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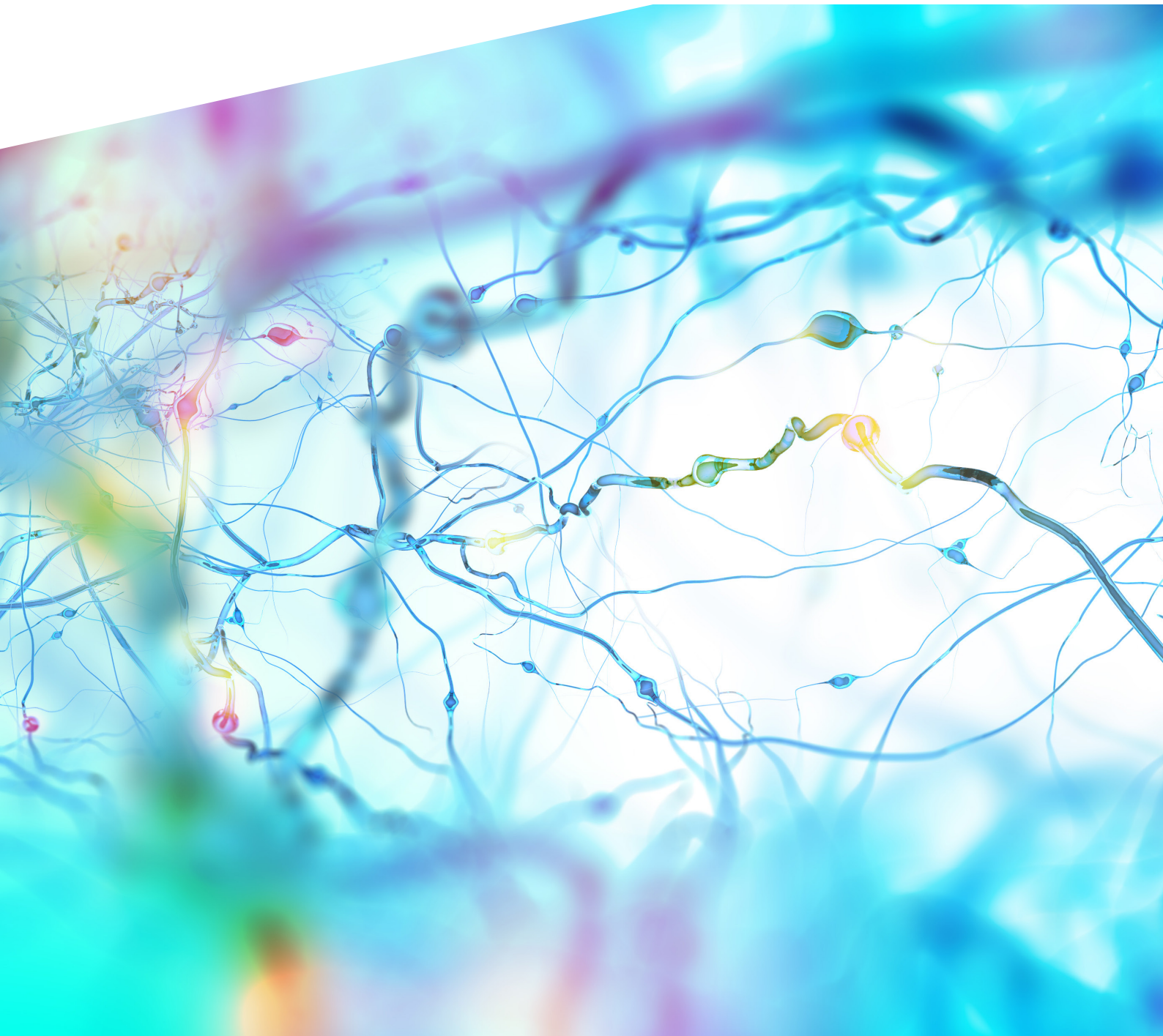

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Aims & Scope

The Ewha Medical Journal (Ewha Med J, http://www.e-emj.org), the official publication of Ewha Womans University College of Medicine and Ewha Medical Research Institute, is published quarterly a year, last day of January, April, July, and October. The first volume was published in March, 1978. It covers all fields of medical science including clinical research and basic medical science. The Journal aims to communicate new medical information between medical personnel and to help development of medicine and propagation of medical knowledges. All manuscripts should be creative, informative and helpful for diagnosis and treatment of the medical diseases and for communication of valuable information about all fields of medicine. Subscripted manuscripts should be written out according to the instructions for the Journal. Topics include original article, case report, images and solution, letter to the editor, invited review article and special issue in the respective field of medicine. The Ewha Medical Journal is indexed/tracked/covered by KoreaMed, KoMCI, KoreaMed Synapse, WPRIM, DOI/CrossRef, EMBASE and Google Scholar.

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Editorial Board

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Editorial

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Gender equity in medical journals in Korea and this issue

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The recommendations by the International Committee of Medical Journal Editors (ICMJE) provide clear guidelines on the selection, description, and representation of study participants. The guidelines emphasize including representative populations in all study types and, at the very least, providing descriptive data for age, sex, ethnicity, and other relevant demographic variables [1]. As of April 7, 2023, there are 280 medical journals in Korea, of which 55 are indexed in the Science Citation Index Expanded (SCIE). It is necessary to investigate the extent to which the 55 SCIE-indexed medical journals in Korea adhere to and implement the ICMJE guidelines on gender equity in their publications. This evaluation involves checking for explicit sex/gender distinctions in the articles and, when missing, seeking justifications and sex/gender-specific interpretations.

The sample included all SCIE-indexed journals published by member organizations of the Korean Association of Medical Journal Editors as of April 7, 2023. The websites of the 55 journals were visited to check for ICMJE guideline adherence. From journals stating that they follow these guidelines, one original article was selected and examined for sex/gender distinction. Cases where sex/gender-differentiated descriptions were not applicable were excluded. The variables included data reflecting sex/gender differences, reasons given when no sex/gender distinction was made, and the interpretation of sex/gender data (Dataset 1). Of the 55 journals, one did not have a statement regarding the ICMJE recommendations and was excluded from the study, leaving 54 for analysis. Table 1 displays the primary results.

As Table 1 indicates, out of 38 articles, excluding 16 that were not applicable, nine (23.7%) did not distinguish participants according to sex or gender, 18 (47.4%) did not provide a sex/

Table 1. Description of sex/gender differences in 54 medical journals in Korea

Sex/gender description	No. of articles
Yes	29
Interpretation (yes)	11
Interpretation (no)	18
No	9
Background (yes)	0
Background (no)	9
Not applicable	16

gender interpretation, and 11 (29.0%) included both sexes/genders and offered a sex/gender-based interpretation. Despite journals' stated adherence to the ICMJE guidelines, the rate of incorporating sex/gender differentiation and interpretation was only 29.0%.

No existing studies on the adequacy of descriptions of sex/gender differences in Korean medical journals were found in KoreaMed (https://koreamed.org/) or PubMed (https://pubmed.ncbi.nlm.nih.gov/), making it challenging to compare this study's results with those of prior research. The present investigation was limited to 55 journals, a fraction of Korea's total 280 medical journals. Only one article was sampled from each journal, representing a minuscule portion of the total annual publications in Korean medical journals. Despite the small sample size, the findings offer insights into how articles published in Korean medical journals describe sex/gender differences. Future research could benefit from randomly sampling a larger number of journals and articles, comparing older and more recent articles to observe trends, and dividing the number of cases in the analysis method for comparative purposes.

The *Ewha Medical Journal* is published by the Ewha Womans University College of Medicine, to which only women are admitted. This unique role of training women leaders in the medical field should also be reflected in the *Ewha Medical Journal's* gender equity policy. I will continue to do my best to promote gender equity in human population studies during my editorship, as I announced in the previous editorial emphasizing diversity, equity, and inclusivity [2].

In this issue, Dr. In-Jeong Cho's review entitled "Sex differences in pharmacotherapy for heart failure [3]" examines the impact of sex on heart failure medication outcomes, highlighting distinct drug responses and side effects between men and women. It underscores the importance of increasing women's participation in clinical trials and developing research methods for sex differences. This topic is essential for precision medicine, aiming to tailor treatments to individual biological and genetic characteristics. The review advocates for a more personalized and inclusive approach to heart failure pharmacotherapy, focusing on the crucial impact of sex-related differences.

To provide the guidelines of gender-equity in scholarly publishing for Korean researchers and editors, two Korean translations are included in this issue. One is the "Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use: a Korean translation [4]," the other is "The Sex and Gender Equity in Research (SAGER) guidelines: implementation and checklist development: a Korean translation [5]." The SGER guidelines and checklist were made by the European Association of Science Editors Gender Policy Committee. Both guidelines and checklist were translated by the members of the Korean Council of Science Editors. Under the help of the Korean Council of Science Editors and the European Association of Science Editors Gender Policy Committee, those two translations can be published in the *Ewha Medical Journal*. It is one of merits of Korean/English journal to be able to publish translated version with importance.

A special article by Drs. Eun Mee Kim, President of the Ewha Womans University and Young-Ju Oh from the Korea National Diplomatic Academy was invited as a secondary publication, entitled "Sustaining Peace on the Korean Peninsula and the role of international organizations [6]." Dr. Kim has served as the 17th President of the university since March 2021. This special article recommended that the Republic of Korea (South Korea) focus on building a solid team of experts in Korean Peninsula affairs and increasing the number of Koreans in critical positions within various United Nations agencies. These efforts will improve engagement with the Democratic People's Republic of Korea (North Korea). Peace between South and North Korea is essential for the Korean Peninsula and the world. Understanding the dynamics of international relations and their impact on peace between South and North Korea can provide physicians and other

health professionals with a broader perspective on the region. Human interaction and exchange could lead to medical challenges in both territories, including the spread of infectious diseases like malaria, tuberculosis, and hepatitis. Addressing the healthcare needs of the North Korean population may require substantial human resources and a significant budget. The medical implications of increased human exchange between the North and South are additional issues that physicians and the South Korean government need to explore.

Dr. Ja Hye Kim's review entitled "Overview of Endocrine Tumor Syndromes Manifesting as Adrenal Tumors" covers adrenal tumor incidence and the clinical features that need to be addressed to improve patient care through early detection, effective management, and targeted treatment [7]. Multiple types of adrenal tumors are clearly presented, providing up-to-date information on this topic for endocrinologists and general physicians.

There are two original articles in this issue: one is to examine the frequency of sleep disorders and the level of sleep quality, as well as their relationship with health-related quality of life in cancer patients in Turkey [8]; the other is to observe the differential expression of exosomal miRNAs in blood and urine [9]. Cancer patients exhibited moderate average sleep quality scores, with over half of them demonstrating poor sleep patterns. Sleep disorders significantly impacted their health-related quality of life. Therefore, to improve the sleep quality of cancer patients, medical care is recommended, including the early detection and social support. In the expression study of exoxomal miRNAs, there was no significant difference in total reads between blood and urine exosomes. It is the study of healthy adults so that the results can be groundwork for the identification of potential biomarkers derived from blood and urinary exosomes.

The year 2024 marks my second year as editor of the *Ewha Medical Journal*. While I proposed several development strategies in the previous editorial, it remains to be seen whether these objectives will be achieved. Nevertheless, with the backing of the publisher and the support of the editorial board members, I am committed to advancing the mission and scope of the journal. Our goal is to publish the highest-quality research and information at the intersection of biomedical science, clinical practice, and medical education.

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Authors' contributions
The article was prepared by a single author.

Conflict of interest
Sun Huh has been the editor-in-chief of the *Ewha Medical Journal* since September 2023. However, he was not involved in the review process. No other potential conflict of interest relevant to this editorial was reported.

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Data availability
Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/SEPRY1

Dataset 1. Raw data of the analysis of gender equity in 55 SCIE-indexed medical journals in Korea

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Not applicable.

Supplementary materials
Not applicable.

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Special Article

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Sustaining peace on the Korean Peninsula and the role of international organizations: a secondary publication

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* This is a secondary publication of Oh YJ, Kim EM. Sustaining peace on the Korean Peninsula and the role of international organizations. *J Peace Unific* 2020;10(1):27-46. http://doi.org/10.31780/jpu.2020.10.1.27 under the permission of the editor of the *Journal of Peace and Unification*. The aim of this secondary publication is to disseminate this invaluable article to the medical society because the health of the North Korean people is of great interest to physicians and health professionals in South Korea. The healthcare system is one of the essential targets of development plans that can be provided by the United Nations. © 2020 Ewha Institute of Unification Studies.

† At the time of the original publication, Ms. Young-Ju Oh was working at the Institute of Foreign Affairs and National Security, Korea National Diplomatic Academy, Seoul, Korea. She is now currently working at the Ministry of SMEs and Startups (MSS), Sejong, Korea.

Keywords
United Nations; Sustainable development; International cooperation; Republic of Korea (ROK); Democratic People's Republic of Korea (DPRK)

The Republic of Korea's potential role in the peacebuilding process on the Korean Peninsula is explored, with the Democratic People's Republic of Korea's earnest efforts to denuclearize and become a normal country. The paper focuses on the United Nations (UN) agencies in the peacebuilding process, considering the UN's engagement in the Democratic People's Republic of Korea during the sanction years with humanitarian assistance, the UN's legitimacy as an impartial international organization for assisting developing countries in forging peace and prosperity, and recently-adopted resolutions on sustaining peace and the Sustainable Development Goals. Policy recommendations are for the Republic of Korea to actively cooperate with the UN's development and humanitarian agencies, conduct a thorough preparatory review and conduct research, and work towards expanding its engagement and role within key UN agencies.

Introduction

The international community has shown great interest and expectation in the possibility of establishing sustained peace on the Korean Peninsula as the peace process appears to manifest itself with the 2018 inter-Korean summits and the 2018 U.S.-Democratic People's Republic of Korea (DPRK, North Korea) Summit in Singapore. Peace on the Korean Peninsula has been a key agenda in the past for international peace and security, which had been focused on the security balance in Northeast Asia and international non-proliferation regime due to the DPRK's determination to develop and possess nuclear weapons.

If the DPRK moves forward with dramatic progress in its complete denuclearization and transition to a normal country, the international community's interest in the Korean Peninsula could expand beyond the elimination of security threats toward establishing sustained peace. The international community will be interested in exploring various ways to engage with the DPRK's transition toward a normal country. A "normal country" is defined as a nation that has developed democracy and achieved progress in reforming the way it operates, as well as being economically advanced and open [1–3]. For the DPRK, many scholars argue that it would mean that the DPRK will join the international community through reform, openness, and denuclearization, including embracing the Joint Declaration on the Denuclearization of the Korean Peninsula, and will respect

the resolutions of the United Nations (UN) Security Council [4,5].

Establishing peace on the Korean Peninsula will mainly depend on bilateral relations between the two Koreas and the relationship with four neighboring countries—the US, China, Japan and Russia. However, once the DPRK moves forward with its reform and opening, there will be more room for other international actors, such as the UN and international financial institutions (IFIs) to engage in bilateral and multilateral relations with the DPRK [5–7]. This projection is based on the assumption that the UN sanctions would be lifted as a result of earnest efforts by the DPRK for denuclearization and transition toward a normal country. Additionally, UN member states and other international organizations must also agree to provide assistance to the DPRK, especially for economic assistance. Although the UN has been criticized for its role in peacebuilding efforts in other parts of the world, there is no other multilateral format that can provide support to the DPRK when the sanctions are lifted. Thus, we need to review the potential role of the UN in the peacebuilding process, including its recent reforms to address criticisms about its peacebuilding mechanism. The role of the private sector and businesses will also be enhanced with the DPRK's reform and opening.

This paper starts with the premise that the Republic of Korea (ROK, South Korea) should play a proactive and important role in denuclearization and building sustained peace on the Korean Peninsula [8–12]. The ROK needs the capacity to lead and coordinate diverse international actors to promote lasting peace on the Korean Peninsula, which includes a thorough understanding of relevant international actors' backgrounds, interests, and potential contributions to the peacebuilding process. This preparation will require a firm commitment, time and effort for preliminary research, and proactive engagement with relevant key agencies. This will be a time-consuming process that requires continued commitment, and thus, it is important that research and preparatory work begin as soon as possible.

Since the 2018 historic inter-Korean Summits and US-DPRK Summits, there is growing interest for the expansion of inter-Korean economic cooperation and the role of international actors in normalizing relations between the US and the DPRK. However, there has been relatively little attention on how the UN and UN agencies can engage in this process. We note that the UN and IFIs have played an important role in advancing global peace and security by supporting developing countries and countries in transition, and we can assume that they could play a crucial role in the DPRK's reform and opening.

Although it is premature to determine the actual roles that the UN and international organizations will perform in establishing peace on the Korean Peninsula, we can learn from their past role in the DPRK during the sanction years. We can also presume that the UN activities for the DPRK will increase when the conditions are ripe for such a transformation, considering the UN's mandate and activities for international peace, security, and development.

IFIs such as the World Bank (WB) and International Monetary Fund (IMF) could actively join efforts to support the DPRK given their extensive experience in supporting transition economies and developing countries. Cooperation between the UN agencies and the World Bank Group has also increased in developing countries with the adoption and implementation of the Sustainable Development Goals (SDGs) since 2016. We assume that there will be close multi-lateral cooperation between the UN and IFIs for the DPRK's reform and opening when the time comes.

This paper focuses on the role of the UN among international organizations in the peacebuilding process on the Korean Peninsula, including the DPRK's reform and opening. This paper focuses on how the UN can be involved in the DPRK's reform and liberalization after the conditions for such support have been created, and not on the conditions for lifting UN

sanctions. In particular, we will explore the ROK's potential role in this process and provide policy recommendations.

Brief overview of the Republic of Korea's peacebuilding efforts on the Korean Peninsula

The Korean Armistice Agreement was signed on July 27, 1953, ceasing all hostilities of the Korean War. It was signed by the United Nations Command represented by the US, the DPRK, and China. However, the Armistice was not a peace treaty, but a cease of fire on the Korean Peninsula. There have been many attempts at reaching peace on the Korean Peninsula for decades with ups and downs, as well as negotiations for eliminating nuclear weapons in the DPRK. The sudden death of Chairman Kim Il-sung in July 1994 happened just days after the US and the DPRK opened talks in Geneva about the DPRK's nuclear programs, and only a few weeks before the first-ever Inter-Korean Summit to take place on July 25, 1994. The Inter-Korean Summit did not take place in 1994, and it was not until 2000 when ROK President Kim Dae-jung and DPRK Chairman Kim Jong-il met in Pyongyang for the first time since the Armistice.

The Six-Party Talks among the ROK, the DPRK, the US, China, Japan, and Russia took place since 2003 after the DPRK withdrew from the Nuclear Non-Proliferation Treaty. This multilateral meeting was an effective method to have a region-wide discussion about the DPRK's development of nuclear capabilities [13]. The meetings took place in Beijing, China, and went through six rounds of talks. However, these meetings discontinued after the DPRK declared that it would pull out of the Six-Party Talks and resume its nuclear enrichment program. The ROK's engagement with the Six-Party Talks and other nuclear negotiations was at times limited as the DPRK and the US often took the lead in the negotiations.

President Kim Dae-jung's (1997–2002) "Sunshine Policy," which signaled a dramatic departure from past ROK Presidents' hard-line policies against DPRK, thawed the relationship between the two Koreas. Several important cooperative projects began, including the Kumgang Mountain tour (1998–2008) and the Kaesong Industrial Park (2004–2016) during the ROK's Roh Moo-hyun (2003–2008) government. The Kumgang Mountain tour was the first joint venture between the two Koreas and brought hard currencies to the DPRK with guided tours. Although President Kim Dae-jung was credited for building a constructive relationship between the two Koreas, and allowed the ROK to have a greater voice in discussions with the DPRK, his soft-line policies were criticized by the conservatives for having aided the DPRK's nuclear program. The Kumgang Mountain tour was halted in 2008 when a ROK civilian was shot dead during a tour. The Kaesong Industrial Park was conceived by President Roh Moo-hyun and Chairman Kim Jong-il, and it began production at the end of 2004 as a symbol of inter-Korean cooperation. This was not without criticisms similar to those against the Kumgang Mountain; after periods of tension, it has been shut down since 2016. President Roh Moo-hyun visited Pyongyang in 2007 for the second Inter-Korean Summit.

A return to a more conservative party in the ROK with Presidents Lee Myung-bak (2008–2013) and Park Geun-hye (2013–2017) ushered in a period of more restrictive policies and programs toward the DPRK. They enjoyed support from the conservative constituents who continued to argue that the Sunshine Policy bolstered the DPRK's nuclear programs, while the progressive constituents argued that the two Koreas were in a more peaceful period with less military provocations. The impeachment of President Park Geun-hye in 2017 and election of President Moon Jae-in (2017–2022) of the progressive party has renewed the ROK's interest in the peace

process on the Korean Peninsula with the ROK playing a more decisive role. President Moon Jae-in and Chairman Kim Jong Un signed the Panmunjom Declaration at the Inter-Korean Summit on April 27, 2018 in Panmunjom. This declaration included transforming the Armistice Agreement of 1953 into a peace treaty with the cooperation of the US and China. As a follow-up, during the 2018 US-DPRK Summit, US President Trump and Chairman Kim Jung-un signed a joint statement that reaffirmed the Panmunjom Declaration [14]. There have been three Inter-Korean Summits since 2018 to help with the Peace Process on the Korean Peninsula, but these Summits have been suspended. The DPRK-US Summits have also been suspended since the second summit in Hanoi, Vietnam on February 27–28, 2019, which was cut short due to disagreements on the issue of easing all or some sanctions against the DPRK.

While there may be some disagreement about the stance toward the DPRK within the ROK, there is a general agreement that peace on the Korean Peninsula should be led by the ROK. With the growing prowess of the ROK in terms of its economic development and growing international presence, South Koreans believe that they should be able to manage and have a greater voice in the peace process on the Korean Peninsula [14]. The recent Moon Jae-in government has been the most active among the ROK presidents, with three Inter-Korean Summits and the DPRK-US Summits. Chairman Kim Jong Un has also been active in engaging with the ROK, the US, and China, and hopes remain that the two Koreas will return to a more active period of summits and negotiations in the near future.

This paper will discuss the role of the ROK in the peacebuilding process on the Korean Peninsula with a special focus on how it may better engage with the UN and IFIs, which are likely to play important functions in the peace process once sanctions toward the DPRK are lifted.

Sustaining peace on the Korean Peninsula and the United Nations

United Nations's view on peace: sustaining peace

While the ROK and the DPRK are central to the peace process on the Korean Peninsula, the UN has been involved in affairs on the Korean Peninsula as an international platform for the DPRK's nuclear and human rights issues as well as a key channel to provide humanitarian assistance. The UN Charter's commitment to international peace, security, and human rights provided the basis for the UN's involvement in the DPRK.

If the DPRK carries out adequate measures for its reform and opening, the international community would agree that the UN, which enjoys legitimacy across the world, should be involved in the transition of the DPRK into a normal country. Thus, it will be important to understand the current discourse and a new approach at the UN for peace and peacebuilding, since it will provide the foundation for the UN's engagement with the DPRK.

There has been growing criticism that the UN should change its approach to peace since its ambitious deployment of UN peacekeepers in the last decade has not led to the elimination or even reduction of war and conflict around the world (Report of the High Level Panel on Peace Operations 2016). Against this backdrop, in 2016 the UN adopted the concept of, and resolution on, "sustaining peace" after much deliberation. The concept of "sustaining peace" first clarifies that peace is a clear and strategic policy objective for all countries regardless of whether they are currently beset in conflict, and that the UN's peace operations aim to sustain peace in all UN member states. By separating the concept of peace from conflict, "sustaining peace" emphasizes that the UN peace efforts should also focus on preventing conflict rather than

merely responding once conflict has occurred. This means that UN peacebuilding activities, which were confined to activities in post-conflict situations, can now be expanded to include a wider range of activities including conflict prevention. Thus, an interface has been created to link various peacebuilding efforts and activities of member states to those of the UN's peace and security activities.

The UN General Assembly and Security Council in 2016 have both adopted a resolution on "sustaining peace" [15,16]. These resolutions were adopted in order to find a new approach to sustaining peace and to redefine the UN's role and function in a rapidly-changing international peace and security context. In 2015, the UN, led by former Secretary-General Ban Ki-Moon, reviewed three aspects of the peace and security system (peace activity; peacebuilding; and women and peace reflected in the UN Security Council Resolution 1325) in order to respond to the rapidly changing international security environment, including the spread of terrorism and extreme violence, and international concerns arising from a complex set of issues including poverty, natural disasters, health security, refugees, and immigration. The UN led a process to reexamine the UN process for peace and security by a group of experts, and the report recommended that the UN use the concept of "sustaining peace" to deal with new challenges to peace and security. Many countries, including the ROK, which was a main champion from the beginning, spearheaded the adoption of the resolution [15].

The UN's discussions on peace and security have centered on the UN's method of engagement in war, conflict, and peacebuilding, which are reflected in the UN Security Council's agenda [16]. The UN engages in international peace and security issues in the form of dispute resolution, managing peacekeeping operations, and participating in the post-conflict peacebuilding process through the Peacebuilding Commission. Over eighty percent of recent UN Security Council discussions have focused on dispatching and managing peacekeeping operations in conflict-affected countries in three stages of conflict: (1) occurrence of conflict; (2) restoration and maintenance of peace; and (3) post-conflict peacebuilding [16].

The resolution for "sustaining peace" argues, first and foremost, that the UN's three pillars of peace and security, development, and human rights must be interlinked in order to achieve sustained peace. Furthermore, the resolution states that the UN must innovate its activities conducted under the UN's three pillars toward an integrated and mutually reinforcing manner for sustaining peace. After the adoption of the resolution on "sustaining peace," measures to link the concept to activities of the UN are being actively discussed, and various reform plans have been proposed and adopted. The UN held high-level talks on sustainable development and sustaining peace to strengthen the peace-development nexus (January 2017), reform of the United Nations Peace and Security System and Development System (2017–19) was conducted, and the UN has reviewed measures to strengthen the role of women and young people in peacebuilding ("Seven-Point Action Plan on Gender-Responsive Peacebuilding") [17,18]. Although some member states have expressed reservations about the expansion of the concept of lasting peace, the UN Secretary-General Antonio Guterres has emphasized that sustainable development is the best guarantee for sustaining peace (United Nations Secretary-General's Report on "Peacebuilding and Continuing Peace"; A/72/707, January 2018, available at https://www.un.org/peacebuilding/policy-issues-and-partnerships/policy/sg-reports) and has developed practical strategies to link peace and development in an integrated way [19].

The resolution on "sustaining peace" also calls for strategic partnerships with various international actors beyond the UN system—in particular, IFIs, bilateral donors and the private sector—in an effort to enhance the ownership of member states in achieving sustained peace.

When the time comes for the UN to engage with the DPRK in its transition to a normal country, it is plausible that the UN will consider its engagement through the lens of sustaining peace and sustainable development. This means that the UN will be likely to use the concept of "sustaining peace" in its internal discussions to provide support the DPRK for UN's "sustaining peace" resolution.

Sustaining peace, sustainable development, and the Democratic People's Republic of Korea

Discussions within the UN about the concept of "sustaining peace" were partly inspired by the Agenda 2030 for Sustainable Development, which was adopted at the 2015 UN Summit. The 2030 Agenda clearly states that there is no peace without sustainable development and vice versa, and argues that peace, justice and strong institutions are key for sustainable development as presented in SDG 16. Furthermore, development gains would be reversed without sustained peace, and inequalities will increase without inclusion and access to justice for all [20]. In January 2017, the UN Secretary-General, Antonio Guterres, emphasized the UN's action to prevent war and sustain peace in the context of SDG 16 [15,21]. Although the primary responsibility for peace will lie with the nations themselves, the UN system and international partners should assist in building resilient capacities for sustaining peace [15,21]. After the adoption of the SDGs and the resolution on "sustaining peace," there has been a clear acknowledgement within the UN that sustainable development is an important outcome of peace and is also an enabler of sustaining peace (UN Secretary-General Antonio Guterres, High-Level Dialogue on "Building Sustainable Peace for All: Synergies between the 2030 Agenda for Sustainable Development and Sustaining Peace" (January, 2017); available at https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/12/Sustainable-Peace-and-2030-Agenda_Concept-note_FINAL.pdf).

In other words, the achievement of the SDGs is meaningful in itself, but it is also important for international cooperation as an investment for peace.

Thus, it is reasonable to expect that the UN will consider the SDGs an important means to achieve sustaining peace on the Korean Peninsula and the normalization of the DPRK. Supporting the implementation of the SDGs in the DPRK will be the UN's first step in playing an important role in establishing peace on the Korean Peninsula. Since sustaining peace is a shared responsibility that needs to be achieved by the DPRK government and other national stakeholders, active cooperation between the UN and the DPRK will be vital [15]. It will be important to critically assess the UN system supporting the implementation of the SDGs. In addition, a review of UN agencies' current assistance to the DPRK will help us better project possible UN engagement with the DPRK.

Implications of the United Nations support system for the Sustainable Development Goals for future United Nations engagement with the Democratic People's Republic of Korea

Agenda 2030 for Sustainable Development, or the SDGs, has 17 goals and 169 targets and has been recognized as a groundbreaking and innovative initiative that expands the current discourse on development cooperation and provides a framework for international cooperation fit for the 21st century.

The key features of the SDGs are: (1) a human-centered approach in line with the motto, "Leave No One Behind" in the process of achieving the SDGs; (2) incorporation of the needs of both the current and future generations; (3) integration of peace, security, and human rights as the foundation for sustainable development; (4) innovative partnership among all international actors (e.g., nation-states, the UN, IFIs, and the private sector); and (5) a set of universal goals that

apply not only to developing countries, but to all 193 UN member states to achieve by 2030.

Since 2015, the UN has put international cooperation for the SDGs as one of its top priorities. The UN Secretary-General Antonio Guterres carried out a sweeping reform of the UN Development System to reorganize the support system for partner countries with a focus on SDGs implementation. They included: (1) strengthening the function of the Resident Coordinator, who oversees UN projects in developing countries; (2) better coordination and reduction of redundancies among the UN projects in developing countries by strengthening the UN Country Team, which is a coordinating body for the UN development and humanitarian agencies; and (3) renaming the UN Development Framework as the UN Sustainable Development Cooperation Framework (UNSDCF), which is designed to be the primary instrument for planning and implementation of the UN development activities at the country level in support of the SDGs implementation [22]. The reform aims to build an integrated UN Development System that is more focused on delivery on the ground with capacities and resources better aligned with the SDGs.

When the UN Development System can actively work with the DPRK, the UN would consider the following to be the first-order priority in accordance with comprehensive reform of the UN Development System: (1) establish the UN Sustainable Development Cooperation Framework for the DPRK to support the DPRK's efforts to achieve the SDGs; (2) empower the Resident Coordinator in the DPRK; (3) secure funding for development programs in the DPRK; and (4) establish partnerships with other international actors operating in the DPRK.

We note that the DPRK has been working with the SDGs since they were announced in 2015. On September 25, 2015, Mr. Tapan Mishra, the UN Resident Coordinator with the Co-Chair Mr. Rim Yong Chol, Division Director of the Ministry of Foreign Affairs of the DPRK, presented the SDGs in Pyongyang [23]. Additionally, the DPR Korea Needs and Priorities 2019 outlines the funding agencies working in the DPRK in order to support 3.8 million people in the DPRK [24]. The DPRK has announced that it will present its voluntary national report for the SDGs at the 2020 High-Level Political Forum for Sustainable Development at the UN [25]. Thus, the DPRK appears to be ready for further UN engagement once the sanctions are lifted.

The United Nations's current humanitarian assistance to the Democratic People's Republic of Korea and implications for future engagement

The UN is actively supporting developing countries to achieve the SDGs through the UN Funds & Program agencies. The UN Development System is the largest multilateral development actor, which provided US$ 33.7 billion in 2017 for assisting developing countries to achieve the SDGs, and these resources largely constitute grant aid from member state donors [26]. The UN Development System reform was based on the UN resolution A/72/279 ("Repositioning of the UN Development System," 2018 https://undocs.org/Home/Mobile?FinalSymbol=a%2Fres%2F72%2F279&Language=E&DeviceType=Desktop&LangRequested=False). However, the DPRK has not benefited from the UN's development assistance during the last decade due to the UN Security Council's sanctions against the DPRK's nuclear program, the most complex in history. A limited number of humanitarian assistance projects have been delivered without a break even under the UN sanctions, since the resolutions do not explicitly prevent humanitarian assistance to the DPRK. According to 2018 UN statistics, a total of US$ 25.9 million in humanitarian assistance was provided to the DPRK through five agencies (WFP, UNICEF, WHO, FAO, and UNFPA). The amounts of aid were, according to the UNOCHA Website as of February 2019: (1) WFP: $14.8 million; (2) UNICEF: $5 million; (3) WHO: $3.5 million; (4) FAO: $2 million; and (5) UNFPA: $600,000. A total of six UN offices are currently stationed in the DPRK, which include

the above five agencies and the UNDP.

Most of the current projects in the DPRK are focused on improving nutrition, providing food security, and improving the basic health environment for the most vulnerable people, such as women and children [24]. UNOCHA estimates that approximately 10.9 million people, or 43% of the DPRK's total population, need basic humanitarian assistance, and it is estimated that of these, 3.8 million people are the most vulnerable (2019 DPRK Needs & Priorities; https://dprkorea.un.org/en/10164-dpr-korea-needs-and-priorities-2019).

