interviews with around 20 participants. Sampling for the survey utilized snowball sampling and promotional efforts through Hana Centers, organizations supporting North Korean defectors, and counseling centers.

Bias

Due to the nature of snowball sampling, the generalizability of this study's findings is limited.

Study size

Assuming a 2-tailed test with a significance level (α) of 0.05, the minimum required sample size for testing mean differences between 2 independent, normally distributed groups (e.g., gender differences) was estimated based on effect size. For a small effect size (0.2), approximately 1,833 participants would be needed; for a medium effect size (0.5), around 295 participants; and for a large effect size (0.8), about 117 participants would be required. Similarly, for independent groups with non-normal distributions, approximately 1,919, 309, and 122 participants would be needed for small, medium, and large effect sizes, respectively.

Statistical methods

The collected survey responses were coded and analyzed using frequency analysis, cross-tabulation analysis, factor analysis, and logistic regression to address the research objectives. In-depth interview data were examined to identify "key domains" and "core ideas," which were later reviewed and categorized by the research team until a consensus was reached.

All statistical analyses were conducted using Stata/MP 17.0 software (Stata Corp.).

Results

Participants

Out of the 300 respondents, 245 (81.67%) were women and 55 (18.33%) were men, with an average age of 52.87 ± 15.90 years. Regarding their North Korean residential origins, the majority (181 individuals, 60.32%) were from Hamgyong Province. A large proportion (258 respondents, 85.66%), reported having held employment (including small-scale trading). The most common marital status in North Korea was "married" (85 individuals, 28.33%).

Regarding defection characteristics, 135 defectors (44.99%) initially left North Korea during the 2000s. The majority (157 individuals, 52.34%) obtained South Korean citizenship in the 2010s. After defection, 181 respondents (60.33%) resided in China, with an average stay of 6.21 ± 4.65 years, while 115 individuals (38.34%) entered South Korea directly without transiting a third country. Among those who stayed in China, approximately 40% experienced arrest by Chinese authorities, 33% were repatriated to North Korea, and about 35% were detained in labor camps or detention facilities.

Regarding post-arrival experiences in South Korea, 147 individuals (49.00%) reported having employment experience, of which only 36 (24.49%) remained employed at the time of the survey. Among those previously employed in South Korea, the primary reasons for job loss were health issues (69 individuals, 60.53%), followed by stress and adaptation difficulties (17 individuals, 14.91%). Concerning marital status after arriving in South Korea—considered separately from North Korean marital status—188 respondents (62.67%) reported being unmarried. Among married respondents, 65 individuals (58.04%) were married to fellow North Korean defectors. Lastly, a majority (251 individuals, 83.67%) still reported having family members remaining in North Korea.

Status of human rights violation trauma experiences

Human rights violation experiences

The most frequently reported human rights violations included being compelled to participate in public self-criticism sessions in North Korea (247 individuals, 82.33%), experiencing severe starvation or illness (188 individuals, 62.67%), and suffering from surveillance or denunciation by neighbors and Party members (171 individuals, 57.00%). Other severe violations included human trafficking of women or children during defection (65 individuals, 21.67%; specifically, 26.53% among women), sexual violence against women in North Korea (22 individuals, 9.0% of women), and witnessing public executions (246 individuals, 82.0%) (Fig. 1).

Trauma experiences

The most common traumatic events in North Korea involved extreme human suffering, including forced labor, chronic starvation or food shortages, persistent homelessness, and torture (192 individuals, 64.00%). This was followed by physical violence such as assaults, beatings, slaps, or kicks (139 individuals, 46.33%) and by natural disasters like floods, typhoons, storms, or earthquakes

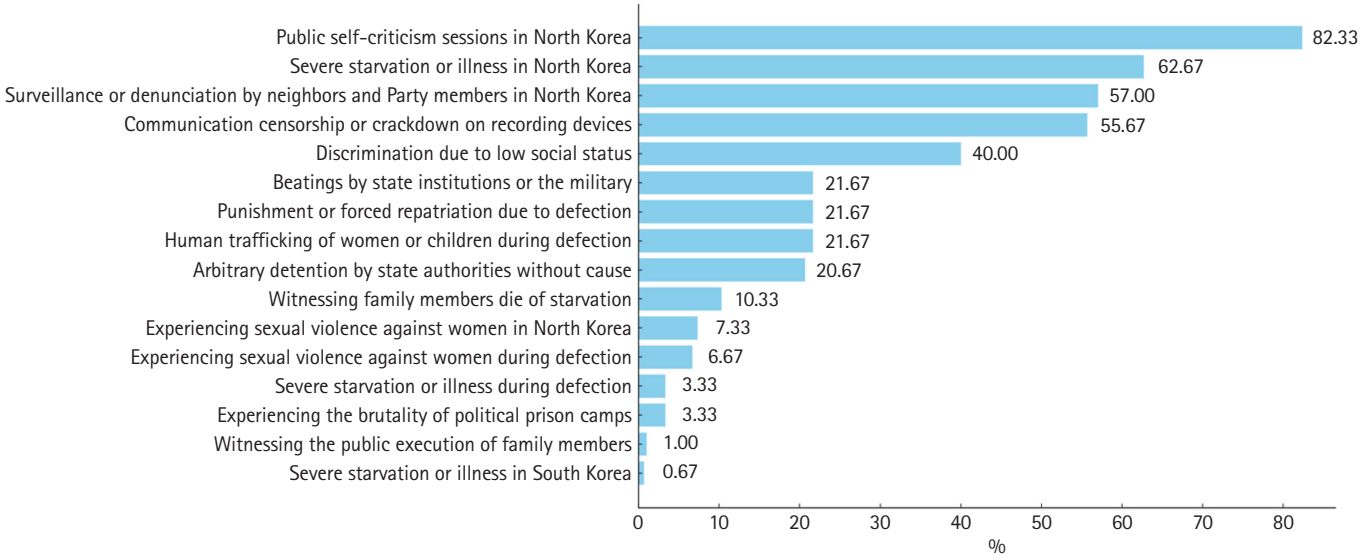

Fig. 1. Prevalence of human rights violations experienced by North Korean defectors.

(133 individuals, 44.33%). During defection, the most frequent traumatic experiences included imprisonment due to abduction, kidnapping, hostage situations, or being taken as a prisoner of war (51 individuals, 27.57%); physical violence including assaults, beatings, or slaps (49 individuals, 26.49%); and attempted sexual assault or coerced sexual acts through force or threat (23 individuals, 12.43%) (Fig. 2).

In South Korea, the primary traumatic experiences reported were traffic accidents involving cars, ships, trains, or airplane crashes (31 individuals, 10.33%), followed by life-threatening illness or injury (13 individuals, 4.33%).

Mental health and quality of life status

Based on total scores from the PTSD Checklist (PCL-5), 168 individuals (56.00%) scored within a range indicating a need for clinical attention (scores of 33 or higher). PTSD levels were significantly higher among defectors under 60 years old compared to those aged 60 or older, and those who resided in China exhibited markedly higher PTSD symptoms than those who entered South Korea directly.

According to the Patient Health Questionnaire (PHQ-9), participants were classified as follows: normal (scores ≤ 4) for 62 individuals (20.67%), mild depression (scores between 5 and 9) for 57 individuals (19.00%), moderate depression (scores between 10 and 19) for 96 individuals (32.00%), and severe depression (scores between 20 and 27) for 85 individuals (28.33%).

Using the Korean version of the Suicidal Tendency Scale (K-MINI) to assess suicidal tendencies, 184 individuals (61.33%) were categorized as having a low suicide risk (scores of 5 or lower), 46 individuals (15.33%) showed moderate risk (scores between 6 and 9), and 70 individuals (23.33%) were identified as having a high suicide risk (scores between 10 and 19).

For anxiety, as assessed by the Generalized Anxiety Disorder Scale (GAD-7), 109 individuals (36.33%) scored within the normal range (scores of 4 or lower), 71 individuals (23.67%) had moderate anxiety (scores between 10 and 14), and 75 individuals (25.00%) exhibited severe anxiety (scores of 15 or higher).

Finally, based on the Insomnia Severity Index (ISI), 80 individuals (26.67%) were within the normal range (scores of 7 or lower), 71 individuals (23.67%) had mild insomnia (scores between 8 and 14), 79 individuals (26.33%) exhibited moderate insomnia (scores between 15 and 21), and 70 individuals (23.33%) were classified as having severe insomnia (scores between 22 and 28).

The impact of human rights violation trauma on mental health, quality of life, and employment

Differences based on defection, entry process, and length of resettlement

Individuals who had lived in China prior to arriving in South Korea exhibited significantly higher levels of depression, suicidal tendencies, and PTSD compared to those who entered South Korea directly. Although the severity of insomnia did not differ significantly between the 2 groups, those who resided in China reported marginally but significantly lower quality of life and, notably, a higher employment rate. There were no significant differences in PTSD, depression, suicidal tendencies, or insomnia based on the length of resettlement in South Korea, suggesting that

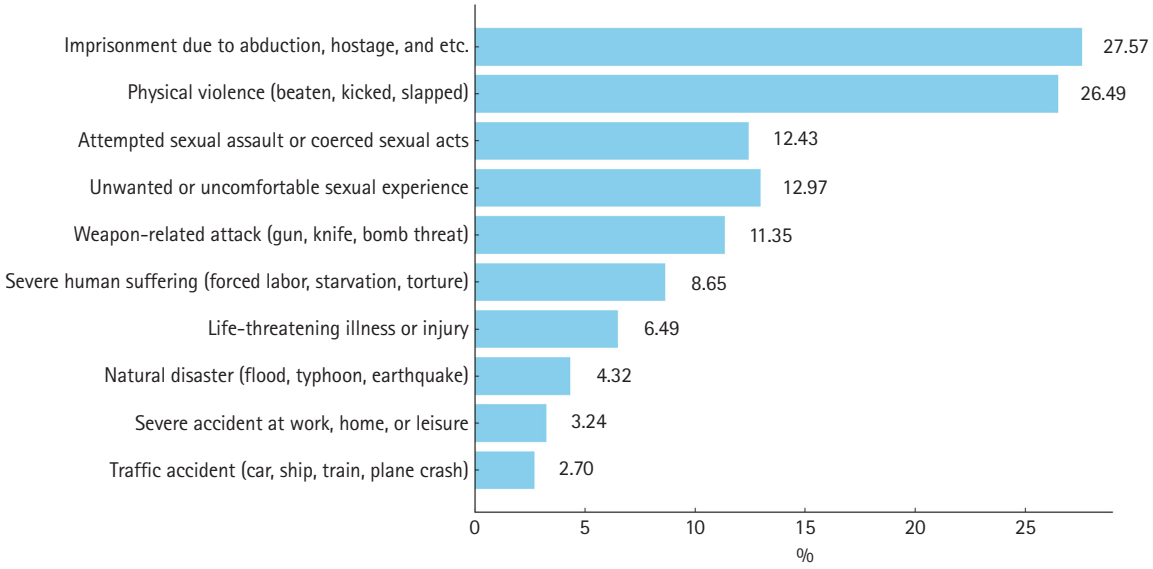

Fig. 2. Prevalence of trauma experiences during defection.

these mental health issues do not naturally resolve over time.

Differences based on experiences of human rights violations

Defectors who directly experienced or witnessed severe human rights violations—including severe starvation or illness, brutality in political prison camps, public executions, punishment for defection attempts, and sexual violence against women in North Korea—displayed significantly higher levels of PTSD symptoms. However, experiencing sexual violence during defection did not significantly alter PTSD levels between groups. In contrast, experiences of human trafficking of women or children during defection were associated with markedly higher PTSD symptoms

Quality of life was significantly lower among individuals who had personally experienced or witnessed public executions, punishments for defection attempts, sexual violence in North Korea, and human trafficking during the defection period.

Paradoxically, employment rates were higher among those who experienced or witnessed human trafficking during defection, suggesting that residence in China might act as a confounding factor influencing employment status.

Differences in mental health based on trauma experiences

An analysis comparing PTSD symptom levels revealed that individuals who directly experienced traumatic events—such as physical violence (attacks, being struck by hands, fists, or clubs), assaults involving weapons (guns, knives, or explosives), life-threatening illness or injury, or natural disasters (floods, typhoons, storms, or earthquakes) in North Korea or during defection—displayed significantly higher PTSD levels than those who did not have such experiences.

Additionally, experiences unique to North Korea, such as witnessing severe injury or death caused by oneself, being imprisoned through kidnapping or hostage-taking, or witnessing sudden violent deaths (murders or suicides), were also significantly associated with elevated PTSD symptoms.

Moreover, during defection, individuals who experienced severe human suffering (such as forced labor, prolonged starvation, chronic homelessness, or torture) demonstrated significantly higher PTSD symptoms compared to those without such exposures.

In South Korea, only experiences involving serious accidents in work, home, or recreational contexts resulted in significantly higher PTSD symptoms compared to those who did not encounter such events.

Differences in quality of life and employment according to trauma experiences

A comparative analysis between groups who directly experienced traumatic events and those who did not revealed significant differences in quality of life. In North Korea and during defection, individuals who directly experienced natural disasters, physical violence, weapon-related attacks, or life-threatening illness or injury scored significantly lower in quality of life than those without these experiences.

Furthermore, in North Korea, respondents who experienced sexual violence, unwanted or uncomfortable sexual encounters, or imprisonment, as well as those who witnessed sudden violent deaths, or serious injury or death caused by themselves, also re-

ported significantly lower quality of life. During defection, severe human suffering further contributed to a reduced quality of life. In South Korea, only those who experienced severe accidents at work, home, or during leisure activities reported significantly lower quality-of-life levels.

Trauma experiences in North Korea did not significantly affect employment status. Interestingly, during defection, experiences such as natural disasters, physical violence, imprisonment, and life-threatening illness or injury were associated with higher employment rates, suggesting that residence in China was a confounding variable influencing employment outcomes. Similarly, in South Korea, individuals who experienced traffic accidents involving cars, ships, trains, or airplane crashes also had higher employment rates, indicating that employment status was more likely a causal factor than a consequence of these traumatic events.

Analysis of in-depth interviews with North Korean defectors

Experiences of trauma from human rights violations

Respondents recounted various traumatic experiences, primarily involving severe starvation, illness, and death in North Korea; brutality in political prison camps; witnessing public executions; physical violence by state institutions or the military; discrimination due to low social status (*songbun*); enforced public self-criticism sessions; and pervasive surveillance through communication censorship or crackdowns on recording devices. Traumatic experiences encountered during the defection process were also documented.

Impact of human rights violation trauma on settlement in South Korea

Respondents described the negative impact of trauma on their interpersonal relationships. Many reported feelings of fear around others, distrust, heightened anger or aggression, and a tendency to avoid social interactions. In the workplace, they cited physical pain, reluctance to participate in company social events, and fear of going outside—factors that often hindered sustained employment. In daily life, defectors frequently experienced trauma-related symptoms, including nightmares, insomnia, anxiety, depression, headaches, fatigue, intrusive recollections of traumatic events, avoidance behaviors, hyperarousal, and persistent negative moods and cognition.

Suggestions for supporting the psychological stability of North Korean defectors

Respondents proposed a range of measures to support their psychological stability. These included providing financial assistance, protection against discrimination and negative perceptions in South Korean workplaces and society, and ensuring stable access to medical care. They also stressed the importance of reducing the stigma associated with psychiatric treatment through targeted awareness campaigns. In addition, respondents emphasized the need for practical and personalized education programs that offer tangible support aligned with individual capabilities after graduating from Hanawon, the official Settlement Support Center for North Korean Defectors. Upon entering South Korea, defectors are required to stay at Hanawon for 3 months, during which they receive education on South Korean society, culture, and practical skills to facilitate integration.

Discussion

Key results

Among 300 North Korean defectors, 81.7% were women, and many experienced severe trauma, including starvation, public executions, physical violence, and trafficking. PTSD, severe depression, and anxiety were prevalent—especially among younger defectors and those who had resided in China. Human rights violations were significantly correlated with increased PTSD symptoms and diminished quality of life. Notably, employment rates were paradoxically higher among those with severe traumatic experiences during defection. Respondents also highlighted persistent psychological distress after arriving in South Korea.

Interpretation

At Hanawon, the primary health services offered to newly arrived North Korean defectors consist of psychiatric care, with mental health specialists conducting initial evaluations and treatments. In addition to this, the current support system provides financial assistance for mental health-related medical services and access to professional counselors specialized in mental health issues. This integrated approach is intended to facilitate defectors' psychological adjustment and overall well-being (Fig. 3).

The findings clearly demonstrate that North Korean defectors experience high rates of human rights violations and trauma, which lead to serious mental health issues such as PTSD. These problems severely diminish their quality of life, adversely affecting interpersonal relationships, work experiences, and daily routines.

However, the current support system—especially through Hanawon and general mental health services—is insufficient. Given the severity and complexity of the trauma faced by these individuals, merely providing financial assistance or basic counseling is inadequate. The existing public healthcare services are not

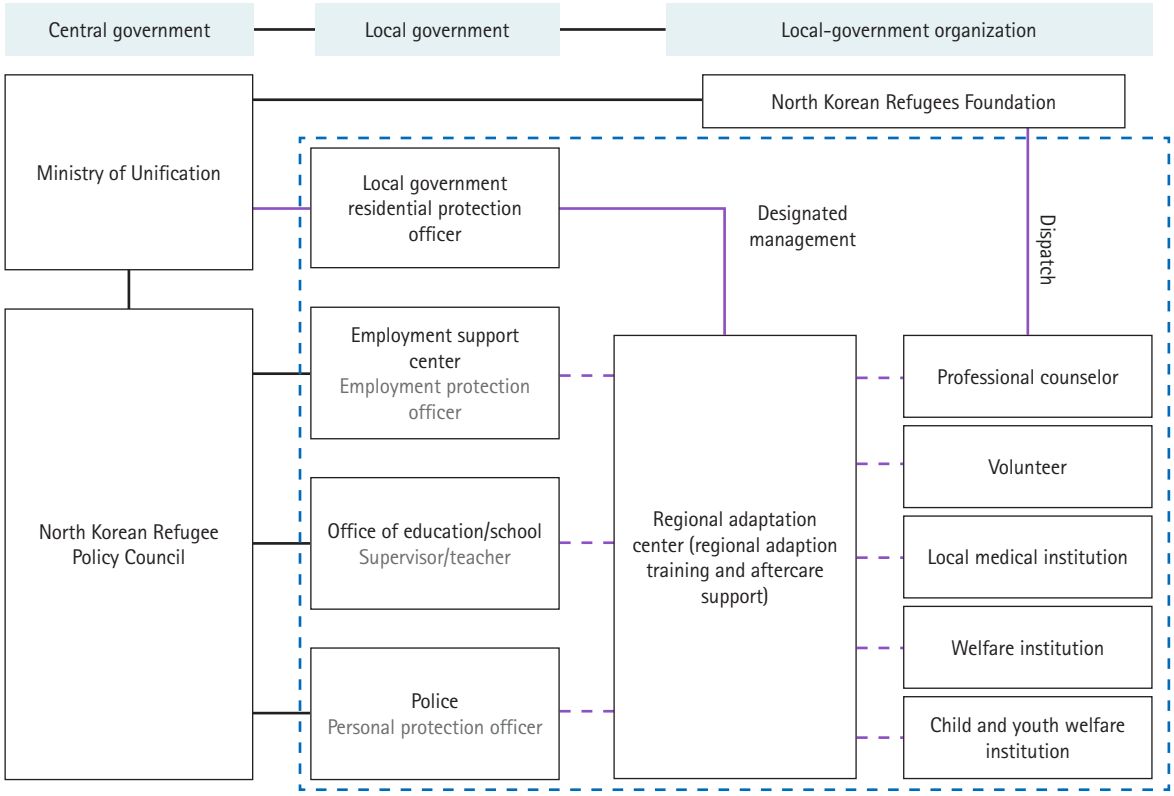

Fig. 3. Overview of the current settlement support system for North Korean defectors (adapted from the Ministry of Unification, Korea).

adequately equipped to address severe trauma-related disorders. Therefore, establishing a specialized trauma treatment infrastructure that can deliver comprehensive care and support is urgently needed.

Recommendations

Establishing medical institution-based trauma treatment centers for North Korean defectors

Given the profound mental health and trauma-related challenges faced by North Korean defectors, it is recommended to establish specialized trauma treatment centers within national and public medical institutions nationwide. Initially, these centers could operate as pilot projects and later evolve into central hub facilities, ensuring comprehensive and systematic treatment and support services. This approach would leverage existing public healthcare infrastructure to facilitate early identification, treatment, and ongoing support, ultimately improving defectors' mental health, quality of life, and integration into South Korean society.

Entrusting medical consultation services for North Korean defectors to relevant healthcare institutions

Instead of relying solely on private organizations, the Ministry of Unification should consider entrusting medical consultation services for North Korean defectors directly to healthcare institutions experienced in providing treatment and support to this population [7]. Furthermore, deploying mental health professionals to these institutions could establish a more structured support system, allowing for continuous and systematic management of healthcare resources. This coordinated, integrated approach overseen by the Ministry of Unification would enhance the efficiency and effectiveness of long-term psychological and medical care for defectors.

Customized support system tailored to entry pathways, gender, and life stages

A support system tailored to the diverse needs of North Korean defectors should account for differences in entry pathways, gender, and specific life stages [8]. Defectors who previously resided in China face unique challenges, including psychological distress from being separated from spouses and children, as well as severe post-traumatic stress from experiences such as arrest by Chinese

authorities and forced repatriation to North Korea. Although some may have achieved economic adaptation during their stay in China, the emotional and psychological difficulties necessitate specialized, trauma-informed care.

Considering gender differences, female North Korean defectors experience significantly higher rates of sexual violence and human trafficking compared to other refugee groups. Therefore, specialized mental health support that addresses issues such as depression, low self-esteem, and trauma recovery is essential. A comprehensive psychological treatment and counseling system involving mental health professionals must be established to effectively manage severe trauma.

Additionally, support measures must consider life-cycle characteristics. Elderly defectors often face severe isolation, loneliness, and guilt related to family separation, whereas younger defectors frequently struggle with adapting to the South Korean education and social systems. Sustainable, mid- to long-term support programs tailored to address the unique challenges at each life stage are necessary. Examples include isolation and emotional distress among older defectors, and educational and social integration challenges among defector youth.

Legal foundation establishment

To establish a solid legal basis for addressing the trauma experienced by North Korean defectors, it is recommended to amend the existing Act on the Protection and Settlement Support for North Korean Defectors. The amendment should specifically mandate the establishment and operation of trauma treatment centers dedicated to North Korean defectors. This legal foundation would ensure structured, long-term psychological support and treatment, which is essential for their successful integration into South Korean society.

Limitations

This study utilized snowball sampling rather than randomized sampling; as a result, it is difficult to generalize the findings to the entire population of defectors.

Conclusion

To overcome prejudice and negative perceptions toward North Korean defectors, it is crucial to shift policy approaches from separation and minimal support to one of localization and integration. Efforts should focus on raising awareness within South Korean society to reduce stigma and discrimination. Specifically, the current support policies—predominantly managed by the Ministry of Unification—must be revised to establish specialized infrastructure capable of professionally addressing the lingering effects of trauma from human rights violations. Collaboration with relevant ministries, such as the Ministry of Health and Welfare and the Ministry of Gender Equality and Family, is necessary to develop integrated systems that offer specialized, trauma-informed care. This comprehensive, sustainable support is essential for facilitating the effective societal integration of North Korean defectors.

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Authors' contributions

All co-authors contributed equally to the research and writing.

Conflict of interest

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

Funding

This study was conducted as part of a research project commissioned by the National Human Rights Commission of Korea for the investigation of human rights conditions (2017).

Data availability

Data cannot be shared due to issues related to the identification of vulnerable participants.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/ZJ4QP3

Supplement 1. Original Korean report of this article.

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e29
https://doi.org/10.12771/emj.2025.00311

Ewha Medical Journal

Immunogenicity of *Anisakis* larvae molting membrane against human eosinophilia sera

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Purpose: This study aimed to investigate whether proteins present in the molting membranes of third-stage (L3) *Anisakis* larvae could serve as potential risk factors for allergic reactions.
Methods: Third-stage larvae (L3) of *Anisakis* spp. were primarily collected from mackerels and cultured in vitro to yield both molting membranes and fourth-stage (L4) larvae. Major soluble proteins in the molting membranes were identified using SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis). Crude antigens extracted from L3, L4, and the molting membranes were subsequently evaluated by western blotting using sera from *Anisakis*-infected rabbits and patients with eosinophilia.
Results: Antigens derived from the molting membranes reacted with sera from *Anisakis*-infected rabbits as well as with sera from 7 patients with eosinophilia of unknown origin. These findings suggest that unidentified proteins in the molting membranes of *Anisakis* L3 may contribute to early allergic reactions, particularly in patients sensitized by specific molecular components.
Conclusion: Our results indicate that proteins present in the molting membranes of third-stage *Anisakis* spp. larvae may be associated with allergic responses. Further studies are required to confirm the correlation between these membranes and *Anisakis*-induced allergies.

Keywords: *Anisakis*; Molting membrane; Hypersensitivity; Eosinophilia

Introduction

Background

Anisakiasis is a food-borne parasitic disease caused by the accidental ingestion of raw or undercooked seafood containing third-stage larvae (L3) of *Anisakis* spp. [1,2]. The first reported human infection, presenting with acute abdominal pain due to a marine nematode, was documented in the Netherlands in 1960 [3]. Since that time, anisakiasis has been reported in several countries, with approximately 2,000 cases in Japan, 20–500 cases in various European countries, and 200 cases annually in South Korea—a reflection of the high consumption of raw fish [4]. Furthermore, the global increase in raw fish consumption over the past decade highlights the ongoing need for the management of food-borne infections such as anisakiasis [5]. Human infections with anisakid larvae commonly produce gastrointestinal symptoms including abdominal or epigastric pain, nausea, and vomiting, which are associated with larval migration and penetration of the gastric mucosa [6]. Allergic anisakiasis may trigger mild to severe immunological reactions on the arms and abdomen, and can also result in angioedema or anaphylaxis [7]. Additionally, some patients exhibit generalized hypersensitivity reactions without accompanying digestive symptoms [8].

There are numerous studies examining allergens of *Anisakis simplex*, which have been classified into excretory-secretory, somatic, and cuticular proteins [4,9,10]. However, no studies have yet explored the allergic components of molting membranes isolated from the outer portion of the larval cuticular layer.

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Received: March 28, 2025 Revised: March 31, 2025 Accepted: April 2, 2025

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Objectives

We have confirmed that proteins in the molting membranes exhibit antigenicity and cross-reactivity with sera from eosinophilia patients. We hypothesized that not only the main body of *Anisakis* larvae but also their molting membranes may function as key allergic antigens. Therefore, we investigated several antigens from the molting membranes that reacted with sera from *Anisakis*-infected rabbits and patients with eosinophilia linked to unknown antigenic components.

Methods

Ethics statement

Mackerels were purchased from local fisheries. Human sera from patients with anisakiasis were collected after obtaining informed consent.

Antigen preparation

L3 of *Anisakis* spp. were collected from mackerels purchased at a wholesale fisheries market in Korea. The collected L3 were washed with phosphate-buffered saline (PBS), and 2 larvae were transferred into each well of a 24-well plate filled with 0.9% sodium chloride solution to obtain the molting membranes and cultured L3. Three days after incubation in a 5% CO_2 incubator, the L3 began to molt over the subsequent 7 days, developing into fourth-stage (L4) larvae. Molting membranes were isolated from the larval bodies in the culture medium under a stereo microscope, then washed with PBS and centrifuged at 4°C to extract proteins for immunoblot analysis. The larvae were also incubated at 4°C for 3 days in PBS containing antibiotics to prevent microbial contamination. Antigens extracted from L3, L4, and the molting membranes were prepared using a protein lysis buffer containing Triton X-100 and analyzed by SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) on a 5%–15% polyacrylamide gel.

Collection of antibody

Anisakis-infected rabbit sera were stored at –80°C until use in immunoblot assays [11]. At the Department of Allergy and Clinical Immunology of Ewha Womans University Mokdong Hospital, a 3 mL venous blood sample was collected from each patient using a serum separator tube. The sample was stored at 2–8°C until initial allergic testing. The remaining specimen was subsequently transferred to the Department of Parasitology and Ewha Medical Research Center at Ewha Womans University College of Medicine for serum separation by centrifugation at 1,300–2,000 × g for 10–15 minutes. The isolated serum was then aliquoted and stored at –20°C until further analysis.

Western blot

Western blot analysis of protein extracts from L3, L4, and the molting membranes of *Anisakis* spp. was performed using sera from *Anisakis*-infected rabbits and eosinophilic patients as described above. A peroxidase-conjugated rabbit/human immunoglobulin G (IgG) antibody (MP Biomedicals) served as the secondary antibody, and immune-reactive bands were visualized using 4-chloro-1-naphthol (Sigma).

Results

After 3 days of incubation, the transparent sheaths isolated from the bodies of *Anisakis* L3 were identified as molting membranes under a stereomicroscope (Fig. 1). Protein extracts from L3, L4, and the molting membranes reacted with IgG from *Anisakis*-infected rabbit sera, as demonstrated by western blot analysis (Fig. 2). Among the various bands observed in the antigen extracts from *Anisakis* L3 and L4, bands of approximately 40 kDa and 14 kDa emerged at 1 week and 3 weeks post-infection, respectively (Fig. 2). Interestingly, proteins extracted from the molting membranes using Triton X-100 elicited a strong response with rabbit sera from the early stages (1 week) of *Anisakis* infection, producing numerous bands that were not observed in the L3 and L4 extracts (Fig. 2). The antigenicity of L3, L4, and the molting membranes, as detected by reactivity with infected rabbit sera, remained at a high plateau for 9 weeks (Fig. 2). Immunoblot assays

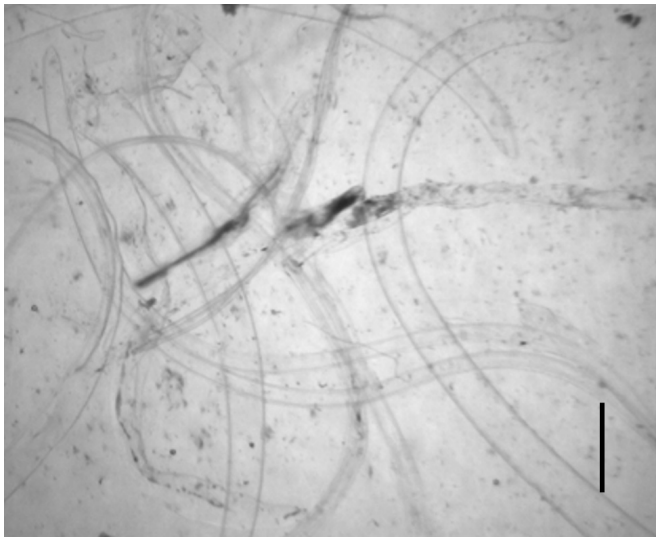

Fig. 1. Molting membranes observed after 3 days of incubation of third-stage larvae (L3) of *Anisakis* spp. Note the transparent sheaths seen under a stereo microscope (scale bar=1 mm).

