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PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Editorial

Peacetime preparedness for the vaccine adverse event

Jong-Koo Lee

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Globally, we are largely moving past coronavirus disease 2019 (COVID-19) and returning to normalcy. The government of the Republic of Korea plans to lower the COVID-19 alert level to the least severe tier, “interest” starting May 1, 2024 [1]. The recommended period of isolation for Covid-19 patients will be shortened from the current five days to patients isolating for one extra day after symptoms have disappeared, and mask-wearing in medical institutions will become voluntary, similar to the protocols for seasonal influenza. Additionally, the 2023–2024 seasonal vaccination campaign will conclude. This fall, the 2024–2025 seasonal vaccination schedule is set to be offered free of charge and will continue to prioritize high-risk groups, including those for influenza. However, it will be necessary to implement pre-emptive measures for respiratory syncytial virus vaccinations, as recommended for high-risk groups in some countries.

The return to everyday life represents a period of calm before the next pandemic, and our use of this time to prepare for future challenges is clearly informed by past experiences. Firstly, the government has committed to improving communication. However, the most crucial strategy for preparing and responding to the next outbreak is vaccination. Nevertheless, due to legislative shortcomings, policies concerning compensation for vaccine-related damages are still being developed.

We have published 2 research papers that investigate adverse reactions to COVID-19 vaccinations in the Republic of Korea. The first paper primarily discusses the research methodology used to study vaccination adverse reactions, titled "A Framework for Nationwide COVID-19 Vaccine Safety Research in the Republic of Korea" [2]. The second paper summarizes the research findings published in this issue [3]. The authors calculated the expected versus observed occurrence ratios for 29 diseases, and validate mechanistic evidence and draw conclusions about causality. The timing of these papers, coinciding with the Global Vaccine Data Network 24 symposium, is particularly opportune, especially given that the United States (US) National Academy of Medicine has also released results on the adverse effects of severe acute respiratory syndrome coronavirus 2 vaccination [4].

Over the past 3 years, the Korea Disease Control and Prevention Agency has entrusted the National Academy of Medicine of Korea with the rapid identification of causal links related to vaccinations. Typically, the evidence is classified into 4 levels: establishes a causal relationship, favors acceptance of a causal relationship, is inadequate to accept or reject a causal relationship, and favors rejection of a causal relationship. However, conditions such as pericarditis, Guillain-Barré syndrome, Bell's palsy, and some other diseases exhibit some differences between the Republic of Korea and the US, necessitating further discussion and research.

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To effectively respond to the potential Disease X, the global community is striving to develop new mRNA vaccines within 100 days, targeting 10 viral families identified by the US National Institute of Health and 25 viral families identified by the Coalition for Epidemic Preparedness Innovations. However, it is even more crucial to evaluate the efficacy and safety of these vaccines. For example, the US Food and Drug Administration withdrew the emergency use authorization for Ad26.COV2.S because it did not update its approval to reflect adaptations needed for the evolving virus [5]. Therefore, ongoing research and the adaptation of vaccines to accommodate viral changes are imperative. During peacetime, it is essential to promptly address issues related to adverse vaccine reactions and to reduce vaccine hesitancy. Several measures are necessary to achieve this.

First, to prepare for emergency vaccinations, we must strengthen both active and passive surveillance networks (pharmacovigilance). This involves establishing investigative methodologies, identifying critical information, and determining methods for minimal data set collection. To achieve this, specific centers should be designated for data collection, and relevant personnel must be trained.

Second, the role of the rapid response team for severe adverse reactions should extend beyond merely identifying causal relationships in individual cases. It should also address recurring incidents through rapid cycle analysis. Establishing a real-time insurance claim platform to confirm associations should be a fundamental part of the operational system. This platform should include investigations into deaths as part of broader epidemiological studies.

Third, addressing vaccine-related injuries and generating scientific evidence are distinct tasks that can be approached in 2 different ways. Some regions, such as Europe and Asia (including Germany, Japan, and Taiwan), treat vaccine injuries as a matter of social solidarity, offering compensation even without definitive causal evidence. In contrast, the US distinguishes between its emergency response compensation (Countermeasures Injury Compensation Program) and its general vaccination compensation (Vaccine Injury Compensation Program), employing a more stringent compensation system. Consequently, the Republic of Korea should weigh the advantages and disadvantages of both models [6]. Although current public sentiment leans towards the former, further legislative improvements are necessary.

In conclusion, ongoing investment in scientific research to address vaccine injuries is crucial for maintaining communication with the public. Additionally, nurturing and sustaining personnel and organizations is essential to achieving our goals. We must avoid prematurely reducing budgets and organizations related to disease management as diseases are being eradicated.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021.

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Special Article

The COVID-19 Vaccine Safety Research Center: a cornerstone for strengthening safety evidence for COVID-19 vaccination in the Republic of Korea

Na-Young Jeong[1,2], Hyesook Park[1,3,4], Sanghoon Oh[1,5], Seung Eun Jung[1,4,6], Dong-Hyun Kim[1,7], Hyoung-Shik Shin[1,8], Hee Chul Han[1,4,9], Jong-Koo Lee[1,4], Jun Hee Woo[1,4], Jaehun Jung[1,10,11], Joongyub Lee[1,12], Ju-Young Shin[1,13,14,15], Sun-Young Jung[1,16,17], Byung-Joo Park[1,4], Nam-Kyong Choi[1,2,18]

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ABSTRACT

The COVID-19 Vaccine Safety Research Committee (CoVaSC) was established in November 2021 to address the growing need for independent, in-depth scientific evidence on adverse events (AEs) following coronavirus disease 2019 (COVID-19) vaccination. This initiative was requested by the Korea Disease Control and Prevention Agency and led by the National Academy of Medicine of Korea. In September 2022, the COVID-19 Vaccine Safety Research Center was established, strengthening CoVaSC's initiatives. The center has conducted various studies on the safety of COVID-19 vaccines. During CoVaSC's second research year, from September 29, 2022 to July 19, 2023, the center was restructured into 4 departments: Epidemiological Research, Clinical Research, Communication & Education, and International Cooperation & Policy Research. Its main activities include (1) managing CoVaSC and the COVID-19 Vaccine

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Safety Research Center, (2) surveying domestic and international trends in AE causality investigation, (3) assessing AEs following COVID-19 vaccination, (4) fostering international collaboration and policy research, and (5) organizing regular fora and training sessions for the public and clinicians. Causality assessments have been conducted for 27 diseases, and independent research has been conducted after organizing *ad hoc* committees comprising both epidemiologists and clinical experts on each AE of interest. The research process included protocol development, data analysis, interpretation of results, and causality assessment. These research outcomes have been shared transparently with the public and healthcare experts through various fora. The COVID-19 Vaccine Safety Research Center plans to continue strengthening and expanding its research activities to provide reliable, high-quality safety information to the public.

Keywords: Causality; Committee; COVID-19; Research center; Safety; Vaccines

Introduction

Since its outbreak in December 2019, coronavirus disease 2019 (COVID-19) rapidly became a global pandemic, with approximately 770 million confirmed cases and 6.9 million fatalities as of October 4, 2023 [1]. To combat the global spread of COVID-19, multiple vaccines have been developed and received emergency use authorization, including vaccines based on an adenovirus vector, protein subunit, and mRNA [2]. In the Republic of Korea, the COVID-19 vaccination program commenced on February 26, 2021, with initial distribution at public health clinics and long-term care centers. As of October 28, 2022, approximately 87.1% of Koreans over 6 months of age had completed their primary vaccine series [3].

When the COVID-19 vaccination program was initially implemented, the Republic of Korea lacked a robust surveillance system to assess the causal link between COVID-19 vaccines and adverse events (AEs). To strengthen surveillance for scientific and systematic safety assessment, the COVID-19 Vaccine Safety Research Committee (CoVaSC) was established on November 12, 2021 at the request of the Korea Disease Control and Prevention Agency (KDCA) [4]. This initiative was primarily led by the National Academy of Medicine of Korea (NAMOK), an organization comprising experts in medicine, pharmacology, and public health. After its inception, the CoVaSC undertook its first year of research during a 10-month period starting on November 19, 2021. The results of this research were used to expand the list of AEs acknowledged to be causally linked with COVID-19 vaccination [4].

The first year of research revealed statistically significant risks associated with COVID-19 vaccination and identified additional diseases for inclusion in the list of suspected conditions. Notably, myocarditis and pericarditis were recognized for their causal relationships with BNT162b2 and mRNA-1273 vaccines. Abnormal uterine bleeding related to frequent and irregular menstruation or bleeding was also added to the list of diseases with a suspected association; however, there was insufficient evidence for causality [4].

During its second year of research, the COVID-19 Vaccine Safety Research Center was established to assume the role of CoVaSC and continue its research mandate. This article describes the research activities of the CoVaSC and the COVID-19 Vaccine Safety Research Center, focusing on COVID-19 Vaccine Safety Assessment. It also outlines the utilization of the findings from the COVID-19 Vaccine Safety Research Center and discusses their implications, providing insights into avenues for future research.

HIGHLIGHTS

- In September 2022, the COVID-19 Vaccine Safety Research Center was established to strengthen the activities of the COVID-19 Vaccine Safety Research Committee (CoVaSC) of the Republic of Korea.
- The CoVaSC has independently conducted research in collaboration with epidemiologists and clinical experts, ranging from protocol development through data analysis to the interpretation of results. This collaboration has facilitated the causality assessment of 27 adverse events of interest to date.
- The COVID-19 Vaccine Safety Research Center plans to continue focusing on ongoing research and expanding its studies to provide reliable and high-quality safety information to the public.

Materials and Methods

Background for Establishing the COVID-19 Vaccine Safety Research Center

Following the completion of its first year of research, CoVaSC's second-year research project began on September 23, 2022

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and lasted for 10 months. The COVID-19 Vaccine Safety Research Center was established on September 30, 2022. In November 2022, pursuant to Article 76.2 of the Infectious Disease Control and Prevention Act, the Notice to Designate Agencies for Research and Investigation of COVID-19 Vaccine Safety was enacted. Through this notice, NAMOK was commissioned to conduct safety research and investigate COVID-19 vaccines. This regulatory framework significantly boosted the efficiency of the research process (Table 1).

Table 1. Timeline of the COVID-19 Vaccine Safety Research Committee and adverse events for causality assessment

Time	Event	Organization of CoVaSC	Adverse events for causality assessment
February 26, 2021	Introduction of COVID-19 vaccine to public in the Republic of Korea		
First-Year Research Project (from November 19, 2021, to September 19, 2022)	Launch of the CoVaSC (November 12, 2021)	3 Committees and 13 teams · Epidemiology committee · Clinical research committee · Communication committee	Abnormal uterine bleeding Acute disseminated encephalomyelitis Acute myocardial infarction Acute transverse myelitis All cause death Aortic dissection Cerebral venous sinus thrombosis Deep vein thrombosis Guillain-Barré syndrome; Miller–Fisher syndrome Heart failure Myocarditis Pericarditis Pulmonary embolism Stroke
Second-Year Research Project (from September 23, 2022, to July 19, 2023)	Launch of the COVID-19 Vaccine Safety Research Center (September 30, 2022) Enactment of the Public Notice on the Designation of the Assigned Agencies to Perform COVID-19 Vaccine Safety Research & Investigations (November 4, 2022)	4 Departments and 17 teams · Department of Epidemiological Research · Department of Clinical Research · Department of Communication & Education · Department of International Cooperation & Policy Research	Acute disseminated encephalomyelitis Acute respiratory distress syndrome Acute transverse myelitis Anaphylaxis Bell's palsy·Disorders of facial nerve Convulsion·Seizure Deep vein thrombosis Encephalitis·Encephalopathy Encephalomeningitis Guillain-Barré syndrome·Miller-Fisher syndrome Herpes zoster Interstitial pulmonary diseases Lupus Lymphadenitis Multiple sclerosis Pulmonary embolism Sepsis Thrombosis with thrombocytopenia syndrome
Third-Year Research Project (from July 31, 2023, to July 30, 2024)	Continuously conducting research at the COVID-19 Vaccine Safety Research Center	5 Departments and 17 teams · Department of Epidemiological Research · Department of Clinical Research · Department of Media Communication · Department of International Cooperation & Policy Research · Department of Causality Assessment	Currently analyzing several adverse events to assess causality with COVID-19 vaccination

CoVaSC, COVID-19 Vaccine Safety Research Committee.

Organization of the COVID-19 Vaccine Safety Research Center

After the establishment of the COVID-19 Vaccine Safety Research Center under the CoVaSC, it was reorganized, expanding from 3 to 4 departments comprising 17 teams. The Department of Epidemiological Research has 5 teams for research on associations between COVID-19 vaccination and suspected AEs, 1 dedicated to the analysis of AE reports following COVID-19 vaccination, and 1 focused on reviewing causality assessment guidelines. The Department of Clinical Research consists of 6 teams specializing in distinct medical fields. The Department of International Cooperation & Policy Research consists of 2 teams: the International Cooperation Team, which is dedicated to collaborative international studies, and the Policy Research Team, which conducts vaccination-related policy research. The Department of Communication & Education contains teams dedicated to developing communication strategies, public education, and training programs. The center also has an advisory committee consisting of experts in medicine, pharmacology, and public health, along with disease-specific *ad hoc* committees that collaborate with Epidemiological Research Teams (Figure 1).

The Department of Epidemiological Research monitors and detects safety signals based on COVID-19 vaccine AE

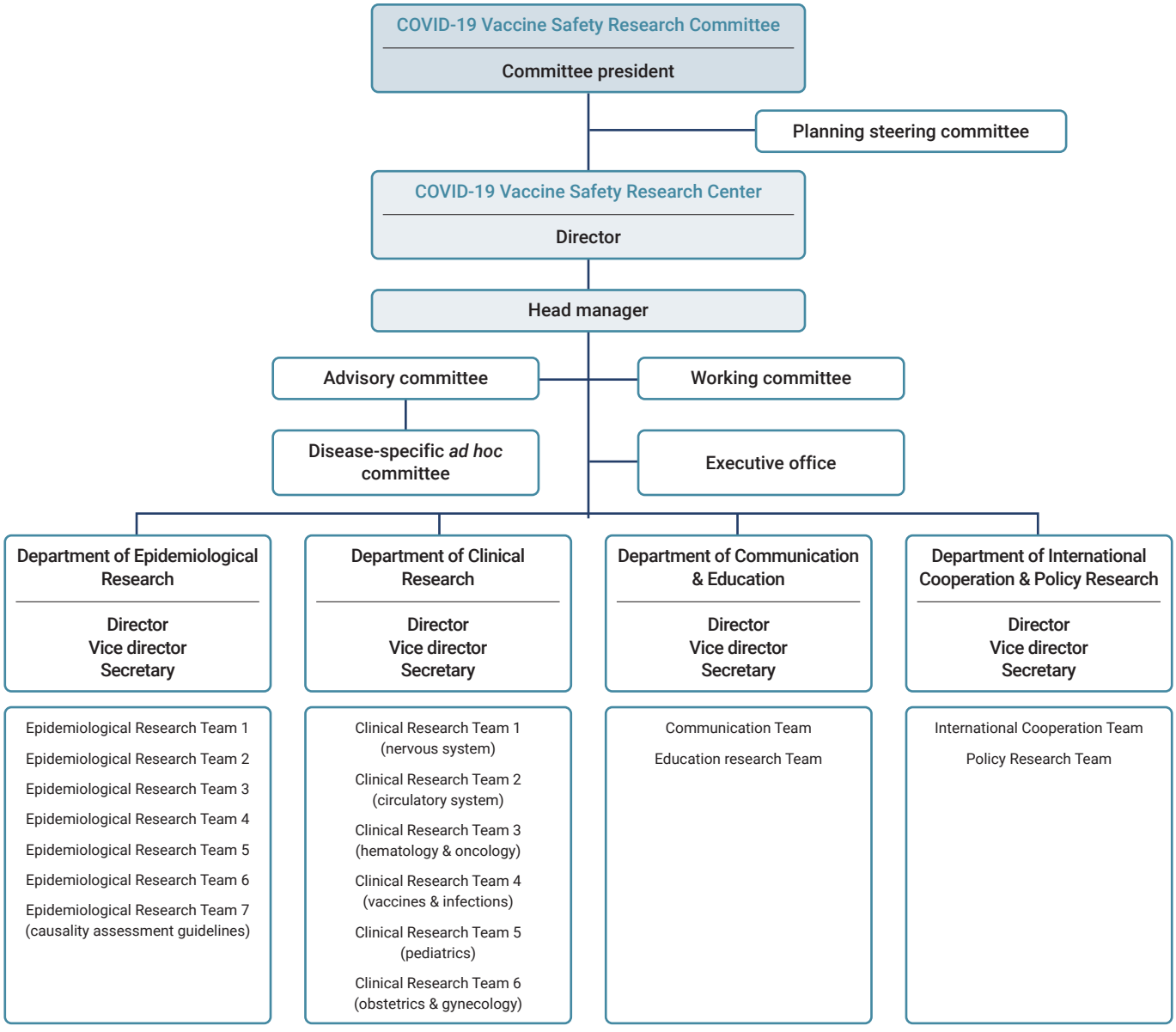

Figure 1. Organization chart of the COVID-19 Vaccine Safety Research Committee during its second year of research.

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reports, establishes plans for epidemiological research, and performs statistical analyses. The Department of Clinical Research formulates research plans considering the clinical environment and operational definitions. This department conducts preliminary literature reviews on the associations between COVID-19 vaccines, AEs, and biological mechanisms.

The Department of Clinical Research collaborates with the Department of Epidemiological Research to develop research protocols and to conduct causality assessments based on literature reviews. *Ad hoc* committees have been organized for each suspected disease of interest by collaboration between the Department of Epidemiological Research and that of Clinical Research, each with clinical experts and epidemiologists related to specific AEs. They have collaboratively developed operational case definitions and interpreted study results to produce high-quality research.

The Department of International Cooperation & Policy Research releases monthly newsletters to provide updates on international research trends related to COVID-19 vaccine safety. Collaborative research projects have been pursued by agencies responsible for international vaccine safety assessments. The department also organized an international symposium to facilitate collaboration in joint research. The Policy Research Team has explored ways to improve vaccine injury compensation systems and proposed pertinent policy recommendations.

The Department of Communication & Education develops communication strategies for clinical experts and the public, hosts fora, and issues press releases to share research findings with the COVID-19 Vaccine Safety Research Center. It has also conducted surveys on public perceptions and experiences of COVID-19 vaccination to identify communication needs.

Scopes and Topics of Research

The main activities of the COVID-19 Vaccine Safety Research Center include (1) managing CoVaSC and the COVID-19 Vaccine Safety Research Center; (2) surveying domestic and international trends in AE causality investigation; (3) assessing the causality of suspected AEs following COVID-19 vaccination; (4) fostering international collaboration and policy research, and (5) organizing regular fora and training programs aimed at raising awareness and communication with both the public and clinical experts.

While operating the COVID-19 Vaccine Safety Research Center, the CoVaSC held regular monthly researcher meetings and planning/steering committee meetings to review research progress. Department-specific meetings were arranged separately, and working committee meetings were convened if necessary. Regular and extraordinary meetings were held between the CoVaSC and KDCA to facilitate discussions regarding the diseases to be analyzed and presented, as well as to address general project matters.

Before commencing its research, the COVID-19 Vaccine Safety Research Center conducted a comprehensive review of the guidelines, protocols, and research findings published by healthcare authorities and vaccine safety surveillance networks in various nations. The center focused on signal detection and causality assessment methodologies and reviewed research methods, previously published articles, and causality assessment algorithms. The COVID-19 Vaccine Safety Research Center selected a causality assessment framework based on an algorithm proposed by the National Academy of Medicine [5] to evaluate the association between COVID-19 vaccines and adverse events of special interest (AESIs).

To assess the safety of COVID-19 vaccination, the center compiled AESI lists, replicating their approach in the first year. This list was then refined through a review of existing literature and by adopting operational definitions devised primarily by the Department of Clinical Research. The center conducted observed-to-expected analyses to compare the expected incidence of AESIs based on the background rate (AESI occurrence prior to the introduction of COVID-19 vaccines) and the observed incidence after vaccine introduction. Epidemiological studies were carried out using nationwide linked data from the COVID-19 Immunization Registry database at the KDCA and the claims database at the National Health Insurance Service (NHIS), and causality assessments were performed. The center also conducted a descriptive analysis of AE reports from those who completed the primary vaccination series or were vaccinated during the winter. Additionally, the center initiated a survey targeting individuals who reported abnormal uterine bleeding or hair loss as AEs after COVID-19 vaccination. The purpose of this survey was to conduct follow-up studies on symptoms that were difficult to confirm using only linked administrative databases. This survey aimed to gain insights into symptom characteristics, severity, and recovery status.

To promote international collaboration and policy research, the COVID-19 Vaccine Safety Research Center translated standardized case definitions published by the Brighton Collaboration, a non-profit global vaccine safety research network. The translated versions have been posted on the Brighton Collaboration and COVID-19 Vaccine Safety Research Center websites. Additionally, to promote joint international vaccine safety research, the center signed a Memorandum of Understanding with the Global Vaccine Safety Network on May 19, 2023, to conduct studies based on a common protocol regarding Guillain-Barré syndrome, myocarditis, pericarditis,

and vaccine-induced thrombosis and thrombocytopenia. The center organized an international symposium on May 19, 2023, titled "Strengthening International Partnership for Vaccine Safety Research and Beyond." The conference served as a platform for sharing the research process and discussing opportunities and considerations for future research [6]. Moreover, CoVaSC published a monthly newsletter to provide up-to-date information and knowledge on vaccination status and safety surveillance, both domestically and internationally.

The Policy Research Team reviewed the compensation programs for post-immunization AEs in the Republic of Korea and abroad to explore ways of improving the existing system. The team examined how vaccine injury compensation programs work globally, paying attention to those that closely resemble the healthcare settings of the Republic of Korea to gain insights into how to improve the current compensation system.

To improve communication between healthcare professionals and the public, the center conducted expert training sessions on the causality assessment of AEs related to COVID-19 vaccination and guidelines for reporting suspected AEs. Monthly fora were live-streamed on YouTube to disseminate the center's research findings to the public. These fora shared causality study results and their clinical interpretations, followed by panel discussions with designated panelists. Furthermore, the COVID-19 Vaccine Safety Research Center surveyed the general population and medical professionals to understand their experiences, attitudes, and perceptions regarding COVID-19 vaccination and improve messaging for future vaccinations against new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

Causality Assessment between COVID-19 Vaccination and Suspected AEs

List of AESIs

During the first year of research, 44 AESIs were identified through a literature review and consultation with clinical experts. In the second year, the list of AESIs was refined by removing diseases for which the analysis had concluded and updated to include only conditions requiring further analysis or reevaluation. The prioritization of AESIs included factors such as the incubation period, latent period post-vaccination, potential for relapse, and the feasibility of defining a risk window. The center also assessed whether the AEs had been captured in existing case reports and if pre-existing studies had provided operational definitions of the AEs based on health insurance claims data.

The final list of AESIs was formulated considering the center's opinions, the KDCA's comments, and the need to establish scientific evidence. Table 1 lists the AESIs for which the COVID-19 Vaccine Safety Research Center performed causality assessments during the first and second years of research.

Data sources

The COVID-19 Vaccine Safety Research Center utilized a nationwide linked database that combined the NHIS insurance claims database and the KDCA's COVID-19 Immunization Registry [4], replicating their approach from the first year. The NHIS database included data on all medical services covered by National Health Insurance for the entire Korean population from January 2002 to the most recent data available at the time of analysis, while the KDCA registry provided information on COVID-19 vaccination, AE reports, and details of previously confirmed SARS-CoV-2 cases starting from January 2020. The NHIS linked the COVID-19 vaccine registry with claims data using national registration numbers and provided it in a pseudonymized format to the COVID-19 Vaccine Safety Research Center for analysis.

Study design

For the analysis of AESIs, the expected incidence after COVID-19 vaccination was predicted based on the incidence before the COVID-19 vaccine roll-out. The center conducted an observed-to-expected analysis by calculating the ratio of the observed to expected incidence rates. A seasonal autoregressive integrated moving average model, a well-known time-series forecasting model, was employed.

For epidemiological association studies on AESIs, the Department of Epidemiological Research and an *ad hoc* committee adopted appropriate research methodologies, such as self-controlled case series and self-controlled risk intervals. The findings of the literature review and clinical insights from the *ad hoc* committee were considered to determine the risk window and follow-up period for each disease.

Causality assessment

Following an investigation into the association between COVID-19 vaccination and an AESI, an independent team performed a causality assessment based on the findings of the investigation and a literature review. This team comprised Epidemiological Research Teams, the *ad hoc* committee from the previous association study, and relevant experts. In the first year of research, the Bradford Hill criteria [7] and the U.S. Surgeon General's epidemiological criteria for causality [8] were used to determine whether each association was

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likely to be causal. During the second year of research, the COVID-19 Vaccine Safety Research Center used a framework based on algorithms proposed by the National Academy of Medicine [5] to conduct a population-level causality assessment. In this framework, epidemiological and mechanistic evidence were first evaluated separately and then assessed in a combined manner.

In performing the causality assessment, the weights of evidence from the epidemiological (including observational studies and randomized controlled trials) and mechanistic literature (including case reports, clinical trials, and clinical and biological studies involving humans, animals, or *in vitro* models) were assessed separately. Weight-of-evidence assessments for epidemiological evidence were categorized as high, moderate, limited, or insufficient. Mechanistic evidence was classified as strong, intermediate, weak, or lacking. Based on these evaluations, the independent causality assessment committee formulated conclusions, categorizing causality as convincingly supported, favoring acceptance, favoring rejection, inadequate to accept, or inadequate to reject [5].

Results

The COVID-19 Vaccine Safety Research Center extensively analyzed the safety of COVID-19 vaccines by monitoring AE reports and examining their potential association with AESIs. The center evaluated the causal relationship between COVID-19 vaccines and AESIs and hosted fora to share its findings. The results of the second year of research were presented at 7 fora held on December 5, 2022, and January 31, February 28, March 30, April 27, May 25, and June 21, 2023.

The center systematically monitored AE reports following COVID-19 vaccination, encompassing both monovalent and bivalent vaccines, including COVID-19 winter booster vaccines. The analysis explored the demographic characteristics, vaccine types, and dosages among individuals who reported AEs and the factors attributable to AE reporting. It also focused on abnormal uterine bleeding, which exhibited a statistically significant risk, analyzing the details of these reports to identify reporting patterns and calculate reporting rates.

The key findings from the COVID-19 Vaccine Safety Assessment for the second year are as follows. Eight diseases showed a statistically significant risk with COVID-19 vaccines: acute transverse myelitis, acute disseminated encephalomyelitis, Bell's palsy/facial nerve disorders, thrombosis with thrombocytopenia syndrome, encephalitis/encephalopathy, herpes zoster, lymphadenitis, and anaphylaxis (Table 2). The results of the studies on each AE were based on announcements at monthly fora and did not undergo formal peer review.

For 5 diseases, evidence was found favoring the acceptance of a causal relationship or evidence convincingly supporting a causal relationship based on epidemiological and mechanistic evidence: acute transverse myelitis, thrombosis with thrombocytopenia syndrome, encephalitis, encephalopathy, lymphadenitis, and anaphylaxis. For acute disseminated encephalomyelitis, the evidence was deemed inadequate for accepting or rejecting a causal relationship at the population level because few patients were included in the study and associations were absent in the existing mechanistic literature. There is also insufficient mechanistic evidence to conclude that COVID-19 vaccination can cause herpes zoster. Epidemiological studies yielded inconsistent results, making it difficult to accept or reject a causal relationship. For Bell's palsy and facial nerve disorders, the results do not align with the epidemiological literature, and there is a lack of mechanistic evidence supporting a causal relationship. Therefore, there was inadequate evidence to accept or reject causality. Given the findings from CoVaSC research, the association for acute transverse myelitis, which was initially included in the list of diseases with a suspected association only for adenovirus vector vaccines, expanded to include mRNA vaccines.

Three diseases showed a low risk after COVID-19 vaccination: Guillain-Barré and Miller-Fisher syndrome, acute respiratory distress syndrome, and interstitial pulmonary diseases. The evidence available to date is inconclusive for accepting or rejecting causal relationships. However, international literature has consistently reported an increased incidence of Guillain-Barré syndrome following the administration of virus vector vaccines. Given its mechanistic possibility, its association with adenovirus vector vaccines was favorable.

Discussion

Since their establishment in late 2021, the CoVaSC and COVID-19 Vaccine Safety Research Center have played pivotal roles in investigating the safety of COVID-19 vaccines using domestic data. The studies conducted by CoVaSC have laid the groundwork for a more comprehensive understanding of the side effects associated with these vaccines and expanded the list of diseases recognized to have a causal association with vaccination. Consequently, those affected have been compensated, and new diseases have been listed with their potential associations with the vaccines. Additionally, these studies used domestic data to generate supporting evidence regarding AEs previously recognized for their association with vaccines or included in the list of diseases with a suspected association.

Table 2. Summary of COVID-19 vaccine safety studies conducted by COVID-19 Vaccine Safety Research Center

Adverse events of interest	Announcement date	Epidemiological study results (statistical significance)[a]	Causality assessment results	Policy Measures on the Association Between COVID-19 Vaccines and Adverse Events (vaccine type and time)[b]
Death				
All cause death	March 4, 2022	NS	-[d]	
Cardio-cerebrovascular disease				
Myocarditis	March 4, 2022	Increased (only for mRNA vaccines)	Several criteria are met[e]	BNT162b2 and mRNA-127; Mar 2022[f] NVX-CoV2373; Dec 2022[g]
Pericarditis	May 12, 2022[c]	Increased (only for mRNA vaccines)	Several criteria are met[e]	BNT162b2 and mRNA-1273; May 2022[f] NVX-CoV2373; Dec 2022[g]
Stroke	March 4, 2022	NS	There are no criteria met[e]	
Acute myocardial infarction	March 4, 2022	NS	There are no criteria met[e]	
Heart failure	May 12, 2022	NS	Several criteria are met[e]	
Aortic dissection	May 12, 2022	NS	Most criteria cannot be evaluated[e]	
Neurological disease				
Acute transverse myelitis	January 31, 2023[c]	Increased	FA	ChAdOx1 and Ad26·COV2·S; Mar 2022[h] BNT162b2 and mRNA-1273; Feb 2023[g]
Acute disseminated encephalomyelitis	January 31, 2023[c]	Increased	I	ChAdOx1[h]
Guillain-Barré syndrome·Miller-Fisher syndrome	January 31, 2023[c]	Decreased	FA (only for adenovirus vector vaccines) or I	ChAdOx1 and Ad26·COV2·S[h]
Multiple sclerosis	February 28, 2023	NS	I	
Convulsion/seizures	May 25, 2023	NS	I	
Bell's palsy/facial nerve disorder	May 25, 2023	Increased	I	BNT162b2, mRNA-1273, and ChAdOx1[h]
Encephalitis/encephalopathy	June 21, 2023	Increased	FA	
Encephalomeningitis	June 21, 2023	NS	I	
Obstetric disease				
Abnormal uterine bleeding	August 11, 2022	Increased	Several criteria are met[e]	All type of vaccines; Aug 2022[g]
Hematologic disease				
Deep vein thrombosis	February 28, 2023[c]	NS	I	
Pulmonary embolism	February 28, 2023[c]	NS	I	
Cerebral venous sinus thrombosis	August 11, 2022	Increased	Several criteria are met[e]	ChAdOx1 and Ad26·COV2·S[h]
Thrombosis with thrombocytopenia syndrome	June 21, 2023[c]	Increased	CS	ChAdOx1 and Ad26·COV2·S[i]
Inflammatory disease				
Herpes zoster	February 28, 2023	Increased	I	
Lymphadenitis	March 30, 2023	Increased	CS or FA	All type of vaccines[i]
Lupus	May 25, 2023	NS	I	
Respiratory disease				
Acute respiratory distress syndrome	March 30, 2023	Decreased	I	
Interstitial pulmonary diseases	April 27, 2023	Decreased	I	

(Continued to the next page)

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Table 2. Continued

Adverse events of interest	Announcement date	Epidemiological study results (statistical significance)[a]	Causality assessment results	Policy Measures on the Association Between COVID-19 Vaccines and Adverse Events (vaccine type and time)[b]
Infectious disease				
Sepsis	April 27, 2023	NS	FR	
Allergic reaction				
Anaphylaxis	April 27, 2023	Increased	FA	All type of vaccines[j]
Surveillance of adverse event reports				
Overall adverse event reports	March 4, 2022; May 12, 2022; January 31, 2023; April 27, 2023	-	-[d]	
Adverse event reports of abnormal uterine bleeding	March 30, 2023	-	-[d]	

NS, not significant; FA, favors acceptance of a causal relationship; I, inadequate to accept or reject a causal relationship; CS, convincingly supports a causal relationship; FR, favors rejection of a causal relationship; I, inadequate to accept or reject a causal relationship.
[a]The terms "increased" and "decreased" refer to significantly increased and decreased risk, respectively. [b]This column indicates the timing of policy measures and whether the events were acknowledged as causally related or reportable, following vaccination with each type of COVID-19 vaccine. It also denotes whether the CoVaSC study results had an impact on these policy measures. [c]The outcome was re-analyzed, and only the date to release the results of final re-analysis was included. [d]Causality assessment was not conducted for the adverse event. [e]The Bradford Hill Criteria and the Surgeon General's epidemiological criteria for causality were used for causal inference. [f]Acknowledgement of causality based on CoVaSC research findings. [g]Added to the list of reportable adverse events based on CoVaSC research findings. [h]Initially listed as reportable adverse events prior to CoVaSC findings. [i]Initially included in the list of adverse events already acknowledged to exhibit a causal relationship before the CoVaSC research.

The research conducted by the CoVaSC and COVID-19 Vaccine Safety Research Center is highly significant. Epidemiological studies using domestic data have produced objective and scientific safety evidence on the association between AEs and COVID-19 vaccination. These findings were disseminated to the public, medical professionals, and governmental bodies. The well-designed research, which was conducted by a wide spectrum of experts (including clinicians specializing in various diseases, epidemiologists, public health experts, and biostatisticians) tapped into the COVID-19 vaccine registry, which included data from the entire population and the health insurance claims database.

The compiled data serve as a cornerstone for evidence-based policy decisions, particularly regarding compensation and medical support for those who experienced AEs after COVID-19 vaccination. The independence of the research—spearheaded by NAMOK, an academic society rather than a governmental entity—further reinforces public trust. In addition, the CoVaSC conducted international collaborative research and organized global symposia, demonstrating its commitment to global vaccine safety assessments. By sharing its expertise and research results, it collaborated with the international community to respond jointly to the global pandemic.

There are some limitations to the research carried out by CoVaSC. First, most studies focused on short-term AEs due to the insufficient duration of follow-up for monitoring long-term AEs. Rapid global vaccine roll-out meant that people received vaccinations within the same timeframe. Given the self-controlled study design employed, only abrupt-onset events were defined as outcomes [9]. Second, concerns were raised regarding the validity of the diagnostic codes for certain AESI diagnoses sourced from health insurance claims. It was also difficult to evaluate the causality of diseases that did not require hospital visits. To address this issue, the center devised a plan to build a registry system for conditions with validity concerns (e.g., cerebral venous sinus thrombosis). Third, near-real-time analyses were hampered by the inherent lag time in claims data. To address data delays in future research, we suggest analyzing data on a rolling basis and employing the results for ongoing, routine active surveillance monitoring [10]. Finally, since the research was conducted to inform policymaking using scientific evidence generated from epidemiological studies and population-level causality assessments, the findings may not precisely align with the causality assessment results for individual cases. Furthermore, even with the advantage of a large dataset, the research could not accurately assess extremely rare outcomes [11].

When the center embarked on its third year of research

on July 17, 2023, it was reorganized from 4 to 5 departments. The Department of Causality Assessment was established to strengthen independent causality evaluation. The Department of Communication and Education was renamed the Department of Media Communication with the aim of crafting diverse communication materials to promote collaboration with a wide array of stakeholders for vaccine safety studies. In addition, a geriatrics and immunology team was formed under the Department of Clinical Research.

Three and a half years after the outbreak of the COVID-19 pandemic, the Korean government lowered the alert level for COVID-19, resulting in the relaxation of several quarantine restrictions. As we transition into the endemic phase, CoVaSC and the COVID-19 Vaccine Safety Research Center are adjusting their research approaches. With routine COVID-19 vaccinations becoming the new norm, the research designs are being redesigned to focus on AEs that may emerge over longer periods. The center also plans to explore as-yet unaddressed issues, including the implications of cumulative vaccine exposure due to multiple booster shots following primary vaccination. In addition, it will strengthen communication efforts with scientists, policymakers, and the public to tackle misunderstandings due to uncertain information and promote open discussions for policymaking to enhance public trust.

Conclusion

Over the past 2 years, the CoVaSC has played a pivotal role in generating scientific evidence to guide policy decisions for potential AEs that may arise from COVID-19 vaccination. Although the global pandemic has subsided and the immediate threat of COVID-19 has diminished, vaccination remains necessary, especially for vulnerable populations. As the COVID-19 Vaccine Safety Research Center has commenced its third-year research project, it will continue to focus on ongoing research and expand its studies to provide reliable safety information to the public.

Notes

Ethics Approval

This study was approved by the Public Institutional Review Board Designated by the Ministry of Health and Welfare (P01-202203-01-005) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021, but had no role in the decision to publish this article. No other potential conflict of interest relevant to this article has been declared.

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Availability of Data

The datasets are not publicly available. If you have any questions about this study, please contact the corresponding author (nchoi@ewha.ac.kr; bjpark@snu.ac.kr).

Authors' Contributions

Conceptualization: NYJ, JKL, BJP, NKC; Methodology: all authors; Project administration: BJP; Visualization: NYJ; Writing–original draft: NYJ, NKC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Review Article

Psychiatric adverse events associated with the COVID-19 vaccines approved in the Republic of Korea: a systematic review

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ABSTRACT

This systematic review evaluated psychiatric adverse events (AEs) following vaccination against coronavirus disease 2019 (COVID-19). We included studies that reported or investigated psychiatric AEs in individuals who had received an approved COVID-19 vaccine in the Republic of Korea. Systematic electronic searches of Ovid-Medline, Embase, CENTRAL, and KoreaMed databases were conducted on March 22, 2023. Risk of bias was assessed using the Risk of Bias Assessment Tool for Non-randomized Studies 2.0. The study protocol was registered in the International Prospective Register of Systematic Reviews (CRD42023449422). Of the 301 articles initially selected, 7 were included in the final analysis. All studies reported on sleep disturbances, and 2 highlighted anxiety-related AEs. Sleep disorders like insomnia and narcolepsy were the most prevalent AEs, while depression was not reported. Our review suggests that these AEs may have been influenced by biological mechanisms as well as the broader psychosocial context of the COVID-19 pandemic. Although this study had limitations, such as a primary focus on the BNT162b2 vaccine and an observational study design, it offered a systematic, multi-vaccine analysis that fills a critical gap in the existing literature. This review underscores the need for continued surveillance of psychiatric AEs and guides future research to investigate underlying mechanisms, identify risk factors, and inform clinical management.