The DPRK was among UNOCHA's 44 most vulnerable humanitarian crisis countries in 2018, but it actually received the least support compared to its need [27]. The required amount for assistance was $111.2 million, and the actual disbursement of assistance was $25.9 million. This amounts to a coverage of 23.4%. This implies that the international community has great reservations for the DPRK's development needs, but also for its humanitarian needs due to the DPRK's nuclear program. Although the UN sanctions allow for humanitarian assistance to the DPRK, there is very little assistance to the DPRK since there are no banks to handle remittances and there is the perception of difficulty in passing through the UN Sanctions Committee. Although the UN's support for the DPRK has been very limited and small in scale, it offers several implications for future UN engagement with the DPRK. First, the UN's assistance to the DPRK will be an important element in the future when sanctions against the DPRK are lifted, with positive transformations in the DPRK and the Korean Peninsula. Since sanctions against the DPRK have been strengthened, bilateral assistance has continued to decrease, and only a few Nordic countries including Switzerland and Finland have provided limited humanitarian assistance to the DPRK. We assume that the UN agencies, which have worked in the DPRK during the sanction years, have accumulated up-to-date and evidence-based data, albeit limited, for the DPRK's development environment and have established channels of cooperation within the DPRK government [24,28].

Since the biggest obstacle to the UN agencies' humanitarian assistance is not only a lack of sufficient resources, but a lack of reliable data, the above UN agencies have been sharing limited information and data collected during project implementation, monitoring and evaluation, or through surveys that each agency conducts on a limited scale [28]. A 2017 survey by UNICEF, "The 2017 DPR Korea Multiple Indicator Cluster Survey," focused on women and children in households [28]. A total of 8,500 households participated in this survey and provided important data on infant and child mortality, and the researchers developed indicators for child health, nutrition and education [28]. The decade-long experience of the UN agencies in collecting data related to development and humanitarian programs in the DPRK could give them a comparative advantage versus international actors when the international community is ready to assist the DPRK.

Second, many donor countries prefer to utilize multilateral assistance when the partner country is perceived to have great uncertainty for development cooperation projects, particularly in terms of impact delivery. The DPRK will fall into this category, and it is likely that many donors will consider multilateral rather than bilateral support for the DPRK, since the former is considered better for project effectiveness, transparency and monitoring of results. Since many donor countries provide about 30% of their official development assistance budget to developing countries through international organizations or, multilaterally, there will be room for support for the DPRK in this format. Thus, when the international community is ready to consider development cooperation with the DPRK, it is likely that donors would consider multilateral channels, especially through the UN system given the UN's mandate and past experience in the DPRK.

Third, the UN agencies' humanitarian assistance has utilized the DPRK's internal system. The

current UN engagement in the DPRK puts the DPRK's central and local government at the center to take full control of the entire project, logistics, distribution and storage of supplies (WFP, "DPRK Interim Country Strategic Plan 2019-21." https://docs.wfp.org/api/documents/WFP-0000103512/download/?_ga=2.222563483.1645215501.1706314546-1188378543.1706314546) [24,29].

In spite of the UN's final authority to determine the project location, beneficiary group, and the method and size of the project, the UN agencies have ensured the DPRK government's self-reliant participation (ownership) through the use of its internal system for the project's full cycle including planning and implementation. For example, the WFP's project, "Project Improving Nutrition and Micronutrient Intakes" produces and distributes super-cereal and biscuits to improve nutrition of pregnant women and children under seven [30]. Under the UN sanctions against the DPRK, the WFP has secured raw materials from China near the border with the DPRK, shipped them to the DPRK, produced cereals and biscuits at its factories in the DPRK, and distributed them through the DPRK's public organizations (local health centers, day-care centers, and schools) [30]. The production, distribution, and storage of biscuits are calculated by in-kind contributions of the DPRK government's plans, using its government system [30]. Thus, the working relationship built between the DPRK government and the UN agencies, and the data collected by the UN agencies while working in the DPRK, would be valuable when UN agencies are able to work at full-scale after the sanctions are lifted.

Fourth, the UN agencies have special advantages in the monitoring and evaluation of development cooperation projects in the DPRK. Monitoring and evaluation would be a key concern for donors, especially for grant aid. The UN agencies operating in the DPRK have noted that project monitoring and evaluation have improved significantly in the last few years [24]. The UN agencies have noted that the DPRK government has recognized the importance of monitoring and has been much more cooperative in providing support for monitoring. We assume that such efforts by the DPRK government will be a positive factor for development cooperation with donor countries and donor agencies when full-scale international assistance can be provided. The UN agencies that have accumulated relevant experience in monitoring aid projects in the DPRK will be sought after as development partners by donor countries.

The UN agencies will be important players when the DPRK is ready for development cooperation with various donors and when earnest changes take place in the DPRK for reform and opening. This is due to the UN's experience that has been accumulated over the years with humanitarian assistance to the DPRK, its changing concept of "sustaining peace," and the crucial nexus between development and peace as recognized in the SDGs.

Prospects for the United Nations's engagement in the Democratic People's Republic of Korea: its roles and sectors for support

The UN's sectoral support to the DPRK will be finalized through an agreement with the DPRK government when "the UN Sustainable Development Framework for the DPRK" is created. The UN adopted "the UN Sustainable Development Framework" on a five-year basis to support the SDGs of recipient countries. The adoption of the framework document is expected to be discussed as a top agenda item if the UN decides to expand its assistance to the DPRK since the DPRK has not yet adopted the SDGs framework. It is plausible that the UN's future engagements with the DPRK for development cooperation will be in line with the SDGs, and in particular with social development targets aimed at improving education, health, poverty, gender equality, and nutrition. Social development will be the first-order priority towards achieving the SDGs since human-centered social development is the foundation for sustainable development

with the SDGs' motto, "Leave No One Behind." Investment in health and education is also an important priority for economic development.

Since the UN agencies have continued to implement humanitarian assistance projects in the DPRK related to social development, it is likely that social development will be an important field of support in the future due to the need for that sector and to take advantage of the accumulated expertise in the DPRK. The UN will work towards mobilizing various international financial resources including grant aid from donors to support the DPRK's social development. There have been many global efforts to establish funding mechanisms in the health and education sectors, and these will become central parts of UN-led multilateral support. As noted above, many donors would prefer UN-led multilateral support for the DPRK, at least in the initial stage of the DPRK engagement.

The UN will be the most important actor for advising the DPRK for its early stage of reform and normalization since it has been performing such functions for many other developing countries especially during the early stage of development and opening. The UN-led international cooperation system on social development will be established in the DPRK, including the formation of a group of donor countries along with the UN agencies for the implementation of SDGs and sustaining peace. When international assistance to the DPRK begins, the UN will have to first expand, reorganize, and strengthen the UN offices in the DPRK starting with the Resident Coordinator, which oversees and coordinates the UN support in the DPRK. The UN DPRK Resident Coordinator has been vacant since September 2019 (before the reform of the UN Development System in 2018, the UNDP's DPRK office director concurrently served as a coordinator in the DPRK). The UN offices in the DPRK will be the focal point of the multilateral development cooperation platform for the UN agencies, donors, and private sector actors.

The Democratic People's Republic of Korea's sustainable development and international financial institutions

Sustainable development in the DPRK will depend on achieving social development goals as well as repairing social infrastructure including railways, roads and energy facilities. SDGs 7, 8, and 9 are in this category. SDG 7 is "ensure access to affordable, reliable, sustainable and modern energy for all"; SDG 8 is "promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all"; and SDG 9 is "build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation." Social infrastructure will require more time, sophisticated strategies, international cooperation, and larger funding compared to social development. Resources for social infrastructure can be mobilized from the ROK's Inter-Korean Cooperation Fund, bilateral cooperation funding from donors (concessional loan), multilateral cooperation funding led by IFIs, and private sector funding [31]. The Inter-Korean Cooperation Fund was established to promote inter-Korean cooperation and contribute to the recovery of the national community by securing necessary funds for inter-Korean cooperation projects. It has various forms and methods to comprehensively support human, physical exchanges and other cooperation. Recent social infrastructure projects in China, Vietnam, and Mongolia suggest that a large volume of resources is needed, and that IFIs would lead the process, which will be the likely scenario in the DPRK. In the process of reform and opening, Vietnam received $3.2 billion in total for 30 projects over 8 years (1994–2001), which accounted for 17% of the total amount, from the International Development Association (IDA) regarding building of social infrastructure. The IFIs refer to

the IMF and five multilateral development banks, including the World Bank Group, the African Development Bank, the Asian Development Bank, the Inter-American Development, and the European Bank for Reconstruction and Development [32]. The IMF and the World Bank Group provide services to their members throughout the world, while the latter regional banks focus primarily on their own region (Ibid.). The World Bank Group and regional banks provide important support for developing countries' economic development. Additionally, developing countries must first become members of the IMF in order to qualify for World Bank loans [33]. Thus, IMF membership will signal that the country can gain membership to relevant regional banks.

The IFIs have mobilized private capital through public-private partnership projects and blended financing when investing in developing countries' social infrastructure projects. The IFIs have also supported former socialist countries in their transition toward a capitalist market system [34]. IFIs' active engagement with the private sector can provide opportunities for the private sector actors to engage in the DPRK. However, there are major challenges in order for this to happen including gaining membership to the IFI by the DPRK. The UN agencies first worked with the IFIs in order to provide technical assistance and policy advice as a first step for further engagement with the private sector in Vietnam [35]. The UNDP and IMF participated in technical assistance and policy advice for finance and macroeconomic management for Vietnam in the late 1980s.

Thus, the DPRK needs to gain membership in the IMF before it can be assessed for loans from global and regional IFIs. If the DPRK gains membership with a commitment to conform to these banks' guidelines for market management, structural reform and investment conditions, it is likely that the DPRK can be eligible for 200–400 million USD in concessional loans per year (Ibid.). IFI support includes technical assistance and more long-term development assistance. The latter will require formal membership to the IMF and other IFIs, and thus, would take longer, while the former can be provided more quickly, as in previous cases of IFI support [36].

The DPRK began active engagement with the IMF in 1997 when IMF sent a delegation to the DPRK for a review, which resulted in the DPRK Fact-Finding Report in 1997 [34]. The DPRK has not gained IMF membership, and is not eligible for support from the IMF or other IFIs. However, many experts argue that it will be important to move from humanitarian assistance during times of crisis toward development cooperation once the sanctions are lifted. Considering the know-how for economic transition and sheer volume of capital that can be mobilized by the IFIs, it will be critical for the DPRK to engage with the IFIs [34]. On the other hand, there remains concern that routine and transparent reporting of the macro-economic conditions and the operation of the financial sector would not be easy in the DPRK [37]. It is also important to note that membership to the IFIs would depend on other member nations' approval and support for the DPRK [37,38].

Conclusion

Peace and security on the Korean Peninsula are important not only for the two Koreas, but for the world since it will bring dividends of peace and other benefits to the region and the world. Sustaining peace and the normalization of the DPRK should proceed with the participation and support of the international community for sustainable and irreversible peace.

The ROK and the neighboring four major powers will most likely play important roles in the denuclearization of the Korean Peninsula and the normalization of the DPRK. The ROK needs to fully understand the capacity of international actors, especially the UN agencies and IFIs, and develop the strategic capability to lead a constructive process for sustaining peace on the

Korean Peninsula in order to play a catalytic role in the peacebuilding process on the Korean Peninsula. The UN agencies and IFIs are important for resource mobilization and implementation of development cooperation projects.

The UN has been the most important international multilateral institution for peace in the world, but it has also had its shortcomings. Thus, the UN has been engaged in reforming its mandate on peacebuilding and agreed on the resolutions on "sustaining peace" in order to respond to some of the criticisms. These reforms have paved the way for the UN to play an important role in the DPRK once the sanctions are lifted since individual nations will take time to become more fully engaged with the DPRK. In particular, the UN can potentially play a significant role in the peacebuilding process on the Korean Peninsula through the SDGs. The UN Development System will most likely lead global efforts for supporting the DPRK's social development in the initial stage due to the following: (1) the UN's legitimacy as a universal and impartial international organization; (2) accumulated experience working in the DPRK; and (3) established support mechanism for the SDGs implementation.

The ROK needs to proactively explore ways to lead and coordinate the UN-led international support for the DPRK in the coming years. If the UN becomes the main coordinating body for international support for the DPRK, the ROK should be ready with preliminary research on multilateral support. This will prepare the ROK to negotiate with major actors, and coordinate the ROK's bilateral support for the DPRK and the UN-led multilateral support. In the short term, the ROK should strengthen its cooperation with the UN agencies currently operating in the DPRK, and broaden its working relationship with the UN's development and humanitarian assistance agencies. These efforts will help to amplify the ROK's voice and enhance its role within the UN system. The ROK's strategic expansion in the UN's development and humanitarian assistance agencies, which have worked (or will work in the future) in the DPRK, will be critical. The ROK needs to actively participate in UN discussions on peace and development, and in particular in the UN development agencies. Gaining membership in the IFIs in the long term and receiving technical assistance in the short term would be critical for the DPRK's development. The ROK can play an important role in assisting the DPRK with preparation for membership to the IFIs, as this will be the first step towards DPRK being eligible for concessional loans from global and regional IFIs, including the IMF, the World Bank Group and the Asian Development Bank [37–39].

Support for the DPRK will likely continue for a long duration once it begins, as has been the case of the UN and IFI engagement with former transition countries. Thus, the ROK needs to build a strong network of personnel who are well-versed in dealing with the Korean Peninsula and place more Koreans in high-ranking decision-making positions in various UN agencies to facilitate such an engagement with the DPRK. Establishing a close working relationship with the UN Secretariat will enhance the ROK's role in the peacebuilding process on the Korean Peninsula and support for the DPRK. In conclusion, it is imperative for the ROK to strengthen its constructive relationship with the UN, conduct a thorough preparatory review and conduct research, and enhance its capability, in order to lead and coordinate the sustaining peacebuilding process on the Korean Peninsula.

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Review Article

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Sex differences in pharmacotherapy for heart failure

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Heart failure (HF) represents a serious public health concern, characterized by substantial morbidity and mortality. Despite advances in pharmacological management, a gap persists in understanding and accounting for sex-related differences in HF treatment. This review was performed to clarify the impact of sex on the clinical outcomes of HF medications. Insights from various clinical trials and studies have highlighted differences between men and women in drug responses and adverse effects, indicating the need for a more nuanced approach to HF management. Promoting greater representation of women in clinical trials and the development of research methodologies that consider sex differences are crucial steps in advancing precision medicine. Such efforts ensure that therapeutic strategies are optimally tailored to the unique biological and genetic profiles of each person. Ultimately, this review emphasizes the vital need for a more inclusive and personalized approach to HF pharmacotherapy, underscoring the critical role of sex-related differences in shaping effective and individualized treatment pathways.

Introduction

Heart failure (HF) is the leading cause of morbidity and mortality worldwide [1]. In Korea, the estimated prevalence of HF rose from 0.77% in 2002 to 2.24% in 2018 [2]. Sex-based stratification reveals that 600,244 women (2.3%) and 599,532 men (2.1%) are affected by this condition [2], indicating a higher prevalence in the Korean female population relative to their male counterparts. The prevalence of HF is anticipated to continue rising, as it generally increases with age. Rapid and accurate diagnosis of HF is crucial for initiating appropriate management and improving outcomes [3]. Based on left ventricular (LV) ejection fraction (EF), heart failure can be classified into three categories: HF with reduced ejection fraction (HFrEF; EF ≤40%), HF with mildly reduced EF (HFmrEF; EF 41%–49%), and HF with preserved EF (HFpEF; EF ≥50%) [4,5]. The recommended pharmacotherapies differ across these categories. Several sets of guidelines have been published for the management of HF [3,6,7], all underscoring the importance of guideline-directed medical therapy (GDMT), particularly for individuals with HFrEF. The GDMT for HFrEF includes angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs), digitalis, ivabradine, and vericiguat. In contrast, SGLT2 inhibitors are the only pharmacological treatment strongly recommended for patients with HFmrEF and HFpEF, with a weaker class of recommendation for both ARNIs and MRAs [7–10].

Sex is a key biological variable in the context of HF. Men and women exhibit distinct pathophysiologies, potentially contributing to sex-specific differences in clinical presentation and diagnosis [11,12]. HFpEF is more common in women, while HFrEF is predominantly observed in men. Notable differences between the sexes in pharmacodynamics and pharmacokinetics have also been documented [11–13]. However, current guidelines do not incorporate sex-based variations into recommendations for treating patients with HF. In this article, we review the evidence for sex-related differences in HF medications and explore pharmacological treatments for HF in consideration of these sex disparities.

Ethics statement

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

Sex-related considerations for heart failure medications

Historically, clinical trials have predominantly included Caucasian men [14]. Despite an increase in enrollment, women continue to be underrepresented in clinical research. In 1994, the National Institutes of Health (NIH) implemented a policy requiring that all NIH-funded human scientific and behavioral studies include women, barring a clear and compelling and rationale for their exclusion [15]. The US Food and Drug Administration introduced a regulation in 1998 titled "Presentation of Safety and Effectiveness Data for Certain Subgroups of the Population in Investigational New Drug Application Reports and New Drug Applications." This policy mandated that new drug applications provide safety and effectiveness data that encompass key demographic subgroups, including those based on sex, age, and race [14]. Furthermore, the NIH issued guidelines in 2015 that obligated researchers to account for sex as a biological variable and to submit valid analyses based on sex, race, and ethnicity to ClinicalTrials.gov [14]. These initiatives have led to recent clinical trials that suggest differences in drug efficacy across subgroups, including sexes.

Comparatively low gastrointestinal motility, intestinal enzymatic activity, and glomerular filtration rate all influence the pharmacokinetics in women, who also tend to have a lower body weight than men [13]. Hormonal differences between the sexes influence drug receptors and responses. Additionally, differences in body composition, gastric motility, cytochrome P450 enzyme activity, drug transporter function, and excretion rates all play roles in the pharmacokinetics of drugs, impacting their absorption, distribution, metabolism, and excretion [11]. Considering the sex-related differences in pharmacokinetics, such as the impacts of smaller body size, decreased intestinal enzymatic activity, and reduced clearance rates, it is reasonable to suggest that women may be at a higher risk of medication overdose compared to male patients [16]. These distinctions underscore the need for a nuanced approach to HF pharmacotherapy, which is essential for maximizing drug effectiveness and reducing the risk of adverse effects across sexes.

Digoxin

The Digitalis Investigation Group study, published in 1997, assessed the impact of digoxin on mortality and hospitalization through a randomized clinical trial that included 6,800 patients with HFrEF (EF ≤45%) [17]. The findings indicated that while treatment with digoxin did not decrease overall mortality, it did lead to a reduction in the rate of hospitalization, both overall and in cases of

worsening HF [17]. Additionally, the study presented intriguing data on the sex-specific effects of digoxin, revealing that in comparison to placebo, digoxin was associated with a significantly higher mortality rate in female, but not male, patients [18]. However, the question of whether these findings are due to sex disparities remains unanswered. Further analysis of the data revealed that higher serum digoxin concentrations, which were more frequently observed in women, were associated with increased mortality [19]. The risk of death has been found to relate independently to the serum digoxin concentration, with significantly elevated risk noted in patients with concentrations of 1.2 ng/mL or higher and 1.6 ng/mL or higher [19,20]. The conclusion drawn was that the observed sex-related disparity in mortality rates associated with digoxin use was attributable to the drug concentration rather than to sex itself. In current practice, digoxin use is approached with caution and is limited to patients with HFrEF who remain symptomatic despite the optimization of GDMT [7]. The prescribed drug concentration is the same for both sexes, with target digoxin plasma concentrations maintained below 1.0–1.2 ng/mL for both men and women [21].

Beta-blockers

Most randomized clinical trials of beta-blockers in patients with HFrEF have included few female participants and minimal analysis of sex-based disparities. Initial research suggested that beta-blockers were similarly effective in women and men; however, this conclusion likely stems from the lower number of women enrolled. The US Carvedilol Heart Failure Study indicated that the impact of beta-blockers was consistent across sexes [22]. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIOR) trial, nebivolol was associated with a reduction in the combined endpoint of all-cause mortality or cardiovascular hospitalization in women, a benefit that was not observed in men (the P for interaction did not indicate significance) [23]. Furthermore, a meta-analysis revealed comparable reductions in mortality for men and women, with no significant sex-related differences [24,25].

Adverse drug reactions associated with the use of CYP2D6-dependent beta-blockers, including carvedilol, metoprolol, nebivolol, and propranolol, are significantly more frequent in women than in men [26]. Moreover, oral contraceptives can interact with the metabolism of metoprolol, leading to increased plasma concentrations in female relative to male patients [27]. Consequently, for several beta-blockers, women may experience the optimal therapeutic effect at doses lower than those required for men [27]. Supporting this notion, the lowest rates of death or hospitalization for HFrEF were observed at 100% of the recommended beta-blocker dose in male patients, whereas female participants experienced approximately 30% less risk at only 50% of the recommended dose. No further decrease in risk was evident at higher doses, according to a post hoc analysis of the Biology Study to Tailored Treatment in Chronic HF (BIOSTAT-CHF) study [28]. Nevertheless, no consensus exists regarding the presence of a sex-based difference in optimal beta-blocker dosage.

Beta-blockers may reduce cardiovascular mortality in patients with HFpEF [7–10]. While female sex was independently linked to the presence of diastolic dysfunction and comparatively poor clinical outcomes in a cohort of elderly individuals with HFpEF [29], sex-related disparities in the effectiveness of beta-blockers remain insufficiently examined among these patients.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Early trials involving ACEIs indicated a benefit exclusively for male patients, with no apparent

advantage for female participants [30,31]. This discrepancy may have been influenced by the sex imbalance in these studies, in which men greatly outnumbered women—a trend also observed in studies on beta-blockers. Consequently, the limited female representation could have skewed the results unfavorably for this group. A subsequent meta-analysis of 30 studies, which encompassed substantial numbers of both male and female participants, established that ACEIs offer comparable benefits in overall mortality and the combined outcome of mortality or hospitalization for HF in both men and women with HFrEF [32]. Large-scale clinical trials later demonstrated that ARBs also provide similar decreases in adverse cardiovascular events among women and men with HFrEF [33–36]. Based on a post hoc analysis of the BIOSTAT-CHF study, Santema et al. [28] noted that the lowest risk of death or hospitalization for HF in women occurred at doses that were only half of the recommended levels, mirroring the findings regarding beta-blockers. This suggests that lower doses of ACEIs or ARBs may be warranted in women with HFrEF.

Recent data have shown that women report adverse drug reactions to ACEIs more frequently than men [37]. This sex disparity may contribute to the less frequent use of ACEIs [38]. Research using administrative databases has revealed that women treated with ARBs experienced a 31% decrease in the risk of all-cause mortality compared to those treated with ACE inhibitors [39]. In contrast, among men, the survival rates did not differ significantly between those prescribed ARBs and those given ACEIs [39]. Sex can be considered when prescribing renin-angiotensin system (RAS) blockers to patients with HF, although this requires further investigation.

Guidelines suggest that ARBs or ACEIs may reduce the risk of hospitalization or cardiovascular mortality associated with HF in patients with HFpEF [7–10]. However, insufficient research has been conducted on sex-related differences in the effectiveness of ACEIs and ARBs for treating HFpEF. Various studies have indicated that estrogen favorably modulates the RAS [40], and the cardioprotective effects of estrogen observed in premenopausal women, which are due in part to RAS inhibition, are lost following menopause [41]. Given that HFpEF is relatively prevalent among postmenopausal women, the role of RAS modulation could be particularly important for managing HFpEF in this demographic.

Mineralocorticoid receptor antagonists

For spironolactone in the Randomized Aldactone Evaluation Study (RALES) [42] and eplerenone in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [43], no significant differences were observed between sexes in terms of prognosis for patients with HFrEF. A secondary analysis of the Aldosterone Antagonist Therapy for Adults With HF and Preserved Systolic Function (TOPCAT) trial, the TOPCAT-Americas, indicated that only women experienced a reduction in all-cause mortality when treated with spironolactone for HFpEF [44]. However, a recent meta-analysis that utilized individual patient data from the RALES, EPHESUS-HF, and TOPCAT-Americas studies showed that MRA treatment resulted in consistent reductions in the risk of adverse events for both men and women, regardless of functional class, LVEF, or other potential confounding factors [45]. Given the absence of sex-related variation in the pharmacokinetics of MRAs [41], the issue of sex-related differences in MRA treatment for HF remains unclear and warrants further investigation.

Angiotensin receptor-neprilysin inhibitor

The ARNI sacubitril/valsartan represents a frontline medical therapy for patients with HFrEF

[7–10]. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which included patients with HFrEF, the effects of ARNI were similar for men and women [46]. The Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial, which compared ARNI to valsartan in patients with HFpEF, found that ARNI did not significantly reduce the primary outcome when compared with valsartan [47]. However, a subgroup analysis indicated that ARNI did reduce the primary outcome in women, but not in men (P for interaction=0.016) [48]. A pooled analysis of the PARADIGM-HF and PARAGON-HF trials revealed that the therapeutic effects of ARNI vary according to LVEF, with benefits that apparently apply to patients with HFmrEF. These benefits demonstrated sex-related differences, with advantages appearing to extend to a higher LVEF in women than in men [49].

The underlying mechanism for the observed sex-related differences in the effects of ARNI on elevated LVEF remains unclear. Given that HFpEF is more prevalent in postmenopausal women, one possible explanation is modulation of the RAS, which undergoes changes after menopause. Furthermore, it is noteworthy that the LVEF is generally higher among the female than the male population [50], which implies that women may experience systolic dysfunction at higher LVEF levels compared to men [48,49]. Nevertheless, further evidence is necessary to substantiate the use of sex-specific ranges when evaluating the efficacy of LVEF-based therapies. Some researchers have noted that the representation of women in the PARAGON-HF trial was markedly higher (51.7%) than in the PARADIGM-HF trial (21.8%) [45]. Therefore, more robust evidence is needed to confirm the existence of sex-based differences in the response to ARNI treatment in HFpEF.

Sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors, initially developed to treat type 2 diabetes, have demonstrated substantial benefits in the management of HF. These medications are effective across all HF categories, irrespective of LVEF, and exhibit clinical advantages in both men and women [51–54]. However, a recent meta-analysis of pooled data from four major randomized controlled trials on SGLT2 inhibitors suggested higher rates of primary composite outcomes in women compared to men [55]. This finding warrants further research to substantiate the hypothesis. The safety profile of SGLT2 inhibitors appears generally consistent between sexes. However, women could be more susceptible to certain adverse effects, such as urinary tract infections, due to anatomical and hormonal differences [56]. Consequently, monitoring and management of these side effects are particularly important for female patients.

Ivabradine and vericiguat

In randomized controlled clinical trials investigating ivabradine [57] and vericiguat [58], researchers observed no significant sex-related differences in the drugs' efficacy or safety profiles among patients with HFrEF. However, the conclusions drawn from these studies are limited by the relatively small number of trials that have been conducted.

Unsolved problems and future direction

Fig. 1 provides a visual summary of sex-related differences in the efficacy of HF pharmacotherapy. Despite advances in the understanding of these differences in the context of

	HFrEF		HFpEF	
	COR		COR	
Digoxin	IIa	· ↑mortality in women due to higher concentration in women		
Beta-blocker	I	· ↓benefit in women in earlier studies due to underrepresentation · ≈benefit with lower dose in women	IIb	· Inadequate date
ACEI	I	· ↓benefit in women in earlier studies due to underrepresentation · ≈benefit with lower dose in women	IIb	· Inadequate date
ARB	I	· ≈benefit · ≈benefit with lower dose in women · ↑benefit compared to ACEI in women	IIb	· Inadequate date
MRA	I	· ≈benefit	IIa	· ≈↑benefit in women
Ivabradine	IIa	· ≈benefit		
ARNI	I	· ≈benefit	IIa	· ↑benefit in women
SGLT2I	I	· ≈benefit	I	· ≈benefit
Vericiguat	IIa	· ≈benefit		

Fig. 1. Sex-related differences in the efficacy of heart failure pharmacotherapy. COR was defined in accordance with the Guidelines for the Management of Heart Failure published by the Korean Society of Heart Failure. Data from Youn et al. [10]. HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; COR, class of recommendation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2I, sodium-glucose cotransporter 2 inhibitor.

HF medications, current guidelines frequently overlook the variations in pharmacodynamics and pharmacokinetics between men and women. Historically, women have been underrepresented in clinical trials, leading to a notable lack of data for analyzing sex disparities in drug responses. Ensuring the balanced representation of women in clinical trials is critical. Emphasis should also be placed on developing sex-specific treatment strategies for HF, regularly updating these strategies with new evidence, and implementing personalized therapeutic approaches.

Furthermore, the growing recognition of sex-related differences in HF presentation underscores the necessity for more sophisticated diagnostic tools that account for these variations. It is imperative to establish educational initiatives aimed at increasing awareness of these sex-related disparities. Moreover, fostering international collaborations can provide a broader perspective, facilitate data sharing, and pave the way for a more unified global approach to the diagnosis and management of HF that recognizes both biological and social sex and gender distinctions. Such a strategy is aligned with the core principles of precision medicine, which emphasizes the development of patient-centered approaches that are customized to the biological and genetic makeup of each individual.

Conclusion

Clinical evidence from HF trials points to sex-related disparities in pharmacotherapy for HF (Fig. 2). However, current guidelines for HF management do not provide distinct recommendations

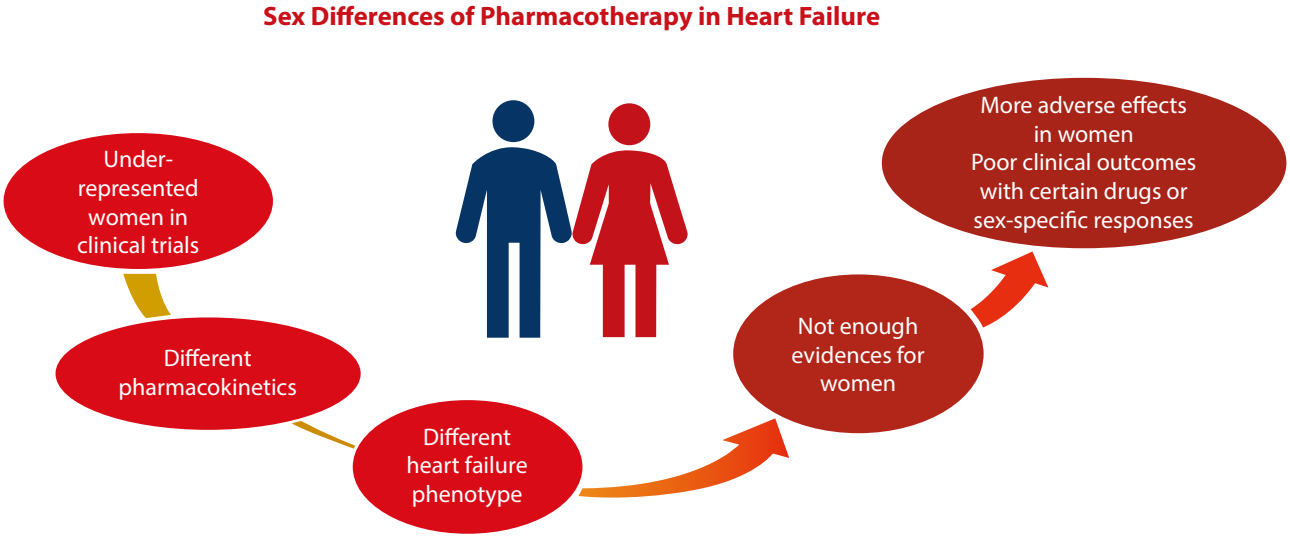

Fig. 2. Overview of sex-based differences in pharmacotherapy for heart failure.

for medication based on these sex-related differences. Adopting a sex-specific pharmacological treatment strategy could be crucial in advancing precision medicine, as it would enhance our understanding of individualized patient characteristics.

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Review Article

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Overview of endocrine tumor syndromes manifesting as adrenal tumors

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Endocrine tumor syndromes constitute a group of disorders characterized by tumors in hormone-producing tissues. These conditions predominantly affect younger patients and often have a familial inheritance. Advances in molecular genetics in recent decades have facilitated the identification of several genes associated with these tumors. The recent World Health Organization classification of adrenocortical tumors integrates the latest developments in pathology, oncology, and molecular biology. In addition, this updated classification includes adrenal cortical diseases based on an understanding of germline susceptibility to these conditions and their clonal-neoplastic nature. Catecholamine-secreting tumors, including pheochromocytoma and paraganglioma, have been found to have a genetic predisposition in as many as 80% of cases. Compared to sporadic cases, endocrine tumor syndromes are more likely to present bilaterally and show synchronous or metachronous disease. This highlights the critical need for early diagnosis, intervention, and ongoing surveillance. This review focuses on the clinical manifestations and genetic basis of endocrine tumor syndromes originating from the adrenal glands.

Introduction

Endocrine tumor syndromes constitute a group of disorders characterized by tumors in hormone-producing tissue. These conditions mainly affect younger patients and often exhibit familial inheritance patterns, with sporadic cases being less common. Patients often initially present with signs and symptoms indicative of hormone overproduction. Nonetheless, non-functional tumors may become apparent due to their mass effect. Pathogenic germline mutations in tumor suppressor genes and oncogenes are implicated in the emergence of various hereditary endocrine tumor syndromes. However, pediatric cases within families may exhibit only subtle clinical signs and minor biochemical alterations, leading to potential misdiagnosis during clinical evaluations.

Over the past few decades, advances in molecular genetics have made it possible to identify many genes associated with the development of endocrine tumors in children. This has improved our understanding of the disease mechanisms, enabling an early diagnosis, timely tumor surveillance, and improved treatment strategies. This review aims to describe the clinical manifestations and molecular genetic basis of endocrine cancer syndromes, focusing on those of adrenal origin.