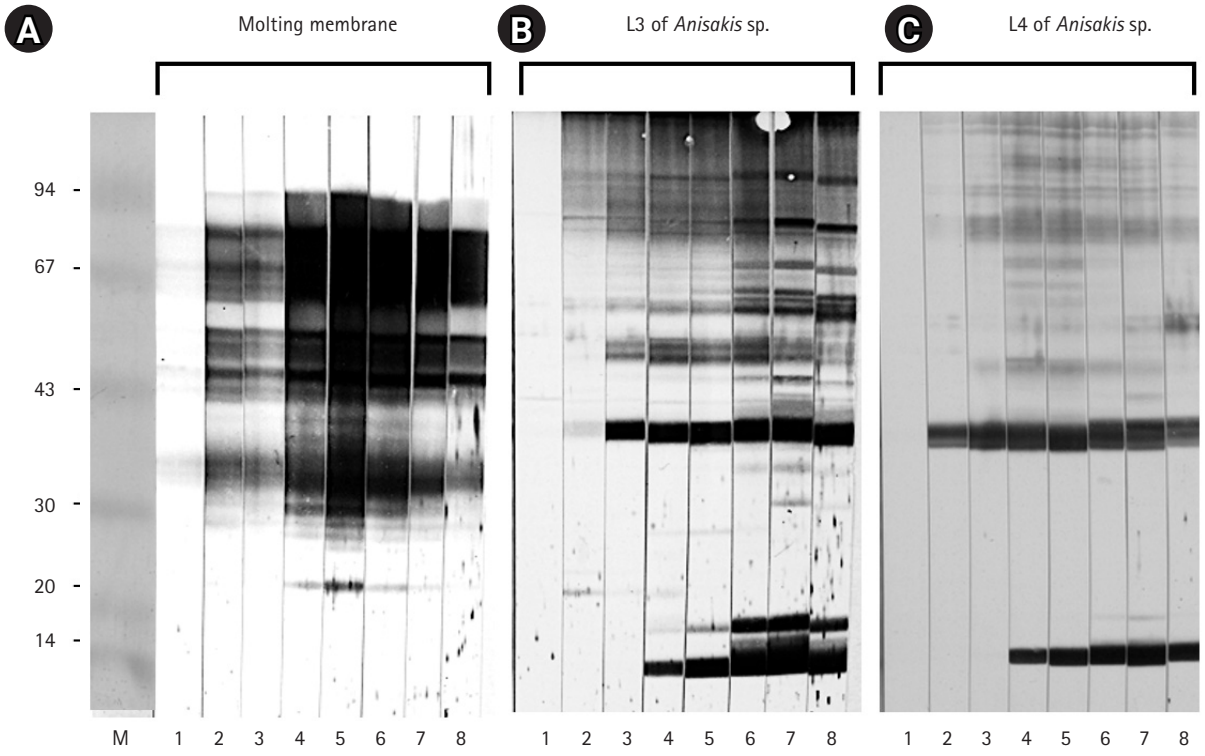

Fig. 2. Immunoblot results for the molting membranes (A), third-stage larvae (L3) of *Anisakis* spp. (B), and fourth-stage larvae (L4) of *Anisakis* spp. (C), reacting with sera from *Anisakis*-infected rabbits. Key time points: 1, 3 days; 2, 1 week; 3, 2 weeks; 4, 3 weeks; 5, 4 weeks; 6, 5 weeks; 7, 7 weeks; 8, 9 weeks after infection.

performed with IgG from sera of 7 eosinophilia patients revealed an irregular pattern of reactivity with protein extracts from the molting membranes of *Anisakis* (Fig. 3). In contrast, sera from patients 2 and 4, as well as those from patients 1, 5, and 7, exhibited regular reaction patterns against antigens extracted from *Anisakis* L3 (Fig. 3).

Discussion

Key results

The molting membranes of *Anisakis* reacted strongly with rabbit IgG during the early stages of infection, displaying numerous unique antigenic bands. In addition, antigens of approximately 40 kDa and 14 kDa from L3 and L4 emerged at 1 and 3 weeks post-infection, respectively. Patient sera exhibited irregular reactivity towards the molting membranes, whereas a regular pattern was observed against *Anisakis* L3 antigens.

Interpretation/comparison with previous studies

It is well established that *Anisakis* infection can trigger a range of allergic reactions in humans, and research into the allergenic factors of *Anisakis* is ongoing. While the structural and biochemical

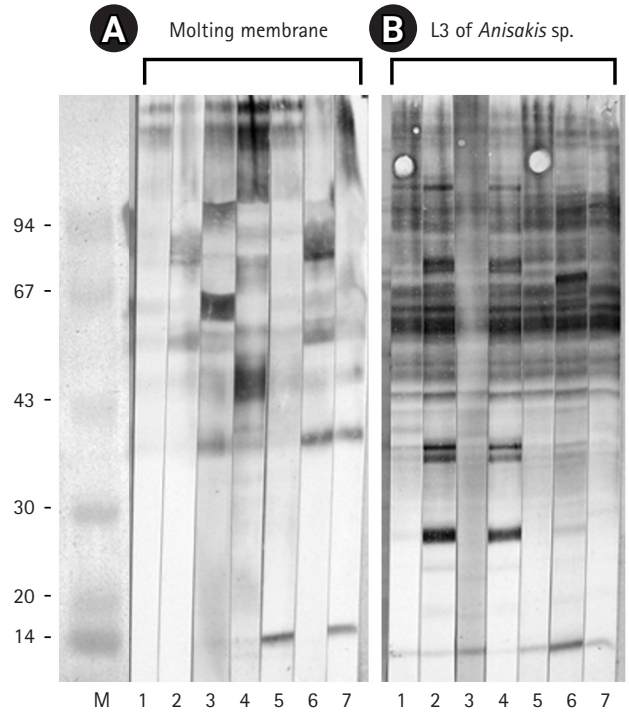

Fig. 3. Immunoblot results for the molting membranes (A) and third-stage larvae (L3) of *Anisakis* spp. (B) reacting with sera from 7 human eosinophilia patients. Note the immunoglobulin G reactivity observed against the molting membranes of *Anisakis* L3.

characteristics of excretory-secretory, somatic, and cuticular allergens in nematodes have been extensively studied, the antigenicity of the molting membranes—isolated from the outer cuticular layer of larvae—remain unexplored. In this study, we demonstrated the strong antigenicity of molting membranes against sera from *Anisakis*-infected rabbits and observed irregular reactivity patterns of these antigens with sera from eosinophilic patients. Our findings suggest that unidentified antigens within the molting membranes may play a role in early allergic reactions occurring within one week of infection. Specific IgG responses to *Anisakis* larvae and their molting membranes were evident from 1 week and maintained at a high plateau for 9 weeks. These results are consistent with previous studies showing that specific IgG production in rats after peritoneal inoculation steadily increased to a high plateau and was sustained for up to 2 months [12]. Moreover, our findings indicate that the diverse antigenic bands present in the molting membranes were absent in L3 and L4 extracts. These distinct immunogenic antigens may have important clinical implications, as they could contribute to allergic reactions. Further research is necessary to identify new major antigens in the molting membranes beyond the already recognized allergens.

Recently, Rahmati et al. [10] in 2020 identified global hotspots for potential allergic anisakiasis, reporting the highest prevalence rates of 18.45%–22.50% in Portugal and Norway. They recommended that allergic anisakiasis be recognized as a significant public health issue in high-risk countries with high consumption of raw fish [10]. Based on this report, we suggest that sensitized individuals may experience hypersensitive reactions upon contact with the outer molting membranes of *Anisakis* larvae, regardless of whether the larvae penetrate the digestive tract.

Suggestions for further studies

Further studies are required to isolate and identify the major antigenic components of the molting membranes that contribute to allergic reactions. Additionally, investigating the structural properties and immunological mechanisms of these proteins may provide valuable insights for allergy diagnosis and prevention. In clinical practice and public health education, it is crucial to raise awareness about the potential allergenic risks posed by molting membranes—even in the absence of direct larval penetration—especially among high-risk populations that consume raw seafood.

Conclusion

This study demonstrated that the molting membranes of *Anisakis* spp. possess strong antigenicity and may serve as significant allergens, particularly in patients with eosinophilia. The unidentified proteins within these membranes could play a critical role in the early allergic reactions following *Anisakis* infection. These findings suggest that molting membranes represent additional candidates for eliciting allergic responses and that their identification could contribute to a better understanding, prevention, and management of allergic anisakiasis, ultimately improving clinical care and public health outcomes.

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Authors' contributions

Conceptualization: HJY. Data curation: BKJ. Methodology/formal analysis/validation: SH, BKJ, HJY. Project administration: HJY. Funding acquisition: not applicable. Writing–original draft: SH. Writing–review & editing: SH, BKJ, HJY.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e30
https://doi.org/10.12771/emj.2025.00094

Ewha Medical Journal

Development of automatic organ segmentation based on positron-emission tomography analysis system using Swin UNETR in breast cancer patients: a prediction study

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Purpose: The standardized uptake value (SUV) is a key quantitative index in nuclear medicine imaging; however, variations in region-of-interest (ROI) determination exist across institutions. This study aims to standardize SUV evaluation by introducing a deep learning-based quantitative analysis method that enhances diagnostic and prognostic accuracy.

Methods: We used the Swin UNETR model to automatically segment key organs (breast, liver, spleen, and bone marrow) critical for breast cancer prognosis. Tumor segmentation was performed iteratively based on predefined SUV thresholds, and prognostic information was extracted from the liver, spleen, and bone marrow (reticuloendothelial system). The artificial intelligence training process employed 3 datasets: a test dataset (40 patients), a validation dataset (10 patients), and an independent test dataset (10 patients). To validate our approach, we compared the SUV values obtained using our method with those produced by commercial software.

Results: In a dataset of 10 patients, our method achieved an auto-segmentation accuracy of 0.9311 for all target organs. Comparison of maximum SUV and mean SUV values from our automated segmentation with those from traditional single-ROI methods revealed differences of 0.19 and 0.16, respectively, demonstrating improved reliability and accuracy in whole-organ SUV analysis.

Conclusion: This study successfully standardized SUV calculation in nuclear medicine imaging through deep learning-based automated organ segmentation and SUV analysis, significantly enhancing accuracy in predicting breast cancer prognosis.

Keywords: Artificial intelligence; Breast neoplasms; Deep learning; Positron emission tomography; Prognosis; Republic of Korea

Introduction

Background

Breast cancer (BC) is the most common cancer among women and one of the leading causes of cancer-related deaths worldwide [1,2]. With recurrence rates of 20%–30%, accurate prognostic prediction is essential for treatment planning [3]. Key prognostic factors include tumor size, nuclear grade, axillary lymph node involvement, hormone receptor status, and the Ki-67 proliferation index [4].

18F fluorodeoxyglucose positron-emission tomography/computed tomography (18F-FDG PET/CT) is widely used to evalu-

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Received: February 26, 2025 Revised: March 11, 2025 Accepted: March 26, 2025

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ate tumor metabolism, stage cancer, and guide treatment decisions [5]. PET-derived parameters such as standardized uptake values (SUVs), metabolic tumor volume, and total lesion glycolysis (TLG) have emerged as significant prognostic indicators in BC [6,7].

Traditional segmentation methods such as region-growing, thresholding, and level-set techniques have been widely used, yet they require manual intervention and suffer from interobserver variability. The Swin UNETR model, which integrates Swin transformers with the UNETR architecture, offers improved spatial feature representation and enhanced segmentation accuracy. However, its computational cost and real-world feasibility remain areas of concern, as discussed later in this study.

Systemic inflammatory responses also influence cancer progression and prognosis [8]. Biomarkers such as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio have been associated with outcomes in multiple cancers [9]. The reticuloendothelial system (RES), which includes the bone marrow, spleen, and liver, plays a key role in systemic inflammation. FDG PET has been used to evaluate metabolic activity in these organs, and increased RES activity has been linked to poor prognosis in BC and other cancers [10,11].

Accurate delineation of BC lesions and RES organs is essential for quantifying PET parameters. Although manual segmentation by nuclear medicine physicians is the current gold standard, it is time-consuming and prone to interobserver variability, which can lead to potential errors [12]. Automated segmentation methods are therefore necessary to reduce variability and improve efficiency.

Objectives

This study employs the Swin-UNETR architecture to segment both the breast and RES organs, highlighting their prognostic significance. Our goal is to develop an advanced diagnostic and prognostic system for BC. We aimed to automate the identification of tumor location and size using SUVs derived from PET/CT scans of BC patients. In addition, we developed a computational tool to calculate SUVs in organs associated with prognosis. A schematic representation of the study flow is shown in Fig. 1.

Methods

Ethics statement

All patient data used in this research were reviewed and approved by the Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital (IRB no., 2023-07-001-002). Obtaining informed consent from individual patients was exempt be-

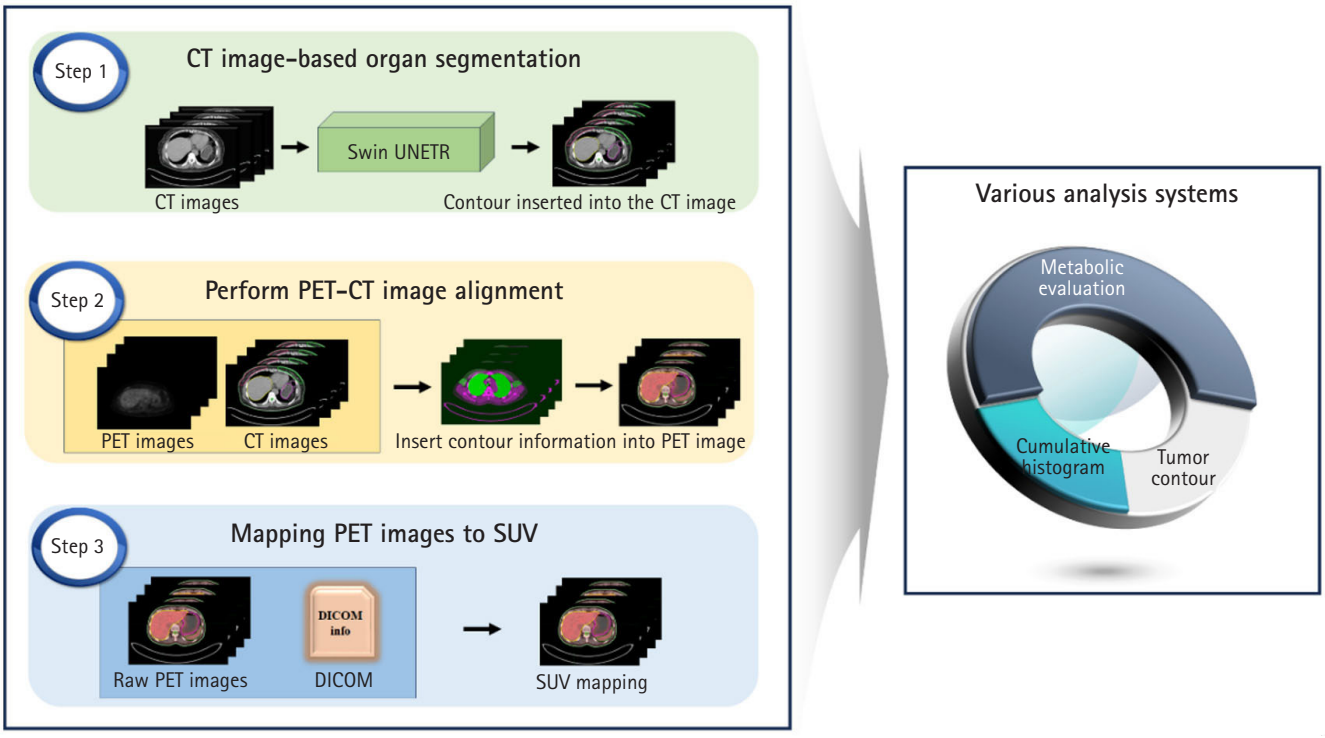

Fig. 1. Schematic representation of the study flow. The left panel summarizes the steps involved in the study, while the right panel illustrates the inherent functionalities of the research findings. CT, computed tomography; PET, positron emission tomography; SUV, standardized uptake value.

cause of the retrospective design of this study.

Study design

This study is a retrospective, medical record-based prediction study. It is reported in accordance with the TRIPOD-artificial intelligence (AI) reporting guidelines for articles on deep learning in the medical field (development or prediction), available at https://www.tripod-statement.org/.

Setting

Data were collected between 2012 and 2014 from female patients (mean age, 54.5 ± 10.3 years; range, 33–77 years) who underwent FDG-PET/CT for initial BC staging at Ewha Womans University Mokdong Hospital in Korea.

Participants

A total of 60 patients were included in the study. All eligible patients diagnosed during the study period were included. Among them, 32 underwent mastectomy, while 28 received breast-conserving surgery.

Data source

PET/CT scans were performed using a Siemens Biograph mCT system (128-slice CT; Siemens Medical Solutions). Patients fasted for at least 6 hours before scanning, and FDG was administered when blood glucose levels were below 140 mg/dL. PET/CT images were acquired 60 minutes after an intravenous FDG injection (5.18 MBq/kg), covering the skull base to mid-thigh. First, non-contrast CT images were obtained (120 kVp, 50 mAs, 1.2 pitch), followed by 3D PET image acquisition (2 minutes per bed position, covering 5 to 7 positions). PET images were reconstructed using a 3D-OSEM iterative algorithm (2 iterations, 21 subsets) with time-of-flight and point-spread function corrections.

Outcome variables

The outcome variables included segmentation results, PET/CT alignment, SUVs, and TLG.

Study size

No sample size estimation was performed, as all eligible subjects were included in the study.

Deep learning models

Auto segmentation

For AI model training, manual segmentation of CT scans from 60 patients was performed using MIM software (MIM Software Inc.), focusing on the breasts, liver, spleen, and bone marrow. An experienced physician performed the segmentation, which was then verified by a second experienced physician. In cases of discrepancy, the 2 physicians reached a consensus. The data were divided into a training set (40 patients), a validation set (10 patients), and an independent test set (10 patients). The Swin UNETR model, a deep learning architecture that integrates the Swin Transformer with convolutional neural networks, was employed for segmentation (Fig. 2).

Encoder: CT images were divided into non-overlapping $2 \times 2 \times 2$ patches, with each patch represented as a 48-dimensional feature vector. These patches were embedded into a sequence representation and tokenized at a resolution of $(H/2 \times W/2 \times D/2)$. The encoded features were processed through 2 consecutive Swin

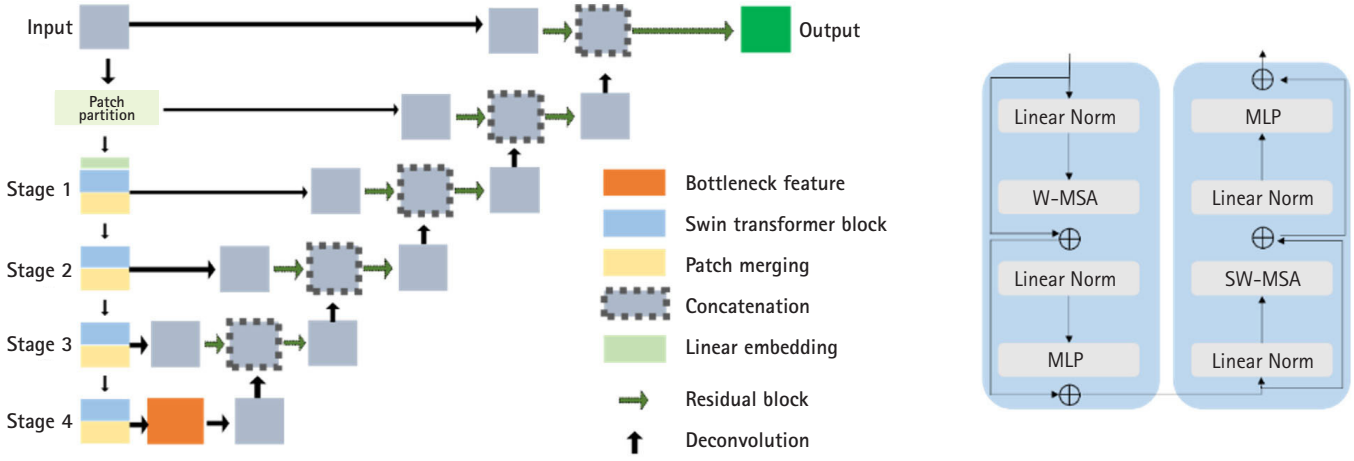

Fig. 2. The architecture (A) and transformer blocks (B) of Swin UNETR. MLP, multilayer perceptron; W-MSA, window-based multi-head self-attention; SW-MSA, shifted window-based self-attention.

Transformer blocks that utilized window-based multi-head self-attention (W-MSA) and shifted window-based self-attention (SW-MSA) (Fig. 2B). A patch-merging layer then reduced the number of tokens while doubling the feature dimensions, and this process was repeated 4 times throughout the encoding stage.

Decoder: The encoded features were reshaped to a resolution of (H/32×W/32×D/32) and processed through residual blocks comprising 3×3×3 convolutional layers with instance normalization. These features were then up-sampled using deconvolutional layers and concatenated with outputs from previous stages. The final encoder output was integrated with these processed features and passed through another residual block. A final 1×1×1 convolutional layer with a SoftMax activation function produced segmentation probabilities.

Model parameters: Various preprocessing techniques were employed to enhance segmentation accuracy. Pixel values were normalized between 0 and 1 by clipping those outside the range of −175 to 250. CT image resolution was standardized at 1.5×1.5×2.0 mm^3, and images were randomly cropped to 96×96×96. Data augmentation techniques included random flipping and rotation (with a probability of 0.1) along all 3 axes, and intensity shifting (with a probability of 0.5 and an offset of 0.1). The model was trained using a combination of dice loss and cross-entropy loss, optimized with the Adam optimizer and stabilized using GradScaler (PyTorch). Training was conducted over 20,000 iterations.

SUV acquisition

PET/CT alignment: To transfer CT-based segmentation to PET images, multimodal image alignment was performed using MATLAB's alignment module. The optimizer was configured with an initial radius of 0.009, an epsilon of 1.5E-4, and a maximum of 1,000 iterations for optimal performance. Segmentation accuracy was evaluated by comparing contour coordinates from CT-based segmentation using the dice coefficient. PET contours were aligned to CT contours using MIM software, and the PET/CT alignment metric was used to assess accuracy. This analysis was conducted on 2 patients, with image details provided in Table 1.

Convert pixel values to SUVs of PET: SUVs were calculated using patient-specific parameters extracted from DICOM data (https://www.dicomstandard.org/), including acquisition time, radiopharmaceutical start time, radionuclide half-life, total dose, rescale slope, and patient weight. These factors enabled accurate SUV quantification per voxel, facilitating metabolic activity assessment for each organ. SUVs were body weight-based and computed using the following formula:

(1)

$$\mathrm{SUV}_{body\ weight\left(\frac{kg}{cc}\right)} = \frac{(pixel\ value\ \times Dicom\ rescale\ factor\ \times Patient\ weight)}{Total\ dose \times e^{\left(\frac{-\log(2)\times(Series\ time\ -\ Radiophamaceutical\ start\ time)}{F^{18}-FDG\ half\ life\ time}\right)}}$$

where pixel value represents the PET image's raw intensity, and the DICOM rescale factor normalizes the pixel arrays. "Series time" refers to the scan initiation time, while "radiopharmaceutical start time" marks the time of 18F FDG administration.

Evaluation metrics

Auto segmentation

The Swin-UNETR model was employed to segment the breasts, spleen, liver, and bone marrow. Evaluation was conducted qualitatively by comparing predicted CT images with manually labeled organ structures, and quantitatively by calculating the average dice coefficient and loss over 20,000 iterations.

Organ-level SUV evaluation

To assess the accuracy of SUV measurements, maximum SUV (SUVmax) and mean SUV (SUVmean) values were compared using different PET image analysis methods. SUVmax was extracted from each contoured organ and compared with values obtained via MIM software, ensuring that the volume of interest (VOI) excluded adjacent organs. SUVmean was evaluated using: (1) a single VOI in MIM software, (2) a single VOI in our program, and (3) A whole-organ contour in our program.

Both SUVmax and SUVmean were consistently derived across methods using a fixed 1.2 cm radius VOI centered at each organ's centroid. Statistical analysis was performed to characterize the results.

Table 1. Image size and slice thickness of the PET/CT images from 2 patients were used to verify PET/CT alignment

	Patient 1		Patient 2	
	CT	PET	CT	PET
Image size (pixels)	512×512×284	200×200×283	512×512×462	200×200×284
Slice thickness (mm)	3	3	2	3

CT, computed tomography; PET, positron emission tomography.

Tumor contour based on SUV

Organ contour labels were aligned with PET images to localize tumors. By using registered contour labels and SUV maps, tumors were identified based on threshold values of 40% and 50% of SUVmax. This approach provided tumor coordinate information and enabled visualization of tumor size and location on CT images.

Total lesion glycolysis evaluation

TLG quantifies metabolic activity by integrating tumor size and SUV. It is calculated by multiplying each lesion's SUV by its corresponding volume and summing these values across all lesions within a given region of interest. In this study, TLG was measured using SUV thresholds of 40% and 50%.

Cumulative SUV histogram

The cumulative SUV histogram represents intertumoral heterogeneity by plotting the percentage of tumor volume that exceeds specified SUV thresholds. This method provides a concise summary of tumor metabolic characteristics. Cumulative SUV histograms were generated for all segmented organs in PET images.

Python code for this study is available at Supplement 1.

Statistical methods

Descriptive statistics were calculated.

Results

Auto segmentation

Fig. 3 presents the segmentation results for the breast, spleen, liver, and bone marrow using the Swin-UNETR model. The left images display the organ labels, and the right images show the predicted segmentation. Fig. 4 provides quantitative results, revealing a maximum dice coefficient of 0.9311 and a minimum loss of 0.3813, which demonstrates the model's effectiveness in accurately segmenting organs with diverse shapes and sizes. These results were obtained from the validation dataset during the training process.

PET/CT alignment

A comparison of the dice scores for the CT-based contours generated by the MIM program versus our alignment program, using datasets from 2 patients, yielded dice coefficients of 0.9114 and 0.9315, respectively (Fig. 5).

SUV acquisition

SUVmax comparisons: Table 2 summarizes the SUVmax comparisons between the MIM software and our method, showing an average difference of 0.23 (range, 0.11–0.35). The liver exhibited the highest difference (0.35) due to its larger volume, whereas the spleen showed the lowest difference (0.11).

SUVmean comparisons: Table 3 presents the SUVmean comparisons. When using a single VOI, the average difference between our program and the MIM software was 0.138 (range, 0.07–0.24), with the highest variation observed in the liver (0.24) and the lowest in the right breast (0.07). When using organ contours, the difference increased to an average of 0.27 (range, 0.26–0.30), with the greatest variation in the spleen (0.30). The differences between the single VOI and organ contour methods were

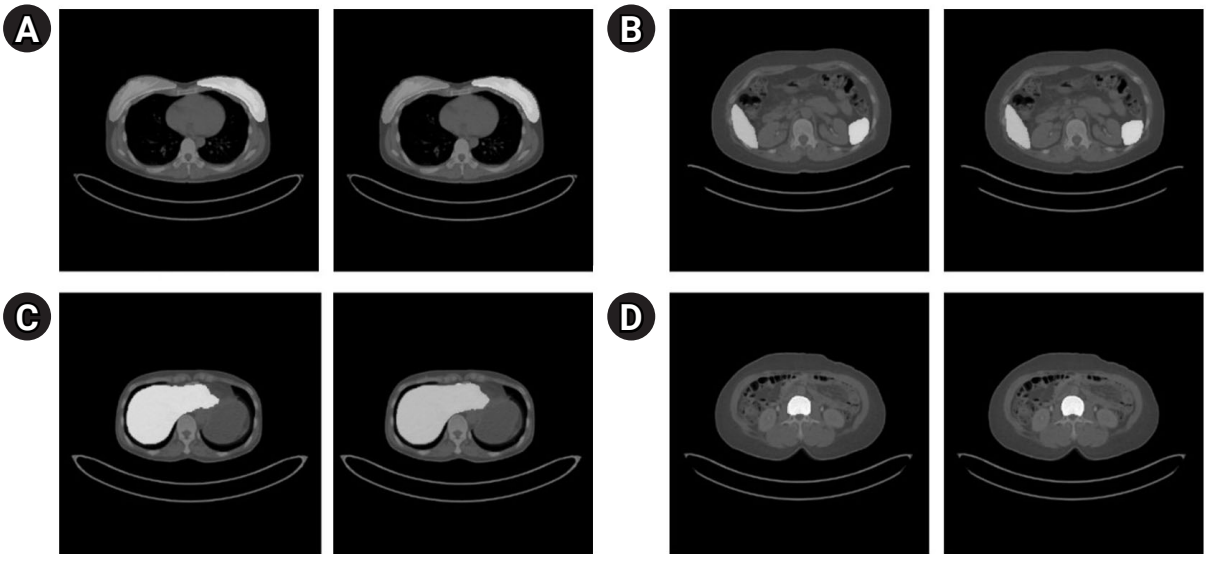

Fig. 3. Segmentation results of the Swin-UNETR model: breast (A), spleen (B), liver (C), and bone marrow (D). In each case, the left image shows the label, and the right image shows the predicted result.

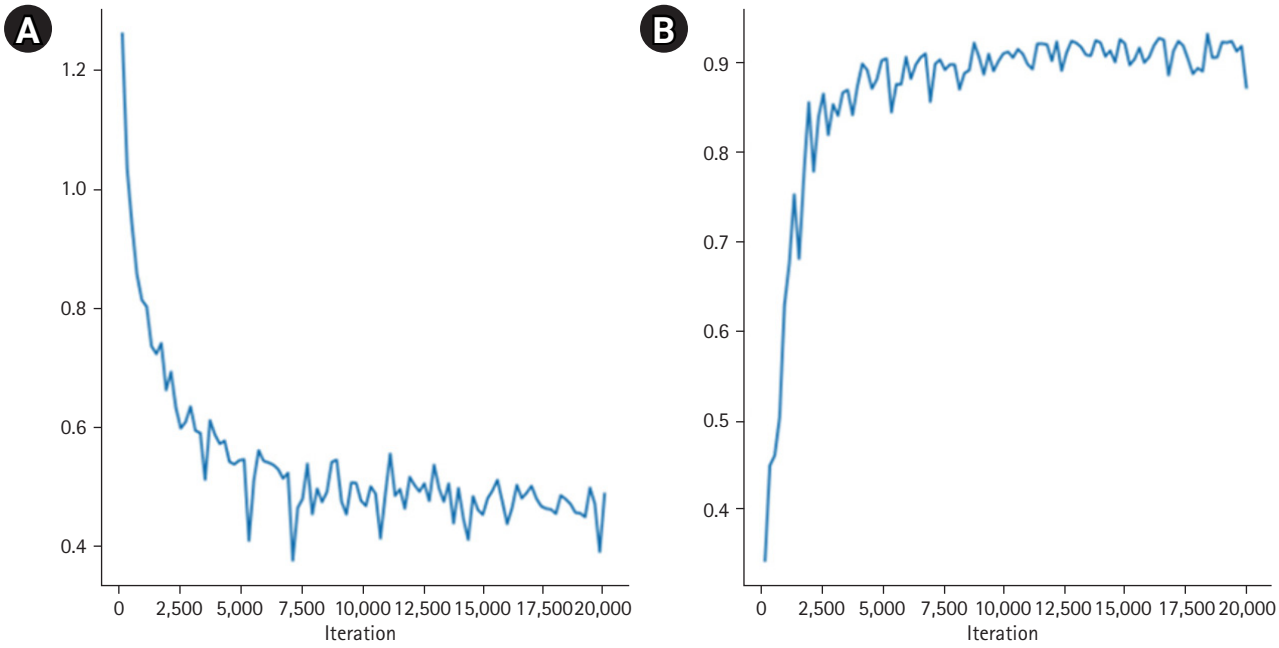

Fig. 4. Quantitative results of organ segmentation using Swin-UNETR: loss (A) and dice scores (B) during 20,000 iterations.

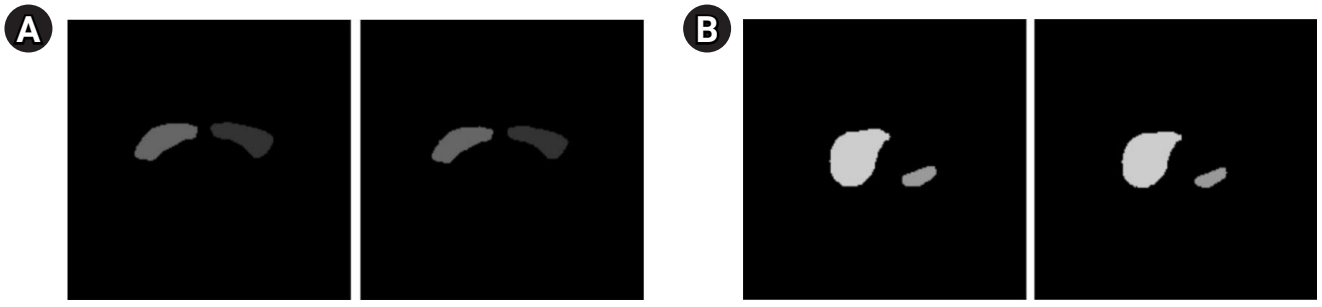

Fig. 5. Results of positron emission tomography/computed tomography alignment using the MIM program for breast (A), and liver and spleen (B). In each image, the left side displays results from the MIM program, while the right side shows results from our technique.

consistently larger than those observed between the 2 single VOI methods, highlighting the impact of VOI selection.

SUV-based tumor contour

Fig. 6 displays the results of contour-based insertion of volumetric information, specifically regions with SUVmax exceeding the 50% threshold based on BC patients' PET images. This approach enables the identification of tumor location and size on both PET and CT images.

TLG evaluation

Table 4 presents the TLG values obtained for 10 patients, focusing on the breast region where the tumors were located.

Cumulative SUV histogram

The cumulative SUV histogram was used to analyze the proportion of organ volume exceeding specific SUV thresholds. Fig. 7 shows cumulative SUV histograms for a BC patient with a right breast tumor and no lesions in the left breast. The tumor histogram exhibits a convex downward shape, indicating a higher proportion of tumor volume with SUV values above the threshold. In contrast, the healthy breast histogram shows a convex upward shape, suggesting a lower proportion of high-SUV regions.

