Aims & Scope
Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health.

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.

Abstracting and Indexing Services
A part of articles, metadata, or full text is available from CrossRef metadata (2010−), PubMed Central (2010−), PubMed (2010−), Scopus (2010−), Embase (2010−), EBSCO Host (2010−), Directory of Open Access Journals (2018−), Korea Citation Index (2011−), and Emerging Sources Citation Index (2020−).

Open Access
PHRP is an open access journal. All contents of the journal are available immediately upon publication without embargo period (https://ophrp.org). All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Editorial Board

Editor-in-Chief
Jong-Koo Lee, MD, PhD
National Academy of Medicine of Korea, Seoul, Korea

Editors

Curie Ahn, MD, PhD National Medical Center, Korea
Roland Brosch, PhD Institut Pasteur, France
Shilpa Buch, PhD University of Nebraska, USA
William Chen, PhD University of Florida, USA
Sun Huh, MD, PhD Hallym University, Korea
Sun Ha Jee, PhD Yonsei University, Korea
Yong Seok Jeong, PhD Kyung Hee University, Korea
Joseph Kamgno, MD, PhD CRFIMT, Cameroon
Cho-il Kim, PhD Korea Health Industry Development Institute, Korea
Jinhyun Kim, PhD Seoul National University, Korea
Yongkuk Kim, PhD Kyungpook National University, Korea
Moo-Song Lee, MD, PhD University of Ulsan College of Medicine, Korea
Soon Young Lee, MD, PhD Ajou University, Korea
Martin Meltzer, PhD CDC, USA
Tippavan Nagachinta, MD, DrPH CDC, USA
Hiroshi Nishiura, MD, PhD Kyoto University, Japan
Chi Eun Oh, MD, PhD Kosin University College of Medicine, Korea
Hyun Joo Pai, MD, PhD Hanyang University, Korea
Hyun-Young Park, MD, PhD Korea Disease Control and Prevention Agency, Korea
Yoon Hyung Park, MD, MPH Soonchunhyang University, Korea
Jeffrey Partridge, PhD WHO/Western Pacific Reginal Office, USA
Kholoud Porter, PhD Medical Research Council, UK
James Sneyd, PhD The University of Auckland, New Zealand
Aeree Sohn, PhD Sahmyook University, Korea
Byoung-Joon Song, PhD National Institutes of Health, USA
Michael Sparks, PhD University of Canberra, Australia
Kyo ou Taniguchi, MD, PhD National Institute of Infectious Diseases, Japan
Tai-Soon Yong, MD, PhD Yonsei University, Korea
Guang Zeng, PhD Chinese Center for Disease Control and Prevention, China

Statistical Editors

Eunok Jung, PhD Konkuk University, Korea
Ho Kim, PhD Seoul National University, Korea
Nam-Kyoo Lim, PhD Korea Disease Control and Prevention Agency, Korea

Journal Management Team

Director
Hee Youl Chai, PhD Korea Disease Control and Prevention Agency, Korea

Managing Editors

Yeoran Yoon Korea Disease Control and Prevention Agency, Korea
Se Hee Hwang, MS Korea Disease Control and Prevention Agency, Korea
Chaeshin Chu, PhD Korea Disease Control and Prevention Agency, Korea

Editorial Coordinator

Hye-Min Cho, MA Infolumi, Korea
Jisoo Yoon, MS Infolumi, Korea

Manuscript Editors

Sue Yeon Chung Infolumi, Korea
Yoon Joo Seo, ELS Infolumi, Korea

© 2023 Korea Disease Control and Prevention Agency
Editorial

149 Neglected issues related to the COVID-19 pandemic
Jong-Koo Lee

Original Articles

151 Risk factors associated with death due to severe fever with thrombocytopenia syndrome in hospitalized Korean patients (2018–2022)
Jia Kim, Hyo-jeong Hong, Ji-hye Hwang, Na-Ri Shin, Kyungwon Hwang

164 Estimating the number of severe COVID-19 cases and COVID-19-related deaths averted by a nationwide vaccination campaign in Republic of Korea
Ji Hae Hwang, Ju Hee Lee, Eun Jung Jang, Ryu Kyung Kim, Kil Hun Lee, Seon Kyeong Park, Sang Eun Lee, Chungman Chae, Sangwon Lee, Young Joon Park

173 Results of contact tracing for SARS-CoV-2 Omicron sub-lineages (BA.4, BA.5, BA.2.75) and the household secondary attack risk
Mi Yu, Sang-Eun Lee, Hye Young Lee, Hye-jin Kim, Yeong-Jun Song, Jian Jeong, Ae Kyung Park, Il-Hwan Kim, Eun-jin Kim, Young-Joon Park

180 The COVID-19 pandemic and healthcare utilization in Iran: evidence from an interrupted time series analysis

188 Vaccine effectiveness and the epidemiological characteristics of a COVID-19 outbreak in a tertiary hospital in Republic of Korea
Seonhee Ahn, Tae Jong Son, Yoonsuk Jang, Ji Hyun Choi, Young Joon Park, Jiseon Seong, Hyun Hee Kwon, Muk Ju Kim, Donghyok Kwon

197 Effectiveness of the COVID-19 vaccine in the Honam region of the Republic of Korea
In-Sook Shin, Yong-Pyo Lee, Seung-Hoon Lee, Jae-Young Lee, Jong-Ha Park, Yoon-Seok Chung

207 Risk factors for COVID-19 outbreaks in livestock slaughtering and processing facilities in Republic of Korea
Seongju Choi, Tae Jong Son, Yeon-Kyung Lee

Short Communication

219 Correlations between regional characteristics of counties and the ratio of intracounty to extracounty sources of COVID-19 in Gangwon Province, Republic of Korea
Seungmin Jeong, Chaeyun Lim, Sunhak Bae, Youngju Nam, Eunmi Kim, Myeonggi Kim, Saerom Kim, Yeojin Kim

Brief Report

224 Temporal association between the age-specific incidence of Guillain-Barré syndrome and SARS-CoV-2 vaccination in Republic of Korea: a nationwide time-series correlation study
Hyunju Lee, Donghyok Kwon, Seoncheol Park, Seung Ri Park, Darda Chung, Jongmok Ha

© 2023 Korea Disease Control and Prevention Agency
Neglected issues related to the COVID-19 pandemic

Jong-Koo Lee
National Academy of Medicine of Korea, Seoul, Republic of Korea

Since June 1, our country has reduced the disaster alert level from “serious” to “caution,” after maintaining it for 3 years and 4 months. We have transitioned to a quarantine system that primarily relies on recommendations and voluntary compliance, except for the requirement to wear masks in medical institutions. The World Health Organization (WHO) declared the end of the Public Health Emergency International Concern (PHEIC) on May 5, prior to its 75th General Assembly. The United States also terminated its public Health Emergency declaration as of May 11. Japan has announced that it will manage the crisis level at the level of seasonal influenza. The easing of measures is attributed to the significant reduction in the fatality rate of coronavirus disease 2019 (COVID-19), which has reached an endemic level. The WHO's Strategic Advisory Group of Experts released a COVID-19 vaccination roadmap in March. Based on analyses of the effectiveness of vaccine administration, guidelines recommended prioritizing the elderly [1]. In accordance with this, recent discussions among Western Pacific countries took place in Manila, Philippines (June 19–23, 2023) to address their respective responses to these guideline changes and prepare alternatives for a potential resurgence in the coming autumn, along with the public health emergency caused by wild poliomyelitis virus and circulating vaccine-derived poliovirus (cVDPV). However, we are overlooking the fact that the PHEIC caused by poliomyelitis remains unresolved. China, which shares borders with Afghanistan and Pakistan, has already experienced an imported polio outbreak. Although we have been preparing effective measures to deal with imported cases of polio, we need to double-check our efforts. Countries that have switched to injectable vaccines from oral vaccines, such as the United Kingdom, Canada, Israel, and United States, have reported positive environmental samples of cVDPV2 and acute flaccid paralysis patient sample in cVDPV3. Therefore, careful attention should be given to procedures such as rapid confirmation tests, the diagnosis of acute flaccid paralysis, and environmental surveillance.

The discussion at hand primarily concerns the repercussions of vaccination and the compensation for vaccine-related injuries. The proposal for a special law in the National Assembly arises from the fact that the existing compensation program for vaccine injuries, which mainly focuses on children, differs in its logic and compensation approach when it comes to COVID-19, especially for adults. This issue relates to the government’s responsibility for adverse events not present during the emergency use authorization, due to the indemnification granted to pharmaceutical companies for vaccine development in crisis management situations. The government actively promoted vaccination to achieve herd immunity. Booster doses were administered to prevent hospitalization, severe complications,
and death among individuals aged 60 and above with underlying health conditions, rather than to prevent transmission. Consequently, it is suggested that the scope of compensation for adverse events should be approached differently compared to the existing national immunization program focused on children. As the mRNA vaccine platform is being used for the first time, it has sometimes been difficult to establish epidemiological and mechanistic causality with adverse reactions. If compensation for severe adverse events is applied based on the WHO criteria, most cases will exceed the compensation scope, leading to discussions on how to handle cases with insufficient evidence. Some countries have observed instances where compensation is provided, taking into account the attribution rate of underlying health conditions that are expected to have contributed to severe adverse events without establishing causality. Therefore, it is necessary to conduct in-depth research on this matter.

The need for active participation in reforming global health governance, which has inadequately addressed international health crises, is often overlooked. Major advanced countries must confront the global chaos resulting from their violations of the International Health Regulations due to state self-interest. The zero draft report, discussed at the recent fourth meeting of the intergovernmental body in Geneva, Switzerland, is aimed to be adopted at the WHO’s General Assembly in May 2024. The draft contains numerous proposed improvements that have not been resolved by the traditional International Health Regulations, which have been in place for over 130 years. These unresolved issues include border closures, disruption of interpersonal exchanges, indiscriminate urban lockdowns, prolonged isolation, human rights and racial discrimination concerns, export-import controls of essential epidemic control supplies, sharing of pathogens, equitable access to vaccines and therapeutics among nations, intellectual property matters, each country’s share of contributions, chronic budget shortages, and insufficient medical support in low-income countries. A fierce battle is underway between developing and developed countries to incorporate these unresolved issues into a new, legally binding treaty. Each provision carries significant implications, involving the assurance of global health security and the protection of the human right to health. In the midst of this, determining the origin of the virus is deemed crucial, and there are arguments in favor of implementing a One Health system to prevent laboratory accidents and the emergence of antimicrobial resistance [2].

Meanwhile, it has been noted that Republic of Korea’s success in containing the spread of the virus through rapid tracing and isolation strategies, utilizing polymerase chain reaction testing in the early stages of the pandemic, serves as a crucial lesson [3]. However, critics of the current zero draft report perceive it as a step backward for human rights and accountability [4].

We must strive for both legitimacy and substantiveness in our efforts. Learning from the past, we must work towards forwards change the future of global public health for the health for all, moving beyond the G7 and towards a new G8 system. The epitaph of Dr. Lee Jong-wook, former Director-General of the WHO, underscores the importance for our nation to actively incorporate our experiences into the Pandemic Prevention Treaty and the revision of the International Health Regulations. These changes will ultimately reshape the tools of global health governance. As a country that has effectively responded to COVID-19, we should exhibit leadership in global health diplomacy.

Additionally, it is crucial to invest in international organizations that address these issues and promote the training of highly skilled personnel capable of effectively managing these organizations. Recently, an unprecedented event took place when the director of the Western Pacific Region (WPR) of the WHO was dismissed, leaving the position vacant. Intense diplomatic battles are currently unfolding on the global stage concerning the election of a new director for the WPR this November [5]. We must not overlook the importance of building our global health diplomacy capabilities to ensure that we are not left behind in these international trends.

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.

Funding
None.

References
ABSTRACT

Objectives: Severe fever with thrombocytopenia syndrome (SFTS) has no vaccine or treatment and an extremely high fatality rate. We aimed to analyze and evaluate the risk factors for death associated with SFTS.

Methods: Among reports from 2018 to 2022, we compared and analyzed 1,034 inpatients aged 18 years or older with laboratory-confirmed SFTS who underwent complete epidemiological investigations.

Results: Most of the inpatients with SFTS were aged 50 years or older (average age, 67.6 years). The median time from symptom onset to death was 9 days, and the average case fatality rate was 18.5%. Risk factors for death included age of 70 years or older (odds ratio [OR], 4.82); agriculture-related occupation (OR, 2.01); underlying disease (OR, 7.20); delayed diagnosis (OR, 1.28 per day); decreased level of consciousness (OR, 5.53); fever/chills (OR, 20.52); prolonged activated partial thromboplastin time (OR, 4.19); and elevated levels of aspartate aminotransferase (OR, 2.91), blood urea nitrogen (OR, 2.62), and creatine (OR, 3.21).

Conclusion: The risk factors for death in patients with SFTS were old age; agriculture-related occupation; underlying disease; delayed clinical suspicion; fever/chills; decreased level of consciousness; and elevated activated partial thromboplastin time, aspartate aminotransferase, blood urea nitrogen, and creatine levels.

Keywords: Epidemiological factors; Risk factors; Severe fever with thrombocytopenia syndrome

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease caused by Phenuiviridae bandavirus. First reported in Henan Province (in Central China) in 2009 [1,2], it most commonly occurs in Asian countries such as China, Korea, and Japan and is transmitted...
by the bite of an SFTS virus (SFTSV)-infected tick. The main carrier is *Haemaphysalis longicornis*, which is found in temperate climate regions and is widely distributed in Korea, Japan, China, and Oceania [3]. Human transmission via exposure to the blood and body fluids of patients with confirmed SFTS has been reported in some regions, and suspected cases have also been reported in Republic of Korea [4].

The incubation period of the disease is 5 to 14 days [5–7]. Clinical symptoms are non-specific, and main symptoms include high fever, digestive problems (nausea, vomiting, diarrhea, anorexia, etc.), and decreased platelet and white blood cell (WBC) counts. If the disease becomes severe, hemorrhagic manifestations, multiple organ failure, and neurological symptoms (muscle tremors and confusion) can occur [8].

In Republic of Korea, nationwide surveillance of SFTS was initiated in 2013, and the first confirmed case was reported in May 2013. The first patient, who tested positive for SFTS when SFTSV was isolated from a blood sample, died of multiple organ failure after developing fever, leukopenia, and thrombocytopenia in August 2012 [9]. After this first case of SFTS was reported in 2013, the number of reported patients continued to increase annually, with the highest number of patients (272 cases) documented in 2017. Thereafter, the number of patients with SFTS remained between 200 and 250 each year, but it later decreased due to limitations on outdoor activities during the coronavirus disease 2019 (COVID-19) pandemic, which reduced the probability of contact with ticks [10].

To date, no approved vaccines or treatments exist for SFTS [11]. From 2013 to 2022, the cumulative SFTS fatality rate in Republic of Korea was high, at 18.7%; China and Japan also had high fatality rates in 2022, with values of 5.1% [12] and 12.1% [13], respectively. Therefore, assessing SFTS and the risk factors for death from this condition is important for reducing the fatality rate associated with SFTS in Republic of Korea.

By analyzing patients with SFTS and associated mortality rates in 2018–2022, this study was conducted to identify the risk factors for death and establish policies for SFTS treatment and prevention.

### Materials and Methods

**Study Target and Case Definition**

**Study target**

We examined records of SFTS cases reported to the surveillance system of the Korea Disease Control and Prevention Agency (KDCA) from 2018 to 2022. Of these, this study included 1,034 inpatients aged 18 years or older who were confirmed by laboratory diagnosis to have SFTSV and who underwent complete epidemiological investigations.

**Case definition**

Of confirmed patients [14] whose clinical symptoms matched the 2022 Legal Infectious Disease Diagnosis and Reporting Criteria, who had epidemiological risk factors, and for whom SFTSV was confirmed through a diagnostic test, SFTS patients were defined as those hospitalized and treated to assess and compare their clinical progress. The following methods and criteria were used to confirm the diagnosis: when SFTSV was isolated from a sample through a culture test, the antibody titer levels in the serum obtained at the convalescent phase showed a 4-fold increase relative to that obtained at the acute phase; the specific immunoglobulin M antibody was detected through indirect immunofluorescence or enzyme-linked immunosorbent assay; or a specific gene was detected in a sample through real-time reverse transcription polymerase chain reaction. After confirmation of SFTS, the cases were divided into death and survival groups, the former consisting of those for which the cause of death was listed as SFTS on the death certificate.

**Research Methods**

This retrospective case-control study was conducted between January 1, 2018 and December 31, 2022 among hospitalized patients with SFTS reported to the KDCA surveillance system. Patients were divided into groups by mortality status for comparison and analysis. For all patients, epidemiological investigations of demographic characteristics, possible route of infection, clinical symptoms, and test results were performed using a standardized form. Each patient’s history
of exposure to risk factors 1 month before symptom onset was examined, and the results of diagnostic tests after hospitalization were collected from the first to the fourth day after admission. The date of SFTS diagnosis was determined based on the information reported in the KDCA surveillance system. Days to diagnosis were calculated from the date of symptom onset to the date of SFTS diagnosis.

Statistical Analysis
All statistical analyses were performed using R ver. 3.6.3 (R Foundation), and a p-value of < 0.05 was considered to indicate statistical significance. Continuous variables were expressed as means (range or standard error), while categorical variables were expressed as frequencies and ratios. Demographic characteristics (sex, age, region, etc.) and epidemiological and clinical characteristics (symptoms, laboratory test results, etc.) were analyzed and compared between the patients who died and those who survived. Finally, the risk factors for death due to SFTS were evaluated by calculating the adjusted odds ratio (OR) through multivariate logistic regression analysis of the risk factors for death identified in univariate logistic regression analysis.

Ethics Statement
This study was approved by the Institutional Review Board of the KDCA (IRB No: 2023-03-03-PE-A) and performed in accordance with the principles of the Declaration of Helsinki. The study was conducted under the Infectious Disease Control and Prevention Act of Republic of Korea, and the requirement for informed consent was waived because of the retrospective nature of the study.

Results

Status of Patients with SFTS by Year and Month
A total of 1,034 inpatients in Republic of Korea were confirmed to have SFTS between 2018 and 2022. The highest number of patients with SFTS was reported in 2018 (n = 249), while the lowest number was reported in 2021 (n = 156). SFTS was found in all 17 cities and provinces nationwide. The 1,034 patients consisted of 488 male (47.2%) and 546 female (52.8%) individuals, and the average patient age was 67.6 years (95% confidence interval [CI], 66.8–68.8). Most patients with SFTS were in their 50s or older (962 patients, 93.0%), and no significant differences in age distribution were observed across years. Of the 1,034 inpatients diagnosed with SFTS, 191 died of the condition. The 5-year average case fatality rate (CFR) was 18.5% (95% CI, 13.6%–23.3%); this slightly decreased after the COVID-19 pandemic began in 2020, but no significant difference was observed in the annual fatality rate (p = 0.768) (Table 1).

SFTS primarily occurs from April to October every year. In this study, the patients began to develop suspicious symptoms in April (19 patients, 1.8%), and September had the highest number of patients with suspected symptoms (201 patients, 19.4%), indicating that SFTS was most prevalent in autumn. This report coincides with the high number of carriers confirmed in September; by then, approximately 3,000 to 8,000 eggs spawned by adult ticks, the main carriers of SFTSV, have begun to hatch, causing a rapid increase in the number of larvae from August onward. Thus, the proportion of patients with SFTS rapidly grows as the probability of a tick bite increases due to the increase in outdoor activities in autumn and the large number of tick larvae hatched from eggs [10].

Table 1. No. of patients and annual CFR by month of symptom onset, 2018–2022

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Total (n = 1,034)</th>
<th>2018 (n = 249)</th>
<th>2019 (n = 218)</th>
<th>2020 (n = 225)</th>
<th>2021 (n = 156)</th>
<th>2022 (n = 186)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>12 (1.2)</td>
<td>2 (0.8)</td>
<td>3 (1.4)</td>
<td>6 (2.7)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0.388</td>
</tr>
<tr>
<td>40–49</td>
<td>39 (3.8)</td>
<td>16 (6.4)</td>
<td>9 (4.1)</td>
<td>5 (2.2)</td>
<td>4 (2.6)</td>
<td>5 (2.7)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>189 (18.3)</td>
<td>47 (18.9)</td>
<td>40 (18.3)</td>
<td>43 (19.1)</td>
<td>28 (17.9)</td>
<td>31 (16.7)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>277 (26.8)</td>
<td>68 (27.3)</td>
<td>61 (28.0)</td>
<td>54 (24.0)</td>
<td>46 (29.5)</td>
<td>48 (28.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>496 (48.0)</td>
<td>112 (45.0)</td>
<td>102 (46.8)</td>
<td>109 (48.4)</td>
<td>76 (48.7)</td>
<td>97 (52.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation.

CFR, case fatality rate.

*p-values for sex and age group were calculated using the chi-square test, while those for age and CFR were calculated using analysis of variance.

https://doi.org/10.24171/j.phrp.2023.0048
Comparison of General Characteristics According to Mortality

Table 2 shows the clinical characteristics of the 2 groups according to mortality status. To analyze the risk factors for death, among the confirmed patients [14] with clinical symptoms, epidemiological relevance, and confirmed SFTSV according to the 2022 Legal Infectious Disease Diagnosis and Reporting Criteria, those receiving inpatient treatment were defined as confirmed SFTS patients and were compared and analyzed by their clinical progress. Next, they were divided into those who died and those who survived.

In terms of sex, the patients who died included more women (96 cases, 50.3%) than men (95 cases, 49.7%), as did the survivors (women: 450 cases, 53.4%; men: 393 cases, 46.6%). Women had a lower risk of death than men (0.88; 95% CI, 0.65–1.21), but the difference was not significant (p = 0.436).