Ethics statement

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

Adrenocortical tumors

Adrenal tumors are classified into those of the adrenal cortex and those of the adrenal medulla and extra-adrenal paraganglia, according to the World Health Organization (WHO) classification of endocrine tumors [1]. Adrenocortical tumors are found in approximately 5% of the general population, with the majority being small, benign, non-functioning adrenocortical adenomas [2,3]. Adrenocortical carcinomas, however, are rare, with an incidence of 0.2 to 0.3 cases per million in adults [2,3]. Most adrenocortical tumors in adults are discovered incidentally, without excess adrenal hormone production, although 15% are functioning tumors [2]. In contrast, in the pediatric population, adrenal hormone excess is observed in about 80% to 90% of patients, with two age peaks: the first 5 years of life and adolescence [4,5]. In pediatric cases, androgen excess is the commonly observed presentation, followed by Cushing syndrome or a combination of both [4]. Therefore, it is important to consider multiple possibilities in the differential diagnosis of virilization, including androgen-secreting tumors and congenital adrenal hyperplasia [6,7]. Cushing syndrome tends to be more prevalent in older age groups [4]. Androgen excess is associated with accelerated growth, whereas cortical excess leads to a reduction in growth velocity. Therefore, clinical suspicion of adrenal tumors is warranted when patients present with symptoms of virilization and Cushing syndrome. Notably, adrenocortical carcinomas are more common in pediatric cases than in adults [8,9]. Furthermore, some cases of adrenocortical carcinomas are linked to various familial cancer syndromes, such as Beckwith-Wiedemann syndrome (BWS), Li-Fraumeni syndrome (LFS), and multiple endocrine neoplasia type 1 (MEN1) [4,10]. Untreated or inadequately treated congenital adrenal hyperplasia can also lead to the development of adrenal tumors [11,12]. Therefore, when diagnosing adrenocortical carcinoma in pediatric patients, the possibility of familial cancer syndromes must be considered. These syndromes increase the risk of other tumors and require a comprehensive management approach. Thus, a thorough differential diagnosis is essential to ensure appropriate and effective treatment strategies.

Li–Fraumeni syndrome

LFS is a hereditary cancer syndrome caused by a pathogenic mutation in the *TP53* gene. This condition is associated with a high risk of developing various childhood and adult-onset tumors, including adrenocortical carcinomas, breast cancer, soft tissue sarcomas, osteosarcomas, leukemia, and brain tumors [13,14]. The estimated lifetime cancer risk for women with LFS exceeds 90%, while it is over 70% for men [14]. Additionally, individuals with LFS face a 5% to 13% lifetime risk of developing adrenocortical carcinoma [12,15–17]. The incidence of germline *TP53* mutations is particularly high in those diagnosed with adrenocortical carcinoma during childhood, with the rate decreasing from 58% in those diagnosed before the age of 12% to 25% in those diagnosed between the ages of 12 and 20 [15]. The typical clinical presentation of LFS includes symptoms arising from glucocorticoid and androgen excess in early childhood [12]. The long-term prognosis is closely linked to the age at diagnosis and the stage of the tumor; pediatric patients with completely resected small tumors generally have a favorable prognosis

[12,18]. LFS should be considered clinically in individuals who develop a diverse range of cancers at a young age or in those with a family history of cancers such as adrenocortical tumors, breast cancer, or brain tumors. It is important to note that genetic testing for *TP53* mutations is strongly recommended for all pediatric cases of adrenocortical tumors, regardless of family history [12,19].

Beckwith-Wiedemann syndrome

BWS is a genomic imprinting disorder characterized by overgrowth and an increased risk of developing various tumors. Individuals with BWS are at a higher risk for embryonic tumors, such as Wilms' tumor, hepatoblastoma, and neuroblastoma. *IGF2* plays a significant role in the fetal development of the adrenal gland and steroidogenesis, and overexpression of *IGF2* has been observed in pediatric patients with adrenocortical tumors [20,21]. While adrenal hyperplasia and adrenal tumors can occur in BWS, they are less common than embryonic tumors. The overall tumor risk associated with BWS is approximately 5%–10%, with adrenocortical carcinoma accounting for about 7% of malignancies [22]. The incidence of adrenocortical carcinoma in patients with BWS is less than 1%. The most common adrenal masses reported in the literature are incidentally diagnosed adrenal cysts during prenatal and postnatal ultrasound screening [23]. There have also been cases of patients diagnosed with adrenal adenomas due to virilization and cortisol excess. Additionally, a few reports exist of patients with BWS and adrenocortical carcinoma presenting with Cushing's syndrome and virilization [23,24]. For patients with BWS, screening for adrenal tumors is recommended, including clinical evaluations for hormone excess, adrenal ultrasound, and monitoring serum dihydroepiandrosterone sulfate levels every 4 to 6 months [25]. However, given the relatively low incidence of adrenal tumors in BWS, there is limited data on the effectiveness of these screening methods [25].

Multiple endocrine neoplasia type 1 and 4

MEN1 is a rare hereditary cancer syndrome characterized by endocrine and extra-endocrine tumors, including parathyroid hyperplasia/adenoma, pituitary adenoma, and gastrointestinal neuroendocrine tumors. Heterozygous mutations in the *MEN1* tumor suppressor gene are identified in 80% to 90% of MEN1 cases [26]. Adrenal involvement is present in 10% of patients, and 1.4% of MEN1 cases develop adrenocortical carcinoma [27]. In approximately 6% of cases, adrenal involvement is the initial manifestation of MEN1 [27,28]. The majority of adrenocortical tumors in this condition are non-functional, although adrenocortical hormone excess is observed in 15% of MEN1 patients. Adrenocortical tumors are rare in the pediatric population [29]. While the incidence of adrenocortical tumors in LFS and BWS is likely to decrease with age, the incidence in MEN1 may increase with age. For adrenal screening in MEN1, abdominal imaging with CT or MRI is recommended every 3 years, and adrenal lesions require ongoing radiologic surveillance for signs of malignancy [30]. Biochemical evaluation is recommended for lesions larger than 1 cm or for those that present with clinical symptoms [30].

MEN4 is a newly identified MEN syndrome with phenotypic characteristics similar to MEN1. It is caused by mutations in the *CDKN1B* gene. The prevalence of *CDKN1B* mutations in patients presenting with neoplasia related to MEN1 is estimated to be approximately 2%–3% [31,32]. However, due to the limited number of reported cases and the likelihood of undiagnosed cases, the exact incidence and prevalence of MEN4 remain unclear. Additionally, there have been reports of adrenal tumors associated with MEN4, including two patients who presented with

non-functioning adrenal masses [31,32].

Bilateral macronodular and micronodular adrenal cortical disease

The understanding of germline susceptibility and the clonal-neoplastic nature of adrenocortical nodules has led to the refinement of their classification into three categories: sporadic nodular adrenocortical disease, bilateral micronodular adrenocortical disease, and bilateral macronodular adrenocortical disease (BMAD) [33]. Sporadic nodular adrenocortical disease typically presents as non-functioning and can involve one or both adrenal glands. In contrast, bilateral micronodular and macronodular adrenocortical diseases usually result in hypercortisolism and affect both adrenal glands [33]. These latter conditions are often associated with germline mutations. BMAD is characterized by adrenal nodules that are 1 cm or larger and commonly leads to Cushing syndrome, predominantly occurring in adults. The growth of adrenal nodules is related to the activation of the cAMP/protein kinase A (PKA) pathway. Activating mutations in *MC2R* and *GNAS* stimulate downstream cAMP/PKA signaling, leading to the development of BMAD [34]. Pathogenic mutations in *ARMC5*, a tumor suppressor gene, have been implicated in familial and sporadic cases of BMAD [35]. Additionally, research has revealed that BMAD is caused by a two-step genetic process in *ARMC5*: an inherited mutation, followed by a somatic second-hit mutation [35,36]. In addition, germline mutations in *MEN1*, *FH*, and *APC* have also been reported in this condition [37]. The typical age of diagnosis is usually between 40 and 60 years, and the condition is rare in children [35–37].

Micronodular adrenal cortical disease is characterized by the presence of multiple small adrenocortical nodules (<1 cm). It is subdivided into isolated micronodular adrenal cortical disease (i-MAD) and primary pigmented micronodular adrenal cortical disease (PPNAD). Carney complex is characterized by the pigmented lesions on the skin and/or mucosa, PPNAD, cardiac myxomas, and both benign and malignant endocrine tumors [38]. Irrespectively of the subtype, this disease is associated with germline mutations in *PRKAR1A* and *PRKACA* [39]. *PRKAR1A* encodes the type 1A regulatory subunit of PKA, and inactivating mutations in this gene lead to PKA dysregulation and are associated with PPNAD and other forms of adrenal cortical disease [38]. *PRKACA* encodes the catalytic isoform of PKA, and genetic defects in *PRKACA* constitutively activate PKA, resulting in cortisol-producing tumors [39]. In recent reports, mutations in *PDE11A* and *PDE8B* have been identified in patients with i-MAD [40,41]. Given the relative rarity of Cushing syndrome in children, careful consideration of the differential diagnosis, especially regarding bilateral MAD [12,42], is of paramount importance when these symptoms emerge during childhood.

Tumors of the adrenal medulla and paraganglia

Pheochromocytomas (PHEOs) are tumors that secrete catecholamines and originate from chromaffin cells in the adrenal medulla. They account for 80%–85% of all catecholamine-secreting tumors, while the remaining 10%–15% are paragangliomas (PGLs), which occur outside the adrenal glands [43]. These conditions are uncommon causes of hypertension, affecting 0.5%–2% of pediatric cases, and they typically manifest in the first decade of life [12,44–46]. Hypertension is noted in 80%–90% of affected pediatric patients and is often accompanied by symptoms such as palpitations, headaches, or sweating [12,44–46]. Historically, the "rule of 10" posited that only 10% of cases were hereditary, malignant, extra-adrenal, and bilateral. However, recent data from the European-American Pheochromocytoma-Paraganglioma Registry (EAPPR) indicate a much higher

incidence of hereditary cases among pediatric patients, with 80% of 164 pediatric patients having a germline mutation [44]. This represents a significant increase from the previously estimated 30%–40% in smaller case series [45,47,48], a change attributed to enhanced mutation screening, the identification of novel mutations, and more comprehensive population-based data from registries such as the EAPPR. These tumors are associated with hereditary cancer syndromes such as MEN2, neurofibromatosis type 1 (NF1), and von Hippel-Lindau (VHL) disease [43,49]. Germline mutations in the *SDHx* genes are frequently identified in these conditions [43]. These syndromes are inherited in an autosomal dominant pattern with variable penetrance.

Genetic testing for VHL and MEN2 is often recommended for patients diagnosed with PHEO or PGL, especially when there is an early onset or a family history of related tumors [50,51]. The presence of bilateral or multifocal PHEOs strongly suggests these hereditary syndromes. Clinical features such as retinal hemangioblastomas or clear cell renal carcinoma may point to VHL [43,50], whereas medullary thyroid cancer (MTC) or primary hyperparathyroidism might be indicative of MEN2 [52,53]. Malignant or atypical presentations are additional indications for genetic testing. This approach is essential as it informs not only the management of the current tumor but also the monitoring for other neoplasms associated with these syndromes.

Von Hippel-Lindau syndrome

VHL disease is an autosomal dominant tumor syndrome that occurs in approximately 1 in 36,000 live births [54]. It results from germline mutations in the *VHL* gene, a tumor suppressor gene that regulates blood vessel formation through the hypoxia-inducible factor [54]. Individuals with this condition are predisposed to developing highly vascularized tumors in multiple organs, including hemangioblastomas of the retina, cerebellum, and spine, renal cell carcinoma, PHEO, PGL, pancreatic cysts, and neuroendocrine tumors [54]. VHL is classified into type 1 and type 2 disease based on genotype-phenotype correlations, with PHEO associated with type 2 VHL in 25%–30% of cases [55]. PHEO in VHL typically presents in the second decade of life [54]. In children, PHEO and PGL may be the initial indicators of VHL, with cases reported in individuals as young as 5 years old [50]. VHL-associated PHEO has a high incidence of bilateral lesions in up to 60% of cases and synchronous or metachronous recurrence in 10%–30% [51]. These findings underscore the significant incidence of PHEO and PGL in patients with VHL and highlight the necessity for early and lifelong screening. In addition to abdominal imaging, annual testing of plasma metanephrines and plasma normetanephrines is recommended starting at the age of 5 [56].

Multiple endocrine neoplasia type 2

MEN2A is characterized by MTC, PHEO, and primary hyperparathyroidism, which affect 70%–80% of individuals with MEN2. The *RET* proto-oncogene plays a role in both MEN2 and sporadic or familial MTC. MTC is the most common manifestation in patients with MEN2A, presenting as early as the first 5 years of life. A smaller proportion of patients develop PHEO, with the likelihood varying based on specific *RET* mutations. Mutations in *RET* codon 634 are highly penetrant for PHEO, with the risk increasing from 25% at 30 years of age to 88% by 77 years of age [57]. PHEOs in patients with MEN2A are predominantly benign, multicentric, and bilateral [53]. Furthermore, in cases where a unilateral PHEO develops, there is a 30%–50% chance of a contralateral PHEO occurring within 10 years [58,59]. Patients with MEN2B almost invariably present with C-cell hyperplasia and MTC, and PHEO occurs in 30%–50% of cases. They also exhibit distinctive

features such as mucosal neuromas, intestinal ganglioneuromatosis, hyperflexible joints, and a Marfanoid body habitus [53]. Screening for PHEO in children is recommended to start at age 11 for those in the high and highest risk categories, and at age 16 for those in the moderate risk category. PHEO in MEN2 typically progresses, with up to 50% of cases developing bilateral lesions and 25% developing a metachronous lesion within 5–10 years [60,61]. The highly variable interval between the first and second PHEO, along with the lack of a direct correlation with the *RET* mutation, necessitates prolonged follow-up.

Neurofibromatosis type 1

NF1 is a multisystem genetic disorder that predisposes individuals to benign and malignant tumors due to mutations in the *NF1* gene [62]. This gene is responsible for producing neurofibromin, a protein that acts as a negative regulator of Ras activity [63]. When neurofibromin is lost, there is an increase in mitogenic signaling, leading to enhanced cellular proliferation or differentiation [63]. PHEOs in NF1 patients are reported in approximately 0.1%–3% of cases, with an average age of onset at 40 years; however, a prospective study has indicated a much higher prevalence of 14.6% [64,65]. The reason for this discrepancy may be the previous lack of biochemical testing, which suggests that some cases may have gone undetected. About half of the cases of PHEOs and PGLs are symptomatic [66]. Biochemical testing for these conditions, which includes measuring urine or plasma catecholamines and metanephrines, is recommended when symptoms are suggestive, during pregnancy, and before elective surgery involving general anesthesia [62]. However, routine biochemical screening for PHEOs and PGLs in adults with NF1 is not currently advised [62]. In a recent notable case, a dopamine-secreting PHEO was discovered in a 13-year-old patient with NF1 [67]. This particular tumor did not exhibit the classic symptoms of PHEO, nor were there elevated levels of metanephrines. Consequently, the physician's clinical suspicion was pivotal in the differential diagnosis of adrenal tumors, particularly in light of the patient's predisposition to cancer.

Succinate dehydrogenase-related pheochromocytomas and paragangliomas

Succinate dehydrogenase (SDH), also known as mitochondrial complex II, is a crucial enzyme for mitochondrial energy production. It is anchored to the inner mitochondrial membrane and consists of four distinct subunits: A, B, C, and D [68]. While the loss of function in *SDHB*, *SDHC*, and *SDHD* is strongly associated with the development of PHEO and PGL, data on *SDHA* are more limited [69]. Approximately 20% of patients diagnosed with PHEO or PGL carry a germline mutation in one of the *SDHx* genes [69,70]. Individuals with *SDHD* mutations exhibit high penetrance, often developing multiple tumors, predominantly in the parasympathetic region of the head and neck [68,69]. In contrast, *SDHB* mutations predispose carriers primarily to retroperitoneal PHEO and sympathetic PGL, and are associated with a more aggressive disease course, including a higher rate of malignancy and metastasis [68,69]. Data on *SDHC* mutations are scarce, but carriers typically present with non-metastatic head and neck PGLs [69]. For asymptomatic carriers of *SDHB* mutations, initial tumor screening is recommended between the ages of 6 and 10 years. For those with asymptomatic *SDHA*, *SDHC*, and *SDHD* mutations, screening should commence between the ages of 10 and 15 years [69]. In children, biochemical measurements are utilized for screening. Additionally, MRI of the head, neck, chest, abdomen, and pelvis is the recommended primary imaging modality for initial tumor screening in childhood [69].

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Conclusion

Over the past 20 years, significant progress has been made in understanding the syndromes that lead to endocrine tumors, greatly improving the diagnostic and therapeutic approaches available to clinicians. These advances include the identification of key genes responsible for these tumors and the elucidation of the pathways that lead to endocrine cell hyperplasia and tumor progression. Nonetheless, challenges remain in pinpointing specific genes and determining their exact role in initiating these tumors. Alongside these genetic insights, this review has effectively outlined the incidence and clinical presentation of adrenal tumors (Table 1). This in-depth knowledge is crucial for improving patient care by facilitating early detection,

Table 1. Endocrine tumor syndromes

Syndromes	Genes involved	Clinical manifestations	Surveillance screening
Endocrine tumor syndrome related to adrenocortical tumor			
Li–Fraumeni syndrome	*TP53*	Adrenocortical carcinoma, breast cancer, soft tissue sarcomas, osteosarcomas, leukemia, brain tumors	Abdominal ultrasound every 3 to 4 months If ultrasound is not possible, blood test every 3–4 months to measure total testosterone, dehydroepiandrosterone, and androstenedione.
Beckwith-Wiedemann syndrome	Abnormal methylation at 11p15.5, *CDKN1C*	Macroglossia, hemihyperplasia, omphalocele, neonatal hypoglycemia, macrosomia, embryonal tumors	Limited data on the utility of these screening methods Clinical evaluations for hormone excess
Multiple endocrine neoplasia type 1	*RET*	Neoplasia of the parathyroid glands, the anterior pituitary gland, neuroendocrine tissue of gastro-entero-pancreatic organ systems	Abdominal imaging with CT or MRI is recommended every 3 years
Bilateral macronodular and micronodular adrenal cortical disease	*ARMC5* *PRKAR1A*, *PRKACA*, *PDE11A*, *PDE8B*	Bilateral adrenal hyperplasia associated with one or more adrenal nodules, Cushing syndrome	
Endocrine tumor syndrome related to pheochromocytoma and paraganglioma			
Von Hippel-Lindau syndrome	*VHL*	Hemangioblastomas of the retina, cerebellum, and spine, renal cell carcinoma, pheochromocytoma, paraganglioma, pancreatic cysts, neuroendocrine tumors	Annual abdominal imaging and plasma metanephrine and normetanephrine testing starting at 5 years of age
Multiple endocrine neoplasia type 2	*RET*	Medullary thyroid cancer, PHEO, primary hyperparathyroidism	Calcium or ionized calcium with PTH levels, plasma metanephrines and normetanephrines or 24-hour urinary metanephrines and normetanephrines starting at 11 years for those in the high and highest categories and 16 years for those in the moderate category
Neurofibromatosis type 1	*NF1*	Plexiform neurofibromas, malignant peripheral nerve sheath tumors, optic pathway gliomas, breast cancer	Limited data on the utility of these screening methods
SDH-related disease	*SDHA*, *SDHB*, *SDHC*, *SDHD*	Early onset, multifocal disease, high rate of recurrence and metastasis	Recommended timing of initial tumor screening between the ages of 6 and 10 years in *SDHB* defects; between the ages of 10 and 15 years in *SDHA*, *SDHC*, and *SDHD* defects

PHEO, pheochromocytoma; SDH, succinate dehydrogenase.

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guiding effective management, and informing the development of targeted treatment strategies.

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The article is prepared by a single author.

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Original Article

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Sleep disorders, sleep quality, and health-related quality of life in patients with cancer in Turkey: a multi-center cross-sectional survey

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Keywords
Disorders of excessive somnolence; Neoplasms; Quality of life; Restless legs syndrome; Sleep initiation and maintenance disorders

Objectives: The present study aims to examine the frequency of sleep disorders and the level of sleep quality, as well as their relationship with health-related quality of life in cancer patients.

Methods: This multi-center cross-sectional survey included 333 cancer patients ranging in age from 16 to 72 years, between June 15, 2017, and August 30, 2018 at the Ankara Oncology Hospital and Erciyes University Kemal Dedeman Oncology Hospital Polyclinic. Data were collected via various surveys conducted through face-to-face interviews, including following measurement tools: Short Form 36 Health Questionnaire, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness, and the Berlin Sleep Questionnaire for obstructive sleep apnea. Face-to-face interviews were carried out with patients who presented for an initial examination or follow-up and were awaiting their appointments.

Results: The most commonly reported sleep disorders were daytime sleepiness (36.9%), sleep respiratory disorders (34.8%), insomnia (29.4%), and parasomnias (28.8%). Good sleepers were found to have significantly higher physical (40.20±10.08 vs. 33.21±8.06; P<0.001) and mental component scores (43.54±8.25 vs. 38.20±7.52; P<0.001) than poor sleepers. Conversely, individuals with insomnia (P<0.01), daytime sleepiness (P<0.001), sleep-respiratory disorders (P<0.05), and bruxism (P<0.001) showed significantly lower scores in both physical and mental components. Additionally, those with restless legs syndrome had a significantly lower physical component score (P<0.001), and those with parasomnias had significantly lower mental component scores.

Conclusion: Cancer patients exhibited moderate average sleep quality scores, with over half of them demonstrating low quality sleep patterns. Sleep disorders significantly impacted their health-related quality of life.

Introduction

Background

Cancer's rising incidence, partly due to an aging population, is noteworthy. By 2030, the number of older adults with cancer is expected to increase by 67% from 2010 in the United States [1]. Advances in early detection and treatment have extended cancer patients' life expectancy. Consequently, effective treatment, minimizing treatment side effects, and improving patients' quality of life (QoL) are vital goals. Identifying factors that hinder cancer patients' daily activities, functional capacity, and QoL is crucial. Factors like pain, depression, fatigue, and sleep disorders

still significantly affect their QoL [2,3].

Sleep disorders, affecting 9%–33% across ages [4], are particularly concerning for cancer patients, impairing their daily life and health-related QoL (HRQoL) [5,6]. These disorders are more severe in cancer patients due to the disease's direct impact, treatment side effects, and comorbid conditions [7]. Insomnia, a common sleep disorder, affects daily activities and is more prevalent in cancer patients (30%–69%) compared to the general adult population (30%) and elderly (23%–50%) [8]. In some cancer cases, insomnia prevalence can be as high as 30%–93% [9].

Sleep disorders and symptom burden greatly diminish older cancer patients' health, functionality, and QoL, potentially worsening disease progression and side effects [10]. Older patients with sleep disturbances face physical and psychosocial challenges, including musculoskeletal, gastrointestinal issues, anxiety, and depression [11]. Insomnia correlates with reduced daily activity, increased fall risk, and cognitive issues [12]. Factors like hospitalization, pain, treatment side effects, immune alterations, and physiological changes contribute to sleep disorders. Insomnia, combined with depression and anxiety, can adversely affect long-term QoL. It impairs immune functions by altering cytokine expression, impacting disease trajectory and mortality [13]. Insomnia is also associated with decreased natural killer cell numbers and activity due to abnormal cortisol synthesis [13,14]. Recognizing, diagnosing, and treating sleep disorders in cancer patients are essential. This helps manage disease prognosis, prevent recurrence, and enhance patient QoL. Despite their importance, sleep disorders are often overlooked in patient care.

Objectives

This study aimed to evaluate sleep disorders and sleep quality, along with their impact on the overall QoL, by using universally recognized measurement tools that are highly sensitive and specific. These tools were based on self-reported data and diagnostic questions administered to cancer patients.

Methods

Ethics statement

The Ethics Committee in Clinical Research on Human Subjects at Erciyes University, Faculty of Medicine, approved this study (Decision date and no.: 2013/232). All participants provided both verbal and written consent before data collection commenced.

Study design

This was a multi-center cross-sectional survey study. It was described according to the STROBE statement (https://www.strobe-statement.org/).

Setting

This study was conducted with 333 volunteer cancer patients ranging in age from 16 to 72 years, between June 15, 2017, and August 30, 2018. Face-to-face interviews were carried out with patients who presented at the Ankara Oncology Hospital and Erciyes University Kemal Dedeman Oncology Hospital Polyclinic for an initial examination or follow-up and were awaiting their appointments. As tools for data collection, we utilized self-administered questionnaires, scales, indexes, and a selection of diagnostic and support questions.

Participants

Participants who were unable to complete the interview and questionnaires due to medical reasons (e.g., cognitive impairment), were excluded from the study. The response rate was 90%.

Variables

Demographic data and topics of questionnaires were outcome variables.

Measurement

The research data were collected using questionnaires that addressed sociodemographic variables (8 questions), the Short Form 36 Health Questionnaire (SF-36; 11 questions) [15], the Pittsburgh Sleep Quality Index (PSQI; 19 questions), the Epworth Sleepiness Scale (ESS; 8 questions) [16,17], and the Berlin Sleep Questionnaire for obstructive sleep apnea (10 questions) [18]. Additional information was obtained through questions derived from the original scales' global diagnostic criteria for insomnia (3 questions) [19], parasomnias (6 questions), restless legs syndrome (RLS; 5 questions) [20], and bruxism (3 questions). A more specific description on the measurement tools are presented in Supplement 1. Socio-demographic data was obtained from the participants that are presented in Supplement 2.

Bias

Since the subject population participated in this survey study voluntarily, there may be sampling bias. The persons who did not participated in the study, may be in worse health or a state of lack of strength.

Study size

Sample size estimations were not made since only voluntary participants were included during the limited period.

Statistical methods

The data were analyzed using the IBM SPSS Statistics Standard Concurrent User V 25 (IBM, Armonk, NY, USA) software. To assess the normality of quantitative variables, the Shapiro-Wilk test was employed. Descriptive statistics for continuous numerical variables that followed a normal distribution are presented as the mean±SD. For variables that conformed to parametric assumptions, Student's t-test was utilized, while the Mann-Whitney U test was applied to those that did not. The chi-square test and Fisher exact test were used for categorical variables. Sleep disorders were converted into dichotomous (yes/no) data by employing global scale/index scores, cut-off points, and diagnostic criteria questions. Linear regression analysis was conducted to determine the impact of sleep disorders and sleep quality on physical and mental health QoL. In this analysis, the physical health QoL summary score (PCS) and mental health QoL summary score (MCS) were treated as dependent variables. Independent variables included the PSQI, RLS, sleep-disordered breathing, parasomnias, daytime sleepiness, and total insomnia scores. The significance level for statistical evaluation was set at $P<0.05$.

Results

Participants

Socio-demographic characteristics were presented in Table 1. A significant proportion

Table 1. Socio-demographic characteristics of oncology patients (n=333)

Variables	No.	%
Gender		
Female	188	56.5
Male	145	43.5
Age group (years), mean±SD: 50.81±11.31 (min-max:16–72)		
16–35	32	9.6
36–45	59	17.7
46–55	109	32.7
56–72	133	39.9
Marital status		
Married	291	87.4
Single/separated/widowed	42	12.6
Educational status		
Primary school	148	44.4
Secondary and high school	103	30.9
University	26	7.8
Monthly income (TL), mean±SD: 1,409.10±818.45 (min-max: 200–5,900)		
Low (200–1,400)	194	58.3
Middle (1,401–5,900)	139	41.7
Active working status		
Working	54	16.2
Not working	279	83.8
Smoking		
Yes	40	12
No	293	88.8
Alcohol consumption		
Yes	24	7.2
No	309	92.8
PSQI, mean±SD: 6.17±3.83		
Good sleepers (≤5 points)	136	40.8
Poor sleepers (>5 points)	181	59.2
Stage of cancer		
Receiving treatment	261	78.3
Completed treatment	72	21.7
Types of treatment		
Chemotherapy	86	25.8
Radiotherapy	5	1.5
Chemotherapy+radiotherapy	47	14.1
Treatment for medical support	9	2.7
Chemotherapy and medical support	80	24
Chemotherapy, radiotherapy, and medical support (e.g., pain control, intake drugs and screening)	70	21
Surgery	48	14.4
Unknown	36	10.8

TL, Turkish lira; PSQI , Pittsburgh Sleep Quality Index.

of cancer patients (83.8%) reported being unemployed, non-smokers (88.8%), and non-alcohol drinkers (92.8%) 1. Regarding treatment, 25.8% of cancer patients underwent isolated chemotherapy, 1.5% received only radiotherapy, and 14.1% underwent a combination of chemotherapy and radiotherapy.

Main results

Number of cancer patients according to the organs or systems, and sex

When assessing the prevalence of cancer by sex, cancers of the respiratory system were the most common in men, accounting for 33.8% of cases. Cancers of the gastrointestinal system followed at 25.5%, and hematological cancers ranked third at 20.0%. In women, cancers of the breast and endocrine organs were the most prevalent, making up 41.5% of cases. Gynecological cancers, including those of the ovary, fallopian tubes, uterus, cervix, vagina, and vulva, were the second most common (18.1%), and hematological cancers were the third most common, representing 13.3% of cases.

Number of cancer patient according to organs or systems are presented in Table 2.

Ages of cancer patients

Approximately 40% of the participants were elderly. The treatments for these patients typically include chemotherapy and radiotherapy. The most common types of cancer among the elderly were breast and endocrine system cancers (including breast and thyroid) at 48.5%, respiratory system cancers (such as lung, bronchus, and oto-rhino-laryngeal) at 33.2%, and gastrointestinal system cancers (including colorectal, hepatobiliary, and pancreatic) at 18.3%. Compared to other age groups, elderly participants tended to have the same types of cancers. The prevalence of sleep disorders among elderly cancer patients was as follows: daytime sleepiness in 41.3% (55 individuals), sleep-related respiratory disorders in 27% (36 individuals), insomnia in 20.3% (27 individuals), and parasomnias in 11.4% (15 individuals). It is noteworthy that RLS and bruxism were not observed as sleep disorders in this group, although they were common among other participants.

Sleep disorders

The prevalence of sleep disorders among cancer patients was presented in Table 3. While sleep disorders did not show statistically significant relationships with sex, with the exception of

Table 2. Distribution of cancer according to organs or systems by gender

Types of cancer	No. (%)			Statistical assessment
	Male	Female	Total	χ^2/P
Gastrointestinal system (esophagus, stomach, duodenal, colorectal, hepatobiliary, pancreatic) cancers	37 (69.8)	16 (30.2)	53 (15.9)	17.692/<0.001
Hematological (lymphoma, leucemia, multiple myeloma, etc.) cancers	29 (53.7)	25 (46.3)	54 (16.2)	1.663/0.231
Breast-endocrine (breast, thyroid, etc.) system cancers	0 (0.0)	78 (100)	78 (23.4)	78.61/<0.001
Gynecological (ovarian, tubal, uterine, cervical, vaginal, vulvar) cancers	0 (0.0)	35 (100)	35 (10.2)	29.205/<0.001
Respiratory system (lung-bronchial, oto-rhino-laryngeal) cancers	49 (84.5)	9 (15.5)	58 (17.4)	33.434/<0.001
Other (skin and its appendages; malignant melanoma, squamous cell, orthopedic, primary bone, etc.) cancers	30 (53.6)	26 (46.4)	56 (16.8)	2.754/0.198

Table 3. Distribution of cancer patients with sleep disorders according to gender

Sleep disorders	No. (%)			χ^2/P
	Male	Female	Total	
Restless legs syndrome	29 (20.0)	48 (25.5)	77 (23.1)	1.409/0.242
Insomnia	48 (33.1)	50 (26.6)	98 (29.4)	1.669/0.196
Parasomnias	50 (34.5)	46 (24.5)	96 (28.8)	4.002/0.045
Excessive daytime sleepiness	56 (38.6)	67 (35.6)	123 (36.9)	0.313/0.576
Sleep respiratory disorders	50 (34.5)	66 (35.1)	116 (34.8)	0.014/0.906
Bruxism	28 (19.3)	26 (13.8)	54 (16.2)	1.810/0.180

parasomnias, they tended to be more severe in men. Excessive daytime sleepiness (38.6% vs. 35.6%), sleep respiratory disorders (38.6% vs. 34.9%), insomnia (33.1% vs. 26.6%), parasomnias (34.5% vs. 24.5%, P=0.045), and bruxism (19.3% vs. 13.8%) were more prevalent in men than in women. Conversely, RLS, which was generally reported in 23.1% of patients, was more common in women than in men (25.5% vs. 20.0%; Table 3).

Sleep quality

The mean PSQI score among cancer patients was 6.17±3.83 (95% CI, 5.75–6.58; P<0.001). Of these patients, 136 (40.8%) had normal (good) sleep quality, with PSQI scores of 5 or less, while 181 (59.2%) experienced poor sleep quality, with PSQI scores ranging from 6 to 16. The mean PSQI score for men was slightly higher at 6.30±3.82, compared to 6.06±3.85 for women, although this difference was not statistically significant (P>0.05; Table 1). All sleep disorders, except for parasomnias, showed significant associations with sleep quality (Table 4).

Upon investigating the relationship between mean PSQI scores, sleep quality level, and sleep disorders, it was revealed that individuals experiencing excessive daytime sleepiness (36.9%) had a mean PSQI score of 7.47±3.99 (P<0.001), with 61.8% of them exhibiting poor sleep quality (χ^2=12.079, P=0.001). Additionally, a significant positive association was noted between daytime sleepiness and sleep quality (χ^2=20.486; P<0.001). Those with sleep-disordered breathing (34.8%) had a mean PSQI score of 8.67±3.83 (P<0.001), and 58.6% were found to have poor sleep quality (χ^2=12.079, P=0.001). Participants with insomnia (29.4%) had a mean PSQI score of 8.67±3.83 (P<0.001), with 73.5% reporting poor sleep quality (χ^2=43.331; P<0.001). The mean PSQI score for patients with RLS (23.1%) was 7.57±3.91 (P<0.001), and 58.4% had poor sleep quality (χ^2=6.590, P=0.010). Lastly, participants with bruxism (16.2%) had a mean PSQI score of 7.59±4.28 (P=0.003), with 66.7% experiencing poor sleep quality (χ^2=11.479, P=0.001). Patients with insomnia, bruxism, and RLS exhibited higher mean PSQI scores than their counterparts, indicating that these groups had lower sleep quality levels.