Discussion

Key results

This study introduces a novel automated method for PET im-

Table 2. Comparison of the SUVmax results obtained from the MIM software and our methodology

Patient index	Methods for obtaining SUVmax	Target organs				
		Breast_R	Breast_L	Liver	Spleen	Bone marrow
1	MIM program result	12.03	1.59	2.51	1.68	1.50
	Program results contour	11.97	1.65	2.48	1.56	1.65
2	MIM program result	4.67	0.66	3.10	1.43	1.13
	Program results contour	4.31	0.68	3.66	1.25	1.23
3	MIM program result	10.96	1.96	5.43	4.47	2.60
	Program results contour	10.79	2.18	5.98	4.71	2.74
4	MIM program result	7.03	1.14	6.12	2.15	2.46
	Program results contour	6.92	1.36	6.44	1.95	2.63
5	MIM program result	1.05	7.38	2.87	2.46	2.32
	Program results contour	0.96	7.37	3.06	2.51	2.68
6	MIM program result	7.89	1.99	2.92	2.05	2.70
	Program results contour	7.15	1.77	2.06	2.00	2.61
7	MIM program result	6.91	2.54	2.38	2.14	2.29
	Program results contour	7.55	2.77	2.18	2.10	2.18
8	MIM program result	5.29	1.50	3.09	2.20	3.90
	Program results contour	5.45	1.60	3.12	2.18	4.14
9	MIM program result	4.68	2.58	6.60	3.69	3.19
	Program results contour	5.47	2.68	6.99	3.68	3.56
10	MIM program result	1.58	3.61	4.54	1.93	2.10
	Program results contour	1.83	3.32	4.19	1.73	2.30
Average difference	MIM program result–Program results contour	0.34 ± 0.27	0.15 ± 0.09	0.35 ± 0.25	0.11 ± 0.08	0.19 ± 0.10

Values are presented as number or mean±standard deviation. Each organ was analyzed in 10 patients.
SUVmax, maximum standardized uptake value.

age segmentation and quantitative evaluation based on the Swin UNETR architecture. The Swin-UNETR model achieved a dice coefficient of 0.9311 and a loss of 0.3813 for precise organ segmentation. PET/CT alignment produced dice scores of 0.9114 and 0.9315. Comparisons of SUVmax values revealed an average difference of 0.23, while SUVmean differences were 0.138 when using a single VOI and 0.27 when using organ contours. Tumor contouring successfully identified regions where SUVmax exceeded 50%. Additionally, TLG values effectively quantified tumor metabolic activity, and cumulative SUV histograms distinguished tumor tissue from healthy tissue through distinct patterns.

Interpretation/comparison with previous studies

Previous methods—including thresholding, gradient-based techniques, and region growing—suffer from limitations such as manual parameter adjustments, sensitivity to noise, and difficulty in handling complex structures [13-15]. Our approach improves segmentation accuracy by leveraging automated CT-based segmentation applied to PET images, which allows for precise organ delineation and accurate SUV extraction. By converting PET pixel values to SUVs using DICOM data, our method ensures reproducibility in SUV measurements [16,17]. In contrast to conventional clinical approaches that rely on variable region-of-interest selection, our method standardizes the calculation of SUVmax and SUVmean for specific organs, thereby enhancing reliability. Moreover, analyzing SUVs from both tumor and normal tissues offers valuable predictions for postoperative outcomes, given that systemic inflammatory responses are key prognostic indicators in cancer. 18F FDG PET/CT is widely used for assessing tumor metabolism and systemic inflammation, especially in organs such as the spleen, liver, and bone marrow, which are pivotal in cancer progression.

Beyond SUV analysis, our method incorporates metabolic tumor volume and TLG, both of which are crucial for evaluating tumor burden and treatment response. By integrating SUV and tumor volume, TLG offers insights into tumor aggressiveness; if used in radiation therapy planning, this approach may lead to more effective treatment strategies.

A comparative analysis revealed differences in SUVmean values between our method and commercially available MIM software. Because MIM calculates SUVmean using a circular VOI that does not fully capture organ shape, slight variations occur. This finding

Table 3. SUVmean results for each of the organs analyzed in 10 patients

Patient index	Methods for obtaining SUVmean	Target organs				
		Breast (right)	Breast (left)	Liver	Spleen	Bone marrow
1	MIM program result	0.76	0.74	2.18	1.30	1.23
	Program results in one VOI	0.84	0.71	1.96	1.30	1.21
	Program results contour	1.14	0.81	1.73	1.16	0.98
2	MIM program result	0.57	0.32	1.14	0.98	0.45
	Program results in one VOI	0.49	0.27	0.98	0.89	0.44
	Program results contour	0.47	0.30	1.11	0.77	0.61
3	MIM program result	1.24	1.53	1.80	2.15	1.13
	Program results in one VOI	1.28	1.40	1.85	2.02	1.17
	Program results contour	0.60	0.43	2.34	1.38	1.10
4	MIM program result	0.64	0.45	2.06	1.97	2.08
	Program results in one VOI	0.54	0.51	1.69	1.71	1.72
	Program results contour	0.59	0.45	1.67	1.48	1.37
5	MIM program result	0.55	0.45	2.19	2.12	1.32
	Program results in one VOI	0.36	0.41	1.79	1.90	1.07
	Program results contour	0.44	0.34	2.02	1.62	1.19
6	MIM program result	0.94	0.76	2.23	1.59	1.67
	Program results in one VOI	0.86	0.86	1.92	1.56	1.40
	Program results contour	0.59	0.40	1.94	1.39	1.39
7	MIM program result	1.09	0.96	1.56	1.49	0.90
	Program results in one VOI	1.13	1.58	1.80	1.66	0.80
	Program results contour	0.69	0.65	1.83	1.40	1.32
8	MIM program result	0.88	0.54	2.44	1.90	0.70
	Program results in one VOI	0.89	0.53	2.23	1.70	0.60
	Program results contour	0.50	0.38	2.13	1.45	1.34
9	MIM program result	0.32	0.41	2.42	1.90	1.77
	Program results in one VOI	0.39	0.44	2.24	2.00	1.76
	Program results contour	0.40	0.35	2.30	1.84	1.68
10	MIM program result	1.02	1.07	1.38	0.52	0.73
	Program results in one VOI	1.02	1.07	1.09	0.44	0.94
	Program results contour	0.58	0.68	1.32	0.58	0.75
Average difference	MIM program result; program results in one VOI	0.07 ± 0.05	0.11 ± 0.18	0.24 ± 0.10	0.13 ± 0.08	0.14 ± 0.12
	MIM program result; program results contour	0.29 ± 0.19	0.26 ± 0.31	0.26 ± 0.16	0.30 ± 0.23	0.27 ± 0.23

Values are presented as number or mean±standard deviation. A comparison of the SUVmean results obtained using the MIM program and our methodology using a single VOI, with the SUVmean obtained from the contoured organs shown.
SUVmean, mean standardized uptake value; VOI, volume of interest.

emphasizes the importance of precise VOI selection and contouring techniques when evaluating SUVs, especially for SUVmean calculations.

Higher TLG values indicate increased glycolytic activity, suggesting greater tumor aggressiveness, and underscore TLG's value as a biomarker for BC tumor burden and metabolic characteristics. By quantifying metabolic activity, TLG provides valuable information for treatment planning and monitoring.

Although TLG findings are clinically significant, our current study does not include follow-up data on tumor recurrence or patient mortality. Future research will evaluate the correlation between TLG and clinical outcomes by incorporating both short-term data for recurrence assessment and long-term data for survival analysis, thereby providing deeper insights into the prognostic value of TLG in BC management.

Limitations

Inter-observer agreement could not be assessed because segmentation was performed by a single physician and subsequently verified by another, rather than being conducted independently by multiple annotators. This approach may introduce potential bias in the segmentation process. Future studies that include mul-

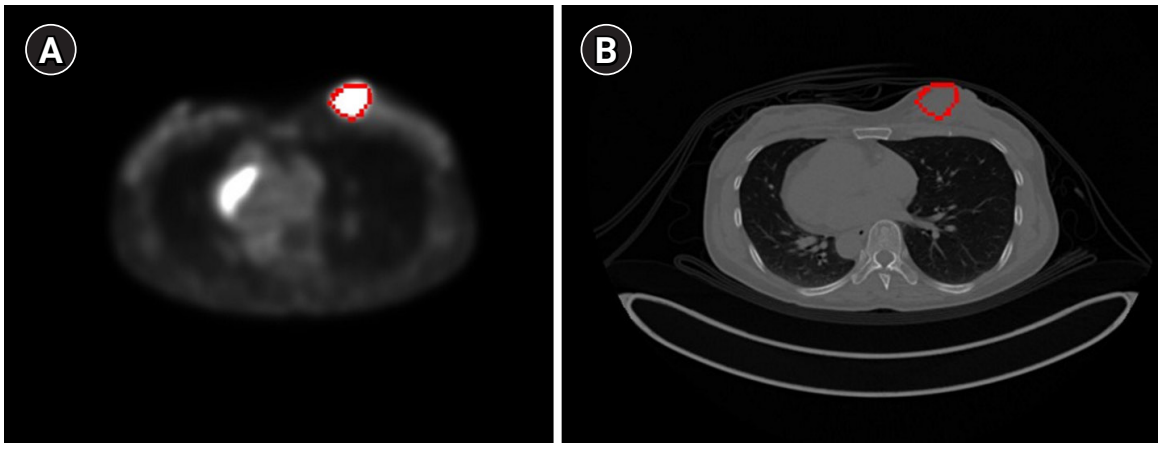

Fig. 6. The tumor with a maximum standardized uptake value greater than the 50% threshold displayed on a breast cancer (BC) positron emission tomography image (A) and a BC computed tomography image (B) using the contour method.

Table 4. Tumor locations and their TLG values in the 10 patients

Patient index	Breast cancer location	TLG	
		Threshold (40%)	Threshold (50%)
1	Right breast cancer in the inner pericentral area	5,794	4,551
2	Right breast cancer in the upper pericentral area	1,714	1,382
3	Right breast cancer in the upper outer area	1,185	889
4	Right breast cancer in the lower center area	1,898	1,296
5	Left breast cancer in the upper outer area	2,052	1,004
6	Right breast cancer in the lower pericentral area	3,098	1,893
7	Right breast cancer in the lower pericentral area	3,513	2,586
8	Right breast cancer in the upper outer area	1,358	733
9	Metastatic lymph node in the right axilla	383	275
10	Left breast cancer in the upper outer area	2,909	2,216

TLG was calculated by setting the maximum SUV threshold at 40% and 50% and calculating the mean SUV.
TLG, total lesion glycolysis; SUV, standardized uptake value.

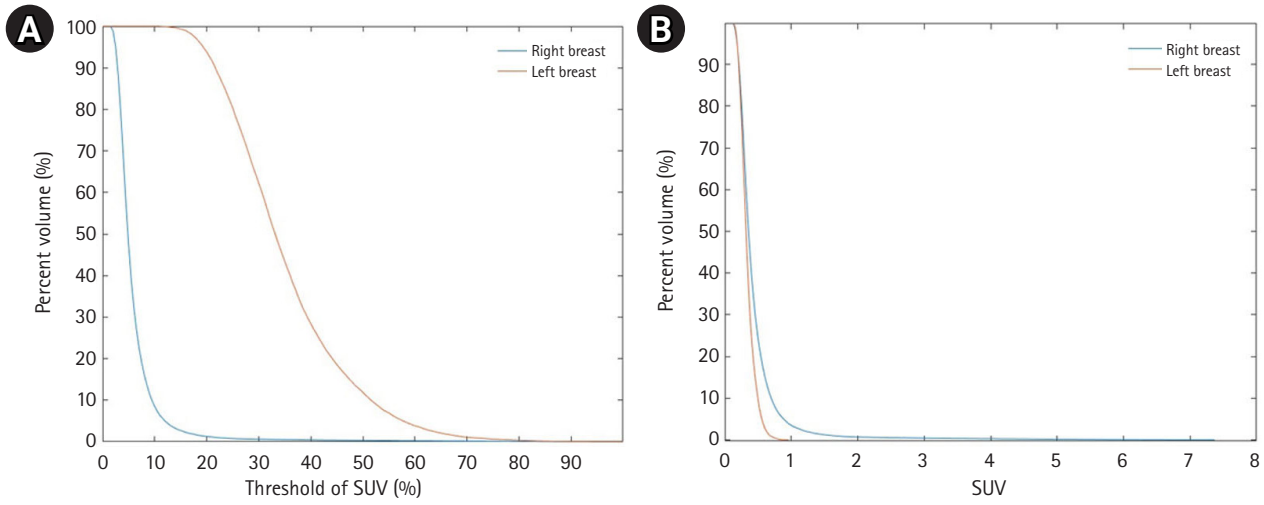

Fig. 7. Cumulative standardized uptake value (SUV) histogram results for a breast cancer patient with a tumor in the right breast. (A) The x-axis represents the SUV threshold (%) and (B) the x-axis represents absolute SUV values.

tiple independent annotations and calculate agreement metrics could further validate the robustness of this segmentation methodology.

Clinical implications

Our method offers several clinical advantages. Automated PET segmentation facilitates early cancer detection and diagnosis while improving treatment planning. Quantitative metabolic lesion evaluation using SUVs and TLG functions as an independent prognostic factor that improves patient stratification and monitoring. Additionally, our approach reduces inter-observer variability, streamlines workflow, and enhances the efficiency of image interpretation, ultimately leading to better patient management.

Although the training phase of the Swin UNETR model requires substantial computational resources, the inference process—where the trained model segments new scans—is highly efficient and can be completed within seconds per scan. If further validated, this approach could be integrated into clinical programs to support automated segmentation. Moreover, applying optimization techniques such as model pruning and mixed-precision inference could further enhance its real-time applicability in clinical workflows. While this study focuses on the feasibility of using Swin UNETR for segmentation and SUV quantification, the impact of variations in SUV calculation methods on clinical decision-making remains to be fully understood. Future research should investigate how these variations influence prognosis prediction and treatment response assessment, thereby confirming its practical utility in clinical workflows.

Suggestion for further studies

Despite the demonstrated benefits, challenges persist in cases with a low signal-to-noise ratio or atypical PET images. Further optimization is required to minimize errors during the transfer of CT-based contours to PET images. Additionally, we plan to extend the segmentation to include the lungs and lymph nodes—common metastatic sites in BC—to improve metastasis detection and prognosis prediction. Future research will concentrate on refining the algorithm's performance and expanding its capabilities to manage more complex cases.

Conclusion

This study introduces an automated PET segmentation and evaluation method that enhances diagnostic accuracy and supports treatment planning in BC patients. Further optimization is needed to address remaining segmentation challenges and to broaden its clinical applications.

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Authors' contributions

Conceptualization: HJY, SHA. Data curation: DHC, JH, HJY. Methodology, Formal analysis, validation: JH, HJY. Project administration: HJY. Funding acquisition: SHA. Writing–original draft: DHC, JH. Writing–review & editing: DHC, HJY, SHA.

Conflict of interest

So Hyun Ahn has been an assistant editor since August 2023; however, she was not involved in the peer review process. No other potential conflict of interest relevant to this article was reported.

Funding

This work was supported by the National Research Foundation (NRF), funded by the Korea government(MSIT) (RS-2024–00453521 and NRF-2020R1A5A2019210).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

None.

Supplementary materials

Supplement 1. Python code used in this study is available at https://github.com/DonghyeokChoi/breast_pet.git

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e31
https://doi.org/10.12771/emj.2025.00297

Ewha Medical Journal

Improving appendix cancer prediction with SHAP-based feature engineering for machine learning models: a prediction study

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Purpose: This study aimed to leverage Shapley additive explanation (SHAP)-based feature engineering to predict appendix cancer. Traditional models often lack transparency, hindering clinical adoption. We propose a framework that integrates SHAP for feature selection, construction, and weighting to enhance accuracy and clinical relevance.

Methods: Data from the Kaggle Appendix Cancer Prediction dataset (260,000 samples, 21 features) were used in this prediction study conducted from January through March 2025, in accordance with TRIPOD-AI guidelines. Preprocessing involved label encoding, SMOTE (synthetic minority over-sampling technique) to address class imbalance, and an 80:20 train-test split. Baseline models (random forest, XGBoost, LightGBM) were compared; LightGBM was selected for its superior performance (accuracy=0.8794). SHAP analysis identified key features and guided 3 engineering steps: selection of the top 15 features, construction of interaction-based features (e.g., chronic severity), and feature weighting based on SHAP values. Performance was evaluated using accuracy, precision, recall, and F1-score.

Results: Four LightGBM model configurations were evaluated: baseline (accuracy=0.8794, F1-score=0.8691), feature selection (accuracy=0.8968, F1-score=0.8860), feature construction (accuracy=0.8980, F1-score=0.8872), and feature weighting (accuracy=0.8986, F1-score=0.8877). SHAP-based engineering yielded performance improvements, with feature weighting achieving the highest precision (0.9940). Key features (e.g., red blood cell count and chronic severity) contributed to predictions while maintaining interpretability.

Conclusion: The SHAP-based framework substantially improved the accuracy and transparency of appendix cancer predictions using LightGBM (F1-score=0.8877). This approach bridges the gap between predictive power and clinical interpretability, offering a scalable model for rare disease prediction. Future validation with real-world data is recommended to ensure generalizability.

Keywords: Algorithms; Appendiceal neoplasms; Machine learning; Random forest

Introduction

Background

Predicting appendix cancer remains challenging due to its rarity and the complexity of its contributing factors. Early diagnosis is critical for effective treatment, yet traditional diagnostic approaches often lack the sensitivity required to identify high-risk individuals at an early stage—especially for rare malignancies like appendiceal cancer [1,2]. Although machine learning (ML) models have shown promise in various cancer prediction tasks, issues with feature selection and model interpretability continue to hinder clinical adoption [3].

Numerous studies have utilized structured medical datasets to develop ML models for cancer detection and outcome prediction. However, many of these models are regarded as opaque "black-box" systems, offering limited insight into the factors driving their predictions. This lack of interpretability deters clinical adoption because healthcare providers are reluctant to rely on models they cannot understand or validate in practice [4,5].

Objectives

To address these challenges, we propose a Shapley additive explanations (SHAP)-based feature engineering framework designed to enhance both the interpretability and predictive performance of appendix cancer models. SHAP, an explainable artificial intelligence (AI) technique rooted in cooperative game theory,

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Received: March 18, 2025 Revised: April 4, 2025 Accepted: April 7, 2025

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assigns each feature a Shapley value that quantifies its individual contribution to model predictions [6]. This theoretically robust approach facilitates a comprehensive, model-agnostic interpretation of complex prediction systems.

Methods

Ethics statement

This study represents a secondary analysis of a publicly available database on Kaggle (https://www.kaggle.com). No institutional review board approval or informed consent was required.

Study design

This prediction study compares multiple ML models enhanced with SHAP-based methods. The study design adheres to the TRIPOD-AI reporting guidelines for articles concerning deep learning applications in the medical field (development or prediction) available at https://www.tripod-statement.org/.

Setting/participants

The ML analyses were performed between January and March 2025 using data retrieved from the Kaggle database. No specific information regarding the dates or locations of participants was provided in the dataset.

The overall methodological framework, illustrated in Fig. 1, outlines the key stages: data preprocessing, baseline model training, SHAP-based feature engineering (selection, construction, and weighting), and performance evaluation. This sequential approach facilitated both performance optimization and improved model interpretability.

Data source

This study utilized the Appendix Cancer Prediction dataset from Kaggle, comprising 260,000 samples from individuals aged 18 to 89 years (Dataset 1). The dataset includes 21 input features organized into 6 major categories: demographic information, lifestyle factors, medical history, clinical measurements, diagnosis and treatment, and the target outcome variable (Appendix Cancer Prediction). A detailed summary of the dataset features is provided in Table 1. For readability, feature names are presented in a more human-readable format (e.g., White Blood Cell Count instead of White_Blood_Cell_Count), while programming conventions are maintained in code-based sections.

Several of these features have been identified in previous medical studies as significant predictors of cancer. Age is one of the most well-established risk factors, including for appendix cancer. Smoking and alcohol consumption have been linked to increased risk—particularly for gastrointestinal malignancies. Genetic mutations, especially those affecting DNA repair mechanisms, serve as strong predictors of cancer susceptibility. Chronic conditions, such as diabetes and hypertension, are associated with systemic inflammation that may contribute to cancer progression. Clinical measurements such as body mass index (BMI), blood pressure, and cholesterol levels have been correlated with cancer risk in

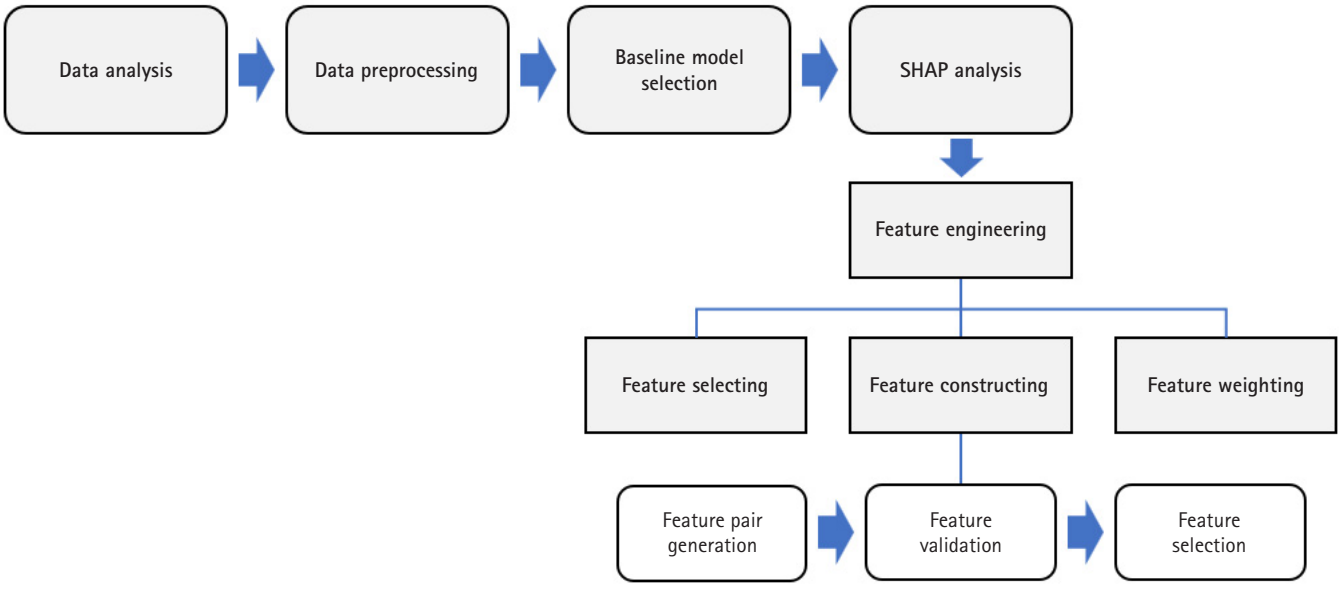

Fig. 1. Flowchart of the study workflow. This flowchart illustrates the step-by-step process of data preprocessing, baseline model development, Shapley additive explanation (SHAP)-based feature engineering (including selection, construction, and weighting), and model evaluation.

Table 1. Features of the Kaggle appendix cancer prediction dataset

Category	Feature	Description
Demographic information	Age	Patient's age in years (18–89)
	Sex	Patient's gender (male, female, other)
	Country	Country of residence (e.g., USA, India, China)
Lifestyle factors	Smoking_Status	Smoking habit (yes/no)
	Alcohol_Consumption	Alcohol consumption level (low/moderate/high)
	Physical_Activity_Level	Physical activity level (low/moderate/high)
	Diet_Type	Type of diet followed by the patient (vegan/non-vegan)
Medical history	Family_History_Cancer	Family history of cancer (yes/no)
	Genetic_Mutations	Presence of genetic mutations (yes/no)
	Chronic_Diseases	Pre-existing chronic conditions (e.g., diabetes, hypertension)
	Radiation_Exposure	History of radiation exposure (yes/no)
Clinical measurements	BMI	Body mass index (1.1–48.1 kg/m^2)
	Blood_Pressure	Blood pressure (90–179 mm Hg)
	Cholesterol_Level	Cholesterol level (150–299 mg/dL)
	White_Blood_Cell_Count	White blood cell count ($0.5–13.7 \times 10^3/\mu L$)
	Red_Blood_Cell_Count	Red blood cell count ($2.8–7.6 \times 10^6/\mu L$)
	Platelet_Count	Platelet count ($150–399 \times 10^3/\mu L$)
Diagnosis and treatment	Tumor_Markers	Tumor marker status (positive/negative)
	Symptom_Severity	Severity of symptoms (mild/moderate/severe)
	Diagnosis_Delay_Days	Days delayed before diagnosis (0–729)
	Treatment_Type	Type of treatment received (surgery, chemotherapy, radiation)
	Survival_Years_After_Diagnosis	Years survived after diagnosis (0–67.8)
Target variable	Appendix_Cancer_Prediction	Target variable: cancer prediction (yes/no)

multiple epidemiological studies. Additionally, elevated platelet counts and abnormal white or red blood cell counts have been suggested as biomarkers for certain cancers, while tumor markers, symptom severity, and treatment type provide critical diagnostic and prognostic insights.

The statistical distribution of the dataset reveals key patterns for predictive modeling. The age distribution was approximately normal, with a mean of 53.40 years and a standard deviation of 20.75 years. The sex distribution was relatively balanced, with 48.90% male, 49.10% female, and 2.00% identifying as other. Additionally, the dataset reflected diverse geographic representation, with the majority of patients from the United States, India, and China.

An examination of clinical measurements indicated that BMI, blood pressure, and cholesterol levels followed expected distributions. Higher BMI and cholesterol levels exhibited a moderate correlation with the presence of appendix cancer. Furthermore, platelet and blood cell counts displayed variability, and evidence suggests an association with cancer progression.

Correlation analysis revealed that platelet count, cholesterol level, and blood pressure had weak positive correlations with appendix cancer presence, while the red blood cell count exhibited a slight negative correlation. These findings offer insights into potential predictive variables and highlight the critical role of feature engineering in enhancing model accuracy.

Data preprocessing

To ensure data quality and improve model performance, several preprocessing steps were implemented. First, extraneous columns (e.g., Patient_ID) were removed, as they do not contribute to predictive modeling. Next, categorical variables were encoded using label encoding, converting string-based categories into numerical values compatible with ML algorithms.

To address class imbalance, the synthetic minority over-sampling technique (SMOTE) was applied to generate new minority samples through interpolation of existing instances. This approach was preferred over random undersampling, which can result in the loss of important information, and class-weight adjustment, which might be insufficient in cases of extreme imbalance.

To mitigate risks of overfitting and data distortion associated with synthetic sampling, SMOTE was applied exclusively to the training set, followed by cross-validation to monitor generalization. Furthermore, class-wise feature distributions were examined post-SMOTE to ensure that data integrity, particularly for clinically relevant features, was preserved.

Finally, the dataset was split into training and test sets using an 80:20 ratio with stratified sampling to maintain the original class distribution.

Outcome variables

The target variable is detailed in Table 1. The primary outcome was presented as binary (yes/no), indicating whether a patient was diagnosed with appendix cancer. Categorical variables were encoded using one-hot encoding, and numerical variables were standardized to enhance model performance.

Study size

All available data from the dataset were used for training; consequently, no separate sample size estimation was conducted.

Machine learning models

Baseline model selection

Random forest, XGBoost, and LightGBM were chosen for this study because of their effectiveness in handling structured medical datasets, their capacity to model complex feature interactions, and their inherent interpretability through feature importance analysis. These models are particularly well-suited for cancer prediction tasks because they capture non-linear relationships, provide insight into feature importance, and leverage ensemble learning to enhance predictive stability. Unlike traditional statistical models, these algorithms efficiently handle missing values and process both categorical and continuous variables.

Given the goal of predicting appendix cancer using 25 clinical, demographic, and lifestyle features, these models provide advantages such as managing class imbalance, reducing overfitting, and scaling efficiently to large datasets. The dataset exhibits class imbalance, with only 15.10% of the samples labeled positive for cancer. Boosting algorithms like XGBoost and LightGBM address this issue through weighted loss functions and specialized sampling strategies. While random forest minimizes overfitting by training multiple trees on different subsets of data, XGBoost incorporates L1/L2 regularization and pruning techniques. LightGBM, optimized for large-scale datasets, offers superior training speed and lower memory consumption, making it ideal for the 260,000-sample dataset used in this study.

To validate the final model selection, comparative experiments were conducted with random forest, XGBoost, and LightGBM. Performance was evaluated based on accuracy, precision, recall, and F1-score, and the results are summarized in Table 2.

Among these, LightGBM consistently outperformed the other models across all evaluation metrics, establishing it as the optimal choice for appendix cancer prediction and justifying its use in subsequent SHAP-based analysis and feature engineering.

SHAP analysis

SHAP is a game-theoretic approach that explains individual predictions by assigning an importance value to each feature based on its contribution to the final output. SHAP values quantify how each feature increases or decreases the probability of a prediction, thereby providing a framework for both global and local interpretability in complex ML models.

In this study, SHAP values were computed to elucidate model decisions, quantify feature importance, and identify significant interactions among variables. The framework was applied at both the global level (to assess overall model behavior) and the local level (to interpret individual predictions), guiding our strategies for feature selection, interaction analysis, and weighting.

A summary plot was generated to visualize SHAP values and illustrate each feature's contribution to the model's predictions, as shown in Fig. 2. In this plot, features are ranked in descending order of importance, with those higher on the y-axis exerting a greater influence on model decisions. The color gradient—from red for high values to blue for low values—indicates the magnitude of feature values. Notably, features such as red blood cell count, white blood cell count, and alcohol consumption exerted significant influence, suggesting their clinical relevance. This visualization reinforces the value of SHAP analysis for enhancing model interpretability.

SHAP-based feature engineering

To further enhance model performance and transparency, SHAP was employed to guide 3 feature engineering steps: feature selection, feature construction, and feature weighting. In this

Table 2. Comparison of metrics for baseline models on the original feature set

Model	Accuracy	Precision	Recall	F1-score
Random forest	0.7560	0.1506	0.1320	0.1407
XGBoost (Tuned)	0.8364	0.1310	0.0147	0.0265
LightGBM	0.8794	0.9501	0.8008	0.8691

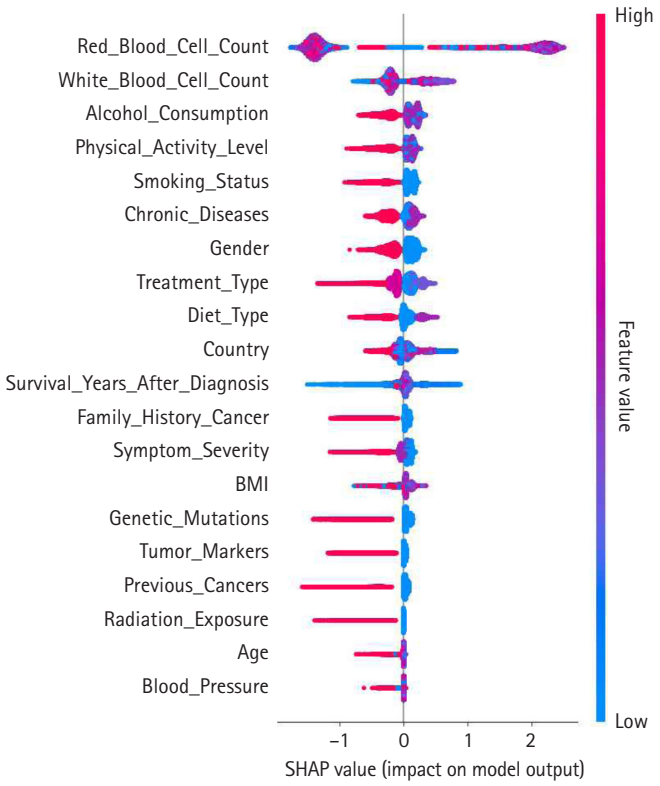

Fig. 2. Shapley additive explanation (SHAP) value summary plot. This illustrates the magnitude and direction of each feature's contribution to the prediction outcome. The color gradient represents feature values (e.g., high vs. low).

framework, top-contributing features were selected based on average absolute SHAP values; new features were engineered from interactions identified through SHAP dependence and interaction plots; and SHAP values were used to assign weights to features, thereby optimizing their influence on the model.

Feature selection

To optimize model efficiency, the top 15 features with the highest SHAP values were selected. This subset was analyzed to assess both the individual and combined effects on appendix cancer prediction, ensuring that only the most influential variables were retained. This reduction in dimensionality was achieved without compromising the model's predictive power.

