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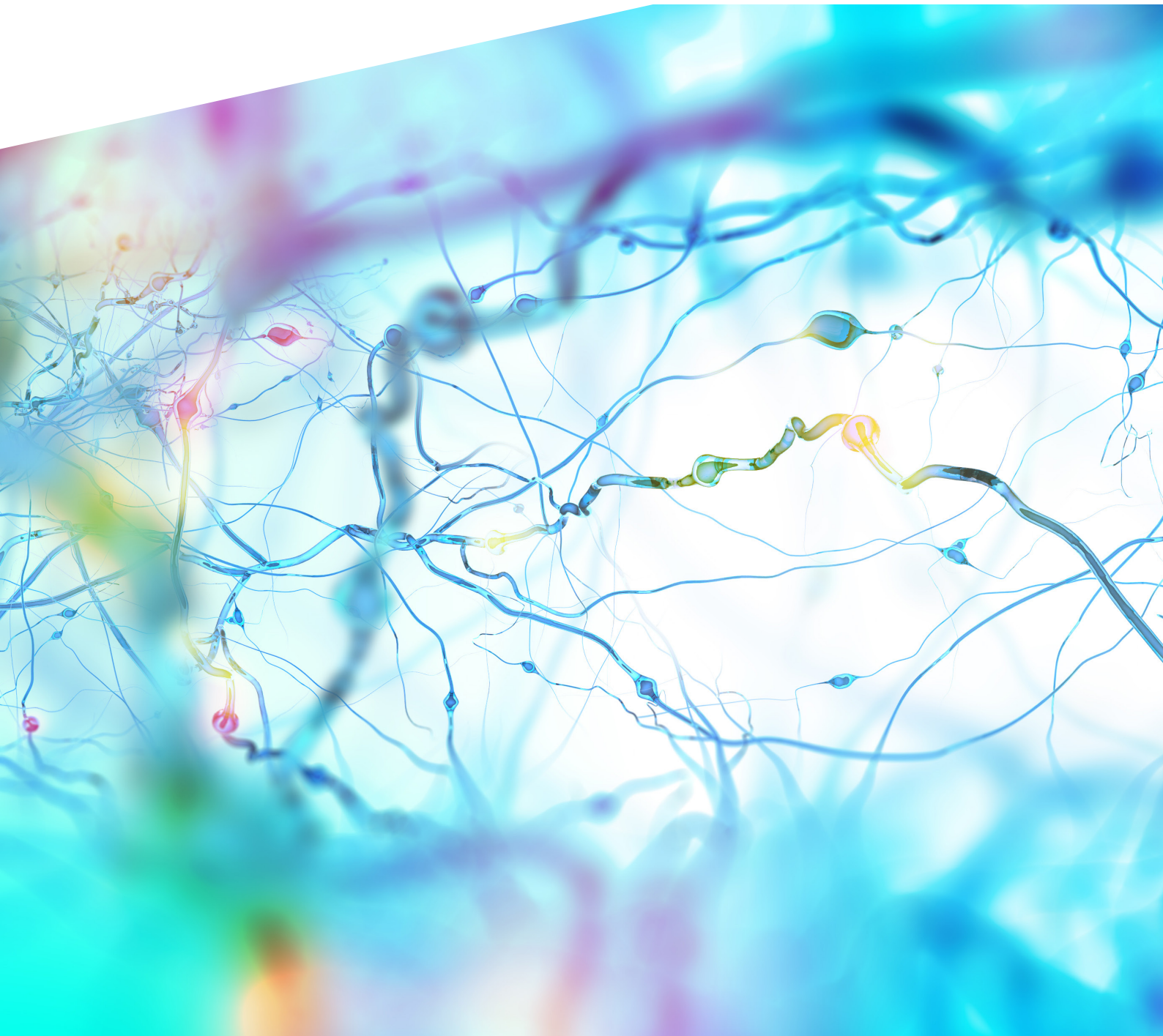

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Aims & Scope

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

Scope: Its scope includes:

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

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

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Protocols

Correspondence

Meeting Report

Editorial

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Unresolved policy on the new placement of 2,000 entrants at Korean medical schools and this issue of *Ewha Medical Journal*

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After the Korean government announced the new placement of 2,000 entrants to Korean medical schools in 2025 [1], approximately 12,700 medical residents have resigned from their training hospitals since February 20, 2024 [2]. The majority have not yet returned to their hospitals. Initially, the government prohibited these resignations, but later reversed this stringent policy and permitted them. A deadline of July 15, 2024, was set for the residents to return to their hospitals, and hospitals were allowed to recruit new residents. By July 17, 2024, 110 out of 151 hospitals that employ medical residents had reported their resignation processing results. According to data from March 2024, 7,648 individuals, representing 56.5% of the 13,531 appointees, have either resigned or declined their appointments. Specifically, among interns, 2,950 out of 3,068 (96.2%) have resigned; among residents, the figure is 4,698 out of 10,463 (44.9%). For the latter half of this year, teaching hospitals have requested 7,707 positions for medical trainees, comprising 2,557 slots for interns and 5,150 for residents [3]. Most medical professors expect that few residents will return to the hospitals.

My primary concern in this situation is the burnout of clinical professors at university hospitals. These dedicated professionals tirelessly engage in patient care, educate medical students and residents, and conduct research. The recent mass resignation of medical residents has further strained these professionals, and it is crucial that we recognize and appreciate their dedication. Five months have already passed. Additionally, there is concern about the sustainability of university hospitals in their current state, as they face financial difficulties stemming from staff shortages caused by resident resignations.

Korean university hospitals are widely recognized for providing world-class medical services at very affordable rates, thanks to the national health insurance system. The potential collapse of these outstanding institutions would represent a significant loss to the medical community and raise concerns among the public about the accessibility and quality of healthcare services.

The Minister of Health and Welfare acknowledged during a National Assembly hearing that the decision to increase medical school admissions by 2,000 starting in 2025 was made without a scientific basis. This policy was formulated by the ministry without consulting medical associations or experts [4]. Since the founding of the Korean government in 1948, no previous administration has implemented such a severe policy that disrupts medical services and maligns the medical community without expert input. It is crucial for both the government and the public to reevaluate what is truly in the best interest of the health and happiness of the Korean people.

In this issue

Academic journals should be easily readable and engaging for a broad audience, not just experts in the field. *Ewha Medical Journal*, as a university publication, welcomes submissions from undergraduate and graduate students. This issue features a meeting report by an undergraduate student, Yerin Lee, which focuses on digital clinical medicine—a rapidly emerging field. Her insights as a medical student, rather than those of a practicing physician, offer an intriguing perspective [5].

This issue's special review section highlights three critical topics on infectious diseases in Korea: multi-drug resistant organisms, including carbapenem-resistant Enterobacterales (CRE) [6], influenza vaccines [7], and antiviral therapy for HIV/AIDS [8]. Drs. Do Hyeon Park and Pyoeng Gyun Choe from Seoul National University discuss the complexities of CRE spread, emphasizing that antimicrobial stewardship should be integrated with infection control strategies to enhance their effectiveness [6]. Dr. Joon Young Song from Korea University reports that high-dose and adjuvanted influenza vaccines have shown improved protection compared to standard-dose vaccines in elderly populations. However, the relative effectiveness of MF59-adjuvanted versus high-dose vaccines remains to be clarified. Despite high vaccination rates among the elderly, the limited effectiveness of current vaccines underscores the need for more potent and durable influenza vaccines specifically designed for this demographic [7]. Dr. Nam Su Ku from Yonsei University notes that over 1,000 new HIV infections have been recorded annually in Korea since 2013. Additionally, since the introduction of zidovudine, about 30 antiretroviral drugs have been approved for HIV treatment. He advocates for early and continuous antiretroviral treatment for all individuals living with HIV as an effective approach to maintain viral suppression and prevent the transmission of HIV [8].

Dr. Dong Wook Shin from Sungkyunkwan University has proposed the use of digital informed consent to standardize the physician's duty to inform, which is deemed a mission-impossible job e. He identified six content areas for digital informed consent and suggested storing these consent forms as non-fungible tokens (NFTs) on a blockchain. This idea stems from a ruling by the Supreme Court of Korea, which found a hospital at fault for not adequately fulfilling its duty to obtain informed consent by allowing insufficient time for the process. This innovative system aims to improve the process of obtaining informed consent, addressing existing challenges. While physicians, patients, and the government might initially be hesitant to adopt this new system, it offers a promising solution to relieve physicians from legal disputes related to their duty to obtain informed consent. Physicians strive to provide the best care for their patients, and facing severe penalties despite their best efforts could hinder their ability to serve. This topic warrants further discussion among all stakeholders involved.

Four protocols for reporting guidelines are introduced. Dr. Soo-Young Kim from Hallym University oversaw the development of these protocols, which focus on community outbreaks, surveillance reports, disease prevention recommendations, and survey reporting. These protocols will serve as the foundation for formal reporting guidelines and will be extremely beneficial for epidemiologists and field researchers.

Chang Ho Ahn at Lunit kindly provided correspondence entitled "My career path at a medical artificial intelligence company, working as a physician outside of clinical practice." Some medical students are interested in working at artificial intelligence companies, and Dr. Ahn's insights will help them understand this new career path as physicians [10].

Dr. Yongho Jee's case-crossover study explores the association between particulate matter

and appendicitis in Korea [11]. It was found that patients with appendicitis had been exposed to higher levels of PM_{10} concentrations 3 and 7 days prior to their hospital admissions in the western area of Seoul. While the association of PM_{10} with appendicitis in boys under the age of 10 may be attributed to their higher breathing rates and immature immune systems, further research with a larger cohort is warranted. Maria Florencia Deslivia and colleagues have developed a new surgical technique involving the insertion of an interlocking screw during intramedullary nailing, utilizing a Steinmann pin and hammer [12]. This technique, tested using Sawbones femurs, shows promise for broader clinical application.

A focus group interview was conducted with six medical students from Ewha Womans University, who participated in an experiential entrepreneurship course from February 13 to 23, 2024 [13]. An analysis of the students' feedback on this innovative curriculum will inform decisions regarding its future implementation. The curriculum aims to enrich students' cognitive, emotional, and behavioral experiences.

It is currently difficult for clinical faculty members to write articles. I commend them for their academic dedication, despite their demanding responsibilities in patient care. I hope the issue concerning the "new placement of 2,000 entrants at Korean medical schools" is resolved efficiently and scientifically in the near future, allowing clinical faculty members to return to their normal routines amidst the current turmoil.

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Authors' contributions

All work was done by Sun Huh.

Conflict of interest

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

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Opinion

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A proposal for digital informed consent to standardize the physician's duty to inform, a mission-impossible job

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Legal ruling on the physician's duty to inform

On January 27, 2022, the Supreme Court of Korea ruled against a hospital for its failure to fulfill its duty to inform. The case involved a patient who underwent spinal surgery in 2018 and subsequently suffered a stroke, leading to paralysis and cognitive impairment. Although lower courts had previously ruled in favor of the hospital, the Supreme Court found that the patient was not given adequate time to consider the risks involved. Only 40 minutes had passed between the explanation of potential complications and the initiation of anesthesia [1].

This ruling has sparked a debate within the medical community concerning the specifics of informed consent, especially regarding the timing of explanations. The Korean Medical Association has expressed strong disagreement with the decision, pointing out that it introduces an undefined concept of "timing of explanation" that is not explicitly outlined in existing medical law.

No physician would oppose the fundamental purpose of the duty to inform, which ensures patients' right to knowledge and self-determination. Additionally, this duty acts as a protective measure for medical professionals, provided they comply with the specified requirements and procedures.

Lawyers often advise that it is safest for doctors to communicate directly with patients, tailoring explanations to their level of understanding and informing family members. Additionally, they recommend that physicians establish a strong rapport with their patients. Moreover, consent forms for operations and other medical procedures differ in format across hospitals, and the style of explanation varies among doctors.

Content of digital informed consent

To address these challenges and improve the informed consent process, I propose the following digital solution:

1. The Korean Medical Association could develop standardized, interactive digital educational materials for a range of surgical procedures. These materials would include 3D imagery and

provide detailed information about the procedures, potential complications, and postoperative care.

2. These materials could be officially certified by expert committees, patient advocacy groups, and legal authorities to ensure compliance with the standards required for patient understanding and legal adherence.

3. The digital format would incorporate intermittent comprehension checks to ensure that patients can only provide consent if they demonstrate understanding.

4. Upon successful completion, patients could provide their electronic signatures, with options for further explanations from physicians if required.

5. The system would enable remote consent from family members or legal guardians when appropriate.

6. This process must be completed at least 24 hours before the scheduled surgery to be considered valid for non-emergency procedures.

Deposition of digital informed consent forms as non-fungible tokens using blockchain technology

The deposition of digital informed consent forms as non-fungible tokens (NFTs) using blockchain technology offers multiple advantages, such as increased security, transparency, and the immutability of consent forms. It has already been implemented in areas such as medical education and credential certification [2]. The procedure can be established as follows:

1. Digitizing the consent form: The informed consent form is first digitized, either by creating it directly in a digital format or by scanning a physical document into a digital file, such as a PDF or image file.

2. Smart contract creation: A smart contract is developed on a blockchain platform, such as Ethereum, to oversee the minting, storage, and access controls of NFTs. This contract contains provisions to verify the authenticity of the consent form and link it to a unique identifier.

3. Minting the NFT: The smart contract associates the digital consent form with an NFT. Metadata linked to the NFT may contain important information such as the patient's identity (anonymized or encoded to protect privacy), the date of consent, and other relevant details.

4. Storing the NFT: The NFT, which represents the consent form, is stored on the blockchain to ensure immutability and traceability. The actual content of the consent form may be stored directly on the blockchain if it is a small file. More commonly, it is stored off-chain, with a reference link (e.g., IPFS, a decentralized storage solution) included in the NFT metadata.

Conclusion

While the system described herein may not address all scenarios, particularly emergencies, it could significantly improve the quality of information provided to patients and reduce legal issues associated with routine operations and treatments. This method would ensure that patients receive standardized, high-quality explanations, while also protecting healthcare providers by clearly documenting the informed consent process. However, a legal framework for establishing NFTs on the blockchain for digital informed consent must be developed. If this innovative technology can be utilized for digital informed consent, it could reduce legal conflicts between physicians and patients or their families, potentially strengthening their rapport.

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Review

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Status of and comprehensive preventive strategies for multidrug-resistant organisms in Korea: a focus on carbapenem-resistant Enterobacterales

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Keywords
Antimicrobial stewardship; Bacterial drug resistance; Carbapenemase; Infection control; Republic of Korea

The rise of multidrug-resistant organisms represents a serious global public health concern. In Korea, the increasing prevalence of carbapenem-resistant Enterobacterales (CRE) is particularly concerning due to the difficulties associated with treatment. Data from the Korea Global Antimicrobial Resistance Surveillance System indicate a yearly increase in CRE cases, with carbapenemase-producing Enterobacterales being the predominant type. The capacity of CRE to resist multiple broad-spectrum antibiotics leads to higher medical costs and mortality rates, underscoring the need for urgent action. Effective prevention is crucial to curbing CRE outbreaks and transmission. Antimicrobial stewardship programs (ASPs) play a key role and require commitment from healthcare professionals to minimize unnecessary antibiotic use, as well as from policymakers to ensure adherence to ASP guidelines. Given the complexity of CRE transmission, ASP efforts must be integrated with infection control strategies for maximum effectiveness. These strategies include adherence to standard and contact precautions, environmental disinfection, preemptive isolation, and comprehensive education and training for healthcare personnel. Additionally, surveillance testing for patients at high risk for CRE and the use of real-time diagnostic kits can facilitate early detection and reduce further transmission. Strategies for the prevention of CRE infection should be tailored to specific healthcare settings. Ongoing research is essential to update and refine infection control guidelines and effectively prevent CRE outbreaks.

Introduction

Background

Antibiotics were originally defined as substances produced by microorganisms that inhibit the growth or proliferation of other microorganisms. This definition has since been expanded to include artificially synthesized compounds. Since the discovery of penicillin, the development and use of various antibiotics have markedly reduced mortality from infectious diseases, positioning antibiotics as one of the most transformative interventions in modern society. This progress has led to bold predictions that humanity might one day conquer bacterial infections. Despite these optimistic projections, bacteria have survived by employing various mechanisms that nullify the effects of antibiotics. The resulting resistant bacteria have proliferated, leading to the emergence

of multidrug-resistant organisms (MDROs) that are unresponsive to conventional treatments. The development of antibiotic resistance is far outpacing the introduction of new antibiotics [1], and multiple studies have highlighted the harmful impacts of antibiotic resistance on socioeconomic and public health indicators, including healthcare costs, length of hospitalization, and mortality [2,3]. In response, at the 68th World Health Assembly in 2015, the World Health Organization (WHO) declared antibiotic resistance a critical threat to human life, calling for international action plans to address the issue across borders. While antibiotic resistance is recognized as a key global challenge, Korea exhibits higher antibiotic prescription rates and antimicrobial resistance than many other countries [4]. The awareness of antibiotic resistance in Korea has gradually improved, with interventions reducing unnecessary antibiotic prescriptions; however, resistance rates remain comparatively high, and some multidrug-resistant bacteria are even on the rise [5]. In particular, the reported incidence of carbapenem-resistant Enterobacterales (CRE), which is increasing worldwide, is also gradually climbing in Korea. With limited antibiotic options available for treating CRE, its increased incidence poses a management challenge, underscoring the importance of prevention and preemptive strategies.

Objectives

This review provides an overview of the present status of multidrug-resistant bacteria in Korea, with a focus on CRE. It also explores infection control strategies for the prevention and preemptive management of CRE infections.

Ethics statement

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

Status of multidrug-resistant organisms in Korea

In 2009, Korea enacted the Infectious Disease Control and Prevention Act, which classified six multidrug-resistant bacterial infections as designated communicable diseases. These included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant enterococci (VRE), multidrug-resistant *Pseudomonas aeruginosa* (MRPA), multidrug-resistant *Acinetobacter baumannii* (MRAB), and CRE. The Korean government established a sentinel surveillance system for healthcare-associated infectious diseases, including these six types of MDROs. In 2017, CRE and VRSA were reclassified as Group 3 infectious diseases, necessitating continuous surveillance and mandatory reporting. In 2020, the Infectious Disease Prevention Act was amended, changing the legal classification system from groups to classes. Consequently, VRSA and CRE were reclassified as Class 2 infectious diseases, and a mandatory surveillance system for these strains has been maintained to date. MRSA, MRPA, and MRAB are designated as Class 4 infectious diseases and are monitored through sentinel surveillance.

In May 2016, aligning with the international effort to combat antibiotic resistance, Korea established the Korea Global Antimicrobial Resistance Surveillance System (Kor-GLASS). This system was modeled after the Global Antimicrobial Resistance and Use Surveillance System (GLASS) proposed by the WHO to assess the national status of antimicrobial-resistant bacteria [6]. Kor-GLASS has been supplemented and adapted to reflect domestic conditions, building

upon the foundation provided by GLASS [6]. Since its inception in 2016, Kor-GLASS has collected data on 12 pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *S. aureus*, *Enterococcus* spp., *Acinetobacter* spp., and *P. aeruginosa*. These bacteria are gathered from nine general hospitals across the nation, with the system confirming antibiotic susceptibility test results and computing resistance rates.

Based on the annual antibiotic resistance rates among the six key strains from 2016 to 2022, as reported in the Kor-GLASS data (Fig. 1), the resistance rate of *S. aureus* to methicillin has been continuously declining since 2016. This trend aligns with observations in other developed countries [7,8]. To date, no VRSA strains have been identified in Korea. Suspected strains have been referred to provincial public health and environment research institutes, as well as the Korea Disease Control and Prevention Agency, for confirmation. However, all have been identified as vancomycin-intermediate *S. aureus* strains [9]. Regarding VRE, carbapenem-resistant *P. aeruginosa*, and carbapenem-resistant *K. pneumoniae* (CRKP), the incidence of infections caused by resistant bacteria has been rising since the initiation of sentinel surveillance. This increase coincides with the escalated use of broad-spectrum antibiotics and mirrors global trends. During the coronavirus disease 2019 pandemic, Korea, like the United States, experienced an uptick in multidrug-resistant bacterial infections. Several factors may have contributed to this pattern, including increased antibiotic prescriptions for patients with respiratory symptoms, the saturation of isolation facilities in medical institutions, staff shortages, and challenges in adhering to infection control guidelines due to work overload [10].

Status of carbapenem-resistant Enterobacterales in Korea

Among the six MDROs, CRE is particularly noteworthy. In 2017, CRE was classified as a Group

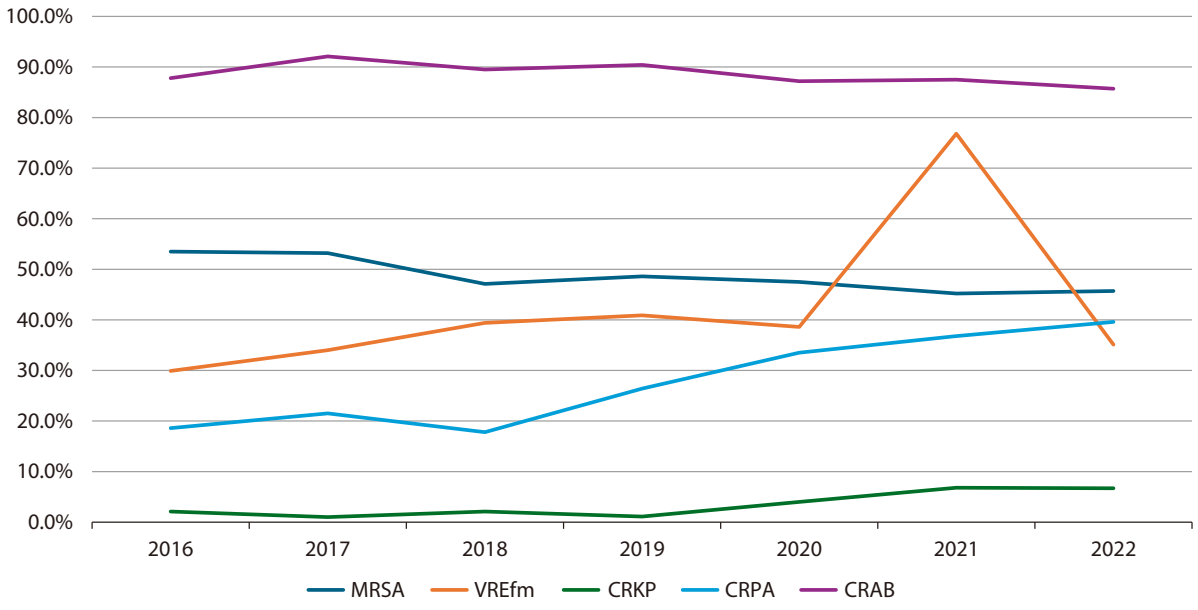

Fig. 1. Rates of antimicrobial resistance for multidrug-resistant pathogens from 2016 to 2020, based on data from the Korea Global Antimicrobial Resistance Surveillance System (Kor-GLASS). MRSA, methicillin-resistant *Staphylococcus aureus*; VREfm, vancomycin-resistant *Enterococcus faecium*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, carbapenem-resistant *Acinetobacter baumannii*.

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3 infectious disease. Following the revision of the Infectious Disease Prevention Act in January 2020, CRE was reclassified as a Class 2 infectious disease. This reclassification mandates that medical personnel report cases within 24 hours in the event of an outbreak or epidemic, as part of a mandatory surveillance system. The reporting rate of CRKP, which has been collected and monitored by Kor-GLASS since 2016, has been continuously increasing. Similarly, the number of reported CRE infections from medical institutions has been rising annually, with an accelerating growth rate (Fig. 2) [11].

In 2022, *K. pneumoniae* was identified as the predominant CRE species, comprising 70.9% of isolated strains, followed by *E. coli* (14.0%) and *Enterobacter* spp. (7.0%). *K. pneumoniae* consistently emerged as the most prevalent species throughout the surveillance period [11]. CRE can be categorized based on the mechanism of carbapenem resistance. Carbapenemase-producing Enterobacterales (CPE) produce enzymes that degrade carbapenems, while non-CPE bacteria demonstrate resistance through other means such as efflux pumps, changes in outer membrane protein permeability, or overproduction of AmpC beta-lactamase or extended-spectrum beta-lactamases. In Korea, CPE accounted for 83.0% of all CRE cases in 2021, surpassing non-CPE pathogens, and this proportion has been rising. The carbapenemases identified to date include *K. pneumoniae* carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded metallo-beta-lactamase (VIM), imipenemase (IMP), and oxacillinase-48 (OXA-48) [12]. Since 2018, KPC has been the most common carbapenemase among domestic CPE strains, followed by NDM and OXA (Fig. 3) [13,14]. The distribution of carbapenemases varies by region and country, with the transmission of new carbapenemases being reported in developed countries [15]. Consequently, maintaining up-to-date molecular epidemiological information on CRE, assessing the domestic context, and performing continuous monitoring of its spread and outbreaks are crucial.

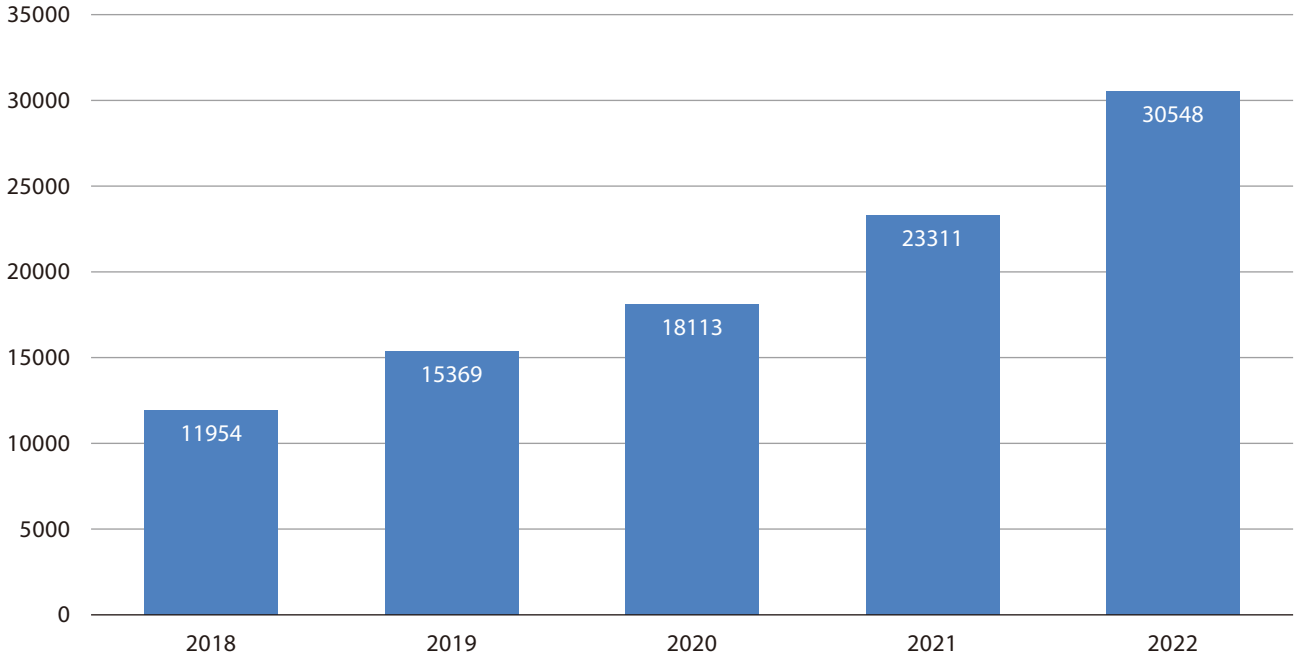

Fig. 2. Annual numbers of CRE infections from 2018 to 2022 based on a mandatory surveillance system. CRE, carbapenem-resistant Enterobacterales.

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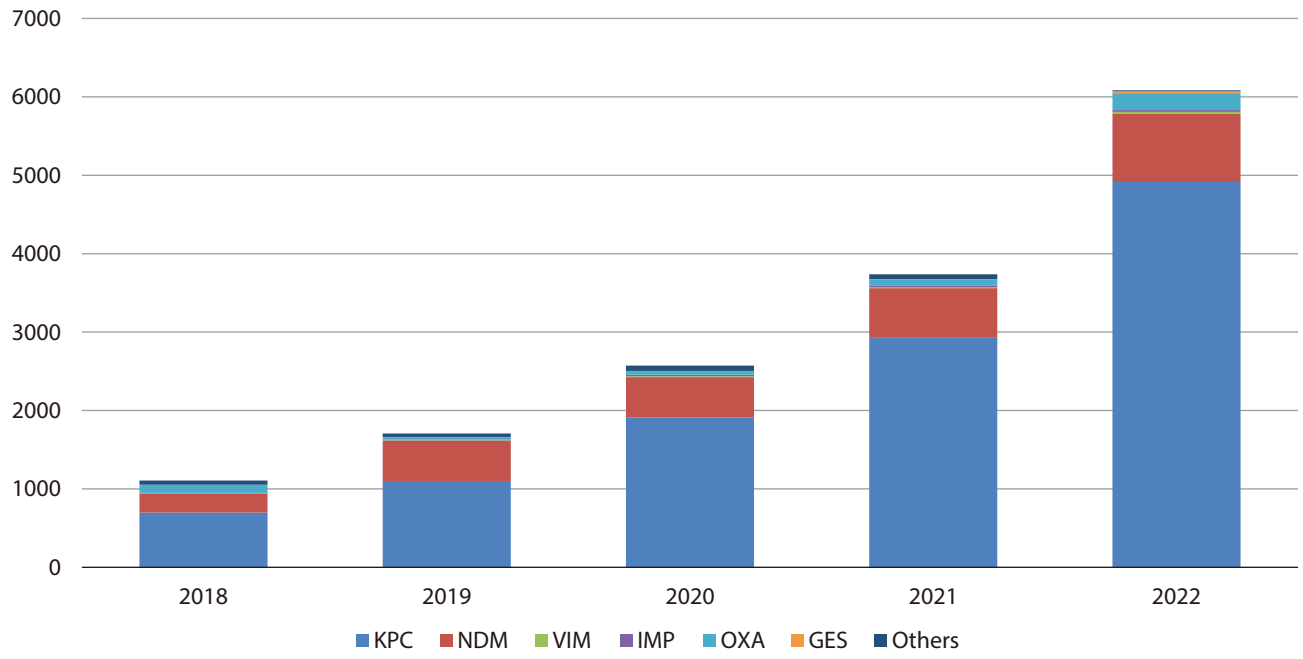

Fig. 3. Annual distributions of carbapenemase-producing Enterobacterales from 2018 to 2022. KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-beta-lactamase; VIM, Verona integron-encoded metallo-beta-lactamase; IMP, imipenemase; OXA, oxacillinase-48; GES, Guiana extended-spectrum beta-lactamase.