Associations between sleep disorders and health-related quality of life

When assessing the relationship between sleep disorders and HRQoL using summary scores for physical and mental health components, it was observed that the average mental health QoL scores across all sleep disorders were significantly higher than those for physical health QoL. However, when evaluating physical health QoL on its own, patients with all types of sleep disorders—except for parasomnia—exhibited significantly lower scores. Conversely, patients with all sleep disorders, with the exception of RLS, had significantly lower mental health QoL

Table 4. Association between sleep disorders and level of sleep quality in cancer patients (n=333)

Sleep disorders	PSQI score		Level of sleep quality			
	Mean±SD	P-value	Good (PSQI: ≤5 points)	Poor (PSQI: 6–16 points)	Total	χ^2/P
			No. (%)	No. (%)	No. (%)	
Restless legs syndrome						
Yes	7.57±3.91	<0.001	32 (41.6)	45 (58.4)	77 (23.1)	6.590/0.010
No	5.75±3.71		149 (58.2)	107(41.8)	256 (76.9)	
Insomnia						
Yes	8.67±3.83	<0.001	26 (26.5)	72 (73.5)	98 (29.4)	43.331/<0.001
No	5.12±3.32		155 (66.0)	80 (34.0)	235 (70.6)	
Parasomnias						
Yes	7.09±3.96	0.005	45 (46.9)	51 (53.1)	96 (28.8)	3.032/0.090
No	5.79±3.72		101 (42.6)	136 (57.4)	237 (71.2)	
Epworth Sleepiness Scale						
Yes	7.47±3.99	<0.001	47 (38.2)	76 (61.8)	123 (36.9)	20.486/<0.001
No	5.40±3.53		134 (63.8)	76(36.2)	210 (63.1)	
Sleep respiratory disorder						
Yes	7.07±3.87	0.002	48 (41.4)	68 (58.6)	116 (34.8)	12.079/0.001
No	5.68±3.73		133 (61.3)	84 (38.7)	217 (65.2)	
Bruxism						
Yes	7.59±4.28	0.003	18 (33.3)	36 (66.7)	54 (16.2)	11.479/0.001
No	5.89±3.68		163 (58.4)	152 (45.6)	279 (83.8)	

PSQI, Pittsburgh Sleep Quality Index.

scores. Additionally, individuals with RLS had the lowest PCS scores, while those with bruxism had the lowest MCS scores (Table 5).

Sleep quality and health-related quality of life

All sub-dimensions of the SF-36 and the summary scores for the physical and mental health components were found to be significantly lower in poor sleepers. The scores for the physical and emotional role difficulty sub-dimensions were particularly impacted, markedly reducing the QoL in these patients. Poor sleep quality was found to affect the physical health component of QoL more significantly than the mental health component, as shown in Table 6. Conversely, patients classified as good sleepers had significantly higher scores in the sub-dimensions of bodily pain, social functioning, and mental health than those classified as poor sleepers. These patients also had relatively higher scores in the sub-dimensions of vitality, general health, and physical functioning.

Predictive factors of health-related quality of life

In the linear regression analysis, the PCS and MCS dimension scores are treated as dependent variables, while sleep quality, parasomnias, sleep-disordered breathing, excessive daytime sleepiness, bruxism, RLS, and insomnia are considered independent variables. Poor sleep quality and sleep disorders accounted for 50.95% (95% CI, 37.10%–64.80%; R^2=0.293; P<0.001) of the

Table 5. Association between sleep disorders and health-related QoL in cancer patients (n=333)

Sleep disorders	No.	SF-36 summary scores			
		PCS score	P-value	MCS score	P-value
		Mean±SD		Mean±SD	
Restless legs syndrome					
Yes	77	31.30±8.38	<0.001	39.10±7.63	0.120
No	256	37.50±9.44		40.77±8.39	
Insomnia					
Yes	98	33.51±9.13	0.002	38.46±7.67	0.006
No	235	37.13±9.56		41.19±8.36	
Parasomnia					
Yes	95	36.23±9.82	0.842	38.20±8.82	0.002
No	238	36.00±9.48		41.27±7.85	
Epworth Sleepiness Scale					
Yes	123	32.05±7.19	<0.001	38.22±7.47	<0.001
No	210	38.42±10.00		41.65±8.42	
Sleep respiratory disorders					
Yes	116	34.30±8.36	0.009	38.67±7.58	0.004
No	217	37.01±10.04		41.30±8.45	
Bruxism					
Yes	54	31.68±7.92	<0.001	36.79±7.31	<0.001
No	279	36.92±9.63		41.08±8.24	
Sleep quality					
Good sleepers (≤5 points)	136	40.20±10.08	<0.001	43.54±8.25	<0.001
Poor sleepers (>5 points)	197	33.21±8.06		38.20±7.52	

QoL, quality of life; SF-36, Short Form-36; PCS, physical component summary; MCS, mental component summary.

Table 6. Association between sleep quality and health-related QoL in cancer patients (n=333)

SF-36 domains	Level of sleep quality			
	Good sleepers (PSQI: 0–5 points)	Poor sleepers (PSQI: 6–16 points)	Overall SF-36	P-value
	(n=181)	(n=152)	(n=333)	
PF	52.48±34.21	34.47±26.95	44.26±32.34	<0.001
RP	40.33±44.83	8.55±23.91	25.82±40.01	<0.001
BP	61.51±24.10	42.90±22.35	53.02±25.07	<0.001
GH	53.76±18.05	41.82±17.11	48.31±18.58	<0.001
VT	54.58±19.23	40.88±17.18	48.33±19.53	<0.001
SF	62.63±25.65	46.62±23.59	55.33±25.95	<0.001
RE	47.14±45.94	15.57±33.42	32.73±43.59	<0.001
MH	62.29±15.81	51.84±14.75	57.52±16.17	<0.001
PCS	40.20±10.08	33.21±8.06	36.07±9.56	<0.001
MCS	43.54±8.25	38.20±7.52	40.38±8.24	<0.001

Values are presented as mean±SD .

QoL, quality of life; SF-36, Short Form-36; PSQI, Pittsburgh Sleep Quality Index; PF, physical function; RP, role difficulty (physical); BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role difficulty (emotional); MH, mental health; PCS, physical component summary; MCS, mental component summary.

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deterioration in physical health QoL and 28.25% (95% CI, 15.60%–40.89%; R^2=0.207; P<0.001) of the impairment in mental health QoL. Additionally, 51.65% (95% CI, 33.46%–69.84%, R^2=0.291; P<0.001) of the physical health QoL deterioration and 35.26% (95% CI, 19.28%–51.23%; R^2=0.283; P<0.001) of the mental health QoL impairment can be attributed to these factors.

Discussion

Key results

It has shown that people who sleep well typically have considerably higher scores in physical (average score of 40.20 compared to 33.21; with a significance level P<0.001) and mental health components (average score of 43.54 compared to 38.20; with a significance level P<0.001) than those who sleep poorly. On the other hand, individuals suffering from insomnia, daytime sleepiness, sleep-respiratory disorders, and bruxism were found to have significantly lower scores in both physical and mental health aspects. Moreover, people with RLS had notably lower physical health scores, and those with parasomnias had significantly lower mental health scores.

Interpretation/comparison with previous studies

Prevalence of sleep disorders

Our analysis of patients with various cancers showed that the most common sleep disorders were excessive daytime sleepiness (36.9%), sleep-disordered breathing (34.8%), and insomnia (29.4%). These findings align with Davidson et al. [21], who reported leg restlessness, insomnia, and excessive daytime sleepiness as most prevalent, though the order varied. Our prevalence of excessive daytime sleepiness was higher than Davidson et al. [21] but lower than Jaumally et al. [14]. We found a 35.8% prevalence of sleep-related breathing disorders, notably high in patients with respiratory system cancers (43.1%). Dreher et al. [22] reported a 49% prevalence in lung cancer patients, and Huppertz et al. [23] found a 90% prevalence in head and neck cancer patients. Insomnia prevalence was 29.5%, with the highest rate (46.6%) in respiratory system cancer patients [24].

Types of cancer and sleep quality

The average PSQI score among our cancer patients was 6.17, indicating moderate sleep quality disorder. Over half (59.2%) were poor sleepers. While no significant relationship was found between cancer type and sleep quality, higher prevalence of poor sleep quality was observed in patients with respiratory system, hematological, and breast cancers. Other studies reported varying rates of poor sleep quality in lung [25] and breast [26] cancer patients, and in those with advanced cancers [27].

Relationship among sleep disorders, sleep quality, and health-related quality of life

Patients with sleep disorders had higher PSQI scores, reflecting worse sleep quality. The prevalence ranged from 16% to 37%, with bruxism and insomnia patients showing the highest PSQI scores. Cheng and Lee [28] identified insomnia as a major troubling symptom for cancer patients. Sleep disorders were linked to reduced physical health QoL, except for parasomnias. RLS and bruxism patients experienced significant declines in physical and mental health QoL, respectively [10]. Chronic insomnia can lead to neuropsychological disorders and weaken immune defenses [9].

Our study found a strong association between poor sleep quality and lower physical health QoL. Poor sleepers showed notable reductions in physical and emotional-role functioning. Linear regression analysis identified poor sleep quality as a primary factor for the decline in physical and mental health QoL. A recent study [29] found a significant negative correlation between sleep disturbances and all QoL domains, with psychological aspects more affected than physical health. Prior studies have linked sleep disorders with reduced QoL, depression [30], concentration difficulties [31], fatigue, and lower survival rates [12]. The connection between sleep problems and physical or mental health concerns remains varied, with some studies [32] finding a stronger link to physical health issues, while others [33] noted a stronger association with mental health factors.

Limitations

As mentioned in the methods section, the sampling is conventional. Only voluntary participants were included.

Suggestion for further studies

Future research should investigate patients' sleep patterns prior to medical care or the onset of illness. Furthermore, present study is a descriptive. Therefore, cohort study or randomized-controlled study is required to compare the QoL of cancer patients with sleep disorders.

Conclusion

Improving the sleep quality of cancer patients through early detection and social support is comparably important to disease treatment. Addressing factors that impact the QoL of cancer patients, such as pain, sleep disorders, fatigue, and anxiety, can lead to improvements in their QoL. Neglecting these issues; however, can have a detrimental effect on patient well-being, as these symptoms can exacerbate each other and lead to further decline. By understanding the importance of social support and motivation, healthcare professionals and family members of patients can actively contribute to alleviating sleep problems and enhancing the QoL of those affected by cancer.

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Data availability
Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/CMG88I

Dataset 1. Raw response data from participants

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Supplement 1. Explanation of survey tools, including validity test
Supplement 2. Survey questionnaire

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Original Article

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Exosomal microRNAs (miRNAs) in blood and urine under physiological conditions: a comparative study

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Keywords
Exosome; Urine; Blood; Physiology, comparative

Objectives: Blood and urine are commonly used specimens for clinical testing, and their contents, particularly exosomal microRNA (miRNA), are diverse, reflecting the metabolic activities of tissues and organs in the body.

Methods: Blood and urine samples were collected from six healthy adults. Exosomes were then enriched from these samples, followed by sequencing and bioinformatic analysis of exosomal miRNA.

Results: The comparative analysis of miRNAs in blood and urine revealed that 41 miRNAs were more abundant in blood, while 61 were found at lower levels. Notably, hsa-miR-934 was among those with higher expression in blood, whereas hsa-miR-425-5p was one of the miRNAs with lower expression. Kyoto Encyclopedia of Genes and Genomes pathway analysis indicated that the target mRNAs of differentially expressed exosomal miRNAs (DEexo-miRNAs) in both blood and urine are implicated in various signaling pathways, including proteoglycans in cancer, axonal guidance, and the regulation of the actin cytoskeleton. Additionally, the target mRNAs associated with DEexo-miRNAs in urine were also linked to processes such as ubiquitin-mediated proteolysis and the phosphatidylinositol signaling system. In contrast, the target mRNAs corresponding to DEexo-miRNAs in blood were involved in the FoxO signaling pathway and chronic myeloid leukemia, among others.

Conclusion: This study observed differential expression of exosomal miRNAs in blood and urine, thereby enriching the available library of exosomal miRNA for these two sample types. It also lays the groundwork for the detection of exosomal biomarkers from blood and urine.

Introduction

MicroRNA (miRNA) is a type of endogenous non-coding RNA (ncRNA) with a regulatory function found in eukaryotes, typically ranging from 18 to 25 nucleotides in length. Mature miRNA is generated through a series of nuclease cleavages and processing of longer precursor transcripts. It is then incorporated into RNA-induced silencing complexes. These complexes recognize target mRNA through base-pair complementarity, guiding the RNA-induced silencing complexes to either degrade the target mRNA or inhibit its translation, depending on the degree of complementarity [1,2]. Recent studies have shown that miRNAs play roles in a variety of regulatory pathways. These include development, viral defense, hematopoiesis, organogenesis, cell proliferation and apoptosis, as well as lipid metabolism [2–5].

Exosomes have recently become a prominent topic, and the analysis of their cargo has

garnered significant attention [6–9]. The double-layered lipid membrane of exosomes ensures the stability of their internal contents, providing a more accurate reflection of the physiological and pathological states of their cells of origin. Consequently, exosome research has been incorporated into the realm of liquid biopsy, complementing studies on circulating tumor cells and cell-free nucleic acids [10]. Our previous research indicated that the detection of exosome-derived miRNAs is more consistent than that of mRNAs [11]. However, several questions remain unanswered: Are exosomal miRNAs uniformly expressed in different bodily fluids, such as blood and urine, within the same human body? Which exosomal miRNA is present across various bodily fluids under normal physiological conditions? Which body fluid is more suitable for the detection of extracellular vesicles in future studies? Currently, these issues remain unresolved. This study presents a comparative analysis of exosomal miRNAs in urine and blood under physiological conditions.

Methods

Ethics statement

This study was approved by the Ethics Committee of Chengdu University (no. 2081920062). All participants understood the purpose and content of the study and signed informed consent.

Specimen source and pre-treatment

Urine samples were obtained from morning midstream collections, and blood samples were drawn from fasting individuals who had not eaten for more than 10 hours—specifically, 10 mL of peripheral venous blood and 100 mL of urine were collected from six healthy adults. These volunteers had not taken any medications for at least seven days prior to sample collection. The basic information for the six individuals is presented in Table 1. Blood samples, treated with EDTA as an anticoagulant, were centrifuged at 1,000×g for 15 minutes, and the resulting supernatant was retained. After further centrifugation at 10,000×g for 10 minutes at 4°C, ammonium sulfate powder was added to achieve a final concentration of 1.06%. The mixture was then centrifuged again at 10,000×g for 15 minutes at 4°C, and the supernatant was aspirated. An equal volume of 16% polyethylene glycol solution was added to the remaining solution and left to stand overnight at 4°C. Following centrifugation at 4,000×g for 1 hour, the supernatant was carefully removed, and the pellet, containing the exosomes, was collected. The enrichment and identification of urinary exosomes were carried out in accordance with established protocols [12,13]. The results of the electron microscopy examination of the exosomes and the particle size analysis are depicted in Fig. 1.

Table 1. The basic information of six healthy individuals

Age	Sex	BMI (kg/m^2)	FBG (mmol/L)	hs-CRP (mg/L)	Urinary pH value	Urine specific gravity
36	Male	22	4.95	9.45	6.5	1.010
27	Female	20	4.80	2.33	6.0	1.015
42	Male	23	6.00	8.55	7.0	1.012
35	Female	23	5.33	3.44	7.5	1.020
23	Male	20	3.98	1.67	5.3	1.024
58	Female	27	6.00	9.88	4.8	1.023

BMI, body mass index; FBG, fasting blood glucose; hsCRP, high-sensitivity C-reactive protein.

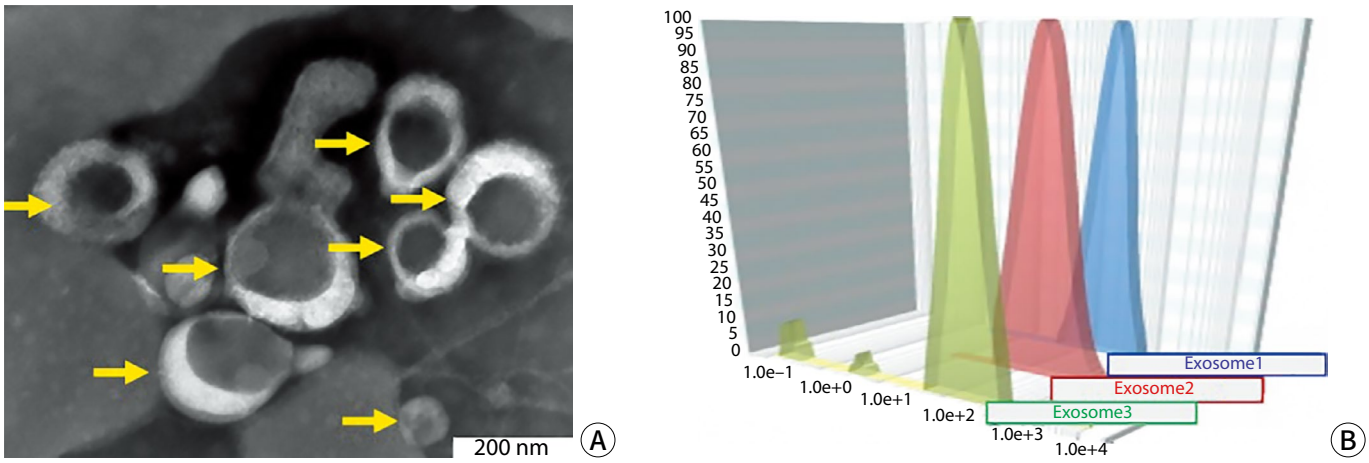

Fig. 1. Identification of exosomes. (A) Electron microscopy of exosomes: the typical single concave tea tray-shaped structure of exosomes (bar=200 nm). (B) Detection of exosomes using a nanoparticle size analyzer: particle aggregation peak with a diameter of approximately 110 nm.

Exosomal microRNA sequencing

The sequencing was conducted in accordance with the manual provided by Illumina, which included steps for library preparation and sequencing experiments. The small RNA sequencing library was prepared using TruSeq Small RNA Sample Prep Kits (Illumina, San Diego, CA, USA). Once the library preparation was complete, the constructed library was sequenced on an Illumina HiSeq 2000/2500 platform, utilizing a single-end read length of 50 bp.

Exosome microRNA analysis

FastQC version 0.10.1 was utilized for data quality control, ACGT101-miR version 4.2 for basic miRNA analysis, ACGTUNAfold version 3.7 for advanced miRNA analysis, TargetScan version 5.0 and Miranda version 3.3a for miRNA target gene prediction, Pathway Network version 1.6 for target gene function analysis, and R software version 3.0.1 for mapping of result files. The databases used in the study are listed in Table 2.

Statistical analysis

The experimental data are expressed as the mean±SE. The input data for miRNA differential expression analysis consisted of normalized values. The P-value was calculated using a model based on the normal distribution. When biological replicates were present, the t-test was used to analyze differences between two groups of samples, and analysis of variance was employed for analyzing differences among multiple groups.

Results

Data quality control results

The total number of reads for urinary exosomes ranged from 23,699,840 to 34,395,054, and the total number of bases ranged from 1,208,691,840 to 1,754,147,754, with averages of 27,871,527.67±5,722,347.37 and 1,421,447,911±291,839,716, respectively. The base composition ratios of adenine (A), thymine (T), cytosine (C), and guanine (G) varied from 21.94% to 31.81%. The Q20 and Q30 quality scores of the reads were between 96.14% and 99.29%, and the overall GC content of the reads ranged from 49.55% to 53.97%. For blood exosomes, the total number

Table 2. Databases used in the experiment

Database	Web address	Version date
miRNA (miRs) database	ftp://miRBase.org/pub/miRBase/CURRENT/	22.0
Pre-miRNA (mirs/MIRs) database	ftp://miRBase.org/pub/miRBase/CURRENT/	22.0
RFam	Collection of many common non-coding RNA families other than miRNA http://rfam.janelia.org	12.0
Repbase	Prototypic sequences representing repetitive DNA from different eukaryotic species http://www.girinst.org/repbase	22.07
Genome database	ftp://ftp.ensembl.org/pub/release-101/fasta/homo_sapiens/dna/	
mRNA database	ftp://ftp.ensembl.org/pub/release-101/fasta/homo_sapiens/dna/	
KEGG pathway database	http://www.genome.jp/kegg	2016.05
Gene Ontology database	http://geneontology.org/	2016.04

miRNA, microRNA; KEGG, Kyoto Encyclopedia of Genes and Genomes.

of reads and total bases were 17,002,521 to 38,704,493 and 867,128,571 to 1,973,929,143, respectively. The averages were 2,588,481.33±11,374,109.12 for reads and 1,320,128,948±580,079,565 for bases. The base composition ratios of A, T, C, and G were between 22.69% and 30.08%. The Q20 and Q30 quality scores of the total reads ranged from 91.61% to 99.40%, with the overall GC content of the reads between 52.55% and 52.91%. As indicated in Table 3, there was no significant difference between the groups ($P>0.05$).

Comparative analysis of the Rfam database

Rfam is a database of ncRNA families, which includes ribosomal RNA (rRNA), transfer RNA (tRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA), miRNA, and other ncRNAs. The annotated sequences of rRNA, snoRNA, snRNA, tRNA, and other RNAs were extracted from the clean data produced by the sequencing machine, using the Rfam database as a reference. The results are presented in Table 4 and have been statistically analyzed and visualized, showing the mean of total reads and unique reads in Fig. 2. There were no significant differences observed between the groups ($P>0.05$).

Comparative analysis of Repbase database

The Repbase database is a comprehensive collection of repeat sequences in eukaryotic DNA, encompassing transposable elements, tandem repeat sequences (such as satellite sequences or microsatellites), scattered genomic repeat sequences, and certain multicopy host genes (including rRNA, tRNA, and histone genes). Annotated repeat-associated sRNA sequences were extracted from the clean data produced by the sequencing machine, using the Repbase database as a reference. The data for total reads and unique reads were analyzed both statistically and visually (Fig. 3). The categorized data from the Repbase database are presented in Table 5. There was no significant difference between the blood and urine groups, with the exception of the total L1 sequence ($P<0.05$).

Candidate RNA length distribution

Based on the analysis and statistics of the original sequencing data, we carried out an assessment of the length distribution for both the total and unique numbers of the filtered valid data. As depicted in Fig. 4, the total reads were primarily concentrated in the 22-nucleotide

Table 3. Quality control results of miRNA sequencing data from blood and urine exosome

Sample_ID	Total_Reads	Total_Bases	A%	T%	C%	G%	Q20%	Q30%	GC%
Urine exosomes	27,871,527.67±5,722,347.37	1,421,447,911±291,839,716	23.87±1.80	23.98±1.03	22.49±0.63	29.67±2.18	99.05±0.34	96.98±0.75	52.15±2.31
Blood exosomes	25,884,881.33±11,374,109.12	1,320,128,948±580,079,565	23.24±0.75	24.01±0.91	23.56±0.86	29.18±0.81	97.87±2.63	95.77±3.60	52.74±0.18
P-value	0.8003	0.8003	0.6056	0.9717	0.1571	0.7336	0.4839	0.5992	0.6820

Q20% reflects the quality of the data, indicating that in the sequencing results, the probability of a base error at a certain position caused by the sequencing instrument is less than 1%; Q30% indicates that in the sequencing results, the probability of a base error at a certain position caused by the sequencing instrument is less than 0.1%.
miRNA, microRNA.

Table 4. Rfam category statistics of blood and urine exosomes

Library	Total reads			Unique reads		
	Blood	Urine	P-value	Blood	Urine	P-value
rRNA	664,436.33±89,892.42	716,135.67±420,629.50	0.8453	16,146.67±4,995.21	11,825.67±1,730.40	0.2298
tRNA	619,247.33±409,943.55	367,148.33±284,480.43	0.4309	9,178.00±5,089.72	6,175.00±3,168.85	0.4346
snoRNA	56,828.33±75,016.46	21,599±12,498.19	0.4673	500.00±357.22	457.33±238.68	0.8718
snRNA	48,305.67±49,710.85	46,866±24,310.35	0.9662	479.67±267.73	491.00±226.30	0.9580
Other Rfam RNA	311,030.67±229,410.06	302,926±103,992.12	0.9582	3,579.33±1,690.04	3,382.00±1,622.64	0.8911

rRNA, ribosomal RNA; tRNA, transfer RNA; snoRNA, small nucleolar RNA; snRNA, small nuclear RNA.

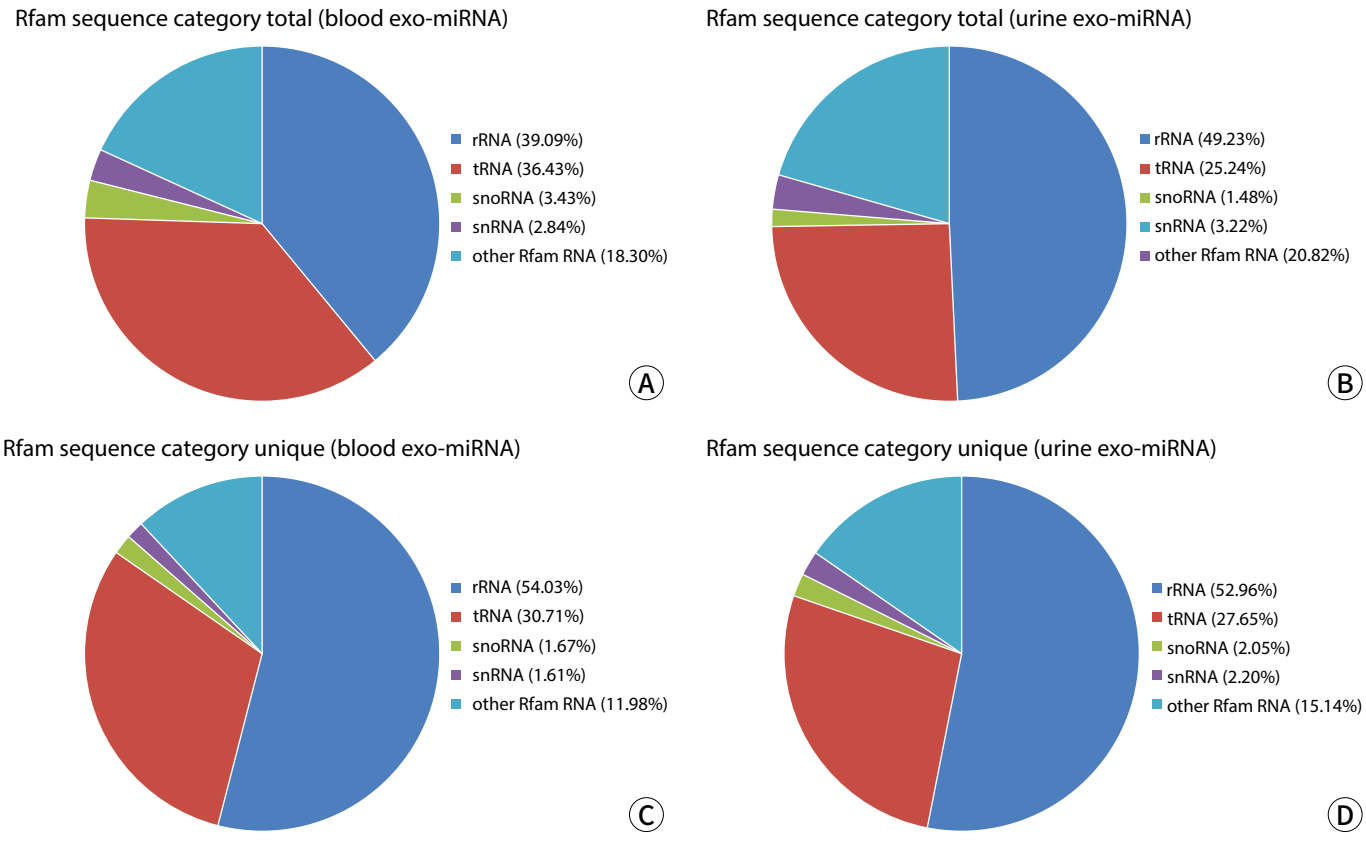

Fig. 2. Pie charts displaying the proportions of rRNA, snoRNA, snRNA, tRNA and some other non-miRNA sequences, referring to the Rfam database. (A,B) Statistics and visualization in total read; (A) blood, (B) urine. (C,D) Statistics and visualization for unique read; (C) blood, (D) urine. miRNA, microRNA; rRNA, ribosomal RNA; tRNA, transfer RNA; snoRNA, small nucleolar RNA; snRNA, small nuclear RNA.

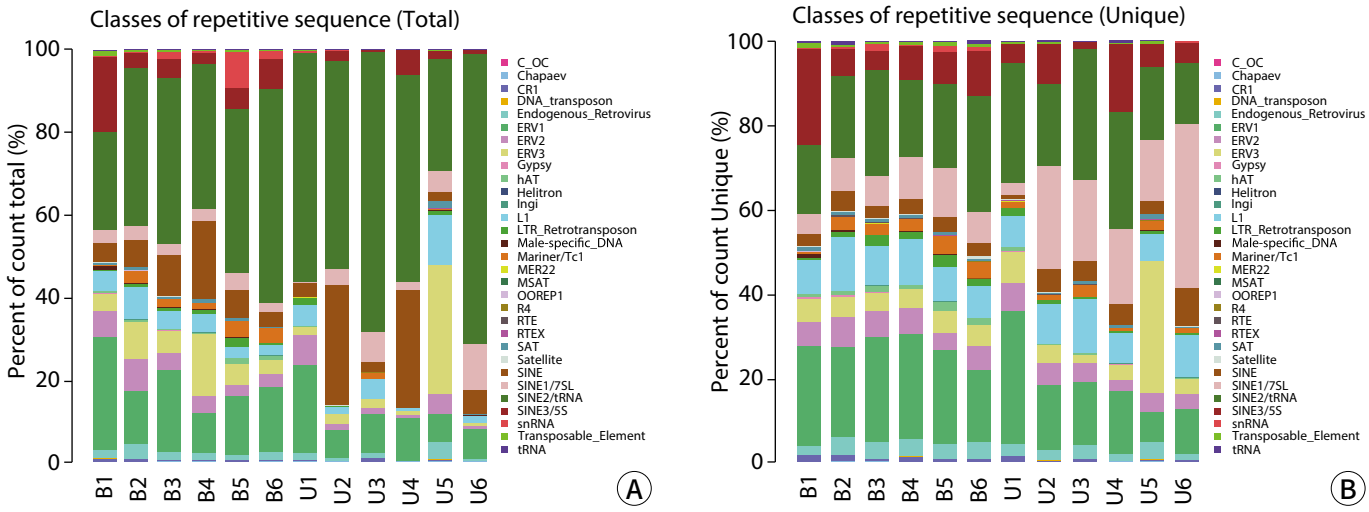

Fig. 3. Stacked graphs presenting a comparison of the two types of data based on the Repbase database. (A) Total reads (%), (B) unique reads (%).

length region. The unique reads were predominantly found within the 19–21 nucleotide range, with a slightly lower distribution at lengths 18 and 22–24, and minimal presence at length 26. When comparing the results from blood and urinary exosomes (Table 6), significant differences were observed between the groups in the 20–23 and 25–26 nucleotide lengths, as well as in the valid reads ($P<0.05$) for unique reads. However, no significant differences were found between blood and urine in total reads and other unique read lengths.

MicroRNA identification and predictive analysis

The accuracy of miRNA identification is highly correlated with the accuracy of miRBase, the genome of the species in question, and the completeness of the database. Clean data, which are essential for analysis, were utilized to identify small RNAs. The miRNA expression levels in each sample were determined using ACGT101 miR software. These expression levels were then used to evaluate the correlation of gene expression characteristics both within and between groups, as well as to evaluate the differential expression of miRNAs. When measuring expression levels, the normalized value (standardized based on the original miRNA read counts) was employed as the metric for miRNA expression, enabling the comparison of miRNA expression across different samples.

Sample correlation analysis

Correlation analysis, utilizing gene expression data from samples, can more accurately determine the clustering relationship among samples. A higher correlation coefficient indicates better clustering of the samples. By employing the Pearson correlation coefficient, we can assess the repeatability among samples and identify potential outliers. As shown in Fig. 4, the correlation coefficients between the six blood and urine samples ranged from 0.49 to 1. Specifically, blood samples had correlation coefficients ranging from 0.49 to 1, while urine samples had coefficients between 0.717 and 1. Notably, the correlation coefficients for the fourth urine sample and the first blood sample were relatively low when compared to the other samples (Fig. 5).