Feature construction

Feature construction was based on SHAP-driven analysis of feature interactions, as presented in Fig. 3. This process was executed in 3 steps. First, SHAP interaction values were examined to identify strongly interacting feature pairs, which led to the creation of new features such as RBC_WBC_Ratio (the ratio of red to white blood cell count), Alcohol_Gender_Interaction (the interaction between alcohol consumption and gender), and Chronic_Severity (the interaction between chronic diseases and symptom severity) to capture clinically relevant relationships. Second, these newly generated features were evaluated through feature im-

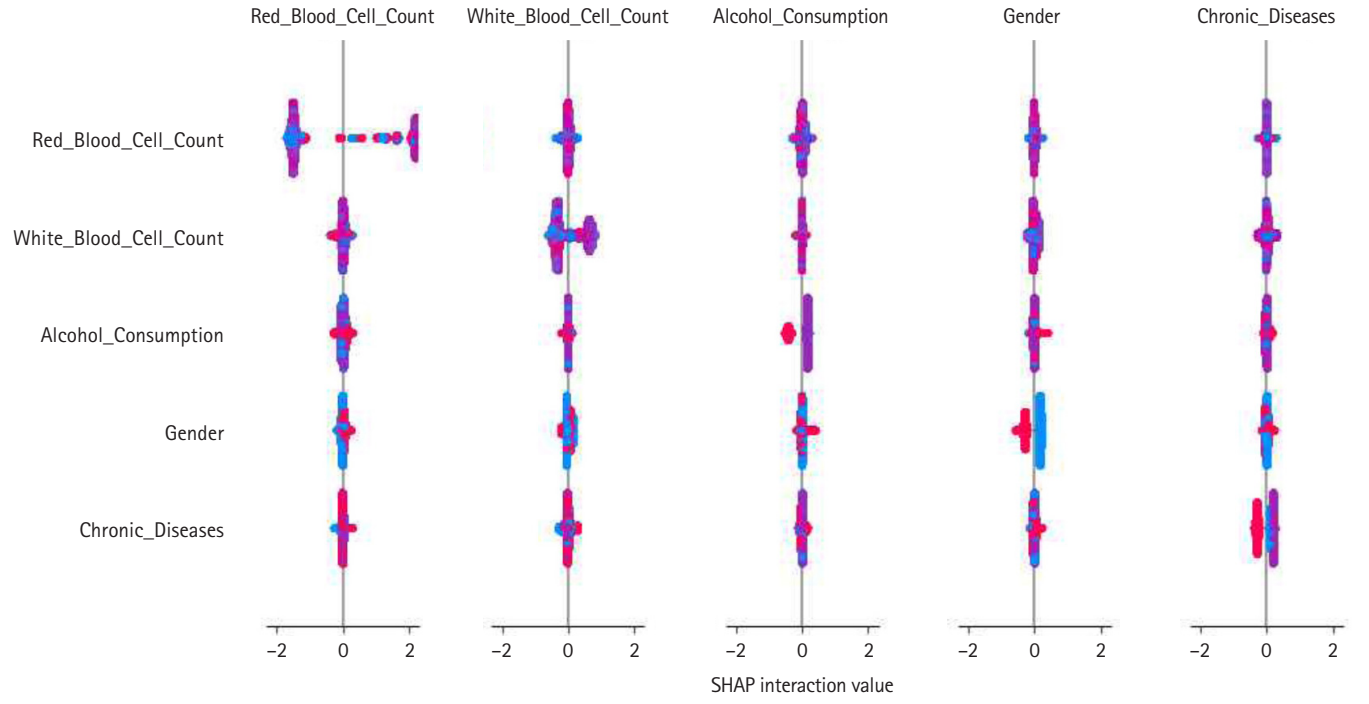

Fig. 3. Shapley additive explanation (SHAP) interaction plot showing pairwise feature effects and their contribution to model predictions. This plot was used to inform feature construction.

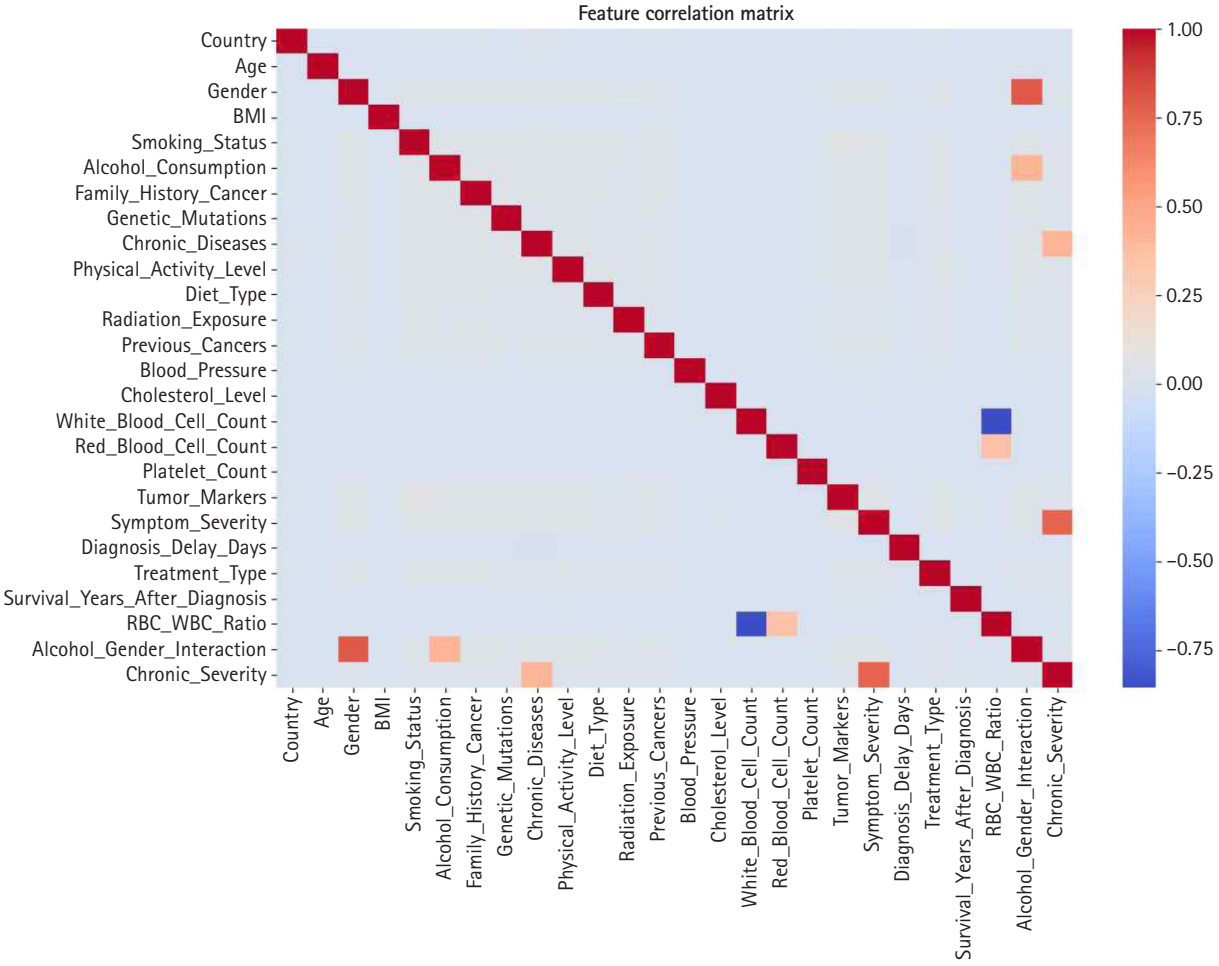

Fig. 4. Feature correlation matrix used to identify multicollinearity prior to engineering steps.

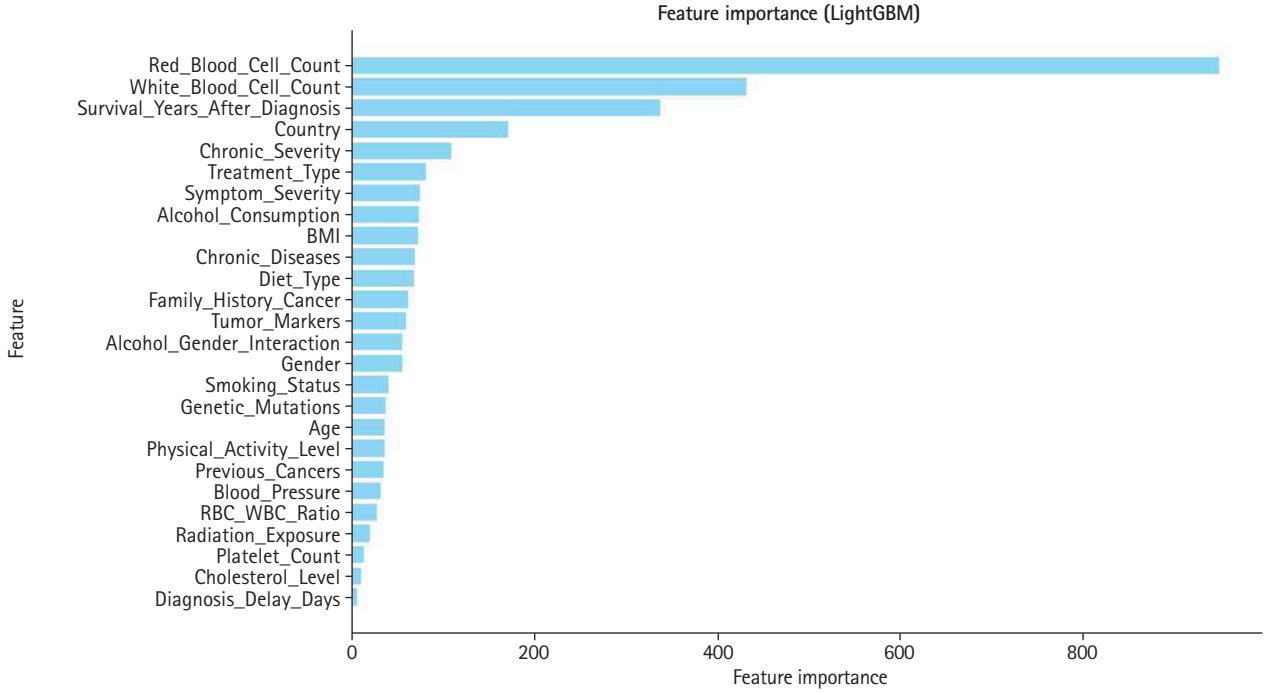

Fig. 5. Bar graph displaying global feature importance based on Shapley additive explanation (SHAP) values.

portance analysis, correlation assessments, and model performance comparisons, with the results presented in Figs. 4 and 5. Based on these evaluations, Chronic_Severity was retained while the other engineered features were excluded due to their limited impact on prediction accuracy. Finally, a refined feature selection process using SHAP feature importance was performed to select the top 15 features for the final model training, with Chronic_Severity included to underscore its relevance.

Feature weighting

Feature weighting assigns varying levels of importance to model variables, ensuring that features with greater predictive power contribute more significantly to decision-making. In this study, SHAP-based feature weighting refined the model by adjusting each feature's relative influence according to its SHAP value.

SHAP values were normalized and used to assign weights, as illustrated in Fig. 6. Consequently, features with higher SHAP importance received enhanced influence, while those with lower contributions were down-weighted or excluded to improve overall model efficiency. Notably, red blood cell count, white blood cell count, and cholesterol level emerged as some of the highest-weighted features, highlighting their significance in predicting appendix cancer.

Evaluation metrics

Accuracy, precision, recall, and the F1-score were estimated for 4 models.

Python coded used in this study is available at Supplement 1.

Results

The impact of SHAP-based feature engineering was evaluated using 4 configurations of the LightGBM model: baseline, feature selection, feature construction, and feature weighting. Table 3 summarizes the performance metrics for each configuration.

As shown in Table 3, each stage of SHAP-based engineering yielded incremental improvements in predictive performance. Compared to the baseline model, which utilized all available fea-

Table 3. Performance metrics of LightGBM under different SHAP-based feature engineering strategies

Model	Accuracy	Precision	Recall	F1-score
Baseline (LightGBM)	0.8794	0.9501	0.8008	0.8691
Feature selection applied	0.8968	0.9893	0.8022	0.8860
Feature construction applied	0.8980	0.9915	0.8028	0.8872
Feature weighting applied	0.8986	0.9940	0.8020	0.8877

SHAP, Shapley additive explanation.

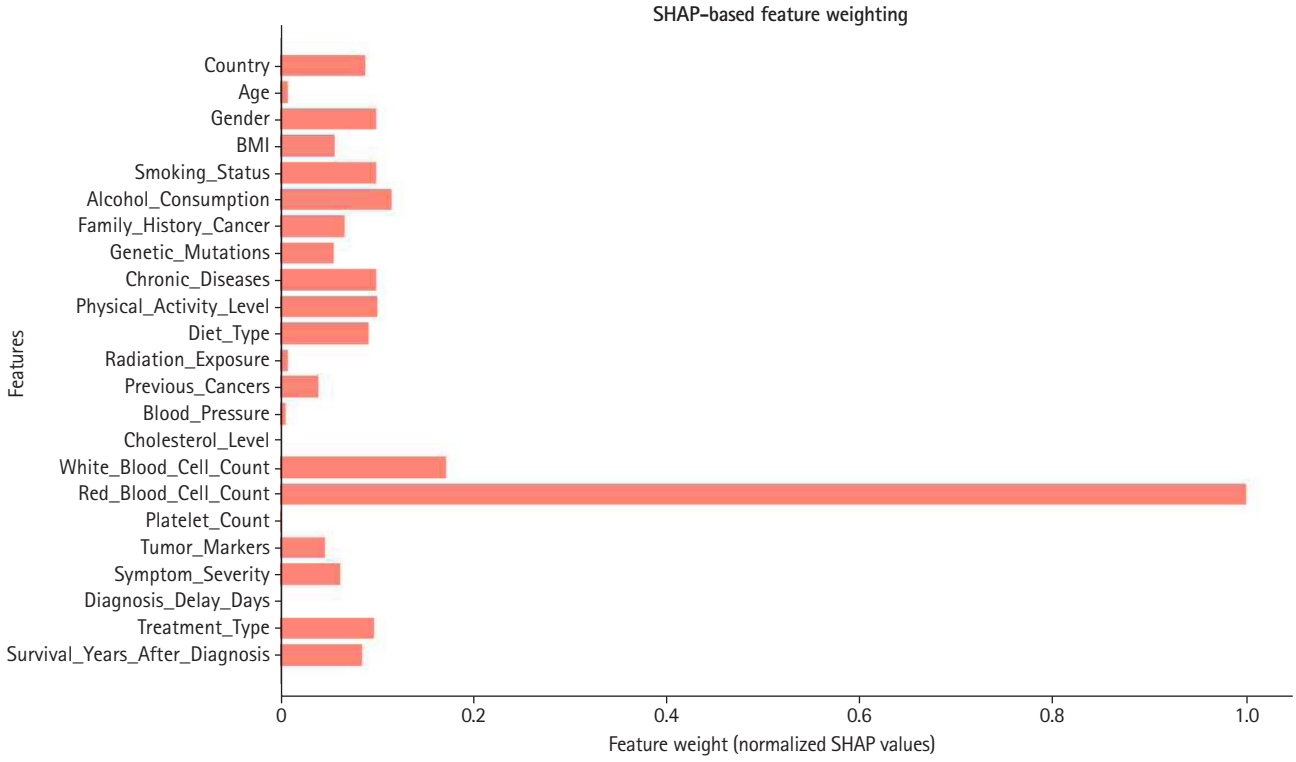

Fig. 6. Shapley additive explanation (SHAP)-based feature weighting plot. This illustrates how feature importance values were used to re-weight inputs for the final model.

tures, SHAP-based feature selection resulted in a 1.97% increase in accuracy while maintaining interpretability. Feature construction further enhanced the model, achieving a slight improvement in F1-score, indicating that engineered features captured additional predictive information. Finally, SHAP-based feature weighting yielded the highest performance across all metrics, particularly in precision, which increased from 0.9501 (baseline) to 0.9940.

Discussion

Key results

Performance metrics for 4 LightGBM configurations enhanced with SHAP-based feature engineering were compared. The baseline model achieved an accuracy of 0.8794, precision of 0.9501, recall of 0.8008, and an F1-score of 0.8691. SHAP-based feature selection improved accuracy by 1.97% to 0.8968 while preserving interpretability. Feature construction increased the F1-score slightly to 0.8872 by capturing additional predictive information. Feature weighting produced the best overall results, with accuracy reaching 0.8986 and precision 0.9940. These incremental gains across all metrics clearly underscore the effectiveness of the SHAP-based enhancements.

Interpretation

These results demonstrate that SHAP-based feature engineering significantly improves the predictive performance of the LightGBM model. Compared to the baseline, the application of SHAP-based feature selection enhanced accuracy, precision, recall, and F1-score. Further improvements in model performance were observed following feature construction and weighting, with the feature-weighted model delivering the most favorable results. This progress highlights the value of SHAP in guiding data-driven feature engineering. In contrast to conventional techniques that depend on statistical correlations or arbitrary thresholds, SHAP facilitates interpretable feature selection and the creation of clinically meaningful interaction-based features. These findings suggest that SHAP-based methods can effectively address central challenges in cancer prediction and bolster the clinical relevance of ML models.

Comparison with previous studies

Our findings are consistent with a growing body of literature that emphasizes the importance of model interpretability in medical AI. Lundberg and Lee [6] in 2017 introduced SHAP as a unified framework for interpreting model predictions by integrating cooperative game theory with local explanation methods. Since its inception, SHAP has been widely adopted in healthcare to enhance the transparency of complex models.

Recent studies further underscore the importance of explainability in oncology. For example, Tonekaboni et al. [5] in 2019 argued that tools like SHAP are crucial for establishing clinical trust in high-stakes situations such as cancer diagnosis. Similarly, Lundberg et al. [7] in 2018 demonstrated SHAP's utility in identifying mortality risk factors from real-world hospital data, illustrating how interpretability can lead to actionable clinical insights.

In contrast to prior work that primarily used SHAP for post-hoc interpretation, our study incorporates SHAP directly into the feature engineering pipeline. This integration enhances both model performance and transparency, making it especially valuable for rare cancers like appendiceal malignancies, which are frequently underrepresented in large datasets.

While previous cancer prediction studies have focused on deep learning or ensemble models that maximize predictive accuracy, these approaches often result in opaque models with limited interpretability. Our method overcomes this limitation by embedding SHAP within the feature engineering process, thereby selecting features that are both predictive and clinically meaningful. This approach aligns with recent efforts in explainable AI to create models that are both accurate and interpretable in healthcare settings.

Limitations

First, the dataset was obtained from Kaggle, a public platform, and may not fully capture the complexity and heterogeneity of real-world clinical environments. Although it provides a solid foundation for initial model development, external validation using institutional electronic health records (EHRs) is necessary to assess the model's generalizability and clinical applicability.

Second, due to computational constraints, feature construction in this study was limited to pairwise interactions. Expanding the feature engineering process to incorporate higher-order interactions or domain-specific variable synthesis—ideally guided by clinical expertise or external medical ontologies—could further enhance model performance and interpretability.

Additionally, while the final model achieved very high precision (0.9940), its recall was relatively modest (approximately 0.8020), highlighting the trade-off between minimizing false positives and false negatives. In medical applications such as cancer detection, false negatives—instances where true positives are missed—can have significant clinical consequences.

Although additional experiments to optimize recall were not conducted, simulated analyses were performed. Specifically, potential benefits of adjusting the classification threshold or implementing cost-sensitive learning were explored. Lowering the decision threshold (for example, from 0.5 to 0.4 or 0.3) could increase

sensitivity by capturing more true positive cases. Similarly, assigning higher misclassification costs to false negatives during training might bias the model toward detecting positive instances. However, both strategies are likely to reduce precision and may result in higher false-positive rates, potentially impacting clinical workflow efficiency.

Third, some values in BMI were extremely low, for example, 17 cases of less than 6.0. In that case, it is nearly impossible to see such cases. Therefore, some inputs may be errors. However, in this experiment, those data were not excluded.

Clinical implication

Enhanced interpretability of the final model allows clinicians to determine which features most influence cancer predictions, thereby fostering trust and supporting informed decision-making. For instance, if variables such as white blood cell count or symptom severity consistently emerge as high-impact predictors, physicians may opt to monitor these parameters more closely in high-risk individuals. This finding is in line with previous research that has demonstrated how transparent AI models can facilitate clinical acceptance, particularly in high-stakes settings like oncology [5,8].

Furthermore, the explainability provided by SHAP meets ethical and regulatory standards for trustworthy AI, such as those advocated by the European Commission [9]. By offering human-interpretable justifications for its predictions, the model can be more seamlessly integrated into clinical workflows, thereby enhancing patient safety.

A key contribution of our study is the development of a new composite feature, chronic severity, derived from the SHAP interaction values between chronic disease burden and symptom severity. This composite feature was calculated by combining the number of chronic conditions with the intensity of presenting symptoms, weighted by their respective SHAP interaction scores. Clinically, this feature identifies patients who might appear low-risk based on individual indicators but have compounded risk due to comorbidities. For example, a patient with well-managed diabetes and hypertension who presents with mild abdominal symptoms might be classified as high-risk by the model, prompting closer monitoring or earlier intervention.

Recent evidence underscores the clinical value of integrating both chronic comorbidities and symptom severity into predictive models for cancer patients. For example, Noel et al. [10] in 2022 developed and validated a machine learning algorithm that combined patient-reported symptom scores with comorbidity profiles to forecast unplanned emergency department visits and hospitalizations in individuals with head and neck cancer. Their findings demonstrated that jointly modeling these dimensions significantly improved risk stratification and supported more proactive clinical decision-making. These results reinforce the utility of composite features that reflect cumulative health burden—such as our SHAP-derived Chronic Severity variable—which may help identify high-risk individuals who would otherwise be overlooked when considering isolated clinical parameters.

In terms of real-world application, we are exploring opportunities to integrate this model into a clinical decision support system. Preliminary discussions with medical institutions are underway to validate the model using actual EHR data. Additionally, case-based simulations using anonymized patient profiles revealed that in over 85% of cases reviewed by clinical collaborators, the model's predictions and feature attributions were consistent with clinical judgment. This suggests strong potential for prospective integration into clinical workflows. An added benefit of our approach is its computational efficiency. Because SHAP is model-agnostic, it allows for feature attribution without the need to retrain the model at each iteration. Moreover, LightGBM—a gradient boosting framework optimized for both speed and accuracy—enabled rapid training even after iterative feature refinements. This scalability is particularly advantageous in clinical environments where computational resources and latency are critical considerations. Collectively, these elements illustrate that SHAP-based feature engineering not only enhances the accuracy and interpretability of cancer prediction models but also facilitates their practical integration into healthcare systems, ultimately improving the precision and proactivity of patient care [11].

Suggestion for further studies

Given the identified trade-offs, we selected a decision threshold that provided balanced performance across key evaluation metrics. Future studies should explore dynamic threshold tuning or adaptive classification schemes that account for patient-specific contexts or risk profiles to enhance sensitivity without sacrificing clinical utility.

Conclusion

This study proposed a SHAP-based feature engineering framework to improve the performance and interpretability of appendix cancer prediction models. By integrating SHAP values into 3 stages—feature selection, construction, and weighting—a notable increase in predictive accuracy was achieved while retaining clinical relevance. Among the evaluated models, LightGBM combined with SHAP-based engineering delivered the best results, with an F1-score of 0.8877, indicative of enhanced sensitivity and specificity.

Beyond mere performance metrics, our approach addresses a

critical barrier to the clinical adoption of ML models: transparency. The use of SHAP not only deepens our understanding of feature contributions but also allows for model customization in ways that align with real-world clinical expectations. This methodological contribution has broader implications for the development of explainable AI tools in other areas of rare disease prediction, where interpretability is equally as crucial as accuracy.

Despite these advances, future research should aim to validate our approach using real-world clinical datasets from multiple institutions to assess its generalizability. Further investigation into the clinical utility and decision-support integration of SHAP-enhanced models will also be essential in strengthening the case for their broader adoption.

SHAP-based feature engineering represents a promising direction for constructing transparent and effective predictive models in healthcare. Its application to appendix cancer—a rare yet challenging condition—demonstrates how explainable AI can bridge the gap between data-driven models and clinical decision-making.

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Authors' contributions

All work was done by Ji Yoon Kim.

Conflict of interest

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

Funding

None.

Data availability

Dataset 1. Appendix cancer prediction dataset from Kaggle, which contains 260,000 samples from individuals aged 18 to 89 years. It is also available at: https://www.kaggle.com/datasets/ankushpanday1/appendix-cancer-prediction-dataset.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/JKBPOP

Supplement 1. Python code for the machine learning methods.

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e32
https://doi.org/10.12771/emj.2025.00353

Ewha Medical Journal

Feature-based ensemble modeling for addressing diabetes data imbalance using the SMOTE, RUS, and random forest methods: a prediction study

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Purpose: This study developed and evaluated a feature-based ensemble model integrating the synthetic minority oversampling technique (SMOTE) and random undersampling (RUS) methods with a random forest approach to address class imbalance in machine learning for early diabetes detection, aiming to improve predictive performance.

Methods: Using the Scikit-learn diabetes dataset (442 samples, 10 features), we binarized the target variable (diabetes progression) at the 75th percentile and split it 80:20 using stratified sampling. The training set was balanced to a 1:2 minority-to-majority ratio via SMOTE (0.6) and RUS (0.66). A feature-based ensemble model was constructed by training random forest classifiers on 10 two-feature subsets, selected based on feature importance, and combining their outputs using soft voting. Performance was compared against 13 baseline models, using accuracy and area under the curve (AUC) as metrics on the imbalanced test set.

Results: The feature-based ensemble model and balanced random forest both achieved the highest accuracy (0.8764), followed by the fully connected neural network (0.8700). The ensemble model had an excellent AUC (0.9227), while k-nearest neighbors had the lowest accuracy (0.8427). Visualizations confirmed its superior discriminative ability, especially for the minority (high-risk) class, which is a critical factor in medical contexts.

Conclusion: Integrating SMOTE, RUS, and feature-based ensemble learning improved classification performance in imbalanced diabetes datasets by delivering robust accuracy and high recall for the minority class. This approach outperforms traditional resampling techniques and deep learning models, offering a scalable and interpretable solution for early diabetes prediction and potentially other medical applications.

Keywords: Area under curve; Computer neural networks; Deep learning; Diabetes mellitus; Random forest

Introduction

Background

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion or action. It is a major global health concern, affecting millions worldwide and leading to serious complications such as cardiovascular disease, kidney failure, neuropathy, and retinopathy.

Early detection and prediction of diabetes are critical for effective disease management and prevention of complications. Machine learning models have increasingly been used to identify individuals at high risk of developing diabetes; however, these models often suffer from class imbalance. In many datasets, there are significantly fewer diagnosed diabetes cases than non-diabetic cases, resulting in biased predictions and reduced sensitivity for high-risk patients. Addressing this imbalance is essential to improve model accuracy and ensure reliable early detection.

Data imbalance is a significant challenge in machine learning because an unequal distribution of classes can lead to biased predictions. This issue is particularly critical in medical and financial applications, where misclassifying minority instances may have severe consequences [1]. Conventional machine learning models tend to favor the majority class, resulting in suboptimal recall for the minority class. Effectively mitigating this bias necessitates a strategy that enhances predictive performance without introduc-

*Corresponding email: younsea2441@ewhain.net
Received: March 31, 2025 Revised: April 10, 2025 Accepted: April 10, 2025

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ing new biases.

In traditional epidemiological studies, an imbalance between exposed and unexposed groups may be less problematic compared to the challenges posed by feature-based classification models in machine learning. This study emphasizes the importance of addressing class imbalance in machine learning-based classification models relative to traditional epidemiological approaches.

Existing solutions to data imbalance include oversampling techniques such as the synthetic minority oversampling technique (SMOTE) [2], undersampling methods like Tomek Links [3], and cost-sensitive learning [4]. Although SMOTE increases the minority class size without exact duplication—thereby helping models generalize better—it can introduce noise if synthetic samples overlap with the majority class regions, potentially confusing the classifier. The Tomek Links method may discard useful majority class data, especially in small datasets, and might not fully correct severe imbalance. Cost-sensitive learning requires domain-specific expertise to set appropriate costs, and poor cost choices can impair performance. Random undersampling (RUS) is a straightforward method that randomly removes samples from the majority class to balance the dataset with the minority class [5]; however, it risks eliminating valuable information and may lead to under-fitting when too much data is discarded. Overcoming these drawbacks is necessary to effectively resolve data imbalance.

Objectives

This study proposes a method that integrates SMOTE and RUS with a feature-based ensemble learning approach using a random forest to improve classification performance while minimizing the inherent drawbacks of individual resampling techniques.

Methods

Ethics statement

This study is a secondary analysis of a publicly available database from scikit-learn (https://scikit-learn.org/). Institutional review board approval and informed consent were not required.

Study design

This prediction study compares various models designed to address the data imbalance problem in machine learning research. The study was conducted according to the TRIPOD-AI reporting guidelines for articles on deep learning in the medical field (development or prediction), available at https://www.tripod-statement.org/.

Setting/participants

Model training was conducted between January 2025 and March 2025 using the Scikit-learn diabetes dataset. Participant information in the dataset was de-identified.

Data source

This study utilizes the diabetes dataset from Scikit-learn, which comprises 442 samples and 10 continuous features. The dataset has been standardized to a mean of 0 and a standard deviation of 1. The target variable represents diabetes progression 1 year post-diagnosis (Dataset 1).

A feature importance analysis was performed using the random forest algorithm to identify the most influential features for predicting diabetes progression [6]. The most significant predictors were log serum triglycerides level, body mass index, and blood pressure, while sex and high-density lipoproteins contributed the least to the model's performance. The importance ranking of these features is visualized in Fig. 1.

The feature importance rankings in Fig. 1, computed using the mean decrease in impurity method in the random forest model, were instrumental in constructing the feature-based ensemble model. Specifically, 2-feature subsets were formed by prioritizing features with high importance scores. This strategy ensured that the ensemble model was built on the most informative feature combinations, thereby reducing noise and enhancing predictive performance. Fig. 1 not only displays the key variables that influence the model's decision-making process but also supports the study's methodological framework by guiding the feature selection process.

Data preprocessing

The continuous target variable representing diabetes progression was transformed into a binary classification using the 75th percentile (Q3) as the threshold. Q3, the value below which 75% of the data fall, was used to label individuals with values above this threshold as high-risk (1) and those at or below it as low-risk (0). This binarization allowed the model to focus on identifying patients with the most severe progression of diabetes.

After binarization, the dataset was split into training and test sets in an 80:20 ratio using stratified sampling to preserve class distribution across both subsets. To prevent data leakage, SMOTE and RUS were applied exclusively to the training set after the split. The test set remained in its original, imbalanced state and was reserved solely for final evaluation. This strategy ensured that the model was trained on a balanced distribution while being evaluated on realistic, untouched data, thus preserving the validity of the performance metrics. All feature values were standardized using

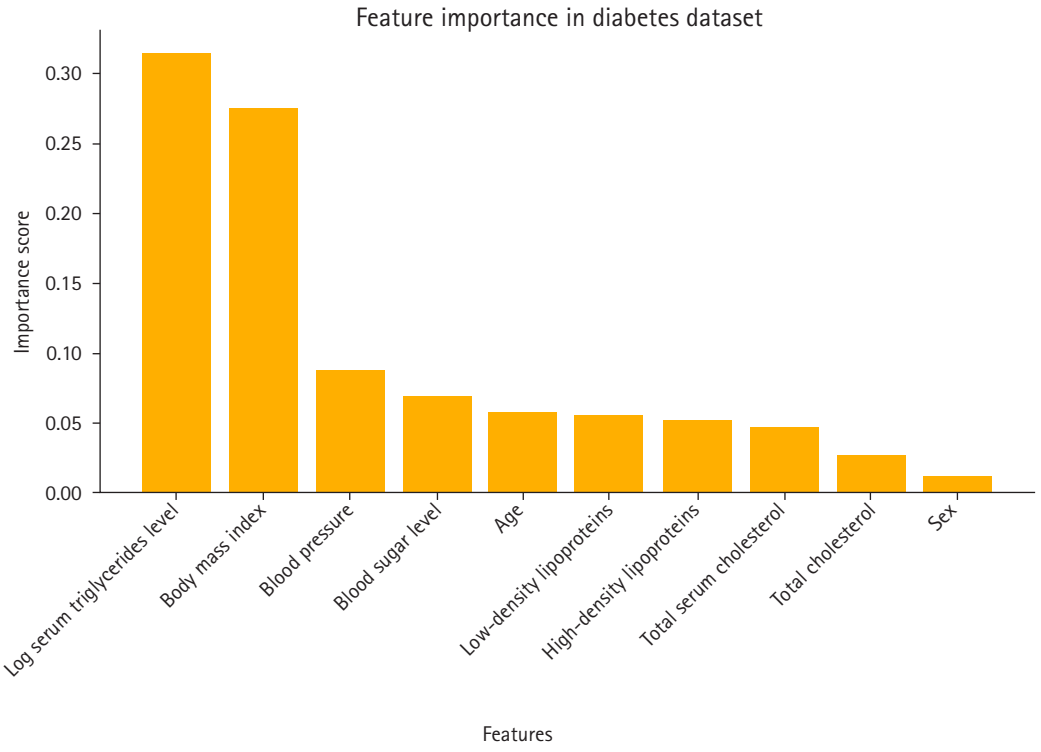

Fig. 1. Feature importance in the Scikit-learn diabetes dataset.