Interventions to prevent carbapenem-resistant Enterobacterales transmission

Infection control strategies to prevent the spread of CRE can be organized into three main components (Fig. 4). Considering the process that facilitates CRE transmission within hospital settings, the first component involves selective pressure from antibiotic use, which creates a favorable environment for CRE to survive and proliferate. The second aspect is the transmission from CRE-infected or colonized patients to others via the hands of healthcare workers or medical devices. The third component is the spread of CRE to the surrounding healthcare environment, where it can form clusters and foster conditions that promote further transmission. At each stage, adherence to an antimicrobial stewardship program (ASP) is crucial to combat the survival advantage of resistant bacteria. Additionally, early screening and isolation of CRE carriers, contact precautions to prevent transmission, and environmental disinfection to eradicate colonies can be effective strategies to inhibit the spread of CRE.

Antimicrobial stewardship programs

Since long-term exposure to broad-spectrum antibiotics is a key risk factor for CRE infection [16,17], adherence to ASPs is essential for reducing the incidence of MDRO infections [18,19], including CRE. ASPs are interventions designed to guide medical staff in selecting appropriate antibiotics and using them for the correct duration. The goal of an ASP is to improve patient safety, reduce healthcare costs and treatment failures, and limit the emergence of multidrug-resistant bacteria. Through the ASP, the selective pressure on CRE can be lessened by curbing the inappropriate use of antibiotics by healthcare providers. ASPs can be implemented through

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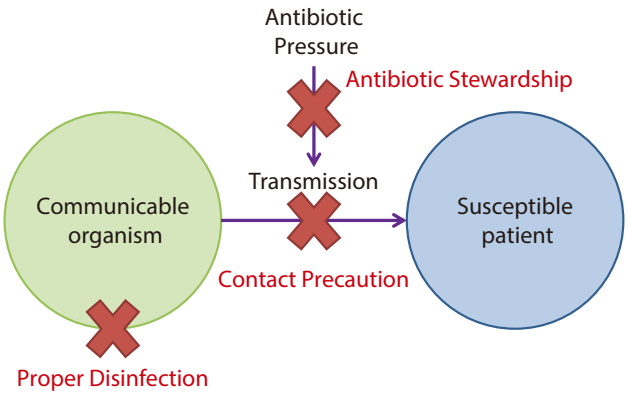

Fig. 4. Conceptual diagram of infection control strategies to prevent the spread of multidrug-resistant organisms.

various practical strategies, such as limiting excessive antibiotic use through antibiotic approval programs and establishing clinical guidelines for standardized first-line antibiotic selection and de-escalation [20]. However, the effectiveness of an ASP is not solely dependent on the participation and adherence of individual healthcare providers who prescribe antibiotics. It also relies on the establishment of policies and cultures at both national and societal levels that enable healthcare providers to engage in and comply with the ASP [21,22]. For instance, in Korea, measures such as incorporating ASPs into healthcare accreditation criteria and evaluating fees for infection prevention and control can act as additional incentives for healthcare providers to adhere to an ASP [23]. Moreover, as the reporting rate of CRE in long-term care facilities (LTCFs) is the second highest after general hospitals [11], and CRE colonization in LTCFs is considered a global risk factor for CRE transmission, it is imperative to establish an integrated ASP that encompasses various healthcare settings, including acute care institutions, LTCFs, and primary, secondary, and tertiary medical institutions. Specific implementation strategies should be tailored to each hospital context [24].

Contact precautions and hand hygiene

CRE is predominantly transmitted within the hospital setting through direct or indirect contact with infected individuals or via contaminated surfaces and environments. Hand hygiene has been recognized as the most effective method for interrupting this mode of transmission for multidrug-resistant bacteria and healthcare-associated infections, as evidenced by multiple studies [25,26]. Infection control guidelines consistently advocate for the implementation of and adherence to standard and contact precautions, which include hand hygiene, to prevent and manage CRE. These guidelines also encourage the use of personal protective equipment and the allocation of individual medical devices for each patient [27]. The WHO guidelines specifically advise that patients colonized or infected with CRE should be physically separated from those who are not, preferably in single-room isolation. When this is not feasible, cohorting patients with the same resistant pathogen is recommended. Additionally, dedicated medical staff should be assigned to care for these patients to minimize the risk of CRE transmission [28]. Monitoring hand hygiene practices is crucial in preventing the spread of CRE and other multidrug-resistant bacteria. Hospitals must ensure that hand sanitizers and other necessary resources are readily available to healthcare workers to facilitate consistent hand hygiene practices [29,30].

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Early detection and surveillance testing

Implementing infection control measures, such as preemptive isolation, at an early stage through CRE surveillance is widely recognized to reduce CRE infections [31]. Guidelines for the prevention of healthcare-associated infections, published by the Korean Disease Prevention and Control Agency, recommend conducting CRE surveillance for groups at high risk [27]. These groups include patients transferred from hospitals with a high prevalence of CRE, critically ill individuals, and those being considered for admission to the intensive care unit with risk factors such as invasive catheter placement or exposure to broad-spectrum antibiotics. For these high-risk groups, a screening test is performed by collecting a stool or rectal swab specimen at the time of admission. The modified Hodge test is a phenotypic assay initially developed as a test for CPE. It has been widely used due to its very high selectivity for KPC-producing CPE—the most common form in Korea—and economical nature. However, since 2018, it has been excluded from the methods recommended by the Clinical and Laboratory Standards Institute due to its subjective interpretation and low sensitivity of around 50% for NDM-producing strains. Molecular assays, such as polymerase chain reaction, are the most expensive of the CPE screening methods but have benefits including quick confirmation (within 4 to 6 hours) and high sensitivity. Culture-based test methods have lower sensitivity than molecular genetic methods and require substantial effort and time, but they are considered cost-effective [32]. CRE can rapidly spread within healthcare facilities because resistance genes such as carbapenemases can be horizontally transferred to other bacteria through plasmids or transposons, and vertical transmission by a single clone is also possible [33,34]. Therefore, rapid diagnosis and response are crucial for inhibiting CRE transmission. Furthermore, the implementation of an ASP requires considerable time to clearly impact the spread of CRE. Additionally, in the Korean context, limitations on staffing and time hinder the application of ASPs [35]. Thus, swiftly diagnosing CRE infections through screening tests and subsequently responding can provide complementary assistance in managing CRE transmission. Previous studies have similarly confirmed that rapid screening tests can reduce the incidence of CRE infections [36,37]. To obtain rapid results, methods such as culturing on chromogenic media (Chromagar KPC, Imipenem-MacConkey method, etc.) followed by confirmation of CPE genotypes using the Carba NP test or immunochromatography can be used [38]. Specifically, commercially available early diagnostic kits can simultaneously detect and differentiate five major carbapenemases— KPC, NDM, OXA-48, IMP, and VIM, which are common in Korea—within 1 to 2 hours using automated equipment [39]. However, these early diagnostic kits can only detect a limited number of enzymes. Furthermore, for clinical application, an additional systematized approach is required to utilize the test results for preemptive isolation or promptly switch to appropriate antibiotics through real-time feedback. Moreover, clearly defined criteria must be available regarding patient selection for rapid diagnostic kits, considering costs, human resources, and other factors specific to each healthcare setting.

Environmental control

The hospital environment can serve as a reservoir for CRE; thus, environmental disinfection is key to preventing CRE transmission. Per the WHO guidelines, CRE isolation rooms should undergo additional cleaning and disinfection, with regular assessments to ensure compliance with environmental cleaning and disinfection protocols [28]. The US Centers for Disease Control and Prevention guidance on CRE management highlights the potential for CRE colonization in sink drains in inpatient rooms. Consequently, it is critical to clean areas around sinks that are

prone to aerosol generation. After patient discharge, comprehensive room disinfection and rigorous monitoring are required to confirm that all surfaces have been adequately disinfected [40]. In short, rooms that have accommodated patients with CRE infection can become a source of infection. It is imperative to disinfect all surfaces, with particular attention to sinks, drains, and faucets, which are recognized as common sites for bacterial colonization [41].

Additionally, both chlorhexidine gluconate baths and staff-focused infection control education contribute to reducing the proportion of CRE carriers, despite their absence from domestic guidelines [42]. Although directly applying recommendations to the Korean context may pose challenges, it is essential to develop CRE transmission prevention guidelines that are tailored to the domestic situation, drawing on local research and evidence.

Conclusion

The ongoing increase in MDROs that are unresponsive to various antibiotics represents a key global public health challenge. In Korea, the incidence of MDRO infections is on the rise, mirroring worldwide trends. This pattern has been identified through the implementation of antibiotic resistance surveillance systems (such as Kor-GLASS) that adhere to international standards, as well as by monitoring critical antibiotic-resistant bacteria that are classified as legal infectious diseases. Thus, continuous surveillance to accurately assess antibiotic resistance is essential for preventing the spread of MDROs. Kor-GLASS currently excludes primary and secondary hospitals, LTCFs, and certain regions, indicating a need for supplementation to establish a comprehensive surveillance system. The establishment of a national real-time alert system, coupled with data sharing between the government, acute care hospitals, and LTCFs, is anticipated to provide additional support in curbing the transmission of MDROs, as observed in other countries.

CRE exhibit resistance to various broad-spectrum antibiotics, including carbapenems, which leads to high mortality rates due to the limited treatment options available. Infections caused by CRE not only raise healthcare costs and place a burden on the healthcare system but also contribute to the spread of healthcare-associated infections through an increase in pathogen carriers. Prevention is paramount in curbing the continuous growth of CRE cases. Individual healthcare providers must adhere to ASPs and minimize unnecessary antibiotic use. Concurrently, robust social systems must be established to support healthcare providers in complying with ASP guidelines. Additionally, it is vital to prevent further transmission through preemptive isolation and surveillance testing of patients at high risk, such as individuals transferred from LTCFs or admitted to intensive care units. While early diagnostic kits can be applied for rapid diagnosis, it is advisable to weigh the advantages and disadvantages of these tests and to use them judiciously, tailored to the circumstances of each medical institution. Beyond the use of early diagnostic kits, infection control interventions—including contact isolation, hand hygiene, environmental cleaning and disinfection, and the education of healthcare workers—should be implemented in conjunction with ASP practices. Ongoing research to verify the effectiveness of these infection control strategies in Korea is essential. Based on the findings, CRE management guidelines suitable for the domestic situation should be developed to curb CRE infections.

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Review

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Influenza disease burden and the need for highly immunogenic vaccines in older adults: a narrative review

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Aged; Hospitalization; Influenza vaccines; Morbidity; Vaccine efficacy

Influenza presents a considerable disease burden, particularly among adults over 65 years old. In this population, the disease is associated with high rates of infection, hospitalization, and mortality. The objective of this study was to assess the impact of influenza on older adults and to evaluate the effectiveness of influenza vaccines within this demographic. A literature search was conducted using PubMed to identify relevant English-language studies published from January 2000 to January 2024. The analysis indicated that influenza-related hospitalization rates (ranging from 10.1 to 308.3 per 100,000 persons) and all-cause excess mortality rates (1.1 to 228.2 per 100,000 persons) were notably high in older adults, although these rates varied over time and by location. Hospitalization rates due to influenza increased considerably after the age of 50 years, with the highest rates observed in individuals aged 85 years and older. Excess mortality attributable to influenza also rose with age, with rates between 17.9 and 223.5 per 100,000 persons in those over 75 years old. The effectiveness of influenza vaccines in preventing severe infections requiring hospitalization was found to be only 37% in individuals aged 65 years and older. The unadjuvanted, standard-dose influenza vaccine had an estimated effectiveness of just 25% against laboratory-confirmed influenza and between 37% and 43.7% in preventing hospitalizations. Therefore, considering the substantial burden of influenza and the limited efficacy of standard vaccines, the use of highly immunogenic influenza vaccines should be prioritized for older adults.

Introduction

Influenza accounts for the highest disease burden in terms of infection, hospitalizations, and mortality rates among acute infectious diseases, leading to high medical expenses and socioeconomic losses [1–3]. Each year, epidemics affect more than 5% to 10% of the global population, with the extent of impact varying based on the antigenic match of circulating strains and vaccination coverage during the season [4]. A community-based prospective cohort study from Korea reported an overall influenza incidence rate of approximately 7 per 100 persons over three seasons from 2012 to 2015 [5]. The number of hospitalizations and deaths from pneumonia and other complications surges following an influenza epidemic, particularly affecting children

under 5 years of age and adults over 65 years. Most deaths occur in the latter population. Due to the consistently high impact of the disease on older adults, a thorough review of the influenza disease burden and the effectiveness of vaccines is crucial.

The objective of this narrative literature review was to evaluate the disease burden of influenza, with a focus on its impact on older adults in terms of infection, hospitalization, and mortality rates. Furthermore, this study aims to assess the effectiveness of influenza vaccines in older adults across different seasons, thereby providing insights that may improve vaccination strategies.

Ethics statement

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

Methods

In this narrative literature review, we first conducted a search on PubMed for relevant English-language articles, published between January 2000 and January 2024. We employed the snowballing search method throughout the review process. The key search terms included "influenza," "influenza-like illness," "older adults," "disease burden," "hospitalization," "excess mortality," efficacy," and "vaccine effectiveness," which were tailored to each topic. After reviewing titles, abstracts, and full manuscripts, we selected relevant studies for inclusion in this review. Furthermore, we manually searched the references cited in the chosen articles to identify additional sources pertinent to this review.

Results

Influenza-related hospitalizations in older adults

Influenza virus infections are more common among socially active young adults; however, hospitalizations due to pneumonia and severe infections predominantly affect older individuals, although rates vary across studies. Comparing influenza-related hospitalization rates between countries is challenging due to differences in the medical environment, including hospital accessibility and admission criteria. A population-based study in the United States estimated age-specific influenza-associated hospitalization rates for respiratory failure (Table 1) [6]. The overall rate was 2.7 per 100,000 person-years, with an increasing trend observed after the age of 50 years: 0.8 for ages 18–49; 4.0 for ages 50–64; 8.7 for ages 65–74; 16.5 for ages 75–84; and 27.9 for those aged 85 and older. In a 15-year study (1998–2012) in Hong Kong, an average of 32.7 per 10,000 persons were hospitalized annually for respiratory viral infections, most commonly due to influenza A (183 per 100,000 persons), respiratory syncytial virus (57 per 100,000 persons), and influenza B (35 per 100,000 persons). Hospitalizations were particularly common among adults aged 65 years and over, with rates two to three times higher than among those 50–64 years old [7]. In France, over eight epidemic seasons from 2010/2011 to 2017/2018, the estimated influenza-associated excess hospitalization rates ranged from 11.6 to 61.9 per 100,000 persons for influenza and pneumonia and from 20.4 to 75.3 per 100,000 persons for respiratory causes across all ages. For adults aged 65 years and over, the rates were 10.1 to 202.6 per 100,000 persons for influenza and pneumonia and 26.3 to 308.3 per 100,000 persons

Table 1. Estimated rates of influenza-related hospitalization

Study [reference]	Years	Country	Category of admission	Annual rates of influenza-related hospitalization (per 100,000 persons)
Ortiz et al. [6]	2003–2009	United States	Respiratory failure	Overall: 2.7
				18–49 years: 0.8
				50–64 years: 4.0
				65–74 years: 8.7
				75–84 years: 16.5
				≥85 years: 27.9
Chan et al. [7]	1998–2012	Hong Kong	Influenza A	≥65 years: 183
			Influenza B	≥65 years: 35
Lemaitre et al. [8]	2010–2018	France	Pneumonia and influenza	Overall: 11.6–61.9
				≥65 years: 10.1–202.6
			Respiratory	Overall: 20.4–75.3
				≥65 years: 26.3–308.3
Hong et al. [9]	2009–2019	Korea	Influenza	20.5–169.9

for respiratory causes [8]. A Korean study utilizing a nationwide healthcare database (associated with the Health Insurance Review and Assessment Service) over the decade from 2009 to 2019 found that the influenza-related hospitalization rate decreased following the 2009 H1N1 pandemic but increased during the 2013/2014 season, peaking at 169.9 per 100,000 people in 2017/2018 [9].

Influenza-attributable excess mortality among older adults

Using time series log-linear regression models based on vital death records and influenza surveillance data, global seasonal influenza-associated respiratory excess mortality rates were estimated for 33 countries. The results revealed an increase in this rate with age. Influenza-associated excess mortality rates ranged from 0.1 to 6.4 per 100,000 persons under 65 years, 2.9 to 44.0 per 100,000 persons between 65 and 74 years, and 17.9 to 223.5 per 100,000 persons over 75 years (Table 2) [10]. These rates varied over time and by location, influenced by factors such as age distribution, prevalence of chronic diseases, dominant influenza subtype, population density, and climate.

A study comparing the 2015/2016 and 2016/2017 influenza seasons across multiple countries indicated that the all-cause excess mortality rates were 4.7 and 14.3 per 100,000 persons in the United States, 20.3 and 24.0 per 100,000 persons in Denmark, and 22.9 and 52.9 per 100,000 persons in Spain, respectively [11]. The estimates for excess mortality due to respiratory and circulatory causes were two to three times lower than those for all causes. Another study in Denmark, spanning from 1994/1995 to 2009/2010, reported a median all-cause excess mortality rate of 35 (range, 6–100) per 100,000 persons; 88% of these deaths were among older adults aged 65 years and above, with higher mortality observed during seasons dominated by the A/H3N2 subtype [12]. In Portugal, from 1980 to 2004, the estimated all-cause excess mortality rate was 24.7 per 100,000 persons, with approximately 90% of these deaths occurring in seniors over 65 years old [13]. Excess mortality rates were three to six times higher during A/H3N2 subtype-dominant seasons compared to those dominated by A/H1N1 or B viruses. Due to more rapid

Table 2. Estimated excess mortality attributable to influenza

Study [reference]	Years	Countries	Category of death	Annual excess mortality rates (per 100,000 persons)
Iuliano et al. [10]	1999–2015	33 Countries	Respiratory	<65 years: 0.1–6.4
				65–74 years: 2.9–44.0
				≥75 years: 17.9–223.5
Schmidt et al. [11]	2015–2017	Denmark	All-cause	Overall: 20.3–24.0
		Spain		Overall: 22.9–52.9
		United States		Overall: 4.7–14.3
Nielsen et al. [12]	1994–2010	Denmark	All-cause	Overall: 35 (range, 6–100)
Nunes et al. [13]	1980–2004	Portugal	All-cause	Overall: 24.7
Giacchetta et al. [15]	1970–2001	Italy	All-cause	Overall: 11.6–18.6
				≥65 years: 91.1
			Pneumonia and influenza	Overall: 1.9–2.2
				≥65 years: 13.3
Lemaitre et al. [8]	2010–2015	France	All-cause	Overall: 0.3–26.6
				≥65 years: 1.1–151.3
			Pneumonia and influenza	Overall: 0.1–4.3
				≥65 years: 2.1–24.5
			Cardiovascular	Overall: 0.3–7.6
				≥65 years: 0.8–42.8
Li et al. [16]	1990–2018	China	All-cause	Overall: 49.6–228.2
			Pneumonia and influenza	Overall: 0.7–30.4
			Respiratory/circulatory	Overall: 30.8–170.2
Jang et al. [18]	2013–2017	Korea	All-cause	Overall: 49.5
Hong et al. [19]	2009–2016	Korea	All-cause	Overall: 10.6
				≥65 years: 74.1
Ohmi et al. [20]	1970–1980s	Japan	All-cause	≥65 years: 6.2
	1990s			≥65 years: 9.4
	2000s			≥65 years: 2.0

mutations and antigenic drifts, A/H3N2 viruses likely pose a greater disease burden—including higher hospitalization and mortality rates—than A/H1N1 and B viruses [14]. In Italy, three studies assessed nationwide excess deaths attributable to influenza between 1970 and 2001 [15]. The findings indicated influenza-related mortality rates of 1.9 to 2.2 per 100,000 persons for pneumonia and influenza, while the all-cause rates were 11.6 to 18.6 per 100,000 persons. Among older adults, the age-adjusted excess death rates were 13.3 per 100,000 persons for pneumonia and influenza and 91.1 per 100,000 persons for all causes. In France, between the 2010/2011 and 2014/2015 seasons, the all-cause influenza-associated excess mortality rates ranged from 0.3 to 26.6 per 100,000 persons for all ages and from 1.1 to 151.3 per 100,000 persons for older adults aged 65 years and above [8].

Several Asian countries have reported comparatively high excess mortality rates, with significant variations by country and season. A systematic review of 17 Chinese studies found

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that influenza-related excess mortality rates for all causes, respiratory and circulatory diseases, and pneumonia/influenza varied widely, with rates of 49.6–228.2, 30.8–170.2, and 0.7–30.4 per 100,000 persons, respectively [16]. Furthermore, Li et al. estimated the average annual influenza-associated excess mortality rates by age group, revealing rates of 0.9, 66.1, and 519.6 per 100,000 persons for the age groups of 0–59 years, 60–79 years, and ≥80 years, respectively, between 2015 and 2018 [17]. In Korea, a nationwide matched cohort study indicated an influenza-associated excess mortality rate of 49.5 per 100,000 persons, with the highest rate observed in older adults aged ≥65 years [18]. Another Korean study, which combined weekly mortality data from Statistics Korea with laboratory surveillance data from the Korea Disease Control and Prevention Agency from 2009 to 2016, estimated the all-cause excess mortality rate at 10.6 per 100,000 persons for all ages and 74.1 per 100,000 persons for older adults [19]. In Japan, age-adjusted average excess mortality rates were relatively low, averaging 6.2 per 100,000 persons during the 1970s and 1980s when vaccination of school-aged children was mandatory [20]. This rate increased to 9.4 per 100,000 persons in the 1990s upon discontinuation of the childhood vaccination program, then decreased to 2.0 when influenza vaccination was administered to older adults in the 2000s.

Low influenza vaccine effectiveness among older adults

Vaccination is recognized as 50% to 80% effective in preventing laboratory-confirmed influenza among young adults [21]. However, a recent meta-analysis revealed that the overall effectiveness of the influenza vaccine among older adults was only 25%, with no statistically significant protection against influenza A/H3N2 in the Northern Hemisphere [22]. Additionally, the analysis indicated that pooled vaccine effectiveness diminished with increasing age in both the Northern and Southern Hemispheres.

Most influenza-related hospitalizations and deaths occur among older adults. Thus, the primary objective of influenza vaccination in this population is to reduce the number of hospitalizations and deaths resulting from severe infections. However, one meta-analysis indicated that the effectiveness of the vaccine in preventing influenza-related hospitalization is only 43.7% (95% CI, 39.7%–47.4%) [23]. Another meta-analysis, which stratified participants by age, indicated that the influenza vaccine was 41% (95% CI, 34%–48%) effective in preventing severe infections that required hospitalization among individuals aged 18–64 years and 37% (95% CI, 30%–44%) effective among those aged 65 years and older [24].

Recent studies have assessed the effectiveness of influenza vaccines in preventing severe outcomes, such as organ failure and death. A study from the United States conducted during the 2022–2023 season found the effectiveness of vaccination against hospitalization due to type A influenza was 37% (95% CI, 27%–46%). This effectiveness varied by age group (18–64 years: 47% [95% CI, 30%–60%]; ≥65 years: 28% [95% CI, 10%–43%]) and by virus subtype (A/H3N2: 29% [95% CI, 6%–46%]; A/H1N1: 47% [95% CI, 23%–64%]) [25]. Additionally, the influenza vaccine was 65% (95% CI, 56%–72%) effective against influenza-related organ failure (involving the respiratory, cardiovascular, or renal systems) and 48% (95% CI, −70% to 84%) effective against death. In a separate study from Norway covering the same season, the effectiveness of vaccination against influenza-associated hospitalization was 34% (95% CI, 26%–42%) for adults aged 65–79 years and 40% (95% CI, 30%–48%) for individuals aged ≥80 years. The effectiveness against influenza-associated death was 6.6% (95% CI, −64% to 47%) for the 65–79 age group and 37% (95% CI, 0.5%–61%) for those aged ≥80 years [26]. While the influenza vaccine does reduce the risk of severe disease, its effectiveness is considerably lower than that

of the vaccines for coronavirus disease 2019 (COVID-19). For preventing COVID-19–associated hospitalization, the effectiveness of vaccination was 65% (95% CI, 61%–69%) among adults aged 65–79 years and 55% (95% CI, 49%–60%) among those aged ≥80 years [26]. Regarding COVID-19–associated death, the effectiveness was 68% (95% CI, 48%–80%) for the 65–79 age group and 78% (95% CI, 65%–86%) for those aged ≥80 years.

Discussion

Given the high rates of hospitalization and death among older adults, reducing the disease burden of influenza through vaccination is essential. In Korea, the vaccination rate for seniors aged 65 years and older has been maintained at over 80% [27]. However, the antibody titer produced in older adult populations following influenza vaccination is approximately 40% to 80% of that in healthy adults, indicating relatively low vaccine effectiveness, ranging from 31% to 58% [28,29].

Influenza vaccines are currently approved based on a hemagglutination inhibition (HI) antibody titer of ≥40 for young adults under 60 years old and ≥30 for seniors over 60 years. However, an HI titer of 1:30 or 1:40 only represents the antibody level that can prevent 50% of influenza virus infections in healthy adults [30]. To achieve vaccine effectiveness greater than 90%, an HI titer exceeding 1:100 may be necessary; however, it is challenging to attain such high immunogenicity among older adults with available conventional vaccines [30]. Furthermore, since seasonal influenza epidemics can persist for more than 6 months, maintaining adequate protective immunity over this duration is crucial. However, HI titers typically start to wane after vaccination and decline sharply after 6 months [31]. The lower vaccine effectiveness observed in older adults aged 65 years and older may also stem from the short duration of vaccine-induced immunity and immune imprinting from repeated exposure, particularly to influenza A/H3N2. Consequently, a need exists for influenza vaccines that are highly immunogenic, induce long-lasting immunity, and minimize immune imprinting. To increase the efficacy of influenza vaccines in older adults, high-dose (Fluzone High-Dose, 60 μg hemagglutinin [HA]/strain), MF59-adjuvanted (Fluad, 15 μg HA/strain), and intradermal (Fluzone Intradermal, 15 μg HA/strain) vaccines have been developed [32-34]. Compared to the conventional standard-dose vaccine, these options have demonstrated higher immunogenicity in terms of their relative HI titer ratios [35]. Although intradermal vaccines are no longer produced, both MF59-adjuvanted and high-dose vaccines have been introduced and are currently available for use.

When evaluating the relative vaccine effectiveness of the MF59-adjuvanted influenza vaccine compared to the unadjuvanted standard-dose vaccine over three consecutive influenza seasons (2017–2018, 2018–2019, and 2019–2020) in the United States, the MF59-adjuvanted, trivalent vaccine displayed superior effectiveness over the quadrivalent alternative. The MF59-adjuvanted option displayed better prevention of influenza-related medical visits, with relative effectiveness estimates ranging from 20.8% (95% CI, 18.4%–23.2%) to 27.5% (95% CI, 24.4%–30.5%) [36]. Additionally, the MF59-adjuvanted trivalent influenza vaccine further reduced influenza-related hospitalizations, demonstrating a relative vaccine effectiveness of 6.5% (95% CI, 0.1%–12.4%). In a meta-analysis comparing the relative effectiveness of high-dose versus standard-dose, unadjuvanted influenza vaccines, the high-dose option displayed superior protection against influenza-like illness compared to the standard-dose vaccine, with a relative effectiveness of 15.9% (95% CI, 4.1%–26.3%) [37]. Moreover, the high-dose vaccine was more effective in preventing hospital admissions, with significant relative effectiveness against

all causes (8.4%; 95% CI, 5.7%–11.0%), pneumonia/influenza (13.4%; 95% CI, 7.3%–19.2%), and cardiorespiratory events (17.9%; 95% CI, 15.0%–20.8%). When the relative effectiveness of the MF59-adjuvanted vaccine was compared to the high-dose vaccine in a meta-analysis that excluded studies sponsored by pharmaceutical companies, no significant difference was found in the prevention of influenza-related emergency room visits, hospitalizations, or pneumonia between the two vaccines [29].

Antigenic mismatches between newly developed vaccines and circulating strains can meaningfully reduce vaccine efficacy. In a randomized study, the MF59-adjuvanted influenza vaccine demonstrated greater cross-reactivity against antigenically drifted, heterovariant A/H3N2 strains compared to the unadjuvanted standard-dose influenza vaccine [14]. Further research is required to ascertain whether the MF59-adjuvanted or the high-dose influenza vaccine is more advantageous in terms of immunological outcomes, including cross-reactive immunity to variant viruses and the capacity to overcome immune imprinting.

In conclusion, influenza imposes a considerable disease burden on older adults, characterized by high rates of infection, hospitalization, and mortality. The effectiveness of influenza vaccines in this demographic fluctuates by season but is substantially lower than that observed in younger adults. Even with high vaccination rates among older adults, the suboptimal effectiveness underscores the need for improved vaccination strategies. These include the use of high-dose and adjuvanted vaccines to increase immunogenicity and afford more robust protection against influenza in this vulnerable age group.

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Authors' contributions

All work was done by Joon Young Song.

Conflict of interest

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

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Not applicable.

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Review

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The epidemiology of HIV/AIDS and the use of antiretroviral therapy in Korea: a narrative review

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Antiretroviral therapy; HIV; Non-AIDS-defining comorbidities

The availability of combined antiretroviral therapy has significantly reduced the number of new HIV infections and the associated mortality, and HIV infection has become a chronic disease with long-term survival. In Korea, more than 1,000 new HIV infections have been registered annually since 2013. After peaking at 1,223 in 2019, the number of new infections decreased between 2020 and 2023. In 2023, the majority of newly HIV-infected people were men, and the proportions of young people under 40 years, homosexual contacts and foreigners increased. Acquired immunodeficiency syndrome (AIDS)-related deaths from opportunistic infections associated with immunosuppression and AIDS-defining cancers are gradually decreasing, whereas non-AIDS defining comorbidities such as non-AIDS defining cancers, cardiovascular disease and metabolic complications are emerging as major causes of death. Since the introduction of zidovudine, approximately 30 antiretroviral drugs have been approved for the treatment of HIV infection. Early and continuous antiretroviral treatment for all people living with HIV is an effective strategy for maintaining viral suppression and preventing transmission of HIV infection. In conclusion, achieving the 95–95–95 target among those living with HIV in Korea requires multifaceted efforts to improve early diagnosis, early and proper treatment of HIV infection including the management of chronic diseases, and adherence to antiretroviral therapy.

Introduction

Since the first report of acquired immunodeficiency syndrome (AIDS) in 1981, the epidemiology of HIV has changed markedly worldwide [1]. Over the past 40 years, the global HIV epidemic has continued, and successful treatments and prevention methods have been developed and disseminated [1]. Before the introduction of antiretroviral therapy (ART) in the late 1990s, HIV infection had a high mortality rate and a devastating effect on people of almost every race, country and class worldwide. The availability of combined ART (cART) has significantly reduced the prevalence and mortality of HIV infection, which has become a chronic disease with long-term survival [1].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has declared a fight against HIV transmission. In 2014, the UNAIDS proposed the 90–90–90 target, i.e., to diagnose 90% of people living with HIV (PLWH) worldwide, provide ART to 90% of PLWH, and achieve viral suppression in 90% of PLWH, by 2020 [2]. The strategy was to diagnose HIV infection early, before PLWH could

become immunocompromised, and put them on ART to achieve sustained viral suppression, thereby halting disease progression, improving morbidity and survival, and reducing HIV transmission [2]. By 2020, the UNAIDS estimated that 84% of PLWH worldwide have been diagnosed, 87% have been offered ART and 90% have achieved viral suppression [2,3]. In December 2020, the UNAIDS raised the target to be achieved by 2025 to 95–95–95, with at least 86% of all PLWH achieving viral suppression [3].

The Korean Centers for Disease Control and Prevention has set a goal of achieving 95–95–95 by 2030, with the aim of reducing the number of new infections in 2030 by 50% compared to 2023 [4]. In this review, I summarize the epidemiology of HIV/AIDS and the use of ART in Korea [5].

Methods

Ethics statement

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

Study design

The present study is a narrative review of studies obtained through a web-based database search.

Literature search and strategy

The following search terms were used in PubMed and KoreaMed.

(Korea) AND {(HIV [tiab]) OR (human immunodeficiency virus [MESH terms]) OR (ADIS [tiab]) OR (acquired immunodeficiency syndrome [MESH terms])}.

The epidemiology of Korean HIV/AIDS

In 1985, the first HIV infection in Korea was reported in a foreigner [6]. Subsequently, the number of new infections has gradually increased every year, and since 1995, more than 100 cases have been reported annually. Since 1999, the number of new infections has increased rapidly every year, and since 2003, more than 500 new infections have been registered each year. Since 2007, the upward trend has slowed, with 700–800 new infections are still recorded each year [7]. In 2011, the upward trend resumed, with more than 1,000 new infections registered yearly since 2013 [8]. After peaking at 1,223 in 2019, the number of new infections decreased from 2020 to 2022 because of the coronavirus disease 2019 (COVID-19) pandemic, with approximately 1,000 new infections registered annually [9]. In 2023, there were 1,005 new HIV infections, a decrease of 61 (5.7%) compared to 2022. However, a recent study comparing HIV infection to diagnosis before and after the COVID-19 pandemic suggested that the actual incidence of HIV infection may have decreased more than the possibility that HIV diagnosis was delayed due to the COVID-19 pandemic because the median time from HIV infection to diagnosis decreased from 5.68 years before to 5.41 years after the COVID-19 pandemic [10]. Over the past decade, there has been an average of 1,100 new cases per year, with 1,191 in 2014, 1,206 in 2018 and 1,005 in 2023, with no clear upward or downward trend (Fig. 1) [11].

After the first diagnosis in 1985, 19,745 cumulative domestic infections were registered by the end of 2023, of which 18,495 (93.7%) were in men and 1,250 (6.3%) in women [10]. In 2023,

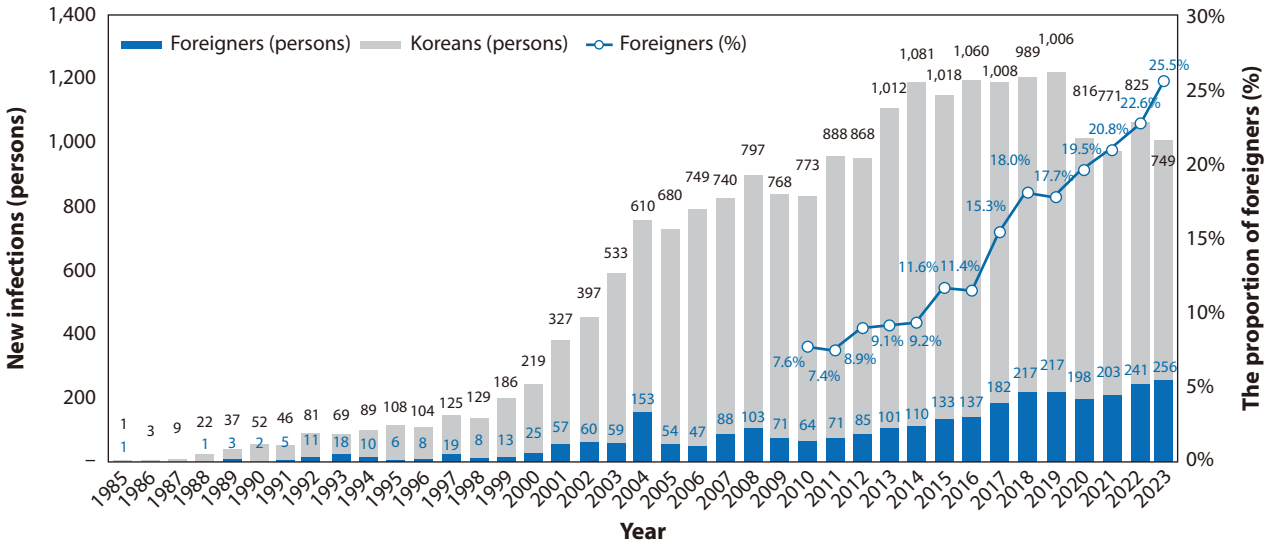

Fig. 1. New human immunodeficiency virus infections in Korea according to year. Adapted from Korea Centers for Disease Control and Prevention [10] with CC-BY.

130 new cases of AIDS were registered, an incidence rate of 0.254 per 100,000 HIV-infected persons. 17.4% of all notifications were of people living with AIDS [10]. Of the total number of infections, the average number of Koreans with HIV infection over the past 5 years was 834. The proportion of foreigners was 9.2% in 2014, 18.0% in 2018 and 25.5% in 2023, and increased each year [11].

The age distribution of new infections has continued to show an increase in the proportion of young people under the age of 40, from 53.3% in 2013 to 61.8% in 2017 and 81.0% in 2023 [11]. In particular, the proportion of young people in their 20s and 30s increased from 576 (53.3%) in 2014 to 572 (57.8%) in 2018 and 478 (63.8%) in 2023 [11,12]. In addition, 158 (15.7%) were in their 40s, 120 (11.9%) in their 50s, 55 (5.5%) their 60s and 16 (1.6%) were ≥70 years of age, with those aged ≥40 years accounting for 34.7% of the total [11]. In 2023 there were new infections in 903 men (89.9%) and 102 women (10.1%), for a gender ratio of 9:1 [11]. The proportion of men was 92.4% in 2014, 91.2% in 2018, and 89.9% in 2023, and showed a slightly decreasing trend.

According to an analysis of cases in which the transmission route of HIV infection was identified, sexual contact was the most common mode of transmission, accounting for 99.6% of infections, of which 54.3% were infected by homosexual contact and 42.0% by heterosexual contact in 2023 [11]. The proportion of transmission by homosexual contact increased from 53.8% in 2019 to 56.2% in 2020, 64.8% in 2021, and 65.4% in 2022 [11]. Although large numbers of transfusion and blood product-related infections were identified early in the HIV epidemic in developed countries such as the United States and Japan, only 46 such infections were identified in Korea, among which 13 were from transfusions performed overseas, 17 from blood products, and 16 from transfusions performed in Korea [8,11]. To reduce the rate of HIV transmission by blood transfusion, HIV antibody testing has been performed on blood donated in Korea since 1987. In addition, nucleic acid amplification testing has been performed on donated blood since February 2005 to prevent missed cases during the testing period. As a result, no case of HIV infection via blood or blood products has been reported since 2006 [11]. Infection via vertical transmission occurred sporadically until 2014, with a total of nine cases reported [8].

The number of deaths among Koreans has not changed significantly, with 142 in 2014, 136 in 2018 and 158 in 2023. There were 158 deaths among PLWH in 2023, an increase of 16 compared to the previous year [11]. However, the causes of death among PLWH have changed; AIDS-related deaths from opportunistic infections associated with immunosuppression and AIDS-defining cancers are declining gradually, whereas chronic diseases such as non-AIDS-defining cancers, liver disease, and cardiovascular disease (CVD) are emerging as important causes of death among PLWH [13]. A study of causes of death among PLWH using National Health Service data from 2004 to 2018 showed that although AIDS was the most frequent (59%) cause of death, chronic conditions such as non-AIDS-defining cancers (8.2%), suicide (7.4%), CVD (4.9%), and liver disease (2.7%) were also important causes [14].

The prevalence of non-communicable diseases among PLWH is projected to increase from 29% in 2010 to 84% in 2030 [15]. The proportion of AIDS-related deaths among PLWH is decreasing and the proportion of deaths from non-AIDS causes is increasing [16]. These findings underscore the importance of treating non-AIDS complications and comorbidities in addition to HIV infection.

Non-AIDS-defining comorbidities in Korean HIV/AIDS

Non-AIDS-defining comorbidities are increasing as a result of advances in treatment and the aging of the patient population [17–19]. In addition to conditions directly related to HIV infection (opportunistic infections, AIDS-specific cancers, central nervous system infections, HIV debilitating syndromes, and co-infection with hepatitis B or C), conditions that are increasingly frequent in patients with HIV and are of clinical concern and need to be treated together are defined as non-AIDS-defining comorbidities. These include CVDs, metabolic complications, kidney diseases, psychiatric disorders, malignancies, and so on [18]. This increase in comorbidities has led to the need for comprehensive internal medicine care for patients with HIV, not just treatment of the infection. There is also an increased need for consultative care with other specialists.

Because PLWH are living longer, the number of older patients is steadily increasing in Korea, and chronic diseases such as malignancies, CVD and diabetes are becoming important issues in HIV care [20]. In a study of the incidence of chronic diseases between PLWH and the general population using data from the National Health Insurance Service, PLWH had higher rates of malignancies, chronic kidney disease, osteoporosis, diabetes, hyperlipidemia and depression than the general population [21].

PLWH have higher rates of CVD, including myocardial infarction and hypertension, compared to people without HIV [18,22], and the mortality rate after acute myocardial infarction or stroke has been reported to be higher in PLWH [23]. A study with claims data from the National Health Insurance of the Korea reported that acute coronary syndrome was confirmed in 2.0% of PLWH, which was 1.3-fold higher than in the general population. The overall mortality rate was 7.1% [24]. In a Korean study, the incidence of CVD in PLWH was 4.11 per 1,000 person-years and CVD was more common in the elderly and in patients with diabetes mellitus [25]. Older PLWH should be encouraged to adopt lifestyle modifications such as regular exercise and a balanced diet.

HIV patients with diabetes need to avoid antiretroviral drugs that can worsen diabetes, including proteinase inhibitors (PIs), which induce insulin resistance and decrease insulin secretion [26]. Weight gain is reportedly greater among PLWH receiving integrase strand transfer inhibitor (INSTI)-based cART as initial therapy [27,28]. In a Korean study, individual INSTI-based regimens were associated with weight gain at the 24-month follow up in both the

treatment-naïve and treatment-experienced groups [20].

In a meta-analysis, bone mineral density was found to be 6.4-fold lower and the rate of osteoporosis 3.7-fold higher in PLWH than in individuals not infected with HIV [29]; the rate of fractures has been reported to be 60% higher [30]. In addition to risk factors for osteopenia and osteoporosis in the uninfected population, the risk of osteopenia associated with HIV medications, including PIs and tenofovir, should be considered [29,31]. In a Korean study, middle-aged men living with HIV had lower hip bone density and higher cortical and trabecular bone deficit rates compared to controls [32]. This finding suggests the need for a tailored strategy for the early detection and prevention of bone deficit in middle-aged men living with HIV.

Although kidney diseases can be caused by HIV infection itself such as HIV nephropathy, several antiretrovirals are associated with renal insufficiency, including tenofovir disoproxil fumarate (TDF), and boosted atazanavir [33]. The most common renal insufficiency observed in clinical practice is associated with the use of TDF [33,34]. In a Korean cohort study of renal insufficiency in male PLWH based on a Korean HIV/AIDS cohort of 830 patients, 32 (3.9%) cases of renal insufficiency occurred during 9,576 person-years of follow-up [35]. Diabetes mellitus, dyslipidemia, exposure to tenofovir or non-nucleoside reverse transcriptase inhibitors (NNRTIs) for >1 year, and AIDS-defining illness were risk factors for renal insufficiency.

PLWH often experience psychological stigma, which is more severe in Korea than in developed countries [36]. This stigma is related to symptoms of both depression and anxiety. Brief screening for depression is recommended for all PLWH [37]. Cognitive behavioral therapy for adherence and depression performed by clinical psychologists is effective for treating depression in PLWH [38]. A Korean study showed that a nurse-delivered cognitive behavioral therapy for adherence and depression was feasible and acceptable for PLWH and could improve their depression and quality of life [39]. HIV-associated neurocognitive disorder screening and the identification of modifiable factors are needed to improve patient compliance with therapy [40]. Among 194 Korean PLWH, the prevalence of HIV-associated neurocognitive disorders was 26.3%. Asymptomatic neurocognitive impairment and minor neurocognitive disorder accounted for 52.9% and 47.1%, respectively, of these patients [41].

Studies on cancer survival in PLWH using data from the National Health Insurance Service found that cancer rates were approximately 1.7-fold higher in PLWH than in the general population, with a decreasing trend in AIDS-related cancers and a gradual increase in non-AIDS-related cancers [42–44]. The incidence rates of HPV-related cancers, including cervical, anal, and oral cancers, were 4.98-, 104.2- and 2.97-fold higher, respectively, than in the general population, and have increased recently [43–45]. Compared with the general population, the incidence rates of lung and liver cancer were higher, whereas that of stomach cancer tended to be lower, among PLWH [42–44]. These findings highlight the need for multifaceted cancer prevention and early detection, including increased cancer screening, HPV vaccination, and smoking cessation.

Antiretroviral therapy for HIV/AIDS in Korea

Zidovudine was the first treatment for HIV infection to be approved by the US Food and Drug Administration (FDA), in 1987 [46]. Several agents were subsequently developed, and by the late 1990s it was recognized that long-term suppression of HIV was possible through a combination of three drugs [47]. This highly active ART is now the standard of care for HIV infection. To date, more than 30 antiretrovirals have been approved by the US FDA: abacavir, embricitabine,

lamivudine, and tenofovir alafenamide, and TDF; the nucleoside reverse transcriptase inhibitor (NRTI) class, which includes doravirine, efarirenz, etravirine, nevirapine, and rilpivirine; the NNRTI class, which includes atazanavir, darunavir, and lopinavir/ritonavir; the PI class, which includes atazanavir, darunavir, and lopinavir/ritonavir; the INSTI class, which includes bictegravir, dolutegravir, elvitegravir, raltegravir, and carbotegravir; the fusion inhibitor class, which includes enfuvirtide; the CCR5 antagonist class, which includes maraviroc; the CD4 post-attachment inhibitor class, which includes ibalizumab; the gp120 attachment inhibitor class, which includes fostemsavir; and the capsid inhibitor class, which includes lenacapavir [48]. In the past, each agent had to be administered separately, resulting in large numbers of pills to be taken daily; however, fixed-dose combinations of multiple drugs into a single formulation have been used more recently.

ART was introduced in Korea in 1991 with zidovudine monotherapy, followed by NRTIs such as didanosine, lamivudine, and stavudine as two-drug combination regimens. The introduction of PIs such as indinavir and later nelfinavir in 1997 and NNRTIs such as efavirenz in 1999 led to the development of triple therapies [49]. Subsequently, NRTIs such as abacavir and tenofovir; PIs such as atazanavir, lopinavir/ritonavir, and darunavir; and NNRTIs such as etravirine and rilpivirine were introduced. The introduction of the raltegravir as a integrase inhibitor in 2010 and its combination with elvitegravir in 2013 paved the way for single-tablet regimens [50]. Since then, several single-tablet regimens have been introduced, including dolutegravir, bictegravir, and doravirine [50]. Long-acting injectable antiretrovirals are used in other nations and will soon be introduced in Korea as a combination of carbotegravir and rilpivirine [51].

Continuous antiretroviral treatment can reduce viral replication in the blood to below the detectable level, leading to long-term suppression of HIV. A study of 141 PLWH in Korea who had received antiretroviral treatment for at least 1 year by 2005 found that 6 months after starting treatment, 73% of patients had suppressed viral replication to ≤400 copies/mL [52]. Antiretroviral treatment can fail due to patient non-adherence to the regimen, and HIV develops resistance-associated mutations. The incidence of resistance mutations in Korea is low, but increasing, and therefore requires attention [53]. Among 248 Korean PLWH, the rate of NNRTI resistance decreased between January 2010 and December 2020 (by 15.3% during 2012–2014, 8.7% during 2015–2017, and 2.4% during 2018–2020), whereas the rates of resistance to PIs and INSTIs increased from 0% until 2018 to 3.5% and 8.2% during 2018–2020, respectively [54]. Therefore, continuous monitoring of the pattern of ART resistance is necessary.

Conclusion

The availability of cART has significantly reduced the prevalence and mortality of HIV infection, which has become a chronic disease with long-term survival. Achieving the 95–95–95 target among those living with HIV in Korea requires multifaceted efforts to improve early diagnosis, early and proper treatment of HIV infection including the management of chronic diseases, and adherence to ART.

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Authors' contributions

All work was done by Nam Su Ku.

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Review

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Epidemiology and management of infectious spondylitis in Korea: a narrative review

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Infectious spondylitis, an infection of the vertebral body, intervertebral disc, or paraspinal tissues, poses diagnostic and therapeutic challenges. This review examines the clinical approach and management of infectious spondylitis in Korea. The incidence of pyogenic spondylitis has increased, primarily due to the aging population, more frequent use of invasive procedures, and higher prevalence of immunocompromising conditions. Conversely, tuberculous spondylitis has declined, reflecting shifts in population demographics and medical practices. *Staphylococcus aureus* remains the predominant causative agent in pyogenic cases, while *Mycobacterium tuberculosis* is the primary pathogen in tuberculous spondylitis. The diagnosis is contingent upon clinical suspicion, inflammatory markers, imaging studies, and microbiological identification. MRI is the preferred imaging modality, offering high sensitivity and specificity. Blood cultures and tissue biopsy are instrumental in isolating the causative organism and determining its antibiotic susceptibility. Treatment involves antimicrobial therapy, spinal immobilization, and vigilant monitoring for complications. Surgical intervention may be necessary in cases involving neurological deficits, abscesses, or spinal instability. The prognosis for infectious spondylitis varies. Long-term complications, including chronic pain, neurological deficits, and spinal deformities, may arise and can meaningfully impact quality of life. Mortality is considerable and is influenced by comorbidities and disease severity. The risk of recurrence, particularly within the first year after treatment, is a concern. This review underscores the importance of ongoing research and education in refining diagnostic and treatment strategies for infectious spondylitis. As this condition becomes more common, these efforts offer hope for improving patient care and reducing the burden of this severe spinal infection.

Introduction

Background

Infectious spondylitis is a disease that affects the vertebral body, intervertebral disc, or surrounding tissues. Although the site of infection can define the condition, terms such as infectious spondylitis, spondylodiscitis, and vertebral osteomyelitis are often used interchangeably. The causative microorganisms are diverse, varying by region and over time. Most bacteria elicit a pyogenic response, while mycobacteria, fungi, *Brucella*, and syphilis lead

to granulomatous reactions [1]. In Korea, bacteria in general and *Mycobacterium tuberculosis* in particular are the predominant causes, corresponding to classifications of pyogenic spondylitis and tuberculous spondylitis.

The diagnosis of infectious spondylitis primarily relies on a high level of clinical suspicion, informed by symptoms such as back pain and fever. However, early identification remains challenging, with diagnosis typically taking 1 to 3 months [2,3]. This delay complicates disease management. Infectious spondylitis places a considerable burden on individuals and society, affecting health, economic stability, and quality of life.

Objectives

This review is designed to provide healthcare professionals with critical insights into the clinical management and treatment of infectious spondylitis. The article thoroughly examines key aspects of this condition within the Korean context, including its prevalence, causative microorganisms, associated comorbidities, diagnostic strategies, therapeutic approaches, and anticipated outcomes. Our goal is to deepen clinicians' understanding and foster improved patient care in cases of infectious spondylitis.

Ethics statement

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

Incidence

The incidence of infectious spondylitis in Korea has varied over time. Prior to the early 2000s, tuberculous spondylitis was believed to predominate, reflecting the high prevalence of tuberculosis [4].

Fig. 1 depicts the incidence of infectious spondylitis, based on national health insurance data from Korea. A nationwide cohort study conducted from 2007 to 2016 identified 9,655 cases of the condition [5]. The findings showed an increase in the number of pyogenic spondylitis cases, risking from 2,431 in 2007 to 4,874 in 2016. Conversely, the incidence of tuberculous spondylitis declined from 1,756 cases to 594 over the same timeframe. These patterns indicate a shift toward bacterial infection as the predominant cause of infectious spondylitis in Korea.

A more recent study covering the period from 2010 to 2019 further confirmed this upward trend (Fig. 1A) [6]. Among 169,244 patients, the number of cases increased from 10,991 in 2010 to 18,533 in 2019. In turn, the incidence rate per 100,000 people climbed from 22.90 to 35.79. This increase is attributed to the aging population, higher prevalence of chronic diseases, increased use of immunosuppressive therapies, and greater frequency of invasive spinal procedures [7–9].

Both pyogenic and tuberculous spondylitis exhibited the highest prevalence in individuals aged 60–79 years (Fig. 1B) [5]. Interestingly, female patients predominated in both groups, which contrasts with some international studies reporting a higher incidence in male patients.

Anatomically, infectious spondylitis predominantly affects the lumbar region, followed by the thoracic and cervical spine, with the latter comprising less than 10% of cases [10]. Pyogenic spondylitis primarily targets the lumbar spine, whereas tuberculous spondylitis more commonly occurs in the thoracic spine, with the lumbar region representing the second most frequent site [3].

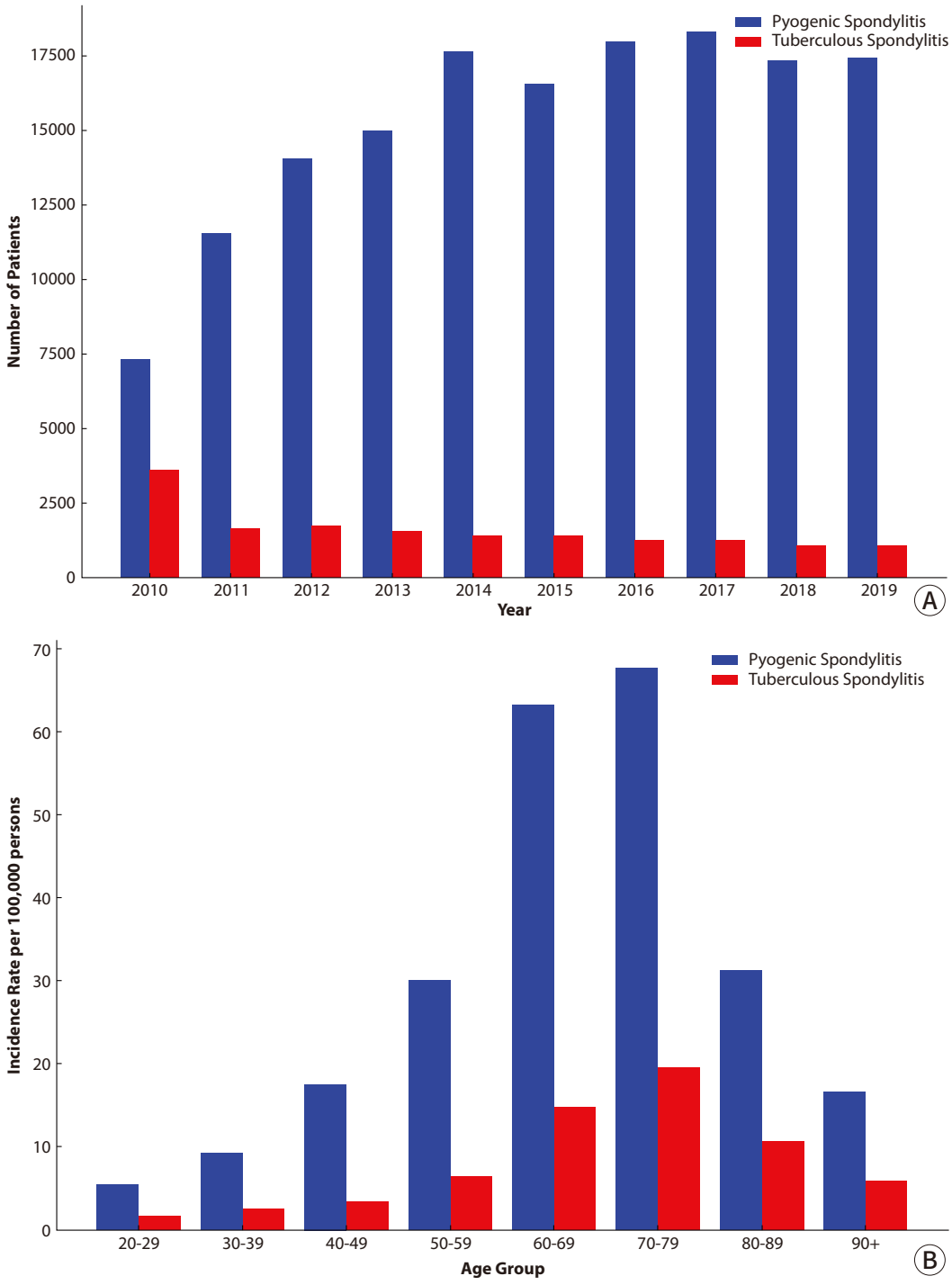

Fig. 1. Incidence of infectious spondylitis in Korea. (A) The number of infectious spondylitis cases recorded between 2010 and 2019 was determined using data provided by the Health Insurance Review and Assessment Service (HIRA) [6]. (B) The incidence rates of pyogenic spondylitis and tuberculous spondylitis were compared from 2007 to 2016 using data from the Korean National Health Insurance Service (NHIS) [5].

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Etiologic microorganisms

In Korea, fungal spondylitis, non-tuberculous mycobacteria, and *Brucella* spondylitis are uncommon [9,11,12]. Microorganisms that cause pyogenic spondylitis typically reach the vertebrae through arterial spread, during spinal surgery or other procedures, or directly from adjacent sites. *Staphylococcus aureus* is the predominant causative agent in pyogenic spondylitis, followed by *Streptococcus* species. Gram-negative bacilli are responsible for 7% to 33% of cases, with *Escherichia coli* being the most common among them [10,13,14]. Coagulase-negative staphylococci are implicated in 30% to 32% of pyogenic spondylitis cases in patients with a history of spinal surgery or other procedures [15]. Gram-negative bacilli are more frequently suspected in female patients or in those with previous or concurrent urinary tract or intra-abdominal infections [10,14]. Table 1 presents the distribution of microorganisms identified in cases of spontaneous or postoperative pyogenic spondylitis based on Korean data [15,16].

Tuberculous spondylitis primarily results from venous spread originating in the lungs or other primary lesions. *M. tuberculosis* can directly infect the spine from adjacent organs, including the lungs, kidneys, and gastrointestinal tract. A literature review by Schirmer et al. [17] indicated that the rate of concomitant pulmonary tuberculosis in patients with tuberculous spondylitis ranges from 8% to 100%. Additionally, a study from Korea found that 16% of patients with tuberculous spondylitis also had extrapulmonary tuberculosis, including miliary tuberculosis as well as renal and lymph node involvement [18].

Comorbidity with other disease

Understanding the distribution of microorganisms based on patient characteristics can guide clinicians in selecting appropriate empirical antibiotics. An analysis of Health Insurance Review and Assessment Service data from 2010 to 2019 showed that patients with infectious spondylitis often exhibit multiple comorbidities. These include diabetes mellitus (55.1%), rheumatoid arthritis (27.3%), chronic obstructive pulmonary disease (15.2%), and end-stage renal disease (12.8%) [6]. In a cohort of 586 patients with culture-proven pyogenic spondylitis, the most common comorbidities were diabetes (30.7%), solid tumors (14.3%), chronic renal disease (10.4%), and liver cirrhosis (9.4%) [16]. The study also revealed that gram-negative infections were relatively prevalent among older patients, women, and those with cirrhosis or solid tumors. Additionally, methicillin-resistant *S. aureus* infection was more frequent in patients with chronic renal disease than in those without this comorbidity [16].

While one report indicated that diabetes was reported in 17% of 94 patients with tuberculous spondylitis, no other comorbidities were specifically associated with this condition [3]. In 2020, Korea had the highest incidence of tuberculosis among Organisation for Economic Co-operation and Development countries, with 49 cases per 100,000 population, and an increasing proportion of new cases were seen in individuals aged 65 and older [19]. Consequently, the range of comorbid diseases in patients with tuberculous spondylitis may be diverse.

Diagnostic approaches

Clinicians should consider infectious spondylitis in patients presenting with new or worsening back or neck pain. The onset of symptoms is often gradual and subtle, with pain typically worsening during weight-bearing activities and subsiding when the patient lies down. The pain is

Table 1. Distribution of microorganisms identified in patients with spontaneous or postoperative pyogenic spondylitis

Microorganisms	Spontaneous pyogenic spondylitis (n=586)	Postoperative pyogenic spondylitis (n=104)
Gram-positive cocci	426 (72.7%)	82 (78.8%)
Staphylococcus aureus	255 (43.5%)	35 (33.6%)
Methicillin-susceptible	157 (26.8%)	13 (12.5%)
Methicillin-resistant	98 (16.7%)	22 (21.2%)
Coagulase-negative staphylococci	31 (5.3%)	32 (31.0%)
Methicillin-susceptible	12 (2.0%)	4 (3.8%)
Methicillin-resistant	19 (3.2%)	28 (26.9%)
Enterococcus species	22 (3.8%)	4 (3.8%)
Enterococcus faecium	4 (0.7%)	1 (1.0%)
Enterococcus faecalis	17 (2.9%)	3 (2.9%)
Enterococcus gallinarum	1 (0.2%)	0 (0%)
Streptococcus species	118 (20.1%)	11 (10.6%)
Streptococcus pneumoniae	6 (1.0%)	0 (0%)
Streptococcus agalactiae	27 (4.6%)	3 (2.9%)
Viridans streptococci	70 (11.9%)	7 (6.7%)
Other streptococci	15 (2.6%)	1 (1.0%)
Gram-negative bacilli	132 (22.5%)	15 (14.4%)
Escherichia coli	69 (11.8%)	6 (5.8%)
Klebsiella pneumoniae	22 (3.8%)	1 (1.0%)
Klebsiella oxytoca	3 (0.5%)	0 (0%)
Klebsiella aerogenes	1 (0.2%)	0 (0%)
Pseudomonas aeruginosa	10 (1.7%)	4 (3.8%)
Enterobacter cloacae	5 (0.8%)	2 (1.9%)
Enterobacter asburiae	1 (0.2%)	0 (0%)
Serratia marcescens	3 (0.5%)	2 (1.9%)
Raoultella ornithinolytica	1 (0.2%)	0 (0%)
Salmonella (non-typhoidal)	2 (0.3%)	0 (0%)
Proteus mirabilis	2 (0.3%)	0 (0%)
Proteus penneri	1 (0.2%)	0 (0%)
Citrobacter koseri	1 (0.2%)	0 (0%)
Morganella morganii	1 (0.2%)	0 (0%)
Campylobacter fetus	3 (0.5%)	0 (0%)
Haemophilus influenzae	1 (0.2%)	0 (0%)
Vibrio cholerae non O1/O139	1 (0.2%)	0 (0%)
Ralstonia mannitolilytica	1 (0.2%)	0 (0%)
Achromobacter xylosoxidans	1 (0.2%)	0 (0%)
Burkholderia cepacia	2 (0.3%)	0 (0%)
Stenotrophomonas maltophilia	1 (0.2%)	0 (0%)
Anaerobes	11 (1.9%)	1 (1.0%)
Polymicrobial	9 (1.5%)	5 (4.8%)
Other*	8 (1.4%)	1 (1.0%)

Data from Kim et al. [15]; Kim et al. [16].
**Granulicatella adiacens*, *Erysipelothrix rhusiopathiae*, *Lactococcus garvieae* (2), *Listeria monocytogenes*, *Neisseria* species (2), *Moraxella* species.

usually well-localized and can be reproduced through palpation or percussion over the affected area. Pyogenic spondylitis is relatively likely among patients who experience back or neck pain along with fever, bloodstream infection, or infective endocarditis [20]. This condition should also be suspected in patients presenting with fever and new peripheral neurologic symptoms, with or without back pain. Radiculopathy, which may manifest as leg pain or weakness, can occur due to nerve root compression or irritation. In cases involving the thoracic spine, patients often describe a "belt-like" pain across the chest wall or abdomen, which can be mistakenly attributed to gastrointestinal, cardiac, or pulmonary conditions.

The initial evaluation of patients with suspected infectious spondylitis should begin with a comprehensive history and physical examination, including a detailed neurological assessment. Patients should be asked about any comorbidities, ongoing infections, and predisposing factors, such as existing non-spinal infections, the presence of indwelling devices, recent application of surgical instruments, and spinal injections [10,15]. Initial diagnostic tests include inflammatory markers (WBC count, ESR, and CRP level), as well as two sets of blood cultures. Spinal imaging is also critical, with MRI being the preferred method when available. Additionally, plain X-rays, including anteroposterior and lateral views, along with flexion/extension views, should be obtained for baseline evaluation in all cases [21]. However, native X-rays exhibit low specificity for diagnosing infectious spondylitis, with these examinations primarily detecting advanced cases characterized by vertebral endplate irregularities or a reduction in intervertebral disc height.

MRI with intravenous gadolinium contrast is the preferred imaging method due to its increased sensitivity and specificity. It offers superior visualization of potential infection spread to the epidural and paravertebral spaces [22]. Clinicians should obtain T2-weighted and post-contrast T1-weighted images with fat suppression. Typical MRI findings indicative of infection include abnormal signals from the intervertebral discs, destruction of the vertebral body endplates adjacent to the disc, and bone marrow edema. However, these findings can also be present in non-infectious spinal conditions, necessitating collaboration between clinicians and radiologists to achieve accurate diagnosis and differentiation [22].

For patients unable to undergo MRI, CT can be used to assess the osseous anatomy and, with the addition of contrast, can also reveal involvement of paraspinal and epidural soft tissues. Recent studies have suggested that fluoro-2-deoxyglucose PET/CT may represent a complementary tool to MRI for differentiating between tuberculous and pyogenic spondylitis [23], as well as for assessing disease activity [23,24]. PET/CT offers superior spatial resolution and improved detection of metastatic infection. The combination of positive blood cultures, imaging findings, and clinical symptoms can often confirm a diagnosis of infectious spondylitis [25]. In blood cultures of patients suspected of having pyogenic spondylitis, when microbial growth is present, the necessity of tissue biopsy remains a topic of debate [20]. A Korean retrospective study involving 141 patients with pyogenic spondylitis, who exhibited positive blood and tissue cultures, reported a 95.7% concordance rate in bacterial identification [26]. Discordant results were typically characterized by the growth of a single species in one sample and multiple species, including the initially identified species, in the other. These findings suggest that in cases with positive blood cultures, tissue biopsy may not be necessary for the microbiological diagnosis of pyogenic spondylitis (Fig. 2).

Inflammatory markers such as WBC count, CRP level, and ESR are typically elevated in acute infections but may be normal in chronic cases [26]. Kim et al. [3] found that patients with pyogenic spondylitis exhibited significantly higher levels of ESR and CRP compared to those with

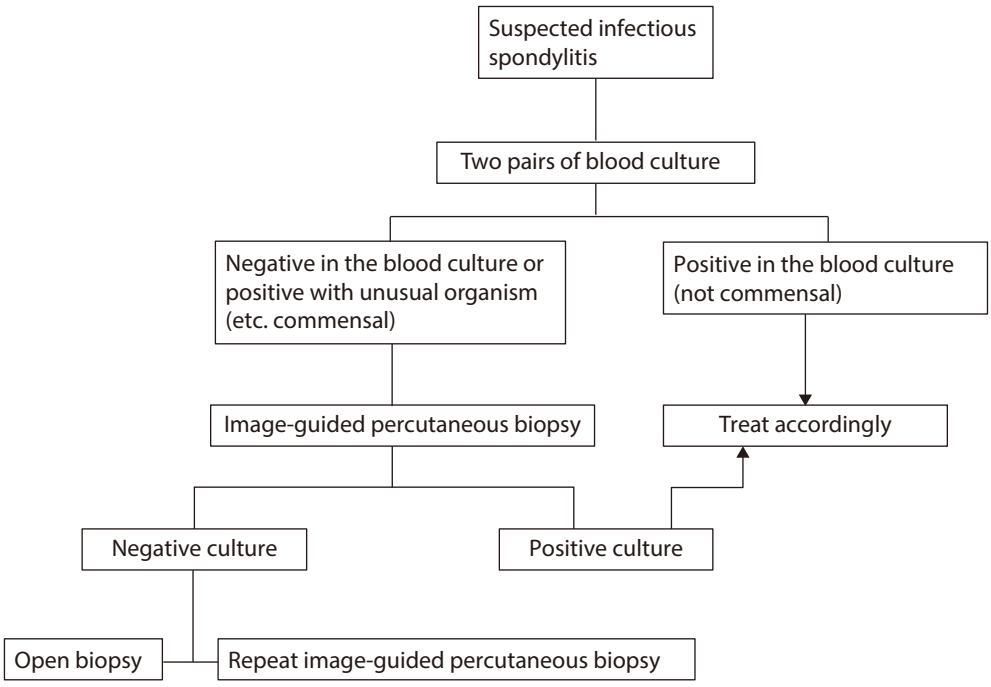

Fig. 2. Approach to diagnosing a patient with suspected infectious spondylitis.

tuberculous spondylitis. Notably, tuberculosis infection rates remain high among elderly Koreans, warranting careful consideration in this demographic [18,27]. Tuberculous spondylitis should be suspected in cases involving slow disease progression over several months or when extraspinal tuberculosis is detected [3,18]. Diagnosis is confirmed through tissue biopsy, with mycobacterial culture positivity rates ranging from 69.0% to 85.3% [28]. Polymerase chain reaction techniques have been employed for the rapid identification of mycobacteria in formaldehyde-fixed, paraffin-embedded tissue specimens. Tissue biopsy is also indicated when blood cultures fail to establish a microbiologic diagnosis for pyogenic spondylitis. The two most widely recognized methods are image-guided percutaneous needle biopsy and open biopsy. Once tissue biopsy is performed, specimens should be sent for both microbiologic and histopathologic examination. Needle biopsy specimens can be obtained percutaneously through CT or fluoroscopically guided biopsy, with diagnostic yields of 44% and 55%, respectively [29]. If needle biopsy is indicated for patients with concurrent paraspinal inflammation or abscess, samples should be collected from paraspinal rather than spinal tissues [30]. Open surgical biopsy is considered the most reliable method, with a 76% diagnostic yield according to a recent systematic review [31]; however, the impact of prior antibiotic use requires further clarification. Some experts suggest that in patients with pyogenic spondylitis who have been exposed to antibiotics but show no signs of sepsis or severe sepsis, a certain interval should elapse before biopsy is performed [32].

A second percutaneous biopsy may be warranted if the initial biopsy does not yield a diagnosis, although the precise benefit of this procedure is still uncertain [33]. It is advisable to wait at least 3 days after the initial biopsy before repeating the procedure, by which time most positive cultures from the first biopsy should have been obtained [34]. Alternatively, if the first image-guided biopsy yields a negative result, proceeding with an open biopsy as the next step is reasonable (Fig. 2).

If the microbial etiology is not identified, empiric treatment becomes necessary. Empiric antibiotics should be promptly administered to critically ill patients showing signs of sepsis or those being taken to the operating room for neurologic compromise. The initiation of empiric treatment should be based on the most likely microbial etiology. To select the appropriate empiric antibiotics for a patient with pyogenic spondylitis of unknown microbial etiology, factors such as medical history, demographic characteristics, clinical features, and imaging results must be considered [4,16]. If the patient has not undergone spinal surgery, vancomycin need not be included in the empiric antibiotic regimen due to the low risk of methicillin-resistant *S. aureus* or methicillin-resistant coagulase-negative staphylococci [13,15,35]. A first-generation cephalosporin is suitable for the treatment of suspected community-acquired pyogenic spondylitis. Alternative options include a fluoroquinolone with rifampin, or a fluoroquinolone plus a beta-lactam/beta-lactamase inhibitor [36,37]. If the patient has exhibited previous or concurrent urinary tract infection or intra-abdominal infection, empiric antibiotics should provide coverage for gram-negative bacilli [10]. Therapy should be adjusted according to bacteriologic test results. Most cases of pyogenic spondylitis are treated conservatively, with favorable outcomes. A recent study has established that a 6-week course of systemic antibiotics is sufficient for most cases [38]. However, a longer duration of therapy may be required in certain situations, such as infections with extensive spread to paraspinal soft tissues, undrained paravertebral abscesses, or extensive bone destruction. Transitioning to oral antibiotics with high bioavailability is considered acceptable.

In cases of culture-negative infectious spondylitis, which typically involve long-term and broad-spectrum antibiotic treatment, this strategy can result in avoidable side effects and contribute to antibiotic resistance. One prior report indicated favorable outcomes with the use of cefazolin in hematogenous pyogenic spondylitis and with vancomycin in post-procedural pyogenic spondylitis among patients with culture-negative pyogenic spondylitis [39].

Treatment

The most severe complication of infectious spondylitis is neurologic impairment, which can occur secondary to either abscess formation or bony collapse. Treatment objectives include saving the patient's life, alleviating pain, preventing or reversing neurologic deficits, eradicating the infection, and restoring spinal stability. To meet these treatment objectives, management principles encompass: (1) establishing an accurate microbiological diagnosis; (2) administering appropriate antimicrobials; (3) immobilizing the spine; and (4) carefully monitoring for clinical and radiographic evidence of spinal instability, as well as for progression of the infection or neurological deterioration.

The treatment regimens for tuberculous spondylitis align with those for pulmonary tuberculosis. For most patients receiving rifampin for susceptible tuberculosis, a 6- to 9-month course of therapy is sufficient [40]. To date, no formal data are available on the efficacy of newer drugs in the treatment of osteoarticular tuberculosis.

While receiving antimicrobial therapy, patients should be carefully monitored for clinical signs of soft tissue extension or abscess, as well as for symptoms of cord compression. Additionally, clinicians should track inflammatory markers, specifically ESR and CRP levels, with weekly assessments [20]. CRP levels tend to normalize more quickly than ESR following successful treatment or after uncomplicated spinal fusion surgery [41]. Routine anteroposterior and lateral radiographs centered on the affected disc are recommended at 1 and 3 months

into antimicrobial therapy, and again 3 months after the cessation of treatment [42]. For the cervical or lumbar spine, orthopedic surgeons advise obtaining follow-up flexion/extension films to reliably detect potential instability or to confirm bone fusion. In patients who are clinically improving while on treatment, routine follow-up MRI is unnecessary, as imaging findings may not correspond with clinical progress [43].

Surgical intervention, which may include procedures such as incision and drainage, decompression, corpectomy, and fusion, is sometimes required. Patients presenting with neurological deficits such as weakness, paresthesia, and urinary retention, as well as those with radiographic signs of epidural or paravertebral abscess or actual or impending spinal cord compression, should be evaluated for surgical decompression. Interventional radiology has become increasingly important in managing psoas muscle abscesses. Continuous monitoring for the development or progression of neurological signs is crucial, yet it is frequently overlooked. Epidural abscesses can lead to abrupt neurological deficits. A spinal epidural abscess, a potentially severe complication of infectious spondylitis, can spread through septic thrombosis of the epidural veins. Since skip lesions, or noncontiguous abscesses, may occur in 15% of overall cases [44], imaging of the entire spine is recommended.

Relative indications for surgery include uncertain diagnosis, lack of clinical improvement following antimicrobial treatment, or significant progressive spinal deformity accompanied by biomechanical instability. However, guidelines do not offer a detailed and practical description of surgical interventions for cases of spondylitis that are resistant to conservative treatment [20]. Decisions regarding surgery should be made in close consultation with surgeons.

In the early phase of infectious spondylitis, bed rest is recommended until the acute pain improves. Both bed rest and spinal immobilization are crucial, particularly in cases of vertebral destruction. Once the acute pain has subsided, ambulation with an appropriate brace is advised. Patients with thoracic infections should use a thoracolumbar sacral orthosis, while those with lumbosacral infections are advised to use a lumbar sacral orthosis. The duration of thoracolumbar sacral orthosis brace usage varies depending on factors such as the patient's response to treatment, the nature of the infection, and the overall health and stability of the spine. Research indicates that approximately 30% of patients may experience a progression of deformity during the first 6 to 8 weeks [45]. Typically, patients may need to wear the brace continuously for several weeks to months, with the duration of use gradually decreasing as healing progresses. Patients should be monitored throughout the treatment and for 1 year after its completion to detect any relapses [46].

Prognosis

Most patients experience a gradual improvement in back pain after the initiation of treatment, with the pain typically resolving after bone fusion occurs. However, clinicians must communicate to patients and their caregivers that back pain may persist. A systematic review of the clinical characteristics of infectious spondylitis reported an attributable mortality rate of 6% [47]. The functional outcome is worse in cases with neurological deficits, which have been noted in 32% of patients. Additionally, 27% of patients experience complications that significantly impact their quality of life [47]. In a large retrospective study from Japan, which included over 7,000 patients with infectious spondylitis, the in-hospital mortality rate was 6% [48]. Comorbidities such as diabetes, end-stage kidney disease, cirrhosis, malignancy, and infective endocarditis were determinants of this mortality rate. Similarly, a retrospective study from a single center in Korea,

which included 116 patients with infectious spondylitis, reported an in-hospital mortality rate of 6% and a relapse rate of 8% [9]. Recurrences typically occur within 6 months, and rarely up to 1 year, after the completion of antibiotic therapy [35].

Conclusion

Infectious spondylitis is a serious condition that necessitates timely diagnosis and effective treatment to reduce the risk of complications, such as neurological impairment. The incidence of pyogenic spondylitis has risen in Korea, while tuberculous spondylitis remains a key concern due to the persistent prevalence of tuberculosis. Accurate microbiological diagnosis, appropriate antimicrobial therapy, and vigilant monitoring are essential for the management of infectious spondylitis. Both medical and surgical interventions are important and are chosen based on the severity and progression of the disease. Clinicians must recognize the variety of etiological microorganisms, consider patient comorbidities, and understand the vital role of a multidisciplinary approach in delivering optimal care. Ongoing education and research are imperative to establish standardized treatment protocols and improve prognoses for patients with infectious spondylitis.

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Authors' contributions

All work was done by Kyung-Hwa Park.

Conflict of interest

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

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Data availability

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Supplementary materials

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Air pollution, including PM_{10}, as a potential risk factor for the development of appendicitis in Korea: a case-crossover study

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Objectives: Interest in the association between particulate air pollution and appendicitis risk has been increasing in recent years, and previous studies have suggested a link between particulate matter ≤ 10 μm in diameter (PM_{10}) and appendicitis. However, robust evidence is currently lacking. This study explored the association between short-term PM_{10} exposure and appendicitis using data from Ewha Womans University Mokdong Hospital, Seoul, Korea, between January 1, 2001 and December 31, 2018.

Methods: We employed a time-stratified case-crossover design using data from 6,526 appendicitis patients taken from the hospital's electronic medical records system. We analyzed the data using a conditional logistic regression model adjusted for daily mean temperature and relative humidity. The effect size of PM_{10} was estimated in terms of each 10 μm/m^3 increase in PM_{10} concentration. Sex, season, and age group were analyzed as subgroups.

Results: Appendicitis patients had been exposed to higher levels of PM_{10} concentrations 3 days (OR 1.045, 95% CI : 1.007–1.084) and 7 days (OR, 1.053; 95% CI, 1.005–1.103) before hospital admission. The case-crossover analysis stratified by sex, age, and season showed that the male sex, being aged under 10, and the cold season were associated with a significantly stronger association between appendicitis and PM_{10} concentrations.

Conclusion: Our study found that PM_{10} concentrations were associated with appendicitis in boys aged under 10. The cold season was also a risk factor. Further research with a larger sample size and with other pollutants is required to clarify the association between PM_{10} and appendicitis.

Introduction

Background

Globally, acute appendicitis affects 1.17 individuals per 1,000 population annually, with a lifetime risk of 8.6% for men and 6.7% for women [1]. In Korea, the incidence rate is 2.27 per 1,000

population [2]. Although numerous studies have explored the pathogenetic roles of various infectious agents in appendicitis, including viral, bacterial, fungal, and parasitic organisms, there is still no consensus on specific causes [3]. A recent study examining the pathological evidence of appendicitis suggests that pressure in the appendix lumen increases due to the proliferation of intestinal bacteria following lumen obstruction and the accumulation of secreted mucus, leading to pain around the navel [4]. However, this does not account for the initial surge in intestinal bacteria that triggers acute appendicitis. It is believed that this increase may be due to immunological changes or environmental factors, rather than the onset of any specific disease state. The incidence of appendicitis in Western countries rose from the 19th to the early 20th century and then declined after the mid to late 20th century [5]. To explain these historical fluctuations, particulate matter ≤10 μm in diameter (PM_{10}) has been hypothesized as a potential risk factor associated with an increased incidence of appendicitis. Previous studies have also investigated the link between air pollution and appendicitis [6,7].

PM_{10} is defined as fine dust composed of particles ≤10 μm in diameter and is one of the most well-known air pollutants, along with fine particulate matter ($PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO). Since the Korean peninsula is exposed to relatively high levels of PM_{10} due to geopolitical reasons, the health effects of PM_{10} on the population have become particularly apparent in recent years [8]. Previous studies have shown that short-term exposure to pollutants can trigger inflammatory processes, potentially contributing to the development of appendicitis [9].

Objectives

We aimed to clarify the association between PM_{10} exposure and the risk of appendicitis to provide better evidence for developing PM_{10} regulation policies and to alleviate the disease burden caused by appendicitis.

Methods

Ethics statement

This study was reviewed and approved by the Ewha Womans University Mokdong Hospital Institutional Review Board (IRB File No: SEUMC 2020-08-026). The requirement for informed consent was waived.

Study design

We conducted a time-stratified case-crossover study design by linking the PM_{10} level during the case event (the date of hospitalization) to each appendicitis case. The study was described according to the STROBE statement, available at https://www.strobe-statement.org/.

Setting

The electronic medical records of all patients diagnosed with acute appendicitis and hospitalized at Ewha Womans University Mokdong Hospital over an 18-year period were collected. Additionally, national Korean air pollution data for the same period were gathered.

To derive time-stratified matched control events (when no admission occurred), we selected control period dates using the same year, month, and day of the week as the appendicitis hospitalization date, but from different weeks. These lags in exposure were referred to as same-day exposure and exposure lagged by "n days" before the event. The control events were

matched with case events on the same day of the week to avoid time trend bias associated with specific weekdays.

Since this study employed a case-crossover analysis, intra-individual comparisons were conducted without accounting for the confounding effects of other risk factors, such as a patient's lifestyle [10]. Instead, we focused on weather variables as potential confounding factors, including daily mean temperature and relative humidity.

Participants

We collected data from 9,886 patients treated for appendicitis at Ewha Womans University Mokdong Hospital, a tertiary medical center in the western part of Seoul, Korea, from January 1, 2001, to December 31, 2018. The information gathered included registration number, gender, age, number of hospitalization days, admission and discharge dates, and residential address. Appendicitis is classified under the International Classification of Disease (ICD) ninth revision (ICD-9) codes 540.9, 540.0, 540.1, or 10th revision (ICD-10) codes K35.0, K35.1, K35.9, along with the in-hospital surgery code 470.

Exclusion criteria

Patients were excluded if they had two or more duplicate records of surgical treatments or if their only surgical records were from the first visit (n=1,107). Additionally, patients were excluded if they had missing data on sex, age, hospitalization date, and/or address (n=1,100). Finally, those missing data on the case period, specifically the date of hospitalization due to appendicitis, were also excluded (n=1,153). This resulted in a total of 6,526 patients being included in the final analysis (Fig. 1).

Variables (study outcomes)

The primary outcome was the PM_{10} exposure level at the time of appendicitis diagnosis.

Data sources and measurement

AirKorea (national air pollution surveillance network) database

Korea's metropolitan area spans 11,861 km^2 and includes Seoul, Incheon, and Gyeonggi-do Provinces. In 2018, 133 monitoring stations were established throughout this region. These stations are part of a national air pollution surveillance network known as "AirKorea," which oversees 240 measurement branches nationwide (https://www.airkorea.or.kr/). The AirKorea database records hourly mean concentrations of air pollutants from continuous monitoring stations, and calculates daily mean and maximum values. PM_{10} measurements were conducted using the beta-ray absorption method, as detailed in previous studies [11]. We linked the exposure data from these monitoring stations to the nearest administrative area corresponding to each patient's residential location. For the two-pollutant model, data were also collected on four additional air pollutants: SO_2, NO_2, CO, and O_3. To assess the effect size and perform sensitivity analysis, we gathered $PM_{2.5}$ measurement data from 2015 to 2018.

Meteorological data from the Korea Meteorological Administration

Meteorological data, including the daily mean values of PM_{10}, temperature, and humidity, were obtained from the Korea Meteorological Administration (http://www.kma.go.kr).

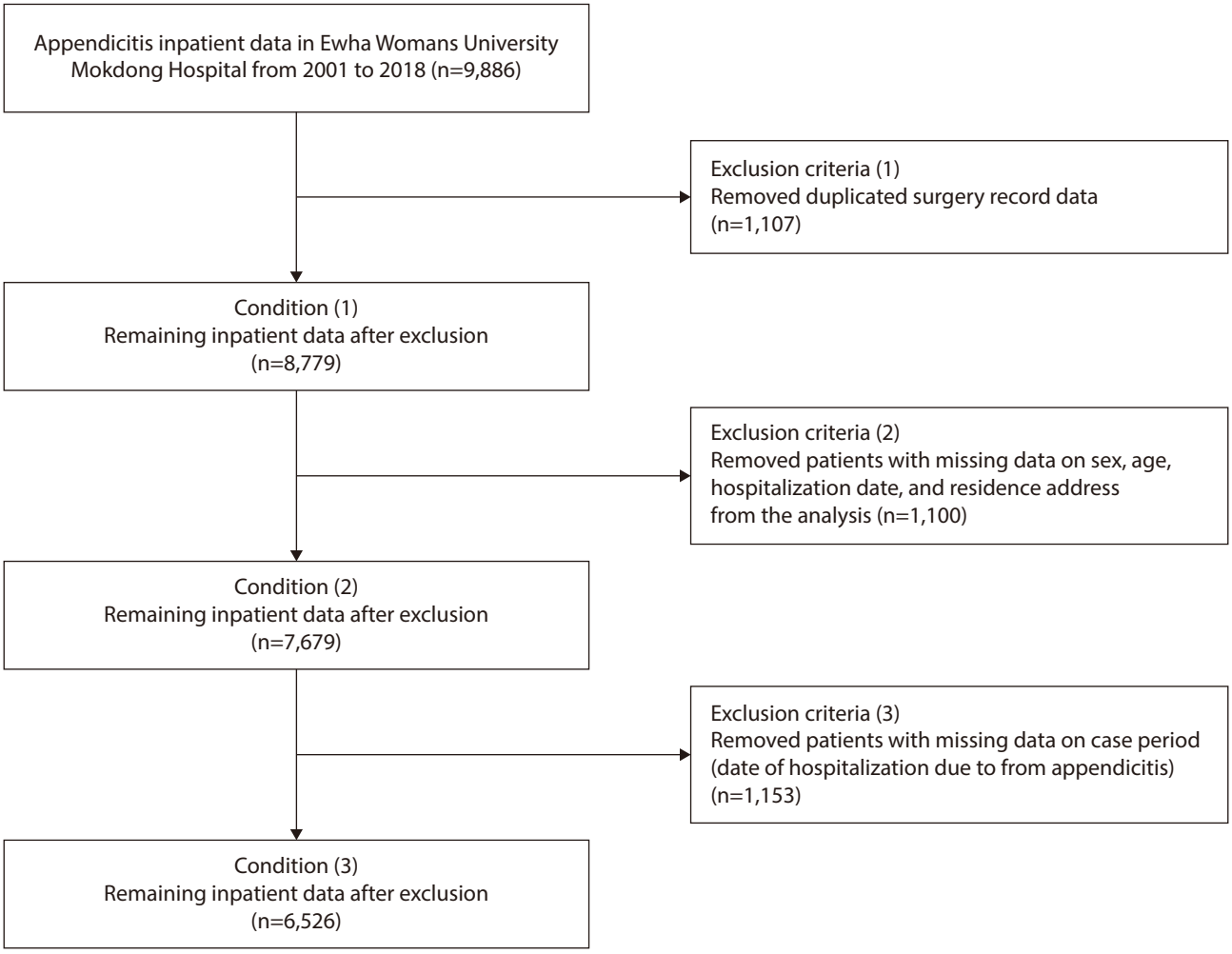

Fig. 1. Identification of appendicitis cases at Ewha Womans University Mokdong Hospital during 2001–2018.

Bias

There was no selection bias reportable in this study.

Study size

Sample size estimation was not performed because this study included all target patients who met the exclusion criteria.

Statistical methods

We analyzed the association between PM_{10} exposure and acute appendicitis using conditional logistic regression (CLR), which is an expanded logistic regression method that accounts for several control periods. This model is particularly effective for case-crossover studies as it accommodates the matched case and control periods within each subject. The CLR model is beneficial in this context because it extends the logistic regression framework to accommodate matched case-control data. This allows for the estimation of exposure-outcome associations while considering the matching structure of the data. Specifically, the CLR model calculates the OR for the occurrence of an event following exposure, taking into account the individual

matching factors [10]. For each case of appendicitis, we matched the day of the appendicitis event with four control periods at weekly intervals, ranging from one to four weeks prior to the event. We then calculated ORs with 95% CIs to assess the relationship between an increase in the interquartile range of PM_{10} levels and the incidence of appendicitis.

We analyzed both the single lag effects (from lag 0 to lag 14) and the moving-average effects (from lag 0–1 to lag 0–14). Subgroup analyses were conducted based on sex (boys/girls), season (warm season: April–September; cold season: October–December), and age groups (under 10, 10–19, 20–29, 30–39, 40–49, 50–59, and 60 years or older). The seasonal categorization reflects the climatic patterns typical of Korea. The selection of specific lag periods was informed by the biological likelihood that the inflammatory response to air pollution exposure could manifest within a few days.

We calculated Spearman's correlation between air pollutants before conducting the two-pollutants model. Pairs of exposure variables that demonstrated a high correlation coefficient (greater than 0.7) were excluded from this analysis. In the two-pollutant model, PM_{10} was set as the main exposure while other air pollutants (SO_2, NO_2, CO, and O_3) were adjusted respectively.

When considering the delay between the actual case date and the date of hospitalization, we calculated the PM_{10} concentrations on the hospital admission day and for 7 and 14 days before admission to evaluate the cumulative effect over several days. The ORs for temperature and humidity were also adjusted and we included the daily average humidity and temperature as confounding variables. The lag effect of exposure considered the moving-average effect. The main results were for those on the The main results were for those on the same-day, 3 day, 7 day, and 14 day moving averages. All the data preprocessing and statistical analysis were performed using R statistical software (Ver. 4.0.0, R Development Core Team, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC, USA), and the α level for statistical significance was 0.05.

Results

Participants' demographic and clinical characteristics

A total of 6,526 appendicitis patients were included in the analysis after excluding those with insufficient essential information, such as duplicated, missing, or unmatched data (Fig. 1). The majority of the study participants resided in Seoul, with the administrative areas detailed in Supplement 1. Overall, 51.09% of the study subjects were male (Table 1); however, gender did not significantly influence the risk of appendicitis (P=0.7141). Analysis of age groups revealed that individuals aged 10–19 years (20.85%) were most susceptible to appendicitis, while those aged 60 years and older (8.99%) were least susceptible. Nonetheless, no significant association was found between age and the risk of appendicitis. The number of appendicitis patients hospitalized during the cold season (52.94%) was higher compared to those admitted in the warm season (47.06%). However, no significant association was observed between the season and the risk of appendicitis (P=0.7408).

Levels of environmental exposure in the case and control periods

Table 2 presents the summary statistics for the exposure data collected during the 2001–2018 study period. We assessed the level of environmental exposure in the case and control groups using the t-test and observed no significant difference in PM_{10} levels between the case and control periods. Supplement 2 contains the summary statistics for daily air pollutant exposure levels measured throughout the study period.

Table 1. Descriptive statistics of the epidemiological characteristics of appendicitis patients (n=6,526) at Ewha Womans University Mokdong Hospital during the study period (2001–2018)

Patients' characteristics	Number of patients (%)	OR (95% CI)	P-value
Sex			
Female	3,192 (48.91)	Ref.	0.7141
Male	3,334 (51.09)	1.011 (0.954–1.072)	
Age, yr			
Age (mean±SD)	31.93±19.08		
<10	704 (11.22)	0.972 (0.853–1.106)	0.6649
10–19	1,308 (20.85)	0.992 (0.884–1.113)	0.8866
20–29	1,066 (17.00)	0.981 (0.870–1.105)	0.7473
30–39	1,189 (18.96)	1.004 (0.893–1.129)	0.9507
40–49	851 (13.57)	0.999 (0.881–1.132)	0.9828
50–60	590 (9.41)	0.999 (0.872–1.145)	0.9932
≥60	564 (8.99)	Ref.	
Season			
Warm season	3,071 (47.06)	Ref.	0.7408
Cold season	3,455 (52.94)	1.010 (0.953–1.071)	

Table 2. Summary statistics for daily exposure variables during the study period (2001–2018)

Exposure variables	Case periods (n=6,526)		Control periods (n=14,539)		Mean difference	95% CI	P-value
	Mean	SD	Mean	SD			
PM_{10} (μg/m^3)	53.31	30.68	52.70	29.43	−0.61	(−1.48, 0.26)	0.19
Mean temperature (°C)	13.41	13.16	13.49	13.32	0.08	(−0.23, 0.38)	0.63
Mean humidity (%)	61.41	15.00	61.48	14.97	0.07	(−0.37, 0.51)	0.75

PM_{10}, particulate matter ≤10 μm in diameter.

Case-crossover analysis: association between PM_{10} exposure and the risk of appendicitis

Table 3 summarizes the results of the case-crossover analysis examining the association between PM_{10} exposure and the risk of appendicitis. The analysis found an association between the risk of appendicitis and the average PM_{10} concentrations 3 days (OR, 1.045; 95% CI, 1.007–1.084) and 7 days (OR, 1.053; 95% CI, 1.005–1.103) prior to hospital admission. However, no association was observed with PM_{10} concentrations on the day of admission or 14 days before admission.

Sex differences: In male patients, the risk of appendicitis was significantly associated with the mean PM_{10} concentrations 3 days (OR, 1.076; 95% CI, 1.023–1.132) and 7 days (OR, 1.103; 95% CI, 1.035–1.176) prior to admission. However, no significant association was observed in female patients at any lag time.

Age differences: Only patients under the age of 10 demonstrated an association between the risk of appendicitis and the PM_{10} concentrations at the time of admission (OR, 1.129; 95% CI, 1.016–1.255), 3 days before admission (OR, 1.140; 95% CI, 1.033–1.258), and 7 days before admission (OR, 1.235; 95% CI, 1.087–1.402).

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Table 3. Risk of appendicitis associated with increases in the interquartile ranges of particulate matter ≤10 μm in diameter (PM_{10}) in various referent time intervals: a case-crossover analysis

Categories	Time intervals			
	Admission day*	3-day moving average†	7-day moving average‡	14-day moving average§
Total	1.027 (0.994–1.060)	1.045 (1.007–1.084)	1.053 (1.005–1.103)	0.938 (0.871–1.009)
Sex				
Male	1.045 (1.001–1.091)	1.076 (1.023–1.132)	1.103 (1.035–1.176)	0.994 (0.897–1.101)
Female	1.003 (0.954–1.054)	1.009 (0.954–1.066)	1.001 (0.935–1.071)	0.883 (0.795–0.981)
Age, yr				
<10	1.129 (1.016–1.255)	1.140 (1.033–1.258)	1.235 (1.087–1.402)	1.042 (0.846–1.282)
10–19	1.013 (0.943–1.089)	1.032 (0.951–1.121)	1.021 (0.919–1.135)	0.897 (0.762–1.056)
20–29	1.013 (0.936–1.096)	1.003 (0.921–1.093)	0.991 (0.891–1.101)	0.839 (0.709–0.993)
30–39	0.998 (0.929–1.072)	1.013 (0.926–1.109)	1.024 (0.914–1.148)	0.900 (0.753–1.075)
40–49	0.985 (0.891–1.088)	1.054 (0.937–1.184)	1.073 (0.936–1.231)	0.940 (0.766–1.153)
50–60	1.063 (0.964–1.171)	1.056 (0.939–1.188)	0.993 (0.859–1.149)	1.053 (0.841–1.319)
≥60	1.069 (0.946–1.207)	1.046 (0.914–1.198)	1.122 (0.955–1.318)	1.111 (0.851–1.149)
Season				
Warm season∏	0.865 (0.817–0.916)	0.807 (0.756–0.860)	0.690 (0.637–0.746)	0.420 (0.369–0.478)
Cold season¶	1.252 (1.192–1.316)	1.424 (1.343–1.509)	1.716 (1.593–1.849)	2.632 (2.334–2.967)

All models were adjusted for daily mean temperature and humidity.
*Current day: PM_{10} exposure level on the day of hospital admission.
†PM_{10} exposure level between current hospital admission day and two days before hospital admission (lag 0–2).
‡PM_{10} exposure level between current hospital admission day and 6 days before hospital admission (lag 0–6).
§PM_{10} exposure level between current hospital admission day and 13 days before hospital admission (lag 0–13).
∏The warm season runs from April to September.
¶The cold season runs from October to March.

Seasonal differences: The risk of appendicitis during the cold season was significantly associated with the mean PM_{10} concentration at various lag times, including at the time of admission (OR, 1.252; 95% CI, 1.192–1.316), three days prior (OR, 1.424; 95% CI, 1.343–1.509), seven days prior (OR, 1.716; 95% CI, 1.593–1.849), and 14 days prior (OR, 2.632; 95% CI, 2.334–2.967). Conversely, no significant association was found between PM_{10} concentration and increased appendicitis risk during the warm season.

Fig. 2 depicts the risk of appendicitis across various reference time intervals, highlighting the associated interquartile ranges of PM_{10} through case-crossover analysis. This analysis includes data from the total patient population, patients aged 0–9, males, and those observed during the cold season over various exposure time intervals. The risk of appendicitis was linked to PM_{10} concentrations when the exposure period ranged from 3 to 7 days prior to hospital admission. In subgroup analyses, a significant association was found between the risk of appendicitis and PM_{10} concentrations during an exposure interval of two to nine days for male patients and those under 10 years of age. Additionally, during the cold season, the risk of appendicitis increased as the exposure interval extended from 1 day to 14 days.

The overall risk of appendicitis during the various reference time intervals associated with increases in the interquartile ranges of PM_{10}, stratified by sex, season, and age are shown in Tables 4, 5. In males, the risk of appendicitis consistently increased over the case period

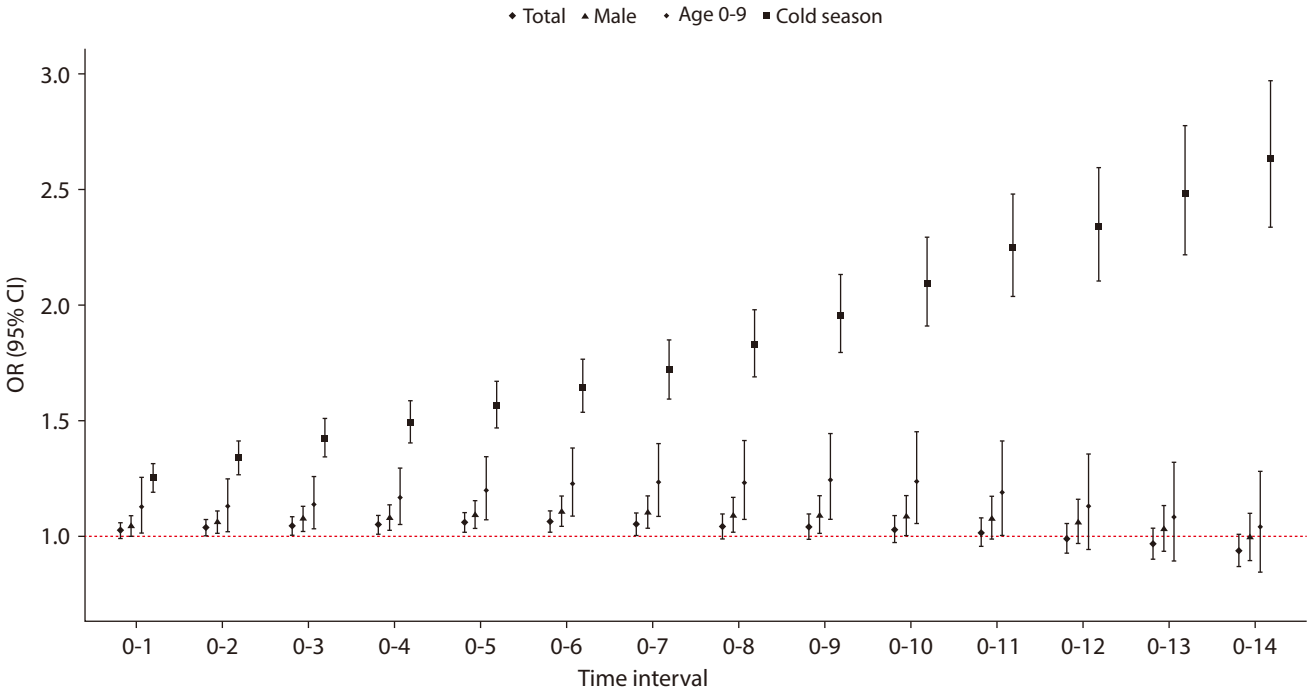

Fig. 2. Risk of appendicitis during various reference time intervals with associated interquartile ranges of PM_{10} using case-crossover analysis, among total patients, patients 0–9 years of age, male patients, and cases that occurred during the cold season. PM_{10}, particulate matter ≤10 μm in diameter.

from one to six days. During the cold season, the longer the case period, the higher the risk of appendicitis, with the greatest risk observed at a 14-day interval (OR, 2.632; 95% CI, 2.334–2.967). The correlation between PM_{10} and other air pollutants is summarized in Supplement 3. Since no air pollutant demonstrated a high correlation with PM_{10}, no variable was excluded from the two-pollutant model. We observed varying trends in the association between PM_{10} and appendicitis across two-pollutant models. While the association remained statistically significant when adjusted for SO_2, CO, and O_3, it was attenuated upon adjustment for NO_2 (Table 6). Since the AirKorea database began recording $PM_{2.5}$ measurements in 2015, we included a sensitivity analysis to assess the impact of $PM_{2.5}$ on the study results using a two-pollutant model with both PM_{10} and $PM_{2.5}$, detailed in Supplement 4.

Discussion

Key results

The present study suggests that short-term exposure to PM_{10} is significantly associated with an increased risk of appendicitis in boys under the age of 10 who were hospitalized during the cold season. To the best of our knowledge, this study is the first to examine the impacts of PM_{10} exposure on acute appendicitis across diverse subgroups and various lag intervals within the Korean population.

Interpretation

Ewha Womans University Mokdong Hospital, affiliated with Ewha Medical School, serves as the sole community-based tertiary medical institution for a population of 1.5 million in

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Table 4. Overall risk of appendicitis during various referent time intervals associated with increases in the interquartile ranges of PM_{10}, stratified by sex and season

Time intervals	Total	Sex		Season	
		Male	Female	Warm season*	Cold season†
0–1	1.027 (0.994–1.060)	1.045 (1.001–1.091)	1.003 (0.954–1.054)	0.865 (0.817–0.916)	1.252 (1.192–1.316)
0–2	1.037 (1.002–1.074)	1.062 (1.014–1.112)	1.007 (0.956–1.061)	0.827 (0.777–0.879)	1.338 (1.268–1.412)
0–3	1.045 (1.007–1.084)	1.076 (1.023–1.132)	1.009 (0.954–1.066)	0.807 (0.756–0.860)	1.424 (1.343–1.509)
0–4	1.051 (1.012–1.091)	1.080 (1.026–1.137)	1.018 (0.963–1.076)	0.800 (0.750–0.854)	1.493 (1.405–1.586)
0–5	1.061 (1.019–1.104)	1.094 (1.036–1.155)	1.024 (0.966–1.086)	0.781 (0.730–0.836)	1.567 (1.469–1.671)
0–6	1.064 (1.020–1.110)	1.107 (1.043–1.174)	1.019 (0.957–1.084)	0.745 (0.693–0.801)	1.647 (1.536–1.765)
0–7	1.053 (1.005–1.103)	1.103 (1.035–1.176)	1.001 (0.935–1.071)	0.690 (0.637–0.746)	1.716 (1.593–1.849)
0–8	1.042 (0.992–1.096)	1.091 (1.018–1.169)	0.991 (0.921–1.066)	0.636 (0.583–0.693)	1.829 (1.688–1.981)
0–9	1.042 (0.987–1.099)	1.092 (1.015–1.176)	0.988 (0.914–1.068)	0.591 (0.538–0.648)	1.956 (1.795–2.131)
0–10	1.031 (0.974–1.092)	1.086 (1.003–1.176)	0.974 (0.897–1.059)	0.552 (0.500–0.611)	2.092 (1.908–2.294)
0–11	1.017 (0.956–1.081)	1.078 (0.990–1.174)	0.956 (0.875–1.044)	0.529 (0.475–0.588)	2.246 (2.034–2.479)
0–12	0.988 (0.926–1.054)	1.061 (0.970–1.161)	0.917 (0.836–1.006)	0.496 (0.443–0.556)	2.335 (2.102–2.594)
0–13	0.966 (0.902–1.035)	1.030 (0.936–1.135)	0.903 (0.818–0.997)	0.462 (0.409–0.522)	2.478 (2.214–2.774)
0–14	0.938 (0.871–1.009)	0.994 (0.897–1.101)	0.883 (0.795–0.981)	0.420 (0.369–0.478)	2.632 (2.334–2.967)

All models were adjusted for daily mean temperature and humidity.

PM_{10} , particulate matter ≤10 μm in diameter.

*The warm season runs from April to September.

†The cold season runs from October to March.

the Yangcheon-gu district of Seoul. Each year, the hospital performs approximately 500 to 600 appendectomies, with the majority of these cases being emergency surgeries for acute appendicitis. Over the 18-year study period, about 72% of the appendicitis patients came from three neighboring administrative districts. In terms of exposure validity, we accessed national air pollution data from AirKorea for analysis. We then correlated this data with our patient records, matching it to the inpatients' home addresses. As for the validity of our outcome definition, all study participants underwent an appendectomy following their diagnosis. This procedure followed a standardized method for critical pathways and was verified by biopsy, ensuring the accuracy and consistency of our outcome definitions.

Regarding sex differences, biological differences, such as variations in immune response and hormonal influences, may make males more susceptible to inflammatory triggers caused by air pollution. Additionally, behavioral factors, including differences in outdoor activities and exposure levels, could contribute to the observed disparity [12].

Children under 10 may be more vulnerable to PM_{10} exposure due to their developing respiratory and immune systems, which are more susceptible to inflammatory agents. Their higher breathing rates relative to body size and increased time spent outdoors can lead to greater exposure to air pollutants. Additionally, because their immune systems are not fully developed, they are less capable of handling environmental insults such as air pollution [13]. Cold weather can exacerbate the effects of PM_{10} on respiratory and immune systems, potentially triggering inflammatory responses more readily [14].

This study observed that seasonal variations in air pollution exposure levels significantly

Table 5. Overall risk of appendicitis during various reference time intervals associated with increases in the interquartile range of PM_{10}, stratified by age groups

Lag days	Age (yr)						
	<10	10–20	20–29	30–39	40–49	50–59	≥60
0–1	1.129 (1.016–1.255)	1.013 (0.943–1.089)	1.013 (0.936–1.096)	0.998 (0.929–1.072)	0.985 (0.891–1.088)	1.063 (0.964–1.171)	1.069 (0.946–1.207)
0–2	1.130 (1.023–1.248)	1.022 (0.949–1.100)	1.022 (0.942–1.109)	1.001 (0.921–1.087)	1.020 (0.915–1.138)	1.066 (0.954–1.190)	1.043 (0.924–1.178)
0–3	1.140 (1.033–1.258)	1.032 (0.951–1.121)	1.003 (0.921–1.093)	1.013 (0.926–1.109)	1.054 (0.937–1.184)	1.056 (0.939–1.188)	1.046 (0.914–1.198)
0–4	1.169 (1.054–1.297)	1.038 (0.953–1.129)	1.008 (0.927–1.095)	1.027 (0.936–1.126)	1.065 (0.944–1.202)	1.034 (0.920–1.162)	1.056 (0.927–1.203)
0–5	1.201 (1.074–1.342)	1.044 (0.955–1.142)	1.012 (0.927–1.106)	1.045 (0.950–1.149)	1.084 (0.955–1.232)	1.017 (0.897–1.152)	1.760 (0.938–1.234)
0–6	1.227 (1.090–1.382)	1.046 (0.948–1.153)	1.016 (0.924–1.118)	1.031 (0.928–1.145)	1.082 (0.954–1.228)	1.005 (0.879–1.148)	1.109 (0.956–1.287)
0–7	1.235 (1.087–1.402)	1.021 (0.919–1.135)	0.991 (0.891–1.101)	1.024 (0.914–1.148)	1.073 (0.936–1.231)	0.993 (0.859–1.149)	1.122 (0.955–1.318)
0–8	1.233 (1.076–1.414)	1.007 (0.899–1.128)	0.972 (0.867–1.090)	1.011 (0.897–1.141)	1.050 (0.908–1.214)	0.997 (0.853–1.165)	1.132 (0.953–1.346)
0–9	1.245 (1.074–1.444)	1.026 (0.908–1.160)	0.964 (0.853–1.090)	0.998 (0.878–1.136)	1.033 (0.886–1.206)	0.982 (0.831–1.160)	1.156 (0.961–1.391)
0–10	1.238 (1.055–1.452)	1.014 (0.890–1.155)	0.947 (0.830–1.080)	0.988 (0.861–1.134)	1.023 (0.869–1.204)	0.979 (0.819–1.170)	1.157 (0.945–1.417)
0–11	1.192 (1.005–1.414)	0.998 (0.869–1.146)	0.915 (0.797–1.050)	0.994 (0.856–1.154)	1.011 (0.848–1.204)	1.003 (0.831–1.211)	1.150 (0.925–1.429)
0–12	1.131 (0.944–1.357)	0.962 (0.831–1.112)	0.879 (0.760–1.017)	0.970 (0.829–1.134)	0.991 (0.823–1.194)	1.031 (0.844–1.259)	1.122 (0.891–1.414)
0–13	1.085 (0.892–1.320)	0.929 (0.795–1.084)	0.866 (0.740–1.013)	0.937 (0.793–1.107)	0.969 (0.798–1.177)	1.058 (0.857–1.308)	1.105 (0.864–1.415)
0–14	1.042 (0.846–1.282)	0.897 (0.762–1.056)	0.839 (0.709–0.993)	0.900 (0.753–1.075)	0.940 (0.766–1.153)	1.053 (0.841–1.319)	1.111 (0.851–1.149)

All models were adjusted for daily mean temperature and humidity.
PM_{10}, particulate matter ≤10 μm in diameter.

impacted the risk of appendicitis. Interestingly, our findings contradict those of previous studies, which suggested that appendicitis incidence was higher in the summer due to increased outdoor activities [15]. Our results lead us to hypothesize that climate factors, such as temperature and humidity, play a more significant role in increasing appendicitis risk than does outdoor activity. Additionally, the distinct weather conditions associated with Korea's four seasons may also influence the results observed in our study.

Our study has several key strengths and novelties. First, it specifically targeted the Korean population. Despite Korea's relatively high air pollution levels compared to Western countries, to our knowledge, this is the first study utilizing Korean data to explore the relationship between PM_{10} and appendicitis. Second, our methodology is distinctive as it aimed to categorize cases across various dimensions, including age, sex, and season. While appendicitis is recognized as an acute condition linked to short-term effects of PM_{10}, the critical exposure period remains unclear. Therefore, diverging from previous research that primarily examined a lag effect of fewer than 3 days, our study investigated the impact of PM_{10} over a 14-day period prior to hospital admission.

Table 6. Risk of appendicitis during various reference time intervals associated with increases in the interquartile range of PM_{10} in the two-pollutant models

Lag	Single mollutant	Two pollutant models			
	PM_{10}	Adjusted SO_2	Adjusted NO_2	Adjusted CO	Adjusted O_3
0–1	1.027 (0.994–1.060)	1.033 (0.995–1.071)	1.005 (0.970–1.042)	1.017 (0.979–1.056)	1.017 (0.979–1.056)
0–2	1.037 (1.002–1.074)	1.041 (1.001–1.082)	1.009 (0.971–1.049)	1.029 (0.988–1.071)	1.029 (0.988–1.071)
0–3	1.045 (1.007–1.084)	1.049 (1.005–1.094)	1.011 (0.970–1.054)	1.035 (0.991–1.081)	1.035 (0.991–1.081)
0–4	1.051 (1.012–1.091)	1.049 (1.005–1.095)	1.018 (0.976–1.061)	1.043 (0.999–1.090)	1.043 (0.999–1.090)
0–5	1.061 (1.019–1.104)	1.058 (1.011–1.108)	1.030 (0.985–1.077)	1.059 (1.011–1.109)	1.059 (1.011–1.109)
0–6	1.064 (1.020–1.110)	1.060 (1.010–1.113)	1.039 (0.991–1.089)	1.067 (1.016–1.120)	1.067 (1.016–1.120)
0–7	1.053 (1.005–1.103)	1.044 (0.990–1.101)	1.032 (0.980–1.086)	1.064 (1.008–1.123)	1.064 (1.008–1.123)
0–8	1.042 (0.992–1.096)	1.029 (0.971–1.090)	1.026 (0.970–1.085)	1.066 (1.006–1.129)	1.066 (1.006–1.129)
0–9	1.042 (0.987–1.099)	1.027 (0.965–1.093)	1.032 (0.972–1.096)	1.077 (1.012–1.147)	1.077 (1.012–1.147)
0–10	1.031 (0.974–1.092)	1.002 (0.938–1.072)	1.020 (0.956–1.088)	1.062 (0.993–1.136)	1.062 (0.993–1.136)
0–11	1.017 (0.956–1.081)	0.995 (0.926–1.069)	1.012 (0.945–1.085)	1.055 (0.981–1.134)	1.055 (0.981–1.134)
0–12	0.988 (0.926–1.054)	0.962 (0.891–1.038)	0.986 (0.916–1.062)	1.029 (0.952–1.111)	1.029 (0.952–1.111)
0–13	0.966 (0.902–1.035)	0.941 (0.868–1.020)	0.975 (0.901–1.055)	1.017 (0.937–1.105)	1.017 (0.937–1.105)
0–14	0.938 (0.871–1.009)	0.913 (0.837–0.996)	0.960 (0.882–1.044)	1.003 (0.918–1.096)	1.003 (0.918–1.096)

All models were adjusted for daily mean temperature and humidity.
PM_{10}, particulate matter ≤10 μm in diameter; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone.

Comparison with previous studies

In Linfen City, China, an increase of 10 μg/m^3 in pollutant levels, considering a 1-day lag, was associated with heightened health risks from January to December 2018. Specifically, the relative risks and their 95% CIs were as follows: PM_{10}: 1.0179 (1.0129–1.0230), SO_2: 1.0236 (1.0184–1.0288), and NO_2: 1.0979 (1.0704–1.1262). The study indicated that men and young adults aged 21–39 years were particularly susceptible to the effects of air pollution. Furthermore, the impact of air pollutants was more pronounced during the colder months, though the seasonal variation was not statistically significant [16]. In Italy, factors predicting perforated appendicitis included consultation delay (OR, 1.621; 95% CI, 1.288–2.039; P<0.001) and the 2-day lag mean concentration of PM_{10} (OR, 1.066; 95% CI, 0.007–1.130; P=0.029) during the period from January 1 to December 31, 2014 [17]. In Taiwan, when temperatures fell below 23°C, higher levels of PM_{10} were linked to a significant increase in hospital admissions for appendicitis between 2009 and 2013 [7]. In New Zealand, no correlation was found between PM_{10} levels and admissions for appendicitis from January to December 2018 [18]. While the above-mentioned three studies found associations between PM_{10} and appendicitis admissions, other results concerning age and climate varied.

Limitations

Our study has several limitations. First, since nationwide air pollutant data are only available by district, we could not account for variations between smaller regional units. Consequently, we cannot ensure a precise match between the pollution data from our database and the actual pollution levels in the patients' neighborhoods.

Second, we did not take into account the socioeconomic and lifestyle data of the patients; therefore, we did not categorize our patients as outdoor or indoor workers to explore any

potential association between outdoor activity and appendicitis. However, it is important to note that appendicitis is an acute condition, and the data were gathered from a single institution located near where most patients reside. We assumed that the levels of air pollution exposure were varied across different neighborhoods. Additionally, the use of a case-crossover data analysis helped to eliminate bias from personal confounders.

Third, since our AirKorea database only began recording $PM_{2.5}$ measurements in 2015, we were unable to assess the effects of $PM_{2.5}$ across all participants. Instead, we conducted a two-pollutant model analysis using PM_{10} and $PM_{2.5}$ data from cases recruited between 2015 and 2018. Our findings indicate that the overall effect size of $PM_{2.5}$ was greater than that of PM_{10}, and it was associated with smaller P-values. Therefore, further studies that focus on $PM_{2.5}$ as the primary exposure are warranted.

Suggestion for further studies

These comprehensive analyses may offer additional insights into preventive measures for appendicitis that are typically overlooked in clinical practice. Further research is essential to enhance our understanding of appendicitis epidemiology and to help decrease the incidence of the condition.

Conclusion

Our study revealed a positive association between PM_{10} concentration and the incidence of appendicitis, suggesting that short-term exposure to PM_{10} may trigger appendicitis. The risk was notably higher in boys under the age of 10 and during the colder seasons. However, these findings should not be interpreted as direct evidence that PM_{10} directly causes appendicitis. To further investigate these relationships, additional ecological and large-scale epidemiological studies are necessary.

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Conflict of interest

Eunhee Ha has been a dean of the Ewha Womans University College of Medicine since August 2021. Ryung-Ah Lee has been an associate editor of the *Ewha Medical Journal* since August 2023. However, they were not involved in the peer review process or decision-making.

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

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Data availability

Research data and R code is available upon request to the corresponding author. Please contact them for the cooperative studies.

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Not applicable.

Supplementary materials

Supplementary materials are available from: https://doi.org/10.12771/emj.2024.e38.

Supplement 1. Distribution of residential areas (administrative districts) of appendicitis (n=6,526)
Supplement 2. Summary statistics for daily air pollutants measured at monitoring stations during the study period of 2001–2018
Supplement 3. Spearman correlation matrix between daily air pollutants during the study period (2001–2018)
Supplement 4. Risk of appendicitis associated with increases in the PM_{10} and $PM_{2.5}$ (study period: 2015-2018)

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Original Article

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Straightforward, safe, and efficient interlocking screw insertion during intramedullary nailing using a Steinmann pin and hammer: a comparative study

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Keywords
Bone screws; Cost-benefit analysis; Femur; Fracture; Radiation dosage

Objectives: Accurately targeting distal nail holes and placing distal interlocking screws pose challenges during intramedullary nailing. This study proposes a straightforward technique for distal locking screw insertion using a Steinmann pin, eliminating the need to reposition the pin or drill bit.

Methods: We utilized 18 Sawbones femur models and intramedullary femur nails. A first-year resident created two distal locking holes on each model, employing both the conventional freehand technique and a novel method involving a Steinmann pin and hammer under image intensification. These techniques were evaluated based on three parameters: (1) the time required to create distal locking holes, measured from the moment the pin was positioned at the center of the hole until the far cortex was drilled through the interlocking hole; (2) the radiation dose (in mrem/h), as estimated with a personal gamma radiation dosimeter; and (3) the number of failures, defined as the creation of more than one hole in the near and far cortex.

Results: The new technique was associated with a lower radiation dose (P=0.0268) and fewer failures (P=0.0367) than the conventional approach. Additionally, the time required to establish distal holes was shorter using the new technique compared to the conventional method (P=0.0217).

Conclusion: The creation of distal interlocking holes with a Steinmann pin and hammer is accurate, efficient, and cost-effective.

Introduction

Background/rationale

Intramedullary (IM) nailing is widely used in orthopedic practice and has recently become the gold standard for treating femoral and tibial diaphyseal fractures. This method is also occasionally employed for humeral shaft fractures due to its load-sharing characteristics [1,2]. To achieve rotational stability, surgeons may insert proximal and distal interlocking screws. While proximal screws are relatively straightforward to place using an aiming device, the placement of distal screws presents a challenge. This difficulty arises from the deformation of the nail within the

medullary canal, which leads to misalignment of the distal locking holes. Consequently, distal interlocking screws must be inserted using a freehand technique.

Targeting the distal nail holes and accurately placing the distal interlocking screws with a freehand approach can be challenging, even for an experienced surgeon. This freehand method of distal screw insertion also involves a radiolucent drive, which may not be available. An alternative is to continuously monitor the projection of the drill bit's tip. However, this approach is difficult and necessitates multiple radiological exposures. Ikpeme et al. reported that the distal interlocking procedure is time-consuming and increases the duration of surgery [3]. If the hole for the interlocking screw is drilled incorrectly, the pre-existing path can interfere with the creation of a new hole, as the drill bit may deviate and slide into the previously drilled hole.

The use of multiple drilling attempts can result in iatrogenic fractures and increased radiation exposure for both patient and surgeon [4,5]. In response, studies have introduced various modifications to the common freehand technique [6–9]. These approaches primarily involve the use of a smooth pin that is subsequently removed and replaced with a drill bit or the placement of a cannulated reamer over the pin. However, procedures that require reinserting the drill after pin removal are time-consuming and prone to failure [10].

Objectives

In this study, we introduce a straightforward method for the insertion of distal interlocking screws using a Steinmann pin. This technique eliminates the need for repositioning the pin or drill bit, offering an accurate and time-efficient alternative to the conventional method.

Methods

Ethics statement

No institutional review board approval or informed consent was necessary for this study, as the materials used were commercially purchased Sawbones.

Study design

In this comparative study, we evaluated the accuracy and time efficiency of the new technique. The findings were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, which is accessible at https://www.strobe-statement.org/.

Setting

A first-year resident with no prior experience in inserting distal interlocking screws experimented on 18 femur Sawbones models (Sawbones, Vashon, WA, USA) with femoral IM nails (unreamed femoral nail; Synthes, Oberdorf, Switzerland). Following the insertion of the IM nail and proximal locking screws, the resident created two distal locking holes using both the conventional freehand technique and the new method, under image intensifier guidance. The study of this surgical technique was conducted at Gyeongsang National University Changwon Hospital.

Surgical technique

A Steinmann pin matching the size of the drill bit was utilized; specifically, 1/8-inch (3.2 mm) and 5/32-inch (4.0 mm) Steinmann pins were employed for the tibia and femur, respectively. In

the proposed technique, the Sawbones model is placed in a supine position on the operating table, with the limb adequately stabilized. Following thorough sterilization of the surgical site, the C-arm is positioned to be perpendicular to the limb. This orientation ensures that the screw holes appear as perfect circles on the fluoroscopic image, a critical factor for accurate visualization and the success of subsequent procedural steps.

The entry point for the Steinmann pin is determined with a high level of accuracy that reflects the precision of the freehand technique. The drill is then equipped with a Steinmann pin, positioning the tip in direct contact with the near cortex. To obtain a clear fluoroscopic image without the interference of a drill shadow, the Steinmann pin is held at an oblique angle to the shaft. Importantly, the tip of the pin must be precisely centered within the locking hole. Adjustments can be made in the proximal, distal, anterior, or posterior directions until optimal centering is achieved. Once the pin is centered, the drill is aligned parallel to the C-arm X-ray beam, and drilling into the near cortex begins.

During the drilling process, the drill is periodically tilted to ensure that the Steinmann pin remains centered in the hole. After confirming the correct positioning, drilling continues toward the far cortex. If the Steinmann pin contacts the nail or deviates from its path relative to the hole, the handpiece is detached from the pin, which remains inserted in the near cortex. The Steinmann pin is then adjusted by bending or tilting, as directed by fluoroscopic guidance, to realign it with the hole (Fig. 1).

Once the orientation is verified, the Steinmann pin is tapped with a hammer to advance it through the interlocking hole until it reaches the far cortex. Once in place, the pin is clamped into the drilling machine, and drilling through the far cortex is completed. An interlocking screw is then inserted through the newly created hole to ensure secure fixation (Figs. 2, 3).

Finally, the correct placement of the interlocking screw is verified using fluoroscopy. The surgical site is then closed in accordance with the standard protocol, and an appropriate dressing is applied. This meticulous technique increases the precision of distal locking hole placement during IM nailing, minimizing potential complications and improving surgical outcomes.

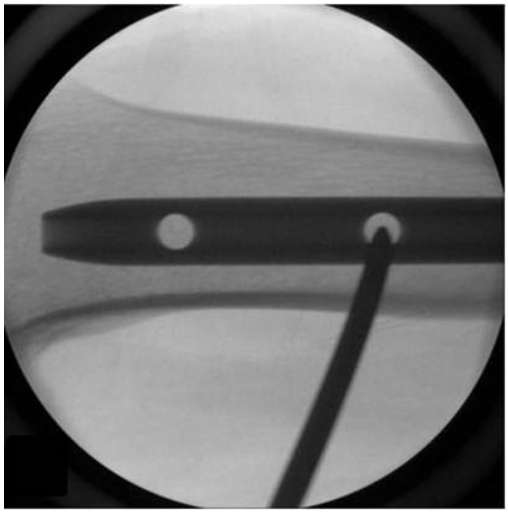

Fig. 1. The drilling machine was detached from the Steinmann pin after insertion into the near cortex. Subsequently, the pin was bent to align with the path to the hole, under image intensifier guidance.

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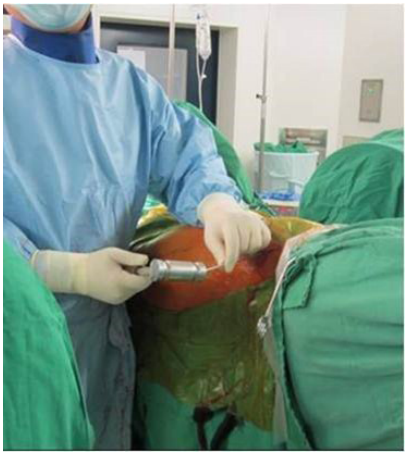

Fig. 2. Once the direction was confirmed, the Steinmann pin was tapped into place with a hammer.

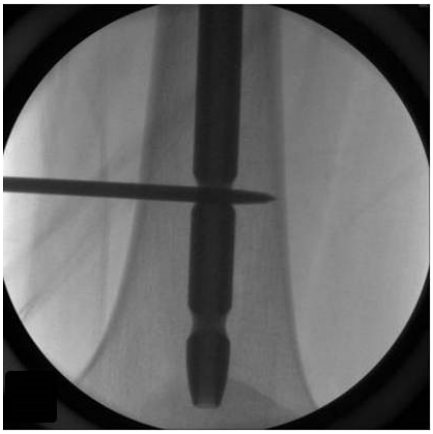

Fig. 3. A Steinmann pin is shown reaching the far cortex after passing through the interlocking hole.

Materials

Each of the 18 Sawbones models was utilized for both new and conventional techniques.

Variables (study outcomes)

The outcome variables included the duration required to perform the surgical technique, the radiation dose to which the Sawbones were exposed, and the number of attempts required to successfully execute the technique.

Data sources and measurement

The measurement methods were as follows. (1) The time taken to create the distal locking holes was recorded. This interval began at the Steinmann's pin was positioned at the center of the hole and continued until the far cortex was drilled through the interlocking hole. (2) Radiation dose (mrem/h) was measured. A personal gamma radiation dosimeter (EcotestCARD; ECOTEST, Lviv, Ukraine) was attached to the lead apron worn by the operator to assess the radiation dose received throughout the entire procedure. (3) The frequency of attempts was noted, with failure defined as the establishment of more than one hole in the near and far cortex. The research

data are available in Dataset 1.

Bias

This study involved no selection bias, as the same purchased models were used for both groups.

Study size

Sample size estimation was not performed.

Statistical methods

We compared the results associated with the conventional and new techniques. Given the absence of normal distribution, all variables were analyzed using non-parametric statistical methods. The P-value was determined through the Wilcoxon rank-sum test. For statistical analyses, we utilized DBSTAT 5.0 (DBSTAT, Seoul, Korea), which can be accessed at http://dbstat.com/.

Results

Participants

The 36 trials involved commercially purchased materials, and no demographic data were collected.

Main results

Surgical duration

The median times required for the conventional and new techniques were 29.5 and 20.0 seconds, respectively. The difference between groups was significant (Wilcoxon W=260.5, corrected Z=−2.963, P=0.0217, Fig. 4).

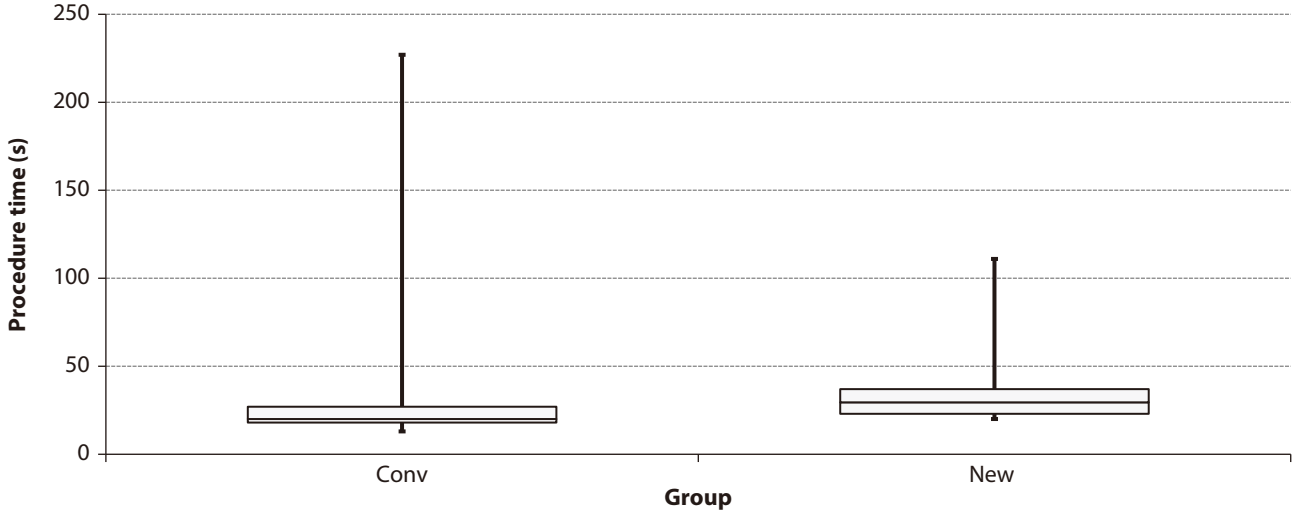

Fig. 4. Comparison of procedure time between the conventional technique (Conv) and the new method (New) for intramedullary nailing. Values are presented in seconds.

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Radiation exposure

The median radiation doses to which the Sawbones were exposed were 1.81 millirem/hour for the conventional technique and 0.87 millirem/hour for the new method. The dose received with the new technique was significantly lower than that received with the conventional approach (Wilcoxon W=263.0, corrected Z=−2.2150, P=0.0268, Fig. 5).

Attempts required for success

The new technique required only one attempt to succeed, whereas the conventional technique took a maximum of four attempts (Wilcoxon W=297.0, corrected Z=−2.0889, P=0.0367, Fig. 6).

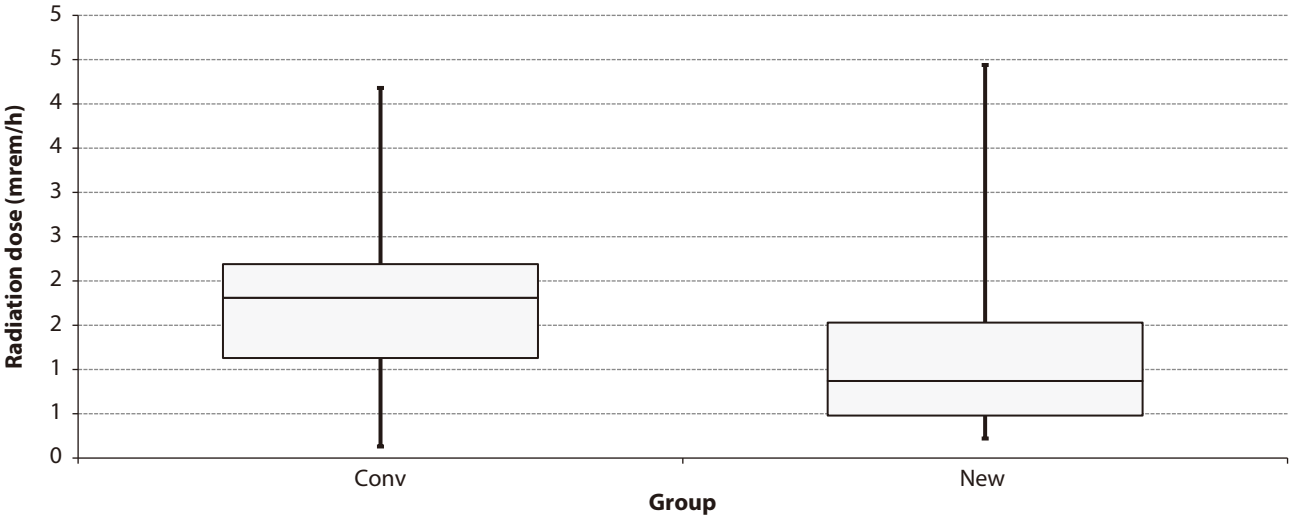

Fig. 5. Comparison of radiation dose administered to the Sawbones between the conventional technique (Conv) and the new method (New) for intramedullary nailing. Values represent doses of radiation, in millirem/hour.

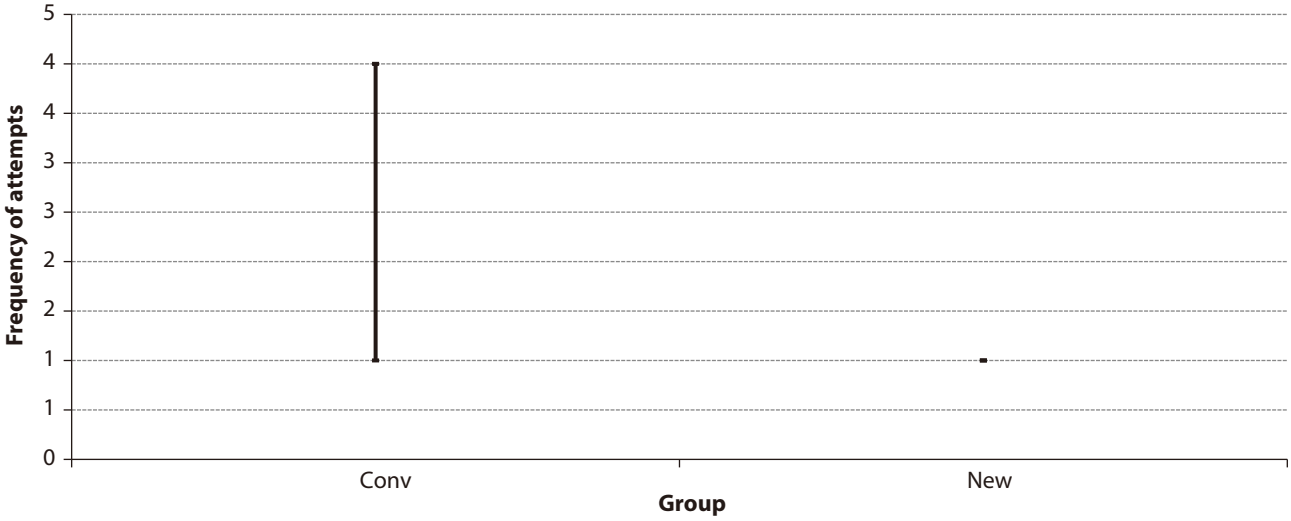

Fig. 6. Comparison of the frequency of attempts between the conventional technique (Conv) and the new method (New) for intramedullary nailing. Values represent frequencies of attempts.

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Discussion

Key results

A new technique for interlocking screw insertion during IM nailing, which utilizes a Steinmann pin and hammer, offers surgeons a time-saving approach with lower radiation exposure and fewer attempts compared to the conventional method not employing a Steinmann pin and hammer.

Interpretation

Two considerations are key when creating interlocking holes: the entry point and the drilling direction. The initial and most critical step involves precisely adjusting the C-arm to align the interlocking holes so they appear as a perfect circle. Drilling should commence only after achieving this circle. Our technique specifically addresses the second consideration, facilitating easy drilling. The most difficult aspect of drilling is that if the drill bit creates an incorrect hole, subsequent attempts to establish a correct pathway often fail because the drill bit tends to slip into the previous hole. In our study, we trained an inexperienced resident who then achieved a near 100% success rate, demonstrating an acceptable learning curve for this challenging procedure. Additionally, our technique resulted in less radiation exposure than the conventional method, despite a longer mean operative time. However, the conventional technique included an outlier value, indicating that once an error occurs, the procedure can take markedly longer to complete (Dataset 1).

Our proposed technique was designed to increase the precision of drill orientation. With the conventional method, the drill bit may not align correctly with the intended bone path, potentially failing to penetrate the near and far cortex holes of the nail at the appropriate angle. If the drill bit passes through the near cortex hole and the tip abuts the far hole, repositioning the drill bit can be challenging due to the pre-existing bone path. Should the surgeon opt to replace the drill bit with a Steinmann pin, the pin can be gently tapped into the far cortex hole of the nail, where it will slide into place. Notably, a Steinmann pin could also be utilized from the outset of the procedure.

A Steinmann pin was chosen over a drill bit for several reasons. First, a drill bit has a smaller core diameter and is stiffer than a Steinmann pin, increasing the risk of breakage when redirecting the bit within the bone. Second, the use of a Steinmann pin eliminates the need for secondary drilling, as the pin matches the drill bit in diameter. Third, unlike a drill bit, a Steinmann pin can be driven into the bone with a hammer. Finally, the Steinmann pin's tip is both narrower and sharper than that of the drill bit, allowing it to gain purchase with the bone even if the initial hole is slightly misaligned.

We opted for a hammer instead of a drill because a drill attached to a Steinmann pin often obscures the radiologic view of the hole. Additionally, the drilling process can cause more damage to both the Steinmann pin and the nail. In contrast, when tapping the Steinmann pin with a hammer, the hole remains constantly visible. This method allows the Steinmann pin to slide into the hole without grinding against the nail. When the entry point is accurate, the success rate of inserting a Steinmann pin is nearly 100%. Even with a slightly inaccurate starting point, an interlocking hole can still be created using the hammer technique. However, this may result in the oblique insertion of the interlocking screw. Our technique appears beneficial and effective when a substantial distance separates the near and far cortices, or when the insertion site is located at the metaphysis rather than the diaphysis. Moreover, using a hammer to insert the Steinmann pin can help prevent damage to the surrounding soft tissue.

Limitations

This study had several limitations. First, the clinical procedure differs from that performed on the Sawbones. In clinical practice, the soft tissues surrounding the femur could impede the accuracy of initial pin placement and the maintenance of the angle and location of the pin during drilling. Moreover, Sawbones are easier to drill than living bones, particularly those of younger individuals. Nevertheless, this study demonstrated significant differences between the two techniques when performed on the same Sawbones model. We expect these differences to be reproducible in real-world scenarios, although it may take longer to complete the procedure with either technique. Second, the sample size was primarily determined by the availability of resources rather than statistical power calculations. Finally, bias is a possibility, as the resident was aware of the technique being used. To address this concern and avoid a ceiling effect, we ensured that the resident was thoroughly trained in both techniques prior to the experiment to minimize any learning curve effects. Furthermore, we randomized the order in which the techniques were applied to each specimen to reduce the impact of systematic bias.

Generalizability

This new technique may aid in the insertion of interlocking screws during IM nailing procedures in hospitals around the world. Several companies manufacture instruments to support the precise placement of distal interlocking screws, such as the Radiolucent Drive (Synthes) and the Trigen Sureshot (Smith & Nephew, London, UK) [8]. However, these tools are expensive, and surgeons in underdeveloped or developing nations often cannot afford them. Our method employs a relatively inexpensive Steinmann pin, eliminating the need for costly equipment. Additionally, this technique is applicable to all types of IM nailing, including that of the humerus and tibia.

Conclusion

Our technique, which employs a Steinmann pin and hammer, is a reliable, reproducible, and cost-efficient approach for the creation of distal interlocking holes.

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Funding acquisition: not applicable
Writing - original draft: Deslivia MF, Lee SJ
Writing - review & editing: Deslivia MF, Kim HJ, Kim SH, Lee SJ

Conflict of interest

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

Funding
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Data availability
Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/ND7IIK

Dataset 1. Results of the comparison between new and conventional methods in terms of time savings, radiation dose exposure to the Sawbones, and number of attempts

Acknowledgments
Not applicable.

Supplementary materials
Not applicable.

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Original Article

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Motivations, positive experiences, and concept changes of medical students in Korea after participating in an experiential entrepreneurship course: a qualitative study

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Keywords
Entrepreneurship; Focus groups; Medical students; Motivation; Republic of Korea

Objectives: This study explored the experiences of medical students enrolled in an elective course titled "Healthcare Innovation and Women's Ventures II" at Ewha Womans University College of Medicine. The research questions were as follows: First, what motivated medical students to participate in the experiential entrepreneurship course? Second, what experiences did the students have during the course? Third, what changes did the students undergo as a result of the course?

Methods: Focus group interviews were conducted with six medical students who participated in the experiential entrepreneurship course from February 13 to 23, 2024.

Results: The analysis identified three domains, seven categories, and 17 subcategories. In terms of motivations for enrolling in the experiential entrepreneurship course, two categories were identified: "existing interest" and "new exploration." With respect to the experiences gained from the course, three categories emerged: "cognitive experiences," "emotional experiences," and "behavioral experiences." Finally, two categories were identified concerning the changes participants experienced through the course: "changes related to entrepreneurship" and "changes related to career paths."

Conclusion: Students were motivated to enroll in this course by both their existing interests and their desire to explore new areas. Following the course, they underwent cognitive, emotional, and behavioral changes. Their perceptions of entrepreneurship and career paths were significantly altered. This study is important because it explores the impact of entrepreneurship education in medical schools from the students' perspective.

Introduction

Background

In 2013, the Korean government launched the Five-Year Plan for University Entrepreneurship Education, marking it as a national project under the leadership of the Ministry of Education, the Ministry of Science, ICT and Future Planning, and the Small and Medium Business Administration. This initiative highlighted the importance of industry-academia collaboration and entrepreneurship education through the Leaders in Industry-University Cooperation project [1]. By recognizing creativity in entrepreneurship education, there is an enhancement in students' engagement with their work, which in turn positively affects their self-efficacy [2]. Programs that focus on case studies, including entrepreneurial mentoring and consulting, offer students valuable indirect entrepreneurial experiences that positively shape their entrepreneurial intentions [3,4].

Entrepreneurship education in medical schools is notably scarce, contrasting with the broader trend in general education. Entering medical school generally implies a commitment to pursuing a career as a physician, which means that medical students experience a distinct process of career exploration and transition compared to their peers in other university programs [5]. Given that the career exploration and choices of medical students profoundly affect their personal fulfillment [6], job satisfaction [7], and overall professional life [8], it is crucial to offer sufficient opportunities for such education during their medical school years. Unfortunately, research on entrepreneurship education within medical schools is virtually nonexistent.

Objectives

This study examined the experiences of students enrolled in the "Healthcare Innovation and Women's Ventures II" course, a free elective practicum offered at Ewha Womans University College of Medicine. The research questions addressed in this study are as follows: First, what motivated medical students to participate in this practice-based entrepreneurship course? Second, what positive experiences did medical students gain from the course? Third, what changes occurred in the medical students as a result of their participation in the course?

Methods

Ethics statement

The students' informed consent was obtained when conducting the survey.

Research team and reflexivity

Personal characteristics of the research team

Interviewer/facilitator: Somi Jeong.

Credentials: Ph.D.

Occupation: Special appointed professor at Ewha Medical Education Center.

Gender: Female.

Experience and training: The researcher who conducted the interviews has a Ph.D. in education and extensive experience in qualitative research, including focus group interviews (FGIs) and consensual qualitative research.

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Relationship with participants

The relationship established: The researcher conducting the interviews explained the research beforehand.

Participant knowledge of the interviewer: The researcher's affiliation, methods, and objectives of this study.

Interviewer characteristics: A homogeneous group interested in entrepreneurship education.

Study design

Theoretical framework

This study is a qualitative analysis conducted through FGIs with medical students who participated in a practice-based entrepreneurship course. Given the focus on the experiences of medical students in this course, there was a lack of prior research and established measurement tools. Therefore, the researchers decided that FGIs would be the most suitable method, as the topic centered on the students' experiences of change through their participation in the entrepreneurship course. The study is reported in accordance with the COREQ statement (https://www.equator-network.org/reporting-guidelines/coreq/).

Participant selection

Medical students enrolled in the practice-based entrepreneurship course were informed about the study to facilitate participant recruitment. Considering that the ideal participant count for an FGI ranges from 6 to 10 [9], we enrolled six fourth-year students from E-Medical School. These students had selected the practice-based entrepreneurship course as a free elective practicum and expressed willingness to participate in the study. Consequently, all students who took part in the practice-based entrepreneurship course were included in this study, totaling six participants. The characteristics of the research participants are presented in Table 1.

Setting

The entrepreneurship course at Ewha Womans University College of Medicine, introduced in 2022, includes a theoretical class titled "Healthcare Innovation and Women's Ventures I" and a hands-on practicum titled "Healthcare Innovation and Women's Ventures II." During the practicum, students visited VRAD, a medical venture company, from February 13 to 23, 2024. There, they engaged in an educational program that employed virtual reality (VR) simulations for the treatment of severe trauma patients. The students actively contributed to the development process by offering feedback and suggesting improvements to the program (Fig. 1).

Table 1. The characteristics of the research participants

Participants	Age	Decision to enroll	Previous experience with program development	Previous experience with virtual reality
Student 1	25	Independent	No	Yes
Student 2	25	Independent	No	No
Student 3	24	Recommendation by a mentor	No	No
Student 4	29	Independent	No	No
Student 5	25	Independent	No	No
Student 6	26	Recommendation by a mentor	No	No

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Fig. 1. Medical students participating in the practice-based entrepreneurship course, (A) visiting companies that develop medical content using virtual reality (VR) technology and engaging in the development process, and (B) experiencing the developed content in an actual lecture.

Data collection

To develop the research and interview questions, two researchers initially crafted a set of questions (Dataset 1) focused on the central research themes. These questions were then reviewed and approved by the other researchers involved in the study.

Prior to the interviews, students received detailed information about the study, including its objectives and methods. They consented to participate in the research and agreed to have their data recorded. The data collection interviews were held in the last week of February 2024, immediately following the conclusion of the entrepreneurship course. These interviews adhered to a structured format, utilizing a guide with open-ended questions. At the start of each interview, participants were informed about the research purpose, the expected duration, the recording of data, and the confidentiality of the interview contents. They were also made aware of their right to withdraw from the study at any time and assured of their autonomy throughout the interview process. The interviews were conducted by two researchers, Somi Jeong and So Hyun Ahn, who took notes on key points discussed. Each interview lasted about one hour. Following the interviews, the recordings were transcribed verbatim to produce the final dataset (Dataset 1).

Data analysis

The analysis was based on transcribed verbatim records and notes taken during the interviews. Initially, one researcher extracted meaningful data from these raw materials. Subsequently, two researchers, Somi Jeong and So Hyun Ahn, convened to discuss the analysis procedure and key considerations. Following this, they independently extracted secondary meaningful data. The researchers later reconvened to cross-verify the secondary data, review the categorizations, and reach a consensus. An external reviewer then examined the derived content. To ensure the validity of the analysis content and process, the research was evaluated using the method proposed by Hoyt and Bhati [10].

Results

Based on FGIs conducted to explore medical students' experiences in a practice-based entrepreneurship course, three domains, seven categories, and 17 subcategories emerged. The identified domains were motivation for participating in the course, experiences gained through participation, and changes experienced as a result of participation. Within the domain of motivation for participation, two categories emerged: "existing interest" and "new exploration." In the domain of experiences gained through participation, three categories were identified: "cognitive experiences," "emotional experiences," and "behavioral experiences." Two categories emerged in the domain of changes experienced through participation: "changes related to entrepreneurship" and "changes related to career." The details are presented in Table 2. Students' precise responses can be found in Supplement 1.

Discussion

Key results

The results yielded three domains, seven categories, and 17 subcategories. The seven emerging categories are as follows: "existing interest" and "new exploration" concerning

Table 2. Group interview results regarding participation in the hands-on entrepreneurship class

Categories	Classification 1	Classification 2
Motivation	Existing interest	To acquire knowledge
		To acquire practical information
	New exploration	To expand possibilities for various career paths
Experience	Cognitive experiences	Thinking from a consumer-centric perspective
		Learning about the effects of VR in medical education
		An understanding of the convergence of medicine and cutting-edge technology
		The need for doctors to participate in research
	Emotional experiences	"It's amazing that VR is being applied to medical education."
		"I was confused because the VR operation did not work as expected."
		"I felt regret that I was ignorant of technologies applied to the medical field."
	Behavioral experiences	Discussing better VR development with colleagues
		Seeking feedback on the experience from the user's perspective
Change experienced	Entrepreneurship	Gaining a deeper understanding of entrepreneurship
		"I want to try starting a business."
		Searching for medical venture companies
		Becoming interested in school/hospital startup support/industry-academia collaboration
	Career	Discovering the potential for various career paths
		"It served as an opportunity to think about incorporating cutting-edge medicine into medical education."

VR , virtual reality.

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motivations for participation; "cognitive experiences," "emotional experiences," and "behavioral experiences" in relation to the experiences gained; and "changes related to entrepreneurship" and "changes related to career paths" regarding the changes experienced.

Interpretation and comparison with previous studies

First, two categories emerged regarding motivation for participating in the practical entrepreneurship class: "pre-existing interest" and "new exploration." Specifically, within the "pre-existing interest" category, subcategories such as "acquiring knowledge about the entrepreneurship process" and "gaining practical information about entrepreneurship" were identified. These motivations reflect a desire to deepen one's experience in entrepreneurship, aligning with Houle's classification of educational program participation motives, which include goal-oriented and learning-oriented motives [11]. In the "new exploration" category, the subcategory "expanding the possibilities for various careers" was identified, indicating that medical students were seeking opportunities to explore diverse career paths beyond traditional clinical practice. These findings align with the objectives of general entrepreneurship education programs, which aim to enhance career exploration and development capabilities [12,13].

Second, three categories of experiences gained from participating in the practical entrepreneurship class were identified: "cognitive experience," "emotional experience," and "behavioral experience." Under "cognitive experience," subcategories including "thinking from a consumer-centric perspective," "learning about the effectiveness of VR in medical education," "understanding the integration of medicine and advanced technology," and "contemplating the necessity of doctors' participation in research" were highlighted. This finding indicates that participants developed an understanding of the role of doctors in the digital healthcare market from a managerial perspective by engaging in the actual operations of startup companies. In the "emotional experience" category, subcategories such as "amazement at the application of VR in medical education," "frustration with operating VR," and "regret over lack of knowledge about technologies used in the medical field" were noted. These results suggest that the innovations in the medical field, though closely related and previously unconsidered, made a significant emotional impact on the participants. Under "behavioral experience," subcategories like "discussing better VR development with peers" and "providing feedback from a user's perspective" were identified. These indicate that participants had opportunities to develop team-building and communication skills, which are crucial components of entrepreneurship [14,15].

Third, two categories emerged in the area of change experienced through participation in the practical entrepreneurship class: "changes related to entrepreneurship" and "changes related to career path." Within the "changes related to entrepreneurship" category, subcategories such as "deepening understanding of entrepreneurship," "increasing desire to try entrepreneurship," "investigating medical venture companies," and "gaining interest in entrepreneurship support and industry-academia collaboration by schools/hospitals" were identified. These findings suggest that entrepreneurship education encourages students to apply their knowledge, thereby enhancing their self-efficacy and motivation, which may lead to entrepreneurial intent [16]. Additionally, under the "changes related to career path" category, subcategories including "discovering the possibility of various careers beyond clinical medicine" and "considering the integration of advanced medical technologies into medical education" were identified. This indicates that students were broadening their perspectives and thought processes, moving beyond textbook knowledge to consider real-world applications of medicine.

Limitations and suggestions

A few limitations and recommendations from this study should be noted. First, the entrepreneurship class focused on a limited selection of companies. Future iterations should include a broader range of experiences, incorporating diverse contents and technologies, to improve entrepreneurship education. Second, the study was confined to fourth-year medical students. There is a need for broader educational interventions at various stages of the medical school curriculum, along with an analysis of their effectiveness. Third, unlike previous studies, the research topic here was explored through qualitative research rather than being grounded in a theoretical framework. To further understand the impact and implications of entrepreneurship classes in medical schools, additional quantitative research is necessary.

Conclusion

Medical students were drawn to this course by both their existing interests and a desire for new exploration. Following the course, students reported cognitive, emotional, and behavioral changes. Their perceptions of entrepreneurship and career paths were notably altered. This study is significant as it provides evidence of the effectiveness of entrepreneurship education in medical schools from the students' perspective. By examining students' experiences in a practical entrepreneurship class, the findings underscore the potential of such education to cultivate biomedical innovators poised to shape the future of healthcare. The next challenge lies in integrating entrepreneurship education into the medical school curriculum, which would allow medical students to further develop their entrepreneurial skills.

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Conflict of interest

So Hyun Ahn has been an assistant editor of the *Ewha Medical Journal* since August 2023, and

Eun Hee Ha has been a dean of Ewha Womans University College of Medicine since August 2021. However, they were not involved in the review process. No other potential conflict of interest relevant to this review was reported.

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Dataset 1. Verbatim obtained from six participants

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Supplement 1. The results of content analyses classified into three domains, seven categories, and 17 subcategories

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Protocol

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Reporting Guidelines for Community Outbreak Investigation Reporting (G-CORE): protocol for guideline development

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Keywords
Outbreak report; Community intervention; Reporting guideline; Study protocol

Objectives: Outbreak reports are essential for documenting the spread of and responses to disease outbreaks. However, there is a lack of standardized reporting guidelines that encompass broader perspectives on outbreaks. We aimed to develop a universal reporting guideline applicable to diverse outbreak reports and community epidemic interventions, the "Guidelines for Community Outbreak Investigation Reporting (G-CORE)."

Methods: G-CORE is designed to address the challenges in documenting various outbreak scenarios, including infectious diseases and non-infectious environmental hazards. The development of G-CORE involved a structured process, including a comprehensive literature review of recent outbreak reports from leading journals and an analysis of existing reporting guidelines. The process also involved project registration with the EQUATOR Network and collaboration with experts in various fields. Following the initial drafting, an internal (team) review was conducted to evaluate the guidelines' robustness and relevance. Subsequently, the guidelines underwent revision based on feedback from external experts and potential users, including authors with experience in outbreak reporting. The project also includes plans for widespread dissemination and periodic revisions to adapt to developments and user feedback.

Results: G-CORE will provide a structured framework for reporting outbreak investigations, comprising a detailed checklist and Explanation & Elaboration documents.

Conclusion: G-CORE establishes a new standard in outbreak reporting, facilitating comprehensive, clear, and actionable public health communications. Its development marks a significant advance in the documentation and management of public health outbreaks.

Introduction

The 21st century has been marked by a series of significant infectious disease outbreaks, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), swine flu, coronavirus disease 2019 (COVID-19), and Mpox. In particular, the COVID-19

pandemic, along with its variants, has highlighted the importance of outbreak reports in public health management. Outbreak reports provide information on an outbreak's progression, the methodologies employed in an investigation, key findings, and public health implications, which are crucial for understanding and managing health crises. The reports elucidate the investigation rationale, symptoms or agents involved, time and place of occurrence, and affected individuals. Notably, outbreak reports are structured to present events and interventions in a sequential, narrative format. During the COVID-19 pandemic, these reports guided interventions at the community, national, and global levels, influenced policy-making, and demonstrated the significant impact of prompt and accurate information in controlling rapidly spreading infectious diseases.

The importance of outbreak reports is not limited to infectious diseases. They also play a vital role in managing non-infectious outbreaks, such as those resulting from environmental hazards or contaminated medical products. An example is an incident in The Gambia during June-September 2022, where children's medications contaminated with diethylene glycol caused acute kidney injury in young patients [1].

Existing reporting guidelines, such as Outbreak Reports and Intervention Studies Of Nosocomial Infection (ORION) [2], often fail to cover the full spectrum of public health emergencies. Reporting guidelines are defined as checklists, flow diagrams, or structured texts that serve as a comprehensive roadmap for authors to report specific types of research [3]. They are crucial tools for various groups, including peer reviewers, authors, and scientific journals. The last update to ORION in 2007 and its subsequent lack of revision indicates a gap in current reporting guidelines, underscoring the need for new, comprehensive reporting guidelines that address public health emergencies beyond nosocomial infections.

In response, we aimed to develop a novel reporting guideline, referred to as Guidelines for Community Outbreak Investigation Reporting (G-CORE). This guideline will provide a comprehensive framework for reporting a wide range of outbreak types. It extends beyond infections of nosocomial origin to include community-level outbreaks and non-infectious environmental hazards. The guideline development process involved an extensive literature review and expert consultations.

Methods

This project's methodology is aligned with the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network standards [4]. The development of our reporting guideline has been officially registered on the EQUATOR Network website [5], ensuring adherence to their rigorous standards for health research transparency and quality. It was first named ORIOCE ("Guidelines for Transparent Reporting of Outbreak Reports and Intervention of Community Epidemics").

Research committee

The research committee is a consortium of experts from diverse fields, each chosen for their unique contributions to developing reporting guidelines. It includes experts in preventive medicine, whose focus on disease prevention and health promotion strategies is pivotal in shaping effective community-level interventions. Epidemiologists who are experienced in the patterns, causes, and effects of health conditions are included to provide a better understanding of the dynamics of community outbreaks. Methodologists, with their expertise

in research design and data analysis, ensure that the guidelines are grounded in scientifically robust principles. Family medicine practitioners offer a practical perspective on managing community health issues, making the guidelines pragmatic and applicable in real-world settings. Public health professionals offer a broader viewpoint on the implications of these guidelines, aligning them with comprehensive public health policies and practices. Lastly, the inclusion of journal editors ensures that the reporting guidelines meet the highest standards for clarity, transparency, and applicability. Through a synergistic blend of workshops, consultations, and collaborative planning, these professionals have integrated their diverse perspectives and expertise to establish a novel reporting guideline.

The research committee discussed the development process and agreed upon the following four steps: 1) literature review, 2) reviewing existing reporting guidelines, 3) development, and 4) ongoing updates and revisions.

Literature review

The literature review is a critical component of our methodology. A team reviewed manuscripts focused on outbreak reports published within the last 3 years in internationally recognized journals. We chose *Public Health Weekly Report* (PHWR), *Morbidity and Mortality Weekly Report* (MMWR), and *EuroSurveillance* for their significant contributions to the field, consistent publication of high-quality outbreak reports, and rich history of publishing extensive and detailed accounts of various outbreak investigations.

The manuscripts from these journals underwent a detailed examination to identify specific characteristics, research designs, and content elements integral to outbreak reporting. We cataloged and presented our findings in a structured format for a comprehensive representation of the data to elucidate the current trends and practices in outbreak reporting.

After the literature review, we held a meeting involving all team members to consolidate findings, discuss the differences and similarities in reporting styles across the selected journals, and identify any existing gaps in the literature. These discussions shaped the new reporting guidelines to ensure that they address the current needs and advance outbreak reporting standards in health research.

Reviewing existing reporting guidelines

This phase of the project involved a detailed examination and categorization of existing reporting guidelines, including a comprehensive analysis of the ORION statement. The primary objective of this review was to assess these guidelines for their relevance and applicability to outbreak reports, including in non-nosocomial settings, particularly in publications in prominent scientific journals.

The process involved evaluating each guideline to understand its structure, specific elements, and overall reporting approach for outbreaks and related health interventions. We focused on how these guidelines address the complexities inherent in outbreak reporting, such as the delineation of epidemiological methods, the presentation of results, and the discussion of public health implications.

Developing new reporting guidelines

The expert committee planned the drafting of G-CORE. This draft was constructed based on insights obtained from an extensive literature review and a detailed analysis of existing reporting guidelines. This approach ensured that the G-CORE guidelines are informed by current practices

and standards and reflect the latest understanding in the field. The inclusion of Explanation & Elaboration (E&E) documents is important, as it provides a detailed rationale for each guideline item. These documents, created through a systematic item-by-item analysis and enriched with expert insight, offer clarity and context, increasing the guidelines' usability and applicability. The committee's role was crucial in this phase. It was responsible for systematically generating guideline items and ensuring that each item is evidence-based and derived from the committee members' collective knowledge and the reviewed literature and existing guidelines. This collaborative process covered all critical aspects of outbreak reporting, prioritizing scientific accuracy, relevance, and practicality.

Subsequently, the initial draft of the guidelines, along with the E&E documents, underwent a series of revisions. This iterative refinement involved applying the draft guidelines and E&E documents to selected literature to test their applicability and effectiveness. The resulting feedback was critically analyzed, and the draft was modified accordingly. We also conducted internal (team) and external peer reviews, including experienced authors in outbreak reporting. The reviewer list included experts in infection, epidemiology, outbreak reporting, and environmental exposures. This collaborative approach ensured that G-CORE addresses real-world needs and maintains scientific integrity. It will involve a scoring system (0–9) enabling a quantitative evaluation of each component of the checklist, E&E documents, and free-text comments. This structured feedback will guide further revisions, ensuring the guidelines are both accurate and user-friendly.

Next, we developed the finalized version of the checklist and an explanatory manual. The checklist will provide a concise guide for researchers, while the manual will offer detailed explanations and examples in various outbreak scenarios. This methodical and evidence-based development approach ensures that the final guidelines are comprehensive, current, and practical.

Ongoing updates and revisions

In light of the dynamic nature of public health and the fluidity of outbreak scenarios, we are committed to regularly updating the G-CORE guidelines. This ongoing process is crucial, as it ensures that the guidelines remain relevant and effective in a field that constantly faces new challenges, scientific advancements, and emerging best practices.

To facilitate these updates, we will consistently monitor and revise the G-CORE guidelines to align with the latest public health and epidemiology developments. First, we will regularly solicit and integrate feedback from a diverse range of users, including researchers, public health practitioners, epidemiologists, and policymakers. This feedback will identify areas for improvement and enhancement, ensuring that the guidelines effectively meet the needs of users. In addition, we will update the guidelines based on new research methodologies, technological advancements, and evolving understandings of disease dynamics. As the field of outbreak reporting progresses, we will update G-CORE to include these new approaches. Lastly, recognizing that the user base of G-CORE may evolve, we will adapt the guidelines to cover a wide range of contexts and applications. This user-focused approach is vital to ensure that G-CORE remains practical and applicable across various public health scenarios.

We will document and share these updates through the EQUATOR Network, ensuring transparency and accessibility. G-CORE's active presence on the EQUATOR Network will result in a wider reach and more engagement with the global research community.

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Results

As of October 2023, the research team has made significant progress in developing a comprehensive reporting guideline for outbreak investigations. This effort is a direct result of the extensive literature review, including diverse outbreak reports from PHWR, MMWR, and *EuroSurveillance*. The review showed various approaches to documenting outbreaks of diseases such as COVID-19, tuberculosis, Mpox, and salmonella. It highlighted the need for a standardized reporting format that includes key elements such as pathogen identification, epidemiological methods, outbreak curves, transmission paths, and public health responses. Meanwhile, the team has been working on a detailed checklist and E&E documents. These tools will guide authors in clearly and consistently reporting outbreak investigations. The finalized versions of the checklist and E&E documents are expected to be published by December 2024.

Discussion

The development of our comprehensive reporting guideline, G-CORE, marks significant progress in addressing the challenges of outbreak reporting. This guideline will fill a gap in current reporting practices for both infectious and non-infectious public health emergencies.

The primary strength of G-CORE lies in its comprehensive nature. By encompassing a broad spectrum of outbreak scenarios, including those involving environmental hazards and medication-induced health conditions, it provides a versatile framework applicable to a variety of public health challenges. The inclusion of specific modules, such as seroepidemiology, molecular epidemiology, and environmental epidemiology, will further strengthen its applicability and relevance. Our emphasis on expert collaboration and literature review throughout the development process will ensure the transparent reporting of outbreak reports and emerging knowledge in the field.

The significance of reporting guidelines in the context of outbreak reports cannot be overstated, as it will provide a future reference for outbreak investigations and preventive or proactive measures. As a repository of vital information, these guidelines are instrumental in guiding responses to future public health emergencies. This is increasingly important as the frequency and diversity of outbreaks are on the rise. In summary, well-structured outbreak reports, guided by comprehensive guidelines, are crucial for improving public health.

However, this study has certain limitations. The rapid pace and unpredictable nature of outbreaks can exceed the guideline's applicability, especially when immediate action is prioritized over structured reporting. Moreover, the standardization of reporting across diverse outbreak types remains complex. Future updates to G-CORE will address these challenges. Regular revisions, informed by feedback from users and changes in the public health landscape, will help to maintain the guideline's relevance and utility. This process will ensure that G-CORE evolves with the ever-changing nature of public health emergencies.

Conclusions

G-CORE will increase the clarity, consistency, and comprehensiveness of outbreak reporting. Its development underscores the need for continual adaptation and improvement in public health reporting and highlights the collaborative effort required to effectively manage public health crises. As we look toward its publication in December 2024, we anticipate that G-CORE will play a crucial role in outbreak reporting and public health strategies.

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Protocol

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Developing Guidelines for Surveillance Reporting (G-SIRE): protocol for guideline development

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Keywords
Surveillance report; Reporting guideline; Study protocol

Objectives: Surveillance reporting, which is integral to public health and safety, involves the systematic collection, analysis, and dissemination of data crucial for various health and security scenarios. Despite its importance, standardized Guidelines for Surveillance Reporting (G-SIRE) are lacking, leading to inconsistencies and affecting data reliability and comparability. To address this gap, this study aimed to develop the G-SIRE, tailored to improve the clarity, transparency, and consistency of surveillance reports, thereby increasing the accuracy and usability of surveillance data for better public health outcomes.

Methods: The methodology adhered to the EQUATOR Network standards, employing a multidimensional approach with a diverse expert team. The process included forming a research committee of multidisciplinary experts, conducting a thorough literature review of recent surveillance report publications, reviewing existing reporting guidelines, and developing a new set of guidelines. Continuous updates and revisions are planned to keep the guidelines relevant and effective.

Results: Significant progress has been made as of November 2023 in developing comprehensive reporting guidelines for surveillance reports. A detailed checklist and Explanation & Elaboration documents have been formulated, which are anticipated to be finalized and published by December 2023.

Conclusion: The G-SIRE guidelines signify a major advancement in standardizing surveillance. They provide a structured approach that increases scientific accuracy, transparency, and practical applicability in this domain. The guidelines are expected to improve the quality of surveillance reporting significantly, contributing to the advancement of public health research and discourse.

Introduction

Surveillance reports play a critical role in the realm of public health and safety. At its core, a surveillance report refers to a document for the ongoing systematic collection, analysis, and dissemination of data related to events or activities that are of importance for public health or security [1]. The significance of this process lies in its ability to provide timely information, which

is crucial for decision-making and effective responses in various scenarios [2]. Whether they involve monitoring the spread of infectious diseases [3], assessing the effectiveness of health interventions [4], or ensuring national security [5], surveillance reports serve as a cornerstone for informed strategies and actions. Their importance is further underscored by their applications across diverse fields, including epidemiology, environmental studies, and national defense, highlighting the versatility and indispensability of these documents in safeguarding public welfare [6].

Despite the significant role of surveillance reports, standardized reporting guidelines are lacking. This absence of a structured framework leads to inconsistencies in reporting practices, thereby affecting the reliability and comparability of surveillance data. Reporting guidelines are checklists, flow diagrams, or organized texts that act as detailed guides for authors when reporting specific kinds of research [7]. These tools are valuable for various groups, including peer reviewers, authors, and scientific journals, helping to ensure accurate and thorough reporting of research. Recognizing this gap, our study aimed to develop the Guidelines for Surveillance Reporting (G-SIRE), a comprehensive set of reporting guidelines specifically tailored for surveillance reports. The objective of this study was to establish a standardized protocol that improves the clarity, transparency, and consistency of surveillance reports. By doing so, the G-SIRE guidelines aim to contribute to the accuracy and usability of surveillance data, ultimately supporting better public health and safety outcomes. This study involved a systematic approach, including literature review, expert consultations, and iterative feedback, to ensure that the guidelines are robust, practical, and applicable across various surveillance contexts.

Methods

This project's methodology aligns with the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network standards [8]. The method involved a multidimensional approach, engaging a diverse team of experts to create solid reporting guidelines.

Formation and role of the research committee

The research committee is a multidisciplinary group that has played a key role in shaping the reporting guidelines. It consists of preventive medicine experts who focus on disease prevention strategies, epidemiologists who study disease patterns and outbreak dynamics, methodologists who ensure scientific accuracy in research design and data analysis, family medicine professionals who provide insights into practical community health management, public health experts aligning the guidelines with wider health policies, and journal editors ensure that the guidelines are clear and applicable. Their combined knowledge, brought together in workshops and team sessions, has formed a basis for developing comprehensive, scientifically sound, and practical reporting guidelines.

Literature review

Our team conducted a thorough review of manuscripts on surveillance reports, published in the last 3 years in well-known international journals. We specifically chose *Public Health Weekly Report* (PHWR) in Korea, *Morbidity and Mortality Weekly Report* (MMWR) in the USA, and *EuroSurveillance* in Europe for their significant contributions to the field and their commitment to publishing top-quality reports on surveillance. These manuscripts were carefully examined to identify unique features, research methods, and key components crucial to surveillance

reporting. Following this extensive review, a joint meeting with all team members was held. The aim was to merge our findings, discuss the differences and similarities in reporting styles among the chosen journals, and identify any gaps in the literature. The insights from these discussions were vital in developing the new reporting guidelines, ensuring that they meet current needs and advance the standards of surveillance reporting in health research.

Reviewing existing reporting guidelines

This stage involved scrutinizing and categorizing existing reporting guidelines, including a detailed study of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [9] and the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement [10]. The main goal was to assess these guidelines for their suitability and effectiveness in surveillance reporting. This included examining each guideline's structure, key components, and overall approach to epidemiological surveillance reporting. In particular, we focused on how these guidelines address the specific challenges of surveillance reports, such as detailing epidemiological methods, presenting research findings, and discussing public health implications.

Developing new reporting guidelines

Developing the G-SIRE guidelines was a systematic process led by our expert committee. The initial draft was based on insights from a detailed literature review and an analysis of existing reporting guidelines, ensuring that G-SIRE aligns with current practices and reflects recent knowledge in the field. The G-SIRE framework is structured into several distinct sections (e.g., title, abstract, summary, introduction, methods, results, discussion, and other information), each requiring specific details for comprehensive reporting. In total, 25 items need to be addressed across these sections.

We included Explanation & Elaboration (E&E) documents for each guideline item, giving clear reasons and context, which increases the guidelines' usability. The committee played a crucial role in this phase, carefully creating each guideline item. These items are evidence-based, drawn from the combined expertise of the committee, reviewed literature, and current guidelines. This joint effort ensures that all important aspects of surveillance reporting are covered, focusing on scientific accuracy and practical use.

We then repeatedly revised the initial draft of the guidelines and the E&E documents, applying them to selected literature to check their effectiveness and refining them based on feedback. Both internal team members and external experts, including those experienced in surveillance reporting, reviewed the drafts. This review process used a scoring system for a detailed evaluation of each part of the guidelines and the E&E documents.

Finally, we produced the final version of the guidelines and a comprehensive manual. The checklist provides a brief guide for researchers, while the manual gives detailed explanations and examples for various surveillance scenarios. This systematic and evidence-based approach ensures the final guidelines are inclusive, up-to-date, and practical for use.

Ongoing updates and revisions

Recognizing the constantly evolving nature of public health and epidemiological surveillance [11], we commit to regularly updating the G-SIRE guidelines. Ongoing revisions are crucial to keep the guidelines relevant and effective amid changing challenges, scientific advancements, and new best practices in the field. To ensure that these updates are timely and effective, the

G-SIRE guidelines will be continually reviewed, aligning them with the latest developments in public health and epidemiology. A key part of this process is gathering and integrating feedback from a wide range of users including researchers, public health experts, epidemiologists, and policymakers. Their input will be invaluable in identifying areas for improvement, making sure the guidelines continue to be responsive to user needs.

Results

As of November 2023, the research team has achieved significant progress in creating detailed reporting guidelines for surveillance reports. Meanwhile, the team has been diligently developing a comprehensive checklist and E&E documents. These instruments are designed to assist authors in reporting surveillance reports with clarity and uniformity. The team anticipates the completion and publication of the finalized versions of both the checklist and the E&E document by December 2024.

Discussion

The development of the G-SIRE guidelines marks a notable progression in the standardization of surveillance system data reporting in the scientific literature. These guidelines aid researchers in effectively articulating both the advantages and limitations of their research findings. Crucially, they also facilitate the interpretation and practical application of these findings. This clarity is essential in the progression of surveillance research, ensuring that the results are not only scientifically sound but also pragmatically relevant in various settings.

In addition, the G-SIRE framework serves as an essential resource for editorial teams and peer reviewers. It offers a systematic method for evaluating the quality and pertinence of research manuscripts, promoting high levels of scientific integrity and clarity in surveillance-related publications. This aspect is increasingly significant in a context where the precision and dependability of health-related data are of utmost importance.

The inclusion of detailed explanations and illustrative examples for each item in the checklist, as referenced in the appendix, increases the utility of the guidelines. This approach facilitates a deeper understanding of the guidelines and offers practical guidance for their application. By providing specific examples, the guidelines become more approachable and user-centric, minimizing the likelihood of misinterpretation or errors during the manuscript preparation process.

Looking forward, the broad implementation of the G-SIRE is likely to significantly improve the caliber of research in the surveillance system domain. The guidelines promote transparency and uniformity in reporting, as well as a deep comprehension of the intricacies involved in handling surveillance data. As the research community becomes more acquainted with these guidelines, an increase in the quality of surveillance research publications is expected, contributing meaningfully to the evolution of the field and improving public health discourse.

Conclusions

In summary, G-SIRE represents a pivotal advancement in the standardization of surveillance system data reporting, offering a framework that enhances the scientific accuracy, transparency, and practical applicability of research findings in this domain. By providing a structured approach for manuscript preparation and evaluation, these guidelines not only facilitate improved clarity

and consistency in research reporting, but also aid in advancing the quality of publications in the field of surveillance. The comprehensive nature of G-SIRE, including its detailed checklist and illustrative examples, makes it a valuable resource for researchers, editors, and peer reviewers alike. This is instrumental in elevating the standards of surveillance research and, consequently, enriching the broader discourse in public health and epidemiology.

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Protocol

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Establishing the Guidelines for Recommendation Reporting (G-RECO): a study protocol for developing reporting guidelines for disease prevention recommendations

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Keywords
Recommendation report; Reporting guideline; Study protocol

Objectives: The objective of this study was to develop the Guidelines for Recommendation Reporting (G-RECO) for use in the *Public Health Weekly Report* (PHWR) in Korea, aiming to improve the standardization, scientific accuracy, and practical applicability of recommendation reports in clinical practice guidelines.

Methods: The methodology of this study aligned with the EQUATOR Network standards. A multidisciplinary research committee was formed, comprising experts in various relevant fields. The development process included a comprehensive literature review, analysis of existing guidelines, and formulation of a structured G-RECO framework with 21 key items. This was supplemented with Explanation & Elaboration documents for each item. The draft underwent rigorous revisions and evaluations by both internal and external experts.

Results: By November 2023, significant progress had been made in developing a detailed G-RECO checklist and accompanying E&E documents. These tools are designed to guide authors in clear and consistent reporting of recommendation reports. The team is poised to finalize and publish the checklist and E&E documents by December 2024.

Conclusion: The G-RECO guidelines represent a significant advancement in the formalization and standardization of recommendation reports for the PHWR. They are expected to improve the quality of research and publications in clinical practice guidelines, contributing to the evolution of the field and enriching public health discourse. The guidelines, with their comprehensive nature and user-friendly design, will become an invaluable resource for researchers, editors, and peer reviewers in public health and epidemiology.

Introduction

Clinical practice guidelines are recommendations systematically developed to assist physicians and patients in making decisions in specific clinical situations. These guidelines not only

provide systematic directions for improving the quality of medical care, but are also a strategy for providing high-quality information to patients. They play a significant role in improving patient satisfaction and treatment efficacy by aiding in decision-making, which can influence appropriate patient treatment.

The Korea Disease Control and Prevention Agency (KDCA) develops numerous clinical practice guidelines. Unlike general clinical practice guidelines, the KDCA's guidelines focus on disease prevention, such as screening and vaccination, and also address certain diseases, such as sexually transmitted infections and tuberculosis.

Currently, there are two reporting guidelines for clinical practice guidelines: RIGHT (Reporting Items for practice Guidelines in HealThcare) [1] and AGREE (Appraisal of Guidelines for Research & Evaluation) [2]. Both are widely used and have similar items, but they also complement each other. Notably, RIGHT includes a public version that can be utilized [3]. These reporting guidelines can be directly applied when reporting on health and disease policy in a weekly report. However, since KDCA's clinical practice guidelines primarily focus on disease prevention and some infectious diseases, it is advisable to select the most relevant items from these guidelines and report accordingly.

In this context, we aimed to develop the Guidelines for Recommendation Reporting (G-RECO) for publications in *Public Health Weekly Report* (PHWR) in Korea. This document is a study protocol that outlines the process of developing G-RECO.

Methods

The methodology employed in this project adheres to the standards set by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network [4]. This approach encompasses a multi-faceted strategy, involving a varied team of specialists, to formulate robust reporting guidelines.

Formation and role of the research committee

The multidisciplinary research committee is instrumental in the development of reporting guidelines. This committee is composed of experts in various fields: specialists in preventive medicine who focus on strategies for disease prevention, epidemiologists analyzing disease patterns and trends, methodologists dedicated to ensuring the scientific rigor of research methodologies and data analysis, family medicine practitioners offering insights on effective community health management, public health professionals who ensure the alignment of the guidelines with broader health policies, and journal editors who contribute to the clarity and practicability of the guidelines. Through collaborative efforts in workshops and team meetings, this diverse group of experts has synthesized their collective expertise to create thorough, scientifically robust, and practically relevant reporting guidelines.

Literature review: *Public Health Weekly Report*

Our team conducted a thorough review of PHWR manuscripts in Korea (https://www.phwr.org/), specifically focusing on recommendation reports. The PHWR is the official academic journal of the KDCA. Its primary objective is to promptly and accurately provide evidence-based scientific information to the public and health professionals both domestically and internationally. This information is based on the KDCA's research, surveillance, and investigation findings. The journal covers a range of topics, including infectious diseases, chronic diseases, environmentally

induced illnesses, injuries and poisoning, and health promotion. It features research papers, outbreak reports, surveillance updates, field reports, reviews and forecasts, and policy reports. Its publications are intended for a wide range of audiences, including healthcare professionals, policymakers, and sometimes the general public, offering timely insights into ongoing public health issues and trends.

The manuscripts were carefully examined to identify unique features, research methods, and key components crucial to report recommendations. Following this extensive review, a joint meeting with all team members was held. The aim was to merge our findings, discuss the differences and similarities in reporting styles among each report, and find any gaps in the literature. The insights from these discussions were vital in forming the new reporting guidelines, ensuring they meet current needs and advance the standards of recommendation reporting in health research.

Reviewing existing reporting guidelines

This stage involved closely scrutinizing and categorizing existing reporting guidelines, including the RIGHT [1] and the AGREE statement. [2] The main goal was to assess the suitability and effectiveness of these guidelines for clinical practice guidelines in the PHWR. This included examining each guideline's structure, key components, and overall approach to report recommendation. Both the RIGHT and the AGREE aim to improve the transparency and quality of guideline reporting, but they focus on slightly different aspects of guideline development and evaluation. The AGREE emphasizes methodological quality assessment, while the RIGHT checklist is considerably shorter and could be easier to use, with similar results [5].

Developing new reporting guidelines

The formulation of the G-RECO guidelines involved a structured procedure orchestrated by our panel of experts. The preliminary version stemmed from comprehensive insights gathered through an extensive review of relevant literature and critical analysis of existing reporting guidelines, ensuring that G-RECO is in line with current practices and integrates the latest field advancements. The structure of G-RECO is segmented into various key sections (including title, abstract, summary, introduction, methodology, results, discussion, and other pertinent information), with each section requiring specific details to ensure thorough reporting. Altogether, these sections encompass 21 key items.

For each item of the guideline, we incorporated Explanation & Elaboration (E&E) documents, providing clarity on the rationale and context, thereby increasing the practicality of the guidelines. During this phase, the committee played an essential role by structurally formulating each guideline item. These items are grounded in evidence, deriving from the collective expertise of the committee, critical review of the literature, and contemporary guidelines. This collaborative process ensured comprehensive coverage of all critical elements of recommendation reporting, with an emphasis on scientific precision and practical utility.

The draft guidelines and E&E documents underwent successive revisions, where they were applied to select literature to evaluate their practicality, with adjustments made based on the feedback received. The drafts were reviewed by both our internal team and external experts proficient in recommendation reporting, employing a scoring method for a detailed assessment of each component of the guidelines and the E&E documents.

Finally, we compiled the final iteration of the guidelines along with an extensive manual. The checklist will serve as a succinct guide for researchers, while the manual provides in-depth

explanations and illustrations for diverse recommendation scenarios. This systematic and evidence-grounded approach ensures that the final guidelines are comprehensive, current, and pragmatically applicable.

Ongoing updates and revisions

The G-RECO guidelines are planned to undergo systematic, ongoing updates. This continuous revision process is essential to maintain their relevance and effectiveness in response to evolving challenges, scientific progress, and emerging best practices within the field. To guarantee that these updates are both timely and impactful, the G-RECO guidelines will undergo regular evaluations, ensuring that they reflect the most current advancements in this domain. A crucial aspect of this updating mechanism involves collecting and incorporating feedback from a diverse array of stakeholders, including researchers, public health professionals, epidemiologists, and policymakers. Their insights will be crucial in pinpointing areas for improvement, thereby ensuring that the guidelines remain attuned to the needs and expectations of their users.

Results

By November 2023, the research team has made considerable advancements in formulating detailed reporting guidelines for recommendation reports. Progressing methodically, the team has been meticulously crafting a thorough checklist and E&E documents. These tools are intended to guide authors in presenting recommendation reports with both clarity and consistency. The team is on track to finalize and release both the checklist and the E&E documents by December 2024.

Discussion

The introduction of the G-RECO guidelines represents a significant advancement in the formalization of clinical practice guidelines and recommendations for the PHWR. Reporting guidelines, identified as checklists, flow diagrams, or structured texts, serve as comprehensive aids for authors in documenting specific research types [6]. These instruments are invaluable to a range of stakeholders, including peer reviewers, authors, and academic journals, ensuring accurate and complete research documentation. The G-RECO guidelines are particularly designed to assist researchers in effectively communicating the strengths and limitations of their findings, thereby enhancing their interpretation and practical application.

Moreover, the G-RECO framework is a vital tool for editorial teams and peer reviewers. It provides a systematic approach for assessing the validity and relevance of research submissions, promoting high standards of scientific accuracy and clarity in publications related to recommendations. This is especially crucial in contexts where the accuracy and reliability of health-related information are paramount.

The G-RECO guidelines are further augmented by the inclusion of detailed explanations and examples for each checklist item, as elaborated in the appendix. This method increases the comprehensibility and practicality of the guidelines, offering concrete guidance for implementation. The provision of specific examples makes the guidelines more accessible and user-friendly, reducing potential misinterpretations or errors during manuscript preparation.

In the future, it is expected that the broad implementation of G-RECO guidelines will significantly improve the standard of research for clinical practice guidelines and

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recommendations. As familiarity with these guidelines grows within the research community, an improvement in the quality of publications related to recommendations is foreseen, which will likely have a substantial impact on advancing the field and enriching discussions in public health.

Conclusions

Our team is committed to developing the G-RECO guidelines to improve the standardization of recommendation reports for the PHWR, providing a framework that bolsters the scientific precision, clarity, and practical relevance of research in this area. These guidelines, by offering a systematic method for manuscript development and assessment, not only promote increased clarity and uniformity in research documentation, but also contribute to elevating the caliber of publications within the realm of clinical practice guidelines. G-RECO's comprehensive design, encompassing a detailed checklist and illustrative examples, positions it as an invaluable tool for researchers, editors, and peer reviewers. This initiative is key in raising the quality of clinical practice guidelines and thus plays a significant role in enriching the wider conversation in public health and epidemiology.

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Conflict of interest

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Reporting Guidelines for Survey Reporting (G-SURE): protocol for guideline development

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Keywords
Survey report; Public health; Reporting guideline; Study protocol

Objectives: The objective of this study was to develop a reporting guideline for epidemiological survey reports, referred to as "Guidelines for Survey Reporting (G-SURE)."

Methods: To develop G-SURE, we adopted a systematic approach, starting with a detailed review of recent survey reports in *Public Health Weekly Report*, *Eurosurveillance*, and *Morbidity and Mortality Weekly Report* and an analysis of current reporting standards. After drafting the guidelines, our team conducted an in-depth internal evaluation to assess their effectiveness and applicability. We then refined the guidelines based on insights from external experts and potential users, particularly those with significant experience in survey reporting. The plan also includes ongoing efforts to widely share the guidelines and update them periodically, incorporating new findings and user feedback.

Results: G-SURE will provide a structured framework for reporting outbreak investigations, comprising a detailed checklist and Explanation & Elaboration documents. These will improve the transparency, consistency, and quality of public health documentation.

Conclusion: In this protocol article, we introduce G-SURE, a guideline developed to improve epidemiological survey research. G-SURE addresses the critical need for uniform reporting standards in epidemiological surveys, aiming to improve the quality and relevance of research outcomes in this area. This guideline is also designed to be a key resource for peer reviewers and editors, aiding them in efficiently assessing the thoroughness and accuracy of survey reports. By providing consistent reporting criteria, G-SURE seeks to minimize confusion and irregularities, which are often encountered in the process of scientific publication.

Introduction

Public Health Weekly Report, which is published by the Korea Disease Control and Prevention Agency, contains various publication types, including survey/surveillance reports. This type includes the analysis and reporting of epidemiological changes in diseases, pathogens, and health issues based on data from national or international survey/surveillance systems. Survey/surveillance reports should be 2,000 words or less, with no more than three tables and figures

each. References should be no more than 10. Each report should include an abstract, core summary, introduction, methods, results, discussion (conclusion), acknowledgments, and references [1].

With the exception of surveillance reports, the purpose of the Guidelines for Survey Reporting (G-SURE), the development of which is discussed herein, is to make it easier for researchers at the Korea Disease Control and Prevention Agency to write survey reports and to ensure that they include all the necessary information. Because a survey report can be understood as a survey questionnaire study, this guideline addresses only epidemiological survey reports and clarifies that they are epidemiological studies. Of course, questionnaire surveys can also be included in epidemiological surveys. Importantly, these surveys should be limited to the disease or health condition of interest, not psychological or educational surveys. Survey reports often cover infectious diseases, but can include all areas of health, including chronic diseases, environmental diseases, and external cause diseases.

A survey is commonly used to describe observations made to measure and record something, while surveillance is used to describe the repetition of a standardized survey to detect changes. In this guideline, surveillance reporting refers to the ongoing and regular investigation and reporting of diseases, health conditions, and other epidemiological data in accordance with national legislation or the Centers for Disease Control and Prevention (CDC) practice guidelines. In other words, survey reporting is not a one-time event, but rather an ongoing practice that is often recognized as necessary for public health.

The difference between periodic survey reporting and surveillance reporting is the legal basis, although periodic survey projects can later be categorized as surveillance reports on their legal basis. In contrast, outbreak reports are investigations in situations where there is an urgent need to respond to a sudden outbreak or epidemic of a disease or health condition.

Survey reporting, surveillance reporting, and outbreak reporting all fall into the category of investigative reporting, but they are categorized as being conducted for specific purposes. The recommended reporting guidelines for each of these study designs are based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [2] and are simplified to make them easier for the Korea Centers for Disease Control and Prevention Agency researchers to use.

Epidemiological survey reports play a pivotal role in epidemiological research, serving as a cornerstone for informed public health decisions and policymaking. They provide critical insights into the prevalence, distribution, and determinants of health-related events in specific populations [3]. By systematically gathering and analyzing data on various health conditions, survey reports contribute to our understanding of disease patterns, risk factors, and the effectiveness of health interventions [4]. Their importance is underscored by their ability to guide health professionals and policymakers in designing targeted strategies to improve health outcomes and allocate resources efficiently. In addition, survey reports promote transparency and accountability in public health, ensuring that interventions are evidence-based and tailored to meet the unique needs of different communities.

To the best of our knowledge, however, there is no reporting guideline for survey reports. Reporting guidelines are defined as checklists, flow diagrams, or structured texts that serve as a comprehensive roadmap for authors to report specific types of research [2]. They are crucial tools for various groups, including peer reviewers, authors, and scientific journals. The objective of this study was to develop better reporting guidelines for epidemiological survey studies; thus, the protocol for the G-SURE, which is developed through expert consensus, is described herein.

Unlike existing guidelines such as the STROBE statement [5], which cater to specific research designs (e.g., cohort studies, case-control studies, or observational studies), the aim of G-SURE is to increase the clarity, transparency, and consistency of survey reports. The ultimate goal is to make survey reports more accessible and valuable to the broader public health community, thereby contributing to more efficient use of time and resources in epidemiological research.

Methods

This project's methodology is aligned with the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network standards [6]. The methodology incorporates a multidimensional approach, involving a diverse team of experts to develop robust reporting guidelines.

Formation and role of the research committee

The research committee, a multidisciplinary consortium, plays a pivotal role in shaping the reporting guidelines. It comprises preventive medicine experts who focus on disease prevention strategies, epidemiologists specializing in disease patterns and outbreak dynamics, methodologists responsible for ensuring scientific rigor in research design and data analysis, family medicine practitioners offering insights on practical community health management, public health professionals aligning the guidelines with broader health policies, and journal editors ensuring the guidelines meet standards of clarity and applicability. Their collective expertise, synthesized through workshops and collaborative sessions, has formed the foundation for developing comprehensive, scientifically robust, and practical reporting guidelines.

Literature review

Our team conducted an in-depth analysis of manuscripts focusing on survey reports, published in the last 3 years in internationally acclaimed journals. We specifically selected *Public Health Weekly Report*, *Morbidity and Mortality Weekly Report*, and *Eurosurveillance*, recognizing their substantial contributions to the domain and their commitment to publishing high-quality survey reports. The chosen manuscripts were meticulously scrutinized to pinpoint distinctive features, research methodologies, and key elements pertinent to survey reporting. Following this comprehensive review, a collaborative meeting with all team members was convened. The purpose of this meeting was to integrate our findings, engage in discussions about the variances and parallels in the reporting styles among the chosen journals, and detect any prevailing gaps in the literature. The insights gained from these deliberations played a crucial role in shaping the new reporting guidelines, ensuring they cater to contemporary needs and propel the standards of survey reporting in health research forward.

Reviewing existing reporting guidelines

This phase focused on closely examining and classifying existing reporting guidelines, including an in-depth analysis of the STROBE statement. The main aim was to evaluate these guidelines for their appropriateness and effectiveness in survey reporting. This involved assessing each guideline's structure, essential components, and overall approach to epidemiological survey reporting. The evaluation particularly concentrated on how these guidelines handle the specific challenges of survey reports, such as detailing epidemiological methods, presenting research findings, and discussing the implications for public health.

Developing new reporting guidelines

The development of the G-SURE guidelines was a methodical process led by our expert committee. The initial draft was based on insights from a thorough literature review and an analysis of existing reporting guidelines, ensuring that G-SURE aligns with current practices and reflects the latest knowledge in the field. We included Explanation & Elaboration (E&E) documents for each guideline item, providing clear reasons and context, which improves the guidelines' practicality.

The committee played a vital role in this phase, meticulously creating each guideline item. These items are grounded in evidence, drawing from the collective expertise of the committee, reviewed literature, and existing guidelines. This collaborative effort ensured coverage of all important elements of outbreak reporting, with a focus on scientific accuracy and practical application.

We then repeatedly revised the initial draft of the guidelines and the E&E documents. This involved applying them to selected literature to evaluate their effectiveness, and then refining them based on the feedback received. Both internal team members and external experts, including those experienced in outbreak reporting, reviewed the drafts. This review process incorporated a scoring system for a detailed evaluation of each part of the guidelines and the E&E documents.

Finally, we produced the final version of the guidelines and a comprehensive manual. The checklist offers a succinct guide for researchers, while the manual provides in-depth explanations and examples for various outbreak scenarios. This systematic and evidence-based approach ensured that the final guidelines are inclusive, up-to-date, and practical for use.

Ongoing updates and revisions

Acknowledging the ever-changing landscape of public health and epidemiological surveys, we are dedicated to continually updating the G-SURE guidelines. This regular revision is essential to maintain their relevance and effectiveness amidst evolving challenges, scientific progress, and new best practices in the field.

To ensure these updates are timely and effective, the G-SURE guidelines will be under constant review, aligning them with the latest developments in public health and epidemiology. Key to this process will be the collection and integration of feedback from a broad spectrum of users including researchers, public health experts, epidemiologists, and policymakers. Their input will be invaluable in identifying areas for improvement and thereby ensuring that the guidelines remain responsive to user needs.

Results

As of November 2023, the research team has made advancements in developing comprehensive reporting guidelines for survey reports. Meanwhile, the team has been working on a detailed checklist and E&E documents. These tools will guide authors in clearly and consistently reporting survey reports. The finalized versions of the checklist and E&E documents are expected to be published by December 2024.

Discussion

The field of epidemiological research is rapidly evolving, underscoring the need for

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standardized reporting methods. Epidemiological surveys, which are fundamentally different from surveillance reports, play a critical role in documenting a wide range of health conditions, including infectious, chronic, and environmental diseases. Unlike surveillance reports that require ongoing monitoring under specific health guidelines, epidemiological surveys are typically one-time or periodic investigations tailored to the specific nature and urgency of health issues. These surveys, whether conducted irregularly or on a regular basis, have distinct objectives and thus require unique reporting methodologies. The transition of a regular survey into a surveillance report is often regulated by the legal framework. For example, outbreak reports are specifically designed for immediate responses to sudden disease outbreaks or epidemics.

The introduction of G-SURE, our comprehensive reporting guideline, represents a significant step forward in addressing the complexities of survey reporting. G-SURE aims to improve the clarity, transparency, and consistency of these reports. However, initially navigating the recommended reporting guidelines based on research design can be challenging and may require a thorough examination of numerous papers and hands-on experience in both conducting research and writing papers. Since epidemiological survey reports generally follow a consistent structure, it is beneficial to consider these guidelines from the outset of the research design process, including during data collection and analysis, and ultimately in the writing phase. While G-SURE covers the essential elements of report formatting, it is not exhaustive. Researchers are encouraged to include additional relevant information that may not be explicitly mentioned in the guidelines. Conversely, some sections of G-SURE may be optional, allowing researchers to omit certain elements if they lack pertinent content; alternatively, they may include these sections with a notation of "not applicable" when appropriate.

Despite these advancements, the standardization of reporting for diverse types of surveys remains a complex endeavor. Future updates to G-SURE will tackle these intricacies. Regular revisions, incorporating user feedback and adapting to changes in the public health landscape, are essential to ensure the continued relevance and effectiveness of the guidelines. This adaptive approach is crucial for G-SURE to keep pace with the dynamic nature of public health emergencies and evolving epidemiological challenges.

Conclusions

In this protocol article, we introduce the G-SURE guidelines, which were developed to improve epidemiological research. G-SURE targets the urgent need for uniform reporting standards in epidemiological surveys, aiming to improve the quality and relevance of research outcomes in this area. This guideline is designed to be a key resource for peer reviewers and editors, aiding them in efficiently assessing the thoroughness and accuracy of survey reports. By providing consistent reporting criteria, G-SURE seeks to minimize confusion and irregularities, which are often encountered in the process of scientific publication.

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Not applicable.

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My career path at a medical artificial intelligence company, working as a physician outside of clinical practice

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After serving as a clinical instructor in the endocrinology department at Seoul National University Bundang Hospital in Seongnam, Korea, I transitioned to Lunit, a medical artificial intelligence (AI) company, in 2023. While my experience as a clinical professor was not extensive, and I am still growing into my new role, I am eager to share my journey through this essay. I hope to provide insights to medical students and junior colleagues who are considering a career in the AI industry.

The artificial intelligence company where I work

The company I work for is dedicated to combating diseases that afflict humanity, using artificial intelligence (AI) as its primary tool. It has specifically prioritized the fight against cancer among various human diseases. Our approach to tackling cancer involves two main strategies: the early and accurate detection of cancer, and recommending the optimal treatment method by understanding the biology of each patient's cancer. I am part of the oncology group, which focuses on developing AI biomarkers from tissue pathology image data to recommend the most effective treatment options [1]. The company was founded in 2013 and went public on the KOSDAQ in 2022. It is currently in a phase of expansion, marked by an increase in both the number of employees and revenue. However, further development is still necessary.

My role in the company

Within the company, I am part of the medical affairs department, which consists of teams focusing on clinical research, biomedical research, data management, and medical product management. As indicated by the names of these teams, our department's responsibilities include conducting various clinical studies with developed AI products, collecting and processing the data necessary for the development of new AI products, maintaining and updating existing AI products, and transforming the primary analysis results from AI models into biomarkers that are more intuitively understandable for humans.

Since AI is a new technology, AI companies are relatively new startups. In the traditional pharmaceutical industry, the role of physicians is well-established; however, in AI companies, this role remains undefined. Drawing on my medical expertise, I engage in a variety of tasks required

by the company. My responsibilities span from direct involvement in AI product development to strategizing on revenue generation with AI products within the business domain. Additionally, I focus on navigating product approvals and building clinical evidence in the clinical research and approval domain. Despite my expertise, I collaborate with field-specific experts who possess even greater knowledge in these diverse areas. One of the highlights of my tenure at the company has been the opportunity to learn from these experts across various disciplines and to demonstrate my value by contributing vital ideas through our interactions.

Product management as an essential task

One common question I receive from acquaintances and juniors curious about my role at the company is whether my work primarily involves simple tasks such as reviewing medical images or pathology tests, and how much programming knowledge is necessary for actual AI development. While my duties do include processing medical data directly, I find that a physician's expertise is most valuable in the area of product management. The company's goal is to sell products that generate profit. Product planning requires identifying what consumers in the healthcare industry—patients, physicians, insurance companies, and government agencies—need, and determining how our products can meet those needs. Physicians have a distinct advantage in this area due to their direct experience with clinical unmet needs. However, product management involves more than just presenting ideas. It also includes the realization of these ideas by leveraging the company's human and material resources. Therefore, launching a product on the market requires knowledge of AI development, software development, product approval processes, and even basic business and accounting principles. These skills collectively address the question of how much programming knowledge is necessary. Although I do not engage in coding at the company, I have studied the fundamentals of programming and have actively pursued knowledge in AI technology. Such a technological understanding is essential to fully utilize medical expertise. To take a more proactive role in the field of medical AI, rather than merely acting as a medical advisor, one must be capable of addressing issues such as why the performance of an AI model under development is unsatisfactory. This involves determining whether the issue stems from specific characteristics of the medical data and deciding which of various solutions—such as modifying the data or altering the training method—has the highest likelihood of success.

Incorporation of various artificial intelligence models

Although I work in the AI industry, I cannot confidently predict how AI technology will transform healthcare. This new technology is characterized by a mix of excessive expectations and high possibilities. At my company, our staff members are constantly striving to remain at the forefront of technological advancements. They are working to integrate foundation models, zero-shot learning, and vision language models into our products. A foundation model [2], also known as a base model or pre-trained model, is a large neural network that has been trained on a vast amount of data in a self-supervised manner without being optimized for any specific downstream task. These models learn general representations and patterns from the data, capturing broad knowledge that can then be adapted or fine-tuned for various downstream tasks through transfer learning. Examples of well-known foundation models include GPT-3 for natural language processing, Bidirectional Encoder Representations from Transformers (BERT),

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and Contrastive Language-Image Pre-training (CLIP) for vision-language tasks.

Zero-shot learning [3] is a paradigm where a machine learning model is trained to generalize and perform tasks without explicit training on examples from those tasks. The model utilizes knowledge gained during pre-training on a broad dataset to make inferences and predictions about new, unseen tasks or classes. In zero-shot learning, the model receives either a natural language description or a few examples of the new task, using its understanding of underlying concepts and relationships to adapt its knowledge accordingly. This approach enables the model to handle tasks it has never encountered during training, potentially diminishing the need for extensive data collection and annotation for each new task.

A vision-language model [4] is a type of multimodal neural network that is designed to simultaneously process and understand both visual and textual data. These models are trained on extensive datasets that include images along with their corresponding textual descriptions or captions. Through this training, they learn to link visual features with related language representations. Vision-language models are utilized in a variety of tasks that involve both visual and textual inputs, such as image captioning, visual question answering, and multimodal retrieval. Notable examples of vision-language models include CLIP, Vision and Language BERT (ViLBERT), and UNiversal Image-TExt Representation (UNITER).

CLIP, developed by OpenAI, employs a contrastive learning method to train on a vast dataset of image-text pairs. It is capable of performing zero-shot classification and image-text matching tasks without the need for fine-tuning. CLIP is celebrated for its flexibility and its proficiency in adapting to new tasks. ViLBERT modifies the BERT architecture to accommodate both visual and textual inputs. It processes images and text through two distinct streams, which are later merged to create a unified representation. ViLBERT is specifically designed for tasks such as visual question answering and image-text retrieval. UNITER offers a unified architecture that integrates image and text processing into a single stream. It leverages a transformer-based model to develop joint representations of visual and textual information. UNITER is adept at handling a variety of vision-language tasks and has demonstrated robust performance in visual question-answering and image-text matching tasks.

Exciting experience of overcoming technical limitations

Participating in such projects is particularly exciting and can be thoroughly enjoyed within the company. While there are moments when I am amazed by the potential of these experiences, there are also times when I clearly see the limitations of current technology. In developing products, engineers do not always apply the latest AI techniques; instead, they sometimes opt for more traditional AI architectures because of their distinct advantages. Overcoming these limitations is a major concern that I share with the AI research team.

The work environment at the company is less structured than in a hospital, with unexpected tasks frequently arising. This can be viewed either as an advantage, lending to a dynamic atmosphere, or as a disadvantage, contributing to instability. I have progressed past the adaptation stage and am now focused on developing my competitiveness. Although I no longer provide direct patient care, I am committed to engaging in meaningful work that extends beyond merely seeking profit. My limited experience may still offer valuable insights to the readers.

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Authors' contributions
All work was done by Chang Ho Ahn.

Conflict of interest
Chang Ho Ahn has been an employee of Lunit since 2023. This article does not promote or advertise the company; instead, it provides an introduction for medical students and junior doctors who are interested in physicians' roles at AI companies. Otherwise, no potential conflict of interest relevant to this article was reported.

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Meeting Report

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Embracing the digital transformation in healthcare: insights and reflections from the Korean Society of Digital Clinical Medicine Summer Conference 2024

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Meeting: The Korean Society of Digital Clinical Medicine Summer Conference 2024
Date: June 2, 2024
Venue: Seoul Dragon City Hotel
Organizer: Korean Society of Digital Clinical Medicine

I participated in the Korean Society of Digital Clinical Medicine Summer Conference 2024 as a medical student, along with members of Ewha Medical School's startup club, E-co (Fig. 1). The conference provided an invaluable opportunity to hear from distinguished speakers in the field of digital clinical medicine and to engage in discussions and idea exchanges with other attendees. It featured an array of booths, presentations, and panel discussions, serving as a platform to

Fig. 1. Photo at the Korean Society of Digital Clinical Medicine Summer Conference 2024 with colleague students and Ewha Womans University College of Medicine preceptors on June 2, 2024.

showcase the latest trends, technologies, and research achievements in digital medicine and clinical practice. The event was organized into sessions held in Rooms A and B. The morning sessions were joint for all attendees, while the afternoon sessions were divided into two separate tracks. Although I am not an expert in digital clinical medicine, I was inspired to briefly describe my experiences at the meeting because it impressed me.

Ethics statement

This was not a human population-based study; therefore, it did not require approval from an institutional review board or obtainment of individual consent.

Session 1. Prospects of digital health

The first session, titled "Prospects of digital health," began with a presentation by Director Ji-Hyun Ahn on "Trends and prospects of digital healthcare in Korea and abroad." This introductory lecture provided definitions of digital health and digital healthcare, discussed current market trends, and addressed regulations and ethical considerations. This comprehensive overview effectively set the stage for the remainder of the conference.

The second lecture, delivered by Professor Sang-Ho Cho from Hallym University Medical School, was titled "Digital health review through CES 2024." CES 2024, known as the world's largest electronics and IT exhibition, served as the focal point of this discussion. The lecture emphasized the technologies that garnered attention at CES 2024, particularly those that received the Best Innovation Awards. Notably, 8 out of the 27 award-winning products were related to wellness, highlighting the increasing significance of digital healthcare. Furthermore, eight of these award-winning products originated from Korean companies, showcasing the strong influence of Korean firms in the global IT market. The trends in Health and Wellness Tech at CES 2024 were summarized into three main categories: artificial intelligence (AI) integration in digital health, the digitization of care, and the personalization of care. During the lecture, Professor Cho introduced notable innovations such as the "motionsleep" smart pillow by 10minds and the "Mand.ro Mark 7D" robotic finger prosthesis by Mand.ro, both products of Korean companies.

The presentation was delivered by Mi-Jung Son, the team leader of the Digital Medical Device Task Force at the Ministry of Food and Drug Safety. Her lecture, titled "Current and future policies of digital medical devices," offered a comprehensive overview of industry and regulatory trends, culminating in a discussion about the Digital Medical Device Act. This act, which was enacted on January 23, 2024, and is set to be implemented on January 24, 2025, is designed to cater to the unique characteristics of digital medical devices. The existing legal framework, primarily focused on pre-market control, is tailored for traditional medical devices and pharmaceuticals and does not adequately address the distinct features of digital medical products. The new legislation defines digital medical devices as those that incorporate advanced digital technologies, such as AI and ICT, for use in diagnosing, treating, predicting, or monitoring diseases, and for maintaining or improving health. The presentation also discussed changes in product classification and grading, clinical trials, and approval processes under the new law. This lecture was particularly informative, providing detailed insights into the legislative history and the forthcoming Digital Medical Device Act, highlighting the importance of evolving regulations in step with the progress of digital healthcare.

Session 2. Directions of digital care: conventional vs. digital

The second session, "Directions of digital care: conventional vs. digital," contained presentations comparing traditional and digital treatments for four diseases: obesity, diabetes, insomnia, and arrhythmia.

Dr. Kyung-Sil Lee from Life Clinic opened the session with a presentation titled "Obesity: conventional vs. digital." Initially, I viewed obesity as irrelevant to my interests, but I quickly recognized that the widespread effort to lose weight is, in fact, a strategy to manage obesity. The presentation covered several apps I had previously used, such as InOut, Milligram, and Yazio, which added a level of familiarity to the discussion. However, I had not considered that these apps were free. The speaker pointed out that digital care is a business that must be viewed from the payer's perspective, as payers are essential for the industry's survival. When the payer is also the user, digital transformation becomes viable. For instance, in weight management, users would need to pay, but the abundance of free apps results in few users opting for paid subscriptions. The presentation also noted exceptions where patients willingly pay for services like Juvis Diet or 365mc Hospital, categorizing these under the "desire" domain rather than the "disease" domain.

The second lecture was given by Professor Soo Im from Seoul National University Hospital and was titled "Diabetes: conventional vs. digital." Professor Im explored the limitations of HbA1c levels, which reflect average blood glucose levels over a period of 2–3 months but fail to capture acute episodes of hypoglycemia and hyperglycemia or daily fluctuations in glucose levels. The importance of monitoring glucose variability stems from its links to oxidative stress, endothelial dysfunction, inflammatory responses, and retinal damage. Continuous glucose monitoring systems, such as Freestyle Libre and Dexcom G7, play a crucial role in addressing this need. The primary objectives of glucose management using continuous glucose monitoring include increasing the time in range and minimizing glucose variability (GV).

The third lecture, delivered by Professor Ho-Jin Choi from Hanyang University Medical School, was entitled "Insomnia: conventional vs. digital." Insomnia, which is recognized as the most prevalent sleep disorder, affects approximately 10%–15% of the population. Treatment options for insomnia encompass cognitive-behavioral therapy (CBT) and pharmacological interventions. CBT for insomnia (CBT-I) comprises several components: sleep hygiene education, stimulus control therapy, sleep restriction therapy, relaxation techniques, and cognitive therapy. A digital therapy device named "Somzz" was introduced during the lecture. This device employs CBT-I techniques via a sequential algorithm, providing real-time feedback, behavioral interventions, and a training program designed to treat chronic insomnia over a period of 6–9 weeks. The presentation also addressed the potential and challenges associated with digital therapy devices, including issues related to reimbursement, discrepancies in clinical trials, and patient willingness to pay.

The fourth lecture, by Professor Sung-Hoon Choi from Hallym University Medical School, was entitled "Arrhythmia: conventional vs. digital." This presentation explored traditional methods of diagnosing arrhythmia, such as ECG, alongside newer, non-invasive techniques. It also discussed the use of wearable devices for heart health monitoring, including Holter monitors and event recorders. The lecture highlighted the digital transformation in the diagnosis of heart disease, featuring advancements in telemonitoring and the application of AI in ECG, imaging, and electrophysiology. Additionally, it addressed the challenges of implementing these new technologies in Korea, including the development of monitoring systems, service providers, and reimbursement mechanisms. The potential of photoplethysmography to detect atrial fibrillation using optical sensors was a particularly intriguing topic. The presentation concluded with an

analogy to the Luddites, emphasizing the need for doctors to adapt to technological changes.

Session 3. MOU Session with the Korean Society of Heart Failure

In the afternoon, I attended sessions in Room B, which featured a session organized by the Korean Society of Heart Failure (MOU session) that included four lectures.

The first lecture was delivered by Dr. Sung-Ji Park from Samsung Medical Center and was titled "Easily conducting echocardiography using AI." Dr. Park discussed the traditional echocardiography process and the enhancements that AI brings to it. AI facilitates both image acquisition and analysis, streamlining the diagnostic process. The integration of AI into echocardiography, encompassing device manufacturing, image sorting, and digital storage, proved to be an exciting development.

Professor Shi-Hyuk Kang from Seoul National University Hospital gave the second lecture in this session, discussing management platforms for heart disease patients. He elaborated on the potential and limitations of digital technologies in 24-hour blood pressure monitoring for patients with hypertension. Professor Kang noted that digital healthcare reimbursement is probable only for conditions with established guidelines and demonstrable benefits for both doctors and patients, such as insomnia. He also emphasized the wider applications of digital technologies in lifestyle management, medication adherence, and rehabilitation.

The third lecture was by Professor Woong Kook from Seoul National University's Mathematics Department, titled "Mathematics, artificial intelligence, and digital medicine." Despite the complexity of topological data analysis, the central theme was that mathematical analysis of medical data can reveal geometric patterns and classify patient groups. Professor Kook demonstrated, using hospital data research, how mathematics, statistics, and AI can deepen medical insights and be applied to big data.

The fourth lecture, delivered by Seong-Eun Moon from Naver, was titled "Digital Health Based on Search Portals." This presentation captured my interest as it explored the ways in which data companies such as Naver are adapting to the digital healthcare environment. I found the discussion on the potential of language models to minimize manual errors in electronic medical records and enhance efficiency particularly intriguing. The lecture also stressed the importance of having access to large volumes of raw data to effectively train these models, underscoring the necessity for extensive data collection in the healthcare sector.

Session 4. Convergence of digital industries and healthcare

The final session in Room B was titled "Convergence of digital industries and healthcare."

Professor Sung-Gyun Kim from Hallym University College of Medicine gave the first lecture on "Predicting chronic kidney disease using AI." This presentation explored the use of AI for monitoring and predicting different facets of kidney disease. It included industry examples such as VUNO's DeepECG and Hativ, showcasing the effective application of AI in the early diagnosis and monitoring of conditions like end-stage renal disease and chronic kidney disease. The ability of AI to detect hyperkalemia through ECG, despite human limitations, was awe-inspiring.

The second lecture, presented by Dr. Gi-Hyun Jeon from Seoul National University Bundang Hospital, focused on the "Utilization of ChatGPT plugins in the clinic." Although I was not familiar with ChatGPT, I found Dr. Jeon's demonstration of its practical applications in a clinical setting

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to be enlightening. Additionally, his YouTube tutorials on using ChatGPT for various educational purposes proved beneficial, illustrating how students can utilize AI to enhance their learning and research capabilities.

The third lecture, delivered by Professor Tae-Ho Heo from Seoul National University, was titled "The reality of medical platforms." This lecture examined the operational status and characteristics of various domestic and international telemedicine platforms. It also addressed the ethical and legal challenges associated with defining the scope of telemedicine and determining responsibility, offering a realistic perspective on the complexities of implementing telemedicine services.

Reflection

As a medical student passionate about biomedical engineering and digital healthcare, I found the Korean Society of Digital Clinical Medicine Summer Conference to be an invaluable experience. The conference covered a wide range of topics, from policy and regulation to the practical applications of AI and digital technologies, providing a comprehensive overview of the current landscape and future potential of digital clinical medicine. The opportunity to interact with experts and peers was particularly enriching, facilitating the exchange of ideas and experiences that will undoubtedly benefit my future studies and career. This conference has reinforced my commitment to integrating digital technologies into medical practice and research, and I am eager to contribute to the advancement of digital healthcare.

This experience has also highlighted the importance of keeping up to date with the latest advancements in digital healthcare, a field that is evolving rapidly. The insights I gained from this conference will be invaluable in shaping my future studies and research. I am dedicated to advancing my education in digital healthcare and biomedical engineering, and I am eager to explore how these technologies can enhance patient outcomes and advance medical practice.

Conclusion

Attending the Korean Society of Digital Clinical Medicine Summer Conference was an enriching experience. The knowledge and insights gained from the lectures and interactions with experts in digital healthcare have greatly enhanced my understanding of this rapidly evolving field. The conference covered a wide range of topics, from foundational knowledge of digital healthcare to in-depth discussions on regulatory frameworks and practical applications, which are all relevant to current and future medical practice. This experience has solidified my interest in digital healthcare and biomedical engineering, and I am eager to continue participating in future conferences and expanding my knowledge in this area.

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Authors' contributions

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