Table 5. Repbase database category data of blood and urine exosomes

Type	Total reads			Unique reads		
	Blood	Urine	P-value	Blood	Urine	P-value
CR1	158.33±105.29	460.67±391.79	0.2663	7.00±2.65	11.33±3.21	0.1458
DNA_transposon	5.33±5.51	23.67±40.99	0.4854	0.67±0.58	0.67±1.15	1.0000
Endogenous_Retrovirus	631.67±203.29	1,172.67±617.80	0.2230	22.00±12.53	35.00±14.80	0.3101
ERV1	7,303.00±3,428.55	12,029.67±9,812.39	0.4749	147.00±75.43	233.67±69.74	0.2178
ERV2	1,541.33±861.59	2,453.67±819.99	0.2547	34.67±10.60	63.67±24.95	0.1375
ERV3	1,729.67±1,011.16	6,242.33±7,672.87	0.3697	35.67±15.14	59.67±39.55	0.3819
Gypsy	20.33±28.57	2.00±3.46	0.3318	1.00±1.00	0.33±0.58	0.3739
hAT	375.67±385.70	70.00±19.47	0.2423	12.00±9.85	5.67±0.58	0.3285
Ingi	16.33±18.23	0	0.1956	1.00±1.00	0	0.1583
L1	1,314.67±642.18	4,333.33±1,739.74	0.0479	55.00±27.07	160.00±123.48	0.2236
LTR_Retrotransposon	498.33±695.27	582.33±121.84	0.8468	13.67±13.87	11.33±4.04	0.7935
Male-specific_DNA	127.33±200.12	2.00±3.46	0.3391	1.67±2.08	0.33±0.58	0.3453
Mariner/Tc1	1,027.00±1,099.83	197.33±118.89	0.2638	24.67±23.01	19.67±10.07	0.7476
OOREP1	12.33±21.36	0	0.3739	0.33±0.58	0	0.3739
MER22	0	126.00±124.53	0.1546	0	2.00±1.73	0.1161
MSAT	0	4.00±6.93	0.3739	0	0.67±1.15	0.3739
RTE	0	2.67±4.62	0.3739	0	0.33±0.58	0.3739
RTEX	0	7.33±12.70	0.3739	0	0.67±1.15	0.3739
R4	5.67±9.81	4.33±7.51	0.8608	0.33±0.58	0.33±0.58	1.0000
SAT	190.33±153.05	291.33±438.60	0.7256	4.33±2.52	5.00±4.58	0.8360
Satellite	21.67±21.03	17.67±26.39	0.8474	2.00±2.65	2.00±2.65	1.0000
SINE	2,050.33±1,447.02	7,130.00±10,174.03	0.4402	22.33±13.80	95.67±138.26	0.4124
SINE1/7SL	1,392.33±946.64	12,243.67±18,914.70	0.3772	63.33±54.24	419.67±605.41	0.3673
SINE2/tRNA	14,275.67±6,922.48	85,443.00±114,958.14	0.3448	147.33±68.85	252.67±147.75	0.3257
SINE3/5S	3,721.33±2,783.05	1,386.33±1,270.52	0.2567	82.33±20.50	71.33±57.36	0.7701
snRNA	1,824.67±2,724.41	0	0.3106	7.00±7.21	0	0.1680
Transposable_Element	223.33±220.37	71.33±14.57	0.2991	6.00±2.65	3.67±0.58	0.2099
tRNA	60.67±60.35	19.00±28.69	0.3409	2.33±1.53	0.67±0.58	0.1518

Differentially expressed exosomal microRNA analysis

The differences in exosomal miRNAs between blood and urine were analyzed using the R language "limma" software package, identifying 102 differentially expressed miRNAs with fold changes greater than 2. Of these, 41 were more highly expressed in blood than in urine samples. The top 10 exosomal miRNAs with significant differences included hsa-miR-934, hsa-miR-30e-3p_1ss22CT, bta-miR-11987_L-1_1ss8TA, hsa-miR-10a-3p_R-1, bta-miR-11987_L-2_1ss8TA, hsa-miR-10b-5p_R-1, hsa-miR-218-5p_R+2, hsa-miR-30d-5p_R+2, hsa-miR-29c-5p_R-1, and hsa-miR-200b-3p. Conversely, 61 exosomal miRNAs were found at lower levels in blood than in urine samples, with the top 10 exosomal miRNAs showing significant differences being hsa-miR-425-5p, hsa-miR-7-5p_R-1, hsa-miR-145-5p, hsa-miR-484, hsa-miR-329-3p, hsa-miR-96-5p_R-2, hsa-

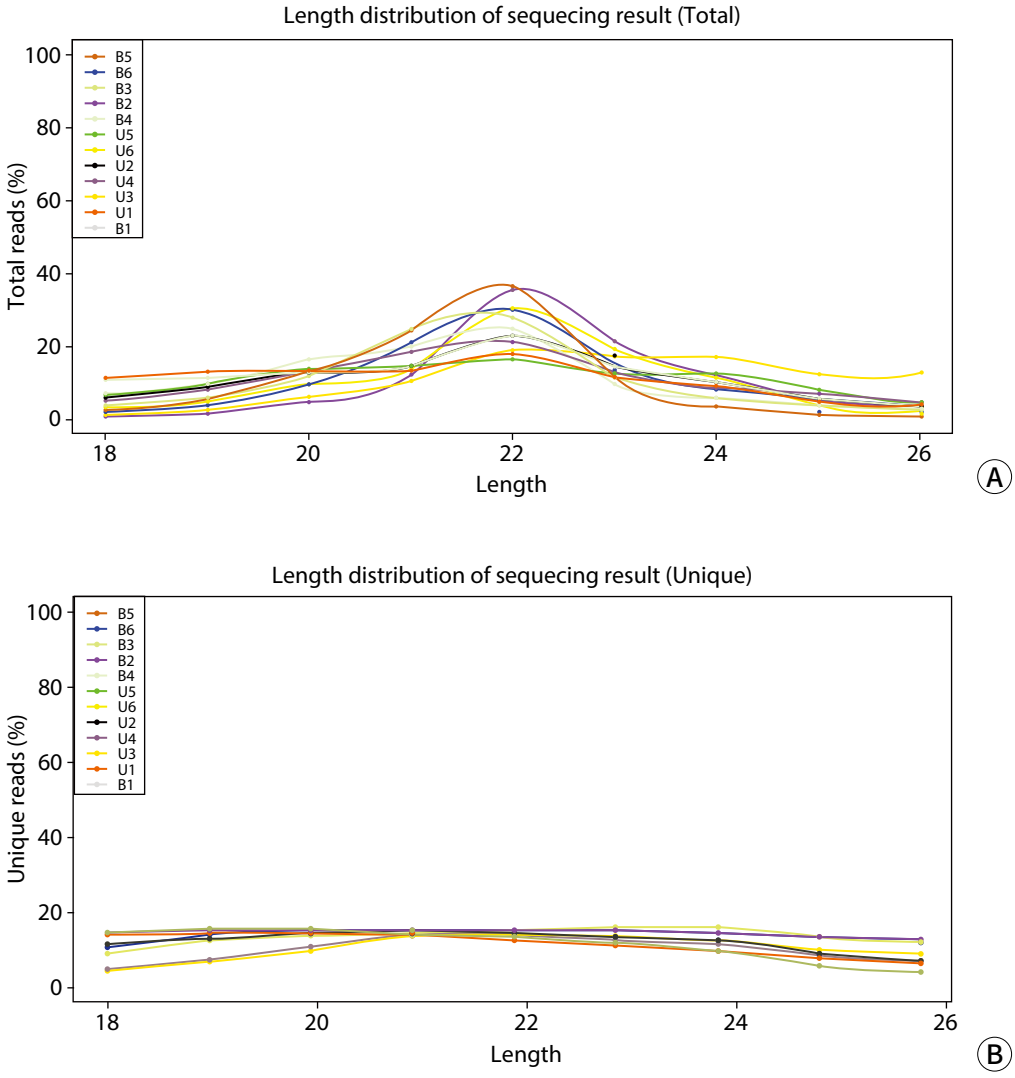

Fig. 4. Length distribution of the sequencing results. (A) Total reads (%), (B) unique reads (%).

Table 6. Length distribution of the sequencing results of blood and urine exosomes

Length	Total reads			Unique reads		
	Blood	Urine	P-value	Blood	Urine	P-value
18	436,361.00±143,478.88	993,080.67±471,516.15	0.1220	50,807.33±28,024.14	109,079.33±36,787.36	0.0945
19	663,565.67±221,921.31	1,328,995.33±611,193.97	0.1509	55,624.00±32,124.51	136,549.00±40,863.32	0.0543
20	1,352,551.67±801,446.33	1,802,782.33±729,445.32	0.5116	57,068.00±31,853.45	154,423.67±51,343.34	0.0493
21	2,530,332.00±1,624,499.74	2,050,522.67±649,025.54	0.6595	57,933.00±30,115.17	161,037.00±55,019.65	0.0465
22	3,577,806.00±2,569,496.50	3,027,407.00±996,219.06	0.7468	53,488.00±27,137.48	149,230.67±48,943.87	0.0414
23	1,448,801.67±815,249.61	2,050,510.33±642,210.98	0.3721	46,007.00±21,993.58	131,136.33±48,280.39	0.0499
24	673,059.33±364,409.83	1,636,292.33±663,391.86	0.0922	39,495.67±16,834.52	118,143.67±48,698.24	0.0574
25	428,329.00±284,580.69	877,942.00±586,115.02	0.2980	25,034.33±7,529.50	90,539.00±31,209.68	0.0241
26	267,313.67±139,584.21	563,885.33±246,623.50	0.1441	18,557.33±3,910.05	69,582.33±16,221.38	0.0061
Valid reads	11,378,120.00±5,998,577.15	14,331,418.00±3,925,298.36	0.5149	404,014.67±193,601.66	1,119,721.00±350,791.92	0.0364

https://doi.org/10.12771/emj.2024.e6

Fig. 5. Correlation analysis of gene expression between three blood samples and three urine samples.

miR-143-3p_R+1, hsa-miR-130b-5p_R+1, hsa-miR-140-3p_R+1, and hsa-miR-338-5p_R-1. The differentially expressed exosomal microRNAs (DEexo-miRNAs) are displayed in Fig. 6, excluding exosomal miRNAs with a log fold change (logFC) of Inf (4 instances) and -Inf (6 instances).

Prediction of target genes for differentially expressed exosomal microRNAs

ENCORI (https://rnasysu.com/encori/) was utilized to predict the target genes (mRNA) corresponding to DEexo-miRNAs. Only those DEexo-miRNAs that matched targets in both TargetScan and Miranda were selected as the final target genes. For the top 10 DEexo-miRNAs in urine, 1,472 target mRNAs were identified, including DDX3Y, RERE, DFFA, RSRP1, PUM1, C1orf216, STK40, YRDC, RRAGC, RAB3B, CC2D1B, ZRANB2, EVI5, ARHGAP29, CLCC1, SORT1, SLC16A1, NRAS, SV2A, GATAD2B, and others. Similarly, for the top 10 DEexo-miRNAs in blood, 2,229 target mRNAs were obtained, including IFFO2, STMN1, FOXJ3, CTSS, RNF11, SRSF11, ATP1B1, LARP4B, AP3M1, TM9SF3, PTEN, LCOR, TIMM10, KMT5B, CREBZF, GNS, HSPB8, EFNB2, CFL2, and POMT2, among others. A total of 578 identical target mRNAs corresponding to DEexo-miRNAs were found between blood and urine (Fig. 7).

Enrichment analysis of target mRNA according to differentially expressed exosomal miRNAs

The target mRNAs corresponding to DEexo-miRNAs underwent Gene Ontology (GO) / Kyoto Encyclopedia of Genes and Genomes (KEGG) functional annotations. In other words, the target mRNA served as an intermediary to link exosomal miRNAs with their respective functions.

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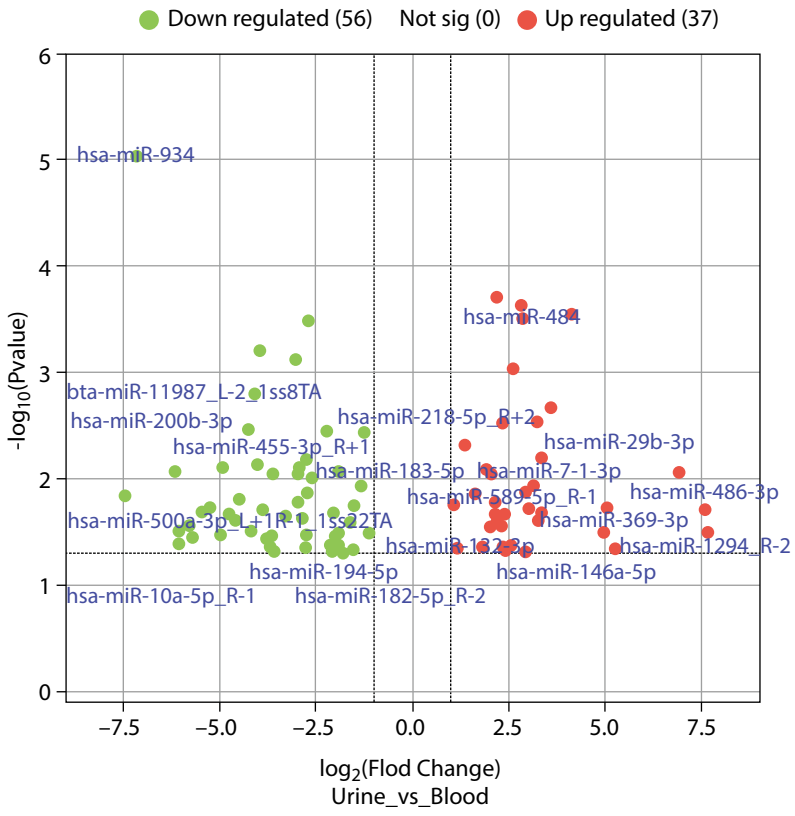

Fig. 6. Volcano map of DEexo-miRNAs derived from blood and urine exosomes. DEexo-miRNAs, differentially expressed exosomal microRNAs.

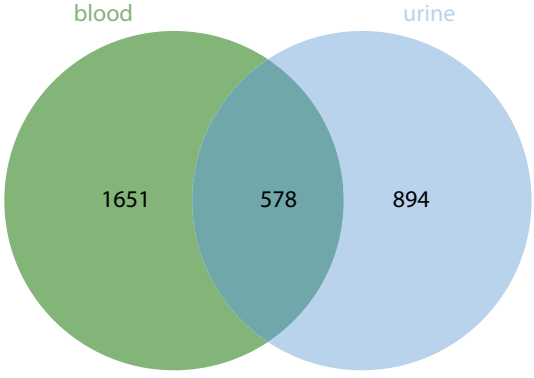

Fig. 7. Venn diagram of the target mRNAs corresponding to the top 10 differentially expressed exosomal microRNAs (DEexo-miRNAs) between urine and blood.

Gene Ontology annotation

The GO annotation bar chart is shown in Fig. 8.

The biological processes (BPs) associated with the target mRNAs of exosomal miRNA in body fluids include positive and negative regulation of RNA polymerase II promoter transcription, DNA template/promoter activities, chromatin structure modulation, nervous system development, cell migration, and protein phosphorylation/polyubiquitination, among others. The BPs

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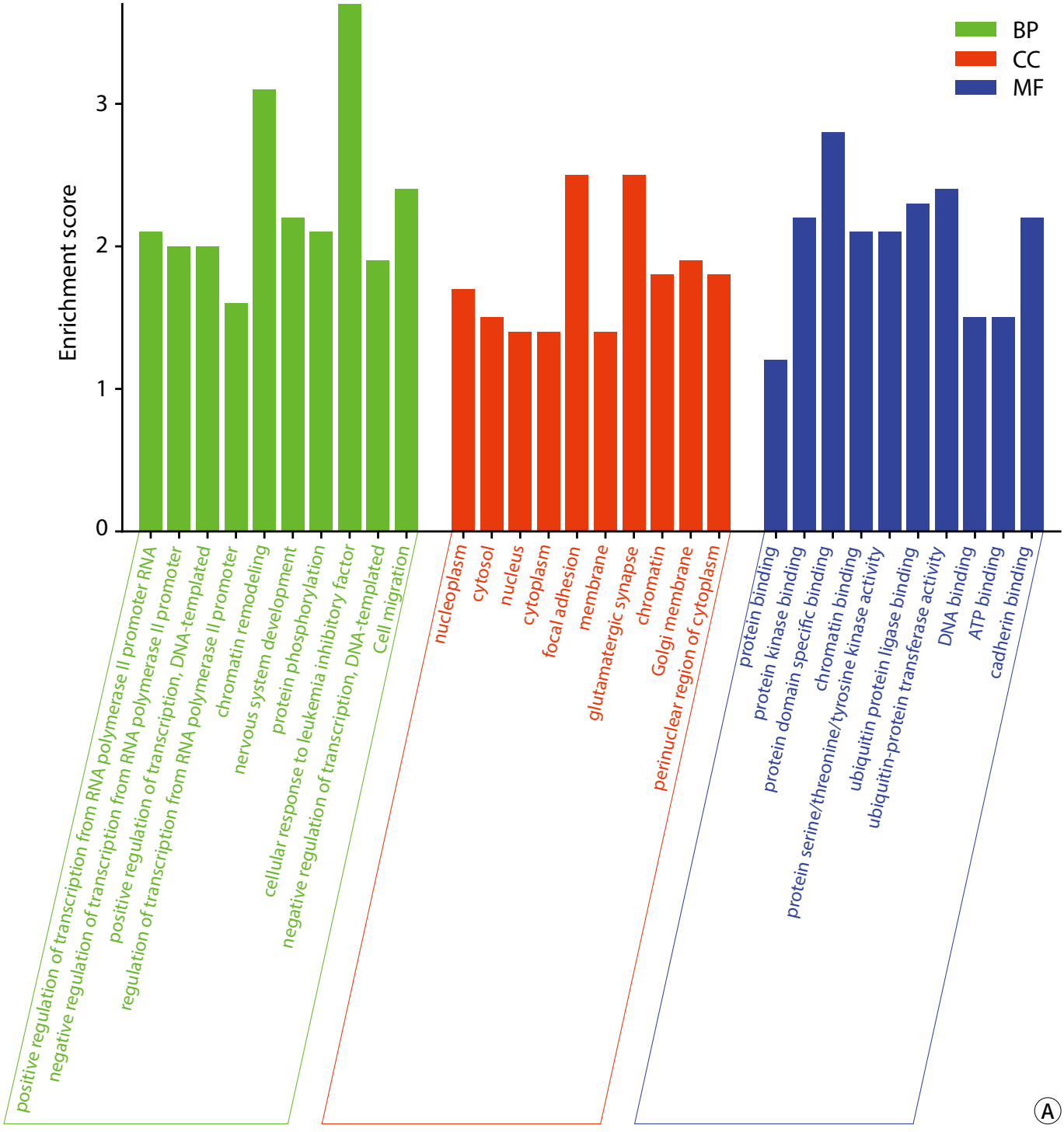

Fig. 8. Bar chart of Gene Ontology annotations. (A) Urine, (B) blood.

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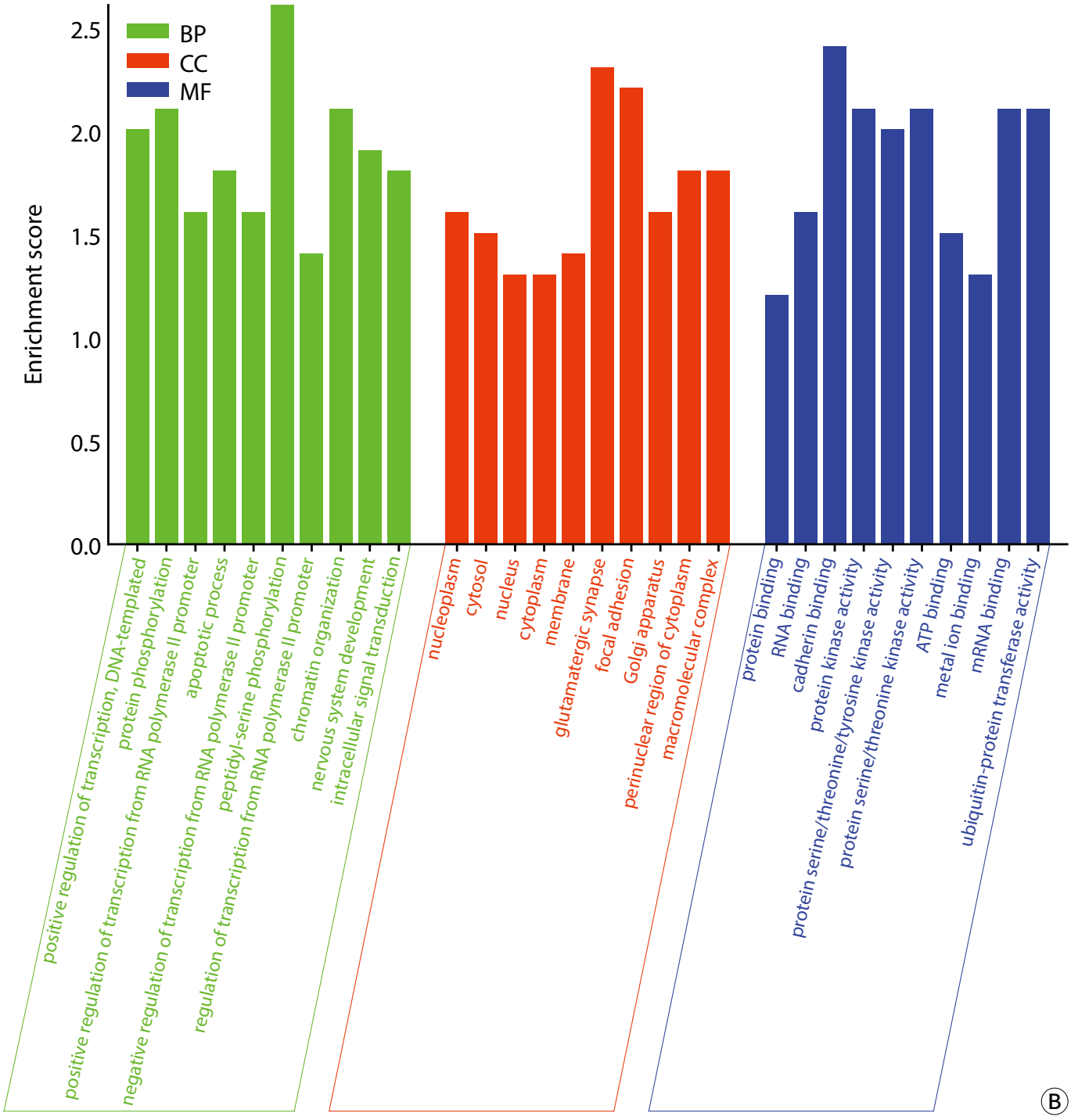

Fig. 8. Bar chart of Gene Ontology annotations. (A) Urine, (B) blood (continued).

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influenced by the target mRNA according to DEexo-miRNAs in urine also encompass chromatin remodeling, cellular response to leukemia inhibitory factor, ubiquitination of protein at the K48 linkage, cell adhesion via plasma membrane adhesion molecules (hemophilic interactions), proteasome-mediated ubiquitin-dependent protein catabolic processes, and peptide-threonine phosphorylation. The target mRNAs of DEexo-miRNAs in blood are involved in BPs such as the apoptosis process, peptide-serine phosphorylation, intracellular signal transduction, negative regulation of gene expression, post-embryonic development, cell cycle regulation, vesicle-mediated transport, the insulin receptor signaling pathway, and protein stability.

The cellular components (CCs) associated with the target mRNAs of exosomal miRNAs in two types of body fluids included the nucleoplasm, cytosol, nucleus, cytoplasm, adhesive spots, endoplasmic reticulum membrane, glutamatergic synapse, chromatin, Golgi apparatus membrane, cytoplasmic perinuclear area, macromolecular complexes, and the actin cytoskeleton, among others. In urine, the CC of the target mRNA encompassed cytoplasmic ribonucleoprotein granules/complexes, cell-cell junctions, cell projections, ubiquitin ligase complexes, and the cytoskeleton. The target mRNAs of DEexo-miRNAs in blood were associated with CC such as intracellular membrane-bounded organelles, nuclear specks, cytoplasmic stress granules, postsynaptic densities, early endosome membranes, and chromatin.

The molecular functions (MFs) associated with the target mRNAs of exosomal miRNA in two types of humor include protein (kinase/domain-specific) binding, protein serine/threonine/tyrosine kinase activity, ubiquitin protein ligase binding/transferase activity, ATP/cadherin/RNA/GDP binding, transcription factor activity with sequence-specific DNA binding, among others. The target mRNAs of DEexo-miRNAs in urine were involved in MFs such as chromatin/DNA/β-catenin/RNA polymerase II core promoter proximal region sequence-specific DNA binding, transcription coactivator/corepressor activity, transcription activator activity, RNA polymerase II transcription regulatory region sequence-specific binding, and protein kinase inhibitor activity. Meanwhile, the target mRNA in blood was associated with MFs including protein serine/threonine kinase activity, metal ion/mRNA/protein kinase/small GTPase binding, and bridging, and others.

Kyoto Encyclopedia of Genes and Genomes enrichment

KEGG enrichment analysis revealed that the signaling pathways targeted by exosomal miRNA-associated mRNAs in blood and urine are implicated in a variety of BPs and diseases. These include proteoglycans in cancer, axonal guidance, regulation of the actin cytoskeleton, cancer pathways, resistance to EGFR tyrosine kinase inhibitors, neurotrophic signaling pathways, endocytosis, cellular adhesion sites, cellular senescence, autophagy in animals, and Salmonella infection, among others. In urine, the targeted mRNAs are involved in pathways such as ubiquitin-mediated proteolysis, the phosphatidylinositol signaling system, the ErbB/Wnt signaling pathway, protein processing in the endoplasmic reticulum, endocrine resistance, gap junction communication, oocyte meiotic division, and Shigellosis. The mRNAs targeted by DEexo-miRNAs in blood are associated with the FoxO, MAPK, PI3K-Akt, Rap1, and Ras signaling pathways, as well as with chronic myeloid leukemia, bacterial invasion of epithelial cells, hepatitis B, and *Yersinia* infection. The KEGG enrichment histogram is presented in Fig. 9.

Discussion

Blood and urine samples are commonly used for clinical testing, as they contain a variety

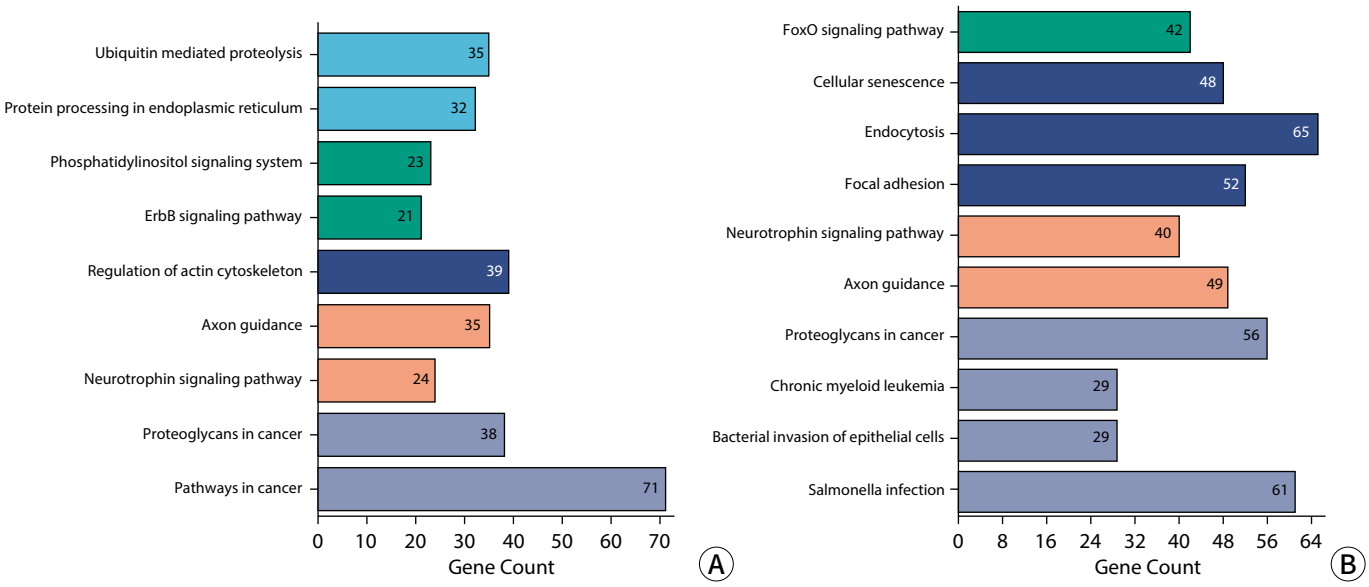

Fig. 9. The KEGG enrichment histogram. (A) Urine, (B) blood. KEGG, Kyoto Encyclopedia of Genes and Genomes.

of substances that reflect the metabolic activity of tissues and organs within an organism. In other words, detecting the same substance in different specimens, such as blood or urine, can yield different results and indicate varying conditions of the body. Therefore, distinguishing the distribution of exosomal miRNAs in different body fluids is crucial for monitoring physiological states and establishing a basis for disease diagnosis. Some studies have reported on blood and urine miRNAs within the same article [14–16]. This paper presents the comparative results for the first time, and the biological analysis of these findings is also being reported for the first time.

The study revealed that the total read counts and the total number of bases in blood and urine samples were essentially identical, and the ratios of the A, T, G, and C bases were also remarkably similar. Comparative analysis of the Rfam database indicated that the content and proportion of rRNA, snoRNA, snRNA, tRNA, and other Rfam RNAs in blood and urine exosomes were fundamentally consistent.

The comparative analysis of the Repbase database revealed that the content and proportion of total reads and unique reads for various genetic elements—including CR1, DNA_transposon, Endogenous_Retrovirus, ERV1, ERV2, ERV3, Gypsy, hAT, Ingi, L1, LTR_Retrotransposon, Male-specific_DNA, Mariner/Tc1, OOREP1, MER22, MSAT, RTE, RTEX, R4, SAT, Satellite, SINE, SINE1/7SL, SINE2/tRNA, SINE3/5S, snRNA, Transposable_Element, and tRNA—in blood and urine exosomes were largely consistent. However, the total reads for L1 were higher in urine exosomes than in blood, although the unique reads showed no difference. The length distributions of candidate RNA exhibited variations between groups at lengths of 20-23 and 25, 26, as well as in the valid unique reads. There were no significant differences in total reads between blood and urine exosomes.

The analysis of DEexo-miRNAs revealed that 41 miRNAs were more highly expressed in blood samples than in urine, while 61 miRNAs showed lower levels in blood compared to urine. The top 10 exosomal miRNAs with higher expression in blood were hsa-miR-934, hsa-miR-30e-3p_1ss22CT, bta-miR-11987_L-1_1ss8TA, hsa-miR-10a-3p_R-1, bta-miR-11987_L-2_1ss8TA, hsa-miR-10b-5p_R-1, hsa-miR-218-5p_R+2, hsa-miR-30d-5p_R+2, hsa-miR-29c-5p_R-1, and hsa-

miR-200b-3p. Conversely, the top 10 miRNAs with lower expression in blood included hsa-miR-425-5p, hsa-miR-7-5p_R-1, hsa-miR-145-5p, hsa-miR-484, hsa-miR-329-3p, hsa-miR-96-5p_R-2, hsa-miR-143-3p_R+1, hsa-miR-130b-5p_R+1, hsa-miR-140-3p_R+1, and hsa-miR-338-5p_R-1. These miRNAs correspond to 1,651 and 894 types of mRNA, respectively, with 578 types being common to both groups.

Studies have found that photosensitive aminotransferase 1 (*PSAT1*) is a target gene for hsa-miR-218-5p and hsa-miR-145-5p, which can be used to predict bone metastasis in gastric cancer [17]. Frørup et al. discovered that extracellular vesicles, particularly those enriched in the plasma exosomes of lactating mothers with Type 1 diabetes, contained abnormal levels of hsa-miR-30d-5p post-delivery [18]. Wu et al. identified plasma exosomal miR-103b, miR-877-5p, and miR-29c-5p as diagnostic biomarkers for early lung adenocarcinoma by combining bioinformatics with experimental verification [19]. Chen et al. reported the upregulation of urinary exosomal hsa-microRNA-200b-3p and hsa-microRNA-206 in patients with steroid-induced osteonecrosis of the femoral head [20].

Sinha et al. found that hsa-miR-425-5p was significantly upregulated, while hsa-miR-663a was downregulated under diabetic conditions [21]. Deng et al. discovered that exosomes derived from the plasma of septic patients inhibited apoptosis of T lymphocytes by downregulating Bcl-2-associated death promoter via hsa-miR-7-5p [22]. Zhang et al. found that hsa-miR-145-5p was significantly differentially expressed in the serum exosomes of patients with polycystic ovarian syndrome (PCOS) and considered these miRNAs as potential biomarkers for PCOS [23]. Hang et al. argued that the downregulation of miR-145-5p in cancer cells and their derived exosomes may contribute to the development of ovarian cancer by targeting connective tissue growth factor [24]. Zhao et al. revealed that the injection of RGD-modified exosomes loaded with miR-484 induced vessel normalization, which in turn sensitized cancer cells to chemotherapy-induced apoptosis [25]. Zhang et al. reported that low serum exosomal miR-484 expression predicted an unfavorable prognosis in ovarian cancer [26]. Li et al. identified cerebrospinal fluid exosomal hsa-miR-96-5p as a biomarker for diagnosing or monitoring the progression of non-small cell lung cancer with leptomeningeal metastases [27]. Tomita et al. considered urinary exosomal hsa-miR-143-3p as a predictive biomarker for persistent psychotic-like experiences [28]. Wang et al. found that hsa-miR-143-3p expression was significantly higher in exosomes from human bone marrow mesenchymal stem cells than in those from human pancreatic cancer cell line exosomes, and suggested that hsa-miR-143-3p might promote apoptosis and suppress cell growth and invasion in pancreatic cancer [29]. Ramanathan et al. detected that poor responders had lower levels of exosomal hsa-miR-338-5p and proposed exosomal hsa-miR-338-5p as a potential biomarker due to its stability and dysregulation in diseases, including complex regional pain syndrome, a chronic pain disorder with persistent inflammation [30].