Z-score normalization, which improved the stability and convergence of the machine learning models.

To address class imbalance in the training set, SMOTE with a sampling strategy of 0.6 was first applied to generate synthetic samples for the minority class. Subsequently, RUS with a strategy of 0.66 reduced the number of majority class samples. The 0.66 ratio was chosen based on the new class distribution after applying SMOTE, ensuring that the final majority-to-minority ratio reached approximately 2:1. These resampling techniques resulted in a final class ratio of approximately 1:2 (minority:majority), achieving improved balance without excessively inflating the minority class or discarding too much majority class information.

Finally, the dataset was examined for missing values and extreme outliers. Since none were detected, no additional imputation or filtering was applied.

Class distribution analysis

Fig. 2 illustrates the impact of SMOTE and RUS on class balance. After resampling, the original imbalance was reduced from approximately 1:3.4 to a more balanced 1:2 ratio, leading to improved training data distribution.

Before resampling, the training set included 89 high-risk (minority) and 264 low-risk (majority) samples. After applying SMOTE (0.6) and RUS (0.66), the class distribution was adjusted to 158 high-risk and 239 low-risk samples, resulting in a 1:1.5 ratio.

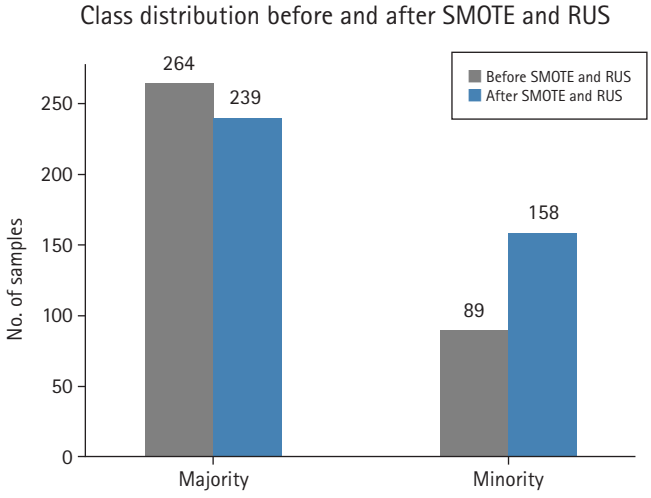

Fig. 2. Class distribution before and after synthetic minority oversampling technique (SMOTE) and random undersampling (RUS).

Outcome variables

Model outcomes were evaluated using the accuracy and area under the curve (AUC) metrics.

Study size

All data in the diabetes dataset were utilized for training; no sample size estimation was performed.

Feature-based ensemble modeling

To enhance interpretability and reduce overfitting, feature importance was first computed using a random forest classifier trained on the resampled dataset. It is important to note that the random forest used within the proposed feature-based ensemble model is conceptually distinct from the standalone random forest model used as a baseline. While the baseline random forest was trained on the original dataset using all features simultaneously, the ensemble model comprises multiple random forest classifiers trained on selected 2-feature subsets from the resampled (SMOTE+RUS) dataset.

Features were ranked based on their importance scores using the mean decrease in impurity criterion. The top-ranked features were then used to construct multiple 2-feature subsets. Based on these scores, the top 5 features were selected to form all possible pairwise combinations (n = 10). Each 2-feature subset was used to train a separate random forest classifier, resulting in a total of 10 base learners.

These individual models were combined using a soft voting ensemble strategy [7]. Each model contributed its predicted class probabilities, which were averaged to yield the final classification. This soft voting approach, which averaged probabilities across all base learners and selecting the class with the highest average, enabled the ensemble to capture diverse patterns across feature pairs while maintaining robust generalization performance.

Random forest was chosen as the base classifier for several reasons. First, compared to deep learning models, random forest offers greater interpretability by providing feature importance analysis, which is particularly valuable in medical applications. Second, the small sample size (442 samples) and inherent class imbalance make the dataset prone to overfitting; random forest is known for its robustness under such conditions. Third, as an ensemble method itself, random forest works synergistically with the higher-level soft voting structure, contributing to stable and consistent performance.

SMOTE and RUS were applied solely to the training data, while the test data remained in its original, non-augmented form (with only standardization applied). This ensured that performance evaluations reflected the model's ability to generalize to unseen, real-world distributions rather than to synthetic, balanced data—a crucial evaluation strategy to avoid overestimating model performance.

Comparative models

Three resampling-based techniques were included for performance comparison: SmoteENN, balanced random forest, and SMOTE combined with Tomek Links. These methods are widely adopted to address class imbalance in medical data classification tasks due to their strong empirical performance and interpretability.

SmoteENN integrates oversampling with data cleaning by removing borderline and noisy samples after synthetic instances are generated [8]. A balanced random forest applies RUS to each bootstrap sample to maintain class balance within decision trees [7]. SMOTE+Tomek Links combines oversampling with a noise-reduction step that eliminates overlapping examples from different classes [9].

These 3 methods were implemented under the same experimental conditions as the other models, with the same Q3 binarization threshold, an 80:20 stratified split, and Z-score normalization applied consistently to ensure fairness in comparison. As a result, any observed performance differences can be attributed to the modeling strategies rather than preprocessing variations.

Furthermore, to evaluate the performance of the proposed feature-based ensemble model, we implemented 10 baseline classification models: logistic regression, random forest, gradient boosting, support vector machine (SVM), k-nearest neighbors (KNN), fully connected neural network (FCNN), deep neural network (DNN), recurrent neural network (RNN), long short-term memory, and wide & deep models.

Ten traditional deep learning and machine learning models were trained on the original, imbalanced dataset—without resampling (i.e., no SMOTE or RUS)—to assess their performance under realistic data conditions. Preprocessing included standard Z-score normalization, and the target variable was binarized using the Q3 (75th percentile) threshold consistently across all models.

For the deep learning models, architectures were designed using TensorFlow/Keras with common configurations (e.g., 2–3 dense layers with ReLU activations, dropout for regularization, and a sigmoid output layer). Training was conducted over 50–100 epochs with early stopping as appropriate. Traditional machine learning models were implemented using Scikit-learn with default hyperparameters, except for SVM, which utilized a radial basis function kernel and probability estimation.

Rather than training a single model on all features simultaneously, 2-feature subsets were created and separate random forest classifiers were trained on each subset. This technique reduced noise interference and mitigated overfitting while leveraging soft voting to aggregate predictions from individual models, thereby enhancing generalization.

Evaluation metrics

Model performance was evaluated using accuracy and AUC, with a particular focus on the minority (high-risk) class—the primary interest of this study.

Statistical methods

No additional statistical analyses were performed beyond the evaluation of accuracy and AUC.

Results

Model performance comparison

Table 1 summarizes the accuracy scores of 14 different models. The feature-based ensemble model achieved an accuracy of 0.8764. Although accuracy alone may not fully capture model performance in imbalanced data, it remains a useful baseline metric for overall classification. Fig. 3 presents a horizontal bar chart comparing AUC scores across all models.

To complement the performance metrics summarized in Fig. 2, Figs. 4–7 and supplementary figures (Supplement 2) illustrate a model-wise comparison of AUC scores. This visualization provides an intuitive overview of each model's discriminative ability, highlighting that the feature-based ensemble model achieved an AUC of 0.9227. Other models, such as balanced random forest, FCNN, and DNN, also demonstrated relatively high AUC values,

Table 1. Comparison of accuracies of 14 models

Model	Accuracy
Feature-based ensemble model	0.8764
Balanced random forest	0.8764
Fully connected neural network	0.8700
SMOTE+Tomek Links	0.8652
K-nearest neighbors	0.8427
Logistic regression	0.8346
Support vector machine	0.8346
Long short-term memory	0.8300
Deep neural network	0.8202
Recurrent neural network	0.8202
SmoteENN	0.8202
Random forest	0.8195
Gradient boosting	0.8195
Wide & deep	0.8090

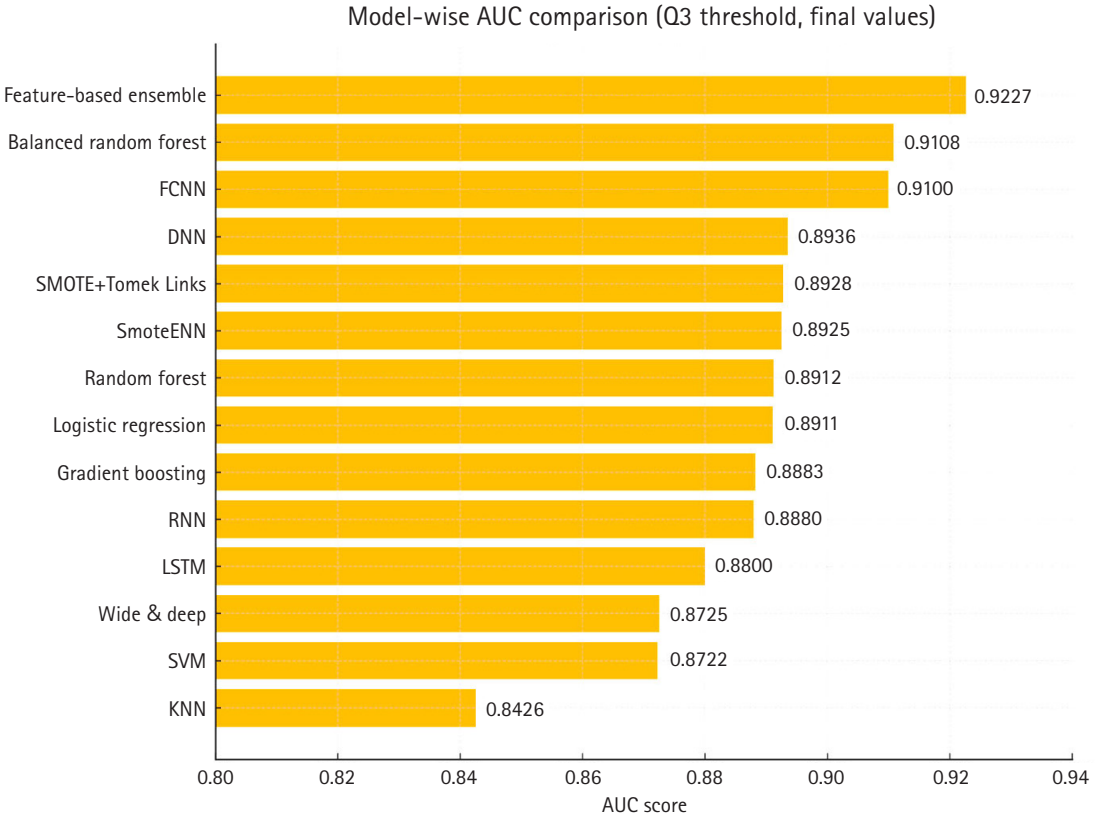

Fig. 3. Comparison of the area under the curve across 14 models. AUC, area under the curve; FCNN, fully connected neural network; DNN, deep neural network; RNN, recurrent neural network; LSTM, long short-term memory; SVM, support vector machine; KNN, k-nearest neighbors.

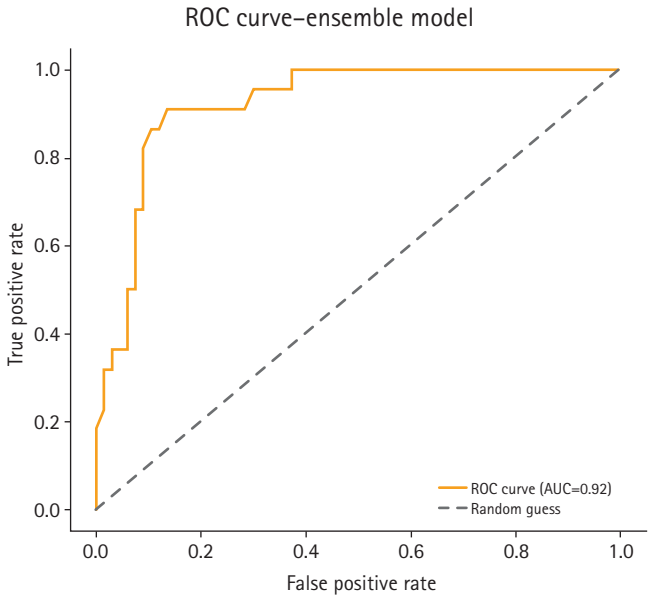

Fig. 4. Receiver operating characteristic (ROC) curve of the feature-based ensemble modeling in this study. AUC, area under the curve.

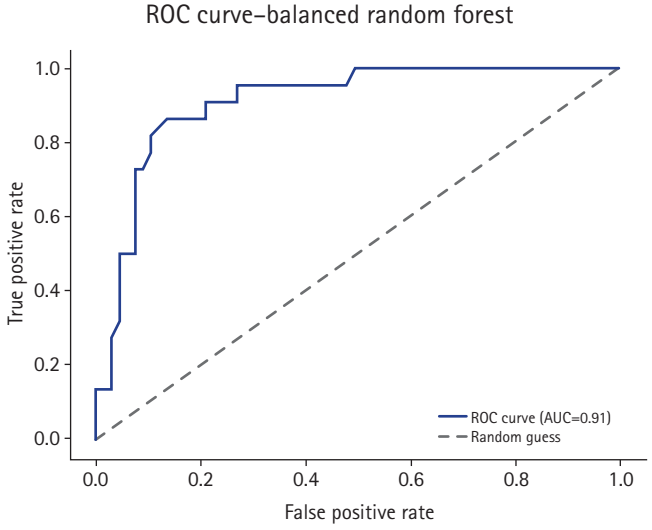

Fig. 5. Receiver operating characteristic (ROC) curve of the balanced random forest model. AUC, area under the curve.

while k-nearest neighbors showed the lowest. This figure reinforces the tabulated metrics by emphasizing the relative ranking in terms of AUC performance.

Discussion

Key results

The feature-based ensemble model and balanced random forest

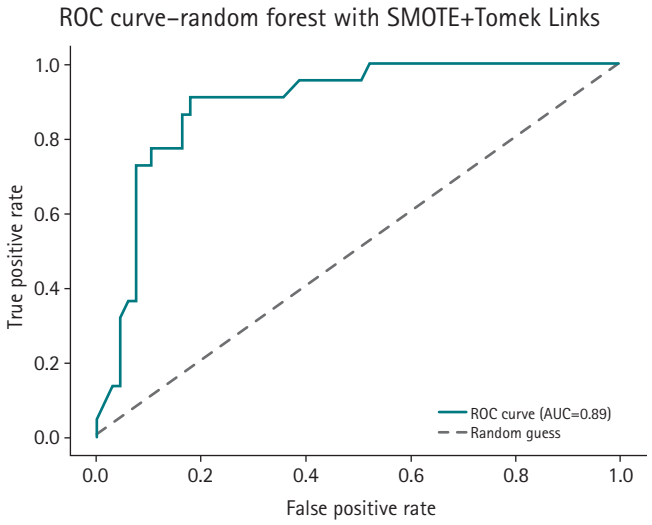

Fig. 6. Receiver operating characteristic (ROC) curve of the SMOTE+Tomek Links model. AUC, area under the curve.

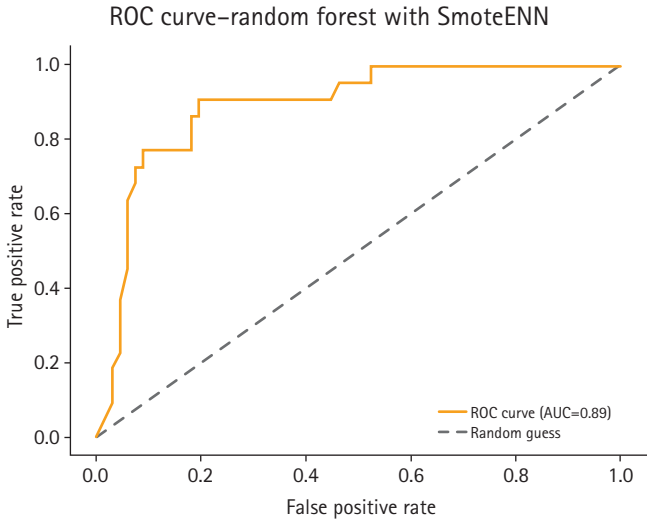

Fig. 7. Receiver operating characteristic (ROC) curve of the SmoteENN model. AUC, area under the curve.

achieved the highest accuracy of 0.8764, followed by the fully connected neural network (0.8700) and SMOTE+Tomek Links (0.8652). Notably, the feature-based ensemble model demonstrated a superior AUC of 0.9227, confirming its effectiveness.

Interpretation

The high AUC score further supports the ensemble model's strong discriminative power, particularly in distinguishing high-risk individuals. These results underscore the effectiveness of integrating SMOTE, RUS, and feature-based ensemble modeling in enhancing both robustness and interpretability—especially in

small, imbalanced medical datasets.

Although deep learning models such as DNN and RNN achieved relatively high AUC scores, they were not adopted as the primary approach in this study, owing to their requirement for large datasets and limited interpretability. In contrast, the random forest offers strong performance, robustness with small sample sizes, and useful feature importance analysis, making it more suitable for our proposed ensemble framework.

This study emphasized AUC due to its relevance to imbalanced classification problems. While accuracy can be misleading in skewed datasets, AUC captures the model's ability to discriminate between classes across a range of thresholds, making it especially suitable for evaluating models in clinical prediction tasks where correctly identifying the minority (high-risk) class is crucial.

To validate the proposed method, we compared its performance against 3 widely adopted resampling-based approaches for imbalanced classification: SmoteENN, balanced random forest, and SMOTE combined with Tomek Links. These methods are frequently cited in recent literature and are considered standard benchmarks in medical data analysis.

Under identical preprocessing and evaluation conditions, the proposed feature-based ensemble model demonstrated comparable or superior performance relative to all 3 baseline methods. This suggests that the ensemble approach offers a compelling, empirically grounded alternative for handling class imbalance, particularly in the small and structured datasets common in healthcare applications.

Comparison with previous studies

Previous studies addressing small data imbalance with the present model remain limited. Salmi et al. [1] noted in their review that, while deep learning is underexplored for structured medical data due to small sample sizes and model complexity, hybrid approaches combining sampling with machine learning models show promise. They discussed how techniques like SMOTE can augment small datasets, thereby improving performance in disease prediction tasks. Rather et al. [10] in 2024 examined how small, imbalanced datasets can benefit from fine-tuning pretrained models, whereas this study leveraged the interpretability of the random forest. These findings align with the findings of Mujahid et al. [11] in 2024 on the efficacy of oversampling in small datasets. Their work compared oversampling techniques such as SMOTE, SVM-smote, borderline SMOTE, k-means SMOTE, and ADASYN on small, imbalanced datasets—for example, twitter sentiment data. Although not exclusively focused on deep learning, the study evaluated these methods with both machine learning and deep learning models and demonstrated improved performance on small datasets (e.g., hundreds of samples) after balancing. Overall, the findings suggest that oversampling enhances deep model consistency, particularly when sample sizes are limited, as validated through k-fold cross-validation.

Strength

This study highlights the effectiveness of combining SMOTE, RUS, and feature-based ensemble learning in managing class imbalance. Unlike traditional methods, this approach improves minority class recall while maintaining overall model accuracy. These improvements are particularly valuable in domains where accurate predictions for the minority class are critical, such as in healthcare and fraud detection.

Limitations

Despite its advantages, our approach has several limitations. First, the computational complexity increases due to the multiple model training steps, although overall performance remained comparable across models. Second, while the feature-based ensemble model enhances generalization, additional optimization is necessary to ensure efficiency when scaling to larger datasets. Furthermore, SMOTE may introduce synthetic samples that do not fully represent real data variations, potentially leading to model biases.

A critical concern is the risk of overfitting when an excessive number of synthetic samples are generated; if the minority class is expanded too much, the model may learn patterns that do not generalize well to unseen data, thus reducing real-world performance. To mitigate this issue, careful tuning of the sampling ratio and validation with independent datasets is essential.

Clinical implications

The method proposed in this study, which integrates SMOTE, RUS, and feature-based ensemble learning, has proven effective in addressing class imbalance in diabetes prediction models. Moreover, this approach is applicable to other medical research fields beyond diabetes. For instance, in cancer prediction, early-stage cancer patients comprise only a small fraction of the total patient population, causing traditional machine learning models to struggle with accurate predictions. By applying the proposed method, the accuracy of predictions for early-stage cancer patients can be improved, thereby aiding early diagnosis.

Suggestion for further studies

Future research should explore expanding the study to larger datasets and diverse application domains to validate the generalizability of the findings. Additionally, integrating hybrid approaches

that combine cost-sensitive learning with ensemble modeling could further balance interpretability and performance.

Conclusion

This study presents a novel approach that combines SMOTE, RUS, and feature-based ensemble learning using the random forest to address the data imbalance problem. Experimental results confirm that this approach significantly enhances predictive accuracy and recall for minority class instances while maintaining overall model robustness.

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Authors' contributions

All work was done by Younseo Jang.

Conflict of interest

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

Funding

None.

Data availability

Files are available from https://scikit-learn.org/stable/datasets/toy_dataset.html#diabetes-dataset

Dataset 1. Diabetes dataset with information on 442 patients.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/MVSFHY

Supplement 1. Python code for all the machine learning and deep learning methods. It is also available on GitHub, https://github.com/YounseoJang/diabetes-imbalance-ensemble.

Supplement 2. Receiver operating characteristic curves for the 10 traditional deep learning or machine learning models.

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e33
https://doi.org/10.12771/emj.2025.00087

Ewha Medical Journal

Comparative evaluation of deep learning architectures, including UNet, TransUNet, and MIST, for left atrium segmentation in cardiac computed tomography of congenital heart diseases

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Purpose: This study compares 3 deep learning models (UNet, TransUNet, and MIST) for left atrium (LA) segmentation of cardiac computed tomography (CT) images from patients with congenital heart disease (CHD). It investigates how architectural variations in the MIST model, such as spatial squeeze-and-excitation attention, impact Dice score and HD95.

Methods: We analyzed 108 publicly available, de-identified CT volumes from the ImageCHD dataset. Volumes underwent resampling, intensity normalization, and data augmentation. UNet, TransUNet, and MIST models were trained using 80% of 97 cases, with the remaining 20% employed for validation. Eleven cases were reserved for testing. Performance was evaluated using the Dice score (measuring overlap accuracy) and HD95 (reflecting boundary accuracy). Statistical comparisons were performed via one-way repeated measures analysis of variance.

Results: MIST achieved the highest mean Dice score (0.74; 95% confidence interval, 0.67–0.81), significantly outperforming TransUNet (0.53; P<0.001) and UNet (0.49; P<0.001). Regarding HD95, TransUNet (9.09 mm) and MIST (5.77 mm) similarly outperformed UNet (27.49 mm; P<0.0001). In ablation experiments, the inclusion of spatial attention did not further enhance the MIST model's performance, suggesting redundancy with existing attention mechanisms. However, the integration of multi-scale features and refined skip connections consistently improved segmentation accuracy and boundary delineation.

Conclusion: MIST demonstrated superior LA segmentation, highlighting the benefits of its integrated multi-scale features and optimized architecture. Nevertheless, its computational overhead complicates practical clinical deployment. Our findings underscore the value of advanced hybrid models in cardiac imaging, providing improved reliability for CHD evaluation. Future studies should balance segmentation accuracy with feasible clinical implementation.

Keywords: Cardiovascular diseases; Congenital heart defects; Deep learning; Heart atria; Precision medicine

Introduction

Background

Accurate segmentation of cardiac structures in chest computed tomography (CT) images is critical for the diagnosis, treatment planning, and management of cardiovascular diseases. Segmentation enables detailed visualization of cardiac anatomy, facilitating the identification of congenital defects, structural anomalies, and pathological changes. Precise segmentation also provides essential information for surgical preparation and interventional procedures, improving surgical outcomes and patient safety. Furthermore, quantitative analyses such as ventricular volume measurements, ejection fraction calculations, and assessments of wall motion are crucial for evaluating cardiac function and diagnosing conditions like heart failure.

Deep learning has revolutionized medical image segmentation, with architectures such as UNet becoming foundational due to their capacity to capture global context and fine-grained details. UNet, introduced by Ronneberger et al. [1] in 2015, follows an encoder-decoder structure with skip connections, yielding remarkable performance across diverse biomedical imaging tasks. However, UNet has limitations in modeling complex spatial rela-

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Received: February 26, 2025 Revised: March 20, 2025 Accepted: April 10, 2025

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tionships and long-range dependencies. To address these shortcomings, advanced models such as TransUNet and MIST have been developed. TransUNet incorporates transformer modules to effectively capture global contextual information [2], while MIST employs multi-scale feature integration strategies and attention mechanisms to further refine segmentation [3]. Collectively, these models represent an evolution from traditional convolutional neural networks (CNNs) toward state-of-the-art hybrid approaches, emphasizing integrated local and global feature representations to increase segmentation accuracy. These 3 models are detailed in Supplement 1.

Despite advancements in deep learning-based segmentation, few studies have comprehensively evaluated state-of-the-art models specifically for cardiac chamber segmentation of chest CT images. Accurate delineation of the left atrium (LA) provides valuable insights into chamber volumes, wall thickness, and morphological abnormalities, which greatly inform early diagnosis and clinical decision-making. However, manual segmentation remains labor-intensive and susceptible to inter-observer variability, underscoring the need for robust and automated segmentation solutions.

Although individual studies have separately investigated UNet, TransUNet, or MIST for cardiac segmentation, a direct comparison of their performance on a common dataset has not yet been reported. While numerous reports have addressed whole-heart or multi-chamber segmentation, this research specifically focuses on the LA, addressing the gap in the literature by evaluating these models to clarify their strengths and limitations. The selection of UNet, TransUNet, and MIST reflects the progressive evolution of segmentation model design.

Objective

The primary objective of this study is to compare the effectiveness of 3 deep learning models—UNet, TransUNet, and MIST—for segmentation of the LA in cardiac CT images of patients with congenital heart diseases (CHDs). Specifically, the study aims to evaluate segmentation performance using the Dice score and HD95 metrics. Additionally, various architectural modifications within the MIST model, including multi-scale attention, skip connections, and hybrid encoders, are investigated to understand their impacts on segmentation accuracy.

Methods

Ethics statement

This study was exempt from institutional review board approval because it used only publicly available, de-identified data. Specifically, we utilized the ImageCHD dataset [4], which contains no personally identifiable information and is licensed under the Apache License 2.0. The dataset was obtained from Kaggle (https://www.kaggle.com/) and used under its open-access terms.

Study design

This is a prediction study involving a comparative analysis of the performance of deep learning models for LA segmentation in cardiac CT images. It follows the TRIPOD+AI reporting guidelines for studies of deep learning models in medical applications (development or prediction), available at: https://www.tripod-statement.org/.

Setting

The ImageCHD dataset comprises 3-dimensional (3D) CT images acquired using a Siemens Biograph 64 scanner (Siemens Healthineers) from 110 patients with CHDs, aged from 1 month to 40 years, predominantly between 1 month and 2 years. The dataset documentation did not specify recruitment dates or the participating institution.

Participants

Participant-specific information was not provided, as all data were de-identified.

Data sources

This study employed the ImageCHD dataset, sourced from Kaggle, for evaluating the UNet, TransUNet, and MIST models. The dataset includes 110 high-quality 3D CT scans annotated with segmentation labels for cardiac structures such as the LA, left ventricle, right ventricle, right atrium, myocardium, aorta, and pulmonary arteries. Designed to facilitate segmentation of major heart structures critical for CHD classification, it contains volumetric scans with LA labels to support the assessment of segmentation accuracy. As an open-source resource, this dataset is dedicated to individuals diagnosed with CHD and emphasizes cardiac structures, particularly the LA. Its annotations facilitate rigorous evaluation and comparative analysis of segmentation models, thereby advancing automated diagnostics in CHD imaging. Of the 110 CT images provided, 108 were included in this study due to quality concerns with 2 images.

Outcome variables

Segmentation performance was quantified using the Dice score (reflecting overall overlap) and HD95 (reflecting boundary accuracy).

Study size

All available cases in the dataset meeting the quality criteria were extracted and utilized; thus, no formal sample size estimation was performed.

Data preprocessing

Data preprocessing was performed to ensure consistency and improve model performance. Two-dimensional (2D) samples were extracted by slicing the 3D H×W×D arrays along the depth axis (D), yielding a series of 2D H×W images for subsequent analysis. The 2D samples were normalized to a standard intensity range (for all models) and augmented to improve model generalizability. The 2D slices were normalized to a standard intensity range (for all models) and augmented to improve model generalizability. Data augmentation included random rotations (±10°), translations (up to 5% width/height shifts), and zooming (±10%) for UNet, applying nearest-neighbor interpolation for image data and constant filling (value of 0) for segmentation masks.

Deep learning models

Experimental setup

All models (UNet, TransUNet, and MIST) were trained on image volumes resized to 512×512 pixels. Experiments were conducted on Google Colab (Google LLC) using NVIDIA GPUs (L4 for UNet and TransUNet, T4 and L4 for TransUNet, and Tesla V100 for MIST; NVIDIA Corp.) and implemented with PyTorch (https://pytorch.org/). TensorBoard (https://www.tensorflow.org/) was employed to monitor training progress, visualizing losses, and performance metrics in real time across epochs.

Model configurations

For UNet, a weighted focal categorical cross-entropy loss function was utilized with an Adam optimizer and a learning rate of 1×10^{-5}. For TransUNet, the loss function combined categorical cross-entropy and Dice coefficient loss; the optimizer was stochastic gradient descent with an initial learning rate of 0.001, subsequently reduced by a factor of 0.1 during training.

The MIST model employed a combined Dice loss and binary cross-entropy loss to manage class imbalance, optimized using Adam with an initial learning rate of 0.001 and similarly reduced by a factor of 0.1 throughout training. Additionally, the MIST decoder was tested with and without the spatial squeeze-and-excitation attention module (SSAM), employing attention-based or concatenation strategies, as depicted in Fig. 1. Output aggregation strategies included summing feature maps from decoder blocks or exclusively utilizing the final feature map (Fig. 1).

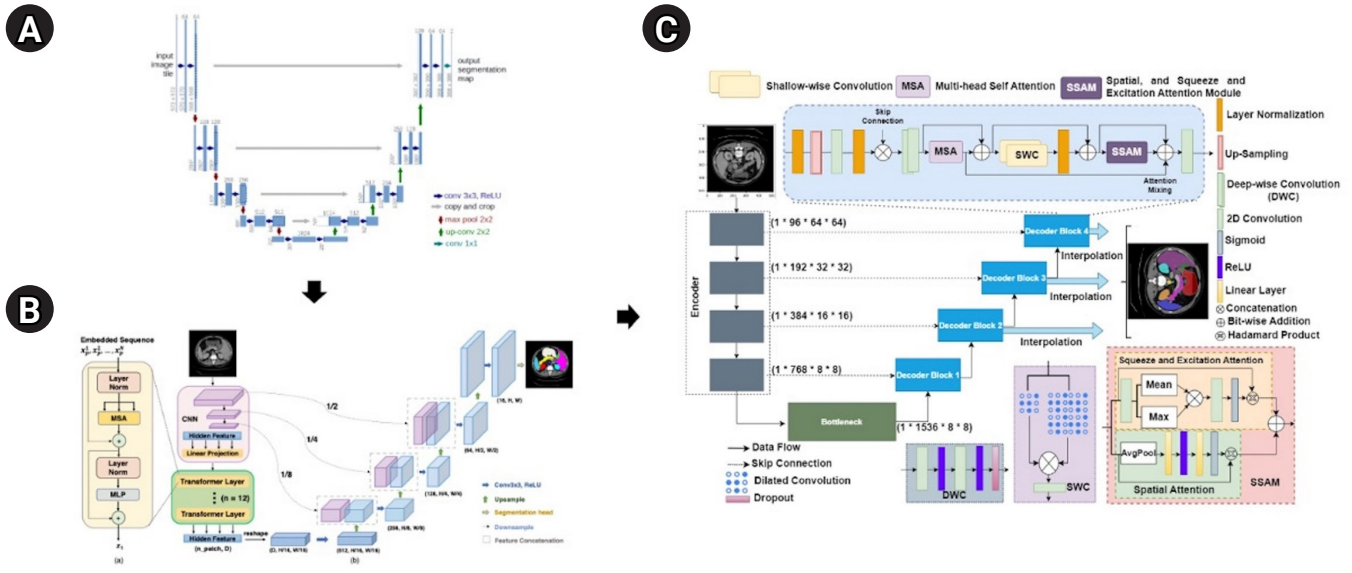

Fig. 1. Model architectures. (A) UNet (Ronneberger et al. [1], 2015), (B) TransUNet (Chen et al. [2], 2021), and (C) MIST (Rahman et al. [3], 2023). A brief overview explains the evolution of transformer and UNet hybrid models. The UNet architecture introduced symmetric encoder-decoder paths with skip connections. TransUNet is built upon UNet by adding transformer attention mechanisms to the encoder, and MIST, a recent model, further integrates multiple attention mechanisms and optimized skip connections to improve performance.