The average age of patients who died was 76.0 years (range, 67.0–80.5), 9 years greater than that of the survivors (67.0; range, 58.0–76.0). None of the patients in the ≤30-year and 30- to 39-year age groups died, and the proportions of patients in their 70s were relatively high in both death and survival groups. Relative to the 50- to 59-year age group, the risk of death was 2.17 times (95% CI, 1.15–4.11) higher in the 60- to 69-year age group (p = 0.017) and 4.58 times (95% CI, 2.57–8.18) higher in the ≥70-year age group (p < 0.001).

### Table 2. General characteristics of the patients with SFTS by mortality status

<table>
<thead>
<tr>
<th>General characteristic</th>
<th>Died (n = 191)</th>
<th>Survived (n = 843)</th>
<th>OR (95% CI)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95 (49.7)</td>
<td>393 (46.6)</td>
<td>1 (ref.)</td>
<td>0.436</td>
</tr>
<tr>
<td>Female</td>
<td>96 (50.3)</td>
<td>450 (53.4)</td>
<td>0.88 (0.65–1.21)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>76.0 (67.0–80.5)</td>
<td>67.0 (58.0–76.0)</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0 (0)</td>
<td>12 (1.4)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>30–39</td>
<td>0 (0)</td>
<td>21 (2.5)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>40–49</td>
<td>3 (1.6)</td>
<td>36 (4.3)</td>
<td>1.04 (0.28–3.81)</td>
<td>0.951</td>
</tr>
<tr>
<td>50–59</td>
<td>14 (7.3)</td>
<td>175 (20.8)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>60–69</td>
<td>41 (21.5)</td>
<td>236 (28.0)</td>
<td>2.17 (1.15–4.11)</td>
<td>0.017</td>
</tr>
<tr>
<td>≥70</td>
<td>133 (69.6)</td>
<td>363 (43.1)</td>
<td>4.58 (2.57–8.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>168 (88.0)</td>
<td>685 (81.3)</td>
<td>1.69 (1.05–2.69)</td>
<td>0.029</td>
</tr>
<tr>
<td>Urban (metropolitan)</td>
<td>23 (12.0)</td>
<td>158 (18.7)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>89 (46.6)</td>
<td>228 (27.0)</td>
<td>2.39 (1.72–3.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Forestry</td>
<td>3 (1.6)</td>
<td>9 (1.1)</td>
<td>2.04 (0.54–7.67)</td>
<td>0.291</td>
</tr>
<tr>
<td>Others</td>
<td>99 (51.8)</td>
<td>606 (71.9)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>Recognition of tick bite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74 (38.7)</td>
<td>282 (33.5)</td>
<td>1.26 (0.91–1.74)</td>
<td>0.165</td>
</tr>
<tr>
<td>No</td>
<td>117 (61.3)</td>
<td>561 (66.5)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>188 (98.4)</td>
<td>652 (77.3)</td>
<td>18.36 (5.80–58.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>3 (1.6)</td>
<td>191 (22.7)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>Time elapsed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From onset to admission</td>
<td>4 (3–6)</td>
<td>4 (3–6)</td>
<td>0.98 (0.93–1.04)</td>
<td>0.56</td>
</tr>
<tr>
<td>From onset to diagnosis (d)</td>
<td>9 (7–11)</td>
<td>6 (5–8)</td>
<td>1.22 (1.17–1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤4</td>
<td>5 (2.6)</td>
<td>174 (20.6)</td>
<td>1 (ref.)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>14 (7.3)</td>
<td>144 (17.1)</td>
<td>3.38 (1.19–9.62)</td>
<td>0.022</td>
</tr>
<tr>
<td>6</td>
<td>21 (11.0)</td>
<td>132 (15.7)</td>
<td>5.54 (2.03–15.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>22 (11.5)</td>
<td>111 (13.2)</td>
<td>6.90 (2.54–18.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>20 (10.5)</td>
<td>99 (11.7)</td>
<td>7.03 (2.56–19.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9</td>
<td>20 (10.5)</td>
<td>53 (6.3)</td>
<td>13.13 (4.70–36.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10</td>
<td>23 (12.0)</td>
<td>40 (4.7)</td>
<td>20.01 (7.17–55.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;10</td>
<td>66 (34.6)</td>
<td>90 (10.7)</td>
<td>25.52 (9.93–65.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>From onset to death</td>
<td>9 (7–11)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data are presented as n (%) or median (range) unless otherwise specified.

SFTS, severe fever with thrombocytopenia syndrome; OR, odds ratio; CI, confidence interval; ref., reference; NA, not applicable.

*<sup>a</sup> p-value calculated using logistic regression.

https://doi.org/10.24171/j.phrp.2023.0048
2.57–8.18) higher in the 70-year age group (p < 0.001) (Figure 1A).

Regarding area of residence, most patients in both groups lived in non-metropolitan areas, and the risk of death in patients living in these areas was 1.69 times higher than in urban regions (95% CI, 1.05–2.69; p = 0.029). Among those who died, the proportion of patients engaged in agriculture-related occupations (89 cases, 46.6%) was lower than that of patients with other occupations (99 cases, 51.8%); similarly, in the survival group, fewer patients were engaged in agriculture-related jobs (228 cases, 27.0%) than in other occupations (606 cases, 71.9%). However, the risk of death was 2.39 times (95% CI, 1.72–3.30) higher in those with agriculture-related occupations than in patients with other occupations (p < 0.001).

A minority of patients recognized the tick bites in both the death (74 cases, 38.7%) and survival (282 cases, 33.5%) groups. Recognizing the tick bites that cause SFTS can be difficult, unlike other tick-borne conditions such as scrub typhus. The eschar created by the ticks that cause scrub typhus resembles that of a scab; however, an SFTS tick-bitten area is small, and the mark often disappears when symptoms develop [14].

Most patients who died had an underlying disease (188 cases, 98.4%); similarly, among the survivors, more patients had an underlying disease (652 cases, 77.3%) than did not. The risk of death in patients with an underlying disease was 18.36 times (95% CI, 5.80–58.07) higher than that in patients without an underlying disease (p < 0.001).

The median interval from first symptom onset to death was 9 days (range, 7–11 days), constituting a rapid disease progression. The time from first symptom onset to hospitalization was the same in both groups (median, 4 days; range, 3–6 days); however, the median time before SFTS diagnosis was 9 days (range, 7–11 days) among those who died and 6 days among the survivors (range, 5–8 days). In other words, the time of diagnosis in the death group was delayed by 3 days relative to the survival group. The risk of death increased 1.22-fold for every 1-day delay in SFTS diagnosis (95% CI, 1.17–1.28; p < 0.001). Compared with a 4-day delay in diagnosis time from first symptom onset, the risk of death increased by a factor of 13.13 (95% CI, 4.70–36.68) when diagnosis was delayed by 9 days, 20.01 (95% CI, 7.17–55.85) when delayed by 10 days, and 25.52 (95% CI, 9.93–65.6) when delayed by more than 10 days (Figure 1B).

**Comparison of Clinical Characteristics According to Mortality**

The clinical characteristics of the 2 groups are presented in Table 3. Most patients who died (188 patients, 98.4%) and most of those who survived (727 patients, 86.2%) experienced fever or chills; meanwhile, 41 patients (21.5%) who died and 164 patients (19.5%) who survived developed a high fever (39 °C or greater). The risk of death was 10.00 times higher (95% CI, 3.14–31.8) in patients who developed fever (p < 0.001) than in those who did not, but no significant difference was found according to the presence or absence of high fever (≥39 °C, p = 0.529). Fatigue was noted in 113 patients (59.2%) and 449 (53.3%) in the death and survival groups, respectively, while headache occurred in 40 patients (20.9%) who died and 207 patients (24.6%) who survived; neither difference was significant (p = 0.139 and p = 0.291, respectively). Myalgia was present in 66 patients (34.6%) and 336 patients (43.4%) in the death and survival groups.

![Figure 1. CFR based on (A) age group and (B) time from onset to diagnosis. SFTS, severe fever with thrombocytopenia syndrome; CFR, case fatality rate.](https://doi.org/10.24171/j.phrp.2023.0048)
Except for fever, the most common report was gastrointestinal symptoms. Overall, gastrointestinal symptoms were present in 114 patients (59.7%) in the death group and 510 patients (60.5%) in the survival group, but no significant difference was found in mortality risk according to the presence or absence of digestive symptoms.

Neurological symptoms were more common among those who died (113 patients, 59.2%) than those who survived (170 patients, 20.2%). Decreased level of consciousness was the most common symptom and was found in 105 patients (55.0%) who died and 118 patients (14.0%) who survived. All neurological symptoms were significantly associated with the risk of death. Neurological symptoms in general were associated with a risk of death 5.74 times higher (95% CI, 4.11–8.01; \( p < 0.001 \)), slurred speech 2.09 times higher (95% CI, 1.34–3.28; \( p = 0.001 \)), decreased level of consciousness 7.50 times higher (95% CI, 5.31–10.6; \( p < 0.001 \)), and convulsions 3.48 times higher (95% CI, 2.03–5.96; \( p < 0.001 \)) than the risk in those without such symptoms.

Hemorrhagic manifestations were present in 37 patients (19.4%) in the death group and 55 patients (6.5%) in the survival group. All hemorrhagic manifestations were significantly associated with the risk of death. The OR of death was 3.44 for hemorrhagic manifestations (95% CI, 2.19–5.40; \( p < 0.001 \)), 3.17 for hematuria (95% CI, 1.54–6.53; \( p = 0.002 \)), 3.75 for petechial bleeding (95% CI, 1.13–12.42; \( p = 0.031 \)), 3.26 for gingival bleeding (95% CI, 1.53–6.94; \( p = 0.002 \)), and 3.83 for melena (95% CI, 1.63–8.99; \( p = 0.002 \)). Lymph node enlargement occurred in 5 patients (2.6%) who died and 22 patients (2.6%) who did not, but no significant difference was observed in mortality risk.

We analyzed the diagnostic test results obtained within 2 weeks after first symptom onset, collected based on an epidemiological survey. Thirty-five patients who were diagnosed with SFTS after 14 or more days from the first symptom date to the first examination performed after admission to a medical institution were excluded from the analysis. The death and survival groups were compared in terms of 11 diagnostic test items identified based on an independent samples t-test performed in patients within 2 weeks after symptom onset: minimum WBC count (\( \times 10^9/L \)),

### Table 3. Clinical characteristics of the patients with SFTS by mortality status

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Died (n = 191)</th>
<th>Survived (n = 843)</th>
<th>OR (95% CI)</th>
<th>( p^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>113 (59.2)</td>
<td>449 (53.3)</td>
<td>1.27 (0.92–1.75)</td>
<td>0.139</td>
</tr>
<tr>
<td>Myalgia</td>
<td>66 (34.6)</td>
<td>336 (34.4)</td>
<td>0.69 (0.50–0.96)</td>
<td>0.025</td>
</tr>
<tr>
<td>Headache</td>
<td>40 (20.9)</td>
<td>207 (24.6)</td>
<td>0.81 (0.56–1.19)</td>
<td>0.291</td>
</tr>
<tr>
<td>Fever/chills</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>188 (98.4)</td>
<td>727 (86.2)</td>
<td>10.00 (3.14–31.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever (( \geq 39 , ^\circ C ))</td>
<td>41 (21.5)</td>
<td>164 (19.5)</td>
<td>1.13 (0.77–1.66)</td>
<td>0.529</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>114 (59.7)</td>
<td>510 (60.5)</td>
<td>0.97 (0.70–1.33)</td>
<td>0.836</td>
</tr>
<tr>
<td>Anorexia</td>
<td>62 (32.5)</td>
<td>272 (32.3)</td>
<td>1.01 (0.72–1.41)</td>
<td>0.958</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (26.2)</td>
<td>227 (26.9)</td>
<td>0.96 (0.67–1.38)</td>
<td>0.833</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>51 (26.7)</td>
<td>234 (27.8)</td>
<td>0.95 (0.67–1.35)</td>
<td>0.768</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (31.4)</td>
<td>224 (26.6)</td>
<td>1.27 (0.90–1.78)</td>
<td>0.176</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (16.2)</td>
<td>173 (20.5)</td>
<td>0.75 (0.49–1.14)</td>
<td>0.178</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>113 (59.2)</td>
<td>170 (20.2)</td>
<td>5.74 (4.11–8.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>32 (16.8)</td>
<td>74 (8.8)</td>
<td>2.09 (1.34–3.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>105 (55.0)</td>
<td>118 (14.0)</td>
<td>7.50 (5.31–10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Convulsions</td>
<td>25 (13.1)</td>
<td>35 (4.2)</td>
<td>3.48 (2.03–5.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic manifestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>37 (19.4)</td>
<td>55 (6.5)</td>
<td>3.44 (2.19–5.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>13 (6.8)</td>
<td>19 (2.3)</td>
<td>3.17 (1.54–6.53)</td>
<td>0.002</td>
</tr>
<tr>
<td>Petechiae</td>
<td>5 (2.6)</td>
<td>6 (0.7)</td>
<td>3.75 (1.13–12.42)</td>
<td>0.031</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>12 (6.3)</td>
<td>17 (2.0)</td>
<td>3.26 (1.53–6.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Melena</td>
<td>10 (5.2)</td>
<td>12 (1.4)</td>
<td>3.83 (1.63–8.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymph node enlargement</td>
<td>5 (2.6)</td>
<td>22 (2.6)</td>
<td>1.00 (0.38–2.68)</td>
<td>0.995</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise specified.

SFTS, severe fever with thrombocytopenia syndrome; OR, odds ratio; CI, confidence interval.

\( ^a \) p-value calculated using logistic regression analysis performed after converting variables into binary values according to the presence or absence of symptoms.

---

https://doi.org/10.24171/j.phrp.2023.0048
minimum hemoglobin level (g/L), minimum platelet count (×10^9/L), maximum activated partial thromboplastin time (aPTT), maximum aspartate aminotransferase (AST, U/L), maximum alanine aminotransferase (ALT, U/L), maximum lactate dehydrogenase (LDH), maximum creatine kinase (CK, U/L), maximum creatine kinase myocardial fraction (CK-MB, U/L), maximum blood urea nitrogen (BUN, mg/dL), and maximum creatine level (mg/dL). The 14-day laboratory parameter dynamics are shown as box plots (Table 4; Figure 2).

The median minimum WBC count was 1.5×10^9/L (range, 1.0–2.1×10^9/L) among all patients, while the median value was lower among the patients who died, at 1.4×10^9/L (range, 0.9–2.0×10^9/L). The median minimum hemoglobin level was 12.5 g/L (range, 11.2–13.8 g/L) among all patients, and the median value of those who died was lower, at 11.5 g/L (range, 9.2–12.8 g/L). However, no significant differences were found between the death and survival groups in either parameter (p = 0.205 and p = 0.560, respectively). The minimum platelet count—which can indicate thrombocytopenia, a primary symptom of SFTS—had a median (range) of 3600×10^9/L (range, 100.3–570.0×10^9/L) across all patients. The median platelet count of those who died was 11.5×10^9/L (range, 9.2–12.8×10^9/L), while that of the survivors was 12.7×10^9/L (range, 11.5–14.0×10^9/L), indicating a lower minimum value. The WBC count differed significantly between the death and survival groups (p < 0.001). The median maximum aPTT values were 430 seconds (range, 36.5–560 seconds) for all patients, 663 seconds (range, 50.8–919 seconds) for the death group, and 405 seconds (range, 357–484 seconds) for the survival group. Thus, the aPTT was significantly longer among the patients who died than among those who survived (p < 0.001).

Moreover, this study compared the maximum AST, maximum ALT, and maximum LDH levels, as indicators of liver function abnormality, between groups. The median maximum AST values were 300.5 U/L (range, 118.8–681.8 U/L) for all patients, 1088.5 U/L (range, 545.0–2297.0 U/L) for the death group, and 228.0 U/L (range, 1030–483.0 U/L) for the survival group; therefore, the maximum AST level was significantly higher among patients who died than among either all patients or survivors. The median maximum ALT values were 1170 U/L (range, 580–2450.0 U/L) for all patients, 2380 U/L (range, 125–4850.0 U/L) for the death group, and 990 U/L (range, 50.8–1970 U/L) for the survival group; thus, the maximum ALT level was much higher among patients who died than among either all patients or survivors. The median maximum LDH values were 9100.0 U/L (range, 4850–18660.0 U/L) for all patients, 2570.0 U/L (range, 1249.8–4762.3 U/L) for the death group, and 7710.0 U/L (range, 4370–1353.0 U/L) for the survival group; as such, the maximum LDH level was also much higher among patients who died than among either all patients or survivors. Significant differences were observed between death and survival groups in the maximum AST, ALT, and LDH levels (p < 0.001).

The median maximum CK values were 574.5 U/L (range, 196.5–1913.0 U/L) in all patients, 1873.0 U/L (range, 4530–6186.0 U/L) in the death group, and 414.0 U/L (range, 166.0–1363.0 U/L) in the survival group; thus, the maximum CK level in the death group was higher than in all patients and in survivors. The median maximum CK-MB values were 4.9 U/L (range, 2.2–15.2 U/L) in all patients, 11.7 U/L (range, 4.3–48.8 U/L) in the death group, and 4.2 U/L (range, 1.8–107 U/L) in the survival group; thus, the median maximum CK-MB value was higher in the death group than in all patients and

**Table 4.** Laboratory parameters of the groups within 2 weeks after symptom onset

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Total (n = 999)</th>
<th>Died (n = 191)</th>
<th>Survived (n = 808)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (×10^9/L)^a</td>
<td>1.5 (1.0–2.1)</td>
<td>1.4 (0.9–2.0)</td>
<td>1.5 (1.1–2.2)</td>
<td>0.205</td>
</tr>
<tr>
<td>Hemoglobin (g/L)^a</td>
<td>12.5 (11.2–13.8)</td>
<td>11.5 (9.2–12.8)</td>
<td>12.7 (11.5–14.0)</td>
<td>0.560</td>
</tr>
<tr>
<td>Platelet count (×10^9/L)^a</td>
<td>360.0 (100.3–570.0)</td>
<td>290.0 (58.0–390.0)</td>
<td>410.0 (112.5–610.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aPTT (s)^a</td>
<td>43.0 (36.5–56.0)</td>
<td>66.3 (50.8–91.9)</td>
<td>40.5 (35.7–48.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)^a</td>
<td>300.5 (118.8–681.8)</td>
<td>1,088.5 (545.0–2,297.0)</td>
<td>228.0 (103.0–483.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (U/L)^a</td>
<td>117.0 (58.0–245.0)</td>
<td>238.0 (125.5–485.0)</td>
<td>99.0 (50.8–197.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDH (U/L)^a</td>
<td>910.0 (485.0–1,866.0)</td>
<td>2,517.0 (1,249.8–4,762.3)</td>
<td>771.0 (437.0–1,353.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK (U/L)^a</td>
<td>574.5 (196.5–1,913.0)</td>
<td>1,873.0 (453.0–6,186.0)</td>
<td>414.0 (166.0–1,363.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB (U/L)^a</td>
<td>4.9 (2.2–15.2)</td>
<td>11.7 (4.3–48.8)</td>
<td>4.2 (1.8–10.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>BUN (mg/dL)^a</td>
<td>20.0 (14.0–31.5)</td>
<td>36.7 (26.1–54.3)</td>
<td>17.8 (13.0–25.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Creatine (mg/dL)^a</td>
<td>1.0 (0.8–1.4)</td>
<td>1.8 (1.2–2.8)</td>
<td>0.9 (0.7–1.1)</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Data are presented as median (range).

WBC, white blood cell; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase myocardial fraction; BUN, blood urea nitrogen.

^a Excluding 35 patients with SFTS for whom no laboratory results were available within 14 days of symptom onset. ^b Minimum, ^c maximum. ^d Value calculated using independent sample t-test.
Figure 2. Dynamic profile of laboratory parameters measured within 2 weeks after symptom onset. (A) White blood cell (WBC) count, (B) platelet count, (C) hemoglobin, (D) activated partial thromboplastin time (aPTT), (E) aspartate aminotransferase (AST), (F) alanine aminotransferase (ALT), (G) lactate dehydrogenase (LDH), (H) creatine kinase (CK), (I) creatine kinase myocardial fraction (CK-MB), (J) blood urea nitrogen (BUN), (K) creatine. SFTS, severe fever with thrombocytopenia syndrome.

Risk factors associated with death due to SFTS

in survivors. Significant differences were observed between the 2 groups in maximum CK ($p < 0.001$) and maximum CK-MB ($p = 0.005$) values.

The median maximum BUN value was 20.0 mg/dL (range, 14.0–31.5 mg/dL) across all patients, while the median maximum value in the death group was 36.7 mg/dL (range, 26.1–54.3 mg/dL), which was higher than that in all patients and in survivors. The median maximum creatine level was 1.0 mg/dL (range, 0.8–1.4 mg/dL) in all patients, while the median value in the death group was 1.8 mg/dL (range, 1.2–2.8 mg/dL). Therefore, the maximum creatine level among patients who died was higher than that of all patients and of the survival group. A significant difference was observed between the 2 groups only in the maximum BUN value ($p = 0.005$).

The diagnostic test patterns of SFTS can be divided into 3
stages by disease period. Stage I is defined by a high fever within 1 week of first symptom onset, stage II is defined by multiple organ dysfunction within 1 to 2 weeks after first symptom onset, and stage III is defined as the recovery period occurring within 2 to 3 weeks after first symptom onset [8]. According to the dynamic profile composed of 11 diagnostic tests performed in both groups within 2 weeks of symptom onset, platelet counts continued to decrease from symptom onset to day 7 (stage I) and were slightly elevated or maintained on days 7 to 14 (stage II) in the survival group; however, platelet counts continued to decrease on days 7 to 14 (stage II) in the death group. The aPTT level was also slightly elevated or maintained during stage I in the survival group but increased rapidly in the death group and continued to increase in stage II. The AST, ALT, LDH, CK, CK-MB, BUN, and creatine levels significantly differed between the survival and death groups. The levels of these parameters increased in stage I and decreased or remained constant in stage II in the survival group, while they remained high and did not return to normal in the death group. These results are similar to the clinical features of inpatients with SFTS in China [8].