The BPs associated with the target genes (mRNA) of DEexo-miRNA in blood and urine encompassed both positive and negative regulation of transcription from an RNA polymerase II promoter on a DNA template, as well as modifications to chromatin structure. The CCs involved included the nucleoplasm, cytosol, nucleus, cytoplasm, adhesive spots, and membranes. The MFs of these target genes were found to be diverse, involving protein binding (including kinase, domain-specific, serine/threonine, and tyrosine kinase interactions), ubiquitin protein ligase binding and transferase activity, as well as ATP, cadherin, GDP binding, and transcription factor activity, which includes sequence-specific DNA binding within the RNA binding transcriptional regulation region. The target mRNAs of DEexo-miRNAs in blood and urine play roles in various signaling pathways. These pathways include proteoglycans in cancer, axonal guidance,

regulation of the actin cytoskeleton, cancer pathways, resistance to EGFR tyrosine kinase inhibitors, neurotrophic signaling pathways, endocytosis, attachment sites, cellular aging, autophagy in animals, and Salmonella infection.

Our analysis of blood and urine exosome sequencing revealed that the ncRNA content, including rRNA, tRNA, snoRNA, snRNA, miRNA, and other ncRNAs, was essentially identical. The database of eukaryotic DNA repeat sequences encompasses transposable elements, tandem repeat sequences (such as satellite sequences or microsatellites), scattered genomic repeat sequences, and some multicopy host genes (including rRNA, tRNA, histone genes, etc.). Additionally, the length distribution of candidate RNA (unique reads) exhibited slight variability. A total of 102 DEexo-miRNAs were identified between blood and urine, with 41 being more abundant in blood than in urine, and 61 showing higher levels in urine than in blood. The corresponding mRNAs of these miRNAs are involved in signaling pathways such as proteoglycans in cancer, axonal guidance, regulation of the actin cytoskeleton, and various cancer pathways. This study lays the groundwork for the identification of potential biomarkers derived from blood and urinary exosomes.

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Conflict of interest
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Data availability
Not applicable.

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Supplementary materials
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Case Report

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Bilateral axillo-breast approach robotic total thyroidectomy without isthmectomy: a case report

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Keywords
Bilateral axillo-breast approach (BABA) robotic thyroidectomy; Isthmus; Thyroid cancer, papillary

Conventional open thyroidectomy is a safe procedure, but it has the disadvantage of leaving noticeable scars on the neck. Bilateral axillo-breast approach (BABA) robotic thyroidectomy was developed as an alternative technique to remove thyroid glands without making incisions in the neck. In traditional BABA robotic thyroidectomy, dividing the isthmus is a routine step to improve the efficiency of the dissection during thyroid surgery. However, there are safety concerns when performing this procedure on patients with thyroid cancer located in the isthmus. We report a case of BABA robotic total thyroidectomy carried out without dividing the isthmus in a patient with isthmic papillary thyroid carcinoma. Our experience suggests that BABA robotic surgery can be a feasible and safe option for selected patients with isthmic papillary thyroid carcinoma.

Introduction

The incidence of thyroid cancer has risen over the past three decades in Korea [1]. This cancer is more common in women than in men and generally has a favorable prognosis [2], raising significant concerns about the quality of life after surgery. While conventional open thyroidectomy is a safe procedure, it has the drawback of leaving noticeable scars on the neck. Given the ongoing increase in thyroid cancer cases, particularly among socially active young women, the cosmetic implications of surgical treatment must be carefully considered [3].

Bilateral axillo-breast approach (BABA) robotic thyroidectomy was developed as an alternative technique for the removal of thyroid glands without making an incision in the neck. Its cosmetic advantages and surgical safety have been extensively documented. Typically, in BABA robotic thyroidectomy, the isthmus is divided early in the procedure to enhance the efficiency of the dissection during thyroid surgery [4]. However, there are safety concerns when performing this procedure on patients with thyroid cancer located in the isthmus. This report describes a case in which BABA robotic total thyroidectomy was successfully performed without dividing the isthmus in a patient diagnosed with isthmic papillary thyroid carcinoma (PTC).

Case presentation

Ethics statement

Informed consent for publication of the images was obtained from the patient.

Case

A 24-year-old female patient presented to Ewha University Medical Center in August 2021 with a palpable mass in the anterior neck. Upon examination, a movable mass measuring 2.5 cm was detected in the thyroid gland's isthmus. Thyroid function tests were within normal limits, with free thyroxine at 1.23 ng/dL and thyroid-stimulating hormone at 2.50 mIU/L. Ultrasonography of the thyroid revealed a hypoechoic nodule in the isthmus, measuring 3.1×1.1 cm (Fig. 1). A fine needle aspiration biopsy was performed, confirming the diagnosis of PTC (Bethesda category VI). The patient was informed of the test results and the implications of surgery. Opting to avoid a visible scar from an open procedure, she chose BABA robotic thyroidectomy. Informed consent was obtained following a thorough discussion about the advantages and disadvantages of robotic thyroid surgery without division of the isthmus. The patient subsequently underwent BABA robotic total thyroidectomy with central compartment neck dissection for the treatment of isthmic PTC.

Skin flaps were marked, and diluted epinephrine was administered in the flap region for hydrodissection. Subsequently, skin flaps were elevated using a tunneler, and bilateral circumareolar and axillary ports were placed [4]. Following the standard flap dissection technique, we carried out en bloc resection of the entire thyroid gland, maintaining the integrity of the isthmus. The procedure was completed without the need for open conversion. The total operation time, defined as the duration from the initial epinephrine injection to the completion of skin closure, was 175 minutes, and the estimated blood loss was minimal (50 mL). The surgical specimen was removed through the site where the left axillary port was inserted, without the need to extend the incision (Fig. 2).

The patient's postoperative recovery was uneventful, and she was discharged on the third day following surgery, resulting in a total hospital stay of 5 days. The excised specimen included the right lobe of the thyroid gland, measuring 5.5×3×1.6 cm, and the left lobe, measuring 5×2.7×1.5 cm, with the entire gland weighing 29 g. The primary tumor was located in the lower portion of the left thyroid, extending through the isthmus to the lower portion of the right thyroid. Pathological examination revealed a 3.0×2.5 cm isthmic PTC and an incidental 0.3 cm microcarcinoma in the right thyroid gland. Two lymph node metastases were identified, each measuring 3 mm, without evidence of extracapsular extension. The resection margins were clear of disease (Fig. 3).

The patient underwent treatment with radioactive iodine, receiving a dose of 50 mCi

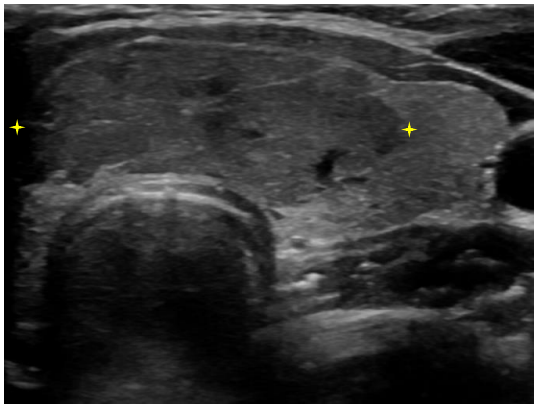

Fig. 1. Thyroid ultrasonography of an isthmic tumor.

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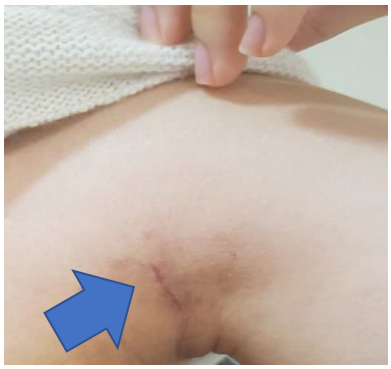

Fig. 2. Left axillary incision scar after 2 weeks.

Fig. 3. Specimen photography showing isthmic thyroid cancer measuring 3 cm.

of I-131. The postoperative examination revealed no complications, including transient hypoparathyroidism or injury to the recurrent laryngeal nerve. Following a 24-month follow-up period, the patient displayed excellent cosmetic outcomes, with the scar being barely noticeable.

Discussion

The anterior transcervical approach has been the standard method for thyroid surgery for over a century, following the introduction of modern thyroid surgery techniques by Sir Theodor Billroth and Theodor Kocher [4]. However, this approach inevitably leaves a noticeable scar on the front of the neck. Given that the incidence of thyroid cancer is increasing, particularly among younger women [2], these surgical scars can cause significant psychological distress [5]. In light of this, robotic thyroid surgery has emerged as an alternative to the traditional anterior transcervical thyroidectomy.

In conventional BABA thyroidectomy, the isthmus is divided with an endoscopic energy device. This step facilitates the lateral and posterior dissection of the gland, allowing for optimal visualization of the superior thyroid pedicle [6]. Additionally, the left axillary trocar site used for specimen retrieval is relatively small, typically 1–2 cm, which makes it challenging to extract the entire thyroid gland without additional incisions to enlarge the opening [6]. Consequently, there have been very few reported cases of BABA robotic total thyroidectomy performed without dividing the isthmus for large isthmic cancer, a technique aimed at ensuring oncologic safety and reducing complications.

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Herein, we performed BABA robotic total thyroidectomy without isthmic division on a 3-cm isthmic PTC, ensuring oncologic and surgical safety. BABA robotic surgery may be a feasible and safe option for selected patients with isthmic tumors.

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Data availability
The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to institutional policy.

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Case Report

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Endoscopically resected duodenal lipoma as an uncommon cause of upper gastrointestinal bleeding: a case report

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Keywords
Duodenum; Lipoma; Gastrointestinal hemorrhage; Endoscopic mucosal resection

Subepithelial tumors in the upper gastrointestinal (GI) tract are often detected during nationwide endoscopic gastric cancer screening in Korea. Most GI lipomas are asymptomatic and do not necessitate further treatment. However, large tumors may lead to complications such as bowel obstruction, intussusception, and bleeding. These GI lipomas require endoscopic or surgical resection. On radiological examination, GI lipomas typically manifest as hypodense lesions with similar density to that of fat tissue. White-light endoscopy generally reveals a yellowish subepithelial tumor exhibiting a positive cushion sign, while endoscopic ultrasonography shows a homogeneous hypoechoic mass within the third layer of the GI tract. We present the case of an 81-year-old woman with symptomatic duodenal lipoma following endoscopic resection.

Introduction

Subepithelial tumors (SETs) in the upper gastrointestinal (GI) tract are often detected during nationwide endoscopic gastric cancer screening in Korea. These GI SETs vary from benign lesions, such as leiomyomas, to malignant ones, including GI stromal tumors and neuroendocrine tumors. Most SETs are asymptomatic and of minimal clinical significance [1]. One type, GI lipomas, constitute approximately 4% of all GI tumors. The colon is the most common site of these lipomas, with only about 4% found in the duodenum [2]. Since most GI lipomas are asymptomatic, they typically do not require further treatment. However, large lipomas may lead to complications such as bowel obstruction, intussusception, and bleeding [3]. These symptomatic GI lipomas necessitate endoscopic or surgical removal. In this report, we present a case of duodenal lipoma that was incidentally diagnosed due to upper GI bleeding, an atypical symptom of GI lipoma.

Case presentation

Ethics statement

Informed consent for publication was obtained from the patient.

Case

An 81-year-old woman with a history of osteoporosis and hypertension was referred to the emergency room of Pusan National University Hospital after experiencing melena for 1 day. Upon admission, her vital signs were normal. Electrocardiography and chest X-ray showed no abnormalities, and the patient's abdomen was soft and non-tender.

A peripheral blood test revealed a hemoglobin level of 9.1 mg/dL, mean corpuscular volume of 80.2 fL, leukocyte count of 6,630/mm^3, eosinophil count of 13/mm^3, and platelet count of 204,000/mm^3. Liver and renal function tests indicated an aspartate aminotransferase/alanine aminotransferase ratio of 18/10, alkaline phosphatase level of 38 IU/L, albumin level of 3.8 g/dL, total bilirubin level of 0.63 mg/dL, blood urea nitrogen level of 25.2 mg/dL, and blood creatinine level of 0.73 mg/dL. Serum electrolyte levels were within normal limits. Prothrombin time was measured at 11.3 seconds, and activated partial thromboplastin time was determined to be 19 seconds.

Initial CT scans revealed a 3-cm hypodense mass lesion, consistent with fat density, in the transverse portion of the duodenum (Fig. 1). Esophagogastroduodenoscopy showed a 3-cm SET in the third portion of the duodenum, with an active ulcer at its apex. Upon retraction of the duodenal lipoma, another ulceration with active bleeding was discovered on the opposite side of the lesion (Fig. 2). Consequently, immediate coagulation therapy was initiated. The patient reported that, while she had undergone endoscopic evaluation as part of Korea's nationwide cancer screening program, she had not been told that she had a duodenal subepithelial lesion (SEL).

Endoscopic ultrasonography was performed 2 weeks after achieving symptom control. This assessment revealed a hyperechoic lesion in the third layer of the duodenal wall (Fig. 2). The patient then underwent endoscopic mucosal resection (EMR) with an endoloop (that is, endoloop-assisted polypectomy) to mitigate the risks of bleeding and perforation. Following EMR, the defect was sealed with additional endoclips to address concerns regarding the potential for delayed perforation (Fig. 3). No postoperative complications were observed.

After EMR, tissue exhibiting the "naked fat" sign was macroscopically identified at the

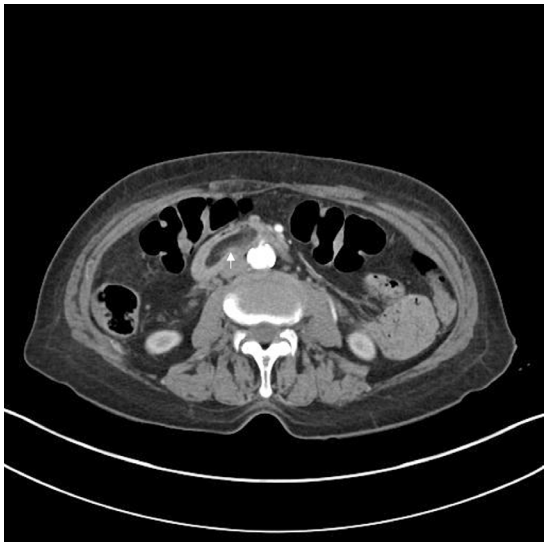

Fig. 1. Abdominal CT revealed a hypodense mass in the third portion of the duodenum (indicated by the white arrow).

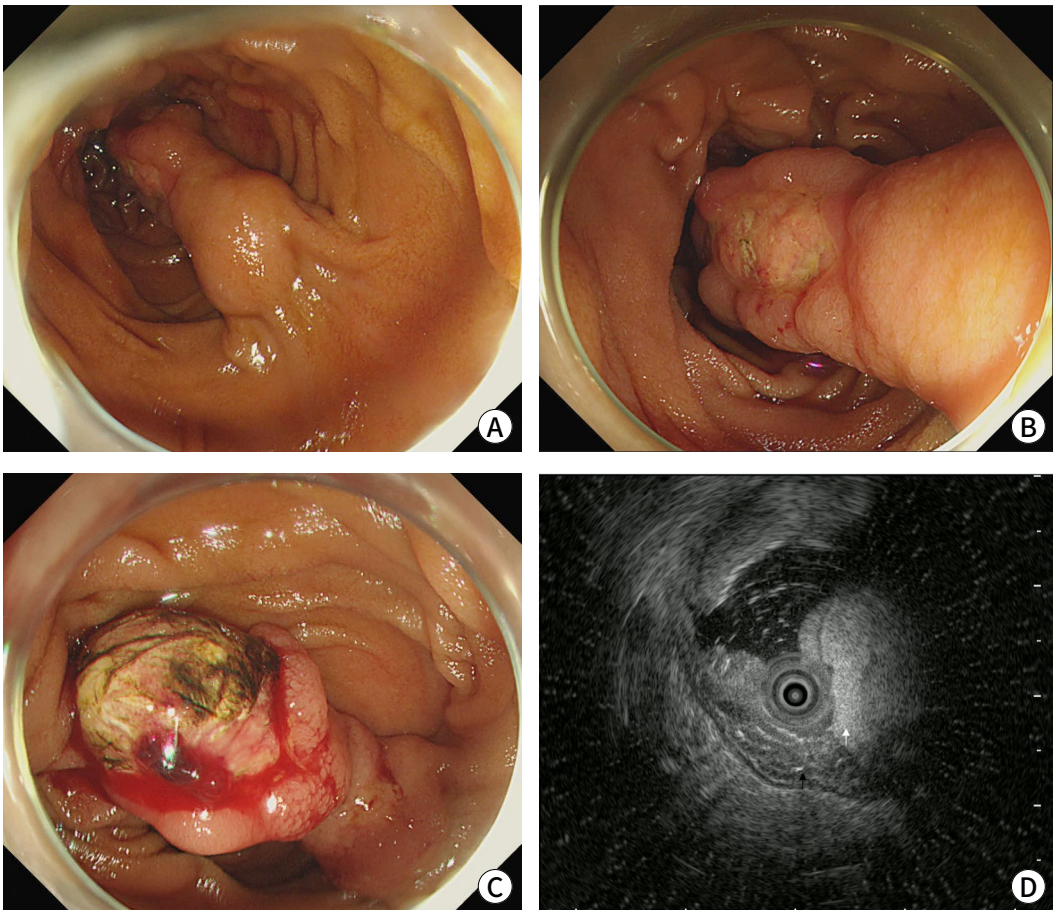

Fig. 2. Endoscopic findings of duodenal lipoma. (A) A 3-cm duodenal lipoma, presenting as a polypoid mass. (B) Multiple ulcerations were observed on the tip of the lesion. (C) A bleeding focus was identified on an ulcer located on the lipoma. (D) Endoscopic ultrasonography revealed a homogeneous hyperechoic mass (indicated by the white arrow). The muscle layer remained intact. The lesion appeared stretched, causing the fold to overlap; consequently, multiple mucosal and submucosal layers were visible beneath the duodenal lipoma (indicated by the black arrow).

resection margin. Pathological examination revealed a polypoid mass lesion, measuring 3.0×2.0×1.3 cm and covered by duodenal mucosa. Microscopically, the tumor consisted of mature adipocytes within the submucosal layer, consistent with duodenal lipoma (Fig. 4). Following the procedure, the patient was discharged from the hospital without complications. Two weeks later, during a follow-up appointment at the outpatient clinic, she reported no further GI bleeding. However, the patient declined follow-up endoscopy due to her advanced age and the long distance between her residence and the hospital.

Discussion

Duodenal lipomas are rare benign lesions that originate from the submucosal adipose tissue of the GI tract. The most common site for lipomas within the GI tract is the large intestine, accounting for 64% of these lesions. In contrast, only 4% are found in the duodenum [2].

Most GI lipomas are asymptomatic and are often discovered incidentally during endoscopic or radiological examination. The duodenal lipoma in the present case was similarly found by

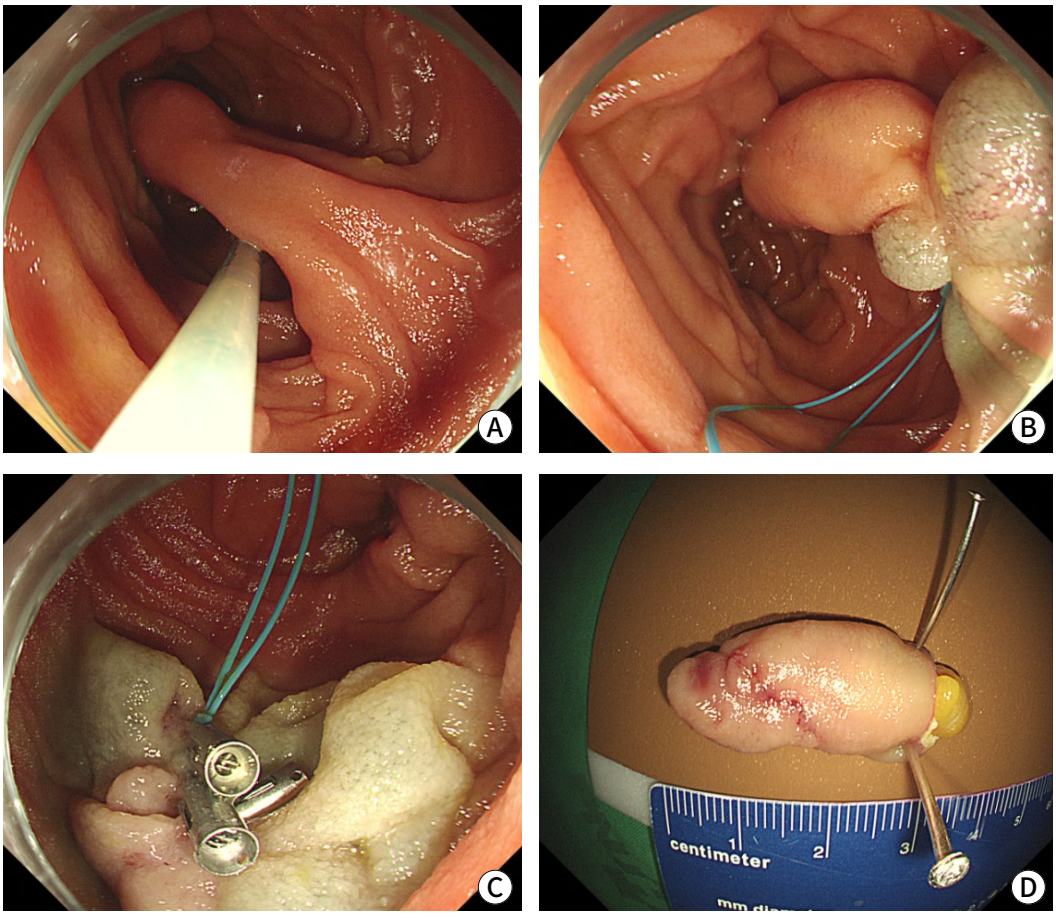

Fig. 3. Endoscopic resection of the duodenal lipoma. (A,B) Submucosal injection and an endoloop were applied to prevent bleeding and perforation. (C) Following polypectomy, the mucosal defect was sealed with endoclips. (D) The resected specimen measured approximately 3.0 cm, and "naked" fat was noted at the resection margin.

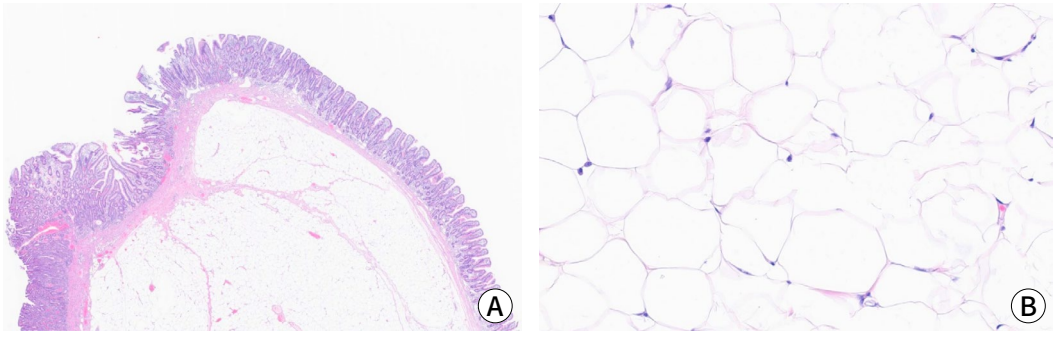

Fig. 4. Microscopic finding showing submucosal lipoma with ulceration. (A) Hematoxylin and eosin (H&E) stain, ×5 magnification. (B) High-power view reveals mature adipocytes, indicating lipoma (H&E stain, ×200 magnification).

chance due to GI bleeding. Despite undergoing endoscopy every 2 years as part of a national cancer screening program, the patient had never been informed of having a duodenal SEL. This is likely because the SEL was located in the third portion of the duodenum, which is not typically examined during national cancer screening endoscopy. Various modalities are available for the

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diagnosis of lipoma, including CT and endoscopic ultrasound. On CT, GI lipomas present as low-density lesions that correspond to the fat density of the submucosal layer of the GI tract [4]. On esophagogastroduodenoscopy, GI lipomas appear as yellowish, solitary SELs that exhibit a cushion sign when compressed with endoscopic forceps. On endoscopic ultrasonography, GI lipomas are revealed as homogenous, hyperechoic lesions situated in the third layer—or submucosal layer—of the GI tract [5].

Typically, GI lipomas are asymptomatic and do not necessitate further treatment [6,7]. However, larger lipomas may cause symptoms such as intussusception, bowel obstruction, and GI bleeding due to ulceration, as observed in our case. One proposed mechanism for ulceration in GI lipomas is the mechanical irritation and pressure exerted by the lipoma on the mucosa of the GI tract. As the lipoma grows, it can continuously press against the duodenal lining, leading to mucosal irritation and eventually ulceration [8]. Symptomatic duodenal lipomas should be removed via endoscopy or surgery [7]. Additionally, growing GI lipomas should also be resected due to the potential for symptom development and the risk of associated malignancy [9,10]. Since most GI lipomas are benign SETs, endoscopic resection may be the preferred treatment when feasible [3]. However, endoscopic resection of duodenal lipomas can result in complications, such as bleeding and perforation. Using an endoloop-assisted endoscopic resection technique, as in our case, can minimize the risks of hemorrhage and perforation following the procedure. In the present case, we administered a submucosal injection before applying the endoloop. This approach has both advantages and drawbacks. It creates a cushion between the lesion and the muscularis propria layer, reducing the risk of perforation. However, this technique also carries a risk of bleeding from the injection site and potential anatomical distortion, which can complicate the placement of the endoloop. Therefore, the decision to use submucosal fluid injection before endoloop application should be made based on the characteristics of the lipoma and the experience of the endoscopist.

To date, fewer than 30 cases of duodenal lipoma with hemorrhage have been reported [7]. To our knowledge, this is the third case report of a duodenal lipoma with hemorrhage in Korea that was successfully treated through endoscopic resection without complications. Previously reported cases of duodenal lipoma with hemorrhage in Korea were located in the bulb or the second portion of the duodenum [7,11,12]. Our case is unique among these in that the lipoma was located in the third part of the duodenum.

Duodenal lipomas are rare benign neoplasms of the GI tract. Although most such lipomas are asymptomatic, some larger tumors can be associated with complications, including bleeding. For symptomatic lipomas, endoscopic resection may be the optimal treatment option.

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Images and Solution

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Disseminated cutaneous gout: a rare manifestation of gout

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A 51-year-old man presented with multiple inflammatory skin lesions on both lower legs that had developed 3 weeks prior. He had a 15-year history of gout and stage 3 chronic kidney disease. Upon physical examination, multiple yellowish, firm papulonodules with evidence of suppuration were noted on his shins, calves, knees, and ankles (Fig. 1). A skin biopsy revealed well-circumscribed deposits of pinkish, amorphous material in the deep dermis, surrounded by histiocytic infiltration and a fibrous reaction. Von Kossa staining did not show any calcium deposition (Fig. 2). The patient was diagnosed with disseminated cutaneous gout, and the skin lesions were treated symptomatically with topical steroids and oral antihistamines.

Gout is a chronic disease characterized by the deposition of monosodium urate (MSU) crystals, which form when urate concentrations are elevated [1]. These MSU crystals can accumulate in joints, bones, and various body tissues, including the skin and soft tissues. The disease can be

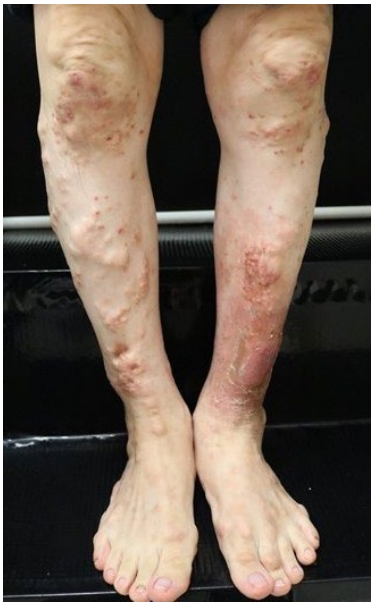

Fig. 1. Multiple yellowish, firm papulonodules had developed on both lower legs. Some lesions showed acute suppuration.

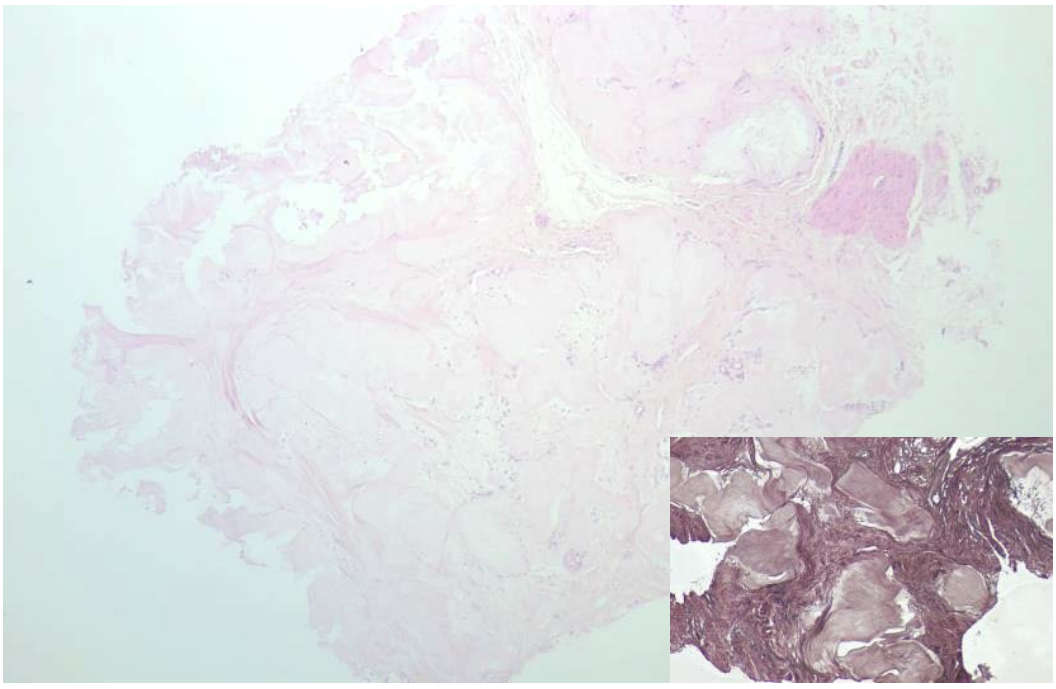

Fig. 2. Well-circumscribed deposition of pinkish amorphous materials was noticed in the deep dermis. Histiocytic infiltration and fibrous reaction were observed surrounding the amorphous materials (hematoxylin and eosin, ×40). Inlet, Von Kossa staining showed no calcium deposition (×100).

categorized into four clinical stages: asymptomatic hyperuricemia, acute gout, intercritical gout (the period between gouty attacks), and chronic tophaceous gout [2]. Chronic tophaceous gout typically emerges after a decade or more of recurrent polyarticular gout. Gouty tophi are deposits of MSU crystals in and around joints, as well as in soft tissues. Cutaneous deposition of MSU crystals is commonly observed over joints or on the ears. Disseminated cutaneous gout is an uncommon skin manifestation of gout, characterized by widespread dermal or subcutaneous tophi that develop at extra-articular sites [3].

The gold standard for diagnosing gout is the identification of negatively birefringent, needle-shaped MSU crystals in synovial fluid or tophi. However, the formalin fixation of skin biopsy specimens can result in the dissolution of crystals, which means that MSU deposition typically appears as pink, amorphous material in routine histological examinations. Alcohol fixation is required for the preservation and identification of the urate crystals [4].

Ethics statement

Informed consent for publication of the images was obtained from the patient.

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Guidelines

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연구에서의 성별과 젠더 형평성: SAGER(Sex and Gender Equity in Research) 지침의 근거 및 이용방법

Sex and Gender Equity in Research (SAGER): rationale for the SAGER guidelines and recommended use: a Korean translation

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성별, 젠더, 지침, SAGER(Sex and Gender Equity in Research), 과학적 연구, 과학계 출판, 젠더 편견, 형평성

Objectives: 성별(sex)과 젠더(gender)의 차이는 연구 설계, 연구 수행, 과학적 결과의 보고뿐 아니라 일반적인 과학 커뮤니케이션에서도 자주 간과된다. 이는 여성의 경우 더욱 그렇지만 남성도 마찬가지이며, 연구 결과의 일반화와 임상 실무에의 적용을 제한하게 된다. 이 글은 국제 지침(가이드라인)의 근거를 설명함으로써 다양한 분야의 연구에서 성별과 젠더 보고에 대한 보다 체계적인 접근을 장려하고자 한다.
Methods: 9개국을 대표하는 13명의 전문가 패널이 일련의 원격 회의, 학술 발표 및 2일간의 워크숍을 통해 지침을 만들었다. 716명의 학술지 편집자, 과학자, 국제 출판계의 구성원들을 대상으로 인터넷 설문 조사를 시행하였으며 과학계 출판에서 성별과 젠더 정책에 대한 문헌 조사도 하였다.
Results: SAGER(Sex and Gender Equity in Research) 지침은 연구 설계, 자료 분석, 결과 및 결과 해석에서 성별과 젠더 정보를 보고하기 위한 포괄적인 절차이다.
Conclusion: SAGER 지침은 일차적으로 저자가 원고를 작성하는 데 도움이 되도록 고안되었다. 그뿐만 아니라 과학의 문지기 역할을 하는 편집자들이 편집 과정에 필수적인, 성별과 젠더에 대한 사정/판단을 원고에 통합시키는 데에도 유용할 것이다.

배경

성별(sex)과 젠더(gender)는 건강과 참살이(well-being)에 있어 중요한 결정 요소이다. 성별은 신체적/생리적 특성과 연관된 인간과 동물의 생물학적 속성으로, 염색체, 유전자 표현형, 호르몬 기능, 생식/성 해부학을 포함한다[1]. 또한, 생물학적 속성과 그것을 표현하는 방법에 따른 차이는 있지만, 일반적으로 여성 또는 남성으로 분류한다.