Training and evaluation

All 3 models (UNet, TransUNet, and MIST) were trained and evaluated using the ImageCHD dataset. Of the 108 cases, 97 were partitioned randomly into training (approximately 80%, 77 cases) and validation (approximately 20%, 20 cases) sets. The remaining 11 cases served as an independent test set for all models. Consistent data splits were maintained across models to ensure fairness in performance comparisons. For evaluation, slices were preprocessed to 512×512 pixels and normalized uniformly.

Performance metrics

Segmentation performance was evaluated using the Dice score and HD95 metrics. The Dice score quantifies the overlap between predicted segmentation and ground truth labels, providing a value between 0 (no overlap) and 1 (perfect overlap). It is mathematically defined as follows:

$$DICE(X,Y) = \frac{2 * |X \cap Y|}{|X| + |Y|} \quad (1)$$

Where X represents the set of predicted pixels and Y the set of ground truth pixels.

The HD95 metric measures the distance between the boundaries of the predicted and true segmentations. It calculates the 95th percentile of the Hausdorff distance to reduce sensitivity to outliers, thus providing a robust measure of segmentation boundary accuracy. HD95 was calculated on 2D slices without applying in-plane voxel spacing (0.25 mm), and thus the reported values are in pixel units rather than millimeters. The out-of-plane spacing (0.5 mm) was not relevant since only axial 2D slices were used.

$$HD95 = max(d_X, d_Y) \quad (2)$$

The software and tools utilized included Python 3.8 (https://www.python.org/), deep learning frameworks PyTorch 1.8 and TensorFlow, and supplementary libraries including NumPy, SciPy, scikit-learn, and OpenCV for image processing. The source code for this study is provided in Supplement 2.

Statistical methods

The metrics (Dice score and HD95) were statistically compared using one-way repeated measures analysis of variance for paired samples. DBSTAT 5 for Windows (DBSTAT Co.) was used for statistical analysis.

Results

Participants/dataset

The ImageCHD dataset is an open-source collection of cardiac CT images available on Kaggle, specifically focused on patients with CHDs (Dataset 1).

Model performance

Detailed loss performance data are available in Dataset 2. Example comparisons of qualitative segmentation outcomes across different model architectures are illustrated in Fig. 2.

Dice scores for the 3 deep learning models are presented in Fig. 3. The results, including Bonferroni's multiple comparison, demonstrate that MIST achieved the highest performance, with a mean Dice score of 0.74 (95% confidence interval [CI], 0.67–

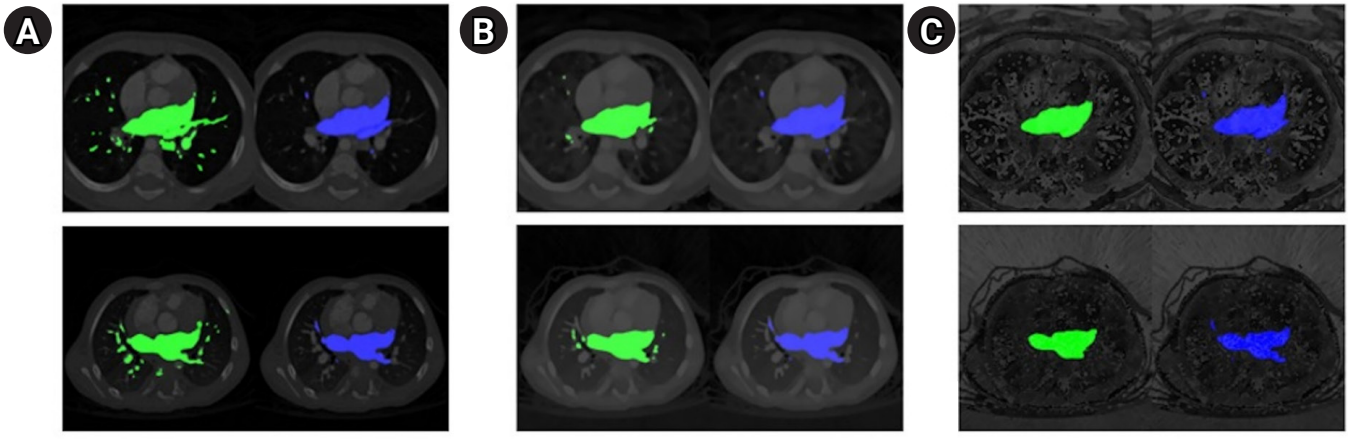

Fig. 2. Qualitative segmentation outcomes across model architectures. The ground truth (blue) is presented in the second column, while the predicted segmentation (green) is shown in the left column. (A) UNet, (B) TransUNet, and (C) MIST. Detailed results, including dice scores and 95th percentile of the Hausdorff distance (HD95) values for individual computed tomography scans, are provided in Supplements 3 and 4.

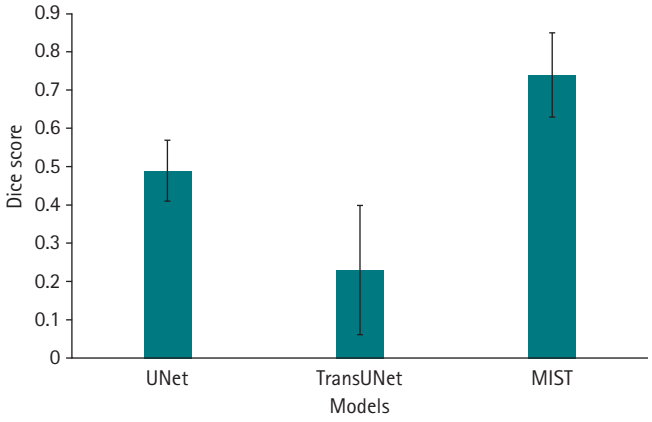

Fig. 3. Dice scores for 11 left atrial cardiac computed tomography images segmented by UNet, TransUNet, and MIST models.

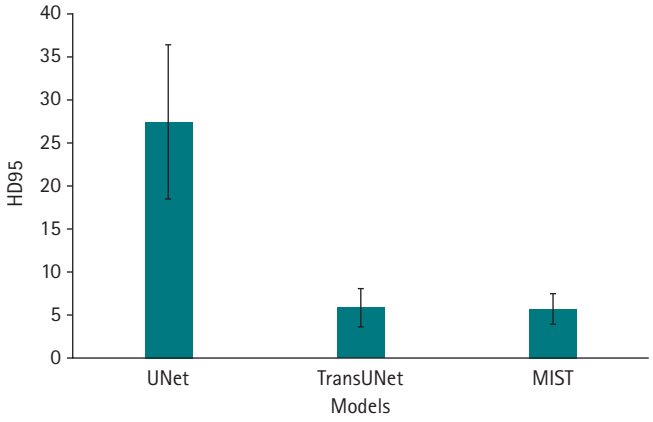

Fig. 4. 95th percentile of the Hausdorff distance (HD95) values for 11 left atrial cardiac computed tomography images segmented by UNet, TransUNet, and MIST models.

0.81), significantly outperforming the other 2 models (P < 0.001). UNet (mean, 0.49; 95% CI, 0.43–0.55) outperforemed TransUNet (mean, 0.23; 95% CI, 0.12–0.34) (P < 0.001) (Supplement 3). Regarding HD95, which measures boundary accuracy, both TransUNet (mean, 5.85 mm; 95% CI, 4.32–7.38 mm) and MIST (mean, 5.77 mm; 95% CI, 4.55–6.98 mm) significantly outperformed UNet (mean, 27.49 mm; 95% CI, 21.45–33.53 mm) (P < 0.001). The difference in HD95 performance between TransUNet and MIST was not statistically significant (P = 1.0000) (Fig. 4, Supplement 4).

Results from ablation experiments, in which individual parameters were varied systematically, are presented in Figs. 5 (Supplement 5) and 6 (Supplement 6), with measured results available in Dataset 3. The MIST model, incorporating SSAM within the decoder blocks and without sum output heads, exhibited a higher Dice score (mean, 0.74; 95% CI, 0.67–0.81) compared to variations employing sum output heads (mean, 0.26; 95% CI, 0.17–0.35). However, the performance of the MIST model without SSAM (mean, 0.66; 95% CI, 0.57–0.76) was comparable to that of MIST with SSAM (Fig. 5, Supplement 5). For HD95, the MIST variant with SSAM and without sum output heads also demonstrated superior performance (mean, 5.77 mm; 95% CI, 4.55–6.98 mm) relative to versions employing sum output heads (mean, 35.88 mm; 95% CI, 29.43–42.32 mm). The HD95 of MIST without SSAM (mean, 5.59 mm; 95% CI, 4.35–6.82 mm) was comparable to the MIST model with SSAM and without sum output heads (Fig. 6, Supplement 6). Example images in Fig. 7 illustrate how the best-performing model accurately delineated the atrial borders and exhibited fewer false predictions in distant anatomical regions.

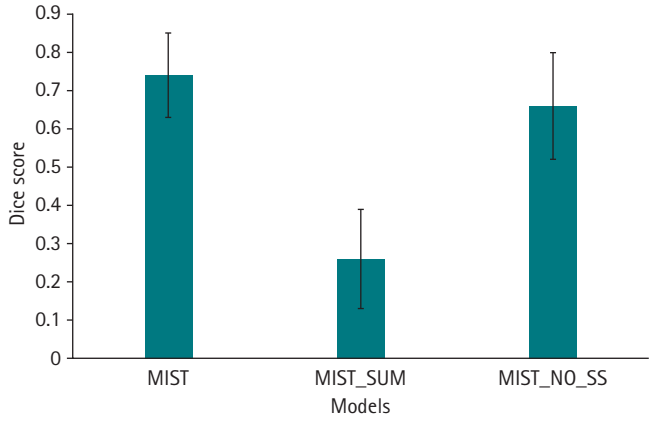

Fig. 5. Dice scores for 11 left atrial cardiac computed tomography images segmented by MIST with or without spatial squeeze-and-excitation attention module (SSAM) or sum output heads.

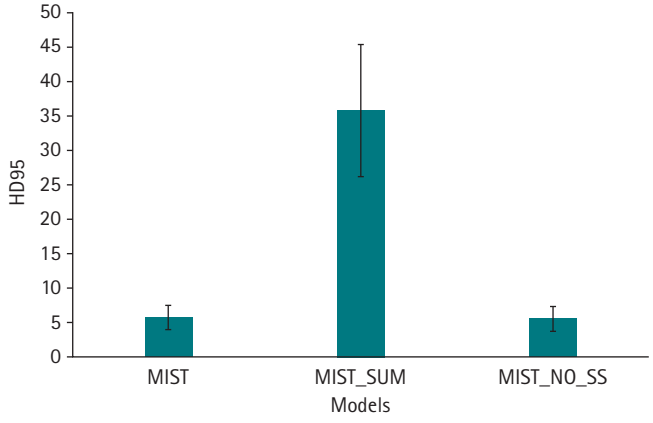

Fig. 6. 95th percentile of the Hausdorff distance (HD95) values for 11 left atrial cardiac computed tomography images segmented by MIST with or without spatial squeeze-and-excitation attention module (SSAM) or sum output heads.

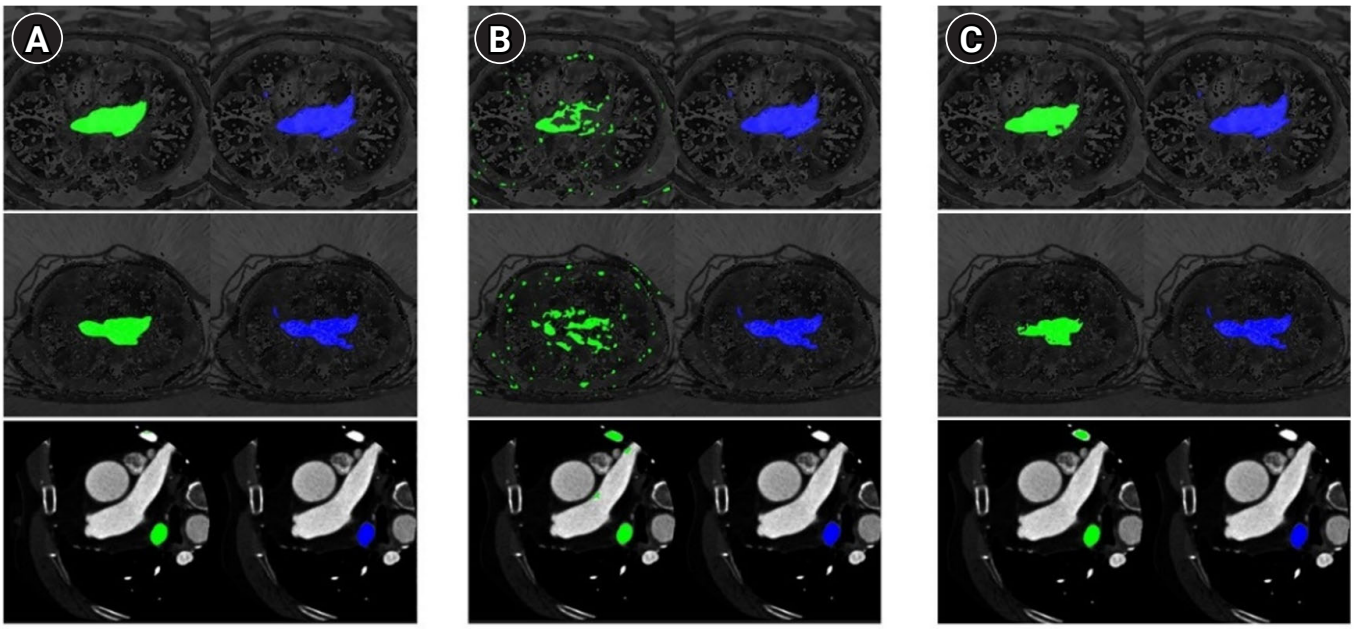

Fig. 7. Qualitative outcomes for MIST variants. The ground truth (blue) is presented in the second column, while the predicted segmentation (green) is shown in the left column. Starting from left: spatial squeeze-and-excitation attention module (SSAM) without summation (A), SSAM with summation (B), and no attention mixer within the decoder and no summation (C).

Discussion

Key results

MIST achieved the highest mean Dice score (0.74; 95% CI, 0.67–0.81), significantly outperforming TransUNet (0.23) and UNet (0.49). TransUNet and MIST also outperformed UNet in HD95, with no significant difference. Parameter variations revealed that incorporating SSAM into MIST while omitting sum output heads yielded the highest Dice score and the lowest HD95 value.

Interpretation

These results suggest that MIST's optimized skip connections and multi-scale attention mechanisms are beneficial for capturing the subtle anatomical variations involved in LA segmentation in children with CHD. Although TransUNet achieved HD95 performance comparable to MIST, the Dice score is generally regarded as the primary indicator of segmentation quality, since it averages performance across the entire region and is less sensitive to localized outliers. In comparison, HD95—while valuable for assessing boundary precision, especially when accurate delineation is critical—can be more sensitive to outliers. Consequently, unless an application explicitly demands extremely precise boundary localization (e.g., surgical planning), overall overlap as captured by the Dice score is typically prioritized. We therefore recommend MIST as the preferred overall segmentation method for LA structures in CHD imaging.

The failure of SSAM to improve LA segmentation performance likely arises from several factors, including the nature of the target anatomy [5], the design of the attention module [6], and the existing capabilities of the MIST model. Accurate segmentation of the LA, a small structure with subtle boundaries, depends on capturing fine-grained features that generic spatial attention mechanisms may overlook.

Comparison with previous studies

Although numerous investigations have applied attention mechanisms or transformer-based architectures to medical image segmentation, a direct comparison of UNet, TransUNet, and MIST on a single, consistent dataset for LA segmentation in cardiac CT images of patients with CHD remains absent. To our knowledge, no prior research has comprehensively benchmarked these 3 models head-to-head under uniform experimental conditions, making this study novel in its direct evaluation.

We therefore must contextualize our findings against earlier studies that employed attention-based or transformer-based architectures for similar segmentation tasks, despite differences in target anatomy or datasets. Our findings align with existing research indicating that CNN-based models such as UNet struggle to capture long-range dependencies due to their fixed receptive fields

[1]. Transformer-based architectures like TransUNet address this limitation by integrating global context [2], although they frequently face challenges in preserving spatial precision, particularly for small or irregular structures [7,8].

Hybrid models such as MIST, which combine multi-scale attention with refined skip connections, have demonstrated superior segmentation performance [3]. Our results further support recent findings suggesting that such attention-driven hybrid architectures outperform both CNN-only and transformer-only models [9].

Unlike prior studies focusing on multi-chamber heart segmentation, our work provides a dedicated evaluation of LA segmentation, offering key insights into which architectural elements most benefit this task.

Strengths

Unlike prior studies that segment multiple chambers or the entire heart, this work targets LA segmentation, enabling a detailed and clinically relevant analysis. Beyond overall performance, we dissect key architectural components, particularly the SSAM and the multi-head attention mechanisms in MIST, thus contributing to future advancements. Specifically, we performed additional ablation experiments to clarify their contributions and inform the model optimization process.

Limitations

This study had several limitations. First, the overall dataset was relatively small, potentially limiting model generalizability. Expanding analysis to larger and more diverse datasets will be crucial for further validation.

Second, the data may have introduced bias due to limitations on scanner diversity and representation of patient populations.

Third, although we used L4 GPUs to ensure consistent hardware conditions, performance and runtime metrics may differ on other GPU architectures. Future studies should normalize batch sizes, standardize training epochs, and benchmark across uniform hardware environments to control for computational heterogeneity.

Finally, some methodological limitations should be noted. Potential biases in study design and dataset selection may have influenced our results, despite efforts to maintain evaluation consistency. Moreover, we did not apply probability calibration to segmentation outputs. Future work should explore calibration techniques such as Platt scaling or isotonic regression to improve confidence estimation and support safer clinical adoption.

Clinical implications

With its high segmentation accuracy, MIST can assist radiologists in detecting subtle LA abnormalities and improve risk assessment for atrial fibrillation. As a pre-screening tool, MIST automates initial LA segmentation and reduces radiologists' workload during final review. We recommend integrating MIST into hospital picture archiving and communication systems (PACS), thus enabling streamlined deployment and improving accessibility in real-world clinical settings.

Suggestion for further studies

To advance the clinical utility and robustness of deep learning-based cardiac segmentation, future research should prioritize the following directions:

First, optimize the MIST framework to reduce computational and memory requirements while preserving segmentation accuracy, enabling real-time clinical deployment.

Second, extend segmentation tasks to other anatomical regions (such as the brain, lungs, and additional cardiovascular structures) to evaluate broader applicability. Conduct multicenter validation using data from diverse clinical settings to improve generalizability across populations and imaging protocols.

Third, develop techniques to increase transparency and foster trust among clinicians, such as attention maps and saliency analysis.

Fourth, explore semi-supervised or unsupervised learning approaches to minimize reliance on large labeled datasets, lowering barriers to adoption in resource-constrained environments.

Fifth, investigate scalable deployment strategies, including integration with PACS and cloud-based platforms, to streamline workflows and facilitate clinical use.

Conclusion

MIST demonstrated superior dice score performance compared with UNet and TransUNet, while also achieving improved boundary accuracy (lower HD95) relative to UNet. These promising results are primarily attributable to its integration of multi-scale attention mechanisms and optimized skip connections. Validation confirmed the model's robustness across various conditions, although its higher computational complexity poses challenges for real-time clinical deployment without further optimization. Overall, this study advances automated cardiac segmentation by incorporating hybrid attention mechanisms, providing insights for future model development.

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Authors' contributions

Conceptualization: SY, JC. Data curation: SY, JC. Methodology/formal analysis/validation: SY, JC. Project administration: JC. Funding acquisition: not applicable. Writing–original draft: SY, JC. Writing–review & editing: SY, JC.

Conflict of interest

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

Funding

None.

Data availability

Files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/VGUF3Z

Dataset 1. The ImageCHD dataset used in this study is publicly available on Kaggle under the Apache 2.0 License: https://www.kaggle.com/datasets/xiaoweixumedicalai/imagechd.

Dataset 2. Dice score and HD95 values for each cardiac CT sample across MIST, UNet, and TransUNet. HD95, 95th percentile of the Hausdorff distance; CT, computed tomography.

Dataset 3. Dice score and HD95 values obtained by MIST with or without SSAM and with or without sum output heads. HD95, 95th percentile of the Hausdorff distance; SSAM, spatial squeeze-and-excitation attention module.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/4EWPMF

Supplement 1. Detailed explanations of the UNet, TransUNet, and MIST models.

Supplement 2. Full source code for UNet, TransUNet, and MIST, including training scripts, model architectures, and evaluation procedures, which is also available at https://github.com/janet-rgb/CardiacSegmentation.

Supplement 3. One-way repeated measures analysis of variance (paired sample) for dice scores across the 3 models.

Supplement 4. One-way repeated measures analysis of variance (paired sample) for HD95 values across the 3 models.

Supplement 5. One-way repeated measures analysis of variance (paired sample) for dice scores of MIST variations (with/without SSAM and with/without sum output heads).

Supplement 6. One-way repeated measures analysis of variance (paired sample) for HD95 values across MIST variations (with/without SSAM and with/without sum output heads).

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eISSN: 2234-2591
Open Access

Original article

Ewha Med J 2025;48(2):e34
https://doi.org/10.12771/emj.2025.00332

Ewha Medical Journal

Cyclic dual latent discovery for improved blood glucose prediction through patient–provider interaction modeling: a prediction study

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Purpose: Accurate prediction of blood glucose variability is crucial for effective diabetes management, as both hypoglycemia and hyperglycemia are associated with increased morbidity and mortality. However, conventional predictive models rely primarily on patient-specific biometric data, often neglecting the influence of patient–provider interactions, which can significantly impact outcomes. This study introduces Cyclic Dual Latent Discovery (CDLD), a deep learning framework that explicitly models patient–provider interactions to improve prediction of blood glucose levels. By leveraging a real-world intensive care unit (ICU) dataset, the model captures latent attributes of both patients and providers, thus improving forecasting accuracy.

Methods: ICU patient records were obtained from the MIMIC-IV v3.0 critical care database, including approximately 5,014 instances of patient–provider interaction. The CDLD model uses a cyclic training mechanism that alternately updates patient and provider latent representations to optimize predictive performance. During preprocessing, all numeric features were normalized, and extreme glucose values were capped at 500 mg/dL to mitigate the effect of outliers.

Results: CDLD outperformed conventional models, achieving a root mean square error of 0.0852 on the validation set and 0.0899 on the test set, which indicates improved generalization. The model effectively captured latent patient–provider interaction patterns, yielding more accurate glucose variability predictions than baseline approaches.

Conclusion: Integrating patient–provider interaction modeling into predictive frameworks can increase blood glucose prediction accuracy. The CDLD model offers a novel approach to diabetes management, potentially paving the way for artificial intelligence-driven personalized treatment strategies.

Keywords: Blood glucose; Biometry; Deep learning; Diabetes mellitus; Hyperglycemia; United States

Introduction

Background

Accurate prediction of blood glucose variability is crucial for effective diabetes management and the prevention of acute complications. In the management of diabetes, predicting blood glucose levels can help prevent hypoglycemia and hyperglycemia [1]. Forecasting drops in glucose levels allows individuals to take preventive measures before they experience dizziness, confusion, or loss of consciousness. Similarly, forecasting hyperglycemic episodes enables timely adjustments in clinical treatments. Early detection and prediction of rising glucose levels aid in adjusting insulin dosages and other clinical treatments [2]. Blood sugar prediction facilitates proactive management, reducing health risks caused by consistently high blood glucose levels, such as heart stroke, nephropathy, neuropathy, retinopathy, and foot problems [3]. Moreover, predictive tools can alleviate patients' anxiety about sudden blood sugar fluctuations. Providing early warnings and reducing the burden of constant monitoring can offer greater flexibility in settings such as the work environment.

Patient–provider interactions influence factors such as medication adherence, dietary choices, and lifestyle modifications [4]. A substantial body of research indicates that variations among healthcare providers may significantly contribute to differences in

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Received: March 30, 2025 Revised: April 3, 2025 Accepted: April 7, 2025

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the prognoses of patients with similar initial conditions [5]. However, traditional prediction models rely primarily on patient-specific biometric indicators and often overlook external influences, including interactions with physicians and other healthcare providers.

To address this gap, our study applies the previously proposed Cyclic Dual Latent Discovery (CDLD) model to the task of prediction based on medical data that include information regarding healthcare providers, leveraging the Cyclic Dual Latent Discovery (CDLD) model [6]. CDLD is a deep learning framework designed to capture the interrelationship between 2 entities to predict the result of their interaction. In contrast to previous artificial intelligence (AI) studies that have not fully incorporated patient–healthcare provider interactions, the CDLD model integrates these relationships to establish a more comprehensive and clinically significant predictive framework for biological parameters such as blood glucose levels.

Objectives

Our work aimed to bridge the gap between individual biometric predictors and a more holistic interaction-based approach. Specifically, we trained the CDLD model to predict the blood glucose levels of patients in the intensive care unit (ICU). The CDLD model discovered latent triats for both patients and providers and used them to predict final blood glucose levels, with predictive accuracy assessed via RMSE on the held-out test set.

Methods

Ethics statement

This study was exempt from institutional review board approval because it used only de-identified, publicly available data (from the MIMIC-IV dataset) [7].

To access this database, we gained credentialed access by completing the "CITI Data or Specimens Only Research" training course and signing the "PhysioNet Credentialed Health Data Use Agreement 1.5.0." Personal patient identifiers were removed in accordance with Health Insurance Portability and Accountability Act regulations, and random integer IDs were assigned instead. Free text data were checked for protected health information and de-identified if needed.

Study design

This is a retrospective cohort study designed to predict glucose levels based on patient–provider relationships. It was described according to the TRIPOD-AI reporting guidelines for articles on deep learning in the medical field (development or prediction), available at https://www.tripod-statement.org/.

Setting

Dates and times were randomly shifted, with a single date shift applied for each patient to maintain internal consistency and different shifts for distinct patients to ensure de-identification.

Participants

The study participants were patients admitted to either the emergency department or the ICU between 2008 and 2019 at Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States. Patients were excluded if they were younger than 18 years at their first visit or if they were on an established list of vulnerable groups requiring enhanced protection.

Data source

The data used in this study were obtained from PhysioNet, specifically from the MIMIC-IV project [7]. After restructuring the data for easier analysis—including de-normalizing, removing audit trails, and reorganizing—de-identification was conducted to maintain patient privacy.

The MIMIC-IV v3.0 dataset was grouped into 2 modules: hosp and icu. The hosp module is sourced from the hospital-wide electronic health record, and the icu module is derived from MetaVision, the in-ICU clinical information system. The full database includes a total of 364,627 individuals who experienced 546,028 unique hospitalizations and 94,458 unique ICU stays.

Within the hosp module, the records from the 546,028 hospitalizations correspond to 223,452 unique individuals. The dataframes include patient demographics (patients), hospitalizations (admissions), and intra-hospital transfers (transfers); laboratory measurements (labevents, d_labitems); microbiology cultures (microbiologyevents, d_micro); provider orders (poe, poe_detail); medication administration (emar, emar_detail); medication prescription (prescriptions, pharmacy); hospital billing information (diagnoses_icd, d_icd_diagnoses, procedures_icd, d_icd_procedures, hcpcsevents, d_hcpcs, drgcodes); online medical record data (omr); and service-related information (services). Provider information was also included in the provider table, with a deidentified character string present in the provider_id column.

The icu module contains data from 94,458 unique ICU stays experienced by 65,366 unique individuals. The dataframes include intravenous and fluid inputs (inputevents), ingredients for these inputs (ingredientevents), patient outputs (outputevents), procedures (procedureevents), information documented as a date or time (datetimeevents), and other charted information (chartevents). All events tables contain a stay_id column, enabling identi-

fication of the ICU patient associated with the stay, as well as an itemid column to identify the concept documented in d_items. The caregiver table, referencing the care provider who collected the data as a deidentified integer (caregiver_id), was also included and linked to all event tables.

From this database, we extracted a subset that suited our objectives. The dataset consisted of 5,014 patients. The sample included 2,696 male and 2,304 female patients, with an average age of 63.173. Individual provider identification codes were used to examine the impact of the patient–provider relationship on blood glucose levels.

We focused on patients who had at least one abnormal blood glucose reading during their hospital stay. The highest blood glucose level during the stay was extracted as a feature of the included patients, and the last measured blood glucose level was extracted as a feature representing the result of the interaction (object of prediction) to evaluate the variability of blood glucose based on ICU management. Consequently, the patient entity included an identification code (subject_id and hadm_id), 8 binary features (corresponding to age and gender), and one numerical feature (the highest blood glucose level during the stay). The provider entity consisted solely of an identification code. One numerical feature (the last measured blood glucose level) was used as the prediction target.

The dataset used in the study includes 5,001 glucose level measurements from 2,551 patients. Some data were excluded for training efficiency. Overall, 80% of the data were used for training, 10% for validation, and the remaining 10% for testing (Fig. 1).

Data preprocessing

To adapt the MIMIC-IV dataset for input into the CDLD model, we performed a series of preprocessing steps to appropriately structure patient and provider data. The dataset was organized into 3 main components as follows: first, patient data (user), which included demographic and clinical features such as gender, age (transformed into 6 categorical variables), and peak blood glucose levels; second, provider data (item), represented by de-identified provider IDs; and third, interaction data (rating), capturing patient–provider interactions, with the final recorded blood glucose level as the target variable.

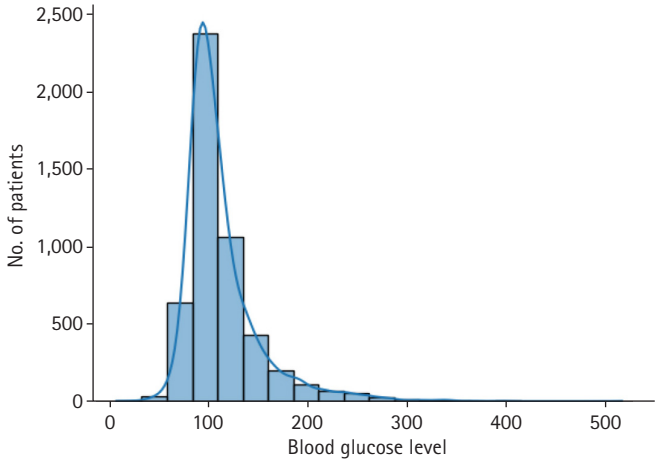

Fig. 1. Distribution of the last measured blood glucose level, the prediction target of this study.

We extracted patient features from the "admissions" and "patients" datasets. Certain attributes, such as race, language, type of insurance, and admission details, were excluded due to cost concerns and because they only minimally affect changes in blood glucose levels. Accordingly, the subject_id, hadm_id, gender, and age of each patient were retained as patient features.

By examining the "labevents" dataset, we selected patients with abnormal blood glucose levels (≥ 125 mg/dL) because these patients are closely monitored and regulated. In the ICU, continuous blood glucose level regulation is considered standard [8,9]. Thus, by extracting the highest and the last blood glucose levels for these patients, we can capture the interaction between medical providers and patients in regulating blood glucose levels.

Beyond clinical considerations, we preprocessed the datasets to improve the accuracy and efficiency of CDLD processing. Rather than using age directly, we categorized patient ages into 10-year intervals, converting these into 6 Boolean features. Similarly, gender was represented with 2 Boolean features. All other numerical features were scaled to a range between 0 and 1 to improve processing accuracy. Because outliers with blood glucose levels over 500 mg/dL influenced the overall standardized values and hindered effective standardization, data points exceeding 500 were assigned a value of 500. As a result, the glucose levels used in the study were limited to a range of 125 to 500 mg/dL and normalized to a numerical range of 0 to 1. Predictions of glucose level were also expressed as normalized values.