To identify the risk factors for death according to the diagnostic test patterns of patients with SFTS, a univariate logistic regression analysis was performed by classifying each diagnostic test item into binary terms according to the reporting criteria mentioned above [15]. Ten diagnostic test items, excluding WBC count, were identified as significant risk factors for death.

The ORs indicating the risk of death were 2.16 (95% CI, 1.58–3.00; p < 0.001) for a hemoglobin level < 12 g/L, 2.08 (95% CI, 1.34–3.22) for a platelet level < 40 × 10^9/L (95% CI, 1.34–3.22; p = 0.001), 9.34 (95% CI, 5.96–14.63; p < 0.001) for an aPTT ≥ 40 seconds, 11.14 (95% CI, 7.52–16.50; p < 0.001) for an AST level ≥ 400 U/L, 4.74 (95% CI, 3.41–6.59; p < 0.001) for an ALT level ≥ 200 U/L, 5.75 (95% CI, 4.09–8.08; p < 0.001) for an LDH level ≥ 1,000 U/L, 4.03 (95% CI, 2.87–5.65; p < 0.001) for a CK level ≥ 1,000 U/L, 7.10 (95% CI, 3.14–16.06; p < 0.001) for a CK-MB value ≥ 100 U/L, 9.22 (95% CI, 6.07–14.02; p < 0.001) for a BUN value ≥ 20 mg/dL, and 11.54 (95% CI, 8.06–16.54; p < 0.001) for a creatine level ≥ 1.5 mg/dL (Table 5).

### Risk Factors for Death in Patients with SFTS

Multivariate logistic regression analysis was performed to analyze the risk factors for death identified in the univariate logistic regression analysis (Table 6). Age; agriculture-related occupations; underlying disease; delayed diagnosis period; fever and chills; decreased level of consciousness; and elevated aPTT, AST, BUN, and creatine levels were identified as risk factors for death in inpatients with SFTS (Figure 3).

### Discussion

In this study, the epidemiological and clinical characteristics and risk factors for death associated with SFTS in the last 5 years were evaluated. Among inpatients diagnosed with SFTS from 2018 to 2022, the proportion of women was slightly higher than that of men, and the average age was 67.6 years, with most patients at least 50 years old. The median period from first symptom onset to death was 9 days, and the average CFR was 18.5%; these findings are consistent with known characteristics of SFTS, which progresses rapidly and has a high fatality rate [8].

### Table 5. Comparison of laboratory parameters of the 2 groups of patients with SFTS

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Died (n = 191)</th>
<th>Survived (n = 843)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &lt; 2.0 × 10^9/L</td>
<td>142 (74.3)</td>
<td>593 (70.3)</td>
<td>1.22 (0.86–1.75)</td>
<td>0.271</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/L</td>
<td>113 (59.2)</td>
<td>337 (40.0)</td>
<td>2.16 (1.58–3.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet &lt; 40 × 10^9/L</td>
<td>34 (17.8)</td>
<td>76 (9.5)</td>
<td>2.08 (1.34–3.22)</td>
<td>0.001</td>
</tr>
<tr>
<td>aPTT ≥ 40 s</td>
<td>167 (87.4)</td>
<td>360 (42.7)</td>
<td>9.34 (5.96–14.63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AST ≥ 400 U/L</td>
<td>155 (81.2)</td>
<td>235 (27.9)</td>
<td>11.14 (7.52–16.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ALT ≥ 200 U/L</td>
<td>112 (58.6)</td>
<td>194 (23.0)</td>
<td>4.74 (3.41–6.59)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LDH ≥ 1,000 U/L</td>
<td>130 (68.1)</td>
<td>228 (27.0)</td>
<td>5.75 (4.09–8.08)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK ≥ 1,000 U/L</td>
<td>85 (44.5)</td>
<td>140 (16.6)</td>
<td>4.03 (2.87–5.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CK-MB ≥ 100 U/L</td>
<td>15 (7.9)</td>
<td>10 (1.20)</td>
<td>7.10 (3.14–16.06)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BUN ≥ 20 mg/dL</td>
<td>162 (84.8)</td>
<td>318 (37.7)</td>
<td>9.22 (6.07–14.02)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatine ≥ 1.5 mg/dL</td>
<td>113 (59.2)</td>
<td>94 (11.2)</td>
<td>11.54 (8.06–16.54)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise specified.

SFTS, severe fever with thrombocytopenia syndrome; OR, odds ratio; CI, confidence interval; WBC, white blood cell; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase myocardial fraction; BUN, blood urea nitrogen.

https://doi.org/10.24171/j.phrp.2023.0048
Among epidemiological characteristics, the risk factors for death were old age, agricultural occupation, underlying disease, and delayed diagnosis. The ORs for death were 2.7 in patients aged 60 to 69 years and 4.82 in those aged 70 years or older, 2.01 in those engaged in agriculture-related occupations, and 7.2 in those with an underlying disease. When the time from the first symptom onset to disease diagnosis was delayed by 1 day, the risk of death increased by a factor of 1.28. This finding implies a high possibility of SFTSV in individuals with continued exposure to risk factors, as most of the patients were older and were engaged in agriculture-related occupations; moreover, the older adults’ risk of death was elevated in the presence of underlying disease and immunosuppression other than SFTS. In addition, the main symptoms of SFTS are non-specific, such as high fever and digestive problems. Thus, the fatality rate of SFTS can be reduced by shortening the diagnosis period through active differential diagnosis from other tick-borne diseases, such as scrub typhus, at medical institutions before early symptoms worsen.

Fever, chills, and decreased level of consciousness are among the clinical characteristics considered risk factors for death. Fever and chills occurred in most patients from the death and survival groups, and the risk of death was 20.52 times higher in those who developed these symptoms than in those who did not. All neurological symptoms were significant in the univariate logistic regression analysis; however, only decreased level of consciousness was a significant risk factor for death in the multivariate logistic regression analysis. Although the exact mechanism of SFTS-induced neurological damage has not been identified, an electrolyte imbalance in the blood can trigger neurological symptoms [17].

This study involved analysis of stage I (high fever) and stage II (multiple organ dysfunction) SFTS among the diagnostic test patterns according to the SFTS disease period. In the death group, the platelet count and hemoglobin levels continued to decrease in stage I; the aPTT, AST, ALT, LDH, CK, CK-MB, BUN, and creatine levels increased but did not return to normal when the diagnostic test pattern progressed to stage II. In the survival group, the platelet count and hemoglobin levels continued to decrease in stage I, while the aPTT, AST, ALT, LDH, CK, CK-MB, BUN, and creatine levels increased; however, these parameters recovered somewhat when the diagnostic test pattern progressed to stage II. Therefore, the active treatment of SFTS in the early stages of the disease (stage I) greatly impacts the risk of progression to death.

Among the laboratory parameters, elevation in aPTT, AST, BUN, and creatine levels were associated with 4.19, 2.91, 2.62, and 3.21 times increased risk of death, respectively. The cause of coagulopathy due to SFTS has not been clearly identified; some studies have suggested acute liver dysfunction as the cause of this condition [18]. Thus, signs of bleeding and changes in aPTT and AST levels should be assessed in the early stages of disease progression. Renal function abnormalities appear relatively late in patients with SFTS. Since the BUN level may increase even if the glomerular filtration rate decreases below 50%, it is necessary to continuously monitor the creatine level rather than the BUN level to obtain an initial differential diagnosis.

Therefore, if non-specific or suspicious symptoms such as fever and chills are reported during the peak of SFTS cases from April to October, epidemiological risk factors such as old age, agriculture-related occupations, and underlying diseases should be assessed in elderly patients who visit medical institutions. In addition, delays in diagnosis should be prevented by confirming the presence of SFTS through active diagnostic testing. Finally, when risk factors for death are identified based on the results of diagnostic tests, such

### Table 6. Multivariate logistic regression analysis of risk factors for death

<table>
<thead>
<tr>
<th>Epidemiologic or clinical feature</th>
<th>Coefficient (β)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (60–69 y)</td>
<td>0.99</td>
<td>2.70 (1.10–6.62)</td>
<td>0.030</td>
</tr>
<tr>
<td>Age group (≥70 y)</td>
<td>1.57</td>
<td>4.82 (2.08–11.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occupation: farmer</td>
<td>0.70</td>
<td>2.01 (1.18–3.43)</td>
<td>0.010</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>1.97</td>
<td>7.20 (1.88–27.58)</td>
<td>0.004</td>
</tr>
<tr>
<td>Time elapsed from onset to diagnosis</td>
<td>0.25</td>
<td>1.28 (1.19–1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>3.02</td>
<td>20.52 (5.25–80.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>1.71</td>
<td>5.53 (2.01–15.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>aPTT ≥40 s</td>
<td>1.43</td>
<td>4.19 (2.21–7.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST ≥400 U/L</td>
<td>1.07</td>
<td>2.91 (1.48–5.69)</td>
<td>0.002</td>
</tr>
<tr>
<td>BUN ≥20 mg/dL</td>
<td>0.96</td>
<td>2.62 (1.43–4.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatine ≥1.5 mg/dL</td>
<td>1.17</td>
<td>3.21 (1.83–5.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen.
as increased aPTT, AST, BUN, and creatinine levels, the rates of SFTS-related mortality can be reduced only through the early provision of treatment (e.g., ribavirin).

This study had some limitations. First, since it was conducted among inpatients, asymptomatic or mildly symptomatic patients with SFTS may have been overlooked. Therefore, the fatality rate of SFTS in the Republic of Korea is likely to be lower than that shown in this study, and the fatality rate may also have been overestimated because the COVID-19 pandemic in 2020 decreased the number of SFTS cases reported. Second, this analysis was based on the results of an initial epidemiological investigation conducted after SFTS was suspected and reported to the system. Therefore, no follow-up study has been carried out, and the effects of certain treatments, such as ribavirin, on SFTS symptoms were not analyzed; thus, effective SFTS treatment options could not be identified. Relative to previously reported SFTS mortality risk factors, this study indicated no new findings. Nonetheless, the COVID-19 epidemic has led to a lack of monitoring and analysis of SFTS; thus, this study is still meaningful in that it provided updated clinical and epidemiological characteristics of inpatients with SFTS by analyzing their clinical progression status and risk factors for death over the past 5 years (2018–2022). As the environment of vectors (here, ticks) changes due to climate change caused by global warming, it is also important
to monitor infectious diseases caused by these vectors. Although changes, such as an increase in the number of vectors, are occurring due to climate change, the present study confirmed that older age, agriculture-related occupation, presence of an underlying disease, delay in diagnosis, fever/chills, decreased level of consciousness, and increased aPTT, AST, BUN, and creatine levels are still important risk factors for SFTS mortality. Based on the study results, a monitoring, patient management, and analysis system for SFTS should be developed by assessing the incidence and fatality rates of SFTS in Republic of Korea.

Conclusion

This study confirmed that risk factors for death in inpatients with SFTS included old age; agricultural occupation; underlying disease; delayed diagnosis; fever and chills; decreased level of consciousness; and elevated aPTT, AST, BUN, and creatine levels. However, the number of patients with SFTS reported in this study was likely low due to the ongoing COVID-19 pandemic, and asymptomatic or mildly symptomatic patients with SFTS may have been omitted since this study included only inpatients. Finally, caution should be observed when interpreting the study results, as the effects of SFTS treatment were not analyzed due to the limited number of follow-up studies.

Notes

Ethics Approval
This study was approved by the Institutional Review Board of the KDCA (IRB No. 2023-03-03-PE-A) and performed in accordance with the principles of the Declaration of Helsinki. The study was conducted under the Infectious Disease Control and Prevention Act of Republic of Korea, and 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
All data generated or analyzed during this study are included in this published article. For other data, or if you have additional questions about the study, please contact the corresponding author, Kyungwon Hwang, E-mail: kirk99@korea.kr.

Authors’ Contributions
Formal analysis: JK; Investigation: JK, HJH, JHH; Supervision: NRS, KH; Writing–original draft: JK; Writing–review & editing: authors. All authors read and approved the final manuscript.

References


Estimating the number of severe COVID-19 cases and COVID-19-related deaths averted by a nationwide vaccination campaign in Republic of Korea

Division of Epidemiological Investigation Analysis, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea

ABSTRACT

Objectives: The Korea Disease Control and Prevention Agency promotes vaccination by regularly providing information on its benefits for reducing the severity of coronavirus disease 2019 (COVID-19). This study aimed to analyze the number of averted severe COVID-19 cases and COVID-19-related deaths by age group and quantify the impact of Republic of Korea’s nationwide vaccination campaign.

Methods: We analyzed an integrated database from the beginning of the vaccination campaign on February 26, 2021 to October 15, 2022. We estimated the cumulative number of severe cases and COVID-19-related deaths over time by comparing observed and estimated cases among unvaccinated and vaccinated groups using statistical modeling. We compared daily age-adjusted rates of severe cases and deaths in the unvaccinated group to those in the vaccinated group and calculated the susceptible population and proportion of vaccinated people by age.

Results: There were 23,793 severe cases and 25,441 deaths related to COVID-19. We estimated that 119,579 (95% confidence interval [CI], 118,901–120,257) severe COVID-19 cases and 137,636 (95% CI, 136,909–138,363) COVID-19-related deaths would have occurred if vaccination had not been performed. Therefore, 95,786 (95% CI, 94,659–96,913) severe cases and 112,195 (95% CI, 110,870–113,520) deaths were prevented as a result of the vaccination campaign.

Conclusion: We found that, if the nationwide COVID-19 vaccination campaign had not been implemented, the number of severe cases and deaths would have been at least 4 times higher. These findings suggest that Republic of Korea’s nationwide vaccination campaign reduced the number of severe cases and COVID-19 deaths.

Keywords: COVID-19; Patient acuity; Republic of Korea; SARS-CoV-2; Vaccination campaign

Introduction

Coronavirus disease 2019 (COVID-19) first emerged in China in 2019 and was declared a
pandemic by the World Health Organization (WHO). As of April 12, 2023, a total of 762,791,152 COVID-19 cases and 6,897,025 COVID-19-related deaths had been reported globally according to the WHO[1]. Following the rollout of COVID-19 vaccinations, infections and deaths were reduced in many countries and regions[2−4]. The WHO reported that COVID-19 vaccinations prevented 14.4 million COVID-19-related deaths in 186 countries in 2021[5].

In Republic of Korea, a national vaccination campaign began in February 2021, promoting 2 viral vector-based vaccines (ChAdOx1 nCoV-19 and Ad26.COV2.S) and 2 mRNA-based vaccines (BNT162b2 and mRNA-1273). The vaccination campaigns were gradually expanded to the entire population older than 6 months of age. As of April 17, 2023, 44,393,483 people (86.7% of the total population) had received 2 doses of the COVID-19 vaccine[6].

The Korea Disease Control and Prevention Agency (KDCA) has advocated for the importance and necessity of vaccination by regularly providing information on the benefits of vaccination for reducing the severity of COVID-19 and COVID-19-related mortality, but the number of severe cases and deaths averted by vaccination has not been sufficiently analyzed[7,8]. As the number of cases continued to increase due to the spread of the Omicron variant, bivalent vaccines were administered beginning in October 2022, and their necessity and importance are being actively promoted to increase vaccination rates.

In Republic of Korea, all confirmed COVID-19 cases, severe COVID-19 cases, and COVID-19-related deaths were reported to the government through the COVID-19 National Surveillance System, and all COVID-19 vaccinations were registered in the National Immunization Registry. Therefore, by linking these 2 databases, we aimed to analyze the public impact of the nationwide vaccination campaign by estimating the number of averted severe COVID-19 cases and COVID-19-related deaths during the mass vaccination campaign in Republic of Korea. Our findings will increase public awareness of vaccination and improve vaccine coverage.

Materials and Methods

Study Population and Design

In this study, we aimed to estimate the number of severe COVID-19 cases and COVID-19-related deaths averted by Republic of Korea’s nationwide vaccination campaign. We analyzed data from February 26, 2021 to October 15, 2022, on people aged 12 years and older. This study excluded those aged 4 to 11 years old due to differences in characteristics between the vaccinated and unvaccinated groups. In this age group, the severity of the disease is low, and vaccination was recommended specifically for high-risk groups. Therefore, the study excluded this age group from the analysis.

According to Republic of Korea’s COVID-19 Response Guidelines, confirmed COVID-19 cases refer to when an individual tests positive for COVID-19 using polymerase chain reaction, rapid antigen testing, or an emergency screening (emergency use-approved products). All confirmed infections, severe cases, and deaths are reported to the government through the COVID-19 National Surveillance System.

In Republic of Korea, vaccinations were first targeted to healthcare workers and high-risk groups, such as residents of long-term care facilities, beginning on February 26, 2021. In August of the same year, large-scale vaccination campaigns were conducted to distribute vaccines to all people over 18 years of age (Table S1).

Data Source

In Republic of Korea, confirmed COVID-19 cases are reported through the COVID-19 National Surveillance System, and COVID-19 vaccination records are reported and managed through the National Immunization Registry. In this analysis, we linked these 2 large databases to organize a database of 54,471,326 COVID-19 vaccination records and 23,008,640 confirmed cases. A total of 46,864,039 eligible people were analyzed (Figure 1).

Case Definition

We estimated the number of averted severe COVID-19 cases and COVID-19-related deaths. According to the COVID-19 Response Guidelines in Korea, we defined severe COVID-19 cases as COVID-19-confirmed cases for which the patient received treatment using high-flow oxygen therapy, mechanical ventilation, continuous renal replacement therapy, or extracorporeal membrane oxygenation within 28 days of a positive COVID-19 test. COVID-19-related deaths were
defined as deaths within 28 days of a positive COVID-19 test.

Vaccination status was defined in this study as follows: (1) the unvaccinated group comprised those who were completely unvaccinated and those for whom only 0 to 13 days had passed after receiving the second dose of a COVID-19 vaccine; (2) the vaccinated group comprised those for whom 14 days had passed since receiving the second dose of a COVID-19 vaccine. Those who received 1 dose of the Janssen vaccine were classified into the vaccinated group.

### Dominant Variants

According to the dates during which certain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants were most dominant, the dominant variant was classified based on the period when >50% of cases were caused by a specific variant. The periods when certain variants were dominant in this study were pre-Delta (February 26, 2021 to July 24, 2021), Delta (July 25, 2021 to January 15, 2022), Omicron (January 16, 2022 to September 3, 2022), and Omicron sub-variants, which included BA.1 (January 16, 2022 to March 19, 2022), BA.2 (March 20, 2022 to July 23, 2022), and BA.5 (July 24, 2022 to October 15, 2022).

### Data Analysis

We estimated differences in age group and sex by vaccination status. We then estimated the number of averted severe cases and deaths for all individuals who were vaccinated through the national vaccination campaign. The classification of vaccination subgroups and the analysis, which were similar to those described in other studies, were undertaken to estimate the projected burden of averted COVID-19 cases.

First, we calculated the daily age-adjusted incidence rates (age ranges [y]: 12−17, 18−29, 30−39, 40−49, 50−59, 60−74, and ≥75) of severe cases and deaths for the unvaccinated group and the vaccinated group. The person-days for the unvaccinated group were calculated for each day by deducting the person-days contributed by those who had received vaccination from the overall demographic approximations for each age group. The person-days for the vaccinated group were determined for each day by multiplying the proportion of individuals who were vaccinated by the demographic approximations for each age group. Individuals with previously confirmed SARS-CoV2 infection were excluded from the susceptible population and the totals for severe cases and deaths. Differences in these rates between the unvaccinated group and the vaccinated group were then calculated for each day and each age group during the study period. The above procedure was repeated for every day during the study period and for severe cases and deaths. The results were then added together to determine the overall projected burden of COVID-19 from averted cases.

The total burden, number of severe COVID-19 cases, and number of COVID-19-related deaths were analyzed using the following formula:

\[
\sum_{\text{age group}} \sum_{\text{day of week}} N \times V_x \geq 2 \text{dose} \left( \frac{\text{COVID unvaccinated} \& 1 \text{dose} - \text{COVID} \geq 2 \text{dose}}{\text{COVID unvaccinated} \& 1 \text{dose}} \right)
\]

N was the daily total susceptible population in each age stratum, with those with a history of COVID-19 diagnosis excluded for each day. \(V_x \geq 2 \text{dose} \) was the cumulative daily vaccination coverage of people within each age group who
had received at least 2 doses of vaccines. \( \text{COVID}_{\text{Unvaccinated \& 1dose}} \) was the daily rate of severe cases and deaths in the unvaccinated group. \( \text{COVID}_{2dose} \) was the daily rate of severe cases and deaths in the vaccinated group. The population of each age group was determined, and the age-adjusted incidence rate of severe COVID-19 cases and COVID-19-related deaths was calculated according to vaccination status. This was calculated as the ratio of the number of severe cases and deaths and the total observation period (person-day) per 1,000,000 people per day. Therefore, according to the aforementioned formula, the number of severe COVID-19 cases and COVID-19-related deaths averted during the study period was estimated through statistical modeling using the number of susceptible people \((N)\), vaccination coverage \((V_{x,2dose})\), and the difference in the incidence rates of severe cases and death \((\text{COVID}_{\text{Unvaccinated \& 1dose}} - \text{COVID}_{2dose})\). All analyses were performed using SAS ver. 9.4 (SAS Institute) and Excel 2016.

**Ethics Statement**

This study was conducted in accordance with the Infectious Disease Prevention and Control Act (no. 12444 and no. 13392) and was approved by the Institutional Bioethics Committee of the KDCA and the requirement for informed consent was waived (No: 2021-12-03-PE-A).

**Results**

From February 26, 2021 to October 15, 2022, 43,601,286 (86.5%) of the total population (50,403,942 people aged \( \geq 4 \) years) were vaccinated through the national vaccination campaign. Of those, 43,157,609 (85.6%) were vaccinated through the national vaccination campaign, and 32,387,611 (64.3%) completed the third and fourth vaccine doses. Republic of Korea recorded its highest number of COVID-19 cases around the BA.1 period (January to March 2022) (Figure 2).

During the same period, of the total study population, 43,096,261 people (92.0%) were vaccinated through the national vaccination campaign. While the difference in vaccination coverage by sex was not statistically significant, the vaccination rate of men was 92.3%, which was 0.6% higher than that of women. The vaccination rate for the third and fourth vaccine doses among women was 69.4%, which was 0.5% higher than the percentage for males (68.8%). Vaccination coverage tended to increase in older age groups. For example, individuals aged 60 to 74 years showed the highest vaccination coverage, with a 95.1% rate of complete vaccination, and the rate of booster vaccinations (third and fourth doses) was also the highest among this age group at 89.3% (Table 1).

Table 2 shows the median daily differences (interquartile range [IQR]) in the rate of severe COVID-19 cases and COVID-19-related deaths per 1,000,000 population in each age group between those who had not been vaccinated and those who were vaccinated through the national vaccination campaign. During the study period, the median daily differences in rate between the unvaccinated group and the vaccinated group were 0.99 severe cases per 1,000,000 population (IQR, 0.30–4.47) and 0.68 deaths per 1,000,000 population (IQR, 0.06–3.73). Although the dominant variant and age group differences were diverse as Republic of Korea recorded the highest number of cases around the BA.1
Table 1. Number and percentage of people in Republic of Korea by sex, age (≥12 years), and vaccination status (February 26, 2021 to October 15, 2022)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
<th>1st dose</th>
<th>2nd dose</th>
<th>3rd dose</th>
<th>4th dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46,864,039</td>
<td>3,348,786 (7.1)</td>
<td>418,992 (0.9)</td>
<td>10,705,357 (22.8)</td>
<td>25,108,518 (53.6)</td>
<td>7,282,386 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23,328,521</td>
<td>1,607,487 (6.9)</td>
<td>200,210 (0.9)</td>
<td>5,460,570 (23.4)</td>
<td>12,525,019 (53.7)</td>
<td>3,535,235 (15.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23,535,518</td>
<td>1,741,299 (7.4)</td>
<td>218,782 (0.9)</td>
<td>5,244,787 (22.3)</td>
<td>12,583,499 (53.5)</td>
<td>3,748,855 (15.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–17</td>
<td>2,764,194</td>
<td>479,613 (17.4)</td>
<td>68,481 (2.5)</td>
<td>1,738,158 (62.9)</td>
<td>477,634 (17.3)</td>
<td>308 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>7,645,787</td>
<td>463,745 (6.1)</td>
<td>72,571 (0.9)</td>
<td>2,698,109 (35.3)</td>
<td>4,388,855 (57.4)</td>
<td>22,507 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>6,762,180</td>
<td>690,817 (10.2)</td>
<td>86,144 (1.3)</td>
<td>2,248,924 (33.3)</td>
<td>3,704,601 (54.8)</td>
<td>31,694 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>8,164,150</td>
<td>610,468 (7.5)</td>
<td>62,293 (0.8)</td>
<td>2,082,978 (25.5)</td>
<td>5,243,537 (64.2)</td>
<td>164,874 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>8,586,091</td>
<td>428,320 (5.0)</td>
<td>44,100 (0.5)</td>
<td>1,191,229 (13.9)</td>
<td>5,557,534 (64.7)</td>
<td>1,364,908 (15.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–74</td>
<td>9,196,464</td>
<td>405,549 (4.4)</td>
<td>46,046 (0.5)</td>
<td>535,463 (5.8)</td>
<td>4,612,996 (50.2)</td>
<td>3,596,410 (39.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>3,745,173</td>
<td>270,617 (2.2)</td>
<td>39,357 (1.1)</td>
<td>210,496 (5.6)</td>
<td>1,123,361 (30.0)</td>
<td>2,101,685 (56.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%).

Vaccination status: doses 1–4, at least 14 days after receipt of doses 1–4; unvaccinated: unvaccinated or < 14 days after receipt of dose 1.

Discussion

In Republic of Korea, a vaccination campaign began with the BNT162b2 vaccine (Pfizer–BioNTech) for healthcare workers and the ChAdOx1 nCoV-19 vaccine (AstraZeneca) for high-risk people (aged ≥65 years), such as residents in long-term care facilities, on February 26, 2021. In June of the same year, vaccinations with the Ad26.COV2.S vaccine (Janssen) and mRNA-1273 vaccine (Moderna) were initiated. Vaccination campaigns then began to distribute vaccines to healthy people (Table S1). Vaccination coverage gradually expanded to the entire population of Republic of Korea, and as of October 15, 2022, 43,096,261 people have been vaccinated through the national vaccination campaign, representing high vaccination coverage (92.0%) among the total population.

COVID-19 vaccination prevents the spread of the SARS-CoV-2 virus; however, it is now aimed at minimizing the disease burden not only at the individual level but also at the national level by preventing severe COVID-19 outcomes. Since it is impossible to directly measure and observe the impact of the COVID-19 vaccination campaign without actual data, though, a mathematical model is needed to quantify the impact of vaccination.

Since the initial outbreak of COVID-19 in 2019, SARS-CoV-2 variants such as the Alpha, Beta, and Delta variants have continued to appear, and the Omicron variant, classified as the fifth variant of concern, has been reported in more than 200 countries worldwide [15]. New SARS-CoV-2 variants can increasingly evade the immune system, which reduces the effectiveness of vaccines in preventing infections [16,17]; however, the effectiveness of vaccination in preventing severe COVID-19 cases and death has been...
### Table 2. Daily differences in the rate of COVID-19 outcomes between unvaccinated and fully vaccinated groups by the dominant variant and age group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age group (y)</th>
<th>Pre-Delta</th>
<th>Delta</th>
<th>BA.1</th>
<th>BA.2</th>
<th>BA.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe cases</td>
<td>Feb. 26, 2021–Oct. 15, 2022</td>
<td>0.99 (0.30–4.47)</td>
<td>2.07 (1.15–3.72)</td>
<td>0.24 (0.00–5.32)</td>
<td>0.16 (0.00–2.07)</td>
<td>0.00 (0.00–0.00)</td>
</tr>
<tr>
<td>Deaths</td>
<td>Feb. 26, 2021–Oct. 15, 2022</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.00 (0.00–0.00)</td>
</tr>
</tbody>
</table>

#### Notes:
- Severe disease: infected person treated with high-flow oxygen therapy, mechanical ventilation, extracorporeal membrane oxygenation, or continuous renal replacement therapy within 28 days of confirmed COVID-19 infection.
- Deaths: infected person who died within 28 days of laboratory confirmation of COVID-19.

#### Analysis:

In a study conducted in Israel, the differences in the daily median incidence by vaccination status were 2.0 severe cases per 100,000 population and 0.5 deaths per 100,000 population, which were much higher than those in this study, which showed estimated differences of 0.99 severe cases per 1,000,000 population and 0.68 deaths per 1,000,000 population. By investigating the ratios of observed instances of severe cases and deaths to prevent further such cases in both countries, the differences could be ascribed to lower incidences rather than to a declining positive impact on immunity and differences in incidence between vaccinated and unvaccinated groups [9]. In Japan, the differences in the daily median incidence by vaccination status were lower than ours. In this study, there were 9.99 deaths per 1,000,000 population among those aged 75 years or older. There were 1.54 cases per 1,000,000 population in Japan among men aged 65 years or older, while the rate was only 1 case per 1,000,000 among women [10].

We estimated that 119,579 (95% CI, 118,901–120,257) COVID-19-related severe cases and 137,636 (95% CI, 136,909–138,363) COVID-19-related deaths would have occurred if vaccination had not been performed for the 597 days from February 26, 2021 to October 15, 2022. We also found that vaccination prevented 95,786 (95% CI, 94,659–96,913) severe cases and 112,195 (95% CI, 110,870–113,520) deaths due to COVID-19, representing reductions in risk of 80.1% (95,786/119,579) and 81.5% (112,195/137,636), respectively. This also indicates that if the nationwide COVID-19 vaccination campaign had not been implemented in Republic of Korea, the number of severe cases and deaths during the same period would have been at least 4 times higher.

When compared to other studies, our study estimated that vaccination averted more COVID-19-related deaths than severe COVID-19 cases, but most other studies estimated that more severe cases or hospitalizations were prevented than deaths [9–11]. This discrepancy is likely due to the limitations of the data sources. First, as the number of confirmed COVID-19 infections increased rapidly, it...
is assumed that there was a difference in the number of deaths in the early stages after infection without passing through the severe stage. Second, the surveillance system for severe cases collects clinical information reported by medical institutions and public health centers; therefore, after the number of confirmed COVID-19 cases increased sharply, underestimation is possible since clinical information about those infected with severe cases was not reported promptly. SARS-CoV-2 can cause infection regardless of age, but symptoms that worsen with age can increase the risk of a severe case and death, especially among the elderly [20,21]. In this study, 80.3% of all severe cases and 94.0% of deaths during the analysis period occurred in infected people older than 60 years of age. The study population aged 60 years and older accounted for only 27.6% of the total population but 83.5% of the total number of averted severe cases and 93.0% of the total averted deaths. Therefore, we believe that the strategy of the Korean COVID-19 vaccination campaign, which prioritized vaccination for high-risk populations such as those aged 60 years or older, had an impact on preventing serious infection and death. Similar findings were reported in Israel and Japan, where the vaccination campaign began early.
Table 3. Cumulative expected and observed COVID-19 outcomes averted by the vaccination campaign (February 26, 2021 to October 15, 2022)

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Population size</th>
<th>Vaccination coverage (≥2 doses, %)</th>
<th>Expected no. of severe cases</th>
<th>Observed severe cases</th>
<th>Averted severe cases</th>
<th>Expected no. of deaths</th>
<th>Observed deaths</th>
<th>Averted deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>46,864,039</td>
<td>92.0</td>
<td>119,579 (118,901–120,257)</td>
<td>23,793</td>
<td>95,786 (94,659–96,913)</td>
<td>137,636 (136,909–138,363)</td>
<td>25,441</td>
</tr>
<tr>
<td>12–17</td>
<td>2,764,194</td>
<td>80.2</td>
<td>193 (166–220)</td>
<td>63</td>
<td>130 (121–139)</td>
<td>95,786 (94,659–96,913)</td>
<td>23,793</td>
<td>112,195 (110,870–113,520)</td>
</tr>
<tr>
<td>18–29</td>
<td>7,645,787</td>
<td>93.0</td>
<td>1,137 (1,071–1,203)</td>
<td>282</td>
<td>856 (822–888)</td>
<td>137,636 (136,909–138,363)</td>
<td>23,793</td>
<td>112,195 (110,870–113,520)</td>
</tr>
<tr>
<td>30–39</td>
<td>6,752,180</td>
<td>88.5</td>
<td>2,016 (1,927–2,103)</td>
<td>662</td>
<td>1,353 (1,303–1,403)</td>
<td>137,636 (136,909–138,363)</td>
<td>23,793</td>
<td>112,195 (110,870–113,520)</td>
</tr>
<tr>
<td>40–49</td>
<td>8,164,150</td>
<td>91.8</td>
<td>4,340 (4,211–4,469)</td>
<td>1,217</td>
<td>3,123 (3,052–3,194)</td>
<td>137,636 (136,909–138,363)</td>
<td>23,793</td>
<td>112,195 (110,870–113,520)</td>
</tr>
<tr>
<td>50–59</td>
<td>5,886,091</td>
<td>94.5</td>
<td>12,775 (12,553–12,997)</td>
<td>2,453</td>
<td>10,322 (10,204–10,440)</td>
<td>137,636 (136,909–138,363)</td>
<td>23,793</td>
<td>112,195 (110,870–113,520)</td>
</tr>
</tbody>
</table>

Data are presented as no. of cases (95% confidence interval).

a) Severe disease: infected person treated with high-flow oxygen therapy, mechanical ventilation, extracorporeal membrane oxygenation, or continuous renal replacement therapy within 28 days of laboratory confirmation of COVID-19.

b) Death: infected person who died within 28 days of laboratory confirmation of COVID-19.

There are some limitations to our study. First, there is a possibility of unmeasured differences from nonpharmaceutical interventions, including wearing face masks, practicing handwashing hygiene, avoiding large gatherings, and maintaining physical distance as well as from the characteristics of different variants in each period. These factors may have influenced the results of the study. Second, when analyzing the impact of COVID-19 vaccination, differences in the risk of infection between the vaccinated and unvaccinated groups may not be solely attributable to the vaccine but also to differences in health status. This increased the possibility of overestimating the impact of the vaccination. Unfortunately, due to data limitations, we were unable to include some factors in our analysis, including socioeconomic status and health status, such as underlying diseases, which could be potential confounders. Data related to these factors were limited and could not be added as additional factors. Therefore, in future studies, more detailed data with a wider range of items such as underlying diseases or comorbidities should be used.

Despite these limitations, this study’s results provide a comprehensive evaluation of the COVID-19 vaccination campaign, showing the substantial impact of vaccinations on the entire population for over 500 days in preventing severe cases and deaths due to COVID-19. Therefore, vaccination was critical for preventing severe cases and deaths, especially among the elderly population, who have a high disease burden.

In Israel, those aged 65 years and older accounted for only 17% of the total population but 74% of severe cases and 91% of deaths. Hence, this age group is an important target population for preventing severe disease and death.

There are some limitations to our study. First, there is a possibility of unmeasured differences from nonpharmaceutical interventions, including wearing face masks, practicing handwashing hygiene, avoiding large gatherings, and maintaining physical distance as well as from the characteristics of different variants in each period. These factors may have influenced the results of the study. Second, when analyzing the impact of COVID-19 vaccination, differences in the risk of infection between the vaccinated and unvaccinated groups may not be solely attributable to the vaccine but also to differences in health status. This increased the possibility of overestimating the impact of the vaccination. Unfortunately, due to data limitations, we were unable to include some factors in our analysis, including socioeconomic status and health status, such as underlying diseases, which could be potential confounders. Data related to these factors were limited and could not be added as additional factors. Therefore, in future studies, more detailed data with a wider range of items such as underlying diseases or comorbidities should be used.

Despite these limitations, this study’s results provide a comprehensive evaluation of the COVID-19 vaccination campaign, showing the substantial impact of vaccinations on the entire population for over 500 days in preventing severe cases and deaths due to COVID-19. Therefore, vaccination was critical for preventing severe cases and deaths, especially among the elderly population, who have a high disease burden.
Estimating averted COVID-19 severe cases, deaths by vaccination campaign

Notes

Ethics Approval
This study was conducted in accordance with the Infectious Disease Prevention and Control Act (no. 12444 and no. 13392) and was approved by the Institutional Bioethics Committee of the KDCA (No. 2021-12-03-FE-A).

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: JHH, SEL, SL, YJP; Data curation: JHH, JHL, SKP, RKK; Formal analysis: JHH, JHL, SKP, EJJ; Investigation: JHH, JHL, Methodology: JHH, JHL, SKP, KHL, CC; Software: JHH, RKK; Validation: EJJ, RKK; Visualization: JHH, JHL; Writing–original draft: JHH, SEL, SL, YJP; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Acknowledgements
We thank the COVID-19 Vaccination Task Force and Division of National Immunization, Korea Disease Control and Prevention, and all relevant ministries (including the Ministry of Interior and Safety and those at the si/do and si/gun/gu levels), medical staff at health centers, and medical facilities for their efforts to respond to the COVID-19 outbreak. This study was part of the Korea COVID-19 Vaccine Effectiveness (K-COVE) Initiative.

References


https://doi.org/10.24171/j.phrp.2023.0096
Introduction

Variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represent a potential risk to global public health. As such, the World Health Organization is diligently
tracking changes in these variants to classify them as either variants of interest (VOIs) or variants of concern (VOCs), underscoring the importance of genotype monitoring. By September 22, 2022, the SARS-CoV-2 Omicron variant B.1.1.529 had emerged as the dominant variant globally, making up over 98% of the viral sequences currently shared through the Global Initiative on Sharing All Influenza Data (GISAID) [1]. In the European Union, Omicron sub-lineages BA.2, BA.4, and BA.5 have been designated as VOCs due to their transmissibility and severity. However, the Omicron sub-lineage BA.2.75 is categorized and managed as a VOI due to inconclusive epidemiological and laboratory evidence [2]. A study of global occurrence trends for these major variants revealed 5,974 cases of BA.2.75 (prevalence, ≤ 0.5%) in 47 countries, 45,536 cases of BA.4 in 100 countries (prevalence, ≤ 0.5%), and 771,047 cases of BA.5 in 132 countries (prevalence, 6%) as of September 20, 2022 [3].

In late March 2022, South Korean disease control authorities implemented the coronavirus disease 2019 (COVID-19) Novel Variant Impact Assessment System to prepare for the domestic outbreak of newly emerging COVID-19 variants and to establish prompt responses to novel variants. Since the first report of the Omicron recombinant variant in Republic of Korea on April 12, 2022, major variant cases have been investigated, and risk assessments have been carried out [4,5]. These epidemiological investigations encompassed cases of variants identified by genome analysis, epidemiologically-linked cases, and contact tracing. If a variant is deemed dangerous based on the results of the epidemiological investigation and response, it is recommended to heighten the control standards [5].

The goal of this study was to compare and evaluate the epidemiological and clinical characteristics, as well as the household secondary attack risk, of confirmed BA.5, BA.4, and BA.2.75 cases, each of which was investigated individually. Moreover, we aimed to utilize these findings as foundational data for shaping and implementing future response policies to variant outbreaks.

Materials and Methods

Subjects
The subjects of this study were confirmed cases of BA.4 and BA.5 variants reported from May 15, 2022, when these variants were first identified in Republic of Korea, through June 30, 2022. The study also included confirmed cases of the BA.2.75 variant reported from July 13, 2022, the date when this variant was first discovered in Republic of Korea, through to September 13, 2022.

Definitions of Variables

Confirmed cases
A confirmed case of a COVID-19 Omicron sub-lineage was used to refer to an individual whose infection with a specific Omicron variant was confirmed through genomic analysis. Domestic and imported cases selected via random sampling were analyzed. The random sampling targeted respiratory patients, high-risk patients, and patients confirmed to have been infected overseas. Random sample targets were selected based on their likelihood of being a COVID-19 Omicron sub-lineage case, with the aim of identifying clinical and epidemiological characteristics.

Epidemiologically-linked cases
An epidemiologically-linked case was defined as a confirmed case that had contact with another confirmed case within a 2-week period before or after the onset of symptoms in the confirmed case. In essence, it refers to an individual who was confirmed to be infected through testing co-workers and family members who had contact during the transmissible period. However, cases involving other variants, identified through genomic analysis, were excluded.

Contacts
The term “contact” was used to refer to an unconfirmed individual who had contact with a confirmed case or an epidemiologically-linked case within a 2-week period before or after the onset of symptoms.

Household secondary attack risk
The household secondary attack risk was defined as the proportion of confirmed cases among household members who had contact with a confirmed (or primary) case, who had
more than 1 household member, after they returned from overseas. This does not include household members who traveled overseas alongside the confirmed (or primary) cases. We calculated the exact binomial 95% confidence intervals and used the chi-square test to determine odds ratios.

Contact Tracing Methods
Investigations were carried out among household contacts who were registered in the COVID-19 information management system. These contacts were either self-reported by confirmed cases or reported through individual case investigations by local authorities. Polymerase chain reaction (PCR) testing for these household contacts was performed 3 times (on day 1, day 3, and day 9) within a 10-day period from the date of last exposure to enhance infection detection. However, for those individuals where 10 days had already passed since the last exposure, PCR testing was performed just once. Furthermore, no PCR testing was conducted for those individuals where 15 or more days had passed since the last exposure. Confirmed cases among household contacts were classified as epidemiologically-linked cases, and a genome analysis was conducted on available samples to ascertain the correlation with the respective confirmed cases. Confirmed cases in which another variant was identified were excluded from this study.

Ethics Approval
This study was granted an exemption from review by the Institutional Review Board (IRB) of the Korea Disease Control and Prevention Agency (IRB No: 2021-12-05-PE-A).

Results
General Demographic Characteristics
The monitoring results for the Omicron sub-lineages BA.4, BA.5, and BA.2.75 revealed that from May 15, 2022, to June 30, 2022, a span of 46 days since the initial confirmation of next-generation sequencing (NGS) analysis results, 97 confirmed cases of BA.4 and 396 confirmed cases of BA.5 were identified. Moreover, 152 confirmed cases of BA.2.75 were detected from July 13, 2022, to September 13, 2022, a period of 62 days since the initial NGS-based confirmation. When comparing the total number of confirmed cases and the occurrence status of confirmed cases by each Omicron sub-lineage during the monitoring period, it was observed that the total number of confirmed cases was decreasing, yet the counts of confirmed BA.4 and BA.5 cases were on the rise. Conversely, throughout the BA.2.75 monitoring period, the total number of confirmed cases consistently increased, though the incidence of BA.2.75 was lower compared to the other sub-lineages (Figure 1).

The epidemiological and clinical characteristics of confirmed cases for the Omicron sub-lineages BA.4, BA.5, and BA.2.75 were as follows: Men had a higher incidence than women across all 3 sub-lineages. The age group of 20 to 40 years constituted the majority of cases, metropolitan areas reported a higher incidence, very few cases had a history of prior infection, and most cases were mild. There were notable differences in the proportion of symptomatic cases and the route of infection. Most BA.4 and BA.2.75 cases were asymptomatic, and the majority of these cases were contracted overseas. For BA.5, most cases reported symptoms, and the majority were infected domestically (Table 1).

The secondary attack risk among household contacts of confirmed Omicron sub-lineages (BA.4, BA.5, BA.2.75) was as follows: There were 33 BA.4 cases with household members, of which 3 were excluded due to having co-primary cases from overseas. This is why Table 2 shows 30 BA.4 primary cases. There were 193 BA.5 cases with household members, with 23 excluded because they had co-primary cases from overseas, resulting in 170 BA.5 primary cases in Table 2. Additionally, there were 72 BA.2.75 cases with household members, and 34 were excluded due to co-primary cases from overseas, leaving 38 BA.2.75 primary cases in Table 2. No statistically significant difference was found between the secondary attack risk of BA.2.75 and those of BA.4 and BA.5 (Table 2). In an analysis according to vaccination status, the secondary attack risk generally decreased with increasing vaccination of household contacts for BA.2.75 and BA.5 but not for BA.4 (Table 3).

Discussion
The epidemiological and clinical characteristics of BA.4, BA.5, and BA.2.75, which are the major VOCs among the Omicron variant sub-lineages, are described below.

In total, 79 cases of Omicron sub-lineage BA.4 and 396 cases of Omicron sub-lineage BA.5 were detected over a span of 46 days, while 152 cases of Omicron sub-lineage BA.2.75 were identified during a period of 62 days. Only 1 severe case was identified among BA.5 confirmed patients, while no severe cases were reported among the BA.4 and BA.2.75 patients. The secondary attack risk among household contacts was 19.6% for BA.4, 27.8% for BA.5, and 24.3% for BA.2.75. Compared to BA.4 and BA.5, BA.2.75 showed no increased tendency for transmissibility, disease severity, or secondary attack risk in household or between household contacts. There were no statistically significant differences among the Omicron sub-lineages.
The number of confirmed cases of the 3 Omicron variant sub-lineages was higher in men than in women, predominantly affecting individuals in their 20s to 40s. These findings align with a United Kingdom (UK) study, which reported that most confirmed BA.2.75 cases affected patients aged 20 to 39 years, with a median age of 30 years [6]. This could be attributed to young people’s active participation in activities such as overseas travel and business trips, potentially exposing them to SARS-CoV-2.

The occurrence of Omicron variant sub-lineages during the monitoring period identified 152 cases (detection rate as of September 10, 1.3%) of BA.2.75 over 62 days (July 13 to September 3), and 396 cases (detection rate as of July 2, 28.2%) of BA.5 over 46 days (May 15 to June 30) [7,8]. The BA.2.75 sub-lineage showed a slower rate of occurrence compared to the BA.5 sub-lineage, consistent with results from a UK study [2]. The term “occupancy rate” refers to the number of detected mutations over the same period. The BA.5 sub-lineage, due to its faster occupancy rate, spread rapidly in Republic of Korea following its introduction into the country, resulting in a higher percentage of domestic BA.5 cases compared to imported ones. Conversely, due to its slower occupancy rate, the percentage of imported BA.2.75 cases was higher than that of domestic cases.

Among the confirmed BA.5 cases, only 1 patient was identified as critically ill, with no critically ill patients or deaths reported among the confirmed BA.4 and BA.2.75 cases. These results support previous findings indicating the severity of the Omicron variant sub-lineages BA.2.75, BA.4, and BA.5 is not as high as that of the existing Omicron variants [9].

The secondary household attack risk for the Omicron sub-lineages BA.2.75, BA.4, and BA.5 were 24.3%, 19.6%, and 27.8%, respectively. Although the BA.5 sub-lineage, which is known for its high transmissibility, displayed the highest secondary attack risk, there was no statistically significant difference among the sub-lineages. Comparatively, a meta-analysis of 135 overseas studies reported a secondary attack risk of 42.7% among household contacts of confirmed Omicron variant cases. On the other hand, a previous study during the initial outbreak of the Omicron variant in Republic of Korea reported a rate of 65.0% [10,11]. The discrepancies between these study results can be attributed to various factors such as sample size, age, underlying diseases, and vaccination status of the study participants. This study also differed by excluding household contacts confirmed to have COVID-19 after entering the country with the primary cases, and only included household contacts infected via domestic transmission.

Additionally, the secondary attack rate might be overestimated because it is calculated based on the single-
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BA.4 (May 15–Jun 30, for 46 d)</th>
<th>BA.5 (May 15–Jun 30, for 46 d)</th>
<th>BA.2.75 (Jul 13–Sep 13, for 62 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>79 (100.0)</td>
<td>396 (100.0)</td>
<td>152 (100.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (60.8)</td>
<td>207 (52.3)</td>
<td>96 (63.2)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (39.2)</td>
<td>189 (47.7)</td>
<td>56 (36.8)</td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>7 (8.9)</td>
<td>45 (11.4)</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td>20–39</td>
<td>38 (48.1)</td>
<td>170 (42.9)</td>
<td>77 (50.7)</td>
</tr>
<tr>
<td>40–59</td>
<td>25 (31.6)</td>
<td>117 (29.5)</td>
<td>47 (30.9)</td>
</tr>
<tr>
<td>60–74</td>
<td>6 (7.6)</td>
<td>56 (14.1)</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>≥75</td>
<td>3 (3.8)</td>
<td>8 (2.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>51 (64.6)</td>
<td>258 (65.2)</td>
<td>77 (50.7)</td>
</tr>
<tr>
<td>Non-metropolitan</td>
<td>28 (35.4)</td>
<td>138 (34.8)</td>
<td>75 (49.3)</td>
</tr>
<tr>
<td>Infection route</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From abroad</td>
<td>54 (68.4)</td>
<td>173 (43.7)</td>
<td>122 (80.3)</td>
</tr>
<tr>
<td>Domestic</td>
<td>25 (31.6)</td>
<td>223 (56.3)</td>
<td>30 (19.7)</td>
</tr>
<tr>
<td>History of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>5 (1.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>No</td>
<td>79 (100.0)</td>
<td>391 (98.7)</td>
<td>151 (99.3)</td>
</tr>
<tr>
<td>Vaccination status(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated &amp; 1st</td>
<td>10 (12.7)</td>
<td>43 (10.9)</td>
<td>27 (17.8)</td>
</tr>
<tr>
<td>2nd</td>
<td>6 (7.6)</td>
<td>61 (15.4)</td>
<td>22 (14.5)</td>
</tr>
<tr>
<td>3rd</td>
<td>61 (77.2)</td>
<td>269 (67.9)</td>
<td>74 (48.7)</td>
</tr>
<tr>
<td>4th</td>
<td>0 (0)</td>
<td>20 (5.1)</td>
<td>12 (7.9)</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (39.2)</td>
<td>214 (54.0)</td>
<td>49 (32.2)</td>
</tr>
<tr>
<td>No</td>
<td>48 (60.8)</td>
<td>182 (46.0)</td>
<td>103 (67.8)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mild</td>
<td>79 (100.0)</td>
<td>395 (99.7)</td>
<td>152 (100.0)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

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

\(^a\)Except for 22 cases for which it was not possible to check the vaccination history (foreigners coming from abroad).

Table 2. SARS-CoV-2 infection attack risk among the household contacts of SARS-CoV-2 Omicron variant sub-lineages

<table>
<thead>
<tr>
<th>Omicron variant</th>
<th>Index</th>
<th>Contacts</th>
<th>Confirmed</th>
<th>SAR (95% CI)</th>
<th>BA.2.75 vs. BA.4(^a)</th>
<th>BA.2.75 vs. BA.5(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA.2.75</td>
<td>38</td>
<td>74</td>
<td>18</td>
<td>24.3 (0.15−0.36)</td>
<td>1.3 (0.6−3.2)</td>
<td>0.8 (0.5−1.5)</td>
</tr>
<tr>
<td>BA.4</td>
<td>30</td>
<td>51</td>
<td>10</td>
<td>19.6 (0.10−0.33)</td>
<td>Ref.</td>
<td>NA</td>
</tr>
<tr>
<td>BA.5</td>
<td>170</td>
<td>288</td>
<td>80</td>
<td>27.8 (0.23−0.33)</td>
<td>NA</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAR, secondary attack risk; CI, confidence interval; ref., reference; NA, not available.

\(^a\)Crude odds ratio (95% CI).

exposure assumption. In other words, estimates tend to inflate the secondary attack rate by assuming that all household contacts are infected by the primary case [12].

The investigation into the household secondary attack risk based on vaccination status revealed no significant difference in the secondary attack risk among household contacts, regardless of the index cases’ vaccination status. However, an observed trend indicated a decrease in the secondary attack rate with an increase in vaccinations among household members of confirmed BA.5 and BA.2.75 cases. This result diverges from a previous study where the secondary attack risk among household contacts of unvaccinated index patients was higher than that with vaccinated index patients. The discrepancy between the 2 studies could have occurred because the previous study did not compare the household secondary attack risk based on the vaccination status of the household contacts, and the incidence rate may have been higher in index cases where
Table 3. SARS-CoV-2 infection attack risk among the household contacts of SARS-CoV-2 Omicron variant sub-lineages by vaccination status

<table>
<thead>
<tr>
<th>Omicron variant</th>
<th>Vaccination status</th>
<th>Household contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Unvaccinated and 1st</td>
</tr>
<tr>
<td>BA.2.75 index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28.6 (17.8−41.4), 18/63</td>
<td>44.4 (21.5−69.2), 8/18</td>
</tr>
<tr>
<td>Unvaccinated and 1st</td>
<td>26.7 (7.8−55.1), 4/15</td>
<td>25.0 (5.4−57.2), 3/12</td>
</tr>
<tr>
<td>2nd</td>
<td>50.0 (6.7−93.2), 2/4</td>
<td>100.0 (1/1)</td>
</tr>
<tr>
<td>3rd and 4th</td>
<td>27.3 (14.9−42.7), 12/44</td>
<td>80.0 (28.3−99.4), 4/5</td>
</tr>
<tr>
<td>BA.4 index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21.3 (10.7−35.6), 10/47</td>
<td>16.7 (0.4−64.1), 1/6</td>
</tr>
<tr>
<td>Unvaccinated and 1st</td>
<td>25.0 (3.1−65.0), 2/8</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>2nd</td>
<td>100.0 (1/1)</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>3rd and 4th</td>
<td>18.4 (7.7−34.3), 7/38</td>
<td>25.0 (0.6−80.5), 1/4</td>
</tr>
<tr>
<td>BA.5 index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29.5 (24.1−35.3), 80/271</td>
<td>41.3 (27.0−56.7), 19/46</td>
</tr>
<tr>
<td>Unvaccinated and 1st</td>
<td>32.4 (17.4−50.5), 11/34</td>
<td>50.0 (15.7−84.3), 4/8</td>
</tr>
<tr>
<td>2nd</td>
<td>23.3 (12.9−36.4), 13/56</td>
<td>33.3 (9.9−65.1), 4/12</td>
</tr>
<tr>
<td>3rd and 4th</td>
<td>30.9 (24.3−38.2), 56/181</td>
<td>42.3 (23.3−63.1), 11/26</td>
</tr>
</tbody>
</table>

Data are presented as proportion (95% CI), number/total number.

More than 5 months had elapsed since vaccination than in unvaccinated index patients [13].

This study has certain limitations. Firstly, the monitoring period was short, resulting in a relatively small number of participants. Secondly, factors such as age, time elapsed since vaccination, and history of infections were not considered. Thirdly, foreign entrants were excluded from the study as it was not possible to ascertain their vaccination status. Lastly, when there was a possibility of simultaneous exposure abroad, household contacts were excluded from the analysis, potentially excluding some secondary cases.

Despite these limitations, the significance of this study lies in its identification of both the epidemiological and clinical characteristics of the less well-known Omicron sub-lineage BA.2.75, and the secondary attack risk among household contacts. Furthermore, this study demonstrated that the Omicron sub-lineage BA.2.75 did not have a higher rate of transmission than the existing BA.4 and BA.5 sub-lineages. Notably, our findings are significant as they represent the first comparative analysis of VOCs in Republic of Korea. The results of this study can guide disease control authorities to continue monitoring major SARS-CoV-2 variants in Republic of Korea, thereby continually refining and developing the disease prevention and response system.

Notes

Ethics Approval
This study was exempted from review by the IRB of the Korea Disease Control and Prevention Agency (IRB No: 2021-12-05-PE-A).

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

Funding
None.

Availability of Data
All data generated or analyzed during this study are included in this published article. For other data, if you have additional questions about the study, please contact the corresponding author (pahmun@korea.kr).

Authors’ Contributions
Formal analysis: MY, HYL, HJK; Software: SEL, YJS; Validation: JJ; Investigation: AKP, IHK; Supervision: YJP, EJK; Writing–original draft: MY; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Acknowledgements
We would like to express our sincere appreciation to the epidemiological investigators at the regional response centers and those in charge of infectious diseases in local governments for their work and efforts in collecting data and on-site responding at front-line quarantine sites for this study.

References
3. outbreak.info. BA.2.75 lineage report [Internet]. outbreak.info; 2022 [cited 2023 Sep 20]. Available from: https://outbreak.info/situation-
The COVID-19 pandemic and healthcare utilization in Iran: evidence from an interrupted time series analysis

Monireh Mahmoodpour-Azari1, Satar Rezaei1, Nasim Badiee23, Mohammad Hajizadeh4, Ali Mohammadi3, Ali Kazemi-Karyani1, Shahin Soltani1, Mehdi Khezeli6

1Research Center for Environmental Determinants of Health, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran
2Institute for Studies in Medicine History, Persian and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran
3Department of Traditional Medicine, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran
4School of Health Administration, Faculty of Health, Dalhousie University, Halifax, NS, Canada
5Department of Health Information Technology, Paramedical School, Kermanshah University of Medical Sciences, Kermanshah, Iran
6Social Development and Health Promotion Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

ABSTRACT

Objectives: This study aimed to examine the effect of the coronavirus disease 2019 (COVID-19) outbreak on the hospitalization rate, emergency department (ED) visits, and outpatient clinic visits in western Iran.

Methods: We collected data on the monthly hospitalization rate, rate of patients referred to the ED, and rate of patients referred to outpatient clinics for a period of 40 months (23 months before and 17 months after the COVID-19 outbreak in Iran) from all 7 public hospitals in the city of Kermanshah. An interrupted time series analysis was conducted to examine the impact of COVID-19 on the outcome variables in this study.

Results: A statistically significant decrease of 38.11 hospitalizations per 10,000 population (95% confidence interval [CI], 24.93–51.29) was observed in the first month of the COVID-19 outbreak. The corresponding reductions in ED visits and outpatient visits per 10,000 population were 191.65 (95% CI, 166.63–216.66) and 168.57 (95% CI, 126.41–210.73), respectively. After the initial reduction, significant monthly increases in the hospitalization rate (an increase of 1.81 per 10,000 population), ED visits (an increase of 2.16 per 10,000 population), and outpatient clinic visits (an increase of 5.77 per 10,000 population) were observed during the COVID-19 pandemic.

Conclusion: Our study showed that the utilization of outpatient and inpatient services in hospitals and clinics significantly declined after the COVID-19 outbreak, and use of these services did not return to pre-outbreak levels as of June 2021.

Keywords: COVID-19; Hospital outpatient clinic; Iran; Patient care
Introduction

The emergence and spread of coronavirus disease 2019 (COVID-19) has challenged and disrupted the functioning of healthcare systems worldwide. Countries have been forced to take swift action to counter the rapid spread of the virus while maintaining the integrity of their health systems [1]. Hospitals have been forced to re-evaluate care and treatment priorities due to the referral and management of new patients infected with COVID-19 in response to the community’s ongoing needs and medical care. During this period, major changes in the provision of non-emergency and elective care in hospitals, outpatient wards, clinics, and surgical centers have also occurred [2]. In particular, strict measures have been taken to control the pandemic worldwide, and healthcare systems have been reorganized to manage the sudden increase in the number of patients infected with the virus [3].

The outbreak of COVID-19 in Iran began on February 19, 2020, following the official announcement of the first 2 cases of COVID-19 in the city of Qom. The virus quickly spread to all provinces of Iran [4]. The spread of COVID-19 and the presence of new coronavirus variants led to high utilization of hospital care, particularly among those with underlying diseases [5]. The most important measures taken by the Iranian government to prevent the spread of COVID-19 were an emphasis on physical distancing, quarantine policies, the control and restriction of travel, restrictions on gatherings, and an increase in the number of hospital beds to isolate COVID-19 patients [6]. As the pandemic continued, several studies reported reduced utilization of healthcare services for reasons that included fear of becoming infected at healthcare facilities, reduced access to healthcare centers due to quarantine or reductions in elective surgery, and the need to separate patients seeking urgent and necessary care from other patients [7]. For example, a study in France reported 68% and 45% reductions in pediatric emergency department (ED) referrals and hospital admissions, respectively [8]. A study in Italy showed a 48.8% reduction in referrals of patients with acute myocardial infarction [9]. A 42% reduction in ED visits was reported in the United States [10]. This unprecedented reduction in healthcare utilization resulting from the COVID-19 pandemic provided an opportunity to identify the most low-value services in healthcare systems and redistribute resources to more essential services to minimize mortality in a crisis [7,11].

Data analysis using an interrupted time series model makes it possible to examine the effect of the COVID-19 pandemic on the pattern of hospitalizations and outpatient visits. The aim of this study was to investigate the effect of the COVID-19 pandemic on outpatient referrals and hospitalizations in hospitals affiliated with the Ministry of Health and Medical Education (MoHME) in the city of Kermanshah. Our study provides valuable insight into the impact of COVID-19 on healthcare utilization in Iran and can be helpful for other developing countries with similar healthcare situations to mitigate the long-term and short-term impacts of the pandemic.

Materials and Methods

Study Setting

This study was conducted in the city of Kermanshah, the capital of Kermanshah Province in the western region of Iran. The total populations of the city of Kermanshah and Kermanshah Province in 2015 were estimated at 1 and 2 million, respectively. The city of Kermanshah contains 7 MoHME-affiliated hospitals that are responsible for providing most healthcare services in the city.

Data Source

The first 2 confirmed cases of COVID-19 in Iran were reported on February 19, 2020. We collected data on the monthly hospitalization rate, rate of patients referred to the ED, and rate of patients referred to outpatient clinics for a period of 40 months (23 months before and 17 months after the COVID-19 outbreak in Iran) from the health information systems of all 7 hospitals. Population data were also extracted from the Statistics Center of Iran.

HIGHLIGHTS

- The study identified 22.6%, 43.1%, and 39.2% reductions in the hospitalization rate, emergency department (ED) visits, and outpatient clinic visits, respectively, following the start of the coronavirus disease 2019 (COVID-19) pandemic.
- A statistically significant decrease of 3811 hospitalizations per 10,000 population was observed in the first month of the COVID-19 outbreak.
- A statistically significant decrease of 191.65 ED visits per 10,000 population was observed in the first month of the COVID-19 pandemic.
- A statistically significant decrease of 168.57 outpatient visits per 10,000 population was observed in the first month of the COVID-19 outbreak.
Statistical Analysis

We conducted an interrupted time series analysis with segmented regression [12,13] to assess the impact of the COVID-19 outbreak on the monthly hospitalization rate per 10,000 population, number of patients referred to an ED per 10,000 population, and number of patients referred to an outpatient clinic per 10,000 population at 7 MoHME-affiliated hospitals in the city of Kermanshah. The interrupted time series method can be used to estimate the impact (not just association) of an intervention on outcomes when no comparison data are available [13]. This method is especially useful when “natural experiments” occur in the real world. The main advantage of this method is that it can fully exploit the longitudinal aspect of the data. However, this approach is unsuitable when trends are not linear (or cannot be transformed to be linear) or the intervention is implemented on a step-by-step basis or at several time points [14].

The specific segmented regression model that follows was used to estimate the effect of the COVID-19 outbreak on the monthly hospitalization rate, rate of ED visits, and number of patients referred to an outpatient clinic [15].

\[
Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_T T_t + \epsilon_t
\]

where \(Y_t\) denotes the number of admissions (hospitalizations, ED visits, and referrals to an outpatient clinic) in the month \(t\), \(T_t\) is the time trend variable, which ranges in value from 1 (first observation) to 40 (last observation), \(X_t\) is a binary variable that represents before and after the outbreak (\(X_t = 0\) for before and \(X_t = 1\) for after), \(X_T T_t\) is coded as 0 for the period before the COVID-19 outbreak and assigned a value between 1 (first observation after the outbreak) and 17 (last observation after the outbreak) for the period after the COVID-19 outbreak, \(\beta_1\) indicates the starting level (intercept) of the outcome variable, \(\beta_2\) represents the slope of the outcome variable before the outbreak (the pre-existing trend), \(\beta_3\) represents the change in the value for the outcome variable immediately after the outbreak (compared to the counterfactual), and \(\beta_4\) represents the difference between the pre- and post-pandemic slopes of the outcome variable.

An interrupted time series analysis was conducted using linear regression (ordinary least squares) with Newey-West errors. The Newey-West approach was used to handle autocorrelation and possible heteroscedasticity in the error term [13]. The Dickey-Fuller statistic test result suggested stationary residuals (i.e., the time series had no unit root). This indicated a normal residual distribution. The seasonality for each of the dependent variables in this study was checked using the 2-way line command. The output graphs indicated no seasonality patterns in our data (Figure S1). All data analysis was performed using Stata ver. 16.0 (StataCorp LLC).

Ethical Approval

This study was approved by the Deputy of Research, Kermanshah University of Medical Sciences (No. IR.KUMS. REC. 1400.856), and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Results

The descriptive results suggested that, while the average hospitalization rate before the outbreak was 105 hospitalizations per 10,000 population, the corresponding figure for the period after the outbreak was 81 hospitalizations per 10,000 population. The results also indicated 22.6%, 43.1% and 39.2% reductions in hospitalization rate, ED visits, and outpatient clinic visits, respectively, following the COVID-19 outbreak. Table 1 reports pre- and post-COVID-19 averages without any time series modeling for all 3 of the variables used in the study. Table 2 and Figure 1 depict the results of the segmented regression analysis for hospitalization rate. The results indicated an initial estimated hospitalization rate of 105.46 hospitalizations per 10,000 population during the study period. Although the hospitalization rate decreased every month before March 2020, this declining trend was not statistically significant (\(p = 0.941\)). A statistically significant decrease of 38.11 hospitalizations per 10,000 population (95% confidence interval [CI], 24.93–51.29; \(p < 0.001\)) was observed in the first month of the COVID-19 outbreak (March 2020). The monthly trend in the hospitalization rate after the COVID-19 outbreak (relative to the pre-COVID-19 trend)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-COVID-19</th>
<th>Post-COVID-19</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>11,430</td>
<td>8,846</td>
<td>-22.6</td>
</tr>
<tr>
<td>Average no. per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 10,000 population</td>
<td>105</td>
<td>81</td>
<td>-43.1</td>
</tr>
<tr>
<td>ED visit</td>
<td>39,778</td>
<td>22,631</td>
<td>-39.2</td>
</tr>
<tr>
<td>Average no. per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 10,000 population</td>
<td>366</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Clinic visit</td>
<td>28,877</td>
<td>17,542</td>
<td></td>
</tr>
<tr>
<td>Average no. per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 10,000 population</td>
<td>265</td>
<td>161</td>
<td></td>
</tr>
</tbody>
</table>

ED, emergency department.
increased by 1.81 hospitalizations per 10,000 population (95% CI, 0.55–3.06; \(p=0.006\)). We also found that the monthly hospitalization rate after the COVID-19 outbreak increased by 1.79 hospitalizations per 10,000 population (95% CI, 0.68–2.90; \(p=0.002\)).

The results of the segmented regression analysis for ED visits are reported in Table 3 and Figure 2. According to this analysis, the pre-pandemic rate of monthly ED visits was higher by 0.81 visits per 10,000 population. This trend, however, was not statistically significant. A statistically significant decrease of 191.65 ED visits per 10,000 population (95% CI, 166.63–216.66; \(p<0.001\)) was observed in the first month of the COVID-19 pandemic (March 2020). Compared to the pre-COVID-19 trend, the monthly trend in ED visits after the COVID-19 outbreak increased by 2.16 visits per 10,000 population, though the change was statistically insignificant (95% CI, −0.41 to 4.74; \(p=0.097\)). In addition, a statistically significant increase of 2.97 ED visits per 10,000 population (95% CI, 0.78–5.17; \(p=0.009\)) was observed following the COVID-19 outbreak.

Table 4 and Figure 3 present the results of the segmented regression analysis for outpatient clinic visits. The initial rate of outpatient clinic visits was estimated at 255.32 visits per 10,000 population. The rate of outpatient clinic visits increased by 0.89 visits per 10,000 population every month before the COVID-19 pandemic, although this trend was not statistically significant (\(p=0.313\)). A statistically significant decline of 168.57 outpatient clinic visits per 10,000 population (95% CI, 126.41–210.73; \(p<0.001\)) was observed in the first month of the COVID-19 outbreak. The monthly trend in outpatient clinic visits after the COVID-19 outbreak, compared to the pre-COVID-19 trend, increased by 5.77 visits per 10,000 population (95% CI, 0.77–10.78; \(p=0.025\)). After the COVID-19 outbreak, the rate of monthly outpatient clinic visits increased by 6.67 visits per 10,000 population (95% CI, 2.02–11.32; \(p=0.006\)).

**Discussion**

Our study results show that the COVID-19 pandemic caused a significant decrease in the total number of hospitalizations, ED visits, and referrals to outpatient clinics in the city of Kermanshah. The results indicate a sharp and significant decrease in the use of health services included in the study in the first month after the outbreak of COVID-19. The results also identified 22.6%, 43.1%, and 39.2% reductions in the hospitalization rate, ED visits, and outpatient clinic visits, respectively, following the outbreak of COVID-19. Similar reductions in the utilization of hospital services have also been observed in studies conducted in other countries.

A study in China by Xiao et al. [16] showed that health facility visits and the number of inpatients decreased by
Table 3. Estimated coefficients of the segmented regression model for emergency department visits before and after the start of the COVID-19 pandemic in Iran

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE(\textsuperscript{a})</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept, $\beta_0$</td>
<td>356.54</td>
<td>7.63</td>
<td>341.06 to 372.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-COVID-19 slope, $\beta_1$</td>
<td>0.81</td>
<td>0.58</td>
<td>-0.37 to 1.99</td>
<td>0.171</td>
</tr>
<tr>
<td>Change in the level of the outcome variable immediately after the COVID-19 outbreak, $\beta_2$</td>
<td>-191.65</td>
<td>12.33</td>
<td>-216.66 to -166.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monthly change in trend, $\beta_3$</td>
<td>2.16</td>
<td>1.26</td>
<td>-0.41 to 4.74</td>
<td>0.097</td>
</tr>
<tr>
<td>Post-COVID-19 linear trend$\textsuperscript{b}$</td>
<td>2.97</td>
<td>1.08</td>
<td>0.78 to 5.17</td>
<td>0.009</td>
</tr>
<tr>
<td>Linear trend, $\beta_{4t}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SE, standard error; CI, confidence interval.
\textsuperscript{a}Newey-West standard errors. \textsuperscript{b}This was obtained from the following time trend equation: $Y_{pt} = \beta_0 + \beta_1 \times \text{time}_{pt} + \epsilon$, where $Y_{pt}$ is the value of the rate of emergency department visits at time $t$ after the start of the COVID-19 pandemic, and $\text{time}_{pt}$ is the time trend variable, which takes values between 1 (first observation after the start of the pandemic) and 17 (last observation after the start of the pandemic).

28.9% and 21.6%, respectively, following the outbreak of COVID-19. Another study in China also showed that hospital visits decreased by 22.6% after the outbreak of the pandemic [17]. Decreasing trends of various degrees were also reported in other countries in terms of hospitalizations, ED visits, and outpatient clinic visits [3,18–20]. A systematic review of 81 studies from different countries showed that the number of hospitalizations and the rate of patient visits to healthcare service providers decreased by an average of 28.4% and 42.3%, respectively [21]. Although it is difficult to compare the rate at which the use of health services decreased between countries due to economic, social, and cultural factors as well as their different healthcare systems, these findings indicate a negative impact on the use of health services following the outbreak of COVID-19.

This sharp decline in hospital care utilization can be attributed to people’s fear of COVID-19 infection and insufficient knowledge about the nature of the disease [22–24]. In EDs, a decrease in daily visits and surgeries could also reflect the population’s fear of being in crowded places [20,25,26]. Changes in ED practices that lowered the admission of general patients may also have resulted in lower overall ED visits [22]. Other issues, such as travel restrictions and quarantine policies, might have played a role in reducing healthcare utilization [27]. Studies have also suggested that care providers might have delayed unnecessary healthcare services to reduce the risk of transmitting the virus to patients and healthcare workers [24,28,29]. Medical centers also suspended outpatient services for non-communicable diseases and non-emergency surgeries [24]. The Centers for Disease Control and Prevention (CDC) recommends the continued use of virtual visits and triage assistance lines and adherence to CDC infection control guidelines to minimize COVID-19 transmission and address public concerns about ED visits during the pandemic [10].

The hospitalization rate, rate of ED visits, and rate of outpatient clinic visits maintained a downward trend compared to similar periods in 2019 after February 19, 2020, but each showed a slight increase following the outbreak. The subsequent increase in healthcare service utilization can be attributed to the different healthcare needs of the population. The increase in all healthcare services identified in this study remained lower than the rate of healthcare service utilization over the same period in the previous year. This shows that, despite the need for hospital, emergency, and outpatient services, people only sought healthcare when their health-related needs became urgent. This suggests that people continue to avoid in-person healthcare services despite the relaxation of restrictive policies to limit the spread of COVID-19 [24,28].

Our study identified an increasing trend in healthcare use following a significant reduction after the initial outbreak of the COVID-19 pandemic. A study in Croatia also found...
that hospital admissions increased from September to December 2020 despite a 51% decrease in total hospital admissions after the outbreak of COVID-19 [30]. A study comparing private and public hospitals in China also identified an increase in the number of admissions to private hospitals in June 2020 [16]. Another study in China also reported that, although a decrease in hospital admissions related to respiratory disease was observed, some health conditions, including diseases of the nervous system, pregnancy and childbirth, congenital anomalies, and chromosomal abnormalities, corresponded to an increase in hospital admissions [17]. These increases in healthcare utilization can be due to previously unmet needs for healthcare services [31] or urgent needs for medical services and healthcare. They may also be due to increased public awareness about COVID-19 and expanded access to care and personal protective equipment.

### Strengths and Limitations

By conducting an interrupted time series analysis, this study aimed to provide a comprehensive picture of changes in healthcare utilization before and after the outbreak of COVID-19. A significant advantage of this model is it could demonstrate the causal impact of the COVID-19 outbreak on healthcare utilization in the absence of a comparison group [12,13]. However, the study had some limitations. First, although an interrupted time series analysis can control for pre-existing time trends and provide a clear and simple mechanism to track the outcome variables of interest, this approach can be misleading when the impact of an intervention or event is not linear over time. Second, the data used in this study were from educational hospitals affiliated with the MoHME; thus, the study results cannot be generalized to other hospitals with different ownership, including private hospitals or social security organization-affiliated hospitals in Iran. Third, although disease peaks are very important and were among the major factors affecting hospital service utilization in our model, we could not include this variable in our analysis.

### Conclusion

Our study findings provide useful insights for healthcare policymakers about the impact of the COVID-19 pandemic on healthcare utilization in Kermanshah Province and Iran as a whole. The results showed that the use of hospital services decreased significantly due to the COVID-19 pandemic, likely due to the changing behaviors of patients and providers, the suspension of health facilities and non-emergency services, and COVID-19-related restrictions. Since the use of healthcare services did not return to pre-outbreak levels 17 months after the outbreak, the government should consider devising and implementing interventions such as telemedicine so that all patients feel safe seeking the care they need.
that they need, even during a pandemic. Future research is needed to identify effective strategies and policies to mitigate the long-term and short-term impacts of the pandemic on healthcare utilization in Iran.

**Supplementary Material**

**Figure S1.** A two-way line graph for checking the seasonality pattern for all outcome variables included in the study. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0041.

**Notes**

**Ethics Approval**
This study was approved by the Deputy of Research, Kermanshah University of Medical Sciences (No. IR.KUMS.REC.1400.856), and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of this study.

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

**Funding**
This research received a grant from Kermanshah University of Medical Sciences (grant no. 4010052). The funder did not have any role in the study's design; the collection, analysis, or interpretation of data, or the drafting of the manuscript.

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

**Authors' Contributions**
Conceptualization: SR, MMA, NB; Data curation: NB, SR, AM, MMA; Formal analysis: SR, AKK, SS, MMA; Funding acquisition: SR, MMA; Investigation: SR, SS, AKK, MK, AM; Methodology: SR, AKK, NB, MMA; Project administration: SR, NB, AM, SS; Resources: SR, MMA, MK, NB; Software: SR; Supervision: SR, NB; Validation: SR, AKK, SS, AM, MH; Visualization: SR; Writing–original draft: SR, SS, NB, MMA, AM, MH; Writing–review & editing: all authors. All authors read and approved the final manuscript.

**References**


Vaccine effectiveness and the epidemiological characteristics of a COVID-19 outbreak in a tertiary hospital in Republic of Korea

Seonhee Ahn¹, Tae Jong Son¹, Yoonsuk Jang¹, Jihyun Choi², Young Joon Park², Jiseon Seong³, Hyun Hee Kwon⁴, Muk Ju Kim⁵, Donghyok Kwon⁶

¹Division of Infectious Disease Response, Gyeongbuk Regional Disease Response Center, Korea Disease Control and Prevention Agency, Daegu, Republic of Korea
²Epidemiological Investigation Team, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
³Division of Infectious Disease Control, Daegu Metropolitan City Hall, Daegu, Republic of Korea
⁴Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Republic of Korea
⁵Department of Infectious Disease, Daegu Catholic University Medical Center, Daegu, Republic of Korea
⁶Division of Public Health Emergency Response Research, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea

ABSTRACT

Objectives: Healthcare facilities are high-risk sites for infection. This study analyzed the epidemiological characteristics of a coronavirus disease 2019 (COVID-19) outbreak in a tertiary hospital after COVID-19 vaccination had been introduced in Republic of Korea. Vaccine effectiveness (VE) and shared anti-infection strategies are also assessed.

Methods: The risk levels for 4,074 contacts were evaluated. The epidemiological characteristics of confirmed cases were evaluated using the chi-square test. The “1 minus relative risk” method was used to determine VE in preventing infection, progression to severe disease, and death. In the largest affected area (the 8th floor), a separate relative risk analysis was conducted. A multivariate logistic regression analysis (with 95% confidence interval [CIs]) was used to identify transmission risk factors with a significance level < 10% via the backward elimination method.

Results: In total, 181 cases of COVID-19 were confirmed, with an attack rate of 4.4%. Of those cases, 12.7% progressed to severe disease, and 8.3% died. In the cohort isolation area on the 8th floor, an adjusted odds ratio was 6.55 (95% CI, 2.99–14.33) and 2.19 (95% CI, 1.24–3.88) for caregivers and the unvaccinated group, respectively. VE analysis revealed that 85.8% of the cases that progressed to severe disease and 78.6% of the deaths could be prevented by administering a second vaccine.

Conclusion: Caregiver training for infection prevention and control is necessary to reduce infection risk. Vaccination is an important intervention to reduce the risk of progression to severe disease and death.

Keywords: COVID-19; Fatality; Outbreak; Tertiary care centers; Vaccine efficacy

© 2023 Korea Disease Control and Prevention Agency.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

Patients with pneumonia of unknown cause in China on December 31, 2019, were subsequently identified as having severe acute respiratory syndrome coronavirus-2 [1–3]. Patients with confirmed coronavirus disease 2019 (COVID-19) exhibited symptoms of fever, cough, and respiratory distress 2 to 14 days after exposure to the pathogen [4]. With COVID-19 spreading worldwide, the World Health Organization declared COVID-19 a public health emergency of international concern on March 11, 2020.

Since its first case was confirmed on January 20, 2020, Republic of Korea has achieved stable management of the COVID-19 pandemic using the 3T strategy (tracing, testing, and treatment) and social distancing measures [5].

In Republic of Korea, 705,900 confirmed COVID-19 cases occurred between January 20, 2020, and January 19, 2022, with 10,882 (1.5%) related to outbreaks in healthcare facilities [6]. Despite robust infection control efforts, nosocomial COVID-19 outbreaks have been reported throughout the pandemic [7–10]. Studies have shown attack rates for nosocomial confirmed COVID-19 cases ranging from 15.5% to 30.9% [8,9]. In addition, hospitalized patients with nosocomial COVID-19 have an increased risk of prolonged hospitalization and death. Heightened public anxiety has resulted in a reluctance to go into healthcare facilities for treatments or diagnostic tests. This may account for the significant reduction in hospital admissions and likely contributed to the high mortality rates [7].

Healthcare facilities are places where both patients and workers commuting from local communities are prone to infection [11–13]. Outbreaks in healthcare facilities burden local healthcare systems and pose a threat to public health because of the high risk of transmission to local communities [14–16].

This study investigated a nosocomial COVID-19 outbreak in a tertiary hospital (hereinafter referred to as hospital A) located in Daegu Metropolitan City that involved 181 confirmed cases following the second round of vaccinations in Republic of Korea. Hospital A had 874 beds and admitted 70 to 100 patients daily. In this 15-story building with 2 underground levels, floors 5 to 14 were inpatient wards, and 1 ward on the 14th floor was operated strictly for COVID-19 isolation. The 8th floor included oncology and internal medicine (ward 1) and 2 orthopedic wards (wards 2 and 3). Although separated by department, patients and caregivers moved between wards, depending on bed availability.

This study analyzed the epidemiological characteristics, transmission risk factors, vaccine effectiveness (VE), and response strategies of a nosocomial COVID-19 outbreak in a tertiary hospital.

Materials and Methods

Case Definitions

• Caregiver: A caregiver association member who provides care and support for a patient with COVID-19.
• Family caregiver: A family member who provides care and support for a patient with COVID-19.
• Healthcare worker (HCW): Anyone working in a hospital setting.
• Severe disease: The stage of COVID-19 for which patients are treated with high-flow oxygen therapy, mechanical ventilation, extracorporeal membrane oxygenation, or continuous renal replacement.
• Unvaccinated: A person who has not received a vaccine or is within 14 days after their first ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine.
• Vaccinated: A person who is at least 14 days past their first vaccine (exception: Ad26.COV2.S).
• Partially vaccinated: 1–14 days after a second vaccination.
• Fully vaccinated: Completed 2 doses of vaccination; 14 days after a second vaccination with a ChAdOx1 nCoV-19, BNT162b2, or mRNA-1273, vaccine or 14 days after the first vaccination with an Ad26.COV2.S vaccine.

https://doi.org/10.24171/j.phrp.2023.0066
COVID-19 outbreak in a tertiary hospital

Field Epidemiological Investigation
Herein, we describe the response strategies to a nosocomial COVID-19 outbreak in a tertiary hospital that occurred from August 21, 2021 to September 10, 2021, as well as an analysis of the infection risk factors and VE. The index patient was a 49-year-old woman who worked as a caregiver in ward 1 (8th floor). She began showing symptoms (runny nose, headache, and dizziness) on August 18, 2021, was tested for COVID-19 on August 20, and was confirmed positive on August 21. After identification of the index patient, 9 patients in ward 1 tested positive for COVID-19 on August 22 during ward-wide testing, confirming the incident as a nosocomial outbreak. On August 23, another 18 confirmed cases were added after testing the contacts of the confirmed cases on the 8th floor, including patients from ward 3.

A joint meeting of the hospital, public health center, city hall, and the Korea Disease Control and Prevention Agency (KDCA) evaluated the ongoing situation and discussed countermeasures. By August 23, a total 28 confirmed cases had been reported, including HCWs and caregivers. Many of the confirmed cases had not worn masks appropriately, and had moved across all floors in the hospital, from the basement to the 14th floor. Furthermore, since there were 3 confirmed cases (1 caregiver, 2 family caregiver) with a symptom onset date of August 17 (prior to the index case), the exposure period in the hospital was lengthened, indicating that many people had been exposed for an extended period of time. Therefore, those who were exposed in the hospital as of August 15 were considered contacts. A decision was made to test all 4,074 contacts within the hospital (1,232 patients, 288 family caregivers, 113 caregivers, and 2,441 HCWs). A field epidemiological investigation was conducted from August 24 to 27, 2021, and monitoring for new cases was continued until September 24, 2021.

We investigated each contact’s sex, age, vaccination record, and exposure location (workplace for workers and caregivers, departments and rooms for patients and family caregivers). The risk levels were categorized as high, medium, or low based on the intensity of the contact’s exposure to confirmed cases (Table S1).

Statistical Analysis
All 4,074 contacts in hospital A were regularly tested until 14 days after the last confirmed COVID-19 case. Attack rates were calculated by sex, age, contact status, and exposure location. Data were analyzed using the chi-square test with the significance level set at \( p < 0.05 \). Severity was calculated by tracing the confirmed cases that led to severe disease or death. The results were then used to calculate the VE in preventing infection, progression to severe disease, and death using the formulae: \( 1 - (\text{vaccination rate/leakage rate}) \times 100 \), \( 1 - (\text{rate of progression to severe disease among the vaccinated/ rate of progression to severe disease among the unvaccinated}) \times 100 \), and \( 1 - (\text{fatality rate among the vaccinated/fatality rate among the unvaccinated}) \times 100 \), respectively, based on a 95% confidence interval (CI). In addition, an epidemic curve was created based on the date of symptom onset (confirmation date in asymptomatic cases) and location.

The relative risk (RR) by sex, age, contact status, and vaccination record was analyzed (95% CI) to identify the transmission risk factors and evaluate their interrelatedness in all 430 contacts on the 8th floor where the index case occurred. Odds ratios (ORs) and 95% CIs were calculated, with statistical significance set at \( p < 0.05 \), by performing multivariate logistic regression analysis using the backward elimination method for variables with a significance level <10%. SPSS ver. 18.0 (SPSS Inc.), and Microsoft Excel 2016 were used for statistical analysis and to create the epidemic curve.

Ethics Approval
Data were collected as part of the public health response to COVID-19 after obtaining a review exemption from the Institutional Review Board (IRB) of the KDCA (IRB No: 2022-09-01-PE-A). Informed consent was not required.

Results
Infection Control Strategies
This event was a nosocomial outbreak that occurred in a tertiary hospital, where 181 cases were confirmed positive on the 8th floor (\( n = 143 \)) and other floors (\( n = 38 \)). The exposure period was August 15, 2021 (2 days before symptom onset on August 17), to September 10, 2021, when the last confirmed case occurred (Figure 1). Confirmed cases requiring intensive care were isolated in a dedicated ward of the hospital for ongoing treatment and those with milder symptoms were rapidly transferred to designated COVID-19 healthcare facilities. High-intensity and medium-intensity contacts were screened with polymerase chain reaction (PCR) testing at 3-day intervals (Table S1). Caregivers and HCWs (including interns and residents on rotation) were prohibited from taking business trips, vacations, and changing workplaces. New hospitalizations and visits were restricted until monitoring of the cohort isolation area was completed. Caregivers and HCWs in high-risk contact areas were provided with level D personal protective equipment, and mobile negative-pressure machines were put in the staff locker rooms. To prevent infection, Ad26.COV2.S vaccination...
was recommended for unimmunized individuals in the low-risk group. After obtaining consent, the initial doses were administered.

**Epidemiological Characteristics**

Of the 181 confirmed cases, 63.5% (n = 115) were women, 54.7% (n = 99) were aged ≥60 years, and those most frequently infected (47.0%, n = 85) were patients, followed by family caregivers (21.5%, n = 39), HCWs (18.8%, n = 34), and caregivers (12.7%, n = 23). The outbreak started with patients and family caregivers, then spread to caregivers and HCWs, and most confirmed cases occurred on the 8th floor (79.0%, n = 143), where the index case occurred (Table 1).

Although the overall attack rate was 4.4% (181/4,074), the attack rate was significantly higher (33.3%, 143/430) in the cohort isolation area (8th floor). Confirmed cases occurred in all wards, except in 5 single-occupancy rooms (total: 31 rooms, 22 multi- and 9 single-occupancy) (Table 1). The rate of progression to severe disease was 12.7% (n = 23), and the fatality rate was 8.3% (n = 15) (Table 2).

**Initial Symptoms**

Among the 181 confirmed cases, 59.7% (n = 108) had symptoms (or exacerbated symptoms), including fever (45.4%), cough (45.4%), sore throat (38.9%), headache (29.6%), and phlegm (27.8%). In total, 40.3% (n = 73) were asymptomatic, and the percentage of asymptomatic cases was lower on the 8th floor than on the other floors (36.4% vs. 55.3%, respectively) (Table 2).

**Vaccine Effectiveness**

Regarding COVID-19 vaccination, 45.3% (n = 82) were unvaccinated, 19.3% (n = 35) were partially vaccinated (1 dose), and 35.4% (n = 64) were fully vaccinated (2 doses) (Table 1). The fully vaccinated rate by contact status was 200% for patients, 77% for family caregivers, 73.9% for caregivers, and 79.4% for HCWs.

Compared with the unvaccinated group, the infection rate was reduced by 58.0% and 66.8% in the vaccinated and fully vaccinated groups, respectively. The rates of progression to severe disease were reduced by 77.0% and 85.8%, and the fatality rates were reduced by 79.3% and 78.6%, respectively. The VE for reducing infection rates, progression to severe disease, and fatality was statistically significant in both the partially and fully vaccinated groups (Table 3).

**Risk Factors for the 8th-Floor Cohort Isolation Area**

The RR was calculated to evaluate the risk factors for infection in the 8th-floor cohort area where 79.0% of all confirmed cases occurred. By contact status, compared with HCWs, the RR was 3.50 (95% CI, 2.23–5.48), 2.70 (95% CI, 1.75–4.18), and 2.27 (95% CI, 1.51–3.41) for caregivers, family caregivers, and patients, respectively. By vaccination status, compared with the fully vaccinated group, the RR was 1.93 (95% CI, 1.44–2.59) and 1.68 (95% CI, 1.14–2.47) in the unvaccinated and partially vaccinated groups, respectively (Table S2).

Multivariate logistic regression analysis was performed on variables with p < 0.1 (i.e., contact and vaccination status), to determine the statistical significance of intergroup differences. Compared with HCWs, the adjusted ORs (aORs) were 6.55 (95% CI, 2.99–14.33), 2.42 (95% CI, 1.14–5.16), and 2.04 (95% CI, 1.09–3.82), in caregivers, family caregivers, and patients, respectively. In addition, the aOR was 2.19 (95% CI, 1.24–3.88) in the unvaccinated group compared with the fully vaccinated group.
Table 1. Demographic characteristics of exposed individuals during a COVID-19 outbreak at a tertiary hospital in Republic of Korea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Contact</th>
<th>Confirmed case (%)</th>
<th>Attack rate</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4,074</td>
<td>181 (100.0)</td>
<td>4.4</td>
<td>0.937</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,471</td>
<td>66 (36.5)</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2,603</td>
<td>115 (63.5)</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>0–19</td>
<td>79</td>
<td>2 (1.1)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>1,607</td>
<td>31 (17.1)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>1,295</td>
<td>49 (27.1)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1,093</td>
<td>99 (54.7)</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Exposure location (floor)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>7th</td>
<td>374</td>
<td>7 (3.9)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>8th</td>
<td>430</td>
<td>143 (79.0)</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>9th</td>
<td>302</td>
<td>2 (1.1)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>10th</td>
<td>229</td>
<td>2 (1.1)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>11th</td>
<td>374</td>
<td>16 (8.8)</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>12th</td>
<td>215</td>
<td>11 (6.1)</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Others&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2,150</td>
<td>0 (0)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Contact status</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Patients</td>
<td>1,232</td>
<td>85 (47.0)</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Family caregivers</td>
<td>288</td>
<td>39 (21.5)</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>Caregivers</td>
<td>113</td>
<td>23 (12.7)</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>2,441</td>
<td>34 (18.8)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Vaccination status&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1,051</td>
<td>82 (45.3)</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>553</td>
<td>35 (19.3)</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Fully vaccinated</td>
<td>2,470</td>
<td>64 (35.4)</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistical analysis: chi-square test. 
<sup>b</sup>Other floors: 2nd and 1st basement, floors 1–6, 13, and 14. 
<sup>c</sup>Partially vaccinated: within 1 to 14 days after the second vaccine; fully vaccinated: >14 days after the second vaccine.

vaccinated group, demonstrating statistically significant intergroup differences (Table 4).

**Discussion**

This study described the response strategies in a COVID-19 outbreak in a tertiary hospital where 181 confirmed cases occurred over a period of 25 days. We also analyzed the risk factors for infection and VE.

On August 23, 2021, a confirmed case of COVID-19 was identified, with symptom onset earlier than the index case. Furthermore, an additional confirmed case occurred in a ward via transfer from the ward where the index patient occurred. The possibility of exposure throughout the hospital could not be ruled out because various facilities in the hospital remained in use for several days, with many people in contact with each other. Therefore, PCR tests were conducted on all contacts (n = 4,074) for 2 days (August 24–25), which led to the confirmation of 82 additional cases.

Given that asymptomatic carriers can transmit COVID-19, when multiple confirmed cases occur in a facility vulnerable to infection, such as a healthcare facility, prioritizing the testing of all relevant contacts in the early screening of symptomatic cases can be an important intervention to prevent a large-scale nosocomial outbreak [17].

In this study, asymptomatic cases accounted for 36.4% (52/143) of all cases on the 8th floor, and 55.3% (21/38) on other floors. Confirmed cases on other floors were identified in the hospital-wide testing implemented after multiple confirmed cases had occurred on the 8th floor. The early identification and isolation of confirmed cases during the initial stage of viral spread reduced the risk of additional transmission by asymptomatic COVID-19 carriers. This was also verified by the proportion of patients among the confirmed cases (43.4%, 62/143) on the 8th floor and (60.5%, 23/38) on other floors. While additional COVID-19 cases were identified on the 8th floor by testing close contacts of the infected, the confirmed cases on other floors were identified through hospital-wide testing, demonstrating that further spread can be forestalled in the early stage of an outbreak.
Table 2. Epidemiological characteristics of infected individuals during an outbreak of COVID-19 in a tertiary hospital in Republic of Korea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 181)</th>
<th>8th floor (n = 143)</th>
<th>Other floors (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>108 (59.7)</td>
<td>91 (63.6)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>49 (45.4)</td>
<td>36 (39.6)</td>
<td>13 (76.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>49 (45.4)</td>
<td>40 (44.0)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>42 (38.9)</td>
<td>37 (40.7)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (29.6)</td>
<td>27 (29.7)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Phlegm</td>
<td>30 (27.8)</td>
<td>21 (23.1)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>24 (22.2)</td>
<td>20 (22.0)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>8 (7.4)</td>
<td>8 (8.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>7 (6.5)</td>
<td>6 (6.6)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (3.7)</td>
<td>1 (1.1)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>3 (2.8)</td>
<td>2 (2.2)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>1 (0.9)</td>
<td>1 (1.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Othera)</td>
<td>5 (4.6)</td>
<td>5 (5.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>73 (40.3)</td>
<td>52 (36.4)</td>
<td>21 (55.3)</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>143 (79.0)</td>
<td>116 (81.1)</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>23 (12.7)</td>
<td>16 (11.2)</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>Death</td>
<td>15 (8.3)</td>
<td>11 (7.7)</td>
<td>4 (10.5)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

*a) Other: nausea, vomiting, diarrhea, general weakness.

Table 3. Vaccine effectiveness during an outbreak of COVID-19 at a tertiary hospital in Republic of Korea

<table>
<thead>
<tr>
<th>Variable</th>
<th>Confirmed case</th>
<th>Total</th>
<th>RR (95% CI)</th>
<th>VE (1–RR)×100 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>82</td>
<td>1,051</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinateda)</td>
<td>99</td>
<td>3,023</td>
<td>0.420 (0.316–0.558)</td>
<td>58.0</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>35</td>
<td>553</td>
<td>0.811 (0.554–1.189)</td>
<td>18.9</td>
<td>0.328</td>
</tr>
<tr>
<td>Fully vaccinated</td>
<td>64</td>
<td>2,470</td>
<td>0.332 (0.241–0.457)</td>
<td>66.8</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td><strong>Severe disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>18</td>
<td>82</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinateda)</td>
<td>5</td>
<td>99</td>
<td>0.230 (0.089–0.593)</td>
<td>77.0</td>
<td>0.002**</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>3</td>
<td>35</td>
<td>0.390 (0.123–1.241)</td>
<td>61.0</td>
<td>0.143</td>
</tr>
<tr>
<td>Fully vaccinated</td>
<td>2</td>
<td>64</td>
<td>0.142 (0.034–0.591)</td>
<td>85.8</td>
<td>0.002**</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>12</td>
<td>82</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinateda)</td>
<td>3</td>
<td>99</td>
<td>0.207 (0.060–0.709)</td>
<td>79.3</td>
<td>0.011*</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>1</td>
<td>35</td>
<td>0.195 (0.026–1.444)</td>
<td>80.5</td>
<td>0.125</td>
</tr>
<tr>
<td>Fully vaccinated</td>
<td>2</td>
<td>64</td>
<td>0.214 (0.050–0.920)</td>
<td>78.6</td>
<td>0.039*</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval; VE, vaccine effectiveness.
a) Partially vaccinated: within 1 to 14 days after the second vaccine; fully vaccinated: > 14 days after the second vaccine.
*p<0.05, **p<0.01, ***p<0.001.

In a large-scale outbreak, testing all relevant people makes it possible to implement self-quarantine of close contacts at an early stage. In this report, caregivers and HCWs who were close contacts self-quarantined, regardless of symptom status, and those in the low-risk group took over their roles. Quarantine of caregivers and HCWs may lead to insufficient patient care and work overload caused by the temporary personnel shortage. However, it is crucial to implement quarantine and place work restrictions on close contacts, whether symptomatic or asymptomatic, to reduce additional viral transmission [17]. In this case, early detection through hospital-wide testing and quarantine of confirmed cases and contacts was an important management strategy that ended an outbreak in a relatively short period.

https://doi.org/10.24171/j.phrp.2023.0066
During the outbreak, caregivers were at high risk of infection due to their close contact with patients needing nursing care and help with activities of daily living. The results of multivariate regression analysis showed that they had a higher RR than other contact status groups. In addition, caregivers do not receive regular education on infection prevention and control [18]. Their insufficient knowledge of infection management and personal hygiene rules makes them more vulnerable to infection than other healthcare professionals [19]. However, this is not a new issue. In the 2015 Middle East respiratory syndrome coronavirus epidemic, 40% of confirmed cases were family caregivers and caregivers [20,21]. During the COVID-19 pandemic, however, hospitals in large-scale outbreak areas in Republic of Korea requested that family caregivers and caregivers submit a COVID-19 PCR-negative certificate within 72 hours or undergo periodic testing. The restriction that only 1 family caregiver or visitor was allowed to enter was also strictly followed. However, hospitals in regions with a relatively low number of confirmed cases, including hospital A, only required a COVID-19 PCR-negative certificate from patients within 72 hours before hospitalization. There were no access controls or restrictions on the number of family caregivers and caregivers.

After the outbreak, hospital A limited caregivers (family or otherwise) to 1 person as much as possible and issued access approval cards, which required proof of a PCR-negative test within 72 hours prior to entering the hospital and allowed access only to the concerned area. In addition, body temperature was checked daily, and PCR testing was administered weekly for every person in the facility. Although this was a labor- and resource-intensive intervention, it was more effective than other caregiver education interventions (e.g., mandatory infection control programs) for preventing infection in the short-term [22,23]. This approach is recommended for high-risk facilities vulnerable to infection, including hospitals and long-term care facilities characterized by frequent close contacts, crowding, and confinement.

The present study demonstrated a VE for preventing transmission of 66.8% in those who were fully vaccinated. Therefore, caregivers must be vaccinated. Caregiver education should also include information on how and when to wash hands, the chain of infection, how to use personal protective equipment, and recognizing signs of infection [24,25].

Immediately after the development of COVID-19 vaccines in November 2020, worldwide vaccination began with high-risk population groups. In Republic of Korea, vaccinations began on February 26, 2021, with persons under 65 years of age living or working at long-term care facilities, HCWs in hospitals, and disinfection workers [26]. Vaccination of those over 65 years of age began on May 27, 2021.

The outbreak described here occurred during the Delta variant wave of COVID-19. The fatality rate in hospital A was 8.3%, which was higher than the national average of 0.78% during the same period [27]. Furthermore, the VE against progression to severe disease and death was lower than the 1-year national average (93% and 95%, respectively) found in a related study of adults ≥18 years from February to September 2021 [28]. This was presumably due to the high percentage of patients with underlying diseases and those in the vulnerable age group (≥60 years) in hospital A.

Nevertheless, the high VE in preventing progression to severe disease and death (85.8% and 78.6%, respectively) in the fully vaccinated group compared with the unvaccinated group, shows that vaccination is essential in high-risk facilities during respiratory infectious disease epidemics such as COVID-19.

### Conclusion

The VE evaluation in this report was performed before the introduction of COVID-19 booster shots in Republic of Korea; thus there are no results on the effect of the booster. A limitation of this study was the inability to analyze the VE according to the interval between the vaccination date and the confirmation of infection. Therefore, if the corresponding data become available, further research is needed.

Although it was impossible to completely block the influx of COVID-19 into hospitals, this study demonstrated...
that, once an outbreak occurred, information sharing and a joint response of the hospital, local government, and public health authorities, along with quick classification and quarantine of all contacts and routine testing for the early detection of confirmed cases, were essential interventions for early termination of the outbreak. In addition, to prevent transmission, infection prevention and control education is required for caregivers at healthcare facilities, and close contacts must be quarantined during the incubation period. Finally, vaccination is the most important measure to prevent infection and transmission, and to reduce the risk of progression to severe disease and death.

Supplementary Material

Table S1. Classification criteria and management of contacts.
Table S2. Risk factors for the 8th floor confirmed cases. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0066.

Notes

Ethics Approval
Obtaining informed consent was exempted by the IRB of the KDCA (IRB No: 2022-09-01-PE-A) as no personal information was included in the 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: DK, YJP, TJS. Data curation: SA, JS, MJK. Formal analysis: SA, YJ, JC. Methodology: YJP, HHK, Project administration: DK. Visualization: JC. Writing—original draft: all authors; Writing—review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions
The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the KDCA or the institutions with which the authors are affiliated.

References


https://doi.org/10.24171/j.phrp.2023.0066
Effectiveness of the COVID-19 vaccine in the Honam region of the Republic of Korea

In-Sook Shin¹², Yong-Pyo Lee², Seung-Hoon Lee², Jae-Young Lee³, Jong-Ha Park², Yoon-Seok Chung²

¹Division of Control for Zoonotic and Vector Borne Disease, Korea Diseases Control and Prevention Agency, Cheongju, Republic of Korea
²Division of Infectious Disease Diagnosis Control, Honam Regional Center for Disease Control and Prevention, Korea Diseases Control and Prevention Agency, Gwangju, Republic of Korea
³Division of Vaccine-Preventable Diseases Control and National Immunization Program, Korea Diseases Control and Prevention Agency, Cheongju, Republic of Korea

ABSTRACT

Objectives: In 2021, the effectiveness of the COVID-19 vaccine was analyzed among people living in the Honam region (Gwangju, Jeollanam-do, Jeollabuk-do, and Jeju) of the Republic of Korea. And we investigated changes in the dominant virus strain.

Methods: This study used the data provided by the Korean Ministry of the Interior and Safety for individuals ≥12 years old in the Honam region, and the Integrated Disease and Health Management System of the Korea Centers for Disease Control and Prevention for COVID-19-vaccinated individuals as of December 31, 2021. Statistical analyzes were performed using IBM SPSS ver. 23.0. The occurrence of confirmed cases by vaccination status, the relative risk, and vaccine effectiveness by vaccine type were calculated.

Results: In 2021, the COVID-19 vaccination rate in Honam was 88.6%. The overall vaccine effectiveness (after 2 and 3 doses) was 98.7% (p < 0.001). and the breakthrough infection rate was 0.16%. From week 21 to week 27 of 2021 (June 27 to July 3), the genome sequencing results were mostly alpha variants. The Delta variant emerged as the dominant variant after 27 weeks and the Omicron variant was found at 50 weeks (December 5–11).

Conclusion: Vaccine effectiveness changed with the outbreak of new variants of the virus as well as over time as antibody levels decreased. that the prevention effectiveness of vaccination in Honam was >98%, and the effect among persons who received 2 doses was >90% regardless of the vaccine type. Although vaccine effectiveness decreased because of reduced antibody levels over time (as observed in breakthrough infections), receiving a booster dose restored the neutralizing antibody levels.

Keywords: Breakthrough infections; COVID-19; Strains; Vaccine efficacy
Introduction

The first coronavirus disease 2019 (COVID-19) case in the Republic of Korea was confirmed on January 20, 2020, in a Chinese woman (aged 35 years) from Wuhan, China who traveled to the Republic of Korea through the Incheon International Airport. The crisis alert level in the Republic of Korea was upgraded from “attention” to “caution.” As 4 additional cases were confirmed, the level was elevated to “alert” on January 27, 2020. Approximately 120,000 cases had been confirmed worldwide in nearly 110 countries by January 31 of the same year, and the World Health Organization (WHO) declared the COVID-19 outbreak a global public health crisis \[1\].

As the number of cases of COVID-19 soared worldwide, the total number of imported and domestically confirmed cases exceeded 500 in the Republic of Korea. On February 23, 2020, the country upgraded the crisis alert level to “severe” and transitioned to an aggressive response system. With the continued spread of infection worldwide, the WHO declared COVID-19 a global pandemic on March 11, 2020. The pandemic is ongoing due to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

A vaccine is an important tool to suppress outbreaks, prevent the spread of infection, and reduce the number of deaths. The COVID-19 vaccine was first administered in the United Kingdom (UK) on December 8, 2020. In the Republic of Korea, vaccination programs began on February 26, 2021, following the approval of COVID-19 vaccines developed by Oxford AstraZeneca (henceforth A vaccine; February 10, 2021), Pfizer BioNTech (C vaccine; March 5, 2021), Janssen (D vaccine; April 7, 2021), and Moderna (B vaccine; May 21, 2021) by the Korea Ministry of Foods and Drug Safety. The features of each vaccine are shown in Table 1 \[2\].

In 2021, 4 COVID-19 vaccines were available in the Republic of Korea, 2 viral vector vaccines (A and D) and 2 mRNA vaccines (C and B). In mRNA vaccines, an intermediate carrier is injected that links the DNA and proteins during protein synthesis based on the DNA containing genetic information and helps human cells to produce an extrinsic protein. Viral vector vaccines deliver a modified virus (vector) to human cells to create antigens and induce an immune response \[3\].

The Republic of Korea imported a total of 194 million vaccine doses (as of October 25, 2021), including 20 million each from COVID-19 Vaccines Global Access (COVAX) and Oxford AstraZeneca, 67 million from Pfizer BioNTech, 7 million from Janssen, and 40 million each from Moderna and Novavax. The vaccines were administered stepwise to the Republic of Korean nationals as well as foreigners, including illegal immigrants. As of March 30, 2022, 44,482,876 individuals (86.7% of the Republic of Korean population) had received 2 vaccine doses, while 32,688,629 (69.4%) individuals had received the third dose. However, the number of confirmed cases increased in March 2022 by >20 times compared with that in December 2021 (from 1,217 to 24,739 per 100,000 population).

No study has yet examined the effectiveness of the COVID-19 vaccine for an entire regional population in the Republic of Korea. Therefore, the current study aimed to analyze the vaccine effectiveness in the Honam region, which has a high proportion of older adults. This region, located south of the Geum River, is comprised of both the mainland landmass and islands, includes both cities and rural areas, and encompasses Gwangju, Jeollanam-do, Jeollabuk-do, and Jeju.

HIGHLIGHTS

- In 2021, the COVID-19 vaccination rate in Honam was 88.6%. The prevention effectiveness of vaccination was >98%, and the effect among persons who received 2 doses was >90% regardless of the vaccine type. The genome sequencing results were mostly alpha variants. The Delta variant emerged as the dominant variant after 27 weeks and the Omicron variant was found at 50 weeks.

Table 1. Comparison of the key features of the COVID-19 vaccines licensed in Korea by the Korea Disease Control and Prevention Agency

<table>
<thead>
<tr>
<th>Platform</th>
<th>Pfizer BioNTech</th>
<th>Moderna</th>
<th>Oxford AstraZeneca</th>
<th>Janssen (J&amp;J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Viral vector</td>
<td>Viral vector</td>
</tr>
<tr>
<td>Age group (y)</td>
<td>≥ 12</td>
<td>≥ 18</td>
<td>≥ 18</td>
<td>≥ 18</td>
</tr>
<tr>
<td>Dose and frequency</td>
<td>2 Doses, 3 wk apart</td>
<td>2 Doses, 4 wk apart</td>
<td>2 Doses, 4–12 wk apart</td>
<td>1 Dose</td>
</tr>
<tr>
<td>Dosage (mL)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cold chain requirements</td>
<td>−90 to −60 °C (6 mo)</td>
<td>−25 to 15 °C (7 mo)</td>
<td>2 to 8 °C (6 mo)</td>
<td>−25 to −15 °C (24 mo)</td>
</tr>
<tr>
<td>Storage requirements</td>
<td>−90 to −60 °C (6 mo) or 2 to 8 °C (5 d)</td>
<td>2 to 8 °C (1 mo)</td>
<td>2 to 8 °C (6 mo)</td>
<td>2 to 8 °C (3 mo)</td>
</tr>
</tbody>
</table>

https://doi.org/10.24171/j.phrp.2022.0308
In this study, the data of persons living in Honam and vaccinated for COVID-19 between January 1, 2021, and December 31, 2021, were retrospectively analyzed (a retrospective cohort study) to investigate vaccine effectiveness by the number of doses and vaccine type. Additionally, the whole genome sequencing results of positive specimens were analyzed to examine changes in the dominant variants. To assess the pandemic in the Republic of Korea, the scale and pattern of confirmed cases were identified based on the type of dominant COVID-19 variant.

Materials and Methods

This retrospective cohort study used data provided by the Korea Ministry of the Interior and Safety of people aged ≥ 12 years who lived in the Honam region and who were vaccinated, according to the regional vaccination registration system of the Integrated Disease & Health Management System of the Korea Disease Control and Prevention Agency (KDCA), as of December 31, 2021.

The database of vaccinated persons aged ≥ 12 years in the Honam region who were registered in the Integrated Disease & Health Management System from January 1 to December 31, 2021 was matched with the database of those with confirmed COVID-19 who were registered in the KDCA Honam Center for Disease Response to identify the COVID-19 case and non-COVID-19 case groups. Unvaccinated persons were identified by subtracting the subset of all vaccinated persons from the Honam population aged ≥ 12 years. Unvaccinated individuals were classified into the COVID-19 case or non-COVID-19 case groups by matching with the database of individuals confirmed to have COVID-19 in Honam.

The Honam region has a total population of 5,665,095 individuals, excluding children aged < 12 years. Of the total population, 2,732,563 were men and 2,932,532 were women, with a sex ratio of 48.2:51.8. Of the vaccinated persons, 3 who received the COVID-19 vaccine abroad and 2 whose date of infection onset was unknown were excluded from the analysis of vaccine effectiveness as it was impossible to identify the type of vaccine (in the former) and timing of infection (in the latter). Additionally, 9,640 persons who were infected before vaccination and 920 who were infected within 14 days after vaccination were excluded because their infections were independent of the vaccine.

A total of 10,565 individuals aged ≥ 12 years were excluded from the total population of 5,665,095 individuals. Hence, 5,654,530 individuals were included in the final analysis, with 14,693 individuals included in the case group (7,786 vaccinated and 6,907 unvaccinated) and 5,639,837 in the non-case group (5,000,261 vaccinated and 639,576 unvaccinated) (Figure 1).

The effects of the second and third doses were examined by assessing the relative risk (RR) in the total population of 5,654,530 persons, and differences in the incidence of infection according to vaccine type were evaluated by estimating the median survival time and by performing a log-rank test using the data of 5,842 persons who received 2 doses. In persons who received the second or third dose, the rate of breakthrough infection was computed by age group, and the period in which each of the dominant variants was detected via whole genome sequencing, and the volume of confirmed cases was examined.

Statistical Analyses

Statistical analyses were performed using IBM SPSS ver. 23.0 (IBM Corp.). The chi-square test was used to determine the proportion of patients in the case group by vaccination status, while survival analysis (Kaplan-Meier, log-rank test) was performed to evaluate the temporal difference in the incidence of infection according to vaccine type. The
attack rate in the vaccinated and unvaccinated persons was computed by vaccine type to assess the RR and to estimate the vaccine effectiveness by vaccine type.

Ethics Statement
The data were collected as part of the public health response to the COVID-19 pandemic. This paper was approved by the Institutional Review Board (IRB) of the KDCA for bioethics examination (IRB No: 2022-11-06-PE-A; 2022-11-28). The informed consent was waived because of the retrospective nature of this study.

Results

As of December 31, 2021, of 5,654,530 persons (the Honam population aged ≥12 years, after excluding persons with missing data on infection occurrence, those infected before vaccination, and those infected within 14 days following vaccination from the total population of 5,665,095 individuals), 14,693 were confirmed to have COVID-19. Thus, the overall infection rate was 0.13% and the sex ratio was 51.49, with COVID-19 more prevalent in men. Among the age groups, individuals aged 60–69 years showed the highest rate of confirmed cases (33.3%), followed by those aged 20–29, 30–39, 40–49, and 12–19 years.

Approximately 5,008,047 persons were vaccinated, with a total vaccination rate of 88.6%. The vaccination rates were 53.2% in the COVID-19 case group and 89.6% in the non-COVID-19 case group. More than half of the vaccinated individuals received mRNA vaccines (53.4%), while 27.75% received V-mRNA vaccines (cross-vaccination with viral vector and mRNA vaccines) and 7.35% received virus vector vaccines.

Regarding the number of vaccine doses, 435,662 individuals received a single dose, 2,373,517 received 2 doses, and 2,198,868 received 3 doses. Most individuals who received a single dose had to wait to be eligible for the second dose. The rate of confirmed cases according to the number of vaccine doses was 0.42% for a single dose, 0.25% for 2 doses, and 0.01% for 3 doses. Thus, the rate of confirmed cases decreased as the number of doses increased.

Among individuals who received a single dose, the rate of confirmed cases was highest (7.9%) in those who received the A vaccine, followed by those who received the D, B, and C vaccines. Among individuals who received 2 doses, the rate of confirmed cases was the highest (0.7%) in those who received the AA vaccines, followed by those who received the CC, AC, BB, and BC vaccines. Among individuals who received 3 doses, the rate of confirmed cases was <0.0% in all vaccine combinations.

Overall, the breakthrough infection rate in vaccinated persons was 0.16% (7,786 of 4,791,820). The rate among those who received 2 doses was 0.12% (5,848 of 4,791,820).

Analysis of the timing of post-vaccination COVID-19 by vaccine type was performed by investigating those who received 2 doses (standard vaccination protocol). Overall, the post-vaccination infection rate was highest (25.25%) at 3 to 4 months after the second dose. By vaccine type, the rate was highest at 1 to 2 months after BB vaccination, at 2 to 3 months after CC vaccination, at 3 to 4 months after AA vaccination, and at 4 to 5 months after AC vaccination.

In the Republic of Korea, COVID-19 vaccination was initiated on February 26, 2021. In the first quarter, A and C vaccines were administered to convalescent hospital/facility inpatients, residents aged <65 years, non-healthcare employees, and employees of healthcare institutions classified as hospitals including infectious disease hospitals. In the second quarter, the A, C, and D vaccines were administered to individuals aged 60 to 74 years, patients with chronic illness, all healthcare institution and pharmacy employees, essential social service personnel, convalescent hospital/facility inpatients, residents aged ≥65 years, individuals aged ≥75 years, and military personnel. In the third quarter, the C, B, and D vaccines were administered to unvaccinated persons in previously targeted groups, high school seniors, individuals aged ≥18 years, and foreigners. In the fourth quarter, the C and B vaccines were administered to pregnant women, persons eligible for the third dose, and children aged 12 to 17 years (Table 2).

The incidence of COVID-19 was 1.07% in unvaccinated persons and 0.16% in vaccinated persons, and the RR was 0.145. The risk of infection was significantly reduced with vaccination (p < 0.05, RR < 1) (Table 3).

Persons who were confirmed to have COVID-19 before receiving the second dose (6 cases infected after vaccination with BC) and those infected <14 days following the second dose were excluded from the analysis because the infection was unrelated to the second dose. Additionally, persons who were administered the BBB, BBC, CCB, or BCC vaccines were excluded because none of them was confirmed to have COVID-19; therefore, it was not possible to assess the effectiveness of those vaccine combinations.

The attack rate was calculated in persons with confirmed COVID-19 after receiving the second dose out of those who received 2 doses of the COVID-19 vaccine (including cross-vaccination) and in persons with confirmed COVID-19 after receiving the booster vaccinations out of those who had received booster vaccinations. The number of patients with confirmed COVID-19 after receiving the second dose was 5,842, which included those with confirmed disease...
Table 2. Characteristics of COVID-19 cases in the Honam region of Korea (2021)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>COVID-19 case</th>
<th>Non-COVID-19 case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5,654,530</td>
<td>14,693</td>
<td>5,639,837</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,727,157 (48.2)</td>
<td>7,445 (50.7)</td>
<td>2,719,713 (48.2)</td>
</tr>
<tr>
<td>Female</td>
<td>2,927,373 (51.8)</td>
<td>7,248 (49.3)</td>
<td>2,920,125 (51.8)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–19</td>
<td>472,806 (8.4)</td>
<td>1,315 (8.9)</td>
<td>471,491 (8.4)</td>
</tr>
<tr>
<td>20–29</td>
<td>701,706 (12.4)</td>
<td>2,326 (15.8)</td>
<td>699,380 (12.4)</td>
</tr>
<tr>
<td>30–39</td>
<td>651,383 (11.5)</td>
<td>2,226 (15.2)</td>
<td>649,157 (11.5)</td>
</tr>
<tr>
<td>40–49</td>
<td>880,249 (15.6)</td>
<td>2,069 (14.1)</td>
<td>878,180 (15.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>951,304 (16.8)</td>
<td>1,870 (12.7)</td>
<td>949,434 (16.8)</td>
</tr>
<tr>
<td>≥60</td>
<td>1,997,082 (35.3)</td>
<td>4,887 (33.3)</td>
<td>1,992,195 (35.3)</td>
</tr>
<tr>
<td>Vaccination status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>5,008,047 (88.6)</td>
<td>7,786 (53.0)</td>
<td>5,000,261 (88.7)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>646,483 (11.4)</td>
<td>6,907 (47.0)</td>
<td>639,576 (11.3)</td>
</tr>
<tr>
<td>Vaccine platform</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>415,765 (7.4)</td>
<td>3,617 (24.6)</td>
<td>412,148 (7.3)</td>
</tr>
<tr>
<td>mRNA</td>
<td>3,023,058 (53.5)</td>
<td>3,687 (25.1)</td>
<td>3,019,371 (53.5)</td>
</tr>
<tr>
<td>Viral-mRNA</td>
<td>1,569,224 (27.8)</td>
<td>482 (3.3)</td>
<td>1,568,742 (27.8)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>646,483 (11.4)</td>
<td>6,907 (47.0)</td>
<td>639,576 (11.3)</td>
</tr>
<tr>
<td>Breakthrough infection(^a) by age group (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–19</td>
<td>386,800 (6.8)</td>
<td>185 (1.3)</td>
<td>386,615 (6.9)</td>
</tr>
<tr>
<td>20–29</td>
<td>688,798 (12.2)</td>
<td>695 (4.7)</td>
<td>688,103 (12.2)</td>
</tr>
<tr>
<td>30–39</td>
<td>604,061 (10.7)</td>
<td>961 (6.5)</td>
<td>603,000 (10.7)</td>
</tr>
<tr>
<td>40–49</td>
<td>825,252 (14.6)</td>
<td>1,128 (7.7)</td>
<td>824,124 (14.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>930,963 (16.5)</td>
<td>1,178 (8.0)</td>
<td>929,785 (16.5)</td>
</tr>
<tr>
<td>≥60</td>
<td>1,572,173 (27.8)</td>
<td>3,639 (24.8)</td>
<td>1,568,534 (27.8)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>646,483 (11.4)</td>
<td>6,907 (47.0)</td>
<td>639,576 (11.3)</td>
</tr>
<tr>
<td>Breakthrough infection(^a) by vaccine type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>379,675 (6.7)</td>
<td>2,678 (18.2)</td>
<td>376,997 (6.7)</td>
</tr>
<tr>
<td>BB</td>
<td>884,634 (15.6)</td>
<td>570 (3.9)</td>
<td>884,064 (15.7)</td>
</tr>
<tr>
<td>CC</td>
<td>851,569 (15.1)</td>
<td>2,200 (15.0)</td>
<td>849,369 (15.1)</td>
</tr>
<tr>
<td>AC</td>
<td>243,244 (4.3)</td>
<td>394 (2.7)</td>
<td>242,850 (4.3)</td>
</tr>
<tr>
<td>BC</td>
<td>14,395 (0.3)</td>
<td>6 (0.0)</td>
<td>14,389 (0.3)</td>
</tr>
<tr>
<td>1 Dose &amp; booster</td>
<td>3,014,205 (46.6)</td>
<td>4,616 (13.2)</td>
<td>3,009,589 (46.7)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>646,483 (11.4)</td>
<td>6,907 (47.0)</td>
<td>639,576 (11.3)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).
A, Oxford AstraZeneca; B, Moderna; C, Pfizer BioNTech.
\(^a\)Breakthrough infection refers here to the occurrence of disease > 14 days after vaccination with dose 2 or 3.

Table 3. RR of COVID-19 according to vaccination status

<table>
<thead>
<tr>
<th>Vaccination status</th>
<th>COVID-19 case</th>
<th>Non-COVID-19 case</th>
<th>Total</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>7,786</td>
<td>5,000,261</td>
<td>5,008,047</td>
<td>0.145 (0.137–0.153)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>6,907</td>
<td>639,576</td>
<td>646,483</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR, relative risk (attack rate of vaccinated/attack rate of unvaccinated); CI, confidence interval.
*p < 0.05 indicates statistical significance.

≥14 days after receiving the second dose and those with confirmed disease < 14 days following the administration of the booster vaccinations. A total of 126 persons had confirmed COVID-19 ≥14 days after receiving the booster vaccinations. The overall attack rate was 0.14%, and 5,968 individuals were confirmed to have COVID-19 after the second dose and booster vaccinations.

The overall effectiveness of the COVID-19 vaccine (2 and 3 doses) was 98.7%. The vaccine effectiveness in persons who received more than 2 doses was 99.7%. In persons who received the second dose, excluding those who received the AA vaccines, the vaccination effectiveness was > 97.4%
We examined the incidence of confirmed cases by vaccine type (viral vector, mRNA, and V-mRNA vaccines). The proportion of confirmed cases was 0.87% in persons who received a viral vector vaccine, 0.12% in those who received an mRNA vaccine, and 0.03% in those who were cross-vaccinated (*p < 0.001*) (Table 5).

Survival analysis was performed on the data of individuals in the COVID-19 case group who had received 2 doses, that is, those who received the second dose at least 14 days earlier and those who received the third dose <14 days before developing COVID-19 (n = 5,842). Individuals with confirmed COVID-19 who received a single dose and who developed COVID-19 <14 days after receiving the second dose were excluded from the analysis.

The overall median survival time was 98.3 days (95% confidence interval [CI], 97.1–99.4 days). The median survival time was longest in individuals vaccinated with AC (110.2 days) and shortest in those vaccinated with BB (63.2 days) (Table 6).

Using the log-rank test, survival analysis of the data from the COVID-19 cases who received 2 doses showed that the difference between AC and CC was not significant, although the differences in other factors were significant (*p < 0.05*) (Table 7; Figure 2).

Of all vaccinated persons in Honam (n = 5,008,047), 7,786 had confirmed COVID-19 at least 14 days after vaccination, and the breakthrough infection rate was 0.16%. The breakthrough infection rates by age group were 0.23% in individuals aged 60 to 69 years and 0.13% each in those aged 20 to 39 and 40 to 59 years. The rate was lowest (0.05%) in individuals aged 12 to 19 years (Table 8).

The periods in which the SARS-CoV-2 variants were found in Honam and the scale of the outbreaks were examined. During the period of week 21 to week 27 (June 27–July 3), the average number of weekly confirmed COVID-19 cases was 170, and the virus identified via whole genome sequencing was the Alpha variant in most cases.

After week 27, Delta emerged as the dominant variant, and the average weekly number of confirmed COVID-19 cases in Honam increased to 426 from July through October. In week 50 (December 5–11), the Omicron variant was detected in specimens, and the average weekly number in weeks 50 to 53 (December 26–January 1) sharply increased to 1,788 (Figure 3).

**Discussion**

As of December 2021, the COVID-19 vaccination rates in Honam were 84.0% for those who received 2 doses and 41.1% for those who received 3 doses. These rates were higher by 1.2% and 6.7%, respectively, than the corresponding rates reported nationwide [4].

The overall effectiveness of vaccination in Honam among all persons vaccinated in 2021, except for confirmed COVID-19 cases unrelated to vaccination, was 98.7%. The vaccine effectiveness rates by vaccine type were 91.3% for viral vector vaccines, 98.8% for mRNA vaccines, and 99.7% for V-mRNA vaccines. In confirmed cases of COVID-19, 0.87% received a viral vector vaccine, 0.12% received an mRNA vaccine, 0.03% were cross-vaccinated, and a significant difference was observed according to vaccine type (*p < 0.001*).

In persons who received 2 doses, the vaccine effectiveness was lowest for AA (93.4%). The prevention effectiveness was 98.5%, 97.4%, and 99.4% in individuals who received AC cross-vaccination, CC vaccination, and BB vaccination, respectively.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>COVID-19 case</th>
<th>Non-COVID-19 case</th>
<th>Total</th>
<th>Vaccinated attack rate (VE %)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>2,678</td>
<td>376,997</td>
<td>379,675</td>
<td>0.71 (93.40)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BB</td>
<td>570</td>
<td>884,064</td>
<td>884,634</td>
<td>0.06 (99.40)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>2,200</td>
<td>849,369</td>
<td>851,569</td>
<td>0.26 (97.40)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>394</td>
<td>242,850</td>
<td>243,244</td>
<td>0.16 (98.48)</td>
<td></td>
</tr>
<tr>
<td>DB</td>
<td>16</td>
<td>108,216</td>
<td>108,232</td>
<td>0.01 (99.86)</td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>4</td>
<td>16,637</td>
<td>16,641</td>
<td>0.02 (99.78)</td>
<td></td>
</tr>
<tr>
<td>Booster</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAB</td>
<td>9</td>
<td>691,047</td>
<td>691,056</td>
<td>0.00 (99.99)</td>
<td></td>
</tr>
<tr>
<td>AAC</td>
<td>52</td>
<td>332,233</td>
<td>332,285</td>
<td>0.02 (99.85)</td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>7</td>
<td>176,658</td>
<td>176,665</td>
<td>0.00 (99.96)</td>
<td></td>
</tr>
<tr>
<td>CCC</td>
<td>38</td>
<td>657,724</td>
<td>657,762</td>
<td>0.01 (99.95)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5,968</td>
<td>4,335,795</td>
<td>4,341,763</td>
<td>0.14 (98.71)</td>
<td></td>
</tr>
</tbody>
</table>

VE, vaccine effectiveness; A, Oxford AstraZeneca; B, Moderna; C, Pfizer BioNTech; D, Janssen (J&J).

*p < 0.05 indicates statistical significance.
Thus, in all vaccine types, the prevention effectiveness was >93%.

Countries such as Israel, the United States (US), and the UK reported on the prevention effectiveness of the 2 COVID-19 mRNA vaccines (developed by Pfizer and Moderna). In Israel, the analysis of approximately 4,710,000 persons who received 2 doses of the Pfizer vaccine showed a 97.2% (95% CI, 96.8%–97.5%) effectiveness in the prevention of hospital admission and a 96.7% (95% CI, 96.0%–97.3%) effectiveness in the prevention of death\(^5\). In a previous US study, the prevention effectiveness of 2 doses of the Pfizer or Moderna vaccines was 90% in healthcare professionals, and the prevention of hospital admission in persons aged ≥65 years was 94% (95% CI, 49%–99%)\(^6\). In the UK, the COVID-19 prevention effectiveness of 2 doses of the Pfizer vaccine among healthcare professionals was 85% (95% CI, 74%–96%)\(^7\). In Honam, which encompasses both mainland landmass and islands, as well as urban and rural areas, and has an age distribution skewed toward older age groups, the prevention effectiveness of the COVID-19 vaccine was higher than that reported in other countries. However,
the prevention effectiveness of a vaccine also depends on various factors, such as the intensity of an outbreak and the level of response. Therefore, the vaccine effectiveness in Honam may change if the period of the Omicron outbreak is included in the analysis.

Breakthrough infection refers to the occurrence of infection >14 days after vaccination. It occurs when the antibodies in vaccines become ineffective because: (1) the individual’s immunity level and physical condition are compromised, (2) the antibody levels have decreased in the body over time following vaccination, and (3) a mismatched antigenic determinant has evolved with the emergence of viral variants. The overall breakthrough infection rate was 0.16%, and this rate was highest in persons aged ≥60 years (0.23%). The breakthrough infection rate was higher in this age group than in other age groups, because persons aged 60 to 79 years were prioritized in the early phase of vaccination and the effect of their vaccines had decreased over time.

As the COVID-19 pandemic continued, several variants emerged. The WHO monitors variants by classifying them into variants of interest and variants of concern according to transmissibility, mortality rate, and the extent of changes in the virus versus the existing vaccines, diagnosis capabilities, and treatments. In Honam, the first confirmed case was identified on January 30, 2020, and the ratio of confirmed cases remained quite low until July 2021. Most cases were infected with the Alpha variant, which was classified as a variant of concern, and the average weekly number of

---

<table>
<thead>
<tr>
<th>Table 8. Breakthrough COVID-19 infections by age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (y)</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>≥12 &amp; &lt;20</td>
</tr>
<tr>
<td>≥20 &amp; &lt;40</td>
</tr>
<tr>
<td>≥40 &amp; &lt;60</td>
</tr>
<tr>
<td>≥60</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

---

Figure 3. No. of cases and coronavirus variants per week in 2021.
confirmed cases was 170 until week 27.

After week 27, Delta emerged as the dominant variant, and the third outbreak occurred in the Republic of Korea. The average weekly number of confirmed cases in Honam from July to October increased to 426. The transmissibility of the Delta variant was 1.6 times higher than that of the Alpha variant and resulted in a sharp rise in the number of confirmed cases, transmitted in public facilities such as karaoke businesses and saunas. In Scotland, the effectiveness of the vaccine against the Delta variant was 87.9% in persons who received 2 doses of the Pfizer vaccine and 59.8% in persons who received 2 doses of the AstraZeneca vaccine [6].

It was reported in the Morbidity and Mortality Weekly Report of the US Centers for Disease Control and Prevention that an mRNA-based vaccine was 91% effective before the Delta variant outbreak, but the effectiveness