젠더는 여성, 남성, 그리고 다양한 젠더의 사회적으로 구성된 역할, 행동 및 정체성을 말한다[1]. 젠더는 사람들이 자신과 서로를 어떻게 인식하는지, 어떻게 행동하고 상호작용하는지에 영향을 미치며, 사회에서의 권력과 자원 분배에도 영향을 미친다. 젠더는 보통 양분적(여자/남자)으로 잘못 인식되어 있다. 그러나 실제로 개인이 자신을 인지하고 젠더를 표현하는 방법을 결정하는 젠더 정체성과 표현들은 매우 다양하다. 부록 1에 성별, 젠더 및 관련 용어의 색인을 제시하였다.

* It is a Korean translation of SAGER guidelines, which the Korean Council of Science Editors did under the support of the EASE Gender Policy Committee. Translated version is also posted at https://www.kcse.org/bbs/others.php. Original guidelines were published as Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;1:2. https://doi.org/10.1186/s41073-016-0007-6

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성별과 젠더는 다양한 방식으로 건강과 참살이에 영향을 미친다. 둘 다 환경적·직업적 위험, 위험 감수 행동, 의료에 대한 접근성, 건강을 추구하는 행동, 의료 서비스의 활용 및 경험에 대한 인지, 그리고 질병 유병률과 치료 결과에도 영향을 미친다. 나아가 약제의 약리 역학과 약 동역학이 성별에 따라 다르므로 부작용도 다르고 치료 효과 또한 영향을 받는 사실은 잘 알려져 있다. 따라서 성별과 젠더는 건강에 중대한 결정 요인이 된다[2].

연구 수행 시 성별 및 젠더 편견

연구 전반에서 성별과 젠더의 중요성을 인지하는데도 지식의 격차가 지속하는 중요한 이유는, 과학적 관심이 특정 성별이나 젠더에 국한되는 일반적인 성향과 성별에 따른 범주화가 가능한 생물체에 성별의 해체를 적용할 수 없다는 잘못된 생각 때문이다[3–6]. 인간을 대상으로 한 연구에서 여성 관련 격차는 쉽게 찾아볼 수 있다[1]. 심혈관 치료 임상시험에 관한 Cochrane Reviews에 따르면 258건의 임상시험에서 총 실험 참가자 중 여성은 27%뿐이었다[7]. 더 중요한 것은 남성과 여성 모두를 모집한 임상시험의 단 3분의 1만이 젠더 기반 분석을 보고했다[8]. 10년 동안 Pain 학술지에 출판된 동물 연구의 79% 이상은 수컷만을 대상으로 했으며, 겨우 4%만이 성별에 따른 차이를 연구했다[9]. 이처럼 연구 대상으로 여성을 고려하지 않으면 부정적 결과를 초래할 수 있다.

1997년과 2001년 사이에 미국 시장에서 철회된 10가지 처방 약 중 8개가 남성보다 여성에게 더 큰 피해를 주었다[10]. 최근 사례로는 미국 식품의약처에서, 여성들은 zolpidem 부작용이 남성보다 더 크기 때문에 기존 복용량의 1/2을 권장한다고 발표했다[11]. 이 모든 사례에서 성별과 젠더에 기반한 분석을 했더라면 승인 전에 남성과 여성의 약물 적용 가능성과 투여량 판단에 필요한 충분한 정보가 마련되었을 것이다.

성별과 젠더에 기반한 분석을 수행하지 못하는 현상은 다양한 학문 분야에서 발생한다. 공학 분야에서는 자동차 좌석 개발에서 남성과 여성의 생리학 및 해부학적 차이에 대한 고려가 부족하여 자동차 사고 시 여성 탑승자들의 목 부상(whiplash injury) 위험이 남성보다 더 커지게 되었다[12,13]. 비록 젠더 격차(gender gap)라는 용어가 여성에게 더 많이 사용되었지만, 성별과 젠더에 기초한 분석이 남성의 건강을 이해하는 데도 도움이 된다는 것 또한 주목해야 한다. 남성과 여성을 모두 모집하는 연구가 증가하고 성별 및 젠더 특이적 데이터가 보고되고 있음에도 불구하고, 이런 정책은 시행되지 않고 있다[3]. 성별과 젠더의 차이에 관한 관심 부족은 우리에게 피해를 줄 뿐만 아니라 혁신을 위한 기회를 놓치게 한다. 성별과 젠더의 잠재적 차이와 유사성을 이해하고, 기술 혁신의 인수 및 영향, 적용 가능성을 탐구하며, 인식의 가변성(cognitive variability)에 대한 깊은 통찰력을 얻는다면, 반드시 사회의 요구를 충족시키기 위한 보다 혁신적인 접근법과 더 나은 해결책으로 이어질 것이다.

학술지 편집자의 역할과 편집 정책

편집자들은 과학의 문지기로서 연구 수행에 영향을 미치는 윤리적 기본 틀을 제시하는 등 중요한 역할을 한다. 출판되는 정보의 양이 계속 증가하면서 출판 논문의 품질에 대한 우려도 커져, 학술지 편집자, 출판사 및 전문가 협회들이 이에 대한 세부 지침을 마련하여 사용하곤 한다. 윤리적 검토 절차는 이제 인간과 동물 연구에 보편적으로 적용되고 있는데, 이는 학술지의 요구사항이기도 하다. 학술지의 의무사항 준수 정책이 미치는 영향은 임상시험 등록[14]이라든가 preferred reporting items for systematic reviews and meta-analysis(PRISMA) 지침 도입 후 체계적 검토 보고 등 다양한 영역에서 명확하게 입증되었다[15]. 또 다른 예로는 Consolidated Standards of Reporting Trials(CONSORT) 지침이 점진적으로 채택됨으로써 무작위 대조시험 관련 보고가 개선되었다[16,17]. PRISMA와 CONSORT에 이어 동물 연구를 위한 ARRIVE 지침을 포함하여 많은 다른 보고 지침이 개발되었다[18]. 정책의 실행과 집행은 여전히 중요한 도전이지만 학술지는 연구 자료의 성별과 젠더 특이적 분석이 정례화되도록 촉진함으로써, 보고되는 자료의 품질과 투명성을 향상하는 데 중요한 역할을 할 수 있다. 2011년 미국 의학한림원(US Institute of Medicine, IOM)이 주최한 "과학 연구의 성별 특이적 보고" 워크숍에서, 젠더에 민감하게 반응하는 연구 결과 보고를 개선하기 위해 학술지와 학술지 편집자가 다루어야 할 주요 쟁점이 확인되었다[3]. 그 예로 성별 특이적 데이터 분석의 필요성과 학

술지 정책상 연구의 설계와 보고에 성별과 젠더 고려 사항을 권고하지 않는다는 점을 들 수 있다.

활용 가능한 근거를 바탕으로 2010년 미국 IOM의 한 위원회는 국제의학학술지 편집위원회(International Committee of Medical Journal Editors, ICMJE)를 비롯한 편집자들에게 임상시험 결과를 보고하는 모든 논문에서 남녀를 별도로 분석해야 한다는 지침을 학술지에 채택하도록 권고했다. 이후에 ICMJE는 성별과 젠더 보고에 관련하여 더욱 활발하게 지침을 발표하고 있으며, 연구자가 모든 연구 유형에 대표 모집단을 포함하도록 권장할 뿐만 아니라 기타 연관된 인구학적 요인 관련 기술적 분석 및 성별에 의한 결과를 보고할 것을 권고했다[19]. 연구에 있어서 남성, 여성(및 기타 모집단)이 충분히 참여하고, 적절한 분석 및 투명하고 완전한 연구 결과의 보고가 이뤄지려면 연구비 후원처, 연구자, 논문 심사자와 편집자 간의 공동 노력이 필요하다[20]. 비록 편집자는 보통 연구 과정 후반부에서 연구가 이미 끝나고 데이터가 분석된 후에 참여하게 되지만, 효과적이고 투명하며 완전한 성별 및 젠더 보고가 이뤄질 수 있도록 중요한 역할을 할 수 있다.

최근 몇 년 동안 과학적 연구에서 성별과 젠더 쟁점을 심의하는 몇몇 심사자들이 지금까지 확인된 문제를 해결하기 위한 모범 사례들을 권고했다. Doull 등은 체계적 검토 방법론과 성별 및 젠더에 기반한 분석 방법을 세분화하고 동시화(synchronize)하여 의사 결정을 위한 근거의 수집, 합성 및 분석을 강화할 것을 제안하였다[21,22]. 나아가 체계적 종설 평가 도구를 개발하여 일차적 연구와 새로운 연구 프로토콜을 평가하는 데 적용하였다[22]. Nowatzki와 Grant는 여자와 남자 사이 불평등의 원인과 결과를 파악하고 이를 해결하는 전략을 개발하기 위해 젠더를 기반으로 한 분석의 근거를 정리하였다[23]. 또한, 2014년 Clinical Orthopedics and Research 학술지는 성별과 젠더에 대한 과학적 보고를 주제로 편집자 사설을 발표했고, 일련의 권고사항도 포함하였다[5]. 편집자 협의회, 출판사, 연구비 지원 기관, 공공 단체도 성별과 젠더 문제에 관심을 기울이고 있다. 2010년에 캐나다 보건연구원(Canadian Institutes of Health Research)은 모든 연구비 지원자들이 연구 설계에 성별과 젠더가 포함되어 있는지를 반드시 답하도록 하는 항목을 의무화했다[24]. 미국이 연구 대상자에 여성을 포함하게 된 것은 1993년 미국 보건국(National Institute of Health, NIH)에서 취한 조치, 즉 여성과 소수 민족을 3상 임상시험에 포함하여 다양한 유효성을 검증하고 분석할 수 있도록 한 조치 덕분이라 해도 과언이 아니다[25]. 최근 NIH는 성별 특이성에 해당하지 않는 경우를 제외하고는, 모든 임상 연구에 대해 남성 · 여성 세포와 동물 간의 균형을 어떻게 맞출 것인지 설명하도록 지원자들에게 요구할 계획이라고 발표하였다[6]. 연구와 과학 출판 분야에서 성별과 젠더 고려의 중요성이 확산하고 있음에도 불구하고 일부 과학계에서는 발전 속도가 더디므로, 학술지, 학술지 편집자, 그리고 전문 학회들이 더 큰 노력을 기울여야 할 것이다. Nieuwenhoven과 Klinge이 지적한 바와 같이[26], 과학자들이 성별과 젠더 이슈를 연구에 통합하도록 장려하기 위해서는 적극적인 권고가 필요하다. 예를 들면, 학제 간을 막론하고 과학 간행물에 성별과 젠더를 더 잘 보고하기 위한 지침에 대한 포괄적 권고사항이 없다. 이를 해결하기 위해, 이 글에서는 모든 분야의 연구에서 성별과 젠더 보고에 관하여 더욱 체계적인 접근을 장려하기 위한 국제 지침의 개발에 관해 설명하고자 한다.

방법

유럽 과학편집자협의회(European Association of Science Editors, EASE)는 2012년에 젠더 정책위원회(Gender Policy Committee, GPC)를 설립하고 연구에서의 성별과 젠더 형평성(Sex and Gender Equity in Research, SAGER)에 대한 일련의 지침을 만들도록 했다. GPC 위원장인 Heidari 박사는 9개국을 대표하는 13명(여성 8명, 남성 5명)의 전문가를 선발했다. 이 중 8명은 다양한 생의학 학술지의 수석 편집자이고, 나머지는 젠더 연구와 과학 출판 관련 전문가였다.

우선 716명의 학술지 편집자, 과학자 및 국제 출판업계 구성원을 대상으로 인터넷 설문 조사를 시행하여 기존의 성별과 젠더 정책에 대한 조사 및 이러한 정책의 필요성에 대한 의견을 수집하였다. 이 설문 조사는 네 가지 정책 영역에 초점을 맞췄다. (1) 가능한 성별과 젠더별로 데이터를 세분화하도록 저자에게 요구하거나 권장하는 지침, (2) 편집자와 편집위원회의 구성에 관한 젠더 정책, (3) 심사자의 젠더 균형을 위해 노력하는 정책, 그리고 (4) 심사자에게 성별 구분 데이터와 젠더 분석을 포함했는지 원고를 평가하도록 요청하는 지침이다. 조사는 다음 네 그룹을 대상으로 삼았는데, EASE 회원, 국제중독학술지 편집자 협의회(International Society of Addiction Journal Editors, ISAJE) 회원, Thomson Reuters의 SCI Expanded 학술지 데이

터베이스의 8,607개 학술지 중에서 무작위 추출한 100개의 학술지, 그리고 관심 있는 경우 누구라도 참여할 수 있는 개방 표본이 그것이었다. 설문 조사를 완료할 수 있는 총 716명의 응답자가 조사에 참여하였으며, 이는 338개의 학술지와 114개의 출판사를 대표하였다.

설문 조사 외에도 정책 옵션 및 전문가 권장 사항을 확인하기 위해 몇 가지 다른 방법이 사용되었다. 먼저, 성별과 젠더에 대한 특정 정책이 있는 학술지를 식별하기 위해 키워드 검색을 수행했다(예: "성별"+"저자를 위한 지침"). 또한, 설문 조사 대상 학술지 중 과학에서의 성별과 젠더 지식 격차에 대해 우려를 표명한 학술지의 웹사이트와 GPC에서 파악하고 있던 동료 심사 학술지의 성별과 젠더 보고 정책을 조사했다.

위원회는 3년 동안 일련의 원격 회의, 학술 발표 및 이틀간의 워크숍을 통해 권고안을 만들었다. 초안 지침이 완성된 후 벨기에의 Blankenberge와 크로아티아의 Split에서 개최된 편집자 회의에서 반대 의견들을 놓고 논의하였다. 또한, 초안 지침을 36명의 성별과 젠더 연구 전문가에게 회람하였고 모든 접수 의견은 문서의 관련 영역에 통합하였다.

결과

설문 조사

설문 조사 결과 설문에 참여한 4개 군에서 학술지가 성별과 젠더 정책을 편다고 밝힌 응답자의 평균 비율은 7%였다. 남성과 여성이 더 평등한(성불평등지수[gender inequality index]가 더 낮은) 국가의 응답자가 이러한 정책이 시행되고 있다고 응답한 경우가 많았다.

무작위로 선택된 100개의 학술지, EASE, 그리고 ISAJE 군에서 대다수(75%)가 저자를 위한 지침에 성별과 젠더 보고를 의무화하는 것에 대해서 잘 모르거나 원하지 않았다. 또한, 여성 응답자가 남성 응답자보다 성별과 젠더 정책을 지지하는 경향이 컸다. 조심스럽게 말하자면, 본 설문은 저자 지침, 동료 심사자 지침, 그리고 편집위원회와 동료 심사자의 젠더 균형에 관한 성별과 젠더 정책이 매우 부족함을 보여준다.

문헌 고찰

문헌 고찰 결과 62개의 학술지에서 개발하여 사용하는 정책과 학술지 원고, 사설, 전문가 위원회 보고서 및 학회 자료집 형태로 발행된 25개의 다른 출판물을 확인하였다.

대부분의 성별 및 젠더 정책과 지침은 저자를 위한 지침에 포함되어, 다양한 과학 분야(예: "동물 과학", "건강-정신의학")와 연구 유형(예: 동물, 인간, 세포 또는 세 가지의 조합)을 다루고 있었다. 대부분의 저자 지침은 해당 시 남성과 여성에 관한 결과를 별도로 보고하라는 것에 그치고 있었다.

몇몇 학술지는 편집자의 글(editorial)에서 새로운 정책의 채택을 알리거나 성별과 젠더 이슈에 대한 인식이 필요함을 강조하기도 하였다[5,20,27]. 예를 들어 Clinical Orthopedic and Related Research의 경우 편집자의 글에서 투고하는 연구자들에게 다음과 같은 지침을 따르도록 권고안을 발표했다[5]. (1) 모든 성별과 젠더에서 건강 문제를 연구하는 경우 남성과 여성 모두를 위한 연구 질문이 충분히 해결되도록 설계할 것, (2) 모든 임상, 기초 과학, 역학 연구에서는 가능한 성별 및/또는 젠더 특이적 자료를 제공할 것, (3) 연구 결과에서 성별과 젠더의 영향력(또는 관련성)을 분석하거나, 이런 분석을 하지 않으면 "방법"에서 밝히고 이를 "논의" 부분에서 연구의 제한점으로 제시할 것, (4) 만약 성별과 젠더가 사후에 분석되었다면 이는 조심스럽게 해석되어야 한다는 것을 명시할 것 등의 내용이다.

IOM이 2011년 개최한 "과학적 연구의 성별 특이적 보고" 워크숍에 참여한 다양한 이해 당사자들은 학술지와 편집자가 다루어야 할 핵심 이슈를 강조한 바, 저자는 인간 대상의 연구뿐 아니라 동물 연구와 인간이나 동물에서 유래한 세포, 조직 및 기타 물질 연구에서도 연구 대상자의 성별에 대해 명시해야 한다고 밝혔다.

Doull 등은 체계적 종설과 성별 및 젠더 기반 분석의 방법론을 개선하고 일원화해야 의사 결정을 위한 증거의 수집, 분석을 향상할 수 있다고 했으며[21], Nowatzki와 Grant는 젠더 기반 분석(gender-based analysis)의 근거를 제시했다[23]. Gender-based analysis는 남녀 간 불평등의 근원과 결과를 파악하고 이를 해결하기 위한 전략을 개발하기 위해 고안되었는데, 건강, 건강 관리, 그리고 이와 연관된 정책에서의 젠더 차이에 중점을 둔다.

SAGER(Sex and Gender Equity in Research) 지침

위에 검토된 정책, 절차 및 권장 사항을 기반으로 하여 SAGER 지침이 개발되었고, 연구에서 성별과 젠더의 체계적 보고를 향상하고자 하였다. 이 지침은 연구자와 저자에게 과학계 출판에서의 성별과 젠더 보고가 필요한 경우, 이에 표준화된 틀을 제공한다. 또한, 편집자의 연구 원고를 평가하기 위한 실질적인 도구로 사용하는 동시에, 저자와 심사자들 간의 인식을 높이는 방법으로 고안되었다. 보고 지침의 경우 일반적으로 연구에서 실제 수행한 것을 어떻게 보고하는지에 중점을 두기는 하지만, SAGER 지침에 포함된 모든 항목이 특정 연구에 적합하거나 적용 가능한 것은 아니라는 점을 인지해야 한다. 이러한 이유로 SAGER는 저자, 편집자, 평가자들이 성별과 젠더가 연구 주제와 관련이 있는지를 고려하고, 해당 시에만 이 지침을 따르도록 권장하는 것이다. 일반적 원칙으로 SAGER 지침에서는 성별과 젠더 용어의 신중한 사용을 권고하는데, 이는 두 용어의 의미를 혼동하지 않도록 하기 위해서이다. 공통된 정의를 사용하는 것은 출판 및 보관 데이터의 메타 분석을 더욱 향상할 수 있다. 성별은 확인 가능한 범위에서 생물학적 구별에 근거한 남성 또는 여성 범주화에만 사용되어야 한다. 저자들은 논문의 방법에서 참여자의 성별 구분이 자가 보고에 따른 것인지, 신체 특성에 대한 외적 또는 내적인 검사인지, 또는 유전적 검사 등을 시행한 것인지 기술해야 한다. 동물 연구에서는 성별(sex)이라는 용어를 사용해야 한다. 세포생물학, 분자생물학이나 생화학 실험에서는 배양된 세포나 조직의 기원과 성염색체에 관해 기술해야 한다. 알 수 없는 경우에는 사유를 명시해야 한다. 기타 학문 영역에서, 예를 들면 기구나 기술의 검정 등의 경우, 저자는 모든 젠더가 사용할 것인지와 사용자의 젠더를 고려하고 실험했는지를 설명해야 한다.

많은 연구가 성별과 젠더에 따른 차이를 분석하도록 "설계"되지는 않았겠지만, 특히 의학 연구에 있어서 본 패널은 이러한 분석이 성별과 젠더에 대한 지식을 발전시키는 데에 필요하다고 인식하였다.

표 1은 SAGER 지침을 제시한다. 인간과 동물 대상 연구, 그리고 인간과 동물에서 유래한 모든 연구(예: 기관, 세포, 조직 등)에 적용될 뿐 아니라, 연구 결과가 인간에게 적용되는 공학 분야와 같은 다른 학문에도 적용된다.

제목과 초록

연구에 한 가지 성별만 포함되거나 연구 결과가 한 성별 또는 젠더에만 적용될 경우, 제목과 초록에는 동물 또는 세포, 조직 및 다른 유래 물질의 성별, 또는 인간 참여자의 성별과 젠더를 명시해야 한다. 응용과학(기술, 공학 등)의 경우 저자는 연구 모델이 한 성별에 기초하였는지 또는 특정 성별의 사용을 고려하였는지를 명시해야 한다. 한 성별만 사용한 (성별 특이적이지 않은) 연구의 경우 "남성에서" 또는 "여성에서"라는 말을 제목과 초록에 포함하여 이 사실을 명시해야 한다. 만약 세포, 조직 등의 배양이 하나의 성별에서 얻어졌다면, 그

표 1. 연구에서의 성별과 젠더 형평성(Sex and Gender Equity in Research, SAGER) 지침

일반 원칙	
저자는 성별(sex)과 젠더(gender) 용어 사용을 신중히 하여 두 용어의 혼동을 피해야 한다.	
연구 대상이 성별 구분이 가능한 경우, 연구 초기에는 기대되지 않았더라도 성별에 따른 차이를 결과에서 드러낼 수 있도록 연구를 설계하고 수행해야 한다.	
연구 대상이 (사회적 문화적 상황에 따라 영향을 받는) 젠더에 따라서 구분이 가능한 경우, 연구는 이 수준에 맞게 수행해야 한다.	
논문의 세부 관련 권고사항	
제목과 초록	연구가 한 가지 성별만 포함하거나 연구 결과가 한 성별 또는 젠더에만 적용될 경우, 제목과 초록에는 동물 또는 세포, 조직 및 다른 유래 물질의 성별, 또는 인간 참여자의 성별과 젠더를 명시해야 한다.
서론	저자는 해당 시 성별과 젠더에 따른 차이가 예상되는지 보고해야 한다.
방법	저자는 연구 설계에 성별과 젠더가 어떻게 고려되었는지, 남성과 여성의 적절한 대표성을 보장했는지를 밝히고, 남성이나 여성이 배제된 경우 그 이유를 정당화해야 한다.
결과	가능한 데이터는 성별과 젠더에 따라 세분화해야 하며, 결과(긍정적/부정적)에 상관없이 성별과 젠더에 기반한 분석을 보고해야 한다. 임상시험의 경우, 철회 및 중단 사례 데이터 또한 성별에 따라 보고해야 한다.
논의	성별과 젠더가 연구 결과와 분석에 미치는 잠재적 영향에 대해 논의해야 한다. 성별과 젠더 분석을 수행하지 않으면 그 근거를 제시해야 하며 저자는 결과 해석에 이런 분석의 적용이 부족하다는 점을 추가로 논의해야 한다.

성별은 제목에 명시되어야 한다[3].

서론

저자는 해당 시 성별과 젠더에 따른 차이가 예상되는지 보고해야 한다. 이러한 연구가 부족한 경우, 저자는 성별 및/또는 젠더가 중요한 변이가 되는지와 차이가 예상되는지를 설명해야 한다.

방법

저자는 연구 설계에 성별과 젠더가 어떻게 고려되었는지, 남성과 여성의 적절한 대표성을 보장했는지를 밝히고, 남성이나 여성이 배제된 경우 그 이유를 정당화해야 한다. 여타 방법론 관련 선택들과 마찬가지로, 연구 모집단과 분석 방법과 관련된 성별과 젠더의 방법론적 선택들을 보고하고 정당화해야 한다.

인간이나 동물 유래 세포나 세포주 배양을 이용하는 체내 및 시험관 연구, 또는 인간이나 동물 유래 조직을 이용한 생체 외 연구는 피험자나 기증자의 성별을 밝혀야 한다.

단, 형질 전환 불멸화 세포주(immortalized cell line)는 제외한다[3]. 다른 경우, 예컨대 배아 또는 태아 초기의 배양이나, 복합 배양액이나 성별을 기록하지 않은 완료된 실험에서 만든 불멸화 세포주의 경우에는, 연구자는 염색체 분석으로 세포나 세포주의 성별을 판단해야 하고, 그 어떠한 방법으로도 성별을 결정할 수 없을 때만 "혼합(mixed)" 또는 "미상(unknown)" 용어를 사용하도록 권장한다.

결과

데이터는 성별에 의해 세분화하여 보고하고, 해당 시 성별과 젠더의 차이와 유사성을 분석하여 서술해야 한다. 남성과 여성의 해부학적, 생리적 차이(키, 몸무게, 체질량, 세포수, 호르몬 주기 등)와 사회적, 문화적 변수(사회-경제적 상태, 교육 수준 등)를 데이터 발표 및/또는 결과 분석에 고려해야 한다. 동물, 조직, 세포 배양 시 젠더 혁신 점검표(gendered innovations' checklist, http://genderedinnovations.stanford.edu/researchers.html)를 사용할 것을 권장한다[28]. 성별과 젠더에 기반한 분석을 수행한 경우에는 결과의 긍정적, 부정적 여부와 상관없이 보고해야 한다. 인간을 대상으로 하는 연구에서는 등록, 참여, 탈락, 중단, 추가 조사 불가 등 관련 자료를 (해당 시) 성별이나 젠더에 따라 세분화해 보고해야 하며, 성별과 젠더 요인의 영향력이 원인, 과정, 치료 효능, 건강에 미치는 영향 및 건강 관련 성과들에 어떤 역할을 하고 영향을 미칠 수 있는지에 근거하여 우선으로 평가해야 한다. 연구의 설계가 젠더 관련 의미 있는 결론을 도출하기에 충분하지 않다면 저자는 젠더 기반 사후 분석을 수행하지 말아야 한다. 모든 경우에 원시 자료(raw data)는 향후 자료 취합과 메타분석이 가능하도록 성별과 젠더에 따라 세분화하여 출판한다.

역학 연구의 경우, 사회 경제학적 변수와 같은 다른 노출이 건강 문제에 미치는 영향에 대해서 모든 젠더를 대상으로 조사하고 젠더 관점에서 비판적으로 분석해야 한다. 보고 지침들은 실제로 수행된 것을 보고하는 방법에 초점을 맞춘다는 것을 인지하고 있으나 SAGER 지침의 모든 항목을 수행할 필요는 없다(그래서 '해당 시'라는 부연이 있다). SAGER 지침은 연구에서 성별과 젠더의 형평성을 향상하기 위한 것이며, 따라서 저자, 편집자, 평가자들이 성별과 젠더가 연구 주제와 관련이 있는지를 판단하고 관련이 있다면 지침을 따르도록 권장하고 있다.

논의

연구 결과의 해석에 있어서 성별과 젠더에 따른 함의를 자세히 서술해야 하는데, 이것은 한 모집단의 모든 성별과 젠더에 일반화될 수 있는 정도를 포함한다. 성별과 젠더에 기반한 분석을 하지 않았다면 저자는 연구의 제한점을 논할 때 이러한 분석을 하지 않은 사유를 서술하고 이로 인해 결과에 어떤 영향을 줄 수 있는지 논의한다.

연구 결과를 해석할 때 과거의 연구들이 절차와 해석에서의 방법론적 엄밀성과 성별 치우침은 없었는지 검토해야 한다. 저자는 성별과 젠더를 혼동하지 말아야 하고 복합적 이거나 상호작용이 고려되어야 할 설명들을 지나치게 단순화하지 않도록 주의해야 한다. 저자는 성별과 젠더 관련 현상들에 대해 가능한 모든 설명, 예컨대 사회적, 문화적, 생물학적, 상황적 요인들을 고려해야 하며, 많은 성 관련 행동들이 문화적 또는 생물학적 요인의 결과일 수 있다는 사실에 유의해야 한다. 성 관련 행동의 변화가 생리학적인 변화의 근거가 될 수는 없다.

부록 2에는 저자들의 인식을 높이기 위한 질문들을 담았다. 이는 고유한 과학적 연구를 수행하는 다양한 학문 분야의 종사자들에게 논문 투고를 위한 기초가 될 수 있을 것이다.

결론

SAGER 지침은 3년에 걸쳐 여러 분야의 학자, 과학자, 학술지 편집자들이 참여하여 문헌 고찰, 전문가 의견 및 학술대회에서의 공청회를 통해 개발되었다. 저자, 학술지 편집자, 출판사, 심사자 및 과학계 기타 구성원 모두가 과학적 출판에서 성별과 젠더 관점에 대한 인지 부족을 해결하는 역할을 해야 한다.

SAGER 지침은 연구자들과 저자들에게 과학적 출판에서 성별과 젠더를 보고하는 표준화된 방법을 제공한다. 이는 과학적 연구에서 성별과 젠더 보고를 향상하고, 저자와 동료 심사자를 위한 지침 역할을 하며, 다양한 연구와 학문 분야를 수용할 수 있을 만큼 유연하고 연구 결과 전달을 향상하도록 설계되었다. 그러나 이 지침은 젠더 다양성 인구 집단에 대해 확정적인 권장 사항을 제시하지는 않는다. 대부분의 연구가 성전환자(transgender)와 같은 젠더 다양성 집단에서의 효과에 대한 차이를 파악할 정도로 설계되지 않았음을 인지하고 있으며, 특히 그러한 다양성이 알려지지 않은 국가에서는 더욱 그렇다. 그렇지만 저자는 자신의 연구 결과가 젠더 다양성 집단에 대해서도 어떤 관련성이 있는지 검토해야 할 것이다.

편집자들은 성별과 젠더 이슈를 통합할 때 더욱 엄밀하고 윤리적인 과학이 가능해진다는 것을 분명히 해야 한다. 수행이 어려울지라도, 학술지 편집자들은 SAGER 지침을 지지하고 각 보고 항목에 관한 우수 사례를 포함하여 각 학술지와 학문 영역의 필요에 맞게 채택할 것을 권고한다. 최소한 원저 논문을 출판하는 학술지라면 저자에게 데이터를 성별과 젠더로 분류하여 제시할 것과 해당하면 성별과 젠더에 따른 차이점 또는 유사성을 충분히 설명하도록 해야 한다. 그림 1은 제출된 원고의 초기 심사에 사용할 수 있는 질문 목록이다. 편집위원장은 초기 투고논문의 사전 점검에 사용될 점검표에 구체적 질문을 포함하여, 편집자들 사이에 성인지적(젠더를 염두에 둔) 평가를 체계화하기 위해 노력해야 할 것이다.

동료 평가자 평가 양식에 소개될 수 있는 질문의 예는 다음과 같다.
- 성별과 젠더가 해당 연구와 관련이 있는가?
- 저자가 성별과 젠더를 적절히 다루었거나 이런 분석의 부재를 정당화했는가?

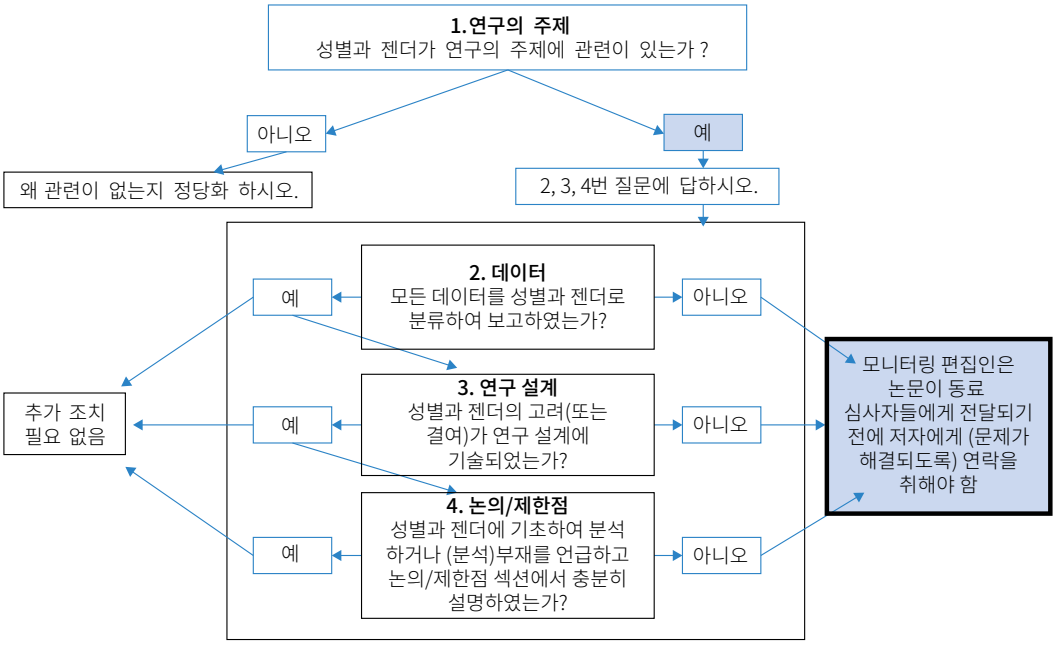

그림 1. 투고 원고에 대한 편집자의 초기 심사를 안내하는 SAGER(Sex and Gender Equity in Research) 흐름도.

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이런 노력이 효과를 거두기 위해서는 학술지 편집자, 출판사, 편집자 단체, 전문 단체, 과학 옹호 단체, 과학 저널리스트 및 기타 과학 관련 소통 채널 등 과학계 전반의 지지가 필요하다.

편집자는 SAGER 지침을 심사자들에게 배포하고 논문 평가에 사용하도록 권장해야 한다. 또한, 동료 심사자가 작성하는 논문 평가서가 성별과 젠더의 중요성과 관련성에 관한 구체적 질문을 포함하고 있는지 확인해야 한다.