For provider data, only the "provider_id" was available from the "poe" dataset. This alphanumeric code was assigned to physicians in the hospital to differentiate them without revealing personal information. To improve the accuracy of CDLD processing, these codes were converted into numerical values. The dataframes used in the study are presented in Supplement 1.

When extracting the provider for each patient during training of the CDLD model, the most frequently recorded provider during the hospital stay was regarded as the interacting provider because no information was available about the providers' clinical hierarchy. We thus assumed that the provider with the most interactions was the one who had the most influence. Although de-

tailed information about physicians was not available and may have been insufficient to reflect each latent feature, we assumed that the CDLD model could appropriately discover the latent features of each provider_id through cyclic training.

Outcome variables

The primary outcome variable was the blood glucose level measured at discharge. Patient variables included sex, age, and peak blood glucose level during hospitalization, while provider was considered as an additional variable. These variables were treated as latent traits.

Study size

All target patient data were extracted from the database; thus, no sample size estimation was performed. For the CDLD deep learning model, a sample of 5,001 participants was deemed sufficient for evaluation based on the estimation power of the model, which delivers performance regardless of the case number.

Deep learning models

CDLD is a recently proposed modeling approach that employs 2 neural networks in a cyclic training loop to uncover hidden (latent) traits of 2 interacting entities from their interaction data. The principle is that each interaction between 2 entities (e.g., a user and an item in a recommender system) contains intrinsic information about both. In the CDLD architecture, one network learns a representation for entity A (e.g., the patient), while a second network learns a representation for entity B (e.g., the provider). These networks are then trained alternately in a cyclic fashion. Through this iterative refinement process, each network's output informs the training of the other, allowing the model to capture complex non-linear relationships more effectively than traditional single-pass or linear models.

In our implementation, the 2 entity types in CDLD are patients (analogous to users) and healthcare providers (analogous to items). The model discovers latent attributes for each patient and provider based on their clinical encounter data, and it cyclically updates these representations to predict the outcome of their interaction—in this case, the patient's post-care blood glucose level. By leveraging CDLD in this manner, we directly incorporate the patient–provider relationship into the prediction framework, yielding a more comprehensive model than one based only on patient features.

To evaluate the effectiveness of the CDLD model in predicting blood glucose variability, we conducted a series of experiments using patient–provider interaction data. The experimental setup involved data preprocessing, model training, and performance evaluation.

We implemented the CDLD model to learn latent representations for patients and providers. As described above, the model consists of 2 neural sub-networks (patient-latent discoverer and provider-latent discoverer) that are trained alternately in a cyclic fashion; the output of one network helps update the other. Key training hyper-parameters were as follows: a latent vector dimension of 32, a batch size of 1,024, and training for 10 epochs (with 10 sub-epochs per cyclic iteration). We used the Adam optimizer and optimized a mean square error (MSE) loss, with root mean square error (RMSE) used as the evaluation metric. To improve generalization, we applied data augmentation by adding small random noise (magnitude 0.1) to input features, effectively increasing the training dataset size fivefold.

Evaluation metrics

The data were split into training (80%), validation (10%), and test (10%) sets. Model performance was evaluated primarily based on RMSE for blood glucose predictions. RMSE was computed for the validation and test sets to assess generalization, as well as for the training set to monitor potential overfitting.

Statistical methods

No statistical tests were performed, aside from error measurement using RMSE.

Results

When discovering the patient latent, the model achieved a training loss of 0.0066 and a validation loss of 0.0089. The RMSE for the training set was 0.0813, and the validation RMSE was 0.0941 (Fig. 2). When discovering the provider latent, the model exhibited a training loss of 0.0066 and a validation loss of 0.0088. The RMSE for the training set was 0.0810, while the validation RMSE was 0.0937 (Fig. 3).

In synthesizing these latent representations to predict blood glucose variability, the model achieved a training loss of 0.0037 and a validation loss of 0.0066. The training set RMSE was 0.0336, the validation RMSE was 0.0852, and the test RMSE was 0.0898 (Fig. 4).

These values are sufficiently low, indicating strong predictive accuracy of the CDLD model regarding blood glucose variability.

Discussion

Key results

The final predictor that synthesized the latent representations

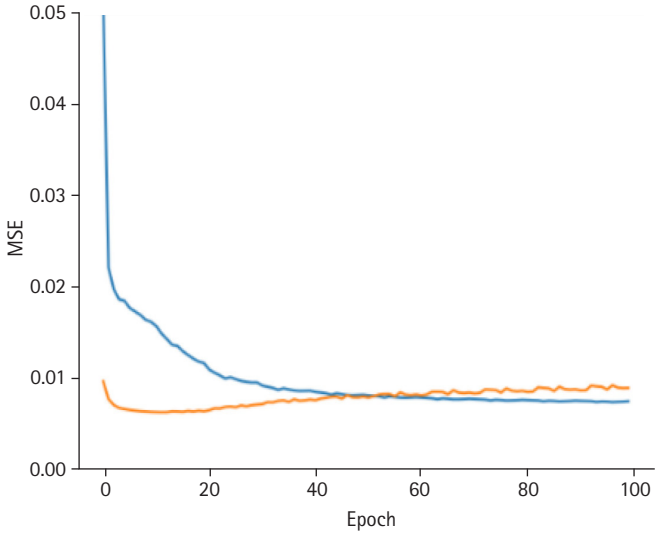

Fig. 2. Graphs depicting the results for model performance when discovering the patient latent. The blue line represents the "train loss," while the orange line denotes the "valid loss." The x-axis is labeled "epoch," indicating the number of training iterations, and the y-axis is labeled mean squared error ("MSE"), which measures the prediction error of the model.

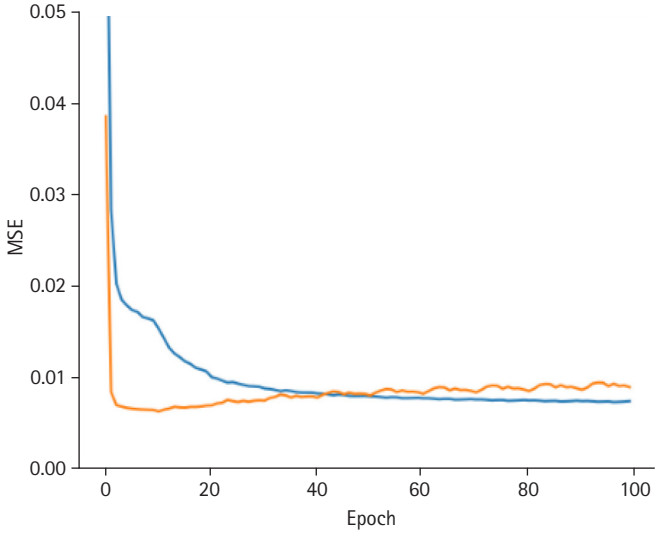

Fig. 3. Graphs depicting the results for model performance when discovering the provider latent. The blue line represents the "train loss," while the orange line denotes the "valid loss." The x-axis is labeled "epoch," indicating the number of training iterations, and the y-axis is labeled mean squared error ("MSE"), which measures the prediction error of the model.

achieved a test RMSE of 0.0898, indicating strong predictive performance. These values are sufficiently low to indicate that the model achieved a balanced and practically significant level of predictive accuracy. Although the slightly higher validation RMSE

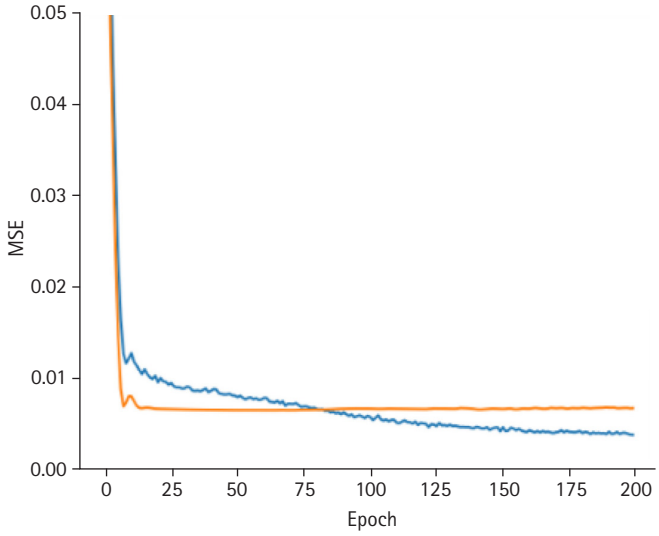

Fig. 4. Graphs depicting the results for model performance when predicting the last measured glucose level. The blue line represents the "train loss," while the orange line denotes the "valid loss." The x-axis is labeled "epoch," indicating the number of training iterations, and the y-axis is labeled mean squared error ("MSE"), which measures the prediction error of the model.

suggests minor overfitting, it remains within an acceptable range, supporting the model's generalizability.

Interpretation

The results demonstrate that the CDLD model effectively captured patient–provider interactions and provided accurate predictions for blood glucose variability. This confirms its viability for enhancing diabetes management strategies based on patient-provider interactions. The findings indicate a well-fitted model that maintains good performance while exhibiting a modest increase in error on unseen data.

Moreover, the CDLD framework handles data with a non-linear structure, overcoming the constraints of single entity-based datasets. This capability enables applications beyond individual predictions, such as evaluating healthcare provider performance and improving patient management strategies. By incorporating provider-related variables, the model can assist in assessing medical quality and optimizing treatment methodologies.

Comparison with previous studies

Traditional blood glucose prediction models predominantly utilize biometric data from individual patients [4], which limits their capacity to incorporate external influences such as physician intervention. The Multi-source Irregular Time-Series Transformer (MITST) uses a transformer-based hierarchical model to inte-

grate data and capture temporal dynamics, thereby eliminating manual feature engineering [10]. Evaluated on the eICU database (including 200,859 ICU stays across 208 hospitals) [11], it outperforms the baseline by 1.7% in area under the receiver operating characteristic curve (AUROC) and by 1.8% in area under the precision-recall curve (AUPRC) ($P < 0.001$). For hypoglycemia, it achieves an AUROC of 0.915 and an AUPRC of 0.247 [12]. Huang et al. [13] in 2023 proposed a graph-based hierarchical network to learn from multiple patients' continuous glucose monitoring data, significantly reducing prediction error by approximately 30% compared to standard models. In critical care, Tang et al. [2] in 2022 reported an RMSE of about 15.8 mg/dL for post-insulin glucose. Outpatient models also perform well; the LSTM of Shao et al. [14] in 2024 achieved an AUROC above 0.97 for hypoglycemia across diabetes types, while the Glu-Ensemble for type 2 diabetes by Han et al. [15] in 2024 improved RMSE without patient-specific calibration. These advanced architectures consistently outperform traditional linear models, improving accuracy and sensitivity regarding glycemic events.

By leveraging entity-to-entity interactions, the CDLD enables a more comprehensive approach, explicitly modeling the relationships between patients and healthcare providers. This advancement facilitates a better understanding of how medical care influences elements of patients' medical status, such as blood glucose levels, beyond direct physiological factors.

Limitations

The primary limitation of this study arises from its use of minimal information. The research could not account for various aspects of the healthcare providers, making it nearly impossible to determine which aspects of patient–provider interactions contribute to fluctuations in glucose levels. This limitation could pose challenges in real-world implementations, as providing actionable feedback to healthcare providers based solely on this information would be difficult. Additionally, privacy concerns regarding medical personnel data present potential obstacles for practical application. Addressing these concerns will be crucial for broader adoption in clinical settings.

Clinical implications

Notably, the CDLD model can predict patients' glucose levels without requiring detailed information about the provider.

Proper management of patients' blood glucose levels is crucial, as hyperglycemia or hypoglycemia can adversely impact overall health by causing various complications, particularly among ICU patients [16]. Therefore, thorough monitoring and prediction of blood glucose fluctuations are essential for preventing both hyperglycemia and hypoglycemia [17]. With a more precise understanding of these fluctuations, clinicians can implement targeted interventions and better prepare to manage high-risk patients, ultimately reducing adverse outcomes. In some cases, overly strict glycemic control can be counterproductive; thus, it is essential to manage blood glucose levels carefully [18].

However, because each patient's condition can vary significantly, tailoring glucose management strategies remains challenging. By incorporating various factors into the CDLD model that affect glucose levels—including data on medical providers, which are often overlooked—clinicians can develop more effective strategies based on accurate predictions. Emerging evidence highlights the importance of personalized treatment for critically ill patients, and integrating diverse factors with precise prediction methods can further enhance these individualized therapies [19].

Predicting changes in glucose levels can also help optimize resource allocation [20]. Serving as an assistive tool for clinical judgment, accurate predictions enable early differentiation between severe and mild cases. This facilitates a more effective distribution of medical resources and personnel, such as ICU beds, ventilators, and intensive monitoring. Early identification of mild cases permits their management in general wards or intermediate care units, preventing unnecessary ICU admissions and reducing bottlenecks. This, in turn, can lower the costs associated with intensive care and contribute to a more sustainable healthcare system.

Predicted blood glucose levels can also support continuous monitoring and early intervention [8]. Detecting fluctuations early and implementing proactive measures can help mitigate the risk of complications, including infections, cardiovascular diseases, and other metabolic disorders. This can lead to improved prognosis and survival among ICU patients.

Generalizability

The results of this study should be interpreted in the context of the described limitations. However, the modeling approach used can be applied to electronic medical records from other medical institutions without difficulty. Since datasets containing information on healthcare providers are often highly sparse, this feature is expected to be useful for other datasets that lack comprehensive provider-related data.

Suggestion for further studies

Since deep learning models can assess the influence of each feature after training, we believe that expanding the dataset for CDLD could enable a more in-depth analysis.

Conclusion

The CDLD model accurately predicted ICU patients' blood glucose levels by incorporating not only patient-specific data but also healthcare provider information. This proof of concept highlights the value of modeling patient–provider interactions and demonstrates improved predictive performance compared to patient-only models. Future work should further validate this approach and explore how to interpret provider-related factors; nevertheless, our findings suggest that integrating provider interactions can enhance personalized diabetes management in critical care settings.

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Authors' contributions

Conceptualization: DR. Data curation: SYP, SK. Methodology, Formal analysis, Validation: SYP, SK. Project administration: DR. Writing-original draft: SYP, SK. Writing-review & editing: SYP, SK, DR.

Conflict of interest

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

Funding

None.

Data availability

Data can be extracted after approval from Physionet (https://physionet.org/).

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/4DTE3N

Supplement 1. Dataframes used in the study. The Cyclic Dual Latent Discovery source code executed is patented and therefore cannot be shared. For further questions, please contact the corresponding author.

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eISSN: 2234-2591
Open Access

Health statistics

Ewha Med J 2025;48(2):e35
https://doi.org/10.12771/emj.2025.00304

Ewha Medical Journal

Dementia-related death statistics in Korea between 2013 and 2023

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Purpose: This study aimed to analyze dementia-related death statistics in Korea between 2013 and 2023.
Methods: The analysis utilized microdata from Statistics Korea's cause-of-death statistics. Among all recorded deaths, those related to dementia were extracted and analyzed using the underlying cause-of-death codes from the International Classification of Diseases, 10th revision.
Results: The number of dementia-related deaths increased from 8,688 in 2013 to 14,402 in 2023. The crude death rate rose from 17.2 per 100,000 in 2013 to 28.2 per 100,000 in 2023, although the age-standardized death rate declined from 9.7 to 8.7 over the same period. The dementia death rate is 2.1 times higher in women than in men, and mortality among individuals aged 85 and older exceeds 976 per 100,000. By specific cause, Alzheimer's disease accounted for 77.1% of all dementia deaths, and by place, the majority occurred in hospitals (76.2%), followed by residential institutions including nursing homes (15.3%) in 2023.
Conclusion: The rising mortality associated with dementia, especially Alzheimer's disease, highlights a growing public health concern in Korea. These findings support the need for enhanced prevention efforts, improved quality of care, and targeted policies addressing the complexities of dementia management. It is anticipated that this empirical analysis will contribute to reducing the social burden.

Keywords: Cause of death; Alzheimer disease; Vascular dementia; International Classification of Diseases; Republic of Korea

Introduction

Background

Dementia is recognized as a major public health problem worldwide, and its prevalence is increasing as the population ages. In Korea, Alzheimer's disease—a primary form of dementia—rose from the 10th leading cause of death in 2013 to the 6th in 2023, representing 3.2% of all deaths [1]. Additionally, the annual cost of Alzheimer's disease treatment in Korea is approximately 2.3 trillion won [2]. The World Health Organization defines dementia as an umbrella term for several diseases that affect memory, cognition, and daily functioning [3]. Because dementia primarily affects the elderly, it leads to memory loss, cognitive decline, and behavioral disturbances. This not only imposes a heavy disease burden on patients but also significantly affects their families, making dementia both a public health and a social issue.

The study of dementia-related deaths is essential for effective clinical management and informed policymaking. Understanding the characteristics and trends of these deaths provides critical data to improve the quality of life for patients and their families.

Objectives

This study aimed to analyze the causes of death and related factors associated with dementia and to examine the death characteristics of dementia patients in Korea from 2013 to 2023.

Methods

Ethics statement

This study analyzed de-identified microdata produced by Statistics Korea; therefore, institutional review board approval or informed consent was not required.

Study design

This descriptive study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which is available at https://www.strobe-statement.org/.

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Received: March 18, 2025 Revised: March 23, 2025 Accepted: March 23, 2025

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Setting, participants, data source, and measurement

Microdata from Statistics Korea's cause-of-death statistics were used to analyze dementia-related mortality rates and death characteristics. These national official statistics are compiled by analyzing death certificates and 22 types of administrative data—including health insurance records and cancer registration data—for all deceased individuals. For the dementia analysis, the International Classification of Diseases, 10th revision codes F01 (vascular dementia), F03 (unspecified dementia), G30 (Alzheimer disease), and G31 (other degenerative diseases of the nervous system, not elsewhere classified) were utilized.

Bias

There was no bias in data collection and analysis.

Study size

The entire population of Korea was included. No sample size estimation was required.

Statistical methods

Descriptive statistics were employed to present the findings. Mortality was analyzed using the number of deaths, the crude mortality rate, and the age-standardized death rate—standardized to the 2005 mid-year population.

Results

Number of deaths and mortality rate due to dementia

In 2023, Korea recorded 14,402 dementia-related deaths, with a crude mortality rate of 28.2 per 100,000 population; dementia accounted for 4.09% of all deaths. In 2013, there were 8,688 dementia-related deaths with a mortality rate of 17.2 per 100,000. Both the number of deaths and the crude mortality rate have shown an increasing trend, with the 2022 mortality rate rising by 36.7% compared to the previous year (Supplement 1). The age-standardized death rate for dementia in 2023 was 8.7 per 100,000, following a decline from 2018 to 2021 and then an increase in 2022 (Fig. 1, Supplement 2).

Deaths due to dementia by sex and age

In 2023, dementia-related deaths in women numbered 9,737 vs. 4,665 in men. The mortality rate for women was 37.9 per 100,000—2.1 times higher than that for men (Table 1). Although the death rate remained minimal before the age of 50, it increased markedly beginning in the 70–74 age group, reaching 976.0 per 100,000 for those aged 85 and older. Mortality rates tended to rise with age. When analyzed by sex and age, the rate for men was higher until age 79, but for individuals aged 85 and older, women experienced a relatively higher rate (Table 2).

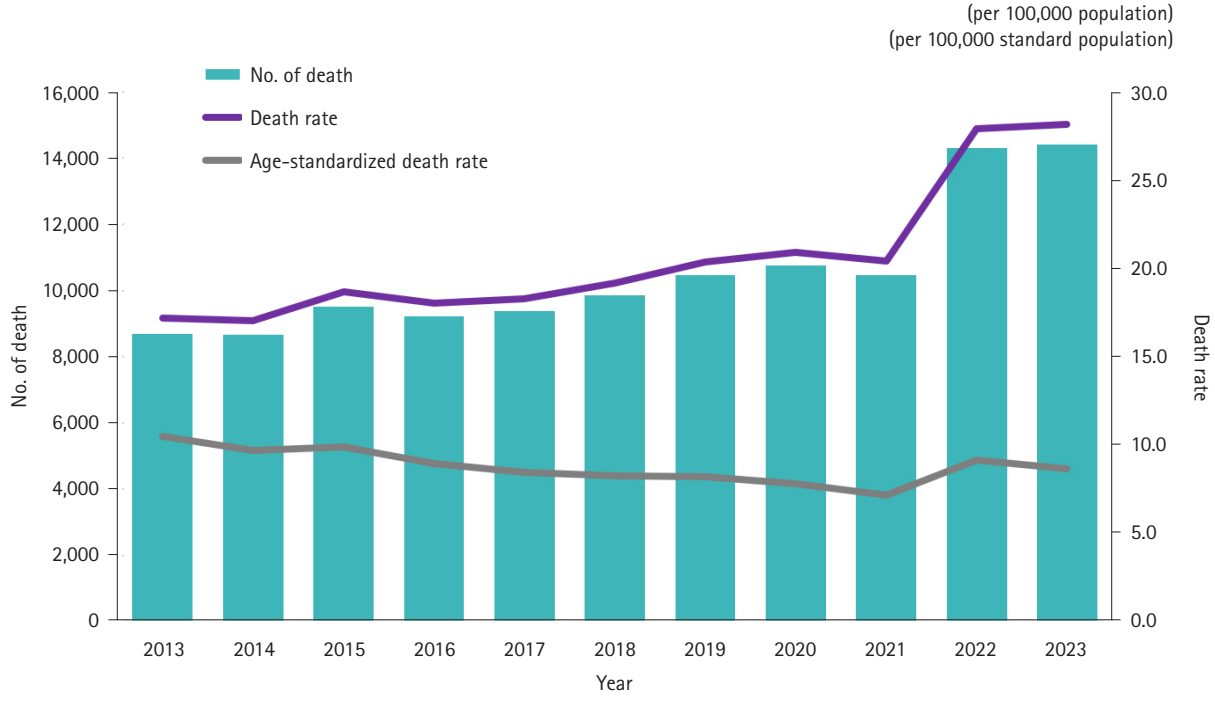

Fig. 1. Number of deaths, death rate, and age-standardized death rate due to dementia-related diseases between 2013 to 2023 in Korea.

Table 1. The number of dementia-related deaths and death rate by sex between 2013 and 2023

Year	No. of deaths (deaths)			Death rate (per 100,000 population)		
	Both sexes	Men	Women	Both sexes	Men	Women
2013	8,688	2,740	5,948	17.2	10.8	23.5
2014	8,663	2,625	6,038	17.1	10.3	23.8
2015	9,519	2,857	6,662	18.7	11.2	26.1
2016	9,223	2,883	6,340	18.0	11.3	24.8
2017	9,375	2,745	6,630	18.3	10.7	25.8
2018	9,847	3,049	6,798	19.2	11.9	26.5
2019	10,453	3,173	7,280	20.4	12.4	28.3
2020	10,747	3,396	7,351	20.9	13.3	28.6
2021	10,476	3,362	7,114	20.4	13.1	27.6
2022	14,301	4,455	9,846	27.9	17.4	38.3
2023	14,402	4,665	9,737	28.2	18.3	37.9

Table 2. The death rate due to dementia by sex and age group in 2023

Age group (yr)	Death rate (per 100,000 population)			Sex ratio (M/W)
	Both sexes	Men	Women	
Total	28.2	18.3	37.9	0.5
< 40	0.0	0.0	0.0	1.4
40–44	0.1	0.1	0.1	1.0
45–49	0.3	0.5	0.1	8.8
50–54	0.3	0.2	0.4	0.5
55–59	1.4	2.2	0.6	3.8
60–64	3.7	4.9	2.6	1.9
65–69	8.7	12.1	5.6	2.2
70–74	21.4	28.9	14.7	2.0
75–79	60.5	71.3	52.0	1.4
80–84	212.1	230.3	200.6	1.1
≥ 85	976.0	809.0	1,044.2	0.8

Mortality rate by specific cause of death due to dementia

In 2023, the mortality rate for Alzheimer's disease was 21.7, for unspecified dementia 5.4, for vascular dementia 0.7, and for other degenerative diseases of the nervous system 0.3. Since 2013, the mortality rate for vascular dementia has continuously declined from 1.9 to 0.7, whereas Alzheimer's disease has shown an increasing trend. In particular, the Alzheimer's mortality rate increased significantly from 15.6 to 22.7 in 2022 (Fig. 2). Among dementia-related deaths in 2023, Alzheimer's disease accounted for 77.1%, a notable rise from 49.7% in 2013.

Place of death due to dementia

In 2023, most dementia-related deaths occurred in medical facilities such as hospitals (76.2%), followed by residential institutions including nursing homes (15.3%), and homes (8.1%). In contrast, the overall distribution of deaths by place was 75.4% in medical facilities, 15.5% at home, and 5.9% in residential institutions.

Since 2013, hospital deaths have declined while home deaths have increased, with a marked change in trend beginning in 2018. Deaths in residential institutions have steadily risen from 10.8% in 2013 to 15.3% in 2023. In 2022, when dementia-related deaths surged, the proportion of hospital deaths decreased from 78.8% to 75.7% (Fig. 3).

Discussion

Key results

In 2023, the dementia death rate was 28.2 per 100,000 population, accounting for 4.09% of all deaths. Due to an aging population, dementia-related deaths have continued to increase, with a sharp rise observed in 2022—when many deaths were attributed to coronavirus disease 2019 (COVID-19), particularly the Omicron variant of severe acute respiratory syndrome coronavirus 2.

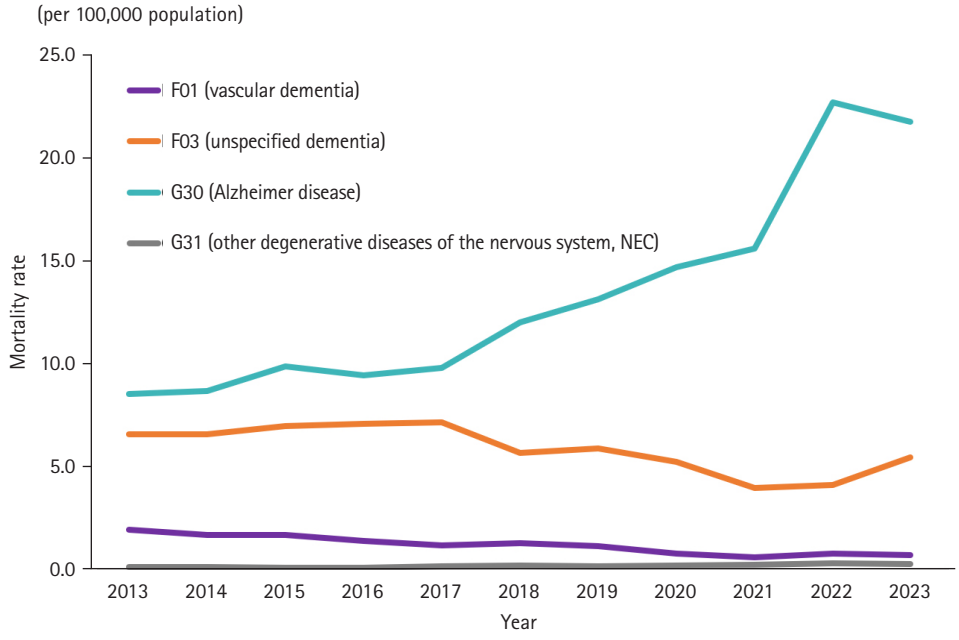

Fig. 2. Specific causes of death among dementia-related deaths between 2013 to 2023 in Korea. NEC, not elsewhere classified.

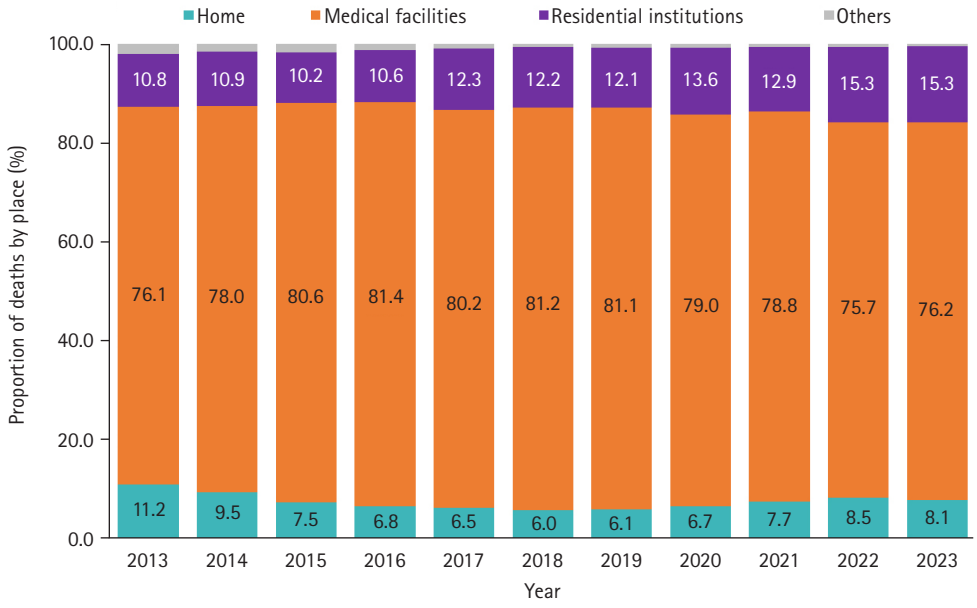

Fig. 3. Place of death due to dementia-related diseases between 2013 to 2023 in Korea.

The dementia death rate is 2.1 times higher in women than in men. Alzheimer's disease accounted for 77.1% of dementia-related deaths in 2023, with its mortality rate increasing sharply in 2022, unlike other dementia types. Additionally, most dementia-related deaths occurred in hospitals (76.2%), followed by residential institutions (15.3%), while the proportion of home deaths has been rising since 2018.

Interpretation

The simultaneous increase in the crude death rate and the decrease in the age-standardized death rate indicate that demographic aging has significantly influenced mortality levels. The burden is disproportionately higher among women (37.9 vs. 18.3 per 100,000) and older adults, peaking at 976.0 per 100,000 for those aged 85 and older. Alzheimer's disease is the predominant cause of dementia deaths (77.1%), with its mortality rate rising sharply,

while the rate for vascular dementia is declining. Furthermore, the increased share of deaths in residential institutions (15.3%) reflects a shift in care settings. These trends underscore the need for targeted interventions—especially for aging women—and enhanced long-term care infrastructure.

How does dementia cause death?

Patients with dementia face an elevated risk of death not only from direct neurodegeneration but also from indirect factors such as pneumonia, malnutrition, and falls. This increased risk is linked to significant lifestyle changes as brain damage progresses. Cognitive decline and reduced physical activity contribute to difficulties with eating, personal hygiene, and medication management, while airway obstruction or aspiration pneumonia may occur from food or secretions. Ultimately, dementia acts as an underlying cause of fatal events including pneumonia, starvation and dehydration, loss of appetite, urinary tract infections, diabetes, infections related to immunosuppression, falls, and airway obstruction due to dysphagia. A previous study analyzing Korean data found that the risk of death for elderly individuals diagnosed with dementia was approximately 8.4 times higher than for those with normal cognition [4].

Korean health policy on dementia

The Korean government has been strengthening its support for dementia management. In 2008, it introduced the "1st Comprehensive Dementia Management Plan," and in 2011, it enacted the Dementia Management Act. Since then, various measures related to dementia have been periodically announced. Given Korea's robust national health insurance system, its dementia management policies emphasize long-term care services and financial support for medical expenses. Notably, dementia-related policies expanded significantly in 2018. Key initiatives included broadening the scope of nursing insurance services to cover patients with mild dementia regardless of physical function, and implementing health insurance coverage for dementia diagnostic tests to reduce patient costs. This policy expansion enabled nursing care for patients with mild dementia who did not require hospitalization, and these changes appear to have influenced the shift in the place of death since 2018.

Impact of COVID-19 on dementia mortality

The COVID-19 pandemic has had multifaceted impacts worldwide, with particularly severe consequences for vulnerable populations, such as dementia patients. During the pandemic, dementia-related deaths can be attributed both to direct COVID-19 infection and to indirect effects from social changes. Previous studies have shown that dementia patients are at higher risk of COVID-19 diagnosis, hospitalization, and death due to weakened immune systems [5]. In Japan, analyses revealed that both the number of dementia patients and the mortality rate increased during the pandemic, attributed to factors such as social isolation from quarantine measures and reduced availability of medical and nursing services [6]. A multivariable analysis in Korea demonstrated that the dementia group had a higher mortality risk than the non-dementia group (odds ratio, 3.05; $P < 0.001$) among a nationwide cohort of 2,800 subjects over 50 diagnosed with COVID-19 between January and April 2020 [7]. According to the 2022 cause-of-death statistics in Korea, the crude death rate increased by 17.4% from the previous year—the largest rise since 1983—while the COVID-19 death rate increased by 522.8% [8]. These findings indicate that although the COVID-19 epidemic peaked in Korea in 2020, its impact on overall mortality was substantial in 2022.

A linear regression model fitted to data from 2013 to 2021 estimated an annual increase in the dementia death rate of approximately 0.48 per 100,000. The predicted value for 2022 (year 9, with 2013 as year 0) was around 21.3 per 100,000—lower than the observed 27.9—even before accounting for the sharp rise in 2023. Alternatively, assuming a linear increase from 2021 to 2023 (an increase of 7.8 over 2 years, or 3.9 per year), the estimate would be 20.4+3.9 = 24.3 per 100,000, consistent with interpolation. Given that the observed dementia death rate in 2022 was 27.9, it can be inferred that the surge in dementia-related deaths that year is linked to the COVID-19 pandemic.

Conclusion

This study examined the demographic characteristics and major trends in dementia-related mortality. The findings provide a basis for developing policy approaches to improve the health and quality of life for dementia patients. Dementia is both a personal health issue and a significant social challenge. Consequently, research on dementia mortality is expected to contribute to alleviating the social burden by identifying preventive strategies to reduce mortality and by guiding improvements in medical services.

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Authors' contributions

Seokmin Lee did all work.

Conflict of interest

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

Funding

None.

Data availability

Raw data are available from microdata on cause of death statistics from Statistics Korea at https://mdis.kostat.go.kr/index.do.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/HJWUF0

Supplement 1. The number of deaths due to dementia in Korea, 2013~2023.

Supplement 2. Data for generating Figures 1 to 3.

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eISSN: 2234-2591
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Ewha Med J 2025;48(2):e36
https://doi.org/10.12771/emj.2025.00381

Ewha Medical Journal

Korea's 2024 reduction in medical research output amid physician residents' resignation

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In February 2024, the Korean government announced it would increase medical school admissions by 2,000 seats—a 65.4% rise from the existing quota of 3,058 [1]. This policy, introduced with minimal consultation with the medical community and lacking a clear scientific rationale, prompted widespread protests [2]. More than 90% of resident physicians resigned, plunging the healthcare system into disarray [3-5]. Over a year later, the dispute between the government and the medical profession remains unresolved, threatening Korea's healthcare infrastructure and academic research productivity.

In Korea, resident physicians constitute nearly 40% of the physician workforce in university hospitals. They bear primary responsibility for inpatient care—including prescriptions, diagnostic tests, and procedures—and play a crucial role in patient monitoring and daily round preparations. Moreover, they assist specialists in the emergency department, intensive care units, and operating rooms. This high reliance on residents meant that their absence overwhelmed university hospitals, forcing faculty members to assume the full spectrum of clinical duties. Professors, who previously balanced patient care, education, and research, have shifted almost entirely to clinical responsibilities, resulting in a marked decline in academic output. Concurrent reductions in government-funded research grants during this period likely exacerbated the downturn in scholarly productivity [6]. The combined impacts of funding cuts and workforce shortages have placed unprecedented strain on university-based research systems.

A downward trend in medical research publications was already evident before 2024. Between 2022 and 2023, publication counts fell modestly by 2.60% in the Web of Science database (20,247 vs. 20,788) and by 5.56% in the Embase database (18,977 vs. 20,094). These databases were chosen for their comprehensive coverage of peer-reviewed medical journals.

The ongoing conflict appears to have significantly accelerated this decline, with a further reduction of 12.01% (17,816 vs. 20,247) in Web of Science and 12.50% (16,604 vs. 18,977) in Embase in 2024 compared with 2023. In contrast, a similar protest in 2020, when resident physicians opposed the expansion of medical school admissions, lasted only one month (August–September) and had minimal impact on research output (Fig. 1, Supplement 1). This sharp decline in medical research contrasts with trends in other fields: based on Web of Science data, medical publications fell by 12.01% in 2024 versus 2023, while publications in the natural sciences and engineering rose by 3.14% and 5.05%, respectively (Fig. 2, Supplement 2). The specific subject categories for natural sciences and engineering used in this comparison are detailed in Supplement 3.

The decline in research output varied widely by specialty. Hematology (–54.2%; 175 vs. 382), rheumatology (–42.7%; 160 vs. 279), dermatology (–39.3%; 300 vs. 494), respiratory medicine (–30.4%; 562 vs. 807), and pediatrics (–29.4%; 266 vs. 377) experienced the steepest drops (Fig. 3, Supplement 4). These fields depend heavily on resident physicians for both clinical service and academic activities. In contrast, some specialties saw modest increases: transplantation (+3.7%; 280 vs. 270), pathology (+4.7%; 179 vs. 171), urology & nephrology (+8.3%; 471 vs. 435), ophthalmology (+9.4%; 430 vs. 393), and critical care medicine

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Received: April 8, 2025 Revised: April 13, 2025 Accepted: April 13, 2025

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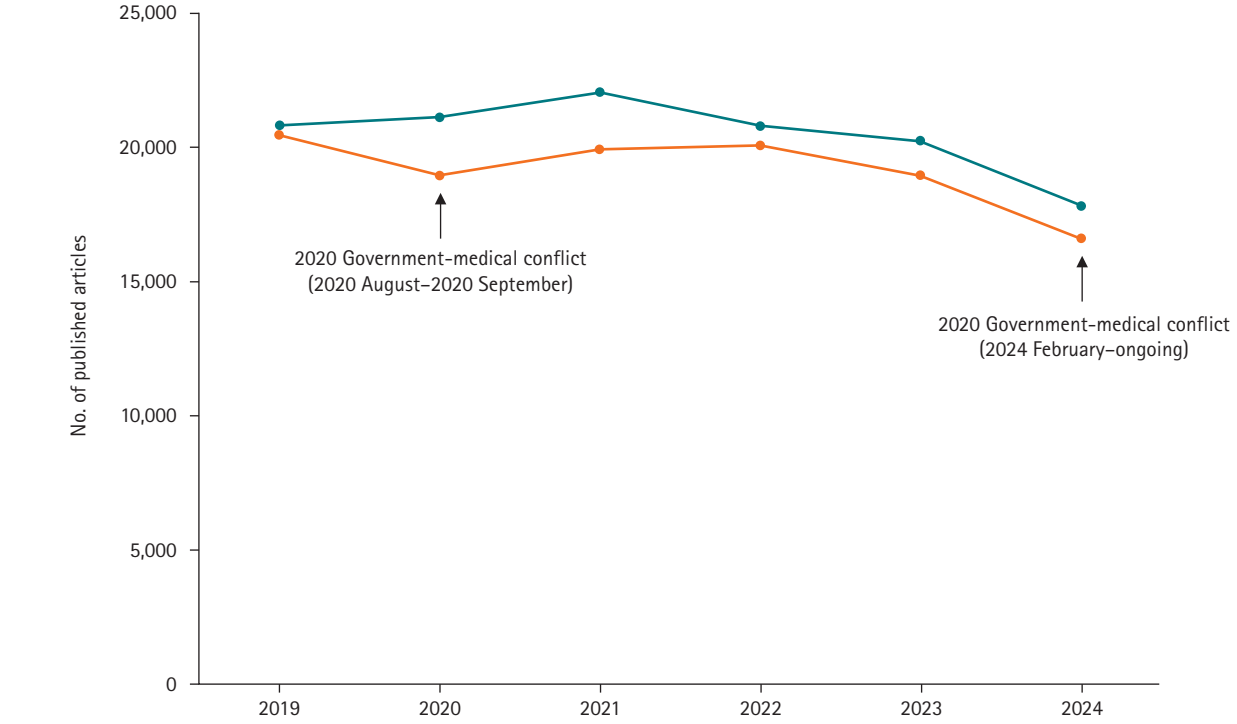
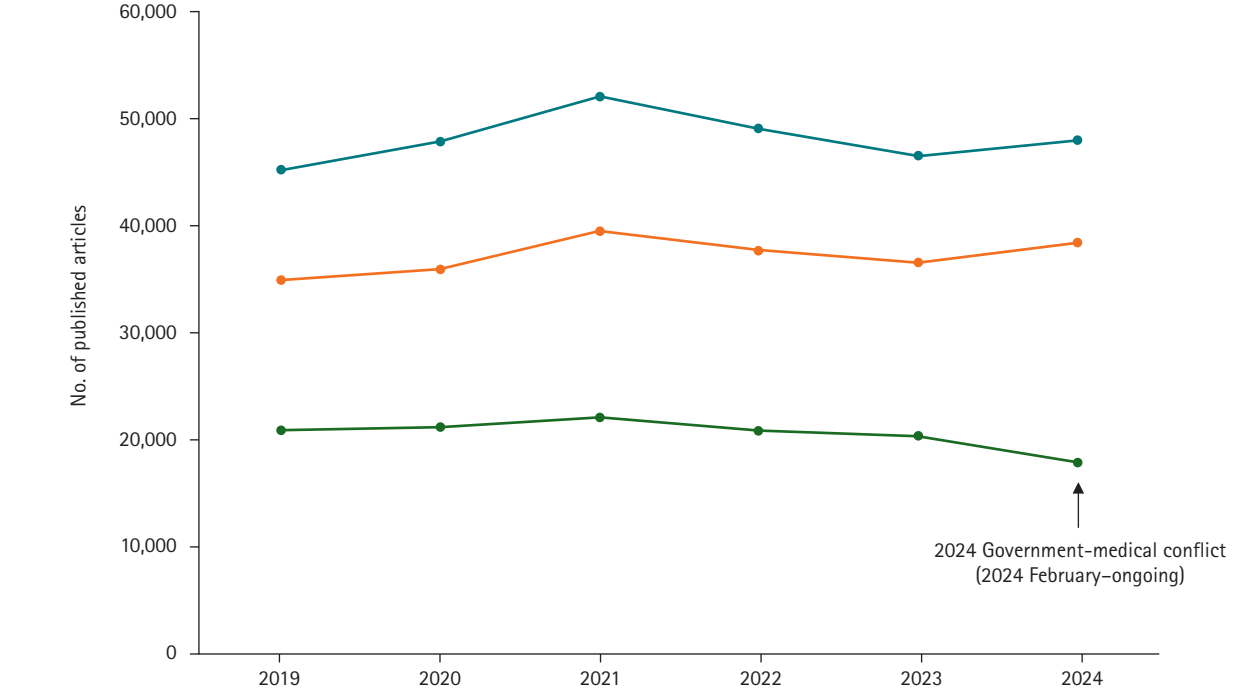


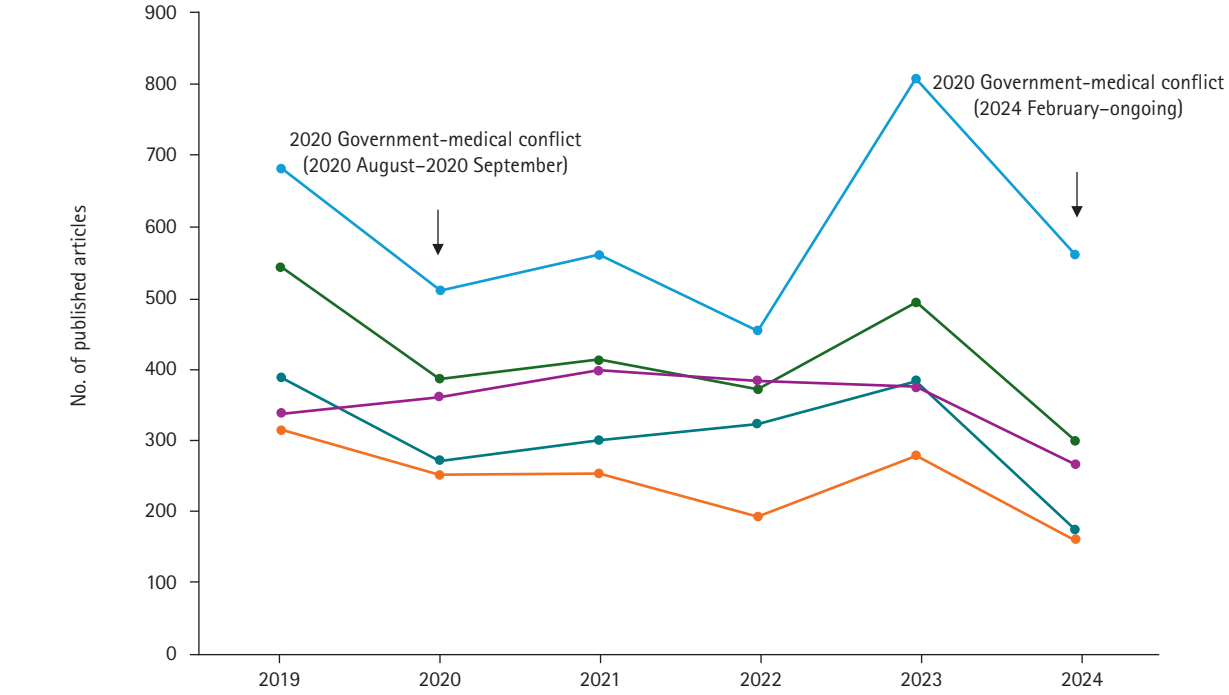
	2019	2020	2021	2022	2023	2024
Web of Science	20,849	21,154	22,074	20,788	20,247	17,816
Embase	20,454	18,957	19,950	20,094	18,977	16,604

Fig. 1. Number of published medical articles by authors with affiliations in Korea (2019–2024) in Web of Science and Embase.



	2019	2020	2021	2022	2023	2024
Natural Science	45,266	47,907	52,116	49,174	46,551	48,013
Engineering	34,864	35,890	39,515	37,717	36,567	38,415
Medicine	20,849	21,154	22,074	20,788	20,247	17,816

Fig. 2. Number of published articles by authors with affiliations in Korea in natural sciences, engineering, and medicine (2019–2024) in Web of Science.



	2019	2020	2021	2022	2023	2024
Hematology	390	271	300	323	382	175
Rheumatology	315	252	253	194	279	160
Dermatology	543	386	414	373	494	300
Respiratory System	682	510	561	455	807	562
Pediatrics	338	361	399	383	377	266

Fig. 3. Number of published articles by authors with affiliations in Korea (2019–2024). Top 5 specialties with the highest reduction rates in 2024 compared to 2023.

(+21.3%; 182 vs. 150). These areas may have been buffered by lower reliance on residents and more established physician assistant systems.

The broader implications extend beyond research productivity. The disruption of clinical workflows has compromised patient care, particularly in tertiary hospitals, where resident physicians play a critical role. Furthermore, the government's response has exacerbated tensions. On December 3, 2025, the Korean President declared martial law, mandating that resident physicians return to their duties within 48 hours—a measure widely criticized as an authoritarian overreach [7]. The decree stated:

"All medical professionals, including medical residents (resident physicians) who are currently striking or have left their medical posts, must return to their duties within 48 hours and perform their roles diligently. Failure to comply will result in punishment under martial law."

The inflammatory rhetoric has further deepened the rift between the government and the medical community, destabilizing the healthcare system. It underscores the indispensable role of resident physicians in sustaining Korea's clinical and academic infrastructures. The unilateral enactment of a policy with such far-reaching consequences—without stakeholder engagement—has inflicted serious harm on both patient care and medical research. An immediate resolution is critical to restore stability and avert lasting damage to Korea's global reputation for healthcare excellence and research innovation. Even if residents return, academic productivity is unlikely to rebound quickly: the prolonged disruption has already caused substantial delays in ongoing studies, weakened mentoring frameworks, and significantly increased faculty clinical workloads—factors that collectively foreshadow a sustained downturn in medical research output.

Future efforts should prioritize collaborative policymaking to rebuild trust between the government and the medical profession. This may include mediated dialogues with medical associations, incentives for resident-physician retention, and the restoration of research funding to offset long-term academic losses. Further studies are warranted to evaluate the lasting impact of these conflicts on patient outcomes and healthcare delivery.

This study has several limitations. In Fig. 3 (Supplement 4), we analyzed the number of published articles by specialty using sub-

ject categories from the Web of Science database. However, individual journals can be indexed under multiple categories in Web of Science; in such cases, we included each journal in all assigned categories rather than designating a single primary classification. Similarly, in Fig. 2, we grouped subject categories under the broader fields of natural sciences and engineering for comparative analysis. Nevertheless, some categories legitimately span both disciplines and were thus included in both. This methodological approach may have resulted in partial duplication of counts across disciplines, which should be considered when interpreting the results.

Korea's healthcare system, long regarded as a model of efficiency and excellence, now stands at a critical crossroads. Resolving this crisis requires not only addressing immediate challenges but also fostering a culture of collaboration and mutual respect to safeguard the future of healthcare and medical research in the country.

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Authors' contributions

Conceptualization: JJY. Data curation: HBC, YSK, SGK. Methodology/formal analysis/validation: JJY, HBC. Project administration: JJY. Funding acquisition: JJY. Writing–original draft: JJY, HBC. Writing–review & editing: JJY, HBC, YSK, SGK.

Conflict of interest

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

Funding

This work was supported by the Soonchunhyang University Research Fund (2025).

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/P3PWGY

Supplement 1. Number of published articles by authors with affiliations in Korea (2019–2024). in Web of Science and Embase.

Supplement 2. Number of published articles by authors with affiliations in Korea in Natural Sciences, Engineering, and Medicine (2019–2024) based on Web of Science.

Supplement 3. The categories of natural sciences and engineering used for this comparative analysis.

Supplement 4. Number of published articles by authors with affiliations in Korea across specialties (2019–2024) based on Web of Science.

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eISSN: 2234-2591
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Ewha Med J 2025;48(2):e37
https://doi.org/10.12771/emj.2025.00318

Ewha Medical Journal

학술출판에서 투명성 원칙과 업무 지침 4판

The Committee on Publication Ethics, DOAJ, the Open Access Scholarly Publishing Association, the World Association of Medical Editors

Principles of Best Practice and Transparency in Scholarly Publishing ver. 4: a Korean translation

The Committee on Publication Ethics, DOAJ, the Open Access Scholarly Publishing Association, the World Association of Medical Editors

서론

Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishing Association (OASPA)와 World Association of Medical Editors (WAME)는 학술출판에서의 투명성 원칙과 업무 지침을 마련하기 위해 협력한 학술단체이다. 이것은 진행 중인 작업의 네 번째 버전(2022년 9월 15일 출판)으로, 널리 보급되기를 바란다.

'학술출판에서 투명성 원칙과 업무 지침'은 학술지 특별호(special issue)와 학술대회 자료집을 포함한 모든 출판 자료에 적용해야 한다. 각 학술지의 지침이 표준지침과 다를 경우 편집인은 학술지가 따르는 절차를 명확하게 밝혀야 한다.

또한 이 지침에 따라 출판사와 편집인은 출판의 모든 측면에서 접근성, 다양성, 형평성, 포괄성을 증진할 책임이 있다. 편집인의 결정은 학문의 가치에 바탕을 두어야 한다. 저자의 국적, 민족, 정치적 신념, 인종 또는 종교 등 투고 원고의 가치를 판단하는 데에 영향을 주어서는 안 된다. 학술지는 모든 참여자에게 배타적인 환경을 조성하지 않아야 하며, 참여자 수용 정책을 늘 점검해야 한다.

학술지 기본 정보(Journal Content)

1. 학술지명(name of journal)

학술지명은

- 독창적이어야 하고, 다른 학술지와 혼동되지 않아야 한다.
- 저자와 독자들이 학술지의 발행처나 범위를 오인하거나 다른 학술지나 기관과 관련이 있다고 잘못 이해하지 않도록 주의하여야 한다.

2. 누리집(website)

- 학술지 누리집은 컴퓨터 바이러스와 악성 프로그램으로부터 사용자를 보호하기 위해 보안을 강화해야 한다.
- 적어도 누리집 URL 프로토콜은 http가 아닌 https(보안 URL

학술지 기본 정보	학술지 정책	조직	출판 비용 및 수익원
1. 학술지 표제	7. 출판윤리 정책과 관련 편집 정책	10. 소유권과 운영	13. 게재료
2. 학술지 누리집	8. 전문가심사	11. 편집위원회 또는 자문위원회	14. 기타 수익
3. 발행 간기		12. 편집실/연락처 정보	15. 광고
4. 자료 보존			16. 마케팅
5. 저작권			
6. 라이선스			

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Received: March 29, 2025 Revised: March 29, 2025 Accepted: March 29, 2025

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protocol)를 사용해야 하며, 모든 트래픽(traffic)은 https를 통해 전송(redirect)되어야 한다. 누리집 관리자는 내용, 구성(presentation)과 응용프로그램(application)에 웹 표준과 표준 윤리지침을 적용해야 한다. 누리집은 독자나 저자에게 오해를 불러일으킬 수 있는 정보를 기술하지 않도록 한다. 누리집에 다른 학술지/출판사의 웹사이트, 디자인, 로고 등을 사용하지 않아야 한다. 다른 누리집의 내용을 복사한 경우, 원본 누리집을 명시해야 한다. 추가로 누리집에는 다음 항목을 분명하게 표시해야 한다.

- 학술지의 목표와 범위
- 목표로 하는 독자층
- 출판할 수 있는 원고의 유형(예시로, 이중게재, 중복게재를 허락하지 않는다는 내용 등 포함)
- 저자 자격 기준(authorship criteria)
- ISSNs (P-ISSN, E-ISSN 모두 기재)

3. 발행 간기(publishing schedule)

학술지의 발행 간기를 명확하게 기술하고, 특별한 사정이 없는 한 발행 일정을 지켜야 한다.

4. 자료 보존(archiving)

학술지나 발행인이 학술지 발행을 중단하는 경우 학술지 전문 전자 백업과 장기 디지털 보존 계획을 밝혀야 한다. 자료 보존을 위한 기관으로는 PMC와 Keepers Registry에 등록된 기관을 포함된다.

5. 저작권(copyright)

- 출판물 저작권 정책은 누리집과 개별 논문에 명시해야 한다.
- 저작권 조건은 누리집 저작권과 별개로 구별되어야 한다.
- 출판된 모든 문헌(HTML과 PDF)의 전문(full text)에 저작권 소유권자를 기재해야 한다.
- 저작권 조건이 별도의 형식으로 설명되어 있는 경우, 누리집에서 누구나 쉽게 찾고 이용할 수 있어야 한다.

6. 라이선스(licensing)

- 라이선스 정보를 누리집에 명확히 설명해야 한다.
- 라이선스 조건은 출판된 모든 문헌(HTML, PDF)의 전문(full text)에 표시해야 한다.
- 오픈 액세스로 지정된 모든 콘텐츠는 오픈 라이선스를 사용해야 한다.
- 제3의 저장소에 저자 원고와 출판된 문헌을 게시하는 데 따른 라이선스 정책을 명시해야 한다.
- Creative Commons License (CCL)을 적용하는 경우, 해당 라이선스의 조건을 Creative Commons 웹사이트의 올바른 라이선스 링크로 연결해야 한다.

학술지 정책(Journal Practices)

7. 출판윤리 정책과 관련 편집 정책(publication ethics and related editorial policies)

학술지는 출판윤리 정책을 누리집에 밝혀야 하며(예: COPE Core Practice 지침), 여기에는 다음 항목을 포함해야 한다.

- 저자와 기여자(contributor) 자격 정책
- 항의와 불만을 처리하는 방법
- 연구윤리 위반 혐의를 처리하는 방법
- 이해관계 정책
- 자료 공유와 재현성 정책
- 연구윤리 준수 정책
- 지적재산권 정책
- 출판 후 논의 정책
- 수정과 취소(철회) 정책

편집인과 발행인은 학술지에 게재된 학술 문헌의 무결성을 보장할 책임이 있다. 표절, 인용 부풀리기, 자료 위조/변조 등 연구윤리 위반 행위가 발생할 때 문제 해결을 위한 정책과 절차를 설명해야 한다. 학술지 정책이나 편집인 성명은 이러한 위반 행위를 장려하거나 의도적으로 허용해서는 안 된다. 편집인이나 발행인이 해당 학술지에서 투고 받은 원고나 이미 발행된 논문에서 연구윤리 위반 행위를 파악한 경우, COPE 가이드라인에 준하는 절차에 따라 처리해야 한다.

8. 전문가심사(peer review)

전문가심사란 원고의 주제 분야의 심사자/전문가로부터 조언을 얻는 것이며, 전문가심사자들은 편집팀의 일원이어서는 안 된다. 그러나 전문가심사의 구체적인 방법은 학술지나 분야에 따라 다를 수 있으므로 다음과 같은 내용을 누리집에 기술해야 한다.

- 투고 원고 심사 여부
- 전문가심사 수행 주체(예: 외부 전문가나 편집위원회 구성원)
- 심사 과정의 유형(단일 가림 심사, 양쪽 가림 심사, 공개 심사 등)
- 심사 절차와 관련된 모든 정책은 아래 같은 경우들을 포함할 수 있음
  - 저자 추천 심사자를 초빙하는지
  - 개인정보가 가려지는지, 가려지는 경우 누가, 누구에게 가려지는지
  - 추가 보충자료(supplementary material)가 심사 대상인지
  - 심사 내용이 논문과 함께 게시되는지
  - 심사자를 명시하는지 여부
- 원고의 최종 결정 과정 및 관련자
- 전문가심사를 받지 않아도 되는 예외적인 특정 논문의 유형

일반적 전문가심사 정책을 따르지 않는 경우라면 해당 논문이

어떤 심사를 받았는지 밝혀야 한다. 학술지는 처음 투고할 때 해당 원고의 수락을 보장해서는 안 된다. 수락된 원고는 심사 기간에 대해 명시된 대로 출판되어야 한다. 심사가 지연될 때는 저자에게 그 이유를 알려야 하며, 저자가 원한다면 원고를 철회(withdrawal)할 기회를 주어야 한다. 출판 일자는 모든 출판 논문에 공표해야 하고, 접수 일자와 채택 일자를 함께 기재하는 것이 바람직하다.

9. 접근성(access)

회원가입, 구독이나 유료 논문과 같이 모든 사람이 자유롭게 접근할 수 없는 온라인 콘텐츠가 있는 경우 접근 방법을 명확하게 설명해야 한다. 인쇄본을 구독할 수 있는 경우라면 구독료를 명시해야 한다.

조직(Organization)

10. 소유권과 운영(ownership and management)

- 학술지 소유권과 운영 관리 정보는 누리집에 밝혀야 한다.
- 투고자나 편집인이 학술지 소유자의 특성에 대해 오해할 수 있는 기관명은 사용하지 않도록 한다.
- 학술지가 학회, 기관이나 스폰서에 소속되어 있는 경우 가급적 누리집 링크(학회, 기관 나 스폰서)를 제공해야 한다.

11. 자문기관(advisory body)

학술지에는 Aims and Scope에 명시된 주제 분야 전문가로 구성된 편집위원회나 자문위원회가 있어야 한다.

- 위원의 이름과 소속을 학술지 누리집에 기재한다.
- 위원회 명단은 최신 정보여야 하며, 위원은 위원회 활동에 동의해야 한다.
- 위원의 최신 정보를 주기적으로 확인하여 갱신해야 한다.

12. 편집실/연락처 정보(editorial team/contact information)

학술지는 누리집에 메일을 포함한 편집사무실 연락정보, 편집위원들의 이름과 소속을 반드시 제시해야 한다.

출판 비용 및 수익원(Business Practices)

13. 저자 비용 또는 게재료(author fees)

- 게재료(논문 처리 비용, 페이지당 비용, 편집 비용, 언어 교정 비용, 컬러 인쇄 비용, 투고 비용, 회비, 기타 부가 비용 등)가 부과된다면 누리집에 그 비용을 명확히 표시한다.
- 게재료가 없다면 이를 분명하게 밝힌다.
- 게재료에 대한 정보는 쉽게 찾을 수 있어야 하며, 투고 과정 중 앞 부분에서 제공해야 한다.
- 향후 게재료를 부과할 가능성이 있는 경우 이를 명시한다.
- 게재료 면제 제도가 있으면 면제 대상이나 자격, 신청 시기, 방법 등의 정보를 밝힌다.
- 게재료나 면제 여부가 편집위원회의 심사와 게재 판정에 영향을 미치지 않아야 하며, 이를 명기한다.

14. 기타 수익(other revenue)

사업 모델 또는 수익원을 누리집에 명시해야 한다. 사례로는 저자 비용(13번 참조), 구독, 후원금과 보조금, 광고(15번 참조), 별쇄본, 부록, 특별호 등을 포함한다. 사업 모델 또는 수익원(예: 별쇄본 수익, 부록, 특별 호, 후원)이 편집위원회의 심사와 게재 판정에 영향을 미치지 않아야 한다.

15. 광고(advertising)

학술지는 광고 게재 여부를 명시해야 한다. 광고를 고려한다면 아래와 같은 광고 정책을 밝혀야 한다.

- 어떤 형태의 광고를 고려할지
- 누가 광고를 수락할지
- 논문 내용이나 독자의 이용 형태에 따라 광고를 연동할지 아니면 무작위로 노출할지 광고가 편집위원회의 의사 결정과 관련되어서는 안 되며, 논문 내용과 무관해야 한다.

16. 마케팅(direct marketing)

원고 의뢰를 포함하여 학술지를 대신해 수행하는 모든 직접 마케팅 활동은 적절하고, 대상이 명확해야 하며, 지나치지 않아야 한다. 발행인이나 학술지 정보를 사실대로 제공하여 독자 또는 저자에게 오해를 불러일으키지 않아야 한다.

Version History

- This is Version 4.0 of the Principles of Transparency and Best Practice in Scholarly Publishing
- Version 3.0: January 2018
- Version 2.0: June 2015 (on the OASPA website)
- Version 1.0: December 2013 (on the OASPA website)

영국출판윤리위원회(COPE, https://publicationethics.org)

COPE는 출판윤리의 모든 측면, 특히 연구 및 출판윤리 위반 사례를 처리하는 절차를 편집인과 발행인에게 제공한다. 또한 회원들이 개별 사례를 토론할 수 있는 장을 제공한다. COPE가 개별 사례를 조사하지는 않지만 적절한 권위자(일반적으로 연구기관 또는 고용주)가 해당 사례를 조사할 수 있도록 편집인에게 권고한다. 모든 COPE 회원은 처리 기준에 명시된 출판윤리에 관한 COPE 원칙을 적용해야 한다.

오픈 액세스 저널 디렉토리(DOAJ, https://doaj.org)

DOAJ는 (1) 오픈 액세스 학술지에 대한 신뢰할 수 있는 누리집 정보를 관리, 유지 및 개발하고, (2) 회원 목록 내 각 항목이 표준을 준수하는지 확인하며, (3) 오픈 액세스 학술지의 가시성, 유통, 검색 및 선호도를 증가시키고, (4) 연구자, 도서관, 대학, 연구비 제공기관, 기타 이해당사자가 DOAJ에서 제공하는 정보와 서비스의 혜택을 누릴 수 있도록 하며, (5) 오픈 액세스 학술지가 도서관 및 서지정보 제공자(aggregator) 서비스에 통합되는 것을 편리하게 하며, (6) 발행인과 학술지가 전자출판 표준을 준수할 수 있도록 지원하고, 나아가 (7) 학술 교류와 출판 시스템이 과학, 고등교육, 산업, 혁신, 사회와 인류에 봉사하는 모델이 될 수 있도록 지원한다. 위와 같은 활동을 통해 DOAJ는 동일한 목표를 향해 노력하는 모든 관련 당사자와 협력할 것이다.

오픈 액세스 학술출판 협회(OASPA, https://oaspa.org)

OASPA는 분야를 막론한 전 세계 오픈 액세스 발행인의 이익을 대변하기 위해 2008년에 설립된 동업자 단체이다. OASPA의 목표는 오픈 액세스 출판을 지원하는 비즈니스 모델, 도구와 표준을 개발함으로써 회원과 학술 커뮤니티의 이익을 위해 지속 가능하고 발전된 미래를 보장하는 것이다. 이런 사명으로 정보를 교환하고 표준을 수립하며, 더 나아가 사업 모델, 홍보, 교육, 혁신을 촉진하고 있다.

세계의학편집인협의회(WAME, http://www.wame.org)

WAME는 편집인 간의 협력과 소통을 증진하고, 편집 수준을 향상시키고, 교육, 자기 성찰, 자기 관리를 통하여 의학학술지 편집의 전문성을 증진하며, 의학 편집의 원칙 및 실무에 관련한 연구를 장려하고자 의학 학술지 편집인들이 자발적으로 만든 국제 비영리 단체이다. WAME는 의학학술지 편집인의 업무 처리에 유용한 정책과 권고안을 마련하고, 회원 편집인을 위한 교재를 개발하고 있다.

위의 내용은 한국과학학술지편집인협의회(https://kcse.org)와 인포루미(https://infolumi.co.kr)에 의해 번역된 문서이다.

Conflict of interest

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

Funding

None.

Data availability

Not applicable.

Acknowledgments

None.

Supplementary materials

None.