Keywords: Adverse effects; Anxiety; COVID-19 vaccines; Mental disorders; Sleep wake disorders; Systematic review

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Introduction

As a global health crisis, the coronavirus disease 2019 (COVID-19) pandemic has had profound

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effects on nearly all aspects of society. In response to the pandemic, several vaccines have been introduced, with Pfizer-BioNTech's BNT162b2, Moderna's mRNA-1273, and Oxford-AstraZeneca's ChAdOx1 nCoV-19 predominantly utilized. As recorded on July 22, 2023, global administration surpassed 13 billion vaccine doses [1]. Despite the substantial benefits of the COVID-19 vaccines, safety concerns about these new vaccines persist. These concerns are often amplified by inaccurate media reporting, potentially heightening vaccine hesitancy in the public [2]. Hence, comprehensive understanding and precise reporting on the nature and prevalence of any adverse events (AEs) related to COVID-19 vaccines are crucial.

No medical intervention is entirely free from the potential for AEs, and COVID-19 vaccines are no exception. Following COVID-19 vaccination, AEs can present as a spectrum of physical symptoms and psychiatric manifestations. Serious, albeit rare, AEs such as myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome, and Guillain-Barré syndrome have been reported [3]. Other less severe but notable symptoms have been consistently reported, including localized pain at the injection site, fatigue, headache, fever, nausea, and psychiatric symptoms such as anxiety and poor-quality sleep [4,5].

Of particular concern is the emergence of psychiatric symptoms after COVID-19 vaccination, an area of study that requires further exploration. The COVID-19 pandemic has already significantly impacted mental health worldwide, influenced in part by fear of the virus, lockdown mandates, and enforced social distancing [6,7]. Therefore, discerning the relationship between COVID-19 vaccination and the onset or exacerbation of psychiatric symptoms is highly important. To date, only one review has sought to synthesize the available evidence on this topic, focusing on published case reports [8].

Therefore, the present systematic review aimed to collate and analyze the existing literature on psychiatric AEs following COVID-19 vaccination. It sought to address the research question: What is the nature and extent of psychiatric AEs after COVID-19 vaccination, and what implications do these findings have for healthcare providers and policymakers?

HIGHLIGHTS

- This review systematically investigated psychiatric adverse events (AEs) following COVID-19 vaccination.
- In the studies reviewed, sleep disturbances such as insomnia and narcolepsy emerged as the most prevalent AEs, while depression was notably absent.
- Biological and psychosocial factors may influence the onset of these psychiatric AEs.
- The study fills a critical gap in the existing literature and calls for ongoing surveillance and further research.

Materials and Methods

The systematic review was conducted in accordance with the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [9], and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement [10]. The study protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (number: CRD42023449422). The authors are psychiatric and epidemiological experts and consultation was received from external reviewers specializing in the epidemiology of vaccine AEs.

Eligibility Criteria

Articles that matched the following criteria were considered: (1) studies of individuals vaccinated against COVID-19 with any vaccine approved in the Republic of Korea, including BNT162b2, mRNA-1273, Ad26.COV2.S, ChAdOx1 nCoV-19, NVX-CoV2373, and bivalent mRNA vaccines; (2) studies that reported on psychiatric AEs, with primary outcomes being anxiety and sleep disorders (e.g., narcolepsy and insomnia) and secondary outcomes covering panic attacks, depression, brain fog, and other psychiatric manifestations; and (3) either population-based or national-level studies.

Information Sources

A systematic electronic search of Ovid-Medline, Embase, CENTRAL, and the Korean database KoreaMed was conducted on March 22, 2023.

Search Strategy

The key terms included in the search were "COVID-19," "vaccine," "mental health," "sleep disorder," "depression," and "psychotic." A librarian was involved in establishing and conducting the search strategy. A manual search of the reference lists of relevant primary and review articles was also conducted to ensure comprehensiveness. The full electronic search strategy for each database is provided in Table S1.

Selection Process

Two reviewers (S.R. and M.C.) independently screened the titles and abstracts of all identified studies to assess eligibility for inclusion. Relevant full-text articles were then independently

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appraised by the same reviewers. Disagreements during the review process were addressed by consensus with a third review author (S.O.). The study selection was performed using Covidence software (Veritas Health Innovation) [11].

Data Collection Process

Two independent reviewers (S.R. and M.C.) conducted the data extraction process with one extracting the data and the other verifying the accuracy of the extracted data. The data extraction form included study characteristics and outcomes.

The data were primarily extracted from tables and figures within the studies, and supplementary files were consulted for additional detail when feasible. If supplementary material was not available, the intention-to-treat principle was used to impute missing data when possible.

Risk of Bias Assessment

The authors used the Risk of Bias Assessment Tool for Non-randomized Studies 2.0 to conduct a paired assessment for the risk of bias in the selected non-randomized studies [12].

Effect Measures

For each included study, continuous outcomes were presented as mean differences or hazard ratios, inverse-variance random-effects analysis and dichotomous outcomes were presented as odds ratios (ORs), and Mantel-Haenszel random-effects analysis with 95% confidence intervals (CIs) was applied to all outcome measures. The AEs in the vaccination studies were quantified using metrics such as rate ratios, ORs, or incidence rates and their 95% CIs.

Synthesis Methods

A meta-analysis was initially planned for studies demonstrating minimal heterogeneity. However, due to considerable heterogeneity and substantial differences in the study populations and methodologies among the included studies, conducting a meta-analysis was not feasible. Consequently, we pooled the results using a narrative synthesis, which provided a qualitative overview of the findings according to the synthesis without meta-analysis reporting guidelines [13].

Results

Study Selection

The initial search of the electronic databases yielded 301 articles. After removing duplicates, 222 articles remained. Of these, 83 were excluded based on title and abstract screenings, leaving 139 full-text reports for eligibility assessment. Ultimately, 7 studies were included in the final systematic review (Figure 1).

Study Characteristics

Of the 7 studies selected, all reported sleep disorders such as narcolepsy and insomnia. In addition, 2 studies documented cases of anxiety, while panic attacks, agitation, and brain fog were each reported in a single study. The characteristics and findings of the included studies are summarized in Table 1 [14–20].

Risk of Bias

The risk of bias assessment is presented in Figure S1 of the supplementary material. Notably, most studies demonstrated a low risk of bias, though there were concerns regarding outcome blinding and comparability of the target groups.

Results of Individual Studies

Sleep disturbance

One study focused on adolescents aged 12 to 18 years and found that the risk of developing sleep disturbances was significantly increased for those who received the BNT162b2 vaccine compared to those who were unvaccinated (IRR, 2.06; 95% CI, 1.01–4.24) [14]. Another self-controlled case-series study reported no significant difference in the

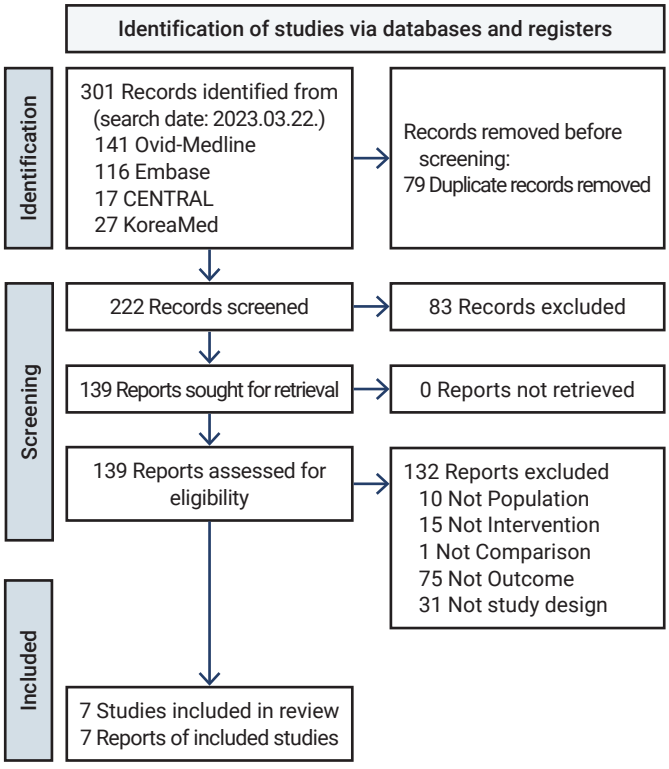

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analysis flow diagram for a systematic review of psychiatric adverse events following COVID-19 vaccination.

Table 1. Studies addressing psychiatric adverse events after COVID-19 vaccination

Study	Study site	Data source	Population (y)	No. of patients included in analysis	Intervention	Comparator	Study design	Outcome	Results
Wan et al. (2022) [15]	Hong Kong	National registry	People with type 2 diabetes (≥16)	141,224 BNT162b2 recipients	BNT162b2	Self-control	Self-controlled case series	Narcolepsy	The incidence of narcolepsy was not significantly different after vaccination with BNT162b2 (1st dose: IRR, 1.02; 2nd dose: IRR, 0.60) than before vaccination.
Wong et al. (2022) [18]	Hong Kong	National registry	Adults (≥18)	BNT162b2 1st: 1,308,820 BNT162b2 2nd: 1,116,677	BNT162b2	N/A	Retrospective observational study	Sleeping disturbance or disorder	The incidence rate of sleep disturbance by vaccine dose was as follows: BNT162b2 1st dose: 122 cases/100,000 doses; 167 cases/100,000 person-years BNT162b2 2nd dose: 91 cases/100,000 doses; 142 cases/100,000 person-years
Lai et al. (2022) [14]	Hong Kong	National registry	12–18	BNT162b2 1st: 138,141 BNT162b2 2nd: 119,664	BNT162b2	Unvaccinated	Retrospective observational study	Sleeping disturbance or disorder	A statistically significant difference in sleep disturbance was observed after the 2nd dose of the Pfizer vaccine compared to the unvaccinated group (IRR, 2.06; 95% CI, 1.01–4.24).
Lloyd et al. (2022) [16]	USA	Claim data	12–64	5,070,372 in Optum 7,445,051 in Healthcore 4,326,594 in CVS Health	BNT162b2, mRNA-1273, Ad26.COV2.S	Historical control (general population or influenza-vaccinated)	Nonconcurrent cohort study	Narcolepsy	The RR of narcolepsy and the frequency of narcolepsy cases per 100,000 doses of vaccine by data source and vaccine type are as follows: Optum: BNT162b2 RR 0.74; 2.6/mRNA-1273 RR 0.78; 3.2/Ad26.COV2.S RR 1.01; 4.9 HealthCore: BNT162b2 RR 1.07; 3.4/mRNA-1273 RR 1.02; 3.6/Ad26.COV2.S RR 0.94; 3.9 CVS Health: BNT162b2 RR 1.35; 3.4/mRNA-1273 RR 1.36; 3.8/Ad26.COV2.S RR 1.63; less than 5.5
Garcia-Alanis et al. (2022) [19][a)]	Mexico	National registry	Adults (≥18)	19,163 Individuals who reported adverse events	BNT162b2, ChAdOx1 nCoV-19, rAd26-rAd5, Ad5-nCoV, CoronaVac	N/A	Retrospective observational study	Anxiety, panic attack, insomnia, agitation	129 Cases of anxiety, 30 cases of panic attack, 25 cases of insomnia, and 11 cases of agitation were reported after COVID-19 vaccination with BNT162b2 or ChAdOx1 nCov-19.
Abdel-Qader et al. (2022) [17]	Jordan	National registry	Adults (≥18)	BNT162b2 1st: 418,517 BNT162b2 2nd: 192,074 ChAdOx1 nCoV-19 1st: 80,281 ChAdOx1 nCoV-19 2nd: 60,562	BNT162b2, ChAdOx1 nCoV-19	N/A	Prospective observational study	Insomnia, brain fog	The incidence of insomnia by vaccine type was as follows: BNT162b2 1st / 2nd dose: 1,182 cases (0.3%)/2,503 cases (1.3%) ChAdOx1 nCoV-19 1st / 2nd dose: 4.702 cases (5.9%)/2,558 cases (4.2%) The incidence of brain fog by vaccine type was as follows: BNT162b2 1st/2nd dose: 449 cases (0.1%)/152 cases (0.1%) ChAdOx1 nCoV-19 1st / 2nd dose: 5,103 cases (6.4%)/2,993 cases (4.9%)

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Table 1. Continued

Study	Study site	Data source	Population (y)	No. of patients included in analysis	Intervention	Comparator	Study design	Outcome	Results
Alkhalifah et al. (2023) [20]	Saudi Arabia	National registry	12–96	28,031 Individuals who reported adverse events	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19	N/A	Retrospective observational study	Anxiety, sleep disruption	The incidence of insomnia (p = 0.48)/sleep disruption (p = 0.022) by vaccine type was as follows: BNT162b2: 221 cases (0.58%)/487 cases (1.27%) ChAdOx1 nCoV-19: 207 cases (0.64%)/463 cases (1.44%) mRNA-1273: 5 cases (0.53%)/17 cases (1.79%)

COVID-19, coronavirus disease 2019; N/A, not applicable; IRR, incidence rate ratio; CI, confidence interval; RR, rate ratio.
[a]An estimated 88% of the total received vaccination with BNT162b2 or ChAdOx1 nCoV-19.

incidence of narcolepsy between the BNT162b2 vaccinated and unvaccinated patients with type 2 diabetes during the risk period versus the comparison period. The dose of the vaccine was also not linked to the outcome[15].

However, 3 studies did provide insights into the incidence rate of sleep disturbance by vaccine type [16–18], reporting 0.16 cases per 1,000 mRNA vaccine doses and 49.79 cases per 1,000 adenoviral vector vaccine doses. Two other studies, instead of reporting the total number of vaccinated individuals, highlighted the total AEs and specific cases of sleep disturbance [19,20]. One of these studies reported 25 cases of insomnia among 19,163 reported AEs after COVID-19 vaccination [19]. Another study revealed 487, 17, and 463 cases of sleep disturbance following vaccinations with BNT162b, mRNA-1273, and ChAdOx1 nCoV-19, respectively, as registered in the Saudi Arabia National Adverse Events Registry for recipients aged 12 to 96 years. These results showed a significant difference in the incidence of sleep disturbances by vaccine type (p = 0.022) [20].

Anxiety and cognitive AEs

Among the studies in our review, 2 reported anxiety-related AEs following COVID-19 vaccination [19,20]. One study noted that, out of 19,163 reported AEs, there were 129 cases of anxiety, 30 cases of panic attacks, and 11 cases of agitation [19]. The other study included 28,031 individuals who had reported 71,480 AEs. Of these, 221 (0.58%), 207 (0.64%), and 5 (0.53%) cases of anxiety were reported after the administration of the BNT162b, ChAdOx1 nCoV-19, and mRNA-1273 vaccines, respectively. However, no statistically significant differences were found in the proportion of anxiety cases between these vaccine types [20]. Regarding cognitive disturbances, another study reported incidences of brain fog following COVID-19 vaccination. Specifically, the mRNA vaccine was associated with 0.93 cases per 1,000 doses, whereas the adenoviral vector vaccine had a significantly higher incidence with 56.09 cases per 1,000 doses [17].

Discussion

The current review compiled findings from 7 studies investigating psychiatric AEs related to COVID-19 vaccines. Of the psychiatric manifestations observed after vaccination, sleep disturbance and anxiety were the most frequently reported. In contrast, depression was rarely documented. The selected studies all investigated AEs following vaccination with BNT162b2, and some studies included evaluations of the mRNA-1273, ChAdOx1 nCoV-19, and other vaccines. The varying incidence of sleep disorders among the different vaccine types suggests that a distinction in vaccine formulation or

its constituents might influence the susceptibility to specific adverse outcomes.

It is noteworthy that all studies included in our review reported sleep disorders such as insomnia or narcolepsy following COVID-19 vaccination. Although the biological mechanisms underlying these sleep disturbances remain elusive, several hypotheses have been proposed [21,22]. One recent study highlighted a link between postvaccination inflammatory reactions and certain hypothalamic circuits crucial to the sleep-wake cycle. Specifically, following peripheral activation of the innate immune system by the novel COVID-19 vaccines, pro-inflammatory cytokines potentially inhibit orexinergic neurons, resulting in enhanced sleepiness [21]. Alternately, the occurrence of postvaccination insomnia may be mediated by hyperarousal as well as inflammatory cytokines [23]. Stress and sleep share a significant correlation, with stressful life events often precipitating acute insomnia [24]. The inherent stress associated with receiving a novel COVID-19 vaccine during a global pandemic might activate the hypothalamic-pituitary-adrenal (HPA) axis, inducing a hyperarousal state that contributes to the onset of insomnia [25].

Two studies in this review reported anxiety and anxiety-related AEs after receiving a COVID-19 vaccination [19,20]. The emergence of postvaccination anxiety symptoms might be attributed to the HPA and immune axes [26], similar to the proposed mechanisms underlying sleep disturbances. Beyond these biological underpinnings, it is also vital to account for social and psychological influences. In the early stages of the COVID-19 pandemic, global anxiety levels escalated and were further exacerbated by the emergency authorization of new vaccines [27]. Given this context of widespread apprehension, we must be cautious about directly linking postvaccination anxiety symptoms solely to the vaccine. Monitoring the persistence of such anxiety reports over time remains essential.

Brain fog following immunization with COVID-19 vaccines was also reported in one study [17]. Brain fog is a nonspecific cognitive symptom characterized by lack of mental clarity, difficulty concentrating, and mental fatigue. This syndrome of cognitive impairment is commonly associated with post-COVID conditions (also called "long COVID") [28]. Several mechanisms have been suggested to explain brain fog after COVID-19 illness [29,30]. However, the association between COVID-19 vaccines and this cognitive impairment remains unclear. Postvaccination brain fog might be more closely linked to flu-like symptoms (e.g., headache, fatigue, fever) than to previously defined cognitive symptoms [31]. Interestingly, active safety surveillance data from Jordan showed a higher incidence of reported brain fog with the ChAdOx1 nCoV-19 vaccine than the BNT162b2 vaccine [17]. This suggests that systemic AEs such as headache, fatigue, and fever appear more prevalent following administration of the adenoviral vector vaccine than the mRNA counterpart [32]. Further research should be done to determine a direct link between the vaccine and genuine cognitive impairment.

One unanticipated observation from the studies included in our review was the absence of reports on postvaccination depression or psychosis. In contrast, a prior review identified 11 articles that documented 14 cases of psychiatric AEs, predominantly psychosis and mood disorders [8]. This discrepancy may be attributed to differences in study design. Our review sourced data from population-based or national-level studies, which are inclined to report the more common, milder AEs. In contrast, the earlier review was based on case reports, which tend to document the less frequent and more severe side effects like psychosis. Despite their relative infrequency in national databases of COVID-19 AEs, case reports of serious psychiatric AEs continue to be published with some regularity [8]. Regarding psychosis in particular, several hypotheses have been proposed to explain the potential mechanisms following COVID-19 vaccination [33,34], underscoring the need for careful monitoring of these reports.

In examining COVID-19 vaccine safety, our review specifically focused on psychiatric AEs. While 2 previous systematic reviews were conducted to assess the range of AEs following COVID-19 vaccination [35,36], it is notable that neither review distinctly categorized the psychiatric AEs. This lack of distinction can be attributed to the multifaceted nature of AE reporting and the challenges in isolating psychiatric symptoms from other systemic reactions. Our review attempts to fill this gap by specifically highlighting and analyzing psychiatric AEs. This focus is crucial, considering the potential impact of these AEs on the quality of life and the psychosocial burden they may impose.

Several limitations to our review need to be acknowledged. First, it predominantly relied on studies evaluating the BNT162b2 vaccine, with fewer studies examining other vaccines. This imbalance could skew the generalizability of our findings to other vaccines. Second, most of the selected articles were observational, which inherently poses a risk of uncontrolled confounding variables. Third, the lack of adequate control arms in most of the included studies precluded meta-analysis, limiting our ability to synthesize data quantitatively. Lastly, the literature we included revealed gaps in reporting serious psychiatric AEs like mood disorders and psychosis, highlighting areas for more comprehensive research.

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Conclusion

The current review identified a spectrum of psychiatric AEs following COVID-19 vaccination, with the notable prominence of sleep disturbances and anxiety. These AEs are relatively uncommon, nonserious, and seem to be multifactorial in nature. A direct causative link between the vaccines and psychiatric symptoms, however, has not yet been definitively established. Therefore, further research is essential to elucidate causality, determine potential risk factors associated with these AEs, and inform proactive measures. We support the need for ongoing surveillance and management of psychiatric reactions to COVID-19 vaccines, while acknowledging the pivotal role that vaccines continue to play in controlling the pandemic.

Supplementary Material

Table S1. Search strategies; **Figure S1.** Risk of bias. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0325.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
All data generated or analyzed during this study are included in this article. Other data are available upon request from the corresponding author.

Authors' Contributions
Conceptualization: MC, SO; Data curation: SR; Formal analysis: SR; Funding acquisition: MC, BJP; Investigation: SR, MC; Methodology: MC, SO; Project administration: MC; Resources: MC; Software: SR; Supervision: MC, BJP, OS; Validation: NKC, HSS, JHW, BJP; Visualization: SR; Writing–original draft: SR, MC, SO; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

AI-powered COVID-19 forecasting: a comprehensive comparison of advanced deep learning methods

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ABSTRACT

Objectives: The coronavirus disease 2019 (COVID-19) pandemic continues to pose significant challenges to the public health sector, including that of the United Arab Emirates (UAE). The objective of this study was to assess the efficiency and accuracy of various deep-learning models in forecasting COVID-19 cases within the UAE, thereby aiding the nation's public health authorities in informed decision-making.
Methods: This study utilized a comprehensive dataset encompassing confirmed COVID-19 cases, demographic statistics, and socioeconomic indicators. Several advanced deep learning models, including long short-term memory (LSTM), bidirectional LSTM, convolutional neural network (CNN), CNN-LSTM, multilayer perceptron, and recurrent neural network (RNN) models, were trained and evaluated. Bayesian optimization was also implemented to fine-tune these models.
Results: The evaluation framework revealed that each model exhibited different levels of predictive accuracy and precision. Specifically, the RNN model outperformed the other architectures even without optimization. Comprehensive predictive and perspective analytics were conducted to scrutinize the COVID-19 dataset.
Conclusion: This study transcends academic boundaries by offering critical insights that enable public health authorities in the UAE to deploy targeted data-driven interventions. The RNN model, which was identified as the most reliable and accurate for this specific context, can significantly influence public health decisions. Moreover, the broader implications of this research validate the capability of deep learning techniques in handling complex datasets, thus offering the transformative potential for predictive accuracy in the public health and healthcare sectors.

Keywords: Algorithms; Artificial intelligence; Computer; Computing methodologies; Deep Learning; Neural networks

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has profoundly impacted countries

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worldwide, including the United Arab Emirates (UAE). The UAE has faced significant challenges in controlling the spread of the virus and in managing its consequences. The accurate forecasting of pandemic dynamics is vital for effective decision-making and resource allocation by healthcare organizations, governments, and policymakers. In recent years, deep learning models have demonstrated remarkable performance in solving various challenges in the fields of healthcare, image processing, text recognition, and natural language processing [1]. These models have been successfully applied to a range of COVID-19 forecasting tasks and their use in predicting the progression of the pandemic in the UAE is of particular interest. This literature review examines the application of advanced deep learning models for COVID-19 forecasting in the UAE and provides a comparative analysis of their performances [2,3].

Several studies have used deep learning models to predict the progression of the UAE pandemic. For example, some studies have applied multi-input, multi-output convolutional neural network (CNN) models to forecast COVID-19 cases in multiple countries, including the UAE [4–6]. Their results indicated that CNN models could effectively capture local patterns in the data and provide accurate forecasts. Similarly, other studies have explored the use of long short-term memory (LSTM) and bidirectional LSTM (Bi-LSTM) models for COVID-19 forecasting in the region, demonstrating their ability to capture complex temporal dependencies in the data and provide reliable predictions [7–11]. The deep learning models discussed in this review include LSTM, Bi-LSTM, CNN, CNN-LSTM hybrid, recurrent neural network (RNN), and multilayer perceptron (MLP) models [6,12–15]. These models have been employed in various studies to forecast COVID-19 cases, deaths, and recoveries as well as to predict the impact of different government interventions and public health measures. The models were used in the context of UAE to find the best-performing model with and without Bayesian optimization, which was selected as one of the best available optimization parameters that could be applied to all the selected models in this study. This study aimed to determine the best model to predict COVID-19 in the UAE. The paper is further divided into Section 2, which provides a detailed background of the COVID-19 pandemic in the UAE; Section 3, which provides information on common models; Section 4, which provides details on preprocessing; Section 5, which provides results and discussion; and Section 6, which presents recommendations, conclusions, and future work.

Contributions to Existing Studies

This study offers several distinct contributions to the academic community and public health policymakers.

HIGHLIGHTS

- This study offers a comprehensive evaluation of various advanced deep-learning models for predicting COVID-19 cases in the United Arab Emirates (UAE), employing a robust dataset that includes demographic and socioeconomic factors.
- A recurrent neural network model emerged as the most accurate and reliable forecasting tool, even without optimization, which has significant implications for public health policy.
- All participants had high COVID-19 vaccine confidence.
- This research goes beyond academic interest, providing actionable insights that empower UAE public health authorities to develop targeted, data-driven interventions, demonstrating the potential of deep learning in managing complex healthcare datasets.

Analysis of advanced deep-learning models

This research is among the first to conduct a comprehensive analysis of multiple deep learning models, including LSTM, Bi-LSTM, CNN, CNN-LSTM, MLP, and RNN models, specifically for predicting COVID-19 cases in the UAE.

Data integration

Unlike previous studies that have focused on a singular aspect, such as confirmed cases, this research incorporates a more comprehensive dataset, including demographic information and socioeconomic indicators, thereby providing a holistic overview for more accurate predictions.

Optimization technique

Utilizing Bayesian optimization, this study goes a step further in fine-tuning the models, which has not been commonly carried out in similar studies. This optimization substantially increased the reliability and accuracy of the predictive models.

Impact on policymaking

This research not only serves academic purposes, but also has substantial real-world applications. It directly aids public health decision-making, enabling authorities to implement targeted and data-driven interventions, which is particularly crucial when pandemics occur.

Future-readiness

Our models, especially the RNN model, which showed the

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best performance without any prior optimization, can serve as a framework for predicting not only COVID-19 cases, but also cases of other infectious diseases, thus having broader implications for healthcare. It has often been pointed out that RNNs have issues of interpretability that can slow down decision-making and may require additional resources to validate the model performance, but this was resolved by developing hybrid models to ensure timely decision-making.

Predictive and perspective analytics

This study is one of the few that uses both predictive and perspective analytics to provide a multidimensional analysis of COVID-19 trends and patterns, thereby adding a layer of depth to data interpretation.

Background

The principal motivation for employing a comparative study of advanced deep learning models lies in the unpredictable nature of the pandemics. Traditional epidemiological models have shown limitations in capturing the dynamic variables that affect virus transmission, such as behavioral changes and policy interventions. By leveraging deep learning, this study aims to offer a more adaptive and accurate framework for COVID-19 forecasting in the UAE.

COVID-19 pandemic in the UAE

Since the first reported case in January 2020, the UAE has implemented strict measures to control the spread of the virus. The country's response evolved over time, adapting to the changing landscape of the pandemic. Some of the key aspects of the UAE's response include lockdowns, travel restrictions, mass vaccination campaigns, healthcare infrastructure expansion, and testing and tracing capacities. This section elaborates on these aspects to provide a more comprehensive understanding of the COVID-19 pandemic in the UAE [16].

Lockdowns and travel restrictions

In the early stages of the pandemic, the UAE imposed strict lockdowns and curfews to minimize the spread of the virus. These measures included closing nonessential businesses, suspending schools and universities, and restricting movement. The UAE has also implemented travel restrictions, including banning flights from high-risk countries, imposing quarantine measures for inbound travelers, and requiring negative polymerase chain reaction (PCR) tests for international passengers [17].

Mass vaccination campaigns

The UAE has been proactive in securing COVID-19 vaccines and in initiating mass vaccination campaigns. The country initiated its vaccination program in December 2020, prioritizing healthcare workers, elderly citizens, and people with chronic diseases. Since then, the UAE has expanded its vaccination efforts to include the general public with several available vaccines, including Sinopharm, Pfizer-BioNTech, and AstraZeneca. By September 2021, the UAE had one of the world's highest vaccination rates, with more than 90% of its population having received at least 1 dose. Currently, the UAE accounts for 100% of all vaccinated residents [18].

Healthcare infrastructure expansion

To effectively combat the COVID-19 pandemic, the UAE invested significantly in expanding its healthcare infrastructure. The country established numerous field hospitals, isolation centers, and testing facilities to accommodate the increasing number of cases. In addition, the UAE increased its healthcare workforce by recruiting more medical professionals and support staff to meet the demand. This expansion not only helped manage the pandemic, but also improved the country's overall healthcare capabilities [19].

Testing and tracing capacities

An essential aspect of the UAE's response to the COVID-19 pandemic was its focus on ramping up the testing and tracing capacities to detect and contain the virus. The country implemented widespread testing, including drive-through testing centers, home testing services, and rapid PCR tests at airports. In addition to testing, the UAE employed advanced contact-tracing methods using smartphone applications and AI-driven tools to identify and isolate individuals who have been exposed to the virus. These efforts played a crucial role in controlling the spread of COVID-19 in the UAE [20,21].

Challenges in COVID-19 forecasting

Predicting the spread of COVID-19 is a complex task owing to various factors, including the evolution of the virus, variable human behavior, and the impact of policy interventions. Moreover, data related to COVID-19 cases can be noisy, incomplete, or inconsistently reported, which further complicates the forecasting process. This section delves into these challenges and provides a deeper understanding of the difficulties involved in COVID-19 forecasting in general [22].

Evolving nature of the virus

COVID-19 has mutated over time, resulting in the development of new variants with distinct characteristics. Some of these variants, such as Delta and Omicron strains, have shown

increased transmissibility and potential resistance to vaccines. These evolving dynamics make it challenging to predict the spread of the virus, because new variants may alter the infection trajectory and require changes in public health measures [23].

Variable human behavior

Human behavior plays a crucial role in the spread of COVID-19, as individual actions and collective responses can significantly impact the transmission of the virus. Additionally, mask-wearing—as an important factor that plays a role in adherence to social distancing guidelines—and vaccination rates can affect the course of the pandemic. Furthermore, human behavior is influenced by various factors such as socioeconomic conditions, cultural norms, and public sentiment, making it difficult to predict and model accurately [24,25].

Impact of policy interventions

Governments and healthcare organizations have implemented numerous policy interventions to mitigate the COVID-19 pandemic's effects. These interventions included lockdowns, travel restrictions, vaccination campaigns and public health messages. The timing, scale, and effectiveness of these interventions can significantly affect the spread of the virus and add complexity to the forecasting process. Additionally, policy interventions can vary across regions and countries, further complicating the creation of accurate models [26].

Data quality and availability

The quality and availability of data related to COVID-19 can pose challenges for forecasting. Data may be noisy, incomplete, or inconsistently reported, owing to variations in testing rates, reporting standards, and healthcare system capacities. In some cases, under-reporting or delays in reporting can lead to data inaccuracies, making it difficult to develop reliable forecasting models. Furthermore, the availability of demographic, economic, and social data related to the pandemic may be limited, constraining the potential of more sophisticated modeling approaches [27,28].

Model selection and evaluation

Selecting appropriate models and evaluation techniques for COVID-19 forecasting can be challenging, given the complex nature of the pandemic and the various factors influencing its spread. Accurate COVID-19 forecasting will help researchers and the community overcome this challenge in the past 100 years and prepare for the future. However, the data are rapidly changing, with daily updates [11]. Researchers must consider several aspects, such as model complexity, interpretability, and generalizability, when developing and evaluating forecasting models. These models can be used for similar pandemics and ongoing COVID-19 cases in the future. Additionally, the rapidly changing dynamics of the pandemic necessitate continuous model adaptation and evaluation, because models that perform well at one point in time may become less accurate as the situation evolves. Despite these challenges, advanced deep learning models have shown promise in capturing complex patterns in data and providing accurate forecasts. By understanding the challenges and intricacies of COVID-19 forecasting, researchers can continue to develop and refine models, ultimately aiding informed policymaking, optimal resource allocation, and effective public health interventions [29].

The initiative behind our comparative study is not merely to create another forecasting model, but also to engineer a model specifically fine-tuned to navigate the complexities of COVID-19 data in the UAE. This distinct focus arises from a thorough understanding of general forecasting challenges, as discussed earlier in this section. Our use of recurrent architectures, such as LSTM and Bi-LSTM, is not arbitrary. These are designed to be highly adaptive, which is a critical feature when dealing with the ever-evolving nature of COVID-19. Their ability to "learn" from new patterns makes them uniquely suited for this task [30].

To deal with variable human behavior, our models integrate additional layers of data, such as mobility trends and vaccination rates. These are not mere add-ons, but are crucial elements that increase the model's forecasting sensitivity to societal variables. Deep-learning models such as CNN-LSTM can learn complex spatiotemporal features, making them particularly responsive to abrupt shifts in data trends owing to government interventions. This is a unique problem-solving feature of our approach that aims to make forecasts more reliable in a rapidly changing policy environment. Our preprocessing strategy is exceptionally comprehensive and involves a multilayered data validation process against official records to rectify issues arising from poor data quality or availability. This is in contrast to models that rely heavily on raw or less-validated data [31]. Finally, the generalizability of findings from a study conducted in the UAE to other regions depends on several factors, particularly when RNNs or other machine learning techniques are involved. This depends on the availability of similar data to countries other than model scalability and adaptability issues. Each country's healthcare policies, practices, and socioeconomic, environmental, and technological factors impact model evaluation and selection.

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Deep learning literature

LSTM-based models

LSTM networks, a type of RNN, have gained considerable attention in time-series forecasting owing to their ability to capture long-range dependencies and model complex sequential patterns. Various studies have demonstrated the effectiveness of LSTM-based models in predicting cases, hospitalizations, and deaths. This section provides an expanded overview of key studies applying LSTM models for COVID-19 forecasting [32] to the daily data of confirmed cases, recovered cases, and deaths to forecast COVID-19 cases [2,33]. A model was trained on data from January 31 to April 6, 2020, and its performance was evaluated using the mean average error (MAE) and mean average percentage error (MAPE) metrics. The LSTM model was able to accurately predict short-term trends in the number of cases, with an MAE of 24.34 and a MAPE of 0.8%. This study highlights the potential of LSTM models to assist policymakers in decision-making and resource allocation during the pandemic. Other studies used LSTM-based models to forecast various scenarios [34,35].

Other studies [1,36,37] applied LSTM models to forecast cases and fatalities in 10 different countries, including the United States, Italy, Spain, and Germany. Those studies used time-lagged features derived from confirmed cases, deaths, and recovery data to train the models. The approach used for model training the model included a rolling window approach. The authors found that the LSTM model provided accurate short-term forecasts (1–3 days ahead), with a root-mean-square error (RMSE) ranging from 2.13% to 8.17% for confirmed cases and from 3.21% to 8.73% for deaths [38].

These studies suggests that LSTM models could be useful tools for monitoring and predicting the evolution of the virus in different countries. Santangelo et al. [39] investigated the use of an LSTM model to predict cases. Their approach involved training the LSTM model on daily confirmed cases, recovered cases, and death data from March 11 to June 8, 2020. The authors compared the LSTM model's performance with other traditional time-series models, including a Holt-Winters exponential smoothing state-space model and a seasonal ARIMA (SARIMA) model. The LSTM model outperformed traditional models in terms of prediction accuracy, demonstrating the potential of deep learning methods as pioneers in predicting COVID-19 cases. By capturing the complex, nonlinear temporal dependencies in the data, LSTM models can provide valuable insights for decision-makers and public health officials [26,40,41].

Gated recurrent unit-based models

Gated recurrent units (GRUs) are a type of RNN that has gained popularity owing to their simplicity and computational efficiency compared to LSTMs, while still achieving comparable performance in many tasks. GRU-based models have been used in several forecasting tasks, with promising results. This section delves deeper into key studies involving GRU models in COVID-19 forecasting. Mohimont et al. [6] explored the potential of a GRU model for forecasting cases in India, a country that faced significant challenges during the pandemic. They compared the performance of the GRU model with that of ARIMA, STL, and ETS models. The study used daily confirmed cases, recovered cases, and death data from January 30, 2020, to August 31, 2020, for model training and evaluation. It was evident that the GRU model provided the best outcome compared to the classical time-series models in terms of prediction accuracy. The authors attributed this superior performance to the ability of the GRU model to capture complex temporal patterns in data. In addition, the GRU model provides more stable forecasts during periods of high case growth, highlighting its usefulness in rapidly changing situations [9,10]. Other studies have employed a GRU-based model for predicting recoveries, and deaths in multiple countries, including the United States, Italy, and Iran [7,8].

Their model incorporated various features, such as government interventions, population demographics, and economic factors, to improve prediction accuracy. The authors compared a GRU model with decision trees and a support vector machine (SVM) model. The GRU performance was better than that of the SVM and decision tree-based models [42]. This demonstrates its capability to capture the complex relationships between the input features and target variables. The authors also noted that the GRU model's performance improved with the inclusion of additional features, emphasizing the importance of incorporating diverse data sources into COVID-19 forecasting [43–46].

Kerr et al. [47] and Lv et al. [48] applied GRU models to cases in Saudi Arabia, which faced considerable challenges during the pandemic. The authors compared the performance of the GRU model with other deep learning models such as LSTMs and feed-forward neural networks. This study also highlights the computational efficiency of the GRU model, which is an important consideration when dealing with large time-series datasets. These studies underscored the potential of GRU-based models for accurate COVID-19 forecasting. By effectively capturing the intricate temporal patterns in the data and offering computational efficiency, GRU models have proven to be valuable tools for decision-makers and public health officials during pandemics [49,50].

CNN-based models

CNNs, which were originally used for image recognition tasks, have recently been adapted for time-series forecasting owing to their ability to detect local patterns and hierarchies in the data. Several studies have explored the potential of CNN models in predicting cases, hospitalizations, and deaths. This section provides an expanded overview of the key studies involving CNN models for COVID-19 forecasting. Sarker et al. [51] developed a multi-input multi-output (MIMO) CNN model to forecast cases in different countries.

Their model incorporated various input features such as daily confirmed cases, recoveries, deaths, and government intervention measures. The authors compared the performance of the MIMO-CNN model with that of ARIMA and ETS models. The results indicated that the MIMO-CNN model outperformed the traditional time-series models in terms of prediction accuracy, particularly for short-term forecasts. The authors attributed this superior performance to the ability of the CNN model to effectively capture local patterns in the data and to generalize these patterns across different countries [12–15]. The study highlighted that CNN can be used to provide accurate forecasts for critical decision-making during a pandemic. Satu et al. [15] and Shastri et al. [52] employed 1-dimensional (1D) CNN models to predict COVID-19 cases in India, a country that faced significant challenges during the pandemic. Their models used daily recoveries, confirmed cases, and deaths to compare with the SVM, linear regression, and decision trees.

The study outcomes were based on the 1D-CNN model, which achieved the highest prediction accuracy among the compared models. The authors also noted that the CNN model was computationally efficient and required less training time than other deep learning models such as LSTMs and GRUs. In 2 other studies [14,53], the use of CNN models to forecast hospitalization was explored. The authors developed hybrid CNN-LSTM-based models that combined both CNNs and LSTMs to capture both local and long-range patterns. They used various features such as daily confirmed cases, hospitalizations, and demographic data. The results demonstrated that the hybrid CNN-LSTM models provided accurate forecasts of hospitalizations, outperforming other deep learning and traditional time-series models. Those studies demonstrated the potential of combining CNNs with other deep learning models to enhance prediction accuracy in pandemic forecasting tasks [54,55].

Deep learning models for COVID-19 forecasting: brief comparative studies

Various studies have conducted comparative analyses based on deep-learning models to determine their performance in pandemic case prediction. These studies provide valuable insights into the relative strengths and weaknesses of different deep-learning approaches for predicting cases, hospitalizations, and deaths. This section provides an expanded overview of key comparative studies involving deep learning models for COVID-19 forecasting [56–59] conducted a comprehensive comparison of GRU, LSTM, and CNN models for forecasting cases. The authors used daily recoveries, confirmed cases, and deaths as input features for the models and evaluated their performance using metrics, such as MAE and RMSE.

This study aimed to determine which deep learning model could best capture complex temporal patterns in the data and provide accurate forecasts. The results indicated that both LSTM and GRU models outperformed CNN models in terms of prediction accuracy [35,60]. The authors attributed this finding to the LSTM and GRU models' ability to capture long-range dependencies in time-series data, which was crucial for accurately predicting the trajectory of the pandemic. These studies highlight the importance of selecting appropriate deep-learning models for forecasting tasks and demonstrate the potential of LSTM and GRU models for predicting the spread of the pandemic.

Several previous studies [56,59,61–63] compared LSTM, GRU, and transformer models to predict COVID-19 cases. They used features similar to those used in previous studies based on daily cases, deaths, and confirmed cases. They used evaluation metrics such as the MAE, RMSE, and MAPE. Those studies aimed to determine the best deep learning model for identifying the complex nature of the relationship between different features. In addition, the transformer model provided the best performance. The authors attributed this finding to the self-attention mechanism of the transformer model, which allows it to capture complex dependencies in the data more effectively than LSTM and GRU models. Additionally, the transformer model demonstrated faster training times and better scalability than other models, making it a more practical choice for large-scale COVID-19 forecasting tasks. Another set of studies [64–66] compared LSTM-, GRU-, and CNN-based models to predict cases in various countries. The authors used daily confirmed cases as input features, evaluated the performance of the models using MAE and RMSE, and study found that the LSTM and GRU models outperformed the CNN models, emphasizing the importance of selecting appropriate deep learning models for pandemic evolution prediction. Dutta and Bandyopadhyay [67] compared LSTM, GRU, and 1D-CNN-based models to predict the cases. The models used features and evaluation metrics similar to those used in the previous studies. The results showed that GRU provided the best overall performance, demonstrating

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the potential of GRU models for predicting cases. Other studies [68–72] conducted comparative research focusing on LSTM, GRU, and CNN models. The authors used features similar to those of previous researchers and evaluation metrics based on MAE and RMSE. They highlighted the importance of selecting appropriate deep-learning models. Another set of studies [23,35,73] compared LSTM, GRU, and Prophet models for forecasting cases. Their evaluation metrics included the MAE and RMSE. They found that the LSTM and GRU models outperformed other models such as Prophet. Still other research [16,40,71] compared LSTM, GRU, and 1D-CNN models. The authors used daily confirmed cases, recoveries, and deaths as input features, and MAE, RMSE, and MAPE to evaluate model performance. The GRU model performed the best on the given data. Comparative studies [43,44,74] have also focused on LSTM, GRU, and CNN models. The authors used features similar to those of previous researchers and metrics such as MAE and RMSE. The GRU model achieved the highest prediction accuracy. Kerr et al. [47] and Sinha et al. [13] compared LSTM, GRU, and CNN models. They used MAE, RMSE, and MAPE, with features similar to those used in previous studies. The LSTM model exhibited the best performance. Other comparative studies [3,71,72,75] evaluated LSTM, GRU, and 1D-CNN models. The authors used features and evaluation metrics similar to those used in the previous studies. The LSTM model achieved the highest prediction accuracy [38].

These comparative studies highlight the importance of selecting the most suitable deep learning model for decoding pandemic evolution. Although LSTM and GRU models have succeeded in capturing long-range dependencies in time-series data, CNN models have also been effective in certain cases. The choice of a deep learning model should be based on the specific requirements and constraints of the forecasting task at hand, as well as the available data and computational resources [76]. Furthermore, these studies highlight the importance of using deep learning models to provide accurate and reliable forecasts, which can assist decision-makers and public health officials in mitigating the impact of the pandemic [39]. The process of selecting appropriate models and evaluation methods for forecasting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be challenging because of the pandemic's complex nature and the various factors that influence its transmission. Researchers must carefully consider several factors such as model complexity, interpretability, and generalizability when developing and evaluating forecasting models. Additionally, the constantly changing dynamics of the pandemic require continuous model adaptation and assessment, because models that perform well at one point may become less accurate as the situation evolves. Despite these challenges, deep-learning models have demonstrated the potential to capture complex data patterns and provide accurate forecasts. By understanding the complexities of SARS-COV-2 forecasting, researchers can persist in developing and refining models, ultimately contributing to informed policymaking, strategic resource allocation, and efficient public health interventions in Malaysia and the UAE.

Computational costs

The complexity of implementing deep learning models, particularly those requiring extensive hyperparameter tuning through Bayesian optimization, may present computational challenges. This requires substantial resources and may limit the efficiency of the model training and evaluation. Training an LSTM network with large datasets can be time-consuming, requiring significant computational power and efficient algorithms. Cost scales with the number of LSTM cells. Bi-LSTM models have 2 layers and are definitely more expensive than LSTM models in terms of computational cost. In contrast, CNN costs are dependent on the complexity of the layers, and CNN-LSTM costs are the same. MLP is a feed-forward neural network that is dependent on the number of layers and neurons, which makes it computationally expensive. RNNs are expensive in terms of their computational costs. In general, the use of deep learning requires extensive computational calculations depending on each factor.

Materials and Methods

This section provides an overview of the materials and methods used in a comparative study of advanced deep-learning models for the accurate forecasting of pandemic dynamics in the UAE. The study involved data collection and preprocessing, model selection, model training and evaluation, and performance comparison.

Data Collection and Preprocessing

Data collection

This study utilized different types of COVID-19 data from the UAE. This included epidemiological data from the World Health Organization and UAE Ministry of Health and Prevention. These included daily confirmed cases, recoveries, and deaths. The data were verified for consistency and cross-validated using data from official government communication. The timing, scale, and nature of the measures were considered for this purpose. The data selected for this study were collected between January 2020 and June 2023. Figure 1 illustrates the proposed framework, which outlines

the primary activities of this study and systematically aligns its objective. The process commences by testing the stationarity and normality of the COVID-19 data to ensure that it adheres to the underlying assumptions of the deep learning models, which is accomplished through statistical methods, such as stationarity and normality tests. Following this, the data were normalized to a range of 0 to 1 using min–max scaling to improve model accuracy.

The framework culminates in the interpretation of results, providing insights, policy implications, and directions for future research encapsulated within conclusions, recommendations, and potential improvements. Additionally, the research includes a dissemination stage aimed at sharing research findings with relevant stakeholders and the scientific community through various channels such as academic publications, conference presentations, and public engagement. Overall, the framework provides a concise yet comprehensive roadmap encompassing primary research activities, from statistical testing to performance evaluation and the dissemination of results. It should be highlighted that the results will differ based on the selected dataset and variables.

Data preprocessing, exploratory data analysis, and feature selection

The collected data were preprocessed to ensure compatibility with the deep learning models. The preprocessing steps are as follows: (1) Data cleaning: (i) Missing values were substituted by the mean or median of the respective column depending on the data distribution. (ii) Outliers were identified through box-plot methods and were either capped or transformed. (iii) Data from multiple sources were checked for consistency with official publications and cross-validated. (2) Feature engineering: (i) Additional features, such as moving averages and growth rates, were created to capture relevant patterns in the data. (ii) 7-day and 14-day moving averages were calculated to smoothen the data. (iii) Daily and weekly growth rates were used to determine the rate of change in various variables. (3) Data normalization: The features were scaled to lie within a given range, often 0–1, to ensure that the gradients do not explode during the backpropagation process. (4) Sequence generation: Time-series data were transformed into input-output sequences with a specified window length for training the models. (5) Several Python libraries were used, including Numpy, Matplotlibm SkLearn, Kera, Scipy, and TensorFlow. (6) Exploratory data analysis was performed to identify anomalies and graphical visualizations. (7) K-fold cross-validation was used to assess model performance on individual datasets.

Model Selection

Six deep learning models were selected for the comparative study. (1) LSTM, (2) Bi-LSTM, (3) CNN, (4) CNN-LSTM, (5) RNN, (6) multilayer perceptron (MLP). These models were chosen based on their demonstrated performance in previous COVID-19 forecasting studies and their ability to capture complex patterns and dependencies in time series data.

Model Training and Evaluation

Model training

LSTM, Bi-LSTM, CNN, CNN-LSTM, RNN, and MLP models were trained on the preprocessed data using a standard

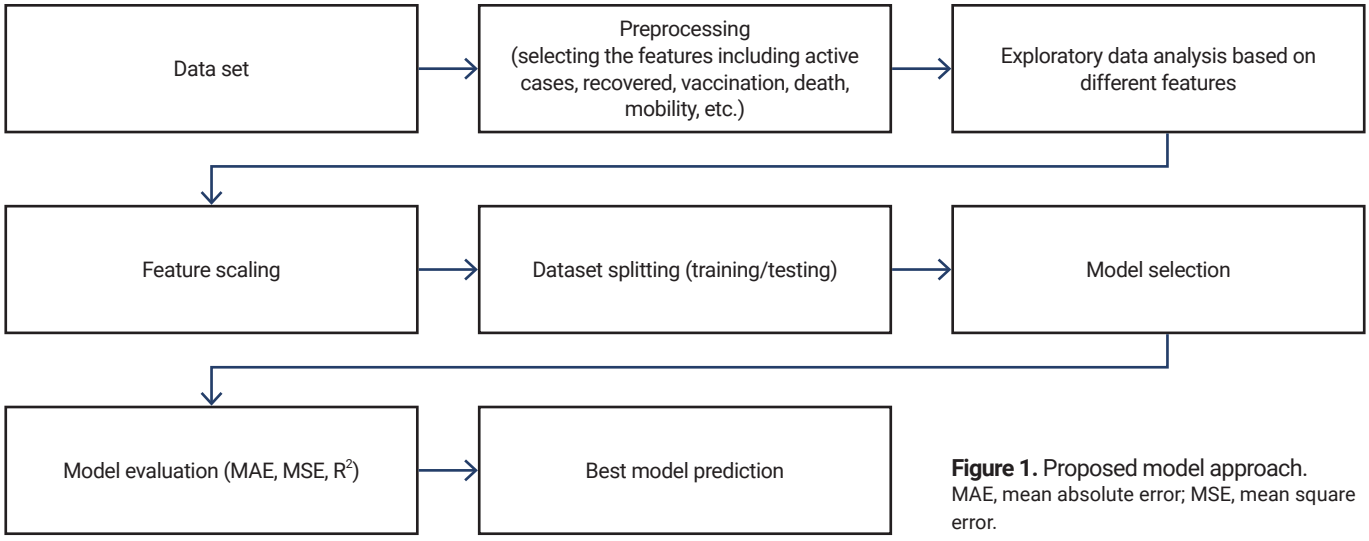

Figure 1. Proposed model approach.
MAE, mean absolute error; MSE, mean square error.

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architecture, loss function, and optimization algorithm. The hyperparameters of the models, including the number of layers, hidden units, and learning rate, were tuned using a grid search or a random search approach. A 3-way split was used. We used a training set for the initial fitting of the model, a validation set for fine-tuning the hyperparameters, and a testing set to assess the final model performance. To create the testing and validation sets from the COVID-19 series data, a time-based split was used rather than a random split because of the temporal nature of the data.

These models were selected based on their proven performance in previous COVID-19 forecasting studies and their capacity to capture intricate patterns and dependencies in time-series data. Further, Bayesian optimization was used to select the best possible hyperparameters for the dataset for each of the algorithms, and the models were evaluated again to determine the best accuracy. The initial parameters used in each algorithm are listed in Table 1.

It is worth noting that each algorithm works differently with a change in the parameters, as with data. We further used a batch size of 1 and trained over 100 epochs for each model.

Table 1. Model parameters

Model	Parameter
Long short-term memory	Units: 50 Activation: relu Optimizer: adam Loss function: mean_squared_error
Bidirectional long short-term memory	Units: 50 Activation: relu Optimizer: adam Loss function: mean_squared_error
Convolutional neural network	Filters: 64 Kernel size: 1 Activation: relu Pool size: 2 Optimizer: adam Loss function: mean_squared_error
Convolutional neural network-long short-term memory	Filters: 64 Kernel size: 1 LSTM units: 50 Activation: relu Optimizer: adam Loss function: mean_squared_error
Recurrent neural network	Units: 50 Activation: relu Optimizer: adam Loss function: mean_squared_error
Multilayer perceptron	Hidden units: varies (10, 20, 50, 100, 200) Activation: relu Optimizer: adam Loss function: mean_squared_error

These parameters were further hyper-tuned using Bayesian optimization.

Bayesian Optimization

Bayesian optimization is not just another tool in the plethora of optimization algorithms; it occupies a unique position in the landscape of optimization techniques due to its theoretical rigor and practical utility. Emerging as a formidable method, especially in scenarios where objective function evaluations are expensive, Bayesian optimization has been hailed as a watershed moment in the evolution of optimization theory. The intellectual and computational efficacy of Bayesian Optimization is predominantly due to its reliance on Bayesian inference. This form of statistical reasoning is based on Bayes' theorem, which enables us to update probabilities based on new evidence. In the context of optimization, particularly hyperparameter tuning, Bayesian inference has emerged as a robust method for intelligently navigating the solution space.

The selection of Bayesian optimization as the primary optimization tool for this study is grounded in its unique ability to efficiently handle the high-dimensional and complex hyperparameter tuning required for the deep-learning models in question. Unlike more traditional optimizers, Bayesian optimization operates on a probabilistic model that is adept at navigating through hyperparameter spaces with greater efficiency and less computational expense. This is particularly advantageous when dealing with the unpredictable nature of COVID-19 data, which often exhibit nonlinear and complex patterns. The effectiveness of Bayesian optimization lies in its capacity to explore the hyperparameter space systematically and intelligently, quickly converging on optimal solutions that might be overlooked or take significantly longer to identify using other methods. This strategic choice is not just about optimization efficiency; it is about achieving a higher level of model-tuning precision, which is essential for the accurate prediction of COVID-19 trends. In this study, the application of Bayesian optimization for tuning deep-learning models in COVID-19 case prediction presents a novel contribution. The innovation lies not only in the use of Bayesian optimization, but also in how it is specifically designed, adapted, and applied to address the unique challenges of pandemic data from the UAE. This approach extends beyond conventional applications in several ways.

The Bayesian optimization process was specially crafted to incorporate cutting-edge deep learning models, such as LSTM and CNN. This customization was specifically carried out to tackle the unpredictable and fluctuating nature of COVID-19 data, which is a novel approach not commonly found in the existing literature. The Bayesian model was iteratively

refined through each round of optimization, representing a dynamic and adaptive approach to model tuning. This ongoing refinement process, especially in the context of evolving pandemic data, demonstrates the flexibility and adaptability that are crucial for accurate forecasting in rapidly changing circumstances. This study systematically evaluated improvements in model performance after optimization. This evaluation not only confirmed the real-world utility of Bayesian optimization, but also uncovered novel insights into the influence of various hyperparameter combinations on model accuracy when applied to epidemiological data.

Performance Comparison

The performances of 6 deep learning models (LSTM, Bi-LSTM, CNN, CNN-LSTM, RNN, and MLP) were compared based on evaluation metrics and visualizations. The models were ranked according to their forecasting accuracy, with the best- performing model being recommended for future COVID-19 forecasting tasks in the UAE. The strengths and weaknesses of each model are discussed, along with potential improvements and future research directions. Through the up-to-date processes discussed in the Materials and Methods section, the study now reflects a new set of deep learning models and provides a comprehensive comparison of their performance in forecasting COVID-19 dynamics in the UAE.

Results and Discussion

Here, we present the outcomes of the study, including the performance of each deep learning model (LSTM, Bi-LSTM, CNN, CNN-LSTM, RNN, and MLP) in forecasting the COVID-19 dynamics in the UAE. The results were summarized using tables and graphs to illustrate the performance of the models based on the evaluation metrics (MAE, R^2, RMSE, MAPE, and mean standard error [MSE]) and to visually compare their predictions with the actual data. The visualization provides a snapshot of the predictions that fit the scaling area.

Model Performance Metrics

Table 2 provides a summary of the evaluation metrics for each model without optimization.

Model Performance Without Optimization

Figure 2 shows a comparison of the actual cases in the UAE with the predictions made by the LSTM model. This visual representation allows an intuitive understanding of the forecasting accuracy of each model. Both the predicted and actual data lines depict an ascending trend, suggesting a steady rise in COVID-19 cases throughout this period. In the initial months, the proximity of the 2 lines indicated high accuracy of the predictive model. However, a noticeable divergence emerges after November, with the model seemingly underpredicting the cases until a slight convergence reappears in later months.

Table 2. Model evaluation metrics without optimization

Model	MAE	MAPE	MSE	R^2	RMSE
LSTM	0.046	1.081	2.18	0.004	0.722
Bi-LSTM	0.0043	1.071	1.88	0.76	0.0043
CNN	0.0062	1.14	3.93	0.55	0.0062
CNN-LSTM	0.0062	1.011	3.93	0.55	0.0062
RNN	0.0017	1.064	3.49	0.96	0.0018
MLP	1,075	0.102	1,291,309	0.98	1,136

MAE, mean average error; MAPE, mean average percentage error; MSE, mean standard error; RMSE, root-mean-square error; LSTM, long short-term memory; Bi-LSTM, bidirectional LSTM; CNN, convolutional neural network; RNN, recurrent neural network; MLP, multilayer perceptron.

Figure 3 provides a comprehensive visual analysis of the actual versus predicted COVID-19 cases in the UAE based on the outputs of the Bi-LSTM model. Both the predicted and actual trajectories exhibit an upward trend, indicating a consistent increase in the number of cases. The beginning of the graph reveals an impressively close alignment between the predicted and actual data, suggesting that the Bi-LSTM model had high accuracy during this timeframe. As time progressed, there was a discernible deviation between the 2 lines, with the model slightly underestimating the surge. However, the model's predictions appeared to be more congruent with actual cases, demonstrating adaptability. This visual representation underscores the significance of continuous model training and validation using real-time data, highlighting the areas of precision and potential improvement in the predictive algorithm.

Figure 4 offers an insightful representation of COVID-19 case trajectories in the UAE by comparing the actual data with the predictions made by the CNN model. From the outset, there is a noticeable proximity between the predicted and actual data lines, indicating the commendable initial accuracy of the model. As time advances, divergence is observed, and the model seems to slightly underestimate the actual cases. This discrepancy widens as we transition into the new year, with actual cases consistently surpassing the model's predictions. The 2 trajectories again come closer, suggesting possible recalibration or changes in data patterns. The overarching trend for both lines remained upward, reflecting the ongoing challenges of the pandemic.

Figure 5 provides a detailed visual analysis of the COVID-19 case trends in the UAE, in contrast with the actual observed data with forecasts made using the CNN-LSTM model. The actual and predicted trajectories were closely aligned,

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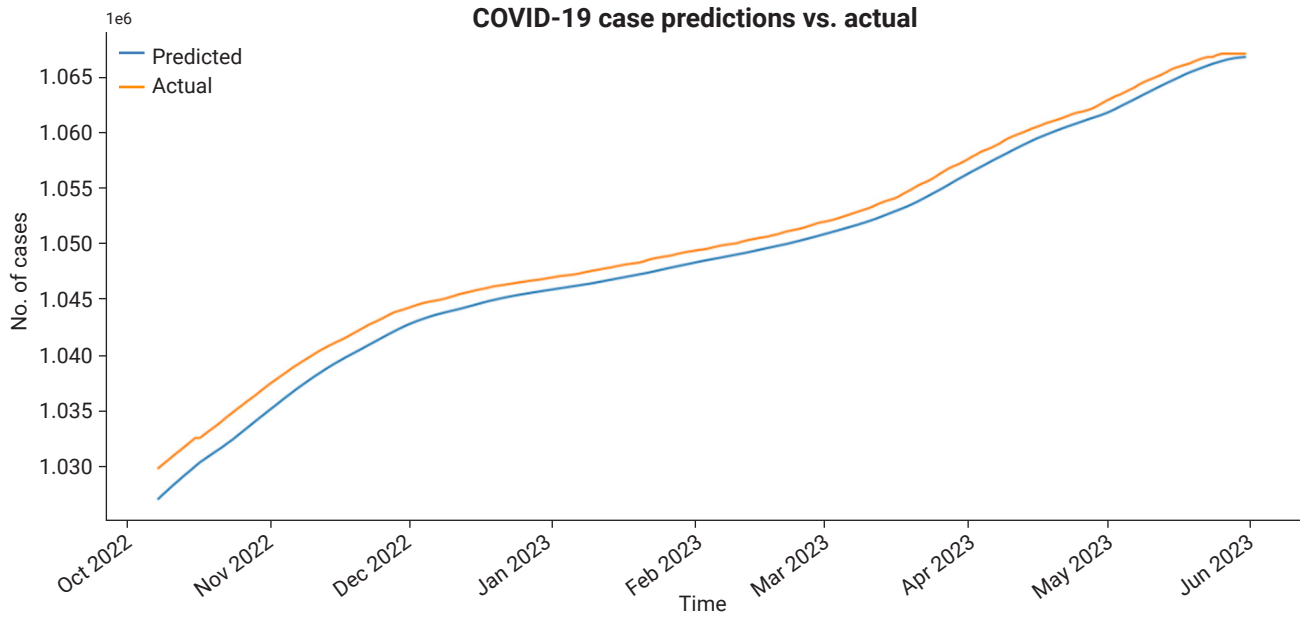

Figure 2. Long short-term memory model performance.

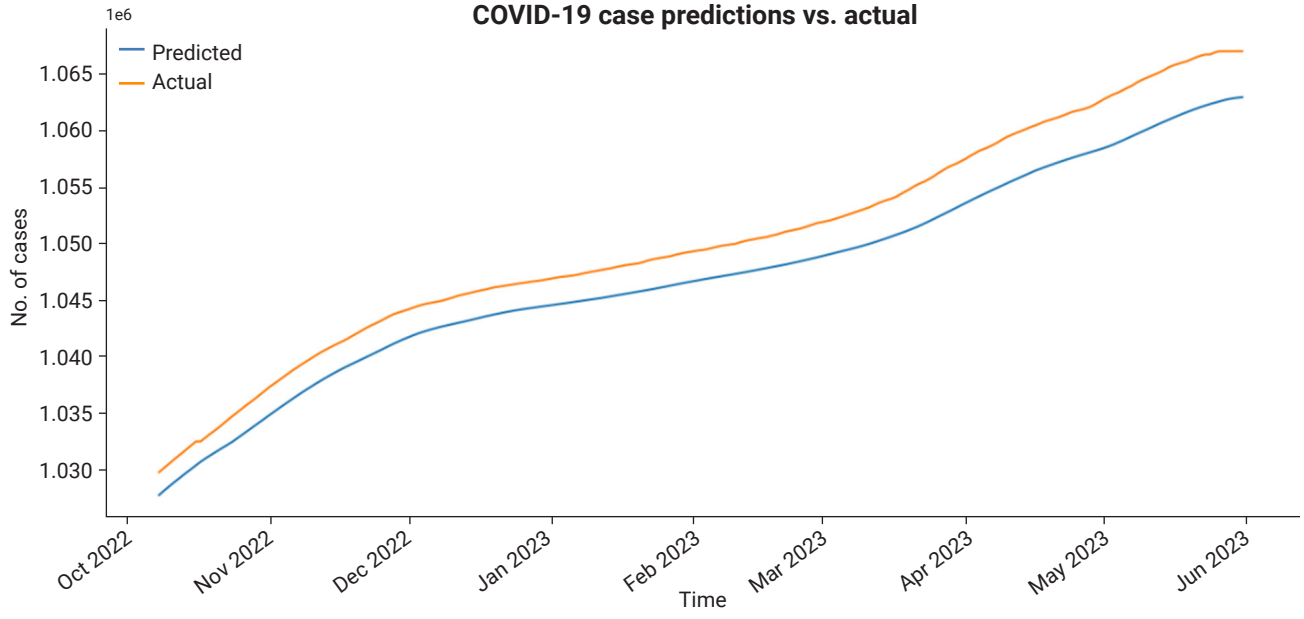

Figure 3. Bidirectional long short-term memory model performance.

thereby demonstrating the initial accuracy of the model. A minor deviation emerges in which the model seems to modestly undervalue the actual number of cases. This pattern persisted until March 2023, when the predicted curve began to closely shadow the actual case trajectory. By April 2023, both curves ascended in a relatively parallel manner, indicating potential stabilization of the predictive capability of the model. The persistent upward trend on both lines emphasizes the continued escalation of the pandemic during this period. Overall, while the CNN-LSTM model exhibited commendable forecasting proficiency, the discrepancies, albeit minor, underscore the dynamic nature of the pandemic.

Figure 6 offers a comprehensive visual analysis contrasting the actual reported cases of COVID-19 against predictions made by the RNN model. The graph displays a notable degree

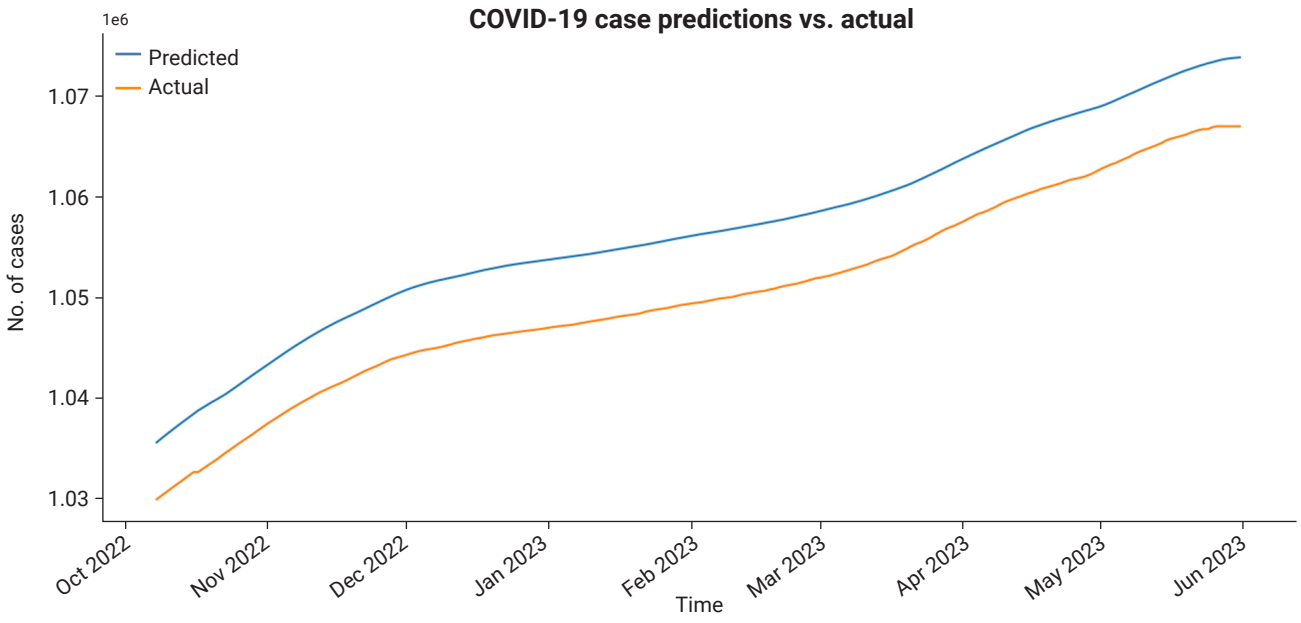

Figure 4. Convolutional neural network model performance.

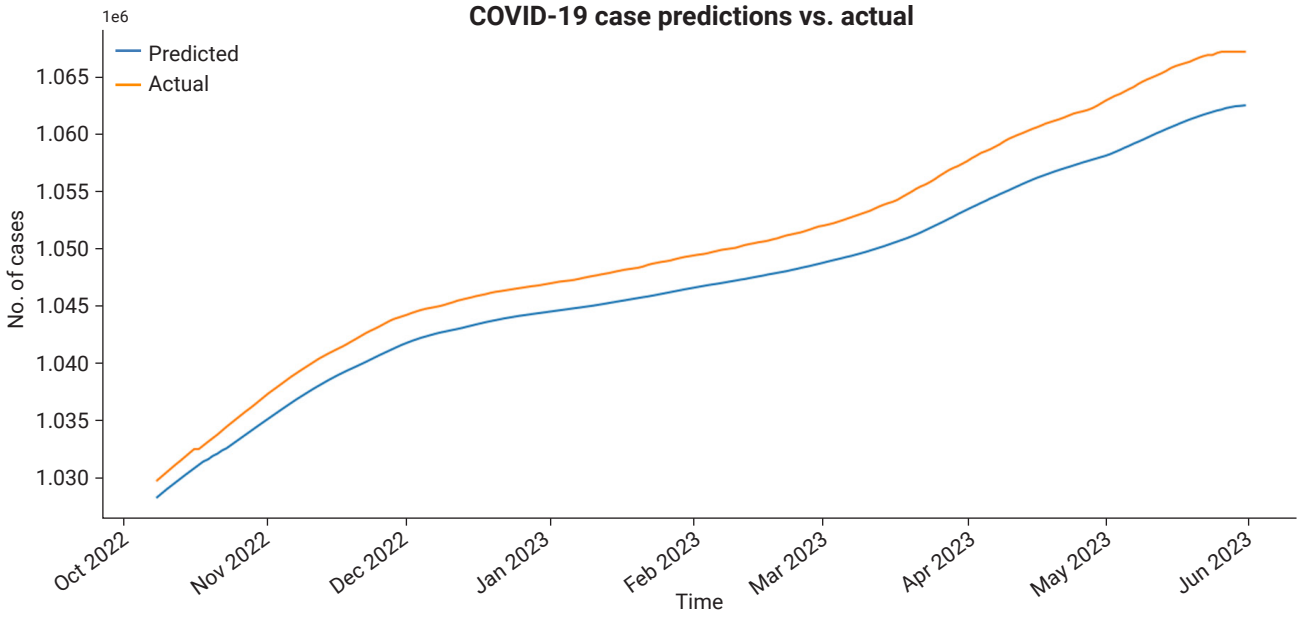

Figure 5. Convolutional neural network-long short-term memory model performance.

of alignment between the actual and predicted trajectories, particularly during the initial months. However, a slight divergence was observed, where the predictions of the RNN model marginally underestimate the actual case count. This underestimation continues until March 2023, after which the predicted values appear to align closely with the actual data, suggesting an adaptation or improved accuracy of the model. Throughout the study period, both curves exhibited an upward trajectory, reflecting the persistent rise in the pandemic. While the RNN model demonstrated appreciable predictive accuracy, the visible discrepancies reiterate the inherent complexities of forecasting dynamic scenarios such as the evolution of a pandemic.

Figure 7 provides a visual representation of the performance of the MLP model for predicting COVID-19 cases. The trends in both the predicted and actual cases showed a steady increase

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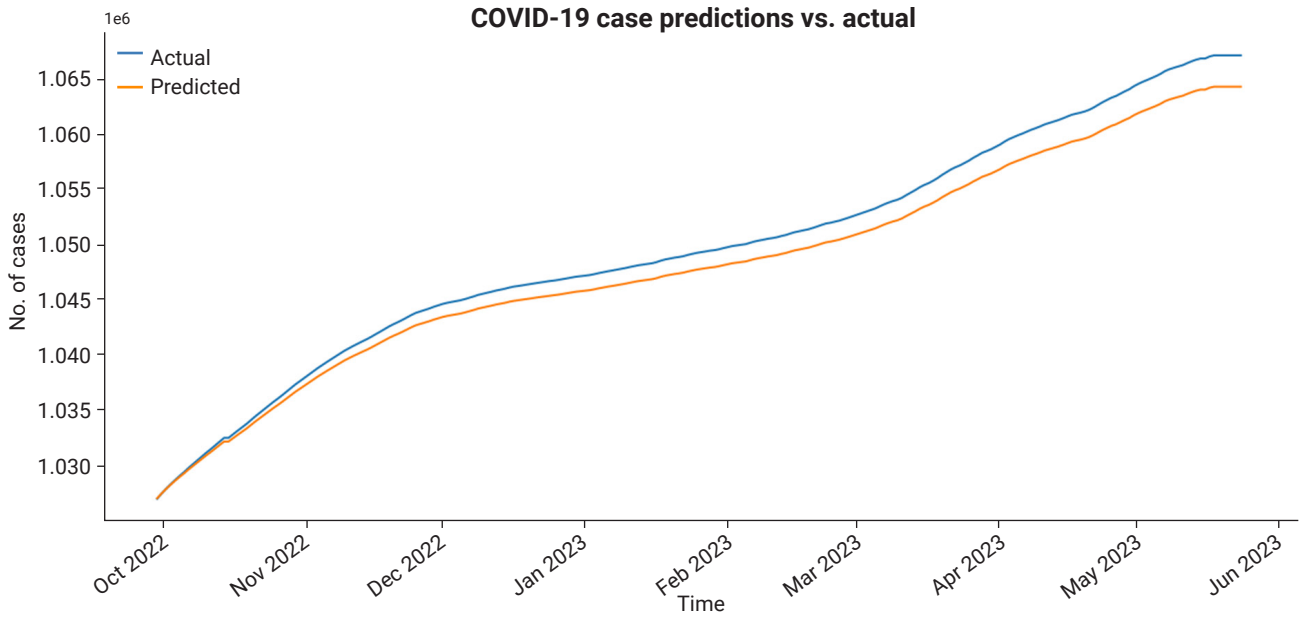

Figure 6. Recurrent neural network model performance.

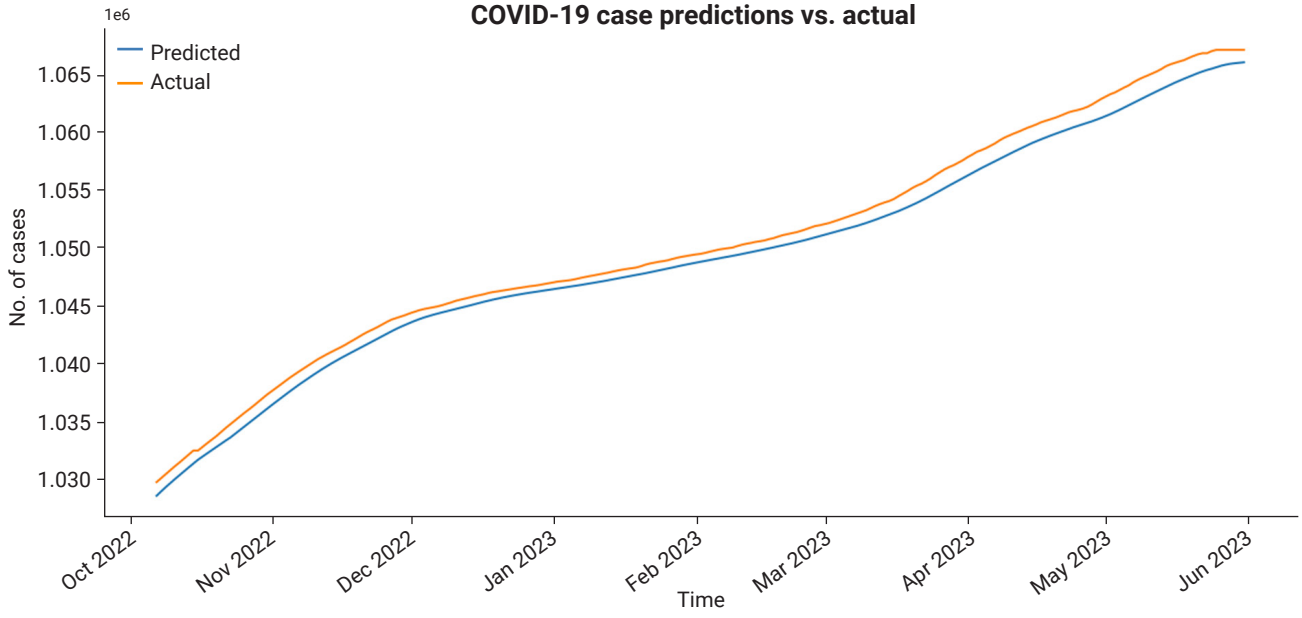

Figure 7. Multilayer perceptron model performance.

over time. In the early stages, the MLP model predictions appear to be tightly aligned with the actual cases, suggesting high accuracy during this period. As the timeline progresses, a slight deviation can be observed from February 2023 onwards, where the predicted values seem to surpass the actual figures, indicating a slight overestimation by the model. This discrepancy highlights the challenges associated with the precise prediction of disease propagation, particularly over longer timeframes. Nonetheless, the overall congruence between the 2 curves demonstrates the MLP model's considerable proficiency in forecasting while also underlining the need for periodic model adjustments to cater to evolving pandemic dynamics.

Model Performance Without Optimization

We used Bayesian optimization based on the parameters

listed in Table 1. The optimizer was provided chosen values of “adam,” “sgd,” “rmsprop," “nadam,” “ftrl,” “adagrad,” and “adadelta.” The tuner was set to a random search with a maximum of 50 trials and the execution per trial was equal to 2. This makes each model optimization trial approximately 100. This is an extensive search for the best parameters and optimization of the models. We wanted to ensure that the models were thoroughly tested before the results were finalized. Table 3 provides a summary of the evaluation metrics for each model with optimization.

Figure 8 shows the performance of the LSTM model with Bayesian optimization and its predictions for the COVID-19 cases. From the initial stages, the forecasted values from the optimized LSTM model appear to adhere closely to the actual cases, suggesting a marked improvement in the predictive accuracy during this interval. The curves progressed in a near-parallel fashion, highlighting the heightened alignment between the predicted and actual values. Notably, the divergence between the 2 sets of data was minimal, even in the later months, demonstrating the efficacy of Bayesian optimization in refining the forecasting capability of the LSTM model. This superior congruence underscores the value of incorporating optimization techniques to increase the precision of predictive models, particularly in the context of public health forecasting, where accuracy can have profound implications.

Table 3. Model evaluation metrics with optimization

Model	MAE	MAPE	MSE	R^2	RMSE
LSTM	0.00023	1.028	7.2045	0.9991	0.00268
Bi-LSTM	0.00028	1.026	1.0681	0.9988	0.00032
CNN	0.00024	1.025	8.1078	0.9990	0.00028
CNN-LSTM	0.00026	1.024	9.4537	0.9988	0.00030
RNN	0.00015	1.022	2.9128	0.9996	0.00017
MLP	0.00017	1.028	3.4843	0.9995	0.00018

MAE, mean average error; MAPE, mean average percentage error; MSE, mean standard error; RMSE, root-mean-square error; LSTM, long short-term memory; Bi-LSTM, bidirectional LSTM; CNN, convolutional neural network; RNN, recurrent neural network; MLP, multilayer perceptron.

Figure 9 shows the performance of the Bi-LSTM model in predicting the total COVID-19 cases in the UAE. The graph contrasts the model’s forecasted values, represented by the dotted line, with the actual number of cases, portrayed by the solid line. A meticulous examination of the graphical representation revealed a closely intertwined pattern between the actual and predicted values throughout the timeline. Especially noteworthy is the manner in which the Bi-LSTM model’s predictions emulate the trend of the actual cases, maintaining remarkably close proximity and accurately capturing the inflection points. It is evident that the optimized Bi-LSTM model achieved a reasonable degree of accuracy, as indicated by the minimal discrepancies between its forecasts and real data. The near-congruence throughout the period under review is emblematic of the model’s robust predictive capabilities.

Figure 10 shows the performance of a CNN in predicting the total COVID-19 cases in the UAE. Upon detailed scrutiny, it became evident that the CNN model exhibited a high degree

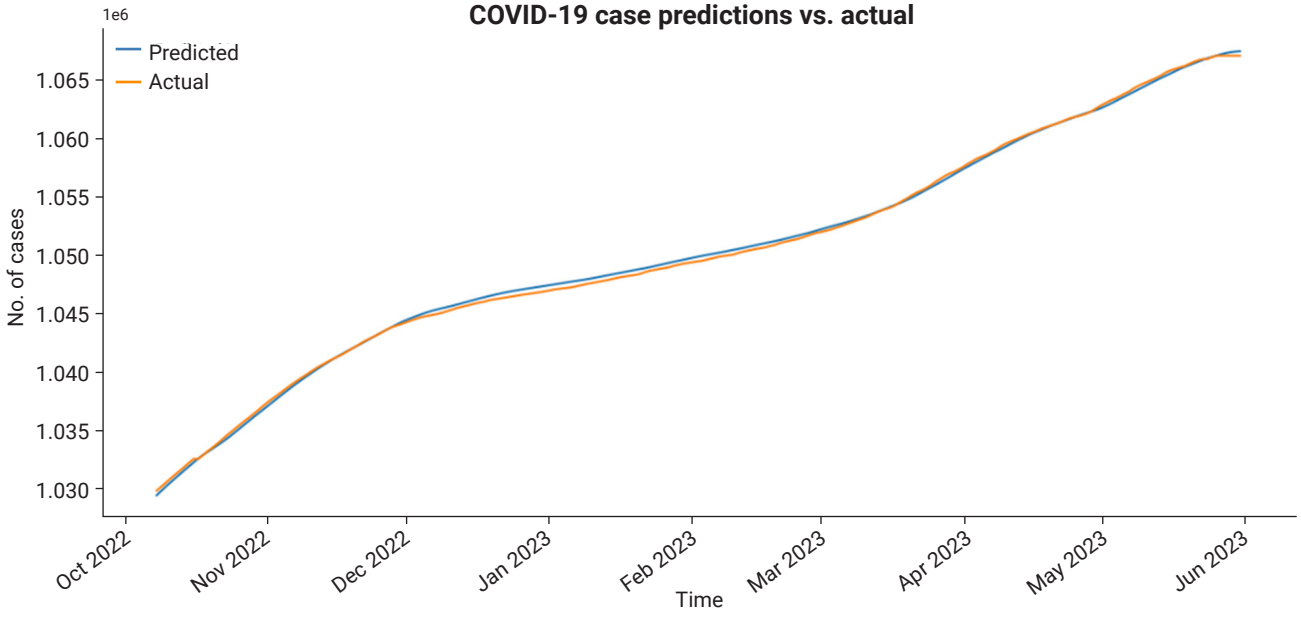

Figure 8. Long short-term memory model performance with optimization.

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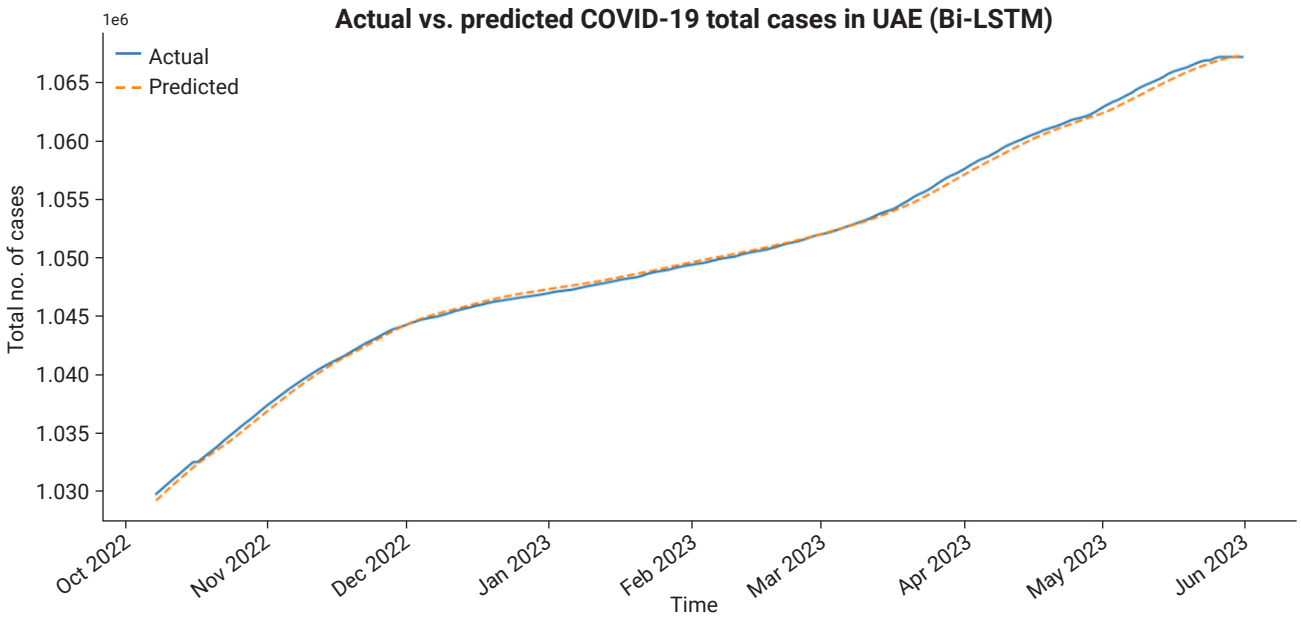

Figure 9. Bidirectional long short-term memory (Bi-LSTM) model performance with optimization. UAE, United Arab Emirates.

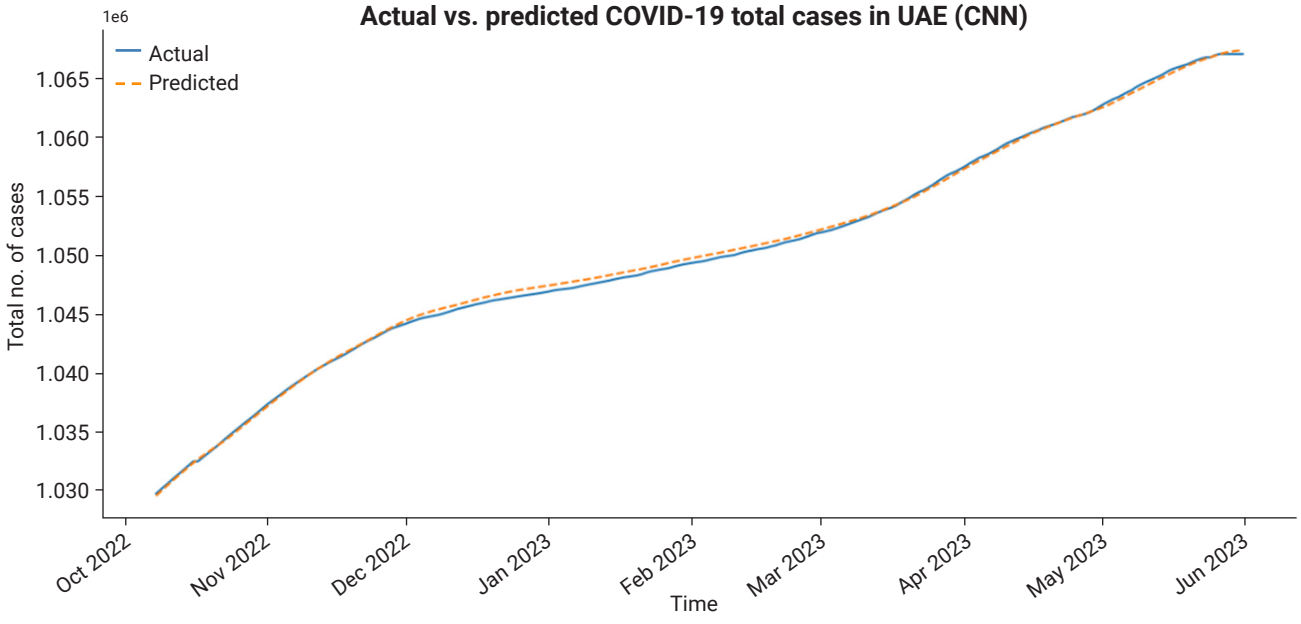

Figure 10. Convolutional neural network (CNN) model performance with optimization. UAE, United Arab Emirates.

of alignment between predicted and actual trajectories. The forecasted values remained in close agreement with the observed data, and the 2 curves followed a largely parallel course. There were subtle areas in which the predicted line veered slightly from the actual trend. However, these divergences were minimal and did not detract from the overall veracity of the model's predictions. The congruity displayed between the forecasted and observed datasets emphasizes the ability of the CNN model to capture the underlying dynamics of the pandemic's spread in the UAE. The capacity of the CNN model to generate such reliable predictions after using Bayesian optimization is invaluable, as it offers stakeholders a more precise tool for devising informed interventions and health policies.

Figure 11 shows the prediction capabilities of a combined CNN-LSTM model with respect to the progression of COVID-19

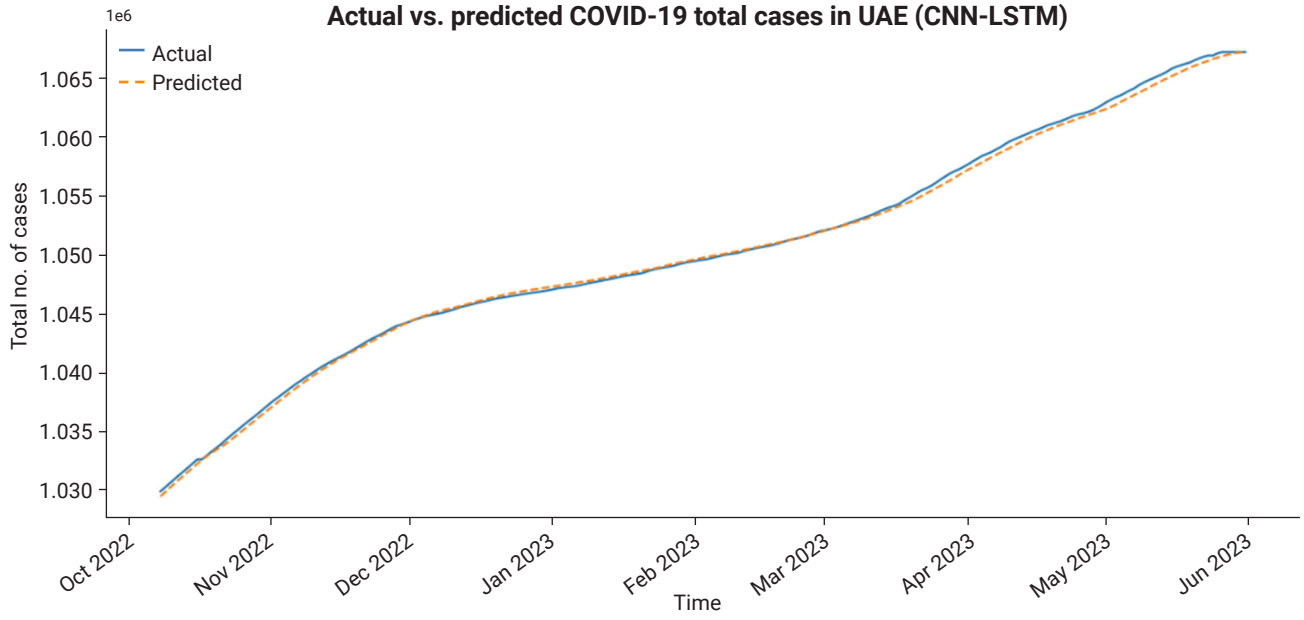

Figure 11. Convolutional neural network-long short-term memory (CNN-LSTM) model performance versus other models with optimization. UAE, United Arab Emirates.

in the UAE. Upon meticulous observation, close congruence can be noted between the model's predictions and the actual data. For the most part, the forecasted values closely shadow the actual counts, indicating commendable predictive accuracy. Although minor deviations can be observed at specific intervals, they are nuanced and do not detract from the overarching trend captured by the model. This harmonization between the forecasted and observed data underscores the efficacy of integrating the CNN and LSTM architectures. This optimized hybrid approach strengthens the model's capability to predict the intricate dynamics of the pandemic's progression, providing an invaluable asset for informed policymaking and strategic health interventions.

Figure 12 shows the predictive performance of an optimized RNN model for the progression of COVID-19 in the UAE. Upon close examination, noteworthy adherence between the model's predicted trajectory and the number of genuine cases becomes evident. Although the optimized model's predictions display minor oscillations from the actual values at certain junctures, they align impressively with the true case trajectory, signaling notable predictive precision. The proximity of the forecasted values to the actual data underscores the utility of RNNs in capturing the temporal patterns in a sequence of data. Given the dynamic and evolving nature of the spread of a pandemic, an RNN's inherent architecture, designed to recognize patterns over time, provides a robust mechanism for understanding and predicting the trajectory of infectious diseases, making it an indispensable tool in epidemiological modelling and planning.

Figure 13 shows the predictive performance of an optimized MLP model for the evolution of the COVID-19 total cases in the UAE. The genuine case counts, depicted by the solid line, are juxtaposed with the model forecasts, which are represented by the dashed line. Upon meticulous observation, one can discern a remarkable congruence between the model's forecasted progression and the actual number of cases. The predicted values from the MLP model commendably traced the trajectory of the actual data, highlighting the nuanced understanding of the underlying patterns.

This striking alignment between the actual and predicted cases is a testament to the success of the MLPs in grasping complex nonlinear relationships in the datasets. The model's capacity to closely mirror the true progression of COVID-19 affirms its efficacy as a robust forecasting tool, especially in scenarios in which historical patterns play a pivotal role in shaping future outcomes.

Comparison of Best-Performing Models with or without Optimization

First, we analyzed each model without optimization based on the results shown in Table 2 and Figures 1–6. Subsequently, the results obtained using Bayesian optimization are shown in Table 3 and Figures 7–12. A comparison of the results is as follows:

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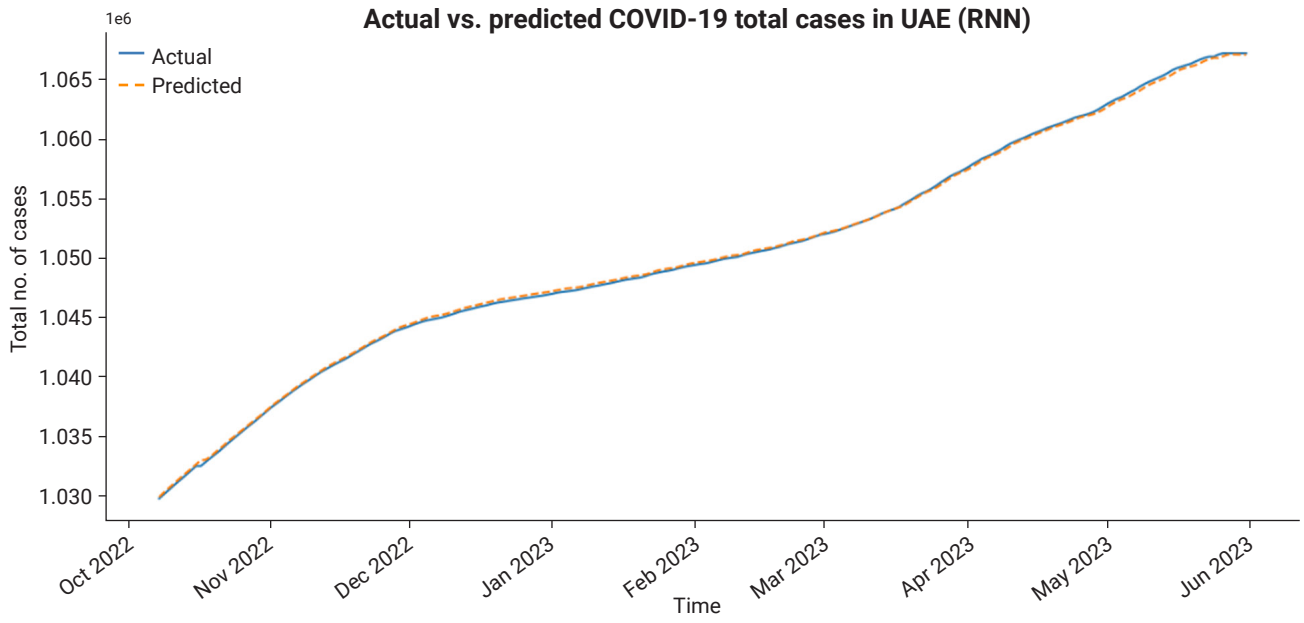

Figure 12. Recurrent neural network (RNN) model performance with optimization. UAE, United Arab Emirates.

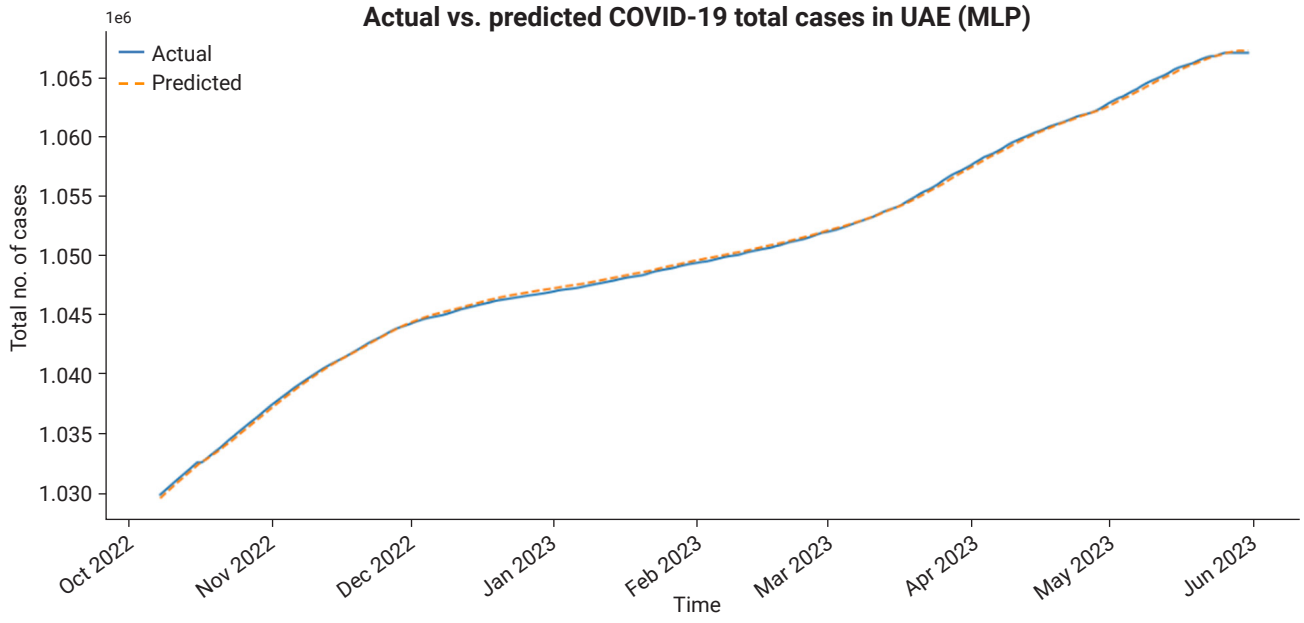

Figure 13. Multilayer perceptron (MLP) model performance with optimization. UAE, United Arab Emirates.

LSTM

Without optimization, the LSTM model exhibited a relatively mid-level performance among the other models in terms of MAE, MAPE, MSE, and RMSE. It performed better than the CNN and CNN-LSTM models. After optimization, it exhibited excellent performance. Although the MSE and RMSE values were on average, the predictions were very close to the actual values.

BI-LSTM

Without optimization, the Bi-LSTM model performed better than the LSTM model, with a lower MAE, MAPE, MSE, and RMSE and a higher R^2 value. This was the second-best performing model. After optimization, the model showed a noticeable improvement in performance compared to the LSTM model. Although the MAE was slightly higher than that of the LSTM, the MSE and RMSE values decreased

significantly. This indicates that the variance and errors were reduced.

CNN

Without optimization, the performance of the CNN model was the worst among the models, with the highest MAE, MAPE, MSE, RMSE, and lowest R^2 values. After optimization, it stands out well with similar metric outcomes to the LSTM model. The R^2 value was lower than those of the LSTM and BI-LSTM models. However, the MAE, MSE, and RMSE values were higher, possibly indicating more errors in the prediction.

CNN-LSTM

Without optimization, the CNN-LSTM model exhibited similar performance to that of the CNN model, showing that a particular LSTM combination did not perform better than the LSTM model itself. After optimization, it performed better than the CNN model only. The prediction errors were significantly reduced and the predictions were closer to the actual values.

RNN

Without optimization, the RNN model exhibited the best performance among all the models. After optimization, the RNN remained the best among all models, with the smallest prediction errors.

MLP

Without optimization, the MLP model had a very high R^2, indicating a good model fit. However, with higher values of other parameters, the model might not perform well. After optimization, the MLP model was the second-best performer and had lower values than LSTM, Bi-LSTM, CNN, and CNN-LSTM.

Overall, the RNN model performed best on all metrics without optimization, as well as with Bayesian optimization. This shows that the model provided accurate predictions than the other models investigated in this study. The second-best was the Bi-LSTM model without optimization, whereas the MLP model was the second-best with optimization. In addition, all the models performed well according to the values after optimization, meaning that optimization is necessary for model improvement.

Limitations of the Study and Ethical Considerations

Despite these promising results, this study had several limitations. First, data quality and completeness may affect model performance. Future studies could explore alternative data sources or use data imputation techniques to address potential data-quality issues. Second, other deep learning models or hybrid models can be investigated to further improve the forecasting accuracy. For example, the transformer model, which has demonstrated promising results in several studies, can be included in future comparisons. In addition, larger trials require more time to run tests and experiments.

Finally, incorporating additional features such as demographic information, mobility data, and information about government interventions may improve the model's predictive capabilities. Future research could explore various feature-engineering techniques to identify the most relevant features for COVID-19 forecasting. Ethical considerations underpin the scope of this study from data collection to model usage. Given that the data utilized involves public health information, it is imperative to ensure the privacy and anonymity of individuals. All datasets were anonymized and aggregated to eliminate markers that could identify individuals. In addition to privacy concerns, the issues of data integrity and representativeness were diligently addressed to avoid any form of bias, such as socioeconomic or geographic bias, that could skew the forecasting models. The chosen deep-learning models were scrutinized for any inherited biases that might inadvertently perpetuate existing health inequities. While the algorithms themselves are neutral, the data that inform them may not lead to biased policy recommendations. Furthermore, the ethical dimensions of automated decision-making in public health were considered. Although these models can forecast with high accuracy, human oversight is vital for interpreting these predictions in a broader ethical and societal context. This approach ensures that model-based recommendations do not inadvertently disadvantage any subgroup of the population or lead to ethical dilemmas such as resource allocation in scarce settings. Finally, transparent reporting and open-source sharing of the models used in this study underscore our commitment to ethical rigor, enabling peer review and the potential for widespread application under ethically sound parameters.

Recommendations for Future Research

Future research could explore alternative feature selection and preprocessing techniques to improve the model performance. The optimization of the models showed a significant improvement over the non-optimized model. This indicates that optimization plays an important role in improving model outcomes. The findings show that all the models can perform at their best once they have been improved. This also depends on the number of trials and execution steps. A larger number of execution trials may overfit the data, whereas a smaller number may underfit

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the data. This requires constant updating of the settings for the models in order to select the best outcome for training.

Our study sets the stage for several significant avenues of future research. First, considering the evolving nature of SARS-CoV-2, subsequent investigations could focus on increasing model adaptability to account for new viral variants, potentially incorporating real-time learning capabilities. Additionally, because human behavior substantially influences the spread of the virus, embedding more granular behavioral variables, such as mobility patterns and public health compliance rates, could provide richer insights. Regional variability in the impact of policy interventions also opens the door for developing geographically tailored models or those that include spatial variables. The exploration of multi-objective optimization methods, allowing for the balancing of multiple conflicting objectives, such as predictive accuracy and model interpretability, also presents a promising area for future work. Future research should aim to integrate additional types of data, such as vaccination rates and healthcare infrastructure availability, to construct more comprehensive and reliable models. Comparative studies that evaluate the performance of deep-learning models against traditional epidemiological or hybrid models that incorporate elements of both would add depth to our understanding of pandemic forecasting methods. Finally, the real-world application of these models, accompanied by a continuous feedback loop for model refinement, served as a robust validation of their practical utility.

Our findings have practical implications for policymakers and public health officials involved in the management of the COVID-19 pandemic. Beyond the academic realm, the broader impact of this study is manifold, particularly in shaping effective public health policy and strategy. First, it provides an empirically validated framework for forecasting COVID-19 dynamics, a tool that can be invaluable to health departments and governmental bodies. By utilizing the deep learning models presented in this study, specifically RNN and MLP, policymakers can achieve a more nuanced understanding of how the virus might spread under various conditions. This insight could be instrumental in the planning and allocation of critical healthcare resources such as ventilators, personal protective equipment, and medical personnel. Furthermore, the findings of this study could inform the design of more targeted and efficient public health interventions, such as lockdowns or vaccine distribution strategies, thereby optimizing the balance between health protection and economic impact. In the context of ongoing vaccination drives, the models can potentially be adapted to forecast vaccine efficacy over time, helping fine-tune vaccination policies. Finally, since the core methodology is not specific to COVID-19, the findings of this study have the potential for application in managing future public health crises, thus laying the groundwork for a more robust and proactive healthcare system.

Conclusion

By using the best-performing models (RNN and MLP) to predict new cases, more informed decisions could be made regarding resource allocation, public health measures, and vaccination strategies. Furthermore, optimization can significantly improve model performance. Additionally, our study contributes to the growing body of research using deep learning models for pandemic forecasting, which can be applied to future public health crises. The accurate forecasting of COVID-19 dynamics is crucial for informed policymaking and resource allocation. The performance of the optimized model can provide valuable insights for public health officials and decision-makers in the UAE. By leveraging these models, authorities can better anticipate the trajectory of the pandemic, implement timely interventions, and allocate resources efficiently to mitigate the impact of the virus on the population. The discussion section highlights the performance of the deep learning models, compares the findings with those of previous studies, acknowledges the limitations, and suggests future research directions. It also emphasizes the implications of the study's findings on public health policy and decision-making in the UAE.

Notes

Ethics Approval

The requirement for informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

Data is publicly available through World Health Organization (WHO), Ministry of Health (UAE), and John Hopkins Github: https://github.com/CSSEGISandData/COVID-19

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Original Article

Effect of Paxlovid in COVID-19 treatment during the periods of SARS-CoV-2 Omicron BA.5 and BN.1 subvariant dominance in the Republic of Korea: a retrospective cohort study

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ABSTRACT

Objectives: This study was conducted to assess the efficacy of nirmatrelvir/ritonavir treatment in patients with coronavirus disease 2019 (COVID-19), particularly those aged 60 years and older. Using real-world data, the period during which the BN.1 Omicron variant was dominant was compared to the period dominated by the BA.5 variant.

Methods: In this retrospective cohort study, data were collected regarding 2,665,281 patients infected with severe acute respiratory syndrome coronavirus 2 between July 24, 2022, and March 31, 2023. Propensity score matching was utilized to match patients who received nirmatrelvir/ritonavir in a 1:4 ratio between BN.1 and BA.5 variant groups. Multivariable logistic regression analysis was employed to assess the effects of nirmatrelvir/ritonavir within these groups.

Results: Compared to the prior period, the efficacy of nirmatrelvir/ritonavir did not significantly differ during the interval of Omicron BN.1 variant dominance in the Republic of Korea. Among patients treated with nirmatrelvir/ritonavir, a significantly lower risk of mortality was observed in the BN.1 group (odds ratio [OR], 0.698; 95% confidence interval [CI], 0.557–0.875) compared to the BA.5 group. However, this treatment did not significantly reduce the risk of severe or critical illness, including death, for those in the BN.1 group (OR, 0.856; 95% CI, 0.728–1.007).

Conclusion: Nirmatrelvir/ritonavir has maintained its effectiveness against COVID-19, even with the emergence of the BN.1 Omicron subvariant. Consequently, we strongly recommend the administration of nirmatrelvir/ritonavir to patients exhibiting COVID-19-related symptoms, irrespective of the dominant Omicron variant or their vaccination status, to mitigate disease severity and decrease the risk of mortality.

Keywords: Antiviral agents; COVID-19; Nirmatrelvir; Retrospective study; SARS-CoV-2 variants

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was first identified in Wuhan, China, at the end of 2019 [1,2]. Since then, the Omicron variant of SARS-CoV-2 has become the dominant strain globally, representing over 98% of the virus samples shared by the Global Initiative on Sharing All Influenza Data [3]. In the Republic of Korea, the first case of the Omicron variant was detected on November 30, 2021 [4]. By January 1, 2022, the predominant variant in the country had shifted from the Delta variant to the Omicron subvariant BA.1 [5,6]. This was followed by the emergence of BA.2 as the dominant subvariant on March 20, 2022, and BA.5 on July 24, 2022. More recently, the BN.1 variant became the dominant subvariant on January 22, 2023, and has spread rapidly in the Republic of Korea, accounting for 50.4% of newly reported infections [7]. This has occurred despite high vaccination coverage and a large portion of the population having been previously infected with Omicron subvariants BA.1, BA.2, or BA.5. The first oral antiviral agents, nirmatrelvir and ritonavir (sold under the brand name Paxlovid), were authorized by the United States Food and Drug Administration on December 22, 2021, for the treatment of high-risk patients with mild-to-moderate COVID-19 [8–10]. Following emergency use authorization in the Republic of Korea on December 27, 2021, nirmatrelvir/ritonavir was first administered on January 14, 2022, to patients experiencing mild-to-moderate symptoms of COVID-19 who were at high risk of progressing to severe disease. The treatment was administered within 5 days of symptom onset (Figure 1) [11]. To date, this combination has primarily been used to treat high-risk patients, in line with the recommendations of the Korea Disease Control and Prevention Agency (KDCA). In recent research, nirmatrelvir/ritonavir was associated with significant decreases in the rates of severe COVID-19 and mortality, with adjusted hazard ratios of 0.54 (95% confidence interval [CI], 0.39–0.75) and 0.20 (95% CI, 0.17–0.22), respectively. The treatment appeared to be more effective in patients who were older, were immunosuppressed, or had underlying neurological or cardiovascular disease (interaction $p < 0.05$ for all) [12,13]. However, these studies were conducted when earlier SARS-CoV-2 variants were more common and may not reflect the current situation of Omicron variant prevalence. Therefore, it is necessary to investigate the effectiveness of nirmatrelvir/ritonavir under the present circumstances, particularly regarding the prevailing Omicron variant. This analysis was performed to assess the efficacy of nirmatrelvir/ritonavir in patients, especially those aged 60 years or older, against COVID-19. We employed real-world data to compare the period of BN.1 Omicron dominance with that of BA.5 Omicron dominance.

HIGHLIGHTS

- We assessed the efficacy of nirmatrelvir/ritonavir in the treatment of COVID-19, particularly among patients aged 60 years and older, in a comparison of Omicron subvariants BN.1 and BA.5 using real-world data.
- Nirmatrelvir/ritonavir remained effective during the period of Omicron BA.1 dominance, significantly reducing mortality risk. A statistically insignificant decrease in severe illness was also noted.
- Regardless of Omicron variant or vaccination status, nirmatrelvir/ritonavir administration is recommended to reduce the risks of severe illness and death from COVID-19.
- This study underscores the continued relevance of nirmatrelvir/ritonavir under Omicron-dominant conditions, offering essential insights for clinical practice and patient care.

Materials and Methods

Data Sources

This study incorporated data from 4 sources: (1) confirmed patient information, (2) primary epidemiological investigation data from the COVID-19 Information Management System of the KDCA, (3) the Drug Utilization Review (DUR) database, and (4) COVID-19 Patient Information Management System data from the Health Insurance Review and Assessment Service (HIRA). The database managed by the KDCA includes information regarding SARS-CoV-2 polymerase chain reaction diagnostic test results, underlying diseases, and vaccination status. The DUR database contains prescription information for oral antivirals used in treating COVID-19. Finally, data from the COVID-19 Patient Information Management System include medical history details, such as critical severity and mortality.

Study Design and Population

This retrospective cohort study included 2,665,433 patients who were infected with SARS-CoV-2 between July 24, 2022, and March 31, 2023. The dominant periods were delineated based on the first week in which over 50% of the weekly SARS-CoV-2 variant tests returned positive results for that variant, based on KDCA variant analysis reporting dates.

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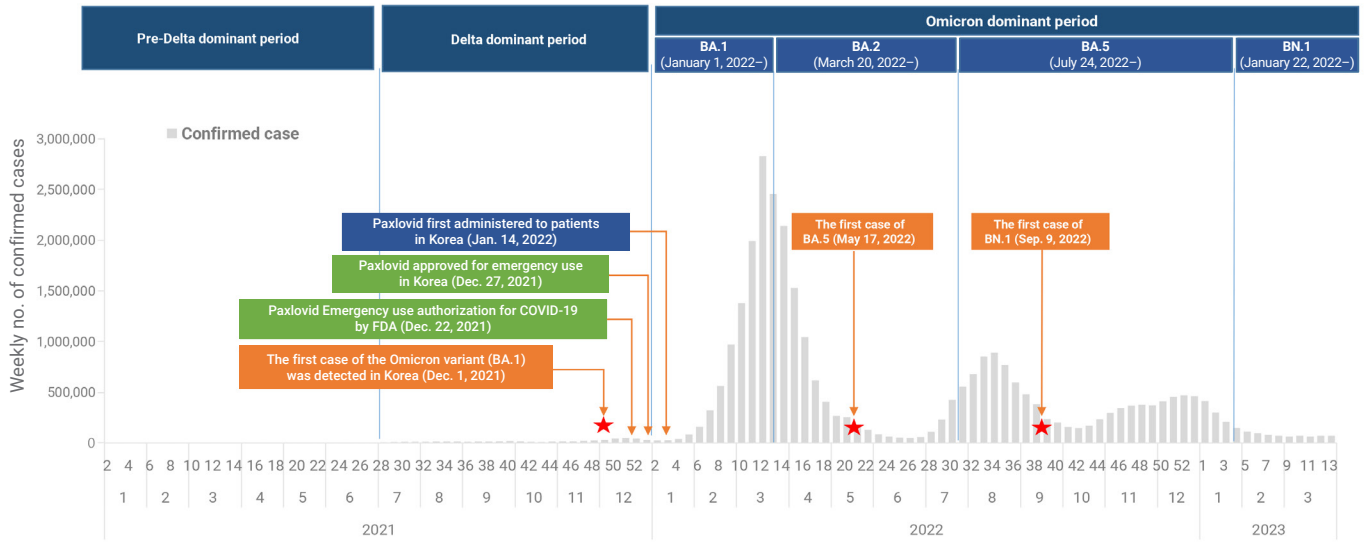

Figure 1. Epidemic waves corresponding to periods of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant dominance in the Republic of Korea from January 1, 2022, to March 30, 2023: pre-Delta, Delta, and Omicron. Data sources: confirmed COVID-19 cases were obtained from the Korea Disease Control and Prevention Agency (KDCA), while the periods of SARS-CoV-2 variant dominance were determined based on a KDCA press release. FDA, Food and Drug Administration.

Consequently, the study population was categorized into 2 groups: (1) the BA.5 group, consisting of 2,470,529 individuals infected between July 24, 2022, and January 21, 2023, during which BA.5 was the prevailing subvariant; and (2) the BN.1 group, comprising 194,904 individuals infected from January 22 to March 31, 2023, when BN.1 predominated.

Nirmatrelvir/ritonavir, administered twice daily for 5 days, is considered for the treatment of patients with mild-to-moderate COVID-19 who are at high risk of progressing to severe illness, including hospitalization or death. The KDCA has recommended the use of nirmatrelvir/ritonavir in its published COVID-19 treatment guidelines [14], specifying the following criteria: (1) any patients aged 60 years or older, (2) patients aged 12 years or older (weighing at least 40 kg) and under 60 years who have underlying disease and/or immunosuppression, and (3) treatment initiation within 5 days of symptom onset in patients not requiring supplemental oxygen.

In the present study, the patient inclusion criteria were as follows: (1) a diagnosis of COVID-19 between July 24, 2022, and March 31, 2023; (2) an age of 12 years or older; (3) infection with SARS-CoV-2 and prescription of nirmatrelvir/ritonavir within 5 days of symptom onset; and (4) those who met the conditions for nirmatrelvir/ritonavir administration according to KDCA guidelines. The exclusion criteria were: (1) incomplete data from the essential epidemiological investigation; (2) treatment with molnupiravir or remdesivir; and (3) ineligibility for nirmatrelvir/ritonavir treatment according to the established KDCA criteria. Follow-up monitoring for each patient was conducted for 28 days following COVID-19 diagnosis.

Study Outcomes

The analysis encompassed cases of severe COVID-19 and related deaths, adhering to the Korean guidelines for COVID-19 response and management [15]. Severe or critical illness, a category that included deaths, was defined as including any patient with a COVID-19 diagnosis who was receiving care in a medical facility and was considered at risk of mortality. These patients required therapeutic interventions such as non-invasive or invasive ventilation, high-flow oxygen therapy, extracorporeal membrane oxygenation, or continuous renal replacement therapy. A death was recorded when it was known or suspected to be caused by COVID-19. Monitoring of severe or critical illness (including death) and mortality in COVID-19 patients continued for 28 days following diagnosis.

In this study, we compared the effectiveness of nirmatrelvir/ritonavir in mitigating the risk of severe or critical illness, including death, among patients with COVID-19 during the periods in which the Omicron BN.1 variant and BA.5 variant predominated. Participants were stratified based on vaccination status (unvaccinated or vaccinated), age group (≥60 years, ≥70 years, or ≥80 years), and sex (male or female).

Statistical Analysis

Descriptive statistics (expressed as frequencies and percentages) were used to characterize the study participants and to compare the groups that were untreated, treated with

nirmatrelvir/ritonavir, unvaccinated, and vaccinated. The chi-square test was employed to compare categorical variables across these groups. To address potential confounders and establish the appropriate sample size, propensity score matching was utilized. This method matched patients who received nirmatrelvir/ritonavir from the BA.5 and BN.1 groups. Specifically, 62,987 patients in the BN.1 group were matched with 251,948 patients in the BA.5 group at a 1:4 ratio (Table 1). The chi-square test was again used to compare categorical variables between these matched groups. Multivariable logistic regression analysis was conducted to evaluate the risk of severe or critical disease, including death, among patients with COVID-19 based on their nirmatrelvir/ritonavir treatment status (treated vs. not treated) within both BA.5 and BN.1 groups. Additionally, within the nirmatrelvir/ritonavir-treated cohort, hierarchical multivariable logistic regression analysis was employed to determine the treatment's effect in the BN.1 group relative to the BA.5 cohort. These analyses were adjusted for age, sex, underlying medical conditions, and vaccination status. All statistical analyses were carried out using SAS ver. 9.4 (SAS Institute). The tests were 2-sided, and *p*-values below 0.05 were considered to indicate statistical significance.

Ethics Statement

The study protocol underwent review and received approval from the institutional review board of the Korea National Institute of Health (approval no: KDCA-2023-07-02-PE-01). The requirement for informed consent was waived.

Results

Study Population Characteristics

During the period of this nationwide retrospective cohort

Table 1. Baseline characteristics of patients who received nirmatrelvir/ritonavir treatment during the BA.5 and BN.1 periods before and after 1:4 propensity score matching

Characteristic	Non-matching			1:4 Propensity score matching		
	BA.5	BN.1	*p*	BA.5	BN.1	*p*
Participants	610,114 (24.7)	62,987 (32.3)		251,948 (80.0)	62,987 (32.3)	
Sex			<0.001			1.000
Male	251,109 (41.2)	24,933 (39.6)		99,732 (39.6)	24,933 (39.6)	
Female	359,005 (58.8)	38,054 (60.4)		152,216 (60.4)	38,054 (60.4)	
Age (y)	69.4±11.2	69.5±11.6	0.911	69.4±11.6	69.5±11.7	0.897
Age group (y)			<0.001			0.999
≤39	9,584 (1.6)	1,277 (2.0)		5,084 (2.0)	1,277 (2.0)	
40–49	14,526 (2.4)	1,569 (2.5)		6,309 (2.5)	1,569 (2.5)	
50–59	40,438 (6.6)	3,992 (6.3)		15,984 (6.3)	3,992 (6.3)	
60–69	255,996 (42.0)	25,786 (40.9)		103,170 (41.0)	25,786 (40.9)	
70–79	173,438 (28.4)	17,972 (28.5)		71,885 (28.5)	17,972 (28.5)	
≥80	116,132 (19.0)	12,391 (19.7)		49,516 (19.7)	12,391 (19.7)	
SARS-CoV-2 immunity[a]			<0.001			0.9150
Unvaccinated	29,858 (4.9)	3,388 (5.4)		13,525 (5.4)	3,388 (5.4)	
Vaccinated	580,256 (95.1)	59,599 (94.6)		238,423 (94.6)	59,599 (94.6)	
Underlying diseases						
Hypertension	245,760 (40.3)	25,431 (40.4)	0.647	101,358 (40.2)	25,431 (40.4)	0.506
Hyperlipidemia	122,472 (20.1)	12,565 (20.0)	0.456	51,204 (20.3)	12,565 (20.0)	0.036
Diabetes	129,218 (21.2)	14,143 (22.5)	<0.001	51,968 (20.6)	14,143 (22.5)	<0.001
Cardiovascular diseases	28,605 (4.7)	2,828 (4.5)	0.025	12,309 (4.9)	2,828 (4.5)	<0.001
Kidney failure	4,036 (0.7)	357 (0.6)	0.005	1,835 (0.7)	357 (0.6)	<0.001
Immunosuppression	5,416 (0.9)	503 (0.8)	0.023	2,404 (1.0)	503 (0.8)	0.001
Chronic obstructive pulmonary disease	5,403 (0.9)	449 (0.7)	<0.001	2,801 (1.1)	449 (0.7)	<0.001
Severe illness or death	1,932 (0.3)	183 (0.3)	0.265	835 (0.3)	183 (0.3)	0.106
Death	1,111 (0.2)	91 (0.1)	0.033	515 (0.2)	91 (0.1)	0.002

Data are presented *n* (%) or mean±standard deviation. Chi-square tests were employed to determine differences between the groups based on nirmatrelvir/ritonavir treatment history.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a](1) Unvaccinated: Individuals who have not been vaccinated or who are within 14 days of receiving their first dose of a vaccine; (2) Vaccinated: Individuals who are 14 days or more past receiving their second dose of a vaccine. Those who received the Janssen vaccine were considered as having received the second dose after the first dose was administered.

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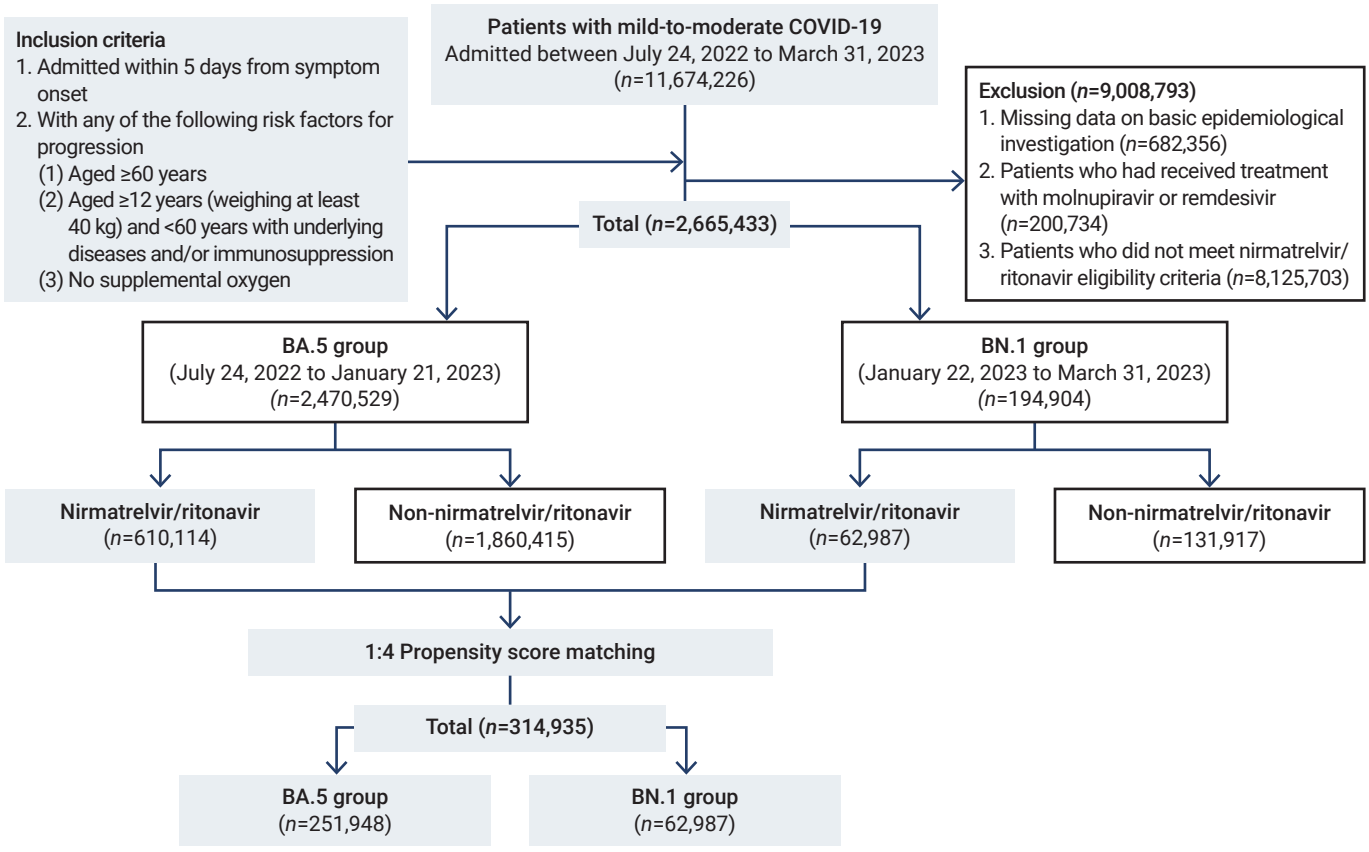

Figure 2. Flowchart of patient selection and grouping. Propensity score matching was employed to match patients who received nirmatrelvir/ritonavir between the BA.5 and BN.1 groups. Specifically, a 1:4 ratio was used to match patients in the BN.1 group (n = 62,987) with those in the BA.5 group (n = 251,948).

study, we screened 2,470,529 patients with mild-to-moderate COVID-19 who were enrolled in the DUR system for patient care. Following the exclusion of 6,965,801 patients, a total of 2,665,433 patients who were eligible for nirmatrelvir/ritonavir treatment were included in the study. The patients were classified into the BA.5 group (n = 2,470,529) and the BN.1 group (n = 194,904) (Figure 2).

In the BA.5 period, of the 610,114 patients (24.7%) who were treated with nirmatrelvir/ritonavir, 545,536 (89.4%) were at least 60 years old. Within this older demographic, the 60–69-year age bracket contained the largest number of patients, with 255,996 individuals (42.0%). The most prevalent comorbidities among these patients were hypertension (245,760, 40.3%), hyperlipidemia (129,218, 21.2%), and diabetes (122,472, 20.1%), as shown in Table 2.

In the BN.1 group, of the 62,987 patients (32.3%) who were treated with nirmatrelvir/ritonavir, 56,152 (89.1%) were aged 60 years or older. Among these older participants, the largest age subgroup was those aged 60–69 years, accounting for 25,786 patients (40.9%). The most common comorbid conditions included hypertension (25,431, 40.4%), hyperlipidemia (14,143, 22.5%), and diabetes (12,565, 20.0%).

Overall, more than 95% of the patients included in the analysis were fully vaccinated against SARS-CoV-2. Factors such as sex, age, presence of underlying diseases (including multiple underlying conditions), and severe or critical nature of the illness (including death) differed significantly based on whether patients received nirmatrelvir/ritonavir treatment (Table 3).

Effectiveness of Nirmatrelvir/Ritonavir in the BA.5 and BN.1 Groups

Multivariable logistic regression was performed to assess the effect of nirmatrelvir/ritonavir use on severe or critical illness (including death) and on death alone. The risk of these outcomes was lower among patients who received nirmatrelvir/ ritonavir treatment than among those who did not, regardless of age, sex, or vaccination status (Table 4).

In the BA.5 group, patients treated with nirmatrelvir/ritonavir had a significantly lower risk of severe or critical illness, including death, compared to the untreated group. The adjusted odds ratio (OR) for receiving nirmatrelvir/ritonavir

Table 2. Baseline characteristics of patients according to nirmatrelvir/ritonavir treatment status during the BA.5 period (July 24, 2022–January 21, 2023)

Variable	No nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir	*p*
Participants	1,860,415 (75.3)	610,114 (24.7)	
Sex			<0.001
Male	781,055 (42.0)	251,109 (41.2)	
Female	1,079,360 (58.0)	359,005 (58.8)	
Age (y)	64.4±12.3	69.4±11.2	<0.001
Age group (y)			<0.001
≤39	36,051 (3.4)	9,584 (1.6)	
40–49	130,499 (7.0)	14,526 (2.4)	
50–59	300,258 (16.1)	40,438 (6.6)	
60–69	773,965 (41.6)	255,996 (42.0)	
70–79	393,648 (21.2)	173,438 (28.4)	
≥80	198,994 (10.7)	116,132 (19.0)	
SARS-CoV-2 immunity[a]			<0.0001
Unvaccinated	83,319 (4.5)	29,858 (4.9)	
Vaccinated	1,777,096 (95.5)	580,256 (95.1)	
Underlying diseases			
Hypertension	865,571 (46.5)	245,760 (40.3)	<0.001
Diabetes	410,376 (22.1)	122,472 (20.1)	<0.001
Hyperlipidemia	469,378 (25.2)	129,218 (21.2)	<0.001
Cardiovascular diseases	92,292 (5.0)	28,605 (4.7)	<0.001
Immunosuppression	9,318 (0.5)	4,036 (0.7)	<0.001
Kidney failure	30,366 (1.6)	5,416 (0.9)	<0.001
Chronic obstructive pulmonary disease	27,036 (1.5)	5,403 (0.9)	<0.001
Severe illness or death	7,351 (0.4)	1,932 (0.3)	<0.001
Death	3,415 (0.2)	1,111 (0.2)	0.8165

Data are presented *n* (%) or mean±standard deviation. Chi-square tests were employed to determine differences between the groups based on nirmatrelvir/ritonavir treatment history.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a](1) Unvaccinated: Individuals who have not been vaccinated or who are within 14 days of receiving their first dose of a vaccine; (2) Vaccinated: Individuals who are 14 days or more past receiving their second dose of a vaccine. Those who received the Janssen vaccine were considered as having received the second dose after the first dose was administered.

treatment, with 95% CI, was 0.516 (0.490–0.543). Among older adults, the ORs (95% CIs) for those aged ≥60 years, ≥70 years, and ≥80 years were 0.494 (0.468–0.520), 0.496 (0.469–0.524), and 0.503 (0.472–0.537), respectively. The ORs (95% CIs) for men and women were 0.503 (0.468–0.541) and 0.527 (0.490–0.567), respectively. For unvaccinated and vaccinated patients, the ORs (95% CIs) were 0.347 (0.312–0.386) and 0.586 (0.553–0.622), respectively (Figure 3A; Table S1). Comparatively, the risk of death was significantly reduced in the nirmatrelvir/ritonavir treatment group compared to the untreated group. The adjusted OR (95% CI) for all nirmatrelvir/ritonavir-treated patients was 0.610 (0.569–0.653). In older adults, the ORs (95% CIs) for those aged ≥60 years, ≥70 years, and ≥80 years were 0.596 (0.556–0.639), 0.598 (0.556–0.643), and 0.603 (0.555–0.654), respectively. For men and women, the ORs (95% CIs) were 0.599 (0.542–0.662) and 0.618 (0.562–0.680), respectively. Similarly, for unvaccinated and vaccinated patients, the ORs (95% CIs) were 0.379 (0.328–0.438) and 0.714 (0.660–0.772), respectively (Figure 3B; Table S1).

In the BN.1 group, the patients treated with nirmatrelvir/ritonavir faced a significantly lower risk of severe or critical illness (including death) than those who did not receive this treatment. The adjusted OR (95% CI) for receiving nirmatrelvir/ritonavir treatment was 0.279 (0.237–0.327). Among older adults, the ORs (95% CIs) for those aged ≥60 years, ≥70 years, and ≥80 years were 0.262 (0.222–0.309), 0.252 (0.211–0.302), and 0.271 (0.218–0.337), respectively. The ORs (95% CIs) for men and women were 0.259 (0.207–0.324) and 0.299 (0.237–0.377), respectively. For unvaccinated and vaccinated patients, the ORs (95% CIs) were 0.215 (0.157–0.294) and 0.307 (0.255–0.370), respectively (Figure 4A; Table S2). Similarly, the risk of death was significantly reduced in the nirmatrelvir/ritonavir treatment group compared to the untreated group. The adjusted OR (95% CI) for all patients treated with nirmatrelvir/ritonavir was 0.373 (0.295–0.471). In older adults, the ORs (95% CIs) for those aged ≥60 years, ≥70 years, and ≥80 years were 0.371 (0.293–0.469), 0.378 (0.295–0.484), and 0.401 (0.302–0.532), respectively. The

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Table 3. Baseline characteristics of patients according to nirmatrelvir/ritonavir treatment status during the BN.1 period (January 22, 2023–March 31, 2023)

Variable	No nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir	*p*
Participants	131,917 (67.7)	62,987 (32.3)	
Sex			<0.001
Male	55,009 (41.7)	24,933 (39.6)	
Female	76,908 (58.3)	38,054 (60.4)	
Age (y)	64.3±12.9	69.5±11.6	<0.001
Age group (y)			<0.001
≤39	5,170 (3.9)	1,277 (2.0)	
40–49	10,206 (7.7)	1,569 (2.5)	
50–59	22,205 (16.8)	3,992 (6.3)	
60–69	51,273 (38.9)	25,786 (40.9)	
70–79	27,239 (20.7)	17,972 (28.5)	
≥80	15,824 (12.0)	12,391 (19.7)	
SARS-CoV-2 immunity[a]			0.029
Unvaccinated	7,415 (5.6)	3,388 (5.4)	
Vaccinated	124,502 (94.4)	59,599 (94.6)	
Underlying diseases			
Hypertension	63,065 (47.8)	25,431 (40.4)	<0.001
Diabetes	29,406 (22.3)	12,565 (20.0)	<0.001
Hyperlipidemia	35,319 (26.8)	14,143 (22.5)	<0.001
Cardiovascular diseases	6,513 (4.9)	2,828 (4.5)	<0.001
Immunosuppression	740 (0.6)	357 (0.6)	0.8723
Kidney failure	2,301 (1.7)	503 (0.8)	<0.001
Chronic obstructive pulmonary disease	1,876 (1.4)	449 (0.7)	<0.001
Severe illness or death	1,003 (0.8)	183 (0.3)	<0.001
Death	360 (0.3)	91 (0.1)	<0.001

Data are presented *n* (%) or mean±standard deviation. Chi-square tests were employed to determine differences between the groups based on nirmatrelvir/ritonavir treatment history.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a](1) Unvaccinated: Individuals who have not been vaccinated or who are within 14 days of receiving their first dose of a vaccine; (2) Vaccinated: Individuals who are 14 days or more past receiving their second dose of a vaccine. Those who received the Janssen vaccine were considered as having received the second dose after the first dose was administered.

Table 4. Effectiveness of nirmatrelvir/ritonavir in the BA.5 and BN.1 groups

Model	Death		Severe/critical illness (including death)	
	No nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir	No nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir
BA.5				
Model 1	Ref.	0.992 (0.927–1.062)	Ref.	0.801 (0.762–0.842)
Model 2	Ref.	0.598 (0.558–0.640)	Ref.	0.511 (0.485–0.537)
Model 3	Ref.	0.610 (0.569–0.653)	Ref.	0.516 (0.490–0.543)
BN.1				
Model 1	Ref.	0.529 (0.420–0.666)	Ref.	0.380 (0.325–0.445)
Model 2	Ref.	0.352 (0.279–0.444)	Ref.	0.266 (0.226–0.311)
Model 3	Ref.	0.373 (0.295–0.471)	Ref.	0.277 (0.236–0.326)

The multivariable logistic regression models were adjusted for age, sex, vaccination status, and underlying diseases. The results are expressed as odds ratios (95% confidence intervals). Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 builds upon model 2 by also adjusting for vaccination status and underlying disease.
Ref., reference.

ORs (95% CIs) for men and women were 0.263 (0.182–0.379) and 0.502 (0.369–0.683), respectively. For unvaccinated and vaccinated patients, the ORs (95% CIs) were 0.337 (0.227–0.501) and 0.394 (0.296–0.526), respectively (Figure 4B; Table S2).

Propensity Score Matching for Sample Size Determination

The proportion of patients who received nirmatrelvir/ritonavir was similar between the BA.5 and BN.1 groups, although the

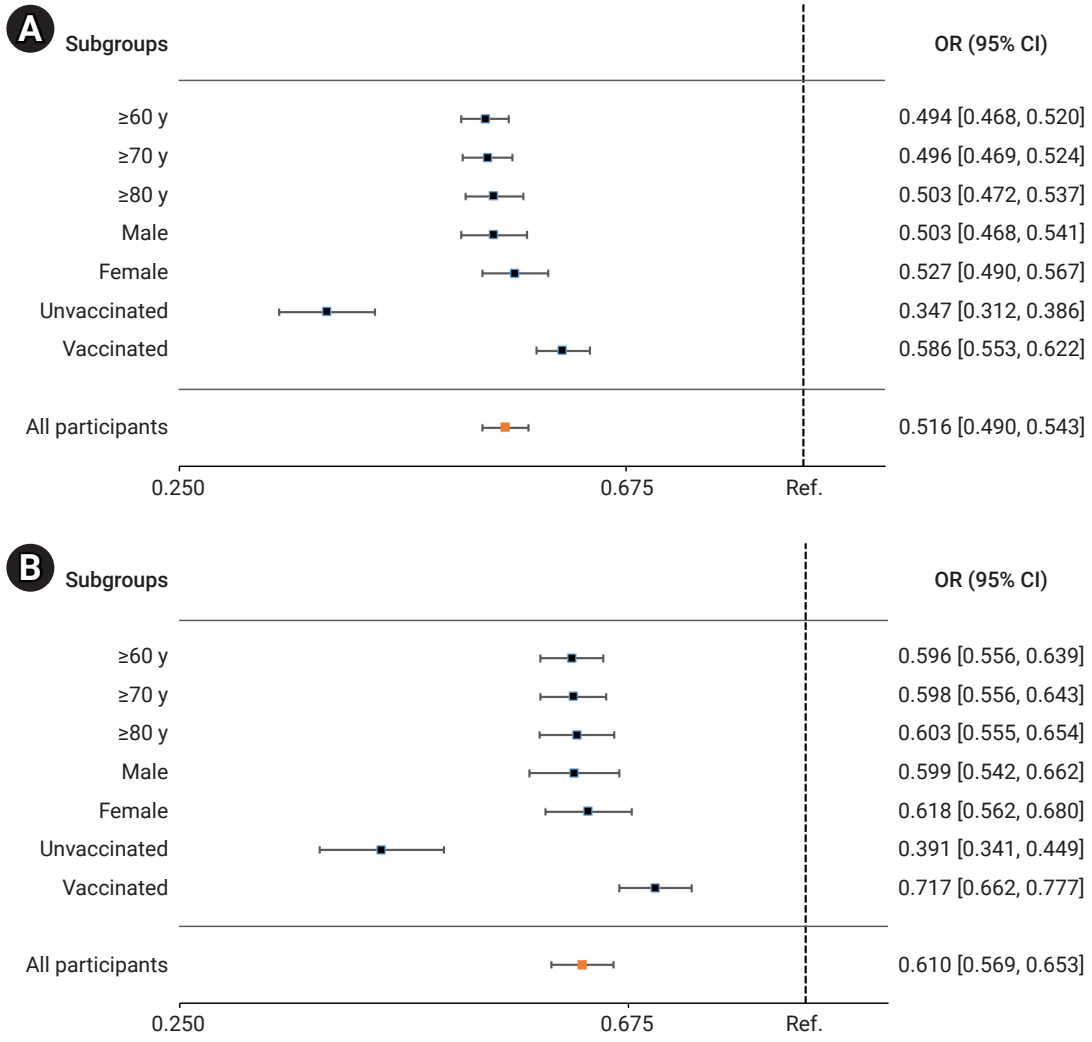

Figure 3. Impact of nirmatrelvir/ritonavir treatment in the BA.5 group. (A) Severe/critical illness (including death). (B) Death. Multivariable logistic regression models were adjusted for age, sex, vaccination status against severe acute respiratory syndrome coronavirus 2, and underlying diseases. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Ref., reference.

BA.5 group included more cases. We therefore employed the propensity score matching technique to match patients who received nirmatrelvir/ritonavir from the BA.5 and BN.1 groups. Specifically, patients from the BN.1 group (n=62,987) were matched with those from the BA.5 group (n=251,948) at a 1:4 ratio. Following propensity score matching, the patient characteristics were found to be balanced across groups, as demonstrated by the chi-square test (p>0.1). For both groups, the percentage of patients aged ≥60 years and the vaccination rates were 89.1% and 94.6%, respectively, with chi-square test p-values of 0.999 and 0.915, respectively (Table 1).

Comparative Effectiveness of Nirmatrelvir/Ritonavir in the BN.1 and BA.5 Groups

Among the patients who received nirmatrelvir/ritonavir treatment, multivariable logistic regression was performed to assess the effect of nirmatrelvir/ritonavir in the BN.1 group compared to that in the BA.5 group (Table 5).

In model 1 (unadjusted), the risk of death was significantly lower for the BN.1 group (OR, 0.707; 95% CI, 0.566–0.883) compared to the BA.5 group. However, no significant reduction was observed in the risk of severe or critical illness (including death) for the BN.1 group (OR, 0.876; 95% CI, 0.747–1.029). In model 2, which was adjusted for age and sex, the risk of death for the BN.1 group was significantly lower (OR, 0.699; 95% CI, 0.559–0.874) than for the BA.5 group. Nonetheless, the risk of severe or critical illness (including death) for the BN.1 group was not significantly reduced (OR, 0.871; 95% CI, 0.742–1.023). In model 3, which included adjustments for vaccination status and underlying disease

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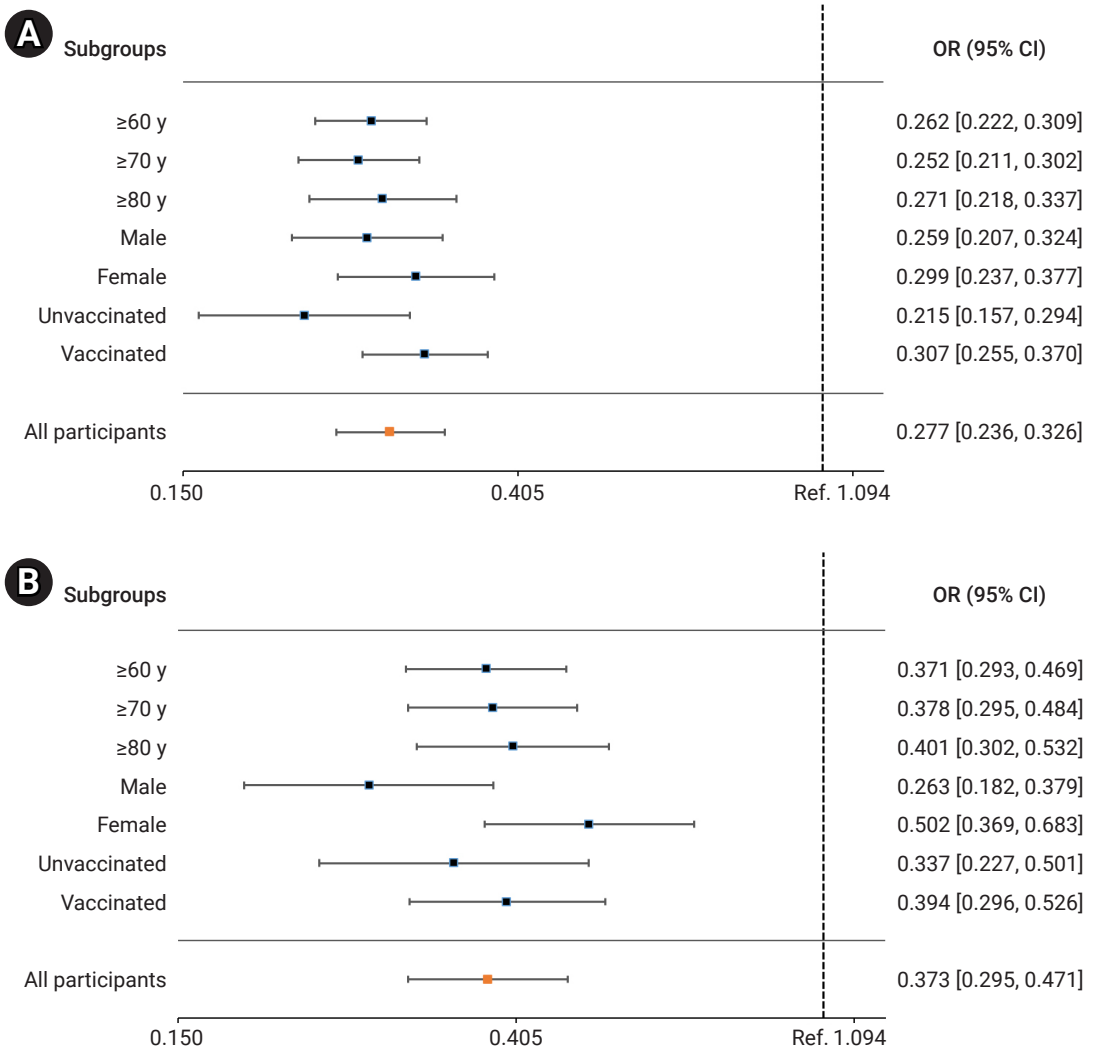

Figure 4. Impact of nirmatrelvir/ritonavir treatment in the BN.1 group. (A) Severe/critical illness (including death). (B) Death. Multivariable logistic regression models were adjusted for age, sex, vaccination status against severe acute respiratory syndrome coronavirus 2, and underlying diseases. Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Ref., reference.

in addition to the factors in model 2, the risk of death for the BN.1 group remained significantly lower (OR, 0.698; 95% CI, 0.557–0.875) compared to the BA.5 group. However, the risk of severe or critical illness (including death) was again statistically similar for the BN.1 group relative to the BA.5 group (OR, 0.856; 95% CI, 0.728–1.007).

Discussion

This nationwide study evaluated the effectiveness of nirmatrelvir/ritonavir throughout the periods dominated by the BA.5 and BN.1 Omicron variants. The sample size was sufficiently large to yield a reliable estimation of risk. Compared to the prior period, the efficacy of nirmatrelvir/ritonavir did not significantly differ during the interval of Omicron BN.1 variant predominance in the Republic of Korea. This was despite initial concerns about a potential reduction in the drug's effectiveness following the transition from BA.5 to BN.1 as the most common viral variant.

Recent studies have indicated that during the Omicron surge, individuals who received nirmatrelvir/ritonavir experienced significantly lower rates of hospitalization and death from COVID-19 compared to those who did not receive the treatment [16–18]. Additionally, our prior research demonstrated that nirmatrelvir/ritonavir effectively decreased the risk of COVID-19 mortality in patients infected with the Omicron BA.5 variant, particularly in older adults, regardless of vaccination status [19]. This analysis further revealed that during periods when each viral variant was predominant, the likelihood of severe or critical illness, including death, was

Table 5. Comparative effectiveness of nirmatrelvir/ritonavir in the BN.1 group versus the BA.5 group

Variable	Model 1	Model 2	Model 3
Severe/critical illness (including death)			
Dominant Omicron subvariant			
BA.5	Ref.	Ref.	Ref.
BN.1	0.876 (0.747–1.029)	0.871 (0.742–1.023)	0.856 (0.728–1.007)
Age		1.114 (1.107–1.121)	1.100 (1.093–1.107)
Sex			
Male		Ref.	Ref.
Female		0.575 (0.507–0.652)	0.547 (0.482–0.621)
SARS-CoV-2 immunity			
Unvaccinated			Ref.
Vaccinated			0.248 (0.212–0.209)
Underlying diseases			
No			Ref.
Yes			2.207 (1.836–2.652)
Death			
Dominant Omicron subvariant			
BA.5	Ref.	Ref.	Ref.
BN.1	0.707 (0.566–0.883)	0.699 (0.559–0.874)	0.698 (0.557–0.875)
Age		1.143 (1.132–1.153)	1.127 (1.117–1.137)
Sex			
Male		Ref.	Ref.
Female		0.635 (0.538–0.749)	0.601 (0.509–0.710)
SARS-CoV-2 immunity			
Unvaccinated			Ref.
Vaccinated			0.253 (0.208–0.308)
Underlying diseases			
No			Ref.
Yes			2.068 (1.629–2.624)

The results are expressed as odds ratios (95% confidence intervals). Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 builds upon model 2 by also adjusting for vaccination status and underlying disease.
Ref., reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

significantly reduced in the group treated with nirmatrelvir/ritonavir compared to the untreated group. Furthermore, among the patients who received nirmatrelvir/ritonavir, the risk of death was significantly lower in patients within the BN.1 cohort than in those within the BA.5 group. We also observed no significant difference in the risk of severe or critical illness, including mortality, between the BA.5 and BN.1 groups. Consequently, our study indicates that the risk of severe outcomes is either significantly lower or similar for cases during the BN.1 period compared to the BA.5 interval. These findings align with the results from *in vitro* studies conducted during the early stages of the Omicron surge, which revealed potent inhibition of this variant by nirmatrelvir [20–23]. Additionally, the antiviral efficacy of nirmatrelvir against 27 SARS-CoV-2 variants, including BA.5 and BN.1, was sustained, suggesting that these drugs remain viable treatment options for COVID-19 [24]. Therefore, our study demonstrates that the use of nirmatrelvir/ritonavir represented a significant independent predictor of reduced mortality risk during the periods dominated by the BA.5 and BN.1 Omicron variants.

COVID-19 vaccines, such as the Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) vaccines, play a crucial role in reducing the risk of SARS-CoV-2 infection and COVID-19–related hospitalization [25,26]. In response to the January 2022 surge of the Omicron variant, the KDCA recommended 2 primary defenses—COVID-19 vaccination and antiviral therapy—to safeguard convalescent hospitals, long-term care facilities, and high-risk populations from severe COVID-19 [27]. As of July 20, 2023, 86.5% of the Korean population aged 5 years and older had been vaccinated against COVID-19 [28]. However, the present study noted a decrease in vaccine effectiveness against infection and hospital admission for Omicron compared to earlier variants [29–31]. This suggests that the Omicron variant may evade the immune response elicited by vaccination or previous infection with other variants, potentially leading to higher transmissibility [32–34]. In the subgroup analyses of study outcomes based on vaccination status, the therapeutic effect of nirmatrelvir/ritonavir was more pronounced among the unvaccinated

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participants than in the vaccinated group during the periods dominated by the BA.5 and BN.1 Omicron subvariants. Our analysis only considered whether patients had received at least 1 vaccine dose prior to the onset of COVID-19, with 95.2% of the study population being vaccinated under this definition. Consequently, additional research is required to assess the real-world efficacy of nirmatrelvir/ritonavir in treating COVID-19, taking into account variations in patient immunity due to vaccination history and prior infection.

This study had several limitations, given its observational and retrospective nature. First, we were unable to confirm whether patients had completed the prescribed 5-day course of nirmatrelvir/ritonavir treatment. As a result, the treatment group may have included patients who did not complete the full course of therapy. Second, factors such as vaccination history (including booster doses) and prior infection play key roles in disease severity and mortality. These were not considered in our study, which could have led to an underestimation of the effects of nirmatrelvir/ritonavir. Third, the KDCA recommend initiating nirmatrelvir/ritonavir therapy within the first 5 days of symptom onset. Our study did not incorporate the timing of symptom onset relative to the COVID-19 diagnosis or the prescription of nirmatrelvir/ritonavir. Fourth, due to the absence of relevant clinical information, we could not determine whether the observed preventive effects against severe/critical illness (including death) and death alone were attributable to nirmatrelvir/ritonavir or to the effectiveness of other treatments, such as monoclonal antibodies. Fifth, while this study analyzed the effectiveness of nirmatrelvir/ritonavir, it did not collect any data on the drug's safety. Consequently, further research into the safety profile of nirmatrelvir/ritonavir is essential to provide patients with accurate information and support informed decision-making.

Conclusion

Our study suggests that treatment with nirmatrelvir/ritonavir remains effective against COVID-19, even with the emergence of the BN.1 variant supplanting BA.5. In both subvariant cohorts, nirmatrelvir/ritonavir treatment was associated with a reduced risk of severe or critical illness, including death, compared to those who did not receive treatment. Consequently, we recommend administering nirmatrelvir/ritonavir to patients exhibiting COVID-19-related symptoms, irrespective of the dominant Omicron variant or the patient's vaccination status. This approach is likely to lower the risk of severe or critical illness, decrease mortality, and help control the spread of COVID-19.

Supplementary Material

Table S1. Effectiveness of nirmatrelvir/ritonavir treatment in the BA.5 group; **Table S2.** Effectiveness of nirmatrelvir/ritonavir treatment in the BN.1 group. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0230.

Notes

Ethics Approval

This study received approval from the institutional review board of the Korea National Institute of Health (approval no: KDCA-2023-07-02-PE-01). Due to the retrospective nature of the research, the requirement for informed consent was waived.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The study's data sets are securely stored in coded form at the KDCA. The KDCA is legally obligated by a data-sharing agreement with the HIRA to prohibit disclosure of the dataset. Nevertheless, researchers who meet certain criteria may access the data for research purposes via the HIRA Bigdata Open portal (https://opendata.hira.or.kr).

Authors' Contributions

Conceptualization: DHK, MGY; Data curation: MGY; Formal analysis: MGY; Investigation: DHK, NYK, MA, SJJ, MJ, SYC; Methodology: MGY; Project administration: DHK; Resources: MGY; Software: MGY; Supervision: JK; Validation: DHK, MGY; Visualization: DHK, MGY; Writing–original draft: DHK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

We would like to extend our sincere gratitude to the DUR program and the HIRA for supplying the necessary datasets for this study.

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Original Article

COVID-19 infection among people with disabilities in 2021 prior to the Omicron-dominant period in the Republic of Korea: a cross-sectional study

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ABSTRACT

Objectives: This study investigated the characteristics of coronavirus disease 2019 (COVID-19) among individuals with disabilities on a nationwide scale in the Republic of Korea, as limited research has examined this population.
Methods: Between January 1 and November 30, 2021, a total of 5,687 confirmed COVID-19 cases among individuals with disabilities were reported through the Korea Disease Control and Prevention Agency's COVID-19 web reporting system. Follow-up continued until December 24, and demographic, epidemiological, and clinical characteristics were analyzed.
Results: Individuals with disabilities represented approximately 1.5% of confirmed cases, with a mean age of 58.1 years. Most resided in or near metropolitan areas (86.6%) and were male (60.6%). Frequent sources of infection included home (33.4%) and contact with confirmed cases (40.7%). Many individuals (75.9%) had underlying conditions, and 7.7% of cases were severe. People with disabilities showed significantly elevated risk of severe infection (adjusted odds ratio [aOR], 1.63; 95% confidence interval [CI], 1.47–1.81) and mortality (aOR, 1.65; 95% CI, 1.43–1.91). Vaccination against COVID-19 was associated with significantly lower risk of severe infection (aORs for the first, second, and third doses: 0.60 [95% CI, 0.42–0.85], 0.28 [95% CI, 0.22–0.35], and 0.16 [95% CI, 0.05–0.51], respectively) and death (adjusted hazard ratios for the first and second doses: 0.57 [95% CI, 0.35–0.93] and 0.30 [95% CI, 0.23–0.40], respectively).
Conclusion: Individuals with disabilities showed higher risk of severe infection and mortality from COVID-19. Consequently, it is critical to strengthen COVID-19 vaccination initiatives and provide socioeconomic assistance for this vulnerable population.

Keywords: COVID-19; COVID-19 vaccines; Disabled persons; SARS-CoV-2

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Introduction

A person with a disability, as defined by Article 2 of the Republic of Korea's Act on Welfare of

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Persons with Disabilities, is an individual whose daily life or social activities are substantially restricted due to a physical or mental impairment that persists over an extended period. "Physical disability" refers to impairments affecting the body's primary external functions or internal organs. In contrast, "mental disability" encompasses disabilities resulting from psychological developmental disorders or mental illnesses [1]. In 2020, the number of people with disabilities in the Republic of Korea reached 2,633,026, representing approximately 5.1% of the country's total population for that year [2].

According to the "COVID-19 Response Guidelines," individuals at elevated risk of coronavirus disease 2019 (COVID-19) include older adults aged 65 years or older, residents of long-term care facilities, and those with underlying health conditions [3]. People with disabilities are also considered to be at high risk of COVID-19 infection. Notably, the proportion of people with disabilities who are over 65 years old has been increasing, and these individuals often have permanent disabilities resulting from diseases and accidents, representing a fixed condition [4]. Additionally, the "Infectious Disease Response Manual for Persons with Disabilities" details the vulnerabilities of this group, including "communication restrictions," "movement restrictions," "infection vulnerability," "care in close quarters," and "group activities." These factors contribute to the increased risk of COVID-19 infection among people with disabilities [5].

As such, individuals with disabilities showed higher risk of COVID-19infection; however, additional research is needed. Previous studies examining COVID-19 infection among this population in the Republic of Korea have been constrained by small sample sizes and limited analysis periods. Moreover, studies from an epidemiological perspective are markedly less common than those approached from a social welfare perspective [6,7].

Therefore, this study was conducted to analyze and present the demographic, epidemiological, and clinical characteristics of confirmed COVID-19 cases among individuals with disabilities from January to November 2021, preceding the Omicron variant.

HIGHLIGHTS

- Individuals with disabilities faced significantly higher risk of severe coronavirus disease 2019 (COVID-19) infection (adjusted odds ratio [aOR], 1.63; 95% confidence interval [CI], 1.47–1.81) and death (AOR, 1.65; 95% CI, 1.43–1.91) compared to those without disabilities.
- Vaccination against COVID-19 was associated with significantly reduced risk. The respective AORs for severe infection after 1, 2, and 3 vaccine doses were 0.60, 0.28, and 0.16, with 95% CIs of 0.42–0.85, 0.22–0.35, and 0.05–0.51. For mortality, the adjusted hazard ratios were 0.57 (95% CI, 0.35–0.93) for 1 dose and 0.30 (95% CI, 0.23–0.40) for 2 doses.

Materials and Methods

Materials

The study period was from the count of confirmed COVID-19 cases as of midnight on January 1, 2021, to the count as of midnight on November 30, 2021. The analysis focused on confirmed COVID-19 cases among individuals with disabilities within this timeframe. During the study period, a total of 386,496 confirmed cases of COVID-19 were reported, with 5,687 of these cases included in our study. Participants were selected according to the following inclusion criteria.

First, we identified 6,735 confirmed COVID-19 cases among people who indicated that they were registered individuals with disabilities in epidemiological reports of the Korea Disease Control and Prevention Agency (KDCA) on the COVID-19 web reporting system. This list was cross-referenced with the KDCA's list of confirmed cases, resulting in the exclusion of 3 cases due to delayed reporting registration and errors in the epidemiological report. Subsequently, the list was compared with documentation of confirmed cases managed by each city and provincial government, as well as in-depth epidemiological reports, leading to the exclusion of 1,045 cases due to error or because of unknown information on specific disabilities. Consequently, a total of 5,687 participants were selected for the study. These cases accounted for approximately 1.5% of the cumulative cases during the study period. The analysis of participants was based on the data as of December 24, 2021. The algorithm for the selection procedure of the study participants is shown in Figure 1.

Epidemiological reports from the COVID-19 web reporting system, along with data regarding confirmed COVID-19 cases provided by the Central Disease Control Headquarters, were used to collect information on demographics, time of infection confirmation, vaccination history, underlying diseases, and routes of epidemiological transmission.

Methods

People with disabilities were categorized based on the presence of physical and/or mental disability, in accordance with the Act on Welfare of Persons with Disabilities [1]. The degree of disability was classified as either non-serious

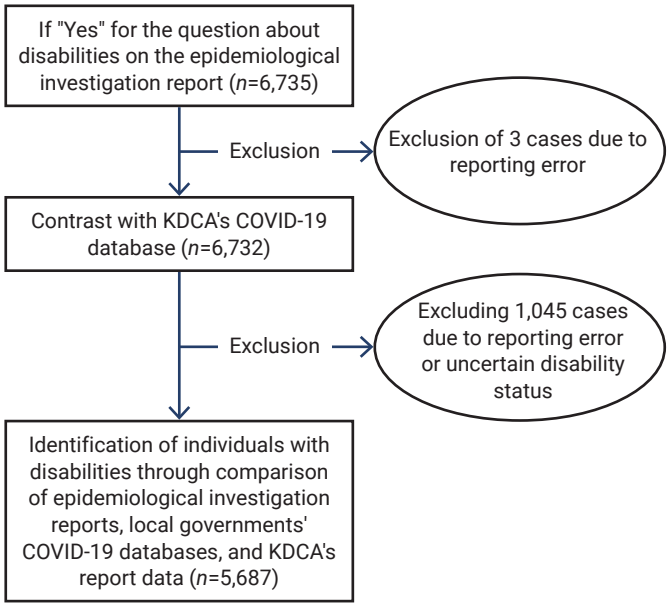

Figure 1. Participant selection process. KDCA, Korea Disease Control and Prevention Agency.

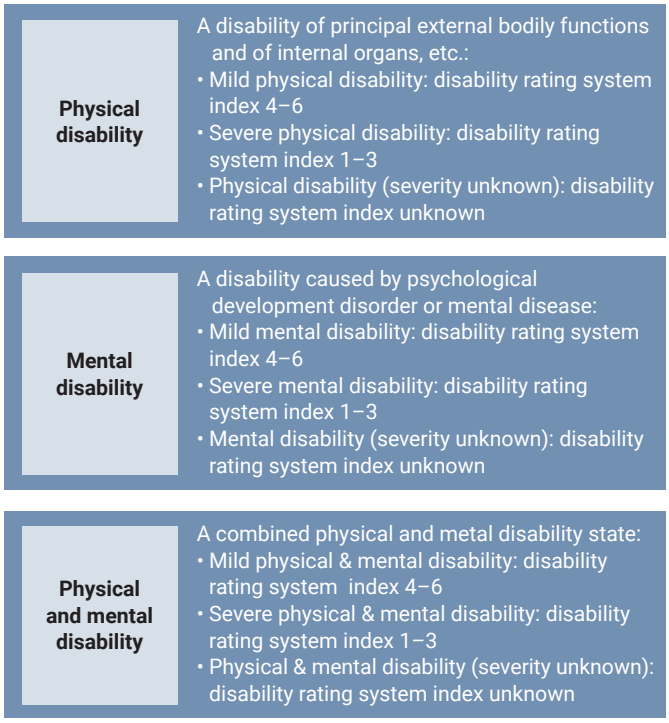

Figure 2. Disability categories.

(mild) or serious (severe). This classification was based on the criteria established by the Korea Disabled People's Development Institute. Mild disability is associated with indices 4 to 6, while severe disability corresponds to indices 1 to 3, according to the disability rating system in use prior to 2019 [8]. The categories of disabilities are detailed in Figure 2.

The following factors were analyzed: general characteristics, which included demographic information; epidemiological characteristics, which considered the route of transmission and the relationship with previously confirmed cases; vaccination history at the time of COVID-19 diagnosis; underlying conditions; prognosis; comparison with confirmed COVID-19 cases in individuals without disabilities; and clinical characteristics, such as the risk of severe infection, in association with vaccination history and the risk of mortality. Descriptive statistics were used to present the results of the frequency analysis, which were expressed as the corresponding number (*n*) and percentage (%). Among the clinical characteristics, multivariate logistic regression was used to estimate the adjusted odds ratio (aOR) for the risk of severe infection based on vaccination history. The outcome variable was a binary indicator of severity, and the independent variable was the number of vaccine doses (none, 1, 2, or 3). Adjusted hazard ratios (aHRs) and Kaplan-Meier curves were computed using survival analysis to estimate the risk of mortality. Furthermore, *p*-values of less than 0.05 were considered statistically significant, and 95% confidence intervals (CIs) were also described. Excel ver. 2013 (Microsoft) and SAS ver. 9.4 (SAS Institute Inc.) were utilized for the statistical analyses.

Institutional Review Board Approval

The study protocol received approval from the institutional review board (IRB) of the KDCA, with the approval number IRB-2023-05-08-PE-01.

Results

General Characteristics of Participants

From January 1 to November 30, 2021, a total of 386,496 cases of COVID-19 were confirmed, with 5,687 of these cases occurring among individuals with disabilities in this study. The temporal trend in the number of confirmed cases is illustrated in Figure 3.

Substantially more confirmed cases were found among men (*n*=3,449, 60.6%) than women (*n*=2,238, 39.4%). The mean age of the patients was 58.1 years, with men averaging 55.9 years and women 61.6 years.

The categories and degrees of disability are presented in Table 1. Most participants had a physical disability (*n*=4,310, 75.8%). A total of 1,226 participants had a mental disability (21.6%), and 151 had both physical and mental disabilities (2.7%). Among those with a physical disability, most had a mild physical disability (*n*=2,637), representing 46.4% of all

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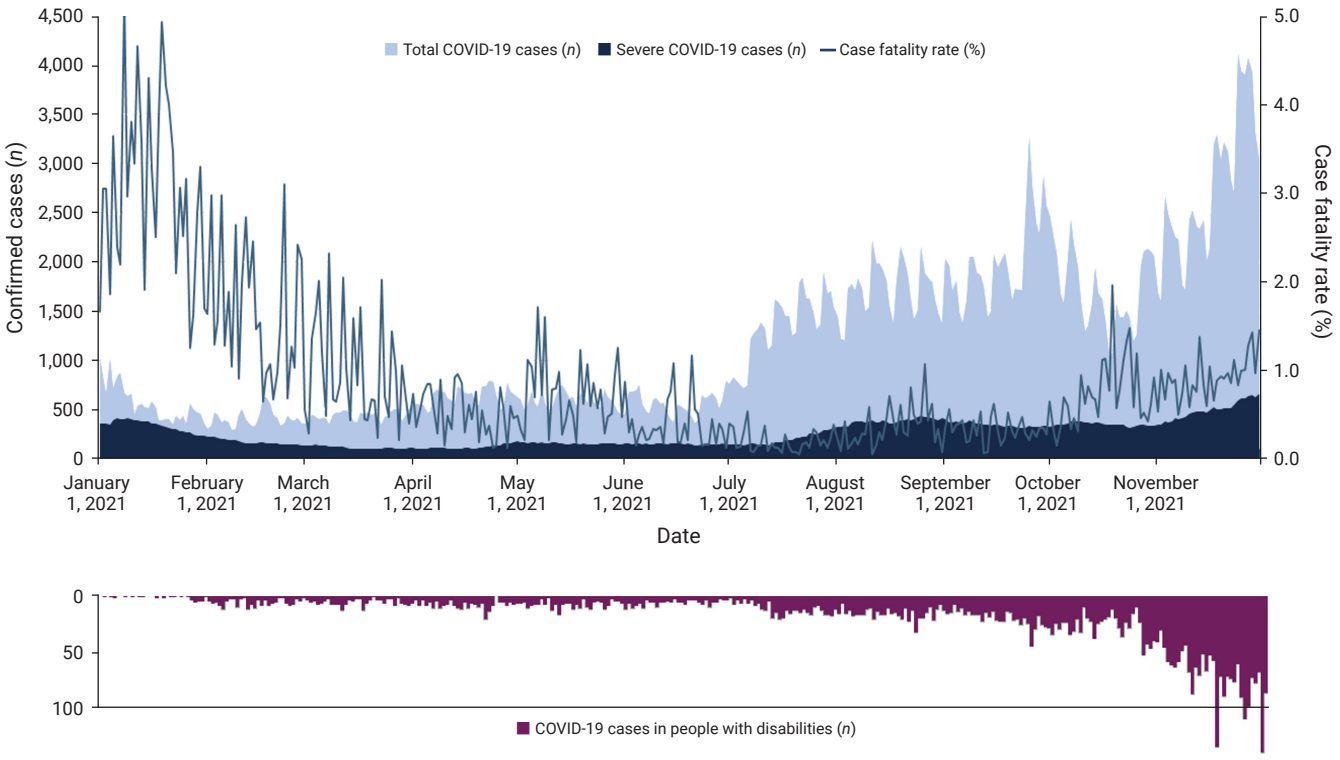

Figure 3. Trends in the incidence of coronavirus disease 2019 (COVID-19) infection, overall and among individuals with disabilities, from January to November 2021.

participants. The distribution of disability categories and degrees was similar between men and women, as shown in Table 1.

Based on the data from the KDCA COVID-19 web reporting system, most cases resided in urban areas, with 46.6% living in Seoul, 35.5% in Gyeonggi, and 2.9% in Gangwon. According to the Korean Standard Classification of Occupations, nearly half of the participants (*n*=2,806, 49.3%) were unemployed, while 24.2% were part of the workforce (*n*=1,378) [9]. The category of "simple labor worker," which typically refers to low-skilled occupations, was the most frequently reported among both men and women, at 8.3% (*n*=286) and 4.4% (*n*=99), respectively.

Epidemiological Characteristics of Participants

The location of transmission was domestic—that is, within the Republic of Korea—for 5,674 cases (99.8%). The most common route of transmission was contact with confirmed cases (*n*=2,316, 40.7%), followed by unknown transmission (*n*=1,631, 28.7%), outbreaks in hospitals and nursing facilities (*n*=955, 16.8%), outbreaks in community settings (*n*=768, 13.5%), and international importation and related transmission (*n*=17, 0.3%).

Excluding unknown transmission sources, the most frequent location of exposure was the home (*n*=1,979, 34.8%), followed by medical facilities (*n*=552, 9.7%) and nursing facilities (*n*=323, 5.7%). When analyzed by sex, the most common exposure locations for men were the home (*n*=1,078, 31.3%), medical facilities (*n*=312, 9.0%), and the workplace (*n*=307, 7.0%). For women, the most common exposure locations were the home (*n*=823, 36.8%), medical facilities (*n*=240, 10.7%), and nursing facilities (*n*=212, 9.5%) (Figure 4).

The most frequent relationship between the participants and previously confirmed cases was either a cohabitating or non-cohabitating family member (*n*=1,857, 32.7%), followed by another type of contact (*n*=1,094, 19.2%) and an unknown relationship (*n*=503, 8.8%).

Clinical Characteristics of Participants

Clinical severity and prognosis

An examination of participant prognosis as of December 24, 2021, revealed that 5,073 individuals (89.2%) had been released from quarantine, 378 (6.6%) remained in quarantine, and 236 (4.1%) had died (4.1%). Additionally, 436 participants (7.7%) were classified as severe COVID-19 cases. These patients required either invasive or non-invasive mechanical ventilation, received high-flow oxygen therapy, or underwent

Table 1. Categories and severity levels of disability in confirmed COVID-19 cases among individuals with disabilities, January–November 2021

Disability category	Total (*n* = 5,687)	Male (*n* = 3,449)	Female (*n* = 2,238)
Physical disability (*n* = 4,310)			
Mild	2,637 (46.4)	1,652 (47.9)	985 (44.0)
Severe	1,226 (21.6)	734 (21.3)	492 (22.0)
Severity unknown	447 (7.9)	266 (7.7)	181 (8.1)
Mental disability (*n* = 1,226)			
Mild	468 (8.2)	231 (6.7)	237 (10.6)
Severe	523 (9.2)	313 (9.1)	210 (9.4)
Severity unknown	235 (4.1)	143 (4.1)	92 (4.1)
Physical and mental disability (*n* = 151)			
Mild	37 (0.7)	25 (0.7)	12 (0.5)
Severe	94 (1.7)	67 (1.9)	27 (1.2)
Severity unknown	20 (0.4)	18 (0.5)	2 (0.1)

Data are presented as *n* (%).

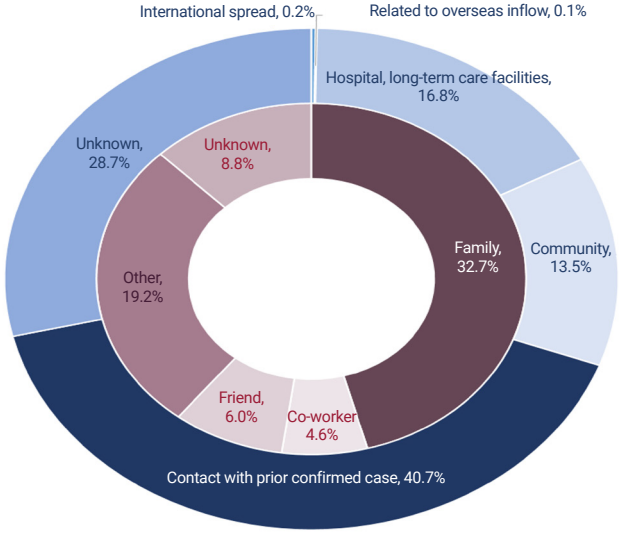

Figure 4. Estimated transmission routes and relationships with previously confirmed coronavirus disease 2019 cases among individuals with disabilities from January to November 2021 (excluding unknown transmission routes).

extracorporeal membrane oxygenation or continuous renal replacement therapy during the quarantine period due to multiple organ failure.

Underlying medical conditions and vaccination status at the time ofCOVID-19 confirmation

Among the participants, 4,318 had underlying conditionss, accounting for 75.9% of the total. For both men and women, hypertension was the most common condition, followed by neurological or psychiatric disorders, diabetes, and cardiovascular disease. The fifth most common underlying condition was urologic disease for men and musculoskeletal disease for women, respectively (Figure 5).

At the time of COVID-19 confirmation, the largest proportion of participants had received 2 vaccination doses (*n* = 2,635, 46.3%). In comparison, 2,388 (42.0%) were unvaccinated, 582 (10.2%) had received 1 dose, and 82 (1.5%) had received 3 doses. When examining the timing of vaccinations, the largest group consisted of unvaccinated individuals (*n* = 2,388, 42.0%). This was followed by 1,307 participants (23.0%) for whom it had been 90 days or more since their second dose, and 649 participants (11.4%) for whom 60 to 90 days had elapsed since their second dose.

Comparison of the risk of severe COVID-19 infection and mortality in confirmed COVID-19 cases between individuals with and without disabilities

Using multivariate logistic regression analysis, aORs were calculated to identify any significant differences in the risk of severe COVID-19 and mortality between participants and confirmed cases without disabilities across the study period. For this analysis, the number of confirmed cases among people without disabilities was estimated at 380,809, after excluding the participants from the total number of confirmed cases during the study period. The results indicated that the participants were 1.63 times more likely to experience severe COVID-19 infection than people without disabilities (aOR, 1.63; 95% CI, 1.47–1.81). Furthermore, the odds of mortality among participants were 1.65 times higher than among those without disabilities (aOR, 1.65; 95% CI, 1.43–1.91).

Analysis of the risk of severe COVID-19 infection and mortality based on COVID-19 vaccination status at confirmation

The risk of severe COVID-19 infection, based on vaccination status at the time of infection confirmation, was analyzed in 4,985 participants (87.7%), excluding those with an unknown degree of disability. The results, adjusted for sex, age, underlying

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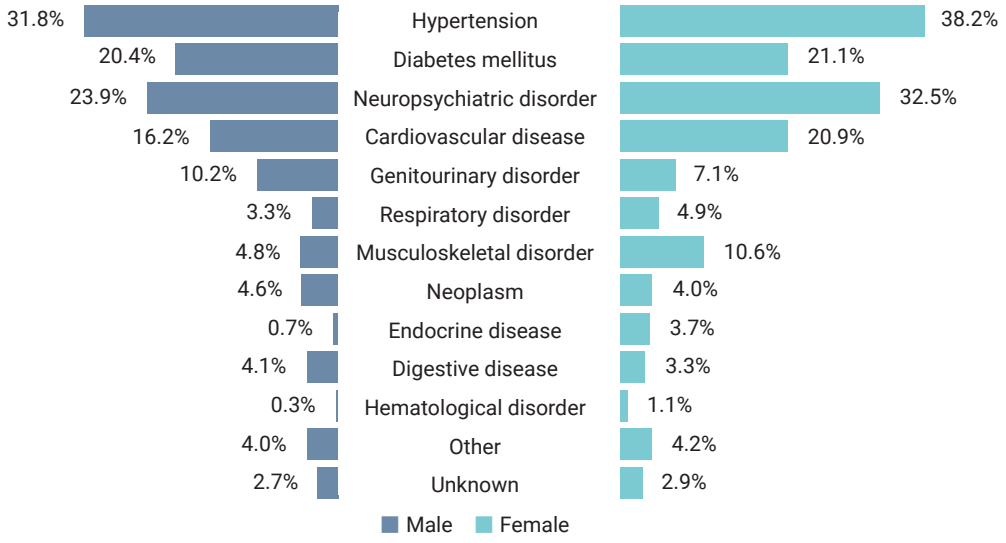

Figure 5. Distribution of underlying diseases among individuals with disabilities from January to November 2021, categorized by sex (n = 4,318). Duplicated counting.

disease, and disability category, are presented in Figure 5. The unvaccinated group served as the reference group. The likelihood of experiencing severe COVID-19 infection was significantly lower in the vaccinated group than in their unvaccinated. Moreover, an inverse relationship was observed between the number of vaccine doses received and the risk of severe COVID-19, indicating that COVID-19 vaccination effectiveness in preventing severe COVID-19 infection (Figure 6).

The time intervals from the date of COVID-19 confirmation to the date of death for deceased participants, and to December 24, 2021, for survivors, were calculated. Survival curves were then constructed and compared using Kaplan-Meier analysis. Significant differences in survival rates were observed based on the history of COVID-19 vaccination and the number of vaccine doses received at the time of COVID-19 confirmation (p < 0.001). Specifically, individuals who were vaccinated at the time of COVID-19 confirmation showed a significantly higher survival rate than those who were unvaccinated. Moreover, an increase in the number of COVID-19 vaccine doses at the time of confirmation was associated with a marked increase in the survival rate (Figure 7).

Table 2 presents the results of an analysis using the Cox proportional hazards model, which was adjusted for variables including sex, age, underlying disease, and disability category. This analysis assessed the risk of mortality associated with overall vaccination status and the number of COVID-19 vaccine doses received at the time of confirmation. The mortality risk among individuals vaccinated against COVID-19 at this time was significantly lower than that of the unvaccinated group

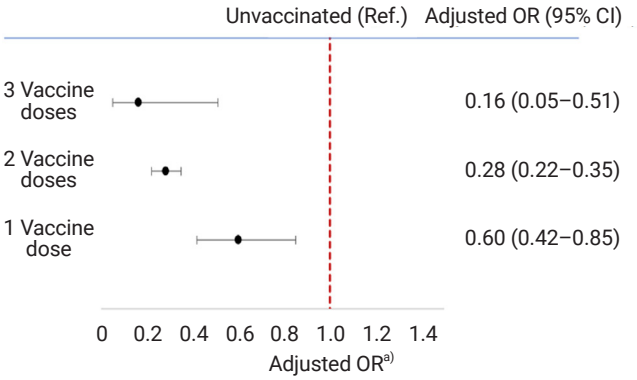

Figure 6. Risk of severe infection according to coronavirus disease 2019 (COVID-19) vaccination status among confirmed COVID-19 cases in individuals with disabilities at the time of COVID-19 confirmation from January to November 2021. Adjusted for sex, age, underlying disease, disabled type.
[a)]Adjusted for sex, age, underlying disease, disability category.
Ref., reference; OR, odds ratio; CI, confidence interval.

(aHR, 0.32; 95% CI, 0.25–0.42). A significantly lower mortality risk was also observed for participants who had received a first vaccine dose (aHR, 0.57; 95% CI, 0.35–0.93) and a second dose (aHR, 0.30; 95% CI, 0.23–0.40). However, among the 82 participants who had received a third vaccine dose, no deaths were reported (Table 2).

Discussion

In this study, we examined the demographical, epidemiological, and clinical characteristics of 5,687 confirmed COVID-19

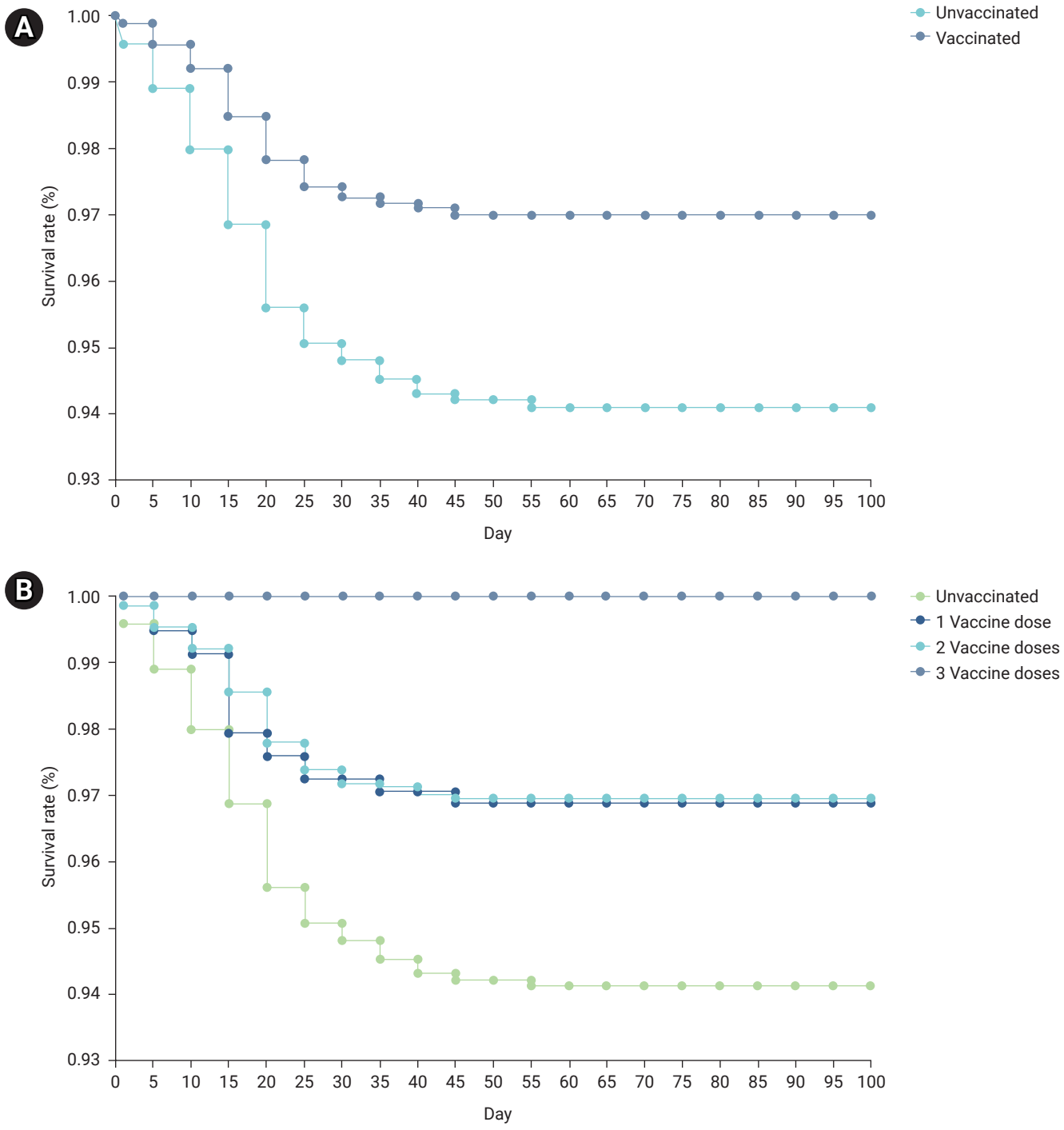

Figure 7. (A) Comparison of survival rates among individuals with disabilities and confirmed coronavirus disease 2019 (COVID-19), categorized by vaccination status at the time of COVID-19 confirmation, from January to November 2021 ($p<0.001$). (B) Comparison of survival rates among individuals with disabilities and confirmed COVID-19, categorized by the number of vaccine doses received at the time of COVID-19 confirmation, over the same period ($p<0.001$).

cases among individuals with disabilities, from January 1 to November 30, 2021. This timeframe preceded the the Omicron variant dominant period in the Republic of Korea.

The study participants, all of whom were individuals with disabilities, represented 1.5% of confirmed COVID-19 cases in the Republic of Korea from January to November 2021. The average age of these participants was 58.1 years, with a higher proportion of . By severity, the largest group

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Table 2. Risk of mortality among confirmed COVID-19 cases in individuals with disabilities by vaccination status, January–November 2021

Variable	Adjusted HR (95% CI)[a]	*p*
Vaccination		
No	1 (ref.)	
Yes	0.32 (0.25–0.42)	<0.0001
No. of vaccine doses		
None	1 (ref.)	
1	0.57 (0.35–0.93)	0.02
2	0.30 (0.23–0.40)	<0.0001
3	0	0.96

HR, hazard ratio; CI, confidence interval; ref., reference.
[a]Adjusted HRs were calculated using Cox regression analysis after adjustment for age, sex, underlying disease, and category of disability.

consisted of those with mild physical disabilities (46.4%), and the majority lived in metropolitan areas. Nearly half of the participants (49.3%) were unemployed, while only 24.2% were economically active, primarily in simple labor work. Consequently, COVID-19 infection is expected to exacerbate not only the health conditions but also the economic conditions of people with disabilities.

Regarding the location of exposure, the most common route of transmission was infection in the home (33.4%). More generally, the most frequent infection source was contact with individuals already confirmed to have COVID-19 (40.7%), most commonly cohabitating or non-cohabitating family members (32.7%). Therefore, to minimize the incidence of COVID-19 infection among individuals with disabilities, it is essential to encourage self-testing within households and to implement routine testing in medical and nursing facilities. Notably, a previous study indicated that the rate of unknown transmission routes was 20% during the early stages of the COVID-19 pandemic in 2020, whereas in our study, this rate was 28.7% among people with disabilities [10].

A total of 75.9% of participants had underlying diseases. Regarding prognosis as of December 24, 2021, 4.1% had died, and 7.7% had experienced severe COVID-19 infection. Individuals with disabilities showed significantly higher risk of severe COVID-19 infection and mortality compared to those without disabilities.

An analysis of vaccination history and the time between COVID-19 vaccination and COVID-19 infection confirmation revealed that the largest group of participants (42.0%) were unvaccinated. This was followed by those for whom 90 days or more had elapsed since the second vaccination dose (23.0%) and those who were 60 to 90 days post-second dose (11.4%). These results indicate that the incidence of COVID-19 increased as the protective effect of the vaccine diminished over time.

The analysis of COVID-19 risk in relation to the number of vaccine doses revealed a significant reduction in the risk of both severity and mortality. Furthermore, we observed a significant increase in survival rates corresponding with an increase in the number of vaccine doses administered. These findings imply that initial COVID-19 vaccination, along with subsequent doses administered within an appropriate timeframe, have a effectiveness in preventing the COVID-19 severe infectionand mortality in individuals with disabilities.

This study has a significant value, as it presents a large-scale analysis of the demographical, epidemiological, and clinical characteristics of confirmed COVID-19 cases among individuals with disabilities. The analysis incorporated various perspectives from January 1 to November 30, 2021. However, one limitation of this study is that it may not account for all confirmed COVID-19 cases in this population due to potential data input errors or missing information within the epidemiological investigation data, which served as the primary data source. Additionally, the lack of information on vaccine type precluded an estimation of vaccine effectiveness based on this parameter. Furthermore, while previous research has identified the heterogeneity of infectiousness as a key factor in COVID-19 transmission [11], this study, relying on a national database, lacked the relevant information to consider this factor.

According to 2021 data from Statistics Korea, 37.7% of all individuals with disabilities are economically active. Among this group, simple labor workers represent the highest proportion, at 28.3%. Furthermore, the percentage of individuals with disabilities aged 65 years or older has been on the rise, increasing from 37.1% in 2010 to 42.3% in 2015 and reaching 48.3% in 2019. Additionally, people with disabilities showed a higher risk of severe COVID-19 and mortality than those without disabilities. Many confirmed COVID-19 cases among people with disabilities involve users of welfare, medical, and nursing facilities. These findings indirectly suggest a high likelihood of chain group transmission if a confirmed case occurs in these facilities. Consequently, people with disabilities are both socially and epidemiologically vulnerable in COVID-19 infection. Therefore, COVID-19 infection is likely to be linked with greater health, economic, and social burden on these individuals.

Conclusion

Considering the decreased number of confirmed COVID-19 cases, the absence of concerning variant viruses, enhanced

medical response capabilities, and increased population immunity, the World Health Organization (WHO) declared on May 5, 2023, that COVID-19 was no longer considered a Public Health Emergency of International Concern (PHEIC). This announcement came 3 years and 4 months after the initial PHEIC declaration on January 30, 2020 [12]. Despite this change, the risk of COVID-19 remains, and the WHO has emphasized the implementation of a long-term management system. The Korean government lowered the COVID-19 pandemic national crisis level from the "serious" to the "warning" level on June 1, 2023, reflecting the changed situation [13].

However, individuals with disabilities still remains as a high-risk group for COVID-19. Therefore, it is crucial to maintain a sustainable means of supporting vulnerable populations, as they are more likely to be affected not only by COVID-19 but also by the next pandemic.

Notes

Ethics Approval
The requirement to obtain informed consent was exempted by the Institutional Review Board of the Korea Disease Control and Prevention Agency (2023-05-08-PE-01), as the study included no identifiable information.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
The datasets are not publicly accessible.

Authors' Contributions
Conceptualization: all authors; Data curation: SKK; Formal analysis: SKK; Investigation: SKK; Methodology: all authors; Project administration: SKK; Resources: SKK; Supervision: BIK; Visualization: SKK; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Factors associated with the timely diagnosis of malaria and the utilization of types of healthcare facilities: a retrospective study in the Republic of Korea

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ABSTRACT

Objectives: This study aimed to analyze trends in the timely diagnosis of malaria cases over the past 10 years in relation to the utilization of different types of healthcare facilities.
Methods: The study included 3,697 confirmed and suspected cases of malaria reported between January 1, 2013, and December 31, 2022, in the national integrative disease and healthcare management system. Some cases lacking a case report or with information missing from the case report were excluded from the analysis. A generalized linear model with a Poisson distribution was constructed to estimate risk ratios and 95% confidence intervals adjusted for other variables, such as distance.
Results: When cases involving diagnosis >5 days after symptom onset in confirmed patients (5DD) were examined according to the type of healthcare facility, the risk ratio of 5DD cases was found to be higher for tertiary hospitals than for public health facilities. Specifically, the risk ratio was higher when the diagnosis was established at a tertiary hospital, even after a participant had visited primary or secondary hospitals. In an analysis adjusted for the distance to each participant's healthcare facility, the results did not differ substantially from the results of the crude analysis.
Conclusion: It is imperative to improve the diagnostic capabilities of public facilities and raise awareness of malaria at primary healthcare facilities for effective prevention and control.

Keywords: Early diagnosis; Health facility; Malaria

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Introduction

Malaria is a representative mosquito-borne infectious disease, caused by protozoan parasites transmitted by female mosquitoes of the *Anopheles* genus [1]. The disease may be caused

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by any of 5 species of protozoa in the genus *Plasmodium*: *Plasmodium vivax* (PV), *Plasmodium ovale* (PO), *Plasmodium malariae* (PM), *Plasmodium falciparum* (PF), and *Plasmodium knowlesi* (PK). Among these, PF and PV pose the greatest threat to humans globally [2]. PF is mainly prevalent in Africa, while PV is commonly found in other regions [3].

In 1979, the World Health Organization declared the Republic of Korea malaria-free [4–6]. However, cases have been reported since 1993, when a soldier experienced a confirmed infection while stationed in Paju, Gyeonggi Province, an area bordering North Korea. By 2000, the annually reported cases had reached 4,000. Due to persistent efforts to eliminate malaria, in recent years the number has fallen to 400 to 500 cases annually [7–9].

The most common symptoms of malaria are fever, chills, and headache. For PV, which is typically found in the Republic of Korea, fever occurs in 48-hour cycles with latency periods that vary from a week to 2 years. This means that symptoms may not develop immediately after transmission via mosquito and that their onset may occur in the following year [10].

In the Republic of Korea, malaria cases occur primarily in regions that border North Korea, such as Incheon, Gyeonggi Province, and northern Gangwon Province. Cases are reported yearly, primarily between May and October, when the vector mosquito is most active. Very few cases are reported during the winter [11–14]. Malaria incidence also differs significantly by sex. In 2022, 420 indigenous malaria cases were reported, with 359 cases (approximately 85%) occurring in men. This trend has remained relatively constant, since approximately 80% of all cases occurred in men both before the COVID-19 pandemic (in 2019) and after it had begun (in 2020). Regarding age, the largest percentage of cases occurs in individuals in their 20s, accounting for more than 30% of cases when the ages of confirmed patients have been categorized as a group aged ≤19 years followed by groups in increments of 10 years [7–9,11,14].

Previous studies have focused primarily on identifying how the infection spreads or on developing diagnostic methods, with little emphasis on understanding how malaria patients use healthcare facilities or the symptoms they experience [4–9,15–17].

To eliminate malaria, it is crucial to interrupt the spread of infection by promptly diagnosing suspected cases [14]. In the Republic of Korea, malaria is classified as a class 3 statutory infectious disease, and all confirmed cases must be reported [14]. Furthermore, the government is actively working towards the eradication of malaria by the year 2030 to align with the World Health Organization's framework and objectives for malaria elimination [18].

HIGHLIGHTS

- To prevent the spread of malaria, the chain of infection can be broken by early detection and initiation treatment of patients. This study aims to analyze the trend of malaria diagnosis.
- When the ratio of cases of diagnosis after 5 days of symptom onset were examined according to the type of healthcare facility, it was found that the risk ratio of diagnosis after 5 days of symptom onset cases increased from public health facilities to tertiary hospitals.
- It is imperative to enhance the diagnostic capabilities of public facilities and raise awareness about malaria at primary healthcare facilities for effective prevention and control.

To achieve the goal of eradication, managing the vector through mosquito control alone is not sufficient. A strategy is needed to proactively block the transmission pathway by diagnosing suspected malaria patients early while reducing the spread of malaria [19]. Thus, the role of healthcare facilities is crucial because they are at the forefront of both diagnosis and treatment. This study aimed to analyze trends regarding the timely diagnosis of malaria cases over the past 10 years, along with factors related to the utilization of different types of healthcare facilities.

Materials and Methods

This cross-sectional study used diagnosis more than 5 days after symptom onset in confirmed patients (5DD) as the dependent variable. Some quantitative variables, such as age, were grouped *a priori* for ease of analysis and interpretation.

A total of 5,204 malaria cases, reported between January 1, 2013, and December 31, 2022, were found in the national integrative disease and healthcare management system, which is a Korea Disease Control and Prevention Agency (KDCA) data platform used for reporting cases of infectious disease according to statutory regulation [20]. Among these cases, 585 of them had no case report, 532 case reports lacked some information, and 6 were diagnosed overseas; these were consequently excluded from the analysis. Additionally, 384 cases confirmed during military service were excluded because the relevant individuals were transferred to a military hospital for diagnosis and treatment, which prevented calculating the distance between their residence and healthcare facilities; addresses within military bases

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could not be identified. Therefore, the final total included in the study was 3,697 cases (Figure 1).

Individuals were grouped into the following age ranges for analysis: ≤19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and ≥60 years.

The KDCA manages malaria risk by designating specific areas at risk due to their high numbers of malaria cases. We defined the risk areas based on 3 years of incidence data, from 2020 to 2022. Most areas were unchanged during that period. As of 2023, the high-risk areas included northern Gyeonggi Province, northern Gangwon Province, and Incheon, comprising a total of 30 municipalities. The moderate-risk areas encompassed 18 municipalities with at least 1 case in the prior 3 years situated close to high-risk areas. Excluding the 48 areas categorized as high or moderate-risk areas, the remaining areas were classified as no-risk areas.

In general, 5 species of malaria parasites can infect people. These parasites are PV, PF, PO, PM, and PK. The only malaria parasite indigenous to the Republic of Korea is PV. For the current study, the infectious source was categorized as PV, PF, PO, or PM by type of protozoa, or as "unknown" when the protozoa was not identified.

Healthcare facilities were categorized as clinics, hospitals, or general hospitals according to the Medical Service Act [21]. This classification included public health facilities responsible for monitoring infectious diseases and managing patients, and capable of diagnosing malaria.

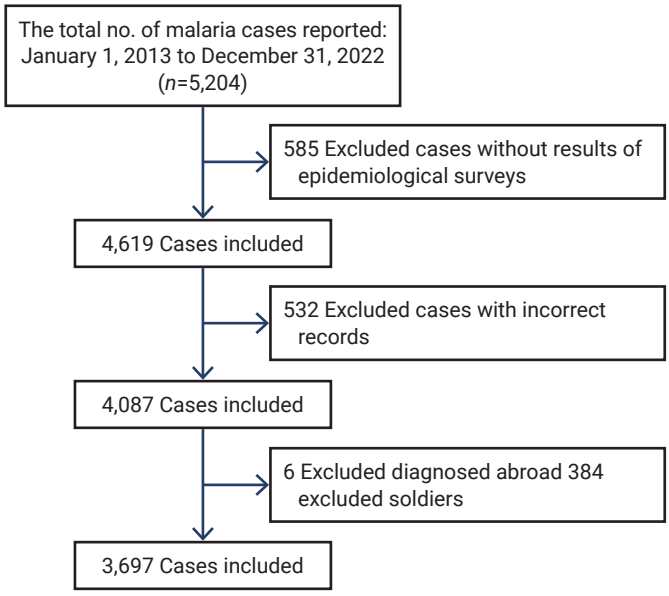

Figure 1. Flow chart of participant selection process. Study subjects were collected from the disease health integrated management system.

General hospitals were subcategorized as general or tertiary hospitals; the latter category was divided further into "tertiary hospital first" or tertiary-first if the diagnosis was confirmed there on a patient's first visit since symptom onset, and "tertiary hospital second" or tertiary-second if a patient was diagnosed there after visiting other clinics or hospitals since symptom onset. In accordance with the above classification, the types of healthcare facilities considered for analysis were tertiary hospital second, tertiary hospital first, general hospital, hospital, clinic, and public health facility.

The distance variable measured the distance between each participant's residence in their case report and the healthcare facility where malaria was diagnosed. Residential addresses were converted into latitude and longitude coordinates using Google's geocoding service. Coordinates for healthcare facilities were determined using the nationwide directory of hospitals, clinics, and pharmacies available on the Health Insurance Review and Assessment Service website as of October 2023 [22]. After the coordinates of each confirmed patient's residence and their healthcare facility were identified, the straight-line distance between these 2 points was calculated using QGIS (https://qgis.org/en/site/)'s distance matrix function.

In the United States, medically vulnerable areas are determined based on physical accessibility by converting a 30-minute travel time to the primary hospital into a distance of 10 km [23]. A study utilizing the Korean medical panel confirmed that the majority of individuals had visited healthcare facilities within 5 km when measuring the distance between the residence of major disease patients and their primary healthcare facilities [24]. Consequently, this study classified the distance between a confirmed patient's residence and the healthcare facility where they were diagnosed into <5 km, 5 to 10 km, 10 to 20 km, 20 to 30 km, and >30 km.

Due to the non-specific nature of malaria symptoms, diagnosing patients based solely on clinical symptoms is very challenging. Clinical symptoms such as fever may manifest from 7 days to up to 2 years after initial infection by mosquito; such broad variation in latency period can delay diagnosis. Past research has confirmed that patients typically seek treatment by visiting a healthcare facility within an average of 4 days after symptom onset [25]. Consequently, as a performance indicator of the malaria eradication project, the KDCA recommends using treatment initiation within 5 days of symptom onset. Recent analysis has revealed that the time to diagnose malaria over the past 5 years averaged 4.6 days (standard deviation=13.0) [26].

Statistical Analysis

In this study, since 5DD was used as a dependent variable and a Poisson distribution was assumed, a generalized linear model with a Poisson distribution was constructed to estimate risk ratios and 95% confidence intervals adjusted for other variables, such as distance. All statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Corp.), and a p-value of <0.05 was considered to indicate statistical significance.

Ethics Statement

The study protocol was approved by the Institutional Review Board (IRB) of the KDCA (no: KDCA-2023-10-08). Informed consent was waived by the IRB.

Results

Table 1 shows the characteristics of confirmed malaria cases that were reported from January 2013 to December 2022. Of the 3,697 total cases analyzed, 2,909 subjects (78.7%) were male and 788 subjects (21.3%) were female. Regarding age groups, the largest percentage was the group in their 20s with 1,001 subjects (27.1%), followed by those in their 40s and 50s with 703 subjects (19.0%) and 687 subjects (18.6%), respectively.

In the classification by the species of malaria protozoa, the majority of infections (3,238 cases, 87.6%) were caused by PV of domestic origin, while the number of cases imported from overseas was 324 cases (8.8%) by PF, 18 cases (0.5%) by PO, and 10 cases (0.3%) by PM. In addition to these, 107 cases (2.9%) were of unknown type, in which the type of protozoa could not be identified since blood could not be collected.

As for the incidence according to the malaria risk areas classified by the KDCA, 2,173 cases (58.8%) were from high-risk areas, 442 cases (12.0%) were from moderate-risk areas, and 1,082 cases (29.3%) were from no-risk areas.

When the distance was measured from each confirmed patient's residential address to the healthcare facility that confirmed their diagnosis, the facility was located within 5 km in 1,808 cases (48.9%), within 5 to 10 km in 723 cases (19.6%), within 10 to 20 km in 594 cases (16.1), within 20 to 30 km in 196 cases (5.3%), and 30 km away or farther in 376 cases (10.2%).

When classified according to the type of healthcare facility where malaria was finally diagnosed, 998 cases (27.0%) were diagnosed at a tertiary hospital and 2,128 cases (57.6%) were diagnosed at a general hospital, accounting for the majority. The final diagnosis occurred at a hospital or clinic in 265 cases (7.2%) and 126 cases (3.4%), respectively, and 180 cases (4.9%) were diagnosed at public health facilities.

Table 1. Distribution of malaria cases reported from January 2013 to December 2022 by demographic and other characteristics ($n=3,697$)

Characteristic	Subtotal	% 5DD
Sex		
Male	2,909 (78.7)	1,549 (53.2)
Female	788 (21.3)	381 (48.4)
Age (y)		
≤19	214 (5.8)	118 (55.1)
20–29	1,001 (27.1)	629 (62.8)
30–39	588 (15.9)	304 (51.7)
40–49	703 (19.0)	352 (50.1)
50–59	687 (18.6)	343 (49.9)
≥60	504 (13.6)	184 (36.5)
Species		
Plasmodium vivax	3,238 (87.6)	1,747 (54.0)
P. falciparum	324 (8.8)	94 (29.0)
P. ovale	18 (0.5)	11 (61.1)
P. malariae	10 (0.3)	8 (80.0)
Unknown	107 (2.9)	70 (65.4)
KDCA risk area		
High risk	2,173 (58.8)	931 (42.8)
Moderate risk	442 (12.0)	285 (64.5)
No risk	1,082 (29.3)	714 (66.0)
Distance from residence to facility (km)		
<5	1,808 (48.9)	973 (53.8)
5–10	723 (19.6)	369 (51.0)
10–20	594 (16.1)	278 (46.8)
20–30	196 (5.3)	92 (46.9)
>30	376 (10.2)	218 (58.0)
Healthcare facility type		
Tertiary hospital second	474 (12.8)	353 (74.5)
Tertiary hospital first	524 (14.2)	320 (61.1)
General hospital	2,128 (57.6)	1,038 (48.8)
Hospital	265 (7.2)	99 (37.4)
Clinic	126 (3.4)	62 (49.2)
Public health facility	180 (4.9)	58 (32.2)
Total	3,697 (100.0)	1,930 (52.5)

Values are presented as number (%).
% 5DD, percentage of final diagnosis for malaria made >5 days after symptom onset; KDCA, Korea Disease Control and Prevention Agency.

From symptom onset to final diagnosis, 53.2% of the cases that occurred in men were 5DD, while 48.4% of the cases in women were 5DD. By age group, 62.8% of the cases occurring in subjects in their 20s were 5DD, while 55.1% of cases occurring in subjects aged ≤19 years were 5DD; in subjects aged ≥60 years, only 36.5% of cases were 5DD.

By the type of protozoa, malaria caused by PV accounted for 87.6% of all cases, and 54.0% of them were 5DD. By risk area, 42.8% of the cases occurring in high-risk areas were 5DD, while 64.5% and 66.0% of the cases occurring in moderate-risk and no-risk areas were 5DD, respectively.

As for the time to diagnosis according to distance, 53.8%

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of the cases diagnosed in a healthcare facility within 5 km were 5DD, whereas 51.0% of the cases diagnosed at a healthcare facility within 5 to 10 km were 5DD. The diagnosis was 5DD in 46.8%, 58.0%, and 46.9% of cases diagnosed at healthcare facilities within 10 to 20 km, within 20 to 30 km, and 30 km or farther from the participant's residence, respectively.

Regarding the time to diagnosis according to the type of healthcare facility, only 32.2% of cases diagnosed at public health facilities were 5DD, whereas 49.2% and 37.4% of the cases diagnosed at clinics and hospitals, respectively, were 5DD. For general hospitals, 48.8% of the cases were 5DD. When subjects were diagnosed at a tertiary hospital, a distinction was made as to whether the initial diagnosis was made at the tertiary hospital (first) or after visiting primary or secondary hospitals (second). The diagnosis was 5DD in 61.1% of tertiary-first cases and 74.5% of tertiary-second cases.

When the trend in healthcare facilities was analyzed based on the time to diagnosis according to distance, it was confirmed that the percentage of time to diagnosis in more than 5 days was higher, based on the distance of 30 km, in cases where public health facilities, hospitals and clinics, general hospitals, or tertiary hospitals were visited first.

Regarding the type of healthcare facility, when the diagnosis was confirmed at a public health facility, the ratio of exceeding 5 days decreased as the distance from a participant's residence increased, then increased again once the distance reached 30 km. In contrast, when the diagnosis was confirmed tertiary-second, the ratio of cases diagnosed after 5 days increased as the distance increased up to 30 km, then decreased again once the distance reached 30 km (Figure 2).

Table 2 shows the characteristics of confirmed malaria cases regarding time to diagnosis in more than 5 days. It was found that a diagnosis was confirmed later in men than women, but the finding was not statistically significant. Considering the group aged ≥60 years as reference, diagnoses were 1.122 times more likely to be confirmed after 5 days for those in their 20s. Though the ratio was found to be 1.127 times for those aged ≤19 years, 1.075 times for those in their 30s, 1.073 times for those in their 40s, and 1.075 times for those in their 50s, statistical significance was found only for the group in their 20s.

When the healthcare facility was within 5 km of the participant's residence, cases were 0.985 times less likely to be 5DD compared to when subjects lived more than 30 km away. For those living within 5 to 10 km of healthcare facilities, the ratio was 0.974 times, followed by 0.961 times for those living within 10 to 20 km, and 0.952 times for those living within 20–30 km.

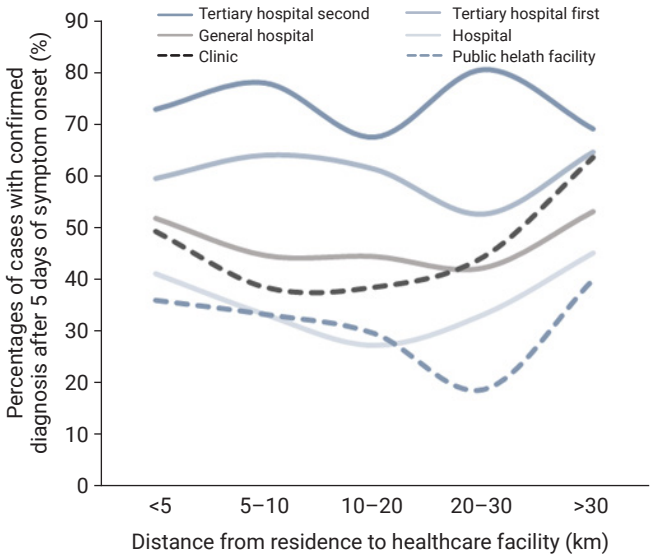

Figure 2. Percentages of cases with confirmed diagnosis more than 5 days after symptom onset, by the distance from residence to healthcare facility and by type of facility.

Those living in high-risk areas were 0.909 times less likely to be diagnosed after 5 days than those living in no-risk areas, whereas those living in moderate-risk areas were 1.008 times more likely to be diagnosed after 5 days.

When the ratio of 5DD cases was examined according to the type of healthcare facility, with public health facilities considered as reference, it was found that the ratio of cases diagnosed after 5 days increased in the order of hospital, general hospital, clinic, and tertiary hospital. Specifically, it was confirmed that the ratio was higher when the diagnosis was made at a tertiary hospital, even after the participant had visited a primary or secondary hospital, although the results of analysis adjusted by the distance to healthcare facilities did not differ greatly from the results of the crude analysis (Table 2).

Discussion

This study analyzed the utilization of healthcare facilities among malaria patients in the Republic of Korea and examined the impact of the distance between their residences and healthcare facilities, as well as the types of facilities they visited, to understand how to prevent the further spread of malaria infection and improve the time to diagnosis and treatment.

Whereas previous studies on malaria cases focused mainly on the distribution of cases, the influence of vector mosquitoes, and methods for timely diagnosis, the current

Table 2. RRs of positively diagnosed malaria cases >5 days after symptom onset

	Crude RR		Adjusted RR	
	Exp(B)	95% CI	Exp(B)	95% CI
(intercept)	1.397*	1.166–1.674	1.368*	1.152–1.625
Sex				
Male	1.000	0.936–1.068	0.999	0.936–1.067
Female	Ref.		Ref.	
Age (y)				
≤19	1.127	0.988–1.286	1.126	0.988–1.285
20–29	1.122*	1.022–1.232	1.122*	1.022–1.232
30–39	1.075	0.972–1.189	1.075	0.972–1.190
40–49	1.073	0.974–1.182	1.072	0.973–1.181
50–59	1.075	0.976–1.185	1.075	0.975–1.184
≥60	Ref.		Ref.	
Distance from residence to facility (km)				
<5	0.985	0.901–1.078	NA	
5–10	0.974	0.880–1.077		
10–20	0.961	0.865–1.069		
20–30	0.952	0.826–1.096		
>30	Ref.			
KDCA risk area				
High risk	0.909*	0.851–0.972	0.907*	0.849–0.969
Moderate risk	1.008	0.923–1.100	1.006	0.922–1.098
No risk	Ref.		Ref.	
Healthcare facility type				
Tertiary hospital second	1.202*	1.034–1.398	1.207*	1.038–1.403
Tertiary hospital first	1.105	0.950–1.286	1.111	0.955–1.292
General hospital	1.072	0.938–1.226	1.077	0.942–1.231
Hospital	1.013	0.859–1.193	1.018	0.864–1.199
Clinic	1.081	0.891–1.311	1.089	0.899–1.320
Public health facility	Ref.		Ref.	

RRs are adjusted for distance.
RR, risk ratio; CI, confidence interval; KDCA, Korea Disease Control and Prevention Agency; ref., reference; NA, not applicable.
*$p<0.05$.

study emphasized patients' utilization of healthcare facilities and the time elapsed from symptom onset to diagnosis.

The characteristics of malaria cases confirmed in this study were similar to those from earlier studies [9,13]. Indigenous malaria cases, whose vector is PV, occur at a relatively high rate in men in their 20s serving at military bases in the northern part of Gyeonggi Province, near the border with North Korea [4,7,8,13,19,27,28]. Even after excluding the occurrences in military personnel, which is the major characteristic of indigenous cases, the largest percentage of cases (78.7%) by age group and sex occurred in men in their 20s, and the high-risk area bordering North Korea had the largest percentage of occurrences (58.8%) by region. In terms of the utilization of healthcare facilities, 48.9% of all confirmed cases reported as malaria were diagnosed at a healthcare facility within 5 km of the participant's residence, while 57.6% of the cases were diagnosed at general hospitals, 27% of which were tertiary hospitals. Those who had visited public health facilities accounted for 4.9%, similar to the 3.4% of subjects who had visited clinics.

It is challenging to diagnose malaria based merely on symptoms at primary healthcare facilities, such as hospitals and clinics, because the clinical symptoms of malaria are non-specific and may easily be mistaken for another disease. In addition, because the national incidence rate in the Republic of Korea is very low, less than 1 case per 100,000 residents, malaria is often diagnosed at general or tertiary hospitals instead of hospitals or clinics.

As a result, patients suspected of having malaria have the shortest time to diagnosis when diagnosed at public health facilities; the time to diagnosis increases for tertiary hospitals. Since malaria is under regulatory supervision in the Republic of Korea and physicians working at public health facilities are required to receive regular training, the physicians at such facilities tend to be more aware of malaria than physicians elsewhere.

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In laboratories, malaria is diagnosed using different techniques: conventional microscopic diagnosis from staining thin and thick peripheral blood smears, molecular diagnostic methods such as polymerase chain reaction, and antigen-based rapid diagnostic tests. However, laboratory methods have some disadvantages for prompt diagnosis. Microscopic diagnosis requires trained healthcare workers with considerable expertise, and molecular diagnostic methods are time-consuming [29–32].

Several previous studies have proposed malaria antigen and antibody tests on febrile patients as a strategy for prompt diagnosis [32–34]. The cost of diagnostic tests for malaria has been included in the medical benefits coverage at primary healthcare facilities in the Republic of Korea. However, as mentioned above, it is not easy to make a differential diagnosis of malaria patients at a primary healthcare facility, and keeping antigen and antibody test kit supplies in stock can be difficult for clinics and hospitals due to the small number of cases.

This study has limitations in that it only reflected information identified in the case reports, and it analyzed the straight-line distance, not the travel distance, between residences and healthcare facilities. However, factors associated with accessibility related to the utilization of healthcare services, such as availability, mutual acceptability, ability to pay, and convenience, seem to have minimal influence on how long malaria diagnosis may take [35]. Malaria diagnosis is covered by health insurance in the Republic of Korea and is available at low cost through public health facilities, such as the Public Health and Environment Research Institute. Therefore, the impact of these related factors is also expected to be minimal.

In addition, the current study did not investigate whether the subjects visited multiple healthcare facilities before receiving a diagnosis, since the available case reports did not include their medical history. Further studies should identify the impact of misclassified facility visit data on the relationship between a delay in diagnosis and the potential spread of community infection.

In addition, although military personnel account for a high proportion of indigenous malaria cases, they were excluded from this study since their exact location of residence could not be identified for security reasons. Considering that the military has its own healthcare system, further research is necessary for analyzing the factors related to timely diagnosis among military personnel.

According to the findings of this study, it is crucial to identify malaria patients promptly by improving the diagnostic capabilities for malaria at public health facilities. However, patients rarely visit public health facilities when experiencing symptoms like fever or chills, and these facilities are less accessible physically than hospitals and clinics.

Therefore, it becomes imperative for primary and secondary hospitals, including clinics, to adopt the malaria diagnostic methods conducted at public health facilities as well as to support patients who present with fever symptoms, thus ensuring timely diagnosis of malaria. A policy advocating for simplified malaria tests at clinics and hospitals should be established, particularly for patients who experience fever between May and October, when the prevalence of malaria is high. Additionally, it is crucial for public health facilities to test potentially exposed individuals, such as the family members and colleagues of confirmed patients.

Conclusion

In conclusion, this study has shown that the highest proportion of malaria diagnoses within 5 days occurred at public health facilities, while tertiary hospitals exhibited the longest time to diagnosis. While it may be expected for tertiary hospitals to have a longer time to diagnosis due to the need for referral from primary or secondary hospitals, the analysis indicated that the ratio of cases diagnosed after 5 days of symptom onset increased for tertiary hospitals, even for tertiary-first cases. In other words, when compared to public health facilities, hospitals, general hospitals, clinics, and tertiary hospitals showed an increasing order in the ratio of cases diagnosed after 5 days. This pattern persisted even when considering the distance between residence and healthcare facilities in the model.

Given that malaria, an infectious disease caused by a vector mosquito, requires blocking the cycle of infection by preventing the spread of infection via the human host as well as managing vector transmission, the timely diagnosis of confirmed cases becomes crucial. It is imperative to enhance the diagnostic capabilities of public health facilities and raise awareness about malaria at primary healthcare facilities for effective prevention and control.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of KDCA (no: KDCA-2023-10-08). The Board waived the requirement for informed consent.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available. If you have any questions regarding this study, contact the corresponding author (kirk99@korea.kr).

Authors' Contributions

Conceptualization: HK, ST; Data curation: HK; Formal analysis: HK, ST; Investigation: SL, JL; Methodology: ST, HK; Resources: HK, SL, SP; Software: HK; Supervision: ST, KH; Writing–original draft: HK, ST; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Brief Report

Gender differences in hepatitis A seropositivity rates according to the Republic of Korea's vaccination policy

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ABSTRACT

Objectives: This study aimed to investigate differences in the anti-hepatitis A virus (HAV) antibody seropositivity rate by age and gender.
Methods: We collected information on anti-HAV immunoglobulin G and immunoglobulin M status from samples submitted for HAV antibody testing in 2012–2022. A total of 1,333,615 cases were included in the analysis.
Results: By age, the seropositivity rate was represented by a U-shaped curve, such that the rate was low for the group aged 20 to 39 years and higher in those who were younger or older. Over time, the curve shifted rightward, and the seropositivity rate declined gradually in the group aged 35 to 39 years and older. A gender-based difference in antibody seropositivity rate was especially noticeable in the group aged 20 to 29 years. This difference between genders widened in the participants' early 20s—when men in the Republic of Korea enlist in the military—and the divergence continued subsequently for older individuals.
Conclusion: These results indicate a higher risk of severe infection among older individuals and a gender-based difference in seroprevalence. Therefore, it is necessary to implement policies to promote vaccination in adults.

Keywords: Anti-hepatitis A immunoglobulin G; Gender differences; Seroprevalence

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Introduction

Hepatitis A virus (HAV) infections can be transmitted by the fecal-oral route, through close contact, or through contaminated food or water. In the Republic of Korea, a total of 17,598 cases of HAV (33.9 cases per 100,000 individuals) were reported in 2019 [1]. This is the largest epidemic since HAV was designated a notifiable infectious disease in 2010; contaminated

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salted clams were the primary source of infection [2–4].

In 2019, 86.6% of the HAV patients reported in the Republic of Korea were aged 20 to 49 years [1], which may be attributable to differences in immunity, not exposure. According to the 2015 Korea National Health and Nutrition Examination Survey, the anti-HAV immunoglobulin G (IgG) seropositivity rate was lowest (11.9%) in the group aged 20 to 29 years and very high (97.8%) in the group aged ≥ 45 years [5].

To understand the epidemiology of HAV infection, surveillance of anti-HAV IgG seroprevalence is important [6]. Anti-HAV IgG seroprevalence in the Republic of Korea has been studied extensively in the past [5,7,8]. Most studies focused primarily on the time-series changes in age-specific seroprevalence. Although the incidence of hepatitis A was higher among men traditionally, the gender ratio in hepatitis A incidence has changed in recent years. In particular, in 2019 the incidence ratio was inverted among individuals aged 20 to 29 years, showing a higher incidence among women than men [9].

This gender-based difference in HAV incidence also seems to be attributable to differences in immunity, not exposure. All men in the Republic of Korea enlist in the military in their early 20s, and mandatory single-dose vaccination against hepatitis A has been enforced for this age group since 2012 [9–11]. The rapid spike in antibody seroprevalence among men aged 20 to 29 years may be considered a result of this policy.

Therefore, this study aimed to investigate differences in the anti-HAV antibody seroprevalence rate by age and gender.

HIGHLIGHTS

- This study analyzed 1,333,615 cases of hepatitis A antibody testing from January 2012 to June 2022 and found an overall increase in seropositivity rates, including a U-shaped curve that shifted rightward by age.
- The seropositivity rate diverged by gender in the participants' early 20s—when men in the Republic of Korea enlist in the military—and the divergence continued subsequently for older individuals.
- Although the study is limited by a lack of socioeconomic data, its strength is its analysis of large-scale data spanning 11 years across all age groups.

Materials and Methods

Study Population

Samples submitted to the Green Cross Labs for HAV antibody testing between January 1, 2012, and June 30, 2022 were used in this study. Data regarding anti-HAV IgG and immunoglobulin M (IgM) status were collected. Cases lacking information about gender or age were excluded from the analysis; cases were also excluded when a positive result was confirmed from an anti-HAV IgM test performed simultaneously with an anti-HAV IgG test. A total of 1,333,615 cases were included in the analysis. Table 1 shows the distributions by year, gender, and age.

Anti-HAV Testing

HAV antibody (anti-HAV IgG, IgM) testing was performed with a Chemiluminescence microparticle immunoassay, using the Architect i2000 analyzer (Abbott, Singapore). The testing methods did not change significantly during the study period.

Statistical Analysis

The anti-HAV IgG positivity rate was determined by year, gender, and age (5-year units), and 95% confidence intervals (CIs) were determined using binomial exact distribution. To examine the difference in the anti-HAV IgG positivity rate by birth year in men and women, we presented the difference in seroprevalence over time in 2-year birth cohorts. Chi-square tests were used to compare seroprevalence between genders, with a significance level of $p < 0.05$. All statistical analyses were performed using SAS ver. 9.4 (SAS Institute).

Ethics Statement

The study was approved by the Institutional Review Board of Green Cross Laboratory (no: GCL-2022-1048-01).

Results

A total of 1,333,615 cases were analyzed in this study. The number of cases per year rose from 61,462 cases in 2012 to 179,009 cases in 2021. From January to June 2022, 79,131 cases were included in the study. Approximately 40.2% of the total cases were male, and 66.5% were aged 25 to 49 years (Table 1). Of the total, 86% were from requests for anti-HAV IgG testing alone, and 14% were from requests for both anti-HAV IgG and IgM testing. Table S1 present the anti-HAV IgG positivity rates and 95% CIs by year, gender, and 5-year units of age from January 2012 to June 2022.

The seropositivity rate by age formed a U-shaped curve, such that seroprevalence was low in the group aged 20 to 39 years and higher in the age intervals younger and older than this group. The seropositivity rate in the group aged 30

Table 1. Characteristics of the study population

Characteristic	No. (%)
Total	1,333,615 (100.0)
Year	
2012	61,462 (4.6)
2013	68,462 (5.1)
2014	91,234 (6.8)
2015	98,330 (7.4)
2016	145,472 (10.9)
2017	151,154 (11.3)
2018	144,377 (10.8)
2019	158,875 (11.9)
2020	156,109 (11.7)
2021	179,009 (13.4)
2022 Jan.–Jun.	79,131 (5.9)
Gender	
Man	536,165 (40.2)
Woman	797,450 (59.8)
Age group (y)	
0–4	2,961 (0.2)
5–9	4,386 (0.3)
10–14	8,856 (0.7)
15–19	36,757 (2.8)
20–24	66,157 (5.0)
25–29	145,192 (10.9)
30–34	245,362 (18.4)
35–39	203,708 (15.3)
40–44	155,878 (11.7)
45–49	136,612 (10.2)
50–54	113,926 (8.5)
55–59	87,193 (6.5)
≥60	126,627 (9.5)

Data are presented as *n* (%).

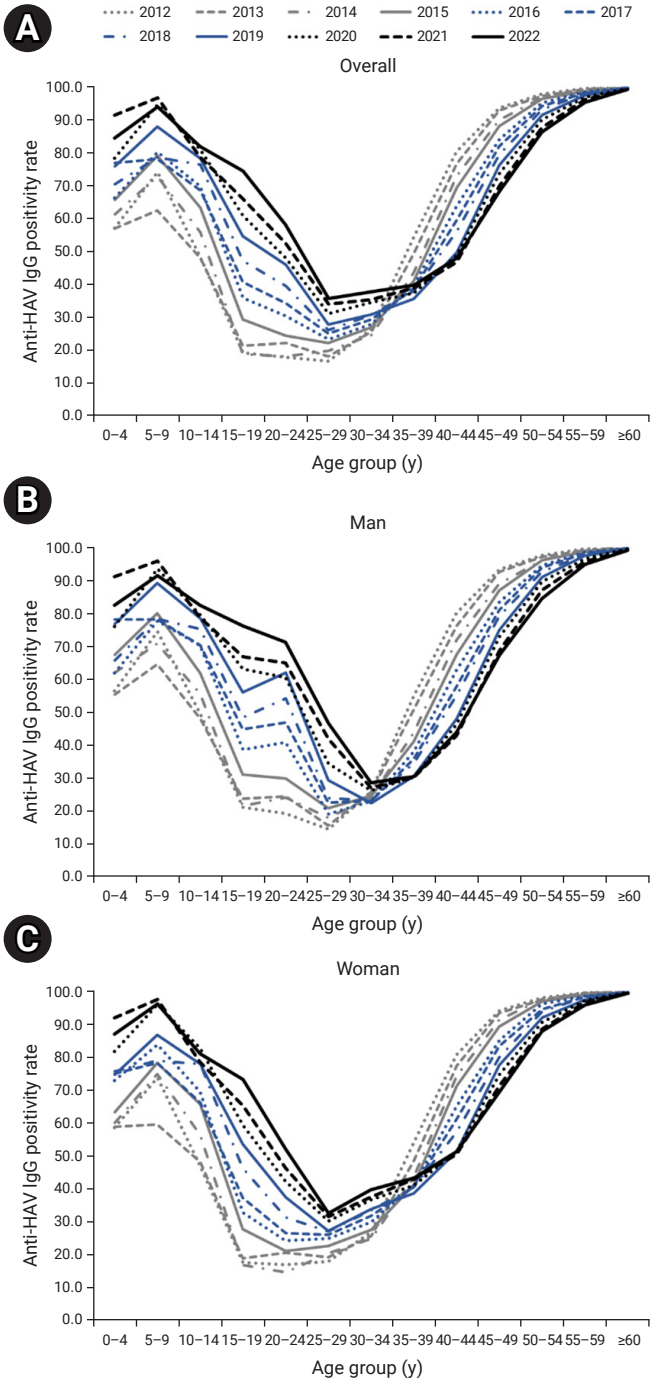

Figure 1. Anti-hepatitis A virus (HAV) immunoglobulin G (IgG) positivity rate by age group. Overall study population (A), man (B), and woman (C).

to 34 years and younger increased over time, while the rate in the group aged 35 to 39 years and older declined over time, resulting in a rightward shift during the study period (Figure 1A).

The rightward shift of the U-shaped curve of the age- and year-specific seropositivity rate was evident even when the cases were separated by gender. However, the seropositivity rate in men aged 20 to 29 years was much higher than that in same-aged women (Figure 1B, C). As a result, in the most recent data in 2022, the seropositivity rate in men aged 30 years and older was relatively low, similar to the rate among women, whereas the seropositivity rate in men aged 20 to 29 years was significantly higher than the rate in women (Figure 2).

Regarding the gender-based difference in seropositivity rate, the rate has diverged more widely by gender since 2014 in the group aged 20 to 24 years. Until 2018, in the group aged 25 to 29 years, the seropositivity rate was slightly higher among women, but after 2019, the rate was higher among men (Figure 3).

Figure 4 illustrates the changes in seropositivity rate by 2-year birth cohorts. In both genders, the rate has risen in all ages across more recent birth cohorts, and within age groups, the rate increased in more recent cohorts. In particular, in

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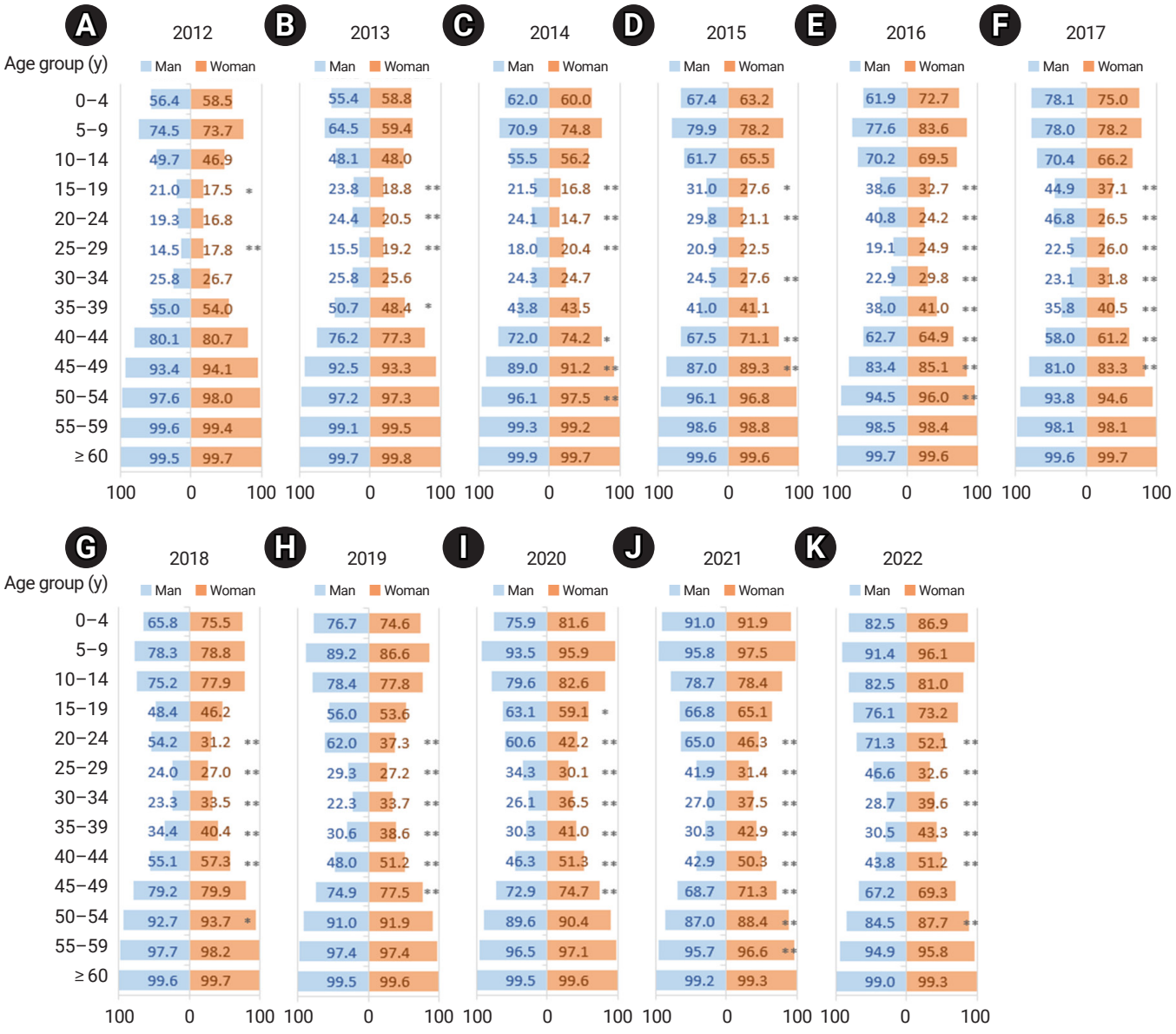

Figure 2. (A–K) Anti-hepatitis A immunoglobulin G positivity rate in each age group by gender and year. *$p < 0.05$, **$p < 0.01$ by chi-square test on gender in each age group.

the 1994–1995 and subsequent birth cohorts, a dramatic rise in the seropositivity rate occurred among men in the group aged 20 to 21 years.

Discussion

Overall, the anti-HAV IgG positivity rate has risen from 2012 to 2022. The depth and width of the U-curve representing the age-specific seropositivity rate have decreased during that period. However, as the U-curve shifts rightward and the seropositivity rate declines gradually among individuals aged ≥40 years, the overall risk of severe infection may increase because of the nature of HAV infection, where the likelihood of severity increases with advancing age [12]. In the Republic of Korea, a hepatitis A vaccine was approved in 1997 and has been included in the national immunization program for infants and toddlers since 2015 [5]. For adults, vaccines are administered to individuals at high risk, but the target population is very small. These results indicate that additional policies must be implemented to facilitate the vaccination of adults [13].

Antibody seroprevalence diverges dramatically by

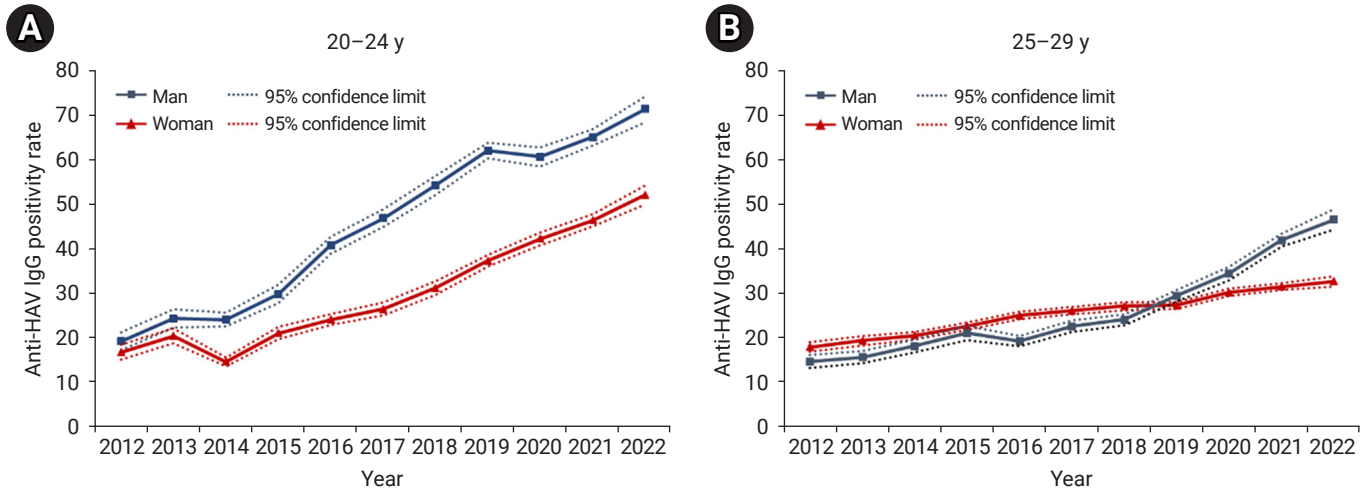

Figure 3. Anti-hepatitis A virus (HAV) immunoglobulin G (IgG) positivity rates by year and gender. (A) Ages 20 to 24 years and (B) ages 25 to 29 years.

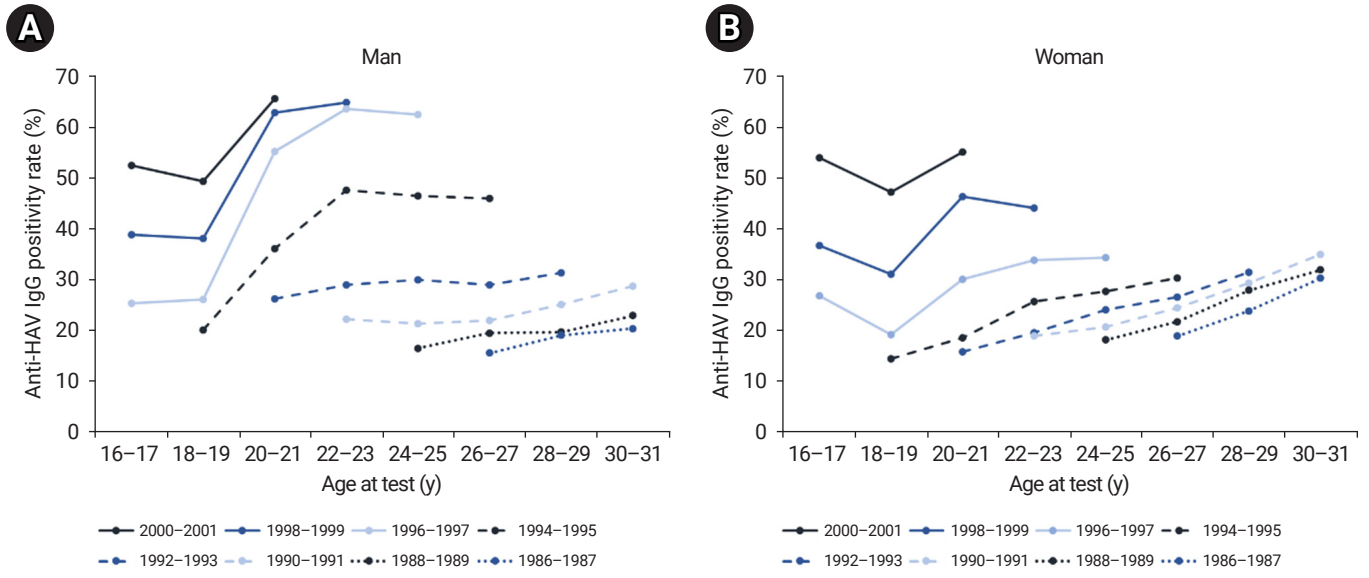

Figure 4. Anti-hepatitis A virus (HAV) immunoglobulin G (IgG) positivity rates per birth cohort by age. (A) Man and (B) woman.

gender in the group aged 20 to 29 years. The divergence is particularly noticeable in participants in their early 20s, and it continues subsequently for older individuals. In the Republic of Korea, mandatory military service is required of adult men; therefore, all men enlist in the military in their early 20s. Additionally, hepatitis A vaccines have been provided to military recruits since 2012 [9–11]. Therefore, the inversion of the incidence rate between men and women, where the incidence of HAV infection among women has outpaced that of men since the year 2019 [9], may be a result of this vaccination policy. The gender-based difference in HAV antibody positivity rates and incidence rates is expected to continue. Furthermore, at 76.1%, the current (2022) HAV antibody seropositivity rate is very high among men aged 15 to 19 years. This is because the vaccination rate has gradually increased in the cohort born after the hepatitis A vaccine was approved in the Republic of Korea in 1997 and began to be used in the private market [5]. Therefore, the current policy for mandatory hepatitis A vaccination for military enlistees must be reviewed and amended.

This study had some limitations. The data used in this study contain information only on gender and age, so we could not examine differences in seropositivity rate according to socioeconomic status. Furthermore, probability

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sampling was not performed. Nevertheless, one of the strengths of this study is that it examined changes in anti-HAV IgG seropositivity over an 11-year period, using large-scale data that spanned all age groups. Utilizing this data will enable surveillance of anti-HAV IgG seroprevalence without additional cost and effort [8].

The anti-HAV IgG positivity rate encompasses both immunity acquired after HAV infection and vaccine-acquired immunity. On average, several thousand cases of HAV infection are reported annually in the Republic of Korea; therefore, any changes in the anti-HAV IgG positivity rate could be understood as a reflection of the vaccination rate. These findings indicate that it is necessary to implement policies to promote the vaccination of adults, due to the higher risk of severe infections among older individuals and the gender-based difference in the seropositivity rate.

Supplementary Material

Table S1. Anti-hepatitis A immunoglobulin G positivity rate and 95% CI by year, age group, and gender. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0263.

Notes

Ethics Approval

The study was approved by the Institutional Review Board of Green Cross Laboratory (no: GCL-2022-1048-01). Informed consent was waived because of the study's retrospective nature.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: HS, UG, EHL, SGL; Data curation: SA, WP, GC; Formal analysis: HS, WP, GC; Writing–original draft: HS, UG, SA, WP, GC; Writing–review & editing: HS, UG, EHL, SGL. All authors read and approved the final manuscript.

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Data Profile

Establishment of a registry of clinical data and bioresources for rare nervous system diseases

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ABSTRACT

Rare diseases are predominantly genetic or inherited, and patients with these conditions frequently exhibit neurological symptoms. Diagnosing and treating many rare diseases is a complex challenge, and their low prevalence complicates the performance of research, which in turn hinders the advancement of therapeutic options. One strategy to address this issue is the creation of national or international registries for rare diseases, which can help researchers monitor and investigate their natural progression. In the Republic of Korea, we established a registry across 5 centers that focuses on 3 rare diseases, all of which are characterized by gait disturbances resulting from motor system dysfunction. The registry will collect clinical information and human bioresources from patients with amyotrophic lateral sclerosis, spinocerebellar ataxia, and hereditary spastic paraplegia. These resources will be stored at ICreaT and the National Biobank of Korea. Once the registry is complete, the data will be made publicly available for further research. Through this registry, our research team is dedicated to identifying genetic variants that are specific to Korean patients, uncovering biomarkers that show a strong correlation with clinical symptoms, and leveraging this information for early diagnosis and the development of treatments.

Keywords: Data collection; Health resources; Nervous system; Rare diseases

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Introduction

According to the World Health Organization, a rare disease is defined as a condition affecting fewer than 6.5 individuals per 10,000. Often, these diseases have hereditary or congenital

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origins. Patients with rare diseases frequently exhibit complex symptoms, many of which are neurological in nature [1]. Despite the identification of numerous rare diseases, the small patient populations for each condition and the diverse range of symptoms pose challenges for early diagnosis. Furthermore, conducting clinical trials with large participant numbers is problematic. Consequently, most rare diseases lack curative treatments, and available therapies tend to be either low in efficacy or expensive. These issues lead to severe disability or death for those affected by rare diseases and contribute to an increased socioeconomic burden [2].

In this study, we sought to establish a registry for motor neuron disease, hereditary spastic paraplegia (HSP), and spinocerebellar ataxia (SCA). These rare motor nervous system disorders are characterized by gait disturbance as a primary symptom. Although these diseases are respectively typified by muscle weakness, spastic paraplegia, and ataxia, they can present with a spectrum of overlapping motor neuron symptoms with similar initial clinical presentations. Furthermore, the absence of precise diagnostic biomarkers and identified genetic variants complicates the accuracy of diagnosis.

Amyotrophic lateral sclerosis (ALS) is a rare and incurable neurodegenerative disease that affects motor nerves in the cerebrum, brainstem, and spinal cord. The clinical manifestations of ALS are highly heterogeneous. Depending on the primary site of pathogenesis, patients may be classified as having progressive muscular atrophy, primary lateral sclerosis, or bulbar ALS [3]. However, because the diagnosis of ALS is based on clinical diagnostic criteria, it is difficult to distinguish the early stages of this disease from other conditions with similar clinical manifestations, such as progressive paraplegia and spinocerebellar atrophy [4]. Moreover, a definitive diagnosis of ALS is often elusive until symptoms have fully progressed [5–7]. According to Brown et al. [8], the pooled prevalence rate of ALS (per 100,000 people) is 6.22 in Europe, 5.20 in North America, and 3.01 in Asia, excluding Japan. Approximately 5.1% of ALS cases are considered familial ALS, with the remainder classified as sporadic ALS [8,9]. Research on familial ALS has identified major pathogenic mutations in genes associated with the disease, such as *SOD1* and *C9ORF72*. While these pathogenic mutations are rare, they have also been found in patients with sporadic ALS. Furthermore, recent findings confirm that ALS clinically and genetically overlaps with several multisystem neurodegenerative diseases [3]. Consequently, research into hereditary ALS is intensifying in an effort to enhance our understanding of the disease and to discover suitable treatments. In the Republic of Korea, the prevalence of ALS is approximately 3 per 100,000 people, markedly lower than in Western countries [10]. The genotypes identified in the Republic of Korea are predominantly *SOD1* genetic variants, in contrast to the *C9ORF72* variants that are more common in Western populations, underscoring a key regional difference in the genetic landscape of the disease [11]. Therefore, collecting clinical and genetic information on Korean patients with ALS is necessary to develop treatments appropriate for this population. To achieve this, a network of ALS researchers must be established and sustained with ongoing support, focusing on the development of diagnostics and therapies.

HSP encompasses a group of inherited neurological disorders that affect the corticospinal tract, leading to stiffness and muscle weakness in the lower limbs. Epidemiological data on HSP are scarce due to its ambiguous clinical diagnosis and classification. However, the prevalence of HSP with a confirmed genetic mutation is approximately 1.8 per 100,000 individuals [12]. HSP prevalence exhibits considerable regional variation, with figures as low as 0.2 per 100,000 in Japan, potentially indicating a lower incidence in Eastern than in Western populations [13]. HSP can be classified based on clinical phenotype, inheritance pattern, or pathogenesis [14]. From a clinical perspective, HSPs are divided into pure and complex forms. Pure HSP typically presents with progressive spastic weakness of the lower limbs, hypertonic urinary bladder disturbance, and a mild reduction in vibratory sensation. In contrast, complex HSP may include additional clinical features such as cerebellar

HIGHLIGHTS

- We established the first registry in the Republic of Korea specifically for rare neurological diseases impacting the motor nervous system: amyotrophic lateral sclerosis, hereditary spastic paraplegia, and spinocerebellar atrophy. This registry involved 5 tertiary hospitals.
- The registry will gather clinical information and bioresources from patients with rare diseases over a 3-year period, with data and materials stored within a web-based clinical research management system and the National Biobank of Korea.
- Our research team aims to identify genetic variants explicitly found in Korean patients, uncover biomarkers strongly correlated with clinical symptoms, and leverage these findings for early diagnosis and treatment development.

dysfunction, cognitive impairment, peripheral neuropathy, and dyskinesia, alongside the characteristic lower limb spastic paralysis. It is therefore important to differentiate HSP from conditions such as motor neuron disease, dementia, and genetic metabolic disorders. Regarding inheritance patterns, HSPs are classified as autosomal dominant, autosomal recessive, sex chromosome-linked, or mitochondrial. The genetic landscape of HSP is diverse, and associations between phenotype and genotype are often unclear. In many instances, genetic variants remain unidentified even when the clinical presentation is consistent with HSP. Consequently, gathering clinical and biological data from patients in the Republic of Korea is vital for advancing our understanding of this condition.

SCA encompasses a clinically and genetically diverse group of autosomal dominant inherited degenerative disorders affecting the cerebellum and its associated structures. SCA represents one of the rarest incurable diseases. The disease primarily affects the cerebellum and progresses to cause a range of cerebellar-related dysfunctions, such as gait disturbances, hand tremors, dysarthria, dysphagia, and balance issues [15]. Due to its rarity, data on national prevalence rates are scarce and variable [16]. In the Republic of Korea, a study estimated the prevalence of SCA to be 4.99 per 100,000 person-years, based on data from the Korean National Health Insurance system [17]. Another study investigating the distribution of SCA genes in this country identified *SCA2*, *SCA3*, and *SCA6* as the most prevalent [18]. However, despite the publication of several Korean studies, including multicenter research utilizing National Health Insurance data, few registries or databases detail the clinical presentation of patients with SCA. Consequently, a critical need exists to establish a registry for Korean patients with SCA. Research into actual clinical presentations can yield valuable evidence for future treatment and care, while supporting the development of initiatives to improve the welfare and legal systems necessary to improve the lives of patients.

Each of the diseases mentioned is rare and characterized by motor symptoms, with numerous genetic variants identified. Consequently, diagnosing based on a single genetic test is challenging, as different genes can lead to a range of clinical manifestations, and phenotypes may overlap across multiple genes (Figure 1). Moreover, genotype distributions vary between national and international reports. With the continuous discovery of new genetic variants, it is essential to gather and share diverse patient information for long-term research. This will enable a more comprehensive understanding along with integration into clinical practice [19].

Overall, epidemiological data on rare motor neuron diseases are limited due to their low prevalence, the complexities of clinical diagnosis, their unclear pathogenesis, and their genetic heterogeneity. Identifying biomarkers and developing targeted therapeutics are further complicated by these factors. Therefore, the need exists to create a comprehensive registry and to gather robust evidence on risk factors and early diagnosis through research efforts. To address this need, the present study was designed to establish a registry for rare neurological diseases in the Republic of Korea and to construct a biobank of high-quality human bioresources. This registry is termed the Korean Research Network for Motor Neuron Disease and Spinocerebellar Ataxia (K-MoSCA). The study also entails the development of an expert network that will lay the groundwork for a range of future studies in this field.

Collection

Five tertiary hospitals in the Republic of Korea will participate in the data collection process: Konkuk University Medical Center, Samsung Medical Center, Chungnam National University Hospital, Soonchunhyang University Cheonan Hospital, and Inje University Haeundae Paik Hospital (Figure 2). Each research center has individually obtained approval from its respective institutional review board. Our goal is to gather data from patients who have been diagnosed with the specified rare diseases within the Department of Neurology at each hospital and who have voluntarily consented to participate in the study. We are aiming for a total of 60 study participants annually over a period of 3 years, amounting to 180 participants in total, with each hospital contributing 12 participants per year. Data collection will take place at

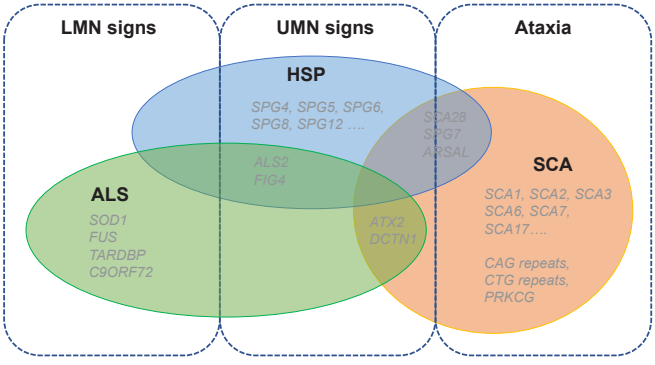

Figure 1. Clinical manifestations and genetic abnormalities observed in a representative group of rare motor neuron diseases.
LMN, lower motor neuron; UMN, upper motor neuron; ALS, amyotrophic lateral sclerosis; HSP, hereditary spastic paraplegia; SCA, spinocerebellar ataxia.

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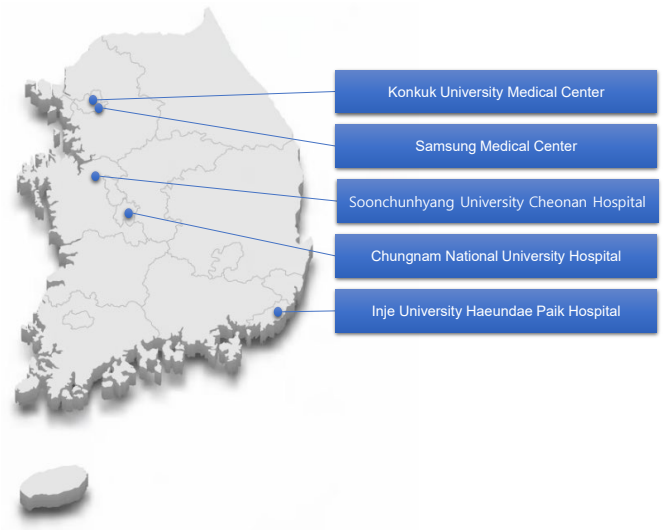

Figure 2. Participating hospitals in the rare motor neuron disease network.

each institution over a 3-year period commencing on the date of approval by the ethics committee of each institution. Additionally, information will be collected from patients who are willing to participate in the study during their baseline visit and at 6-month follow-up appointments.

Patients who agree to participate in the study will provide written informed consent and will receive a copy of the consent form. Potential participants will be clearly informed that their decision to participate or decline will not affect their clinical care. They will also be told that they have the right to withdraw their consent at any time before data collection is finalized. Patients will be given the contact details of the research team, allowing them to withdraw without the need to discuss their decision with others. Research staff will be made aware that patients may refuse to participate and withdraw their consent at any point before the completion of data collection.

Participants must be at least 19 years old and have a diagnosis of ALS, HSP, or SCA. For those with ALS, eligibility will be determined based on whether they meet any of the following diagnostic requirements: the Revised El Escorial criteria, the Awaji Criteria, or the Gold Coast Criteria [5–7]. Patients with HSP or SCA will be considered eligible if they possess relevant genetic variants and exhibit a clinical presentation that aligns with their diagnosis [12,15]. Enrollment of participants with these conditions will occur after they have completed adequate differential diagnostic testing, as determined by the investigating researcher. Conversely, individuals with other systemic diseases, vulnerable populations such as minors or those with cognitive impairments, participants from whom clinical information and biological samples cannot be obtained, and any individuals deemed unsuitable for the study by the investigator will be excluded (Table 1).

After consenting to participate in the study, during the initial visit, patients will be asked to provide a range of information. These data include demographics, personal medical history, family history, comorbidities, clinical information, treatment details, disability assessments, and patient-based quality of life measures obtained through questionnaires (Table 2). Disability assessments will employ disease-specific scales: the Korean version of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (K-ALSFRS-R) for ALS, the Spastic Paraplegia Rating Scale (SPRS) for HSP, and the Scale for the Assessment and Rating of Ataxia (SARA) for SCA [20–22]. Quality of life will be evaluated using the Fatigue Severity Scale, the Beck Depression Inventory-II, the Pittsburgh Sleep Quality Index, the World Health Organization Quality of Life-BREF, and the Korean version of the Zarit Burden Interview as a measure of caregiver burden [23–26].

Patient clinical information will be de-identified, and all centers will utilize a standardized case record form. These case notes will document standard demographic data, categorized by disease, and a registry will be established via a web-based clinical research management system (iCreaT; https://icreat.nih.go.kr/) [27]. To ensure the efficient operation of this system, each institutional researcher will receive training on its use and be assigned identification.

Prospectively, blood samples and (when possible) cerebrospinal fluid will be collected. Each blood sample will consist of approximately 25 mL, distributed as follows: 3 ethylenediaminetetraacetic acid (EDTA) tubes (12 mL total), 1 serum separator tube (8 mL), and 1 Paxgene tube (5 mL). An additional 10 mL of blood will be collected and stored if patients consent to provide peripheral blood mononuclear cells and RNA. The blood in the EDTA tubes will be separated into DNA (10 μg per vial in 3 vials), plasma (300 μL per vial in 10 vials), and buffy coat (1.8 mL in a single vial). The blood in the serum separator tube will be processed to obtain serum (300 μL per vial in 5 vials). From the Paxgene RNA tube, 3 to 4 mL of RNA-stabilized blood will be extracted. Furthermore, if a lumbar puncture is performed for medical treatment or diagnosis and the patient consents, approximately 5 to 10 mL of cerebrospinal fluid will be collected. No cerebrospinal fluid will be collected solely for research purposes, and this material will only be stored if an excess is available over the amount required for medical procedures. Blood and cerebrospinal fluid samples will be collected, processed, and stored by the Global Clinical Central Lab and then sent to the National Biobank of Korea annually [28]. At each 6-month

Table 1. Inclusion and exclusion criteria for study participants

	Contents
Inclusion criteria	1. Adults aged 19 years or older with the ability to provide informed consent 2. Diagnosed with one of the following diseases: 1) Amyotrophic lateral sclerosis: diagnosed using the Revised El Escorial criteria, Awaji Criteria, or Gold Cost Criteria 2) Hereditary spastic paraplegia 3) Spinocerebellar ataxia 4) Others[a]: primary lateral sclerosis, progressive muscular atrophy, ALS-FTD complex, progressive bulbar palsy, benign focal muscular atrophy, and other motor neuron disease
Exclusion criteria	1. Patients with systemic diseases 2. Vulnerable research participants: minors, cognitively impaired patients 3. Participants for whom clinical information and human derivatives cannot be collected 4. Other patients who, in the judgment of the investigator, are inappropriate for the study

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia.
[a]Atypical motor neuron diseases, for which diagnosis is not explained by other diseases.

Table 2. Case record items

Category	Specific item
Demographics	Age at registration, sex, place of birth, smoking history, drinking history
Personal medical history	Comorbidities: tumors, cardiovascular disease, Parkinson's disease, autoimmune disease, neurodegenerative disease, genetic neuropathy
Family history	Three or more generations of family tree
Clinical information	Date of onset, diagnosis, diagnosis subclassification, degree of neurological involvement at onset and at present, clinical course
Test results	Imaging tests: brain MRI, spine MRI Neurophysiology tests: NCS, EMG, EP Genetic tests: simple gene tests, gene panel tests, NGS, WES, WGS Cerebrospinal fluid tests Cognitive function tests (K-MMSE-2, MoCA-K), Pulmonary function tests (test date, test availability, FCV, FEV1)
Treatment and support	Medical treatment: riluzole, edaravone, others Invasive treatment: gastrostomy, tracheostomy Support: use of mechanical ventilator, non-invasive ventilator, and/or wheelchair
Disability level	ALS: K-ALSFRS-R HSP: SPRS SCA: SARA
Patient-based quality of life index	FFS, BDI-II, PSQI, WHOQOL-BREF, Zarit Burden Interview
Follow-up items	Disability level on each clinical scale (K-ALSFRS-R, SPRS, and SARA), application of invasive treatment, date of death

MRI, magnetic resonance imaging; NCS, nerve conduction study; EMG, electromyography; EP, evoked potential; NGS, next-generation sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing; K-MMSE-2; Korean version of the Mini-Mental State Examination-2; MoCA-K, Korean version of the Montreal Cognitive Assessment; FCV, forced vital capacity; FEV1, forced expiratory volume in 1 second; ALS, amyotrophic lateral sclerosis; K-ALSFRS-R, Korean version of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; HSP, hereditary spastic paraplegia; SPRS, Spastic Paraplegia Rating Scale; SCA, spinocerebellar atrophy; SARA, Scale for the Assessment and Rating of Ataxia; FFS, Fatigue Severity Scale; BDI-II, Beck Depression Inventory-II; PSQI, Pittsburgh Sleep Quality Index; WHOQOL-BREF, World Health Organization Quality of Life-BREF.

follow-up, clinical scales will be reassessed for each disease. Additional information will be gathered regarding wheelchair use, gastrostomy, tracheostomy, and, if applicable, the date of death.

Data Resource Use

Descriptive statistics will be applied to the data collected from participants to estimate national demographic trends for each disease. Using the clinical information gathered, predictive determinants and risk factors associated with disease-specific clinical assessment scales—the K-ALSFRS-R for ALS, SPRS for HSP, and SARA for SCA—can be identified. Furthermore, these data will enable the discovery of factors that could be leveraged for the prevention of each disease. Genetic analysis of the collected human derivatives will be conducted to identify variants specific to the Korean population, based on the genetic profiles associated with

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each disease. An additional objective is to uncover potential biomarkers by analyzing associations between changes in clinical scales and genomic or transcriptomic data. We anticipate the discovery of specific biomarkers in these samples, particularly from participants who have provided cerebrospinal fluid. Our approach includes integrating clinical information, clinical scale assessments, genetic testing results, and detailed examinations such as imaging and electromyography to perform extensive association analyses.

Strengths and Weaknesses

The aim of this study was to develop the first registry focused on rare neurological diseases affecting the motor nervous system in the Republic of Korea. We have created a web-based platform that facilitates multi-institutional collaboration within this country, allowing for the collection of patient information on rare conditions. Previously, these data were managed independently by each institution for individual diseases. By focusing exclusively on rare motor nerve diseases and engaging experts from various institutions, we anticipate that specialized data can be more easily gathered and shared. Moreover, a broad range of data will be obtained through initial evaluation questionnaires that cover depression, sleep, quality of life, and caregiver burden. This approach is expected to aid in the identification of potential biomarkers and the discovery of genetic variants that are prevalent in the Korean population. Additional data acquired from patient follow-ups will further enhance our understanding of the epidemiology of rare movement disorders in the Republic of Korea. The insights gained from this data will help to facilitate early diagnosis, determine the appropriate timing of medical intervention, establish patient-centered management strategies, and inspire the development of novel treatments. In Europe, national registries for rare diseases, including neurological conditions, have been established. These registries facilitate information sharing, the development of diagnostic and management guidelines, and the provision of training programs based on these guidelines [29]. It is our hope that these European models will inform the creation of national registries in Asia and provide a valuable resource to support personalized medicine for patient populations that differ from those in Western countries.

Our registry has the potential to be utilized for expanded studies of the targeted diseases. Data will be collected from patients and their progress monitored under current standards of care, aiding in the identification of progressive genetic variants and analyses of treatment effectiveness in Korean patients. Additionally, it will provide information on cost-effective testing and the tracking of highly relevant biomarkers and genes for patients who are unable to participate. Biomarker monitoring, the application of new therapeutic agents, and appropriate gene therapy are expected to be prioritized to help surviving patients, and the existing genetic information can assist in the analysis of subgroups for each disease.

Ultimately, the registry will serve as a basis for medical policy decisions concerning motor neuron diseases and related disorders. It is designed to gather data on the diagnostic process and medical treatments for each rare disease. Additionally, extending our research to include the estimation of healthcare costs associated with diagnosis, treatment, and medical intervention could form a foundation for future health insurance budget allocations and coverage policies. Additionally, the registry will compile data on factors such as fatigue, sleep patterns, depression, quality of life, and caregiver burden. This information will be instrumental in understanding the real-world needs of patients and their caregivers, allowing for the prioritization of services and the reform of relevant policies.

The study does have certain limitations. Like other registries, it offers no direct benefits to participating patients. Those enrolled in the registry and contributing specimens will not gain direct financial or therapeutic incentives. They should not anticipate any specific benefits until new treatments are formulated from the analysis of their provided data, or until they are assessed for suitable interventions. These points are clearly communicated in the informed consent documentation.

Participant selection bias within the registry is also a possibility. The number of participating centers is limited, and not all patients diagnosed at each center can be enrolled. Moreover, as outlined in the exclusion criteria, patients experiencing cognitive decline who do not have a guardian are not suitable for inclusion in the registry, as it is unlikely that sufficient information can be obtained from them. Additionally, the limited participant capacity and brief enrollment window mean that patients diagnosed outside of this period, as well as those diagnosed after the target number of patients has been reached, will be excluded from the registry, potentially contributing to bias. Geographically, 2 of the 5 centers are situated in Seoul; this complicates the process of evenly recruiting patients from each region, especially when factoring in travel distance. Patients who are more educated, younger, have better mobility, or have caregivers who can readily travel to the centers and are attuned to their medical needs are relatively likely to be represented in the registry.

Limitations in the maintenance and persistence of the registry should also be expected. Enrolled patients will undergo follow-up every 6 months to evaluate their clinical symptoms, clinical measures, and the utilization of invasive treatments. However, we anticipate challenges in data management and updates following the conclusion of the 3-year study period. The diagnosis and classification of individual rare diseases may evolve, and the registry may only partially capture these changes for patients whose initial diagnosis is subject to revision due to new findings over the course of the study. Additionally, compatibility with registries from other healthcare organizations and forthcoming advancements should be considered.

Access

While the registry is under construction, clinicians and researchers involved in studies can access clinical data through iCReaT; this information will not be made public. After the data assembly is finalized, the collected data will be de-identified to the greatest extent possible in preparation for public release and will be stored under the Korea Disease Control and Prevention Agency. The stored data and human biological resources will be accessible as public resources via the National Biobank of Korea and its website [30]. Contributors will retain priority access to up to 30% of the deposited resources for a period of 3 years. Once this priority period has lapsed, the human bioresources will become fully public. Regarding these biological deposits, data may be requested through an export application even before the deposit process is complete. In such instances, the donor's right to priority distribution is considered to have been exercised. Other researchers may also request access. If their applications are approved, they will be provided with clinical information and specimens for research purposes, and any results obtained must be submitted.

Notes

Ethics Approval

Ethical approval for this study was obtained from the institutional review board of each participating research center: Konkuk University Medical Center (IRB No: KUMC 2023-04-060), Samsung Medical Center (IRB No: SMC 2023-04-045-001), Chungnam National University Hospital (IRB No: CNUH 2023-06-066), Soonchunhyang University Cheonan Hospital (IRB No: SCHCA 2023-04-042-003), and Inje University Haeundae Paik Hospital (IRB No: HPIRB 2023-05-004-003). Participants and their guardians were informed about the study, and written consent was obtained.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets are not currently publicly accessible; however, they can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: JO, JP, JMS, BJK, ES; Data curation: MYJ; Methodology: JMS, EO, KJS; Project administration: all authors; Resources: all authors; Supervision: BJK; Writing–original draft: DK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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Commentary

Challenges in capacity building of national immunization programs and emergency or pandemic vaccination responses in the Global Health Security Agenda member countries

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Coronavirus disease 2019 (COVID-19) triggered a global crisis and economic collapse. Infectious diseases have been reported to impact over 1,430 cities across 210 countries at any given time (United Nations [UN] 2020). During the COVID-19 pandemic, the World Trade Organization (WTO) estimated a 5.3% decline in global trade (WTO 2021), while the International Monetary Fund (IMF) reported a 13.1% increase in global financial debt (IMF 2020). More than 350 million individuals lost full-time employment (African Development Bank 2020). In light of this experience, it has been pointed out that pandemic preparedness was inadequate and must be improved with greater transparency (Organisation for Economic Co-operation and Development 2022). Equity and solidarity are essential principles in pandemic preparedness (World Health Organization [WHO] 2022). The pandemic has starkly revealed and intensified severe and systemic inequalities (UN 2020).

The Global Health Security Agenda (GHSA) Immunization Action Package is developing a methodology that will act as a strategy to enhance and supplement existing resources for national immunization programs (NIP) capacity. It also aims to establish a dynamic library of these resources that will expand over time. Efforts to increase global vaccination coverage are ongoing, as immunization is acknowledged to be one of the most effective and cost-efficient global health interventions for saving lives and preventing diseases [1]. Immunization efforts are carried out through a national vaccine delivery system, which includes efficient distribution, accessibility for marginalized populations, sufficient cold chain infrastructure, and continuous quality control. These elements are crucial for building resilience against public health threats and emergencies [1]. The Joint External Evaluation (JEE) assesses immunization using 2 indicators: vaccine coverage within the national program and the national vaccine access and delivery.

Indeed, the GHSA Immunization Action Package aims to raise the vaccination rate for vaccine-preventable diseases. As part of this initiative, various meetings have been held to share and develop strategies and initiatives of member countries. To assess the challenges and strengths of the NIPs of GHSA member countries, the Immunization Action Package has gathered data for statistical analysis from literature reviews and WHO/United Nations International Children's Emergency Fund sources. At the Expert Forum of the Seventh GHSA

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Ministerial Meeting, which took place on November 28, 2022, participants discussed 4 key capacities of NIPs: infrastructure, sustainable financing, and other vaccine-related capacities, including vaccine awareness, access, and development. The forum also addressed several challenges that NIPs may face, along with related emergency responses, such as an insufficient health workforce, inadequate education or training, cold chain issues, and a lack of information management systems and government funding at both central and local levels. These topics were chosen for their relevance as identified in the JEE and other data sources, and for their significance in strengthening NIPs. This paper will explore 4 such topics.

The Expert Forum concentrated on addressing the specific needs and challenges that countries participating in the Seventh GHSA Ministerial Meeting encountered while striving to enhance their NIP capacities. The countries involved in these discussions included Australia, Japan, Finland, Kenya, Lao PDR, Malawi, Pakistan, Saudi Arabia, Sweden, Thailand, Senegal, South Africa, Peru, Singapore, Philippines, Nigeria, Malaysia, Madagascar, Georgia, Gambia, DR Congo, El Salvador, Ethiopia, Bangladesh, Cameroon, Uganda, Argentina, Switzerland, Denmark, Burkina Faso, Liberia, the Republic of Korea, The Netherlands, United Kingdom, United States, and Zimbabwe as of November 14, 2022.

The Expert Forum offered a platform for nations to assess the capacity of their NIPs to develop strategies aimed at preventing potential challenges arising from insufficient capabilities.

Due to COVID-19, each member country of the GHSA has recognized the importance of strengthening NIP capacities during peacetime. A study found a correlation of 0.63 between the vaccination rates for diphtheria, tetanus, and pertussis (DTP), polio, and measles in 2019, before the COVID-19 pandemic, and the COVID-19 vaccination rate in 2022 across the 71 GHSA member countries [2]. This indicates a strong relationship between routine immunization coverage and the ability to achieve high vaccination rates during a public health emergency such as COVID-19. This correlation suggests that countries need to maintain high vaccination rates even in the absence of a pandemic to be prepared for public health emergencies. Resilient infrastructure is a critical component in this effort, as it can alleviate the strain on emergency response systems. The JEE assessed the average score for infrastructure among the 71 GHSA member countries at 3.57 out of 5. A low score highlights that infrastructure is a significant area for improvement in the NIP and has become a topic for discussion.

Health system infrastructure is divided into various components, including physical infrastructure, information and communication technology, and medical equipment [3]. The COVID-19 pandemic, in particular, has underscored the importance of a robust public health data infrastructure [4]. The Republic of Korea serves as a prime example of resilient infrastructure, as seen in its management of routine immunization during the pandemic. This involved examining the capacities of information technologies, such as stock management tools and vaccine data management, integrating private sector activities and data into the national immunization system, and utilizing this information infrastructure to enable the government and other institutions to develop more efficient and equitable vaccination strategies [4]. Successful interventions hinge on a strong health system infrastructure and investment [5]. Indeed, the COVID-19 pandemic has revealed vulnerabilities in the current infrastructure, necessitating that key stakeholders undertake initiatives to reinforce infrastructure, thereby enhancing vaccination coverage [5]. The Expert Forum provided an opportunity for countries to present national case studies and deliberate on strategies for building resilient infrastructure.

Sustainable financing aims to improve the generation, allocation, and use of public and pooled funds in healthcare [6]. The financial sustainability of the NIP is increasingly important to meet current and future immunization performance targets, including access, utilization, quality, safety, and equity. It also supports the prevention and early detection of, and effective response to, infectious disease threats, as well as the introduction of new vaccines and technological advancements. Following the JEE Report by the WHO, financial challenges were identified in 15 low- and middle-income countries, spanning 10 in Africa, 2 in the Western Pacific, and 1 each in Europe, South-East Asia, and the Eastern Mediterranean regions [1]. According to the World Bank's 4 income classifications, the 71 member countries of the GHSA include 22 high-income

HIGHLIGHTS

The Immunization Action Package of the Global Health Security Agenda (GHSA) aims to protect vaccine-preventable diseases by increasing the vaccination rate. GHSA member countries must implement sustainable national immunization programs and respond to emergency vaccination plans. This article emphasizes four significant capacities—infrastructure capacity, sustainable financing capacity, vaccine access and equity, and vaccination hesitancy—to achieve the goals of the Immunization Action Package.

(31.0%), 19 lower-middle-income (26.8%), 17 low-income (23.9%), and 13 upper-middle-income (18.3%) countries [1].

Financial sustainability is a key factor influencing vaccine coverage, access, and delivery. To improve vaccine coverage, a government's strong commitment is essential; this includes co-financing, campaign support, and budget allocation across central and local governments, as well as the development of human resources. Moreover, maintaining vaccine access and delivery requires financial independence, effective negotiation with vaccine manufacturers, and the cultivation of technical professionals. For financial sustainability, the national immunization strategy has developed the national immunization schedule to estimate the costs and implement a realistic vaccine budget [7,8]. A successful strategy will depend on the continuous evolution of previous initiatives, as challenges differ by region and income level. There is still a need for further analysis and action to increase efficiencies in various settings.

Vaccine equity is predicated on the principle that access to and allocation of healthcare should be impartial, regardless of race, religion, political belief, economic status, or any other social condition [9]. However, the inequitable distribution and access to vaccines for COVID-19 have exacerbated the pandemic's effects, leading to an increase in the number of cases and deaths, as well as significant political and economic repercussions [10]. Consequently, the challenges of vaccine access and equity have become a primary focus of discussion at global, regional, and national levels, both before and during the COVID-19 pandemic. According to the JEE of the GHSA, among the 71 member countries, 80% of those in the African region have faced difficulties with vaccine access due to geographic constraints and limited vaccination sites. As of August 2022, the COVID-19 vaccination rates (excluding Ukraine) are as follows: a vaccination rate of 0% to 20% in 17 GHSA member countries (15 in Africa, 1 in the Eastern Mediterranean, and 1 in the Americas); 20% to 40% in 10 countries (9 in Africa, 1 in the Eastern Mediterranean); 40% to 60% in 4 countries (1 in Africa, 3 in the Eastern Mediterranean); 60% to 80% in 22 countries (1 in the Eastern Mediterranean, 10 in Europe, 4 in the Americas, 3 in South-East Asia, and 4 in the Western Pacific); 80% to 90% in 15 countries (1 in Africa, 4 in Europe, 3 in the Americas, and 7 in the Western Pacific); and over 90% in 2 countries (1 in the Americas and 1 in the Eastern Mediterranean). The inequity in COVID-19 vaccine distribution is anticipated to have a deep and enduring impact on the socio-economic recovery of low and lower-middle-income countries. Without immediate measures to increase supply, share vaccines equitably, and ensure universal accessibility, the consequences will be far-reaching.

Vaccine campaigns aimed at combating COVID-19 depend not only on the efficacy and safety of the vaccines, but also on the level of vaccination hesitancy among the public and healthcare workers. This factor is critical for achieving control over the pandemic [11]. The Strategic Advisory Group of Experts on Immunization defines vaccination hesitancy as a "delay in acceptance or refusal of vaccination despite the availability of vaccination services" [12]. Consequently, vaccination hesitancy can be assessed by the vaccine acceptance rate, which represents the proportion of the population indicating in national surveys that they have been vaccinated or are willing to be vaccinated. Research indicates considerable variability in COVID-19 vaccine acceptance rates across different regions and countries. Acceptance rates falling below 60% can pose various challenges to national COVID-19 pandemic programs [11]. Notably, low vaccine acceptance rates have been observed in the Middle East, Eastern Europe, and Russia [11]. In contrast, high acceptance rates in East and South-East Asia are indicative of effective pandemic control in these regions [11]. Addressing the widespread issue of COVID-19 vaccination hesitancy necessitates a collaborative effort involving governments, health policymakers, and a range of institutions and stakeholders.

As part of category R.7.2 of the JEE, vaccination hesitancy has emerged as a significant topic on the global health agenda. The Seventh GHSA Ministerial Meeting included sessions designed to further the discussion on identifying the primary causes of vaccination hesitancy across various regions and to develop strategies aimed at preventing reductions in vaccine coverage rates due to low acceptance.

Overall, countries have encountered limitations and challenges with their existing NIPs through experiences of health emergencies such as COVID-19. Consequently, they have established common goals to develop practical solutions. At the Seventh GHSA Ministerial Meeting, the Expert Forum convened to discuss the visions for the action package and its implementation process. It is evident that numerous factors contribute to the success of NIPs, including resilient infrastructure, sustainable financing, vaccine equity, and addressing vaccination hesitancy. To overcome these challenges, the Expert Forum served as a catalyst for collaboration between countries with underdeveloped NIP capacities and those with more robust capabilities. Participants in the 7th GHSA Ministerial Meeting selected relevant member countries to discuss specific issues and explore practical approaches. The Immunization Action Package aims to motivate GHSA member countries, as well as non-member countries, to participate in the NIP capacity-building project. This project focuses on 3 areas for countries with lower capacities. It also includes monitoring the cooperation

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process and developing a tool to measure improvements in NIP capacities.

Notes

Ethics Approval
The requirement for informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Availability of Data
The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: SL; Data curation: SHP, YJJ; Formal analysis: SL; Investigation: SL, SHP, YJJ, DR; Methodology: SL; Project administration: SL; Resources: SL; Software: JJO; Supervision: SYK; Validation: SL, SHP; Writing–original draft: SL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Instruction for authors

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- **Journal articles**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  1. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. Academic Press; 2020.
  2. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. CRC Press; 2017. p. 627-80.
  3. Ministry of Employment and Labor. Statistics on occupational injuries and illnesses, 2008. Ministry of Employment and Labor; 2009.
- **Websites**
  1. World Health Organization (WHO). COVID-19 vaccines [Internet]. WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  1. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Springer; 2002. p. 182-91.
- **Dissertation**
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