윤리적 행동과 편집 업무에 대한 정기 교육의 목적으로 성별과 성 인지적(젠더를 염두에 둔) 보고의 중요성에 대한 교육을 편집자들에게 제공해야 한다.

Authors' contributions

Conceptualization: Heidari S
Formal analysis: De Castro P, Tort S, Curno M
Investigation: Heidari S, De Castro P, Curno M
Methodology: Heidari S
Project administration: Heidari S, Tort S
Writing – original draft: Heidari S, Babor TF
Writing – review & editing: Heidari S, Babor TF, De Castro P, Tort S, Curno M

Conflict of interest

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Supplementary materials

Not applicable.

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부록 1. 용어 해설

젠더(gender): 젠더는 여성, 남성 및 다양한 젠더를 지향하는 사람의 사회적으로 구성된 역할, 행동 및 정체성을 말한다[1]. 이는 사람들이 자신과 서로를 어떻게 인식하고, 행동하고 상호작용을 하는지와 사회에서의 힘과 자원 분배에 영향을 미친다. 젠더는 보통 이원적 요소(여성/남성)로 잘못 개념화된다. 그러나 사실 젠더 정체성과 표현에는 다양한 범위가 있고, 이에 따라 개인이 어떻게 자신을 식별하고 젠더를 표현하는지를 정의한다.

젠더 정체성(gender identity): 남성과 남자다움, 여성과 여자다움, 또는 양가적으로 스스로 생각하는 개인의 개념으로, 어느 정도는 신체적 특성, 부모의 반응, 심리적 및 사회적 압력에 기인한다. 이는 젠더 역할의 내부적 경험이라 할 수 있다(MeSH 용어, 1991년 도입, 1975년 개정)

젠더 기반 분석(gender-based analysis): 계획하고 의사 결정하는 과정뿐 아니라, 정책, 프로그램 및 입법 과정의 개발에 젠더 관점을 체계적으로 통합하는 분석 도구를 말한다. 이 분석은 여성-남성, 소년-소녀 간의 차이점을 파악하고 명확히 하는 데 도움이 되며, 이러한 차이가 건강 상태, 건강 관리 체계에 대한 접근성 및 상호작용에 어떻게 영향을 미치는지 보여준다(https://women-gender-equality.canada.ca/).

성 인지적(젠더를 염두에 둔) 분석(gender-sensitive analysis): 성별에 따라 단순히 데이터를 분

리하는 것 이상의 통계 분석이다(예: 단순한 "성별에 따른 집계"로는 충분하지 않음). 성 인지적 분석은 데이터에 반영된 저변의 젠더 관계에 대해 의문을 제기해야 한다(http://www.oecd.org/dac/gender-development/44896238.pdf).

젠더 관점(gender perspective): 젠더 관점은 젠더의 영향이 사람들의 기회, 사회적 역할 및 상호작용에 미치는 영향을 본다. 젠더는 국제 및 국가기구의 정책, 프로그램 및 사업 목표가 성공적으로 수행되는 데 직접적인 영향을 미치며, 결과적으로 사회적 발전과정에 영향을 미친다. 젠더는 개인과 사회의 경제적, 사회적, 일상적 및 사적 삶의 모든 측면과 사회가 남성과 여성에게 부여하는 다른 역할에 있어서 필수 불가결한 요소이다(http://www.fao.org/docrep/003/x2919e/x2919e04.htm).

성별(sex): 성별은 인간과 동물의 신체적, 생리적 특징과 관련된 생물학적 속성의 묶음으로, 염색체, 유전자 발현, 호르몬 기능 및 생식/성 해부학을 포함한다[1]. 성별을 구성하는 요소와 그러한 생물학적 특성이 어떻게 표현되는지는 다양하지만, 성별은 대개 여성 또는 남성으로 분류된다.

성별과 젠더 기반 분석(sex- and gender-based analysis): 건강 계획과 의사 결정 과정은 물론, 건강 연구, 정책 및 프로그램 개발에 있어 성별과 젠더 관점을 통합하는 분석적 접근을 말한다. 이 분석은 여성-남성, 소년-소녀 간의 차이점을 파악하고 명확히 하는 데 도움이 되며, 이러한 차이가 건강 상태 및 건강 관리체계에 대한 접근성과 상호작용에 어떻게 영향을 미치는지 보여준다(https://women-gender-equality.canada.ca/).

성별 분리 통계(sex-disaggregated data): 남성과 여성에 대해 개별적으로 수집하고 분석한 데이터. 젠더 주류화 수행 틀(Gender Mainstreaming Implementation Framework) – UNESCO, 2003.

성차별주의(sexism): 젠더에 따른, 또는 젠더 관련한 사회적 역할에 대한 고정관념을 조장하는 행동이나 태도에 근거한 편견 또는 차별(MeSH 용어, 2013년 도입).

성전환자(transgender persons, transexual persons, transgenders): 출생 시의 해부학적 성별과 일반적으로 관련되지 않는 젠더 코드화된 행동에 지속해서 동일시되고 이를 표현하는 사람으로, 성전환 절차를 밟을 의사가 있거나 없을 수 있다(MeSH 용어, 2013, 2016).

부록 2. 성 인지적 보고를 위한 저자 점검표

연구 접근
연구 과제에 사용된 젠더와 성별 개념이 활용되었습니까?
그렇다면, 젠더 및/또는 성별의 개념을 명시적으로 정의했습니까? 연구에서 젠더 및/또는 성별의 어떤 측면을 조사하는지 분명합니까?
그렇지 않다면, 이것이 중요한 제한점이라고 생각합니까? 관련 문헌의 기존 지식에 의하면 고려해야 할 타당한 젠더 및/또는 성별 요소가 있습니까? 성별 및/또는 젠더는 귀하가 제안한 연구와의 관련성이 높다고 생각하는 경우, 연구 설계에서 이를 반영해야 합니다.
연구의 질문 및 가설
연구 질문이나 가설이 젠더 및/또는 성별 또는 이와 관련된 집단이나 현상을 참고합니까? (예를 들어, 남성과 여성의 차이, 여성 간의 차이, 남자다움과 같은 젠더화된 현상의 이해를 위한 노력)
문헌 고찰
문헌 고찰에서 여자-남자, 소년-소녀, 또는 수컷-암컷 간에 의미 있는 차이가 있다는(또는 부족하다는) 것을 뒷받침하는 선행 연구를 인용했습니까?
문헌 고찰에서 과거의 연구들이 젠더 또는 성별에 대한 고려 정도를 명시하고 있습니까?
연구 방법
표본은 젠더 및/또는 성별 기반 요인들을 포괄하는 데 적절합니까?
젠더 및/또는 성별에 따라 분리된 자료수집이 가능합니까?
선정 및 제외 기준이 젠더 및/또는 성별과 관련하여 타당합니까? (주: 이는 인간, 동물 개체, 완전 유기체가 아닌 생물학적 시스템에도 해당함)
연구에서 제안된 자료수집 방법이 젠더 및/또는 성별 조사에 적합합니까?
분석 접근법은 젠더 및/또는 성별에 기반한 요인을 파악하기에 적절하고 충분히 엄격합니까?
윤리적 측면
연구 설계가 젠더 및/또는 성별에 특별한 의미가 있을 수 있는 관련 윤리적 이슈를 반영하였습니까? (예: 임상시험에서 임산부 포함)

Data from Canadian Institutes of Health Research [24].

Guidelines

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연구에서의 성별과 젠더 형평성(Sex and Gender Equity in Research, SAGER) 지침: 시행 및 체크리스트 개발

The Sex and Gender Equity in Research (SAGER) guidelines: implementation and checklist development: a Korean translation

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성별(sex)과 젠더(gender)의 차이를 이해하는 것은 질병 관련 병태생리학 연구, 사회인구학적 건강결정요인, 의학적 또는 사회적 중재의 긍정적 영향 및 위해성 등을 막론하고 엄밀하고 포용적연구에 있어 필수적이다. 다양한 젠더를 포함한 연구가 활발해졌지만 성별과 젠더를 변수로 명시하는 연구는 여전히 부족하다. 2016년에 발표된 성별과 젠더 형평성(Sex and Gender Equity in Research, SAGER) 지침은 널리 지지되고 있지만, 소수의 과학 학술지와 기관들에서만 이를 공식적인 편집 및 출판 정책에 반영하고 있다. *Lancet* 학술지들의 SAGER 지침의 준수와 모니터링을 촉진하기 위해 본 연구진은 비공식 예비 연구를 실시하여 체크리스트를 개발했다. 이는 신속한 편집 검토를 가능하게 하고 많은 편집인과 학술지들이 SAGER 지침을 받아들이며, 심사자와 저자들의 인식도를 높이기 위함이다. 원고 점검 또는 심사 과정의 일부로 이 체크리스트를 활용함으로써, 학술지 편집인들은 성별과 젠더를 변수로 고려해 보고함에 있어 출판 권고 사항(best publishing practices)의 준수를 지지할 수 있게 되며, 이는 출판되는 연구의 일반화 수준을 향상시킬 수 있을 것이다.

배경

역사적으로 과학 연구는 남녀/암수간 차이를 고려하지 않고 남성 모델에 편중되었다. 21세기의 도래 이후 이러한 비뚤림(bias)은 비과학적이고 동시에 비윤리적이라는 인식이 점차 높아지고 있지만[1,2], 연구에서 남성을 표준으로 간주하는 경향은 여전히 젠더 불형평성의 주된 요인으로 남아 있다[3].

성별과 젠더의 차이를 고려하는 것은 과학 연구에 필수적이다[3,4]. 그러나 임상 및 사회과학에서 여성 및 다양한 젠더의 참여자가 과소 표집되거나 심지어 배제되는 현상은 여전히 문제가 되고 있다[5,6]. 이처럼 건강을 결정하는 요인으로서 성별 및 젠더가 중요하다는 인식이 높아지고 있음에도 불구하고, 젠더 격차는 여성 및 다양한 젠더의 사람들에게 여전히 존재하며 불균형적인 위험(예를 들면, 오진 또는 부적절한 치료 등)을 초래한다[6]. 뿐만 아니라, 성별과 젠더의 차이는 공학, 기술, 그리고 사회경제학적 연구 결과에도 영향을 미친다[7,8].

현재 많은 연구비 발주 기관들은 연구 대상자 간 성별 및 젠더의 균형을 맞추거나 그렇지 않을 경우 발생한 불균형에 관해 정당한 근거를 제시할 것을 요구하고 있다. 미국 국립보건원(NIH)의 '생물학적 변수로서의 성별에 관한 미국 국립보건원 정책'('NIH Policy on Sex as a Biological Variable') 및 '여성건강연구를 위한 범 기

* It is a Korean translation of check list of SAGER guidelines, which the Korean Council of Science Editors did under the support of the EASE Gender Policy Committee. Original guidelines were published as Van Epps H, Astudillo O, Del Pozo Martín Y, Marsh J. The Sex and Gender Equity in Research (SAGER) guidelines: implementation and checklist development. *Eur Sci Ed* 2022;48:e86910. https://doi.org/10.3897/ese.2022.e86910

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관 차원의 미국 국립보건원 전략 방안('Trans-NIH Strategic Plan for Women's Health Research')이 그 예시이다[9]. 규제 기관들도 임상시험에서 소외된 소수집단이 포함될 수 있도록 임상시험 의뢰자 대상 지침[10]을 발표하였다. 또한 연구 참여자가 성별과 젠더, 인종, 민족, 연령 및 성적 성향과 관련하여 실제 환자 모집단을 보다 정확하게 대표해야 한다는 필요성이 점점 더 강조되고 있다[11]. 이러한 정책은 긍정적인 효과를 거두고 있다. 임상시험 참여자의 지리적, 인종적/민족적, 그리고 젠더 다양성을 다룬 미국 식품의약국(FDA) 연례 보고서에 따르면, 여성의 임상시험 참여율은 2015년 43%에서 2019년에 51%로 증가했다[12].

많은 논문에서 연구 참여자의 성별이나 젠더를 명시하지 않는다는 사실을 인지하고 2015년에 유럽과학학술지편집인협의회(European Association of Science Editors, EASE) 전문가들이 협력하여 "연구 설계, 데이터 분석, 결과 및 해석에서 성별 및 젠더를 보고하는 포괄적인 절차"인 SAGER(Sex and Gender Equity in Research) 지침을 개발했다[5]. SAGER 지침에 대한 지지는 신속히 나타났지만 지침의 준수와 편집 정책으로의 채택은 더뎠다. 이는 아마도 의무화에 대한 우려, 편집인의 시간 부족, 그리고 기술적 장벽(전자 투고 시스템에 저자들이 따라야 할 새로운 요구 사항을 통합하는 문제 등)과 같은 이유와 일부 관련 있을 것이다[13]. 현재 대규모의 변화가 일어나고 있으며, Elsevier와 Springer Nature와 같은 대형 출판사들은 수백 개의 학술지에서 편집 및 심사 지침에 SAGER 지침을 반영하는 작업을 진행하고 있다[14,15].

SAGER(Sex and Gender Equity in Research) 지침의 이행

The Lancet 학술지들은 국제의학학술지편집인협의회(International Committee of Medical Journal Editors)가 발행한 일반적인 지침을 준수하고 있지만[16], 저자를 위한 안내에 성별 및 젠더에 관한 보고를 현재 명시하지 않고 있다. 그럼에도 SAGER 지침의 요건을 가장 효과적으로 적용하기 위해 내규를 점차적으로 발전시켜왔다. 예를 들어, 인구사회적 자료표에서 특정 젠더만이 아닌 모든 젠더의 숫자 보고를 요구하고 있으며 성별 및 젠더 데이터 수집 방법과 참여자들의 자발적인 선택을 위해 제공되는 선택안에 관한 정보 제시를 장려한다.

2021년, *The Lancet Rheumatology*, *The Lancet Haematology*, *The Lancet Psychiatry* 편집위원회는 시범 프로그램을 도입했다. 이는 생물학적 성별, 젠더, 그리고 인종에 따른 인구사회적 자료 보고에 더욱 주의를 기울이고 성별 및 젠더를 세분화한 데이터가 연구결과, 이상 반응 및 환자 보고 지표에 추가되도록 저자들에게 요청하기 위함이었다[17,18]. 이 일환으로 *The Lancet Rheumatology*와 *The Lancet Haematology* 편집인은 모든 주요 논문의 SAGER 지침의 준수 여부를 모니터링했으며 저자들이 성별 및 젠더별로 세분화한 결과 및 이상 반응(일반적으로 부록에 포함되는) 데이터를 보고하도록 권장하였다. 그러나 항상 적절하거나 유용한 것은 아님을 인정하기에(예를 들어 대상자 수가 매우 작은 경우) 이러한 데이터를 추가할지 여부는 저자의 재량에 맡겼다. 이 시범 프로그램의 주요 목표는 SAGER 지침을 기존 편집인 업무 과정에 통합하는 것이 실현 가능한지와 저자들이 이러한 추가적인 요청을 얼마나 따라주는지를 가늠하려는 것이었다.

The Lancet Rheumatology 편집인들은 다음 다섯 가지 항목에 중점을 두었다: (1) 초록에 성별과 젠더에 관한 데이터의 수록, (2) 인구사회적 자료를 제시하는 표에 성별 또는 젠더에 관한 모든 보고된 데이터의 수록, (3) 성별과 젠더에 따라 세분화된 이상 반응 데이터의 수록, (4) 성별 및 젠더에 따라 세분화된 환자 보고 지표 데이터의 수록, 그리고 (5) 성별과 젠더에 따른 자료분석 수록이다. 저자의 호응 정도에 대한 지표로, 이 시범 프로그램 시행을 발표하기 전(2021년 1월~5월)과 후(2021년 6월~8월)에 출판된 논문 중 위의 다섯 가지 항목을 충족하는 논문의 비율을 계산했다[17]. 이 단계에서 실행 가능성에 대한 공식적 측정방법(예를 들면 편집인이 원고를 검토하고 저자에게 데이터를 요청하거나 출판사가 수정된 자료를 구현하는 데 소요되는 추가적인 시간 등)은 포함하지 않았다.

전반적으로 저자들은 추가적인 요청에 호의적이었으며 성별 및 젠더에 따라 세분화한 자료를 논문에 어떻게 포함할지 편집위원회와 생산적인 논의를 하는 것에도 적극적이었다. 2021년 1월부터 5월 사이에 출판된 20편의 논문이 성별과 젠더와 관한 데이터를 전혀 초록에 포함하지 않은 반면, 2021년 6월부터 2022년 8월 사이에 출판된 56편의 논문 중 46편(82%)은 초록에 이를 명시했다(그림 1). 이상 반응을 보고한 논문의 경우, 성별 및 젠더에 따른 세분화된 자료가 2021년 1월부터 5월 사이에 발행된 논문의 0%(13편 중 0편)이

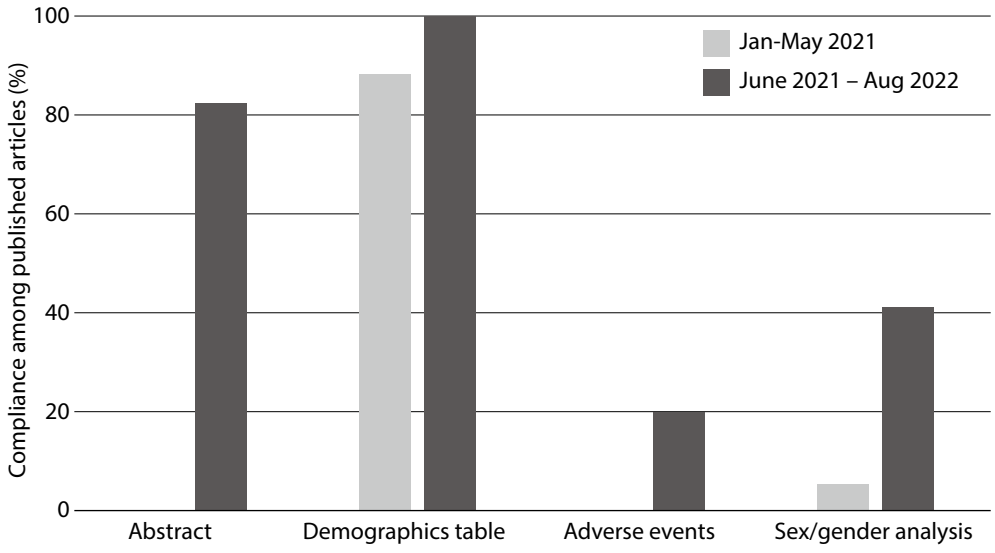

그림 1. *The Lancet Rheumatology*에 출판된 논문의 SAGER(Sex and Gender Equity in Research) 지침 준수 비율. 시범 프로그램 개시 전인 2021년 1월~5월, 개시 후인 2021년 6월~2022년 8월에 출판된 논문 중 성별/젠더 데이터를 초록에 보고한 비율, 인구사회적 특성 표에 구분하여 제시한 비율, 이상 반응 분석에 성별/젠더에 따른 세분화 자료를 제시한 비율, 그리고 자료분석에 성별/젠더를 적용한 비율.

었던 반면 2021년 6월부터 2022년 8월 사이에 발행된 논문의 28%(18편 중 5편)로 증가했다. 마찬가지로, 성별 및 젠더 분석을 포함한 논문도 5%(20편 중 1편)에서 41%(59편 중 24편)로 증가했다. 단, 시범 프로그램 개시 전이나 후에도 환자 보고 지표에 성별 및 젠더를 세분화한 자료를 포함한 연구는 없었으며, 이는 해당되는 논문이 현저히 적은(개시 전 3편, 개시 후 6편) 것과 관련이 있을 수 있다. 반면 인구 사회적 특성 표에 성별 및 젠더 관련 자료를 포함한 논문의 비율은 시범 프로그램 개시 전에도 이미 높았으며, 개시 후에 그 비율은 더욱 증가했다(그림 1).

궁극적으로 의미 있는 데이터의 생성을 위해서는 성별과 젠더에 대한 고려가 새로운 임상시험 및 연구 설계(그리고 해당 연구의 통계 분석)에 반드시 통합돼야 한다. 따라서 진행 중이거나 완료된 연구에 대한 보고를 개선하려는 노력은 고무적이며 이는 저자, 규제 기관, 그리고 정책 입안자들의 인식 고양에도 도움이 되기를 기대한다.

SAGER(Sex and Gender Equity in Research) 체크리스트 개발 및 사용

시범 프로그램을 진행하면서 우리는 SAGER 지침의 활용과 준수 여부를 모니터링하는 데 체크리스트가 유용하다는 것을 깨닫게 되었다. 따라서 SAGER 논문의 표[5]를 CONSORT 체크리스트[19]의 구조에 맞도록 변환하였다. 인간 대상 연구(표 1)와 응용과학 및 세포생물학 분야와 같이 인간 참여자를 포함하지 않는 연구(표 2) 각각에 적용할 수 있는 체크리스트 두 종류를 만들었다.

또한 원 SAGER 표에는 포함되지 않았으나 세 종 *Lancet* 학술지 시범 프로그램에서 시험한 내용에 따라 다음 요건들을 포함하였다: (연구결과 또는 데이터와 분석에 대한 사전 명시 여부와 관계없이) 모든 참가자의 젠더 또는 성별 데이터를 초록과 기초 인구학적 특성 표 모두에 포함하는 것, 그리고 부록에 성별과 젠더에 따라 세분화된 데이터와 분석을 포함하는 것이다.

SAGER 체크리스트는 저자들에게 제공되어야 하며 성별 및 젠더 데이터 보고에 대한 안내가 학술지의 '투고 규정'에 명시되어야 한다. 저자에게 명확한 안내를 제공하는 것은 연구에서 성별과 젠더 고려의 중요성에 대한 인식을 높이고 학술지의 기대 사항을 정확하게 전달하는 데 도움이 될 것이다.

편집인의 관점에서 SAGER 체크리스트는 심사와 학술지 출판의 작업 단계별로 학술지의 업무 흐름에 따라 다양하게 사용될 수 있다. 현 단계에서 *Lancet* 학술지들은 초기 심사 완료 후 저자에게 수정 원고 제출을 요

표 1. SAGER(Sex and Gender Equity in Research) 지침 체크리스트: 사람 대상 연구

섹션/주제	항목	체크리스트 설명	[해당] 페이지 번호
일반적 사항	1	성별/젠더 용어의 적절한 사용	
제목	2	대상자의 성별/젠더가 하나뿐인 경우 제목에 이를 명시	
초록	3a	대상자의 성별/젠더가 하나뿐인 경우 초록에 이를 명시	
	3b	연구 모집단을 성별/젠더 세부 분류로 기술*	
서론	4a	해당하면, 성별/젠더에서의 차이 또는 유사점 여부를 보여주는 선행 연구의 인용	
	4b	성별/젠더가 중요한 변수가 될 수 있는지와 이에 따른 차이가 예상되는지 여부 언급	
	4c	연구 모집단의 성별/젠더에 따른 인구학적 특성(예: 남성/여성 연구 대상자의 질병 유병률) 기술*	
연구방법	5a	성별/젠더 정의 방법(예: 자가 보고, 유전자 검사)	
	5b	연구 설계에서 성별/젠더가 어떻게 고려되었는지, 남성 및 여성 연구 대상자의 적절한 대표성을 확보했는지 여부, 남성이나 여성이 배제된 경우 그 이유에 대한 정당성 제시, 또는 고려되지 않았을 경우 해당 이유에 대해서 설명하는 기술. 연구 설계에서 성별/젠더 기반 특정 중재(예: 여성에 대한 피임 의무화)에 대한 정당성 제시* 피임 요건과 임신 및 수유자 배제에 대한 과학적 근거를 명시적으로 보고*	
결과	6a	연구 모집단 기술에 고려된 모든 범주에 대한 성별/젠더 세부 분류의 온전한 제시*	
	6b	해당하면, 성별/젠더에 따라 세분화한 데이터와 성별/젠더에서의 차이점 및 유사점 기술	
	6c	결과와 관계없이 성별 또는 젠더 기반 분석을 보고(사전에 명시된 경우 본문에, 그렇지 않은 경우 부록에 포함)*	
	6d	임상시험의 경우, 성별/젠더에 따라 세분화한 이상반응 데이터(사전에 명시된 경우 본문에, 그렇지 않은 경우 부록에 포함)*	
	6e	성별/젠더에 따른 세분화된 환자 보고 지표 데이터 제시(사전에 명시된 경우 본문에, 그렇지 않은 경우 부록에 포함)*	
	6f	역학 연구의 경우, 건강문제 관련한 다른 노출 요인의 영향에 대해 모든 젠더를 고려하고 젠더 관점에서 비판적으로 분석	
	6g	표 1에 남성 성별/젠더, 여성 성별/젠더, 그리고 기타 범주(수집된 경우)에 대한 별도의 행이 포함됨*	
논의	7a	모집단의 모든 성별/젠더에 일반화 가능한 정도를 포함하여, 성별/젠더가 연구 결과 및 분석에 미치는 잠재적 함의 기술	
	7b	성별/젠더 분석을 수행하지 않은 경우, 그 근거를 제시하고 해당 분석의 부재가 결과 해석에 미치는 영향에 대해 논의	

SAGER 지침을 근간으로 조정하였음.
*원 SAGER 표에 추가된 항목임.
Adapted from Heidari et al. [5] with CC-BY.

청할 때 체크리스트를 사용하며, 편집인은 게재 결정에 대한 통지에 성별 및 젠더 보고와 관련된 요구사항을 저자들에게 전달하고 있다. 성별 및 젠더 데이터와 분석에 대한 전문가 검토가 중요하다는 점을 고려할 때, 사실 초기 심사 의뢰 "전"에 체크리스트를 사용하여 투고 원고를 스크리닝 하는 것이 이상적이다. 이런 접근은 논문 수정 단계에서 심사자의 부담 가중이 될 수 있는(예를 들면 한번 더 심사해야 하는 상황) 새로운 보고 요건이 도입된다는 우려를 피할 수 있게 한다. 하지만 심사 전의 SAGER 지침 집행이 저자의 호응 정도에 따라 작업 진행에 병목현상을 야기할 수도 있다.

체크리스트의 모든 항목이 모든 연구에 적용되지 않을 수 있다. 사실 각 항목은 결과를 보고하는 시점이 아니라 연구 설계 단계에서 고려되어야 바람직하다. 설계 단계에서 성별 및 젠더 차원을 포함하지 않은 연구는 이러한 문제들을 통계적으로 유의미하게 다룰 수 있는 기반이 충족되지 않을 경우, 성별 또는 젠더에 따른 세분화 데이터와 분석을 적절하게 논의 및 신중하게 해석해야 한다. 이러한 데이터는 기술적 보고 및 가설 설정에 충분히 유효할 수 있으므로, 논문의 부록에 데이터를 포함시키는 것이 유용하고 잠재적으로 유익하다고 생각한다.

논의

출판된 논문에 SAGER 지침을 적용하려는 본 연구진의 노력은 성공적이었으며, 심사 과정에 체크리스트가

표 2. SAGER(Sex and Gender Equity in Research) 지침 체크리스트: 기타 연구(응용 과학, 세포생물학 등)

섹션/주제	항목	체크리스트 설명	[해당] 페이지 번호
일반적 사항	1	성별/젠더 용어의 적절한 사용	
제목	2a	동물뿐 아니라 동물에서 유래한 모든 세포, 조직 등에도 성별을 제목에 명시	
	2b	응용과학(기술, 공학 등) 분야에서 연구 모델이 특정 성별/젠더를 기반으로 하는지 또는 기술의 응용이 특정 성별/젠더에 한정되는지를 제목에 제시	
초록	3a	동물뿐 아니라 동물에서 유래한 모든 세포, 조직 등에도 성별을 초록에 명시	
	3b	응용과학(기술, 공학 등) 분야에서 연구 모델이 특정 성별/젠더를 기반으로 하는지 또는 기술의 응용이 특정 성별/젠더에 한정되는지를 초록에 제시	
서론	4a	해당하면, 성별/젠더에서의 차이 또는 유사점 여부를 보여주는 선행 연구의 인용	
	4b	성별/젠더가 중요한 변수가 될 수 있는지와 이에 따른 차이가 예상되는지 여부 언급	
연구방법	5a	세포 생물학, 분자 생물학 또는 생화학 실험에서 세포 또는 조직 배양의 기원 및 성염색체 구성을 명시(알 수 없는 경우, 그 이유를 명시)	
	5b	기기 또는 기술을 실험하는 연구에서 제품이 모든 젠더에 적용되거나 사용될지 여부와 사용자의 젠더를 염두에 두고 실험했는지 설명	
	5c	해당하면, 연구 설계에 성별/젠더가 어떻게 고려되었는지 기술	
	5d	세포 배양을 하는 생체내(*in-vivo*) 및 시험관(*in-vitro*) 연구, 인간이나 동물 유래 세포주 연구, 또는 인간이나 동물 유래 조직을 이용한 생체 외(*ex-vivo*) 연구의 경우, 피험자나 출처 기증자의 성별을 명시(단, 고도로 변형된 불멸화 세포주는 제외)	
결과	6	동물 모델을 사용하는 연구의 경우, 동물의 성별 세부 분류 제시*	
논의	7	해당하면, 모집단의 성별/젠더에 일반화 가능한 정도를 포함하여, 성별/젠더가 결과 및 분석에 미치는 잠재적 함의 기술	

SAGER 지침을 근간으로 조정하였음.

*원 SAGER 표에 추가된 항목임.

사용됨으로써 (1) 학술지 편집인들이 용어 표준화에 기여할 수 있도록 돕고, (2) 성별 및 젠더를 변수로 포함함으로써 성별/젠더에 기반한 선정기준의 정당성을 보장할 수 있는 보고 권고 사항(best reporting practices)을 지지하며, (3) 학계의 인식을 높일 것으로 기대한다.

최근 학술지 편집인들은 연구자들이 연구의 포용성(inclusion) 및 다양성(diversity)에 대한 세부 사항을 보다 공개하는 의식 고양 및 기회 마련을 위해 다른 전략을 채택하기도 했다. Cell Press는 2021년 1월부터 저자들이 논문의 과학적 내용의 다양성뿐만 아니라 저자됨(authorship)과 각 저자의 연구에 기여한 바를 포함할 수 있도록 포용성 및 다양성 양식 작성을 가능하게 하였다. 저자들은 해당 답변에 따라 출판될 논문에 포용성 및 다양성에 관한 문구를 포함할 수 있다. 이는 연구 수행 및 보고의 투명성을 높이고 학계에서 포용성 및 다양성에 대한 인식을 제고하기 위해 이런 문구를 명시하는 논문을 부각하려는 것이다[20]. *New England Journal of Medicine*도 마찬가지로 저자는 논문의 온라인 출판에 맞춰서 연구 대상자의 질병, 문제, 또는 상태와 연구 대상자의 대표성에 대한 배경 정보를 부록 표(supplement table)에 작성하도록 하고 있다[11]. 이와 같은 새로운 요구사항은 연구 설계의 투명성과 환자 모집단의 대표성 확보에 대한 강화로, 진일보하고 있음을 나타낸다.

성별과 젠더, 그리고 정체성 관련한 여러 차원 간의 복합적인 상호작용은 불평등의 원인이 되고 있다. 포용적인 연구와 교차의학(intersectional medicine)은 정체성의 다양한 요소들이 (성별, 젠더, 인종, 민족, 성적 성향, 장애, 그리고 사회경제 및 문화적 요인 등이) 개인에게 어떻게 영향을 미치는지 이해하는 데 힘써야 한다. 이런 점에서 SAGER 체크리스트는 차후 SAGER 지침의 수정보완을 위한 모델이 될 수 있으며 이는 성별과 젠더가 정체성 관련한 다른 중요한 요소와 통합되고 이들 간의 교차성이 건강에 어떤 영향을 미치는지 확인할 수 있기를 기대한다.

데이터와 데이터 사이언스는 점점 더 우리 세계를 형성하고 연구 및 의료 분야에 폭넓은 변화를 가져오고 있다. 데이터 사이언스에서 성별과 젠더를 포함하여 정체성의 다양한 측면들을 통합 개선하는 것이 시급하

다. 인공지능이 연구 성과에 혁신을 가져올 것이라 약속했지만, 이러한 알고리즘은 학습된 데이터만큼만 유효할 뿐이다. 예를 들어, 연구 대상자가 모집단을 대표한다는 가정이 잘못되면 기존의 비뚤림이 악화되고 잘못된 연관성이 도출될 수 있다. 성별 또는 인종으로 편중된 데이터에 기반하여 알고리즘을 개발했기 때문에 [21,22] 개발된 진단 알고리즘이 여성 또는 유색 인종을 대상으로 실험했을 때 성과가 부진한 사례가 많이 있다. 이처럼 대표성 있는 데이터를 사용하지 않는 것은 대변되지 못한 집단(underrepresented)에 영향을 미치며 연구의 적용 가능성을 제한한다. SAGER 체크리스트는 이러한 유형의 연구에도 적용될 수 있으며, 현재 형식으로도 데이터의 대표성과 알고리즘의 적용 가능성을 판단할 수 있도록 도움이 되는 핵심 항목을 이미 제공하고 있다.

진정으로 포용적인 연구의 실현은 연구 설계에서 시작된다. 연구 설계에 새로운 항목이 적용되려면 연구지원 기관, 연구자, 기관연구윤리위원회 및 데이터를 생성하는 기타 조직들의 지지와 함께 정책 입안자, 옹호자, 그리고 사회 전반의 지원이 필요하다[18,23,24].

교차연구(intersectional research)가 표준이 될 때까지, 저자와 편집인이 SAGER 지침을 준수하여 보고할 수 있도록 이 체크리스트가 도움이 되기를 기대한다. 과학은 모두를 위한 것이며, 성별과 젠더에 관한 포괄적인 보고를 한다면 포용성을 고려하지 않은 연구의 부적절함을 드러낼 것이다.

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Conflict of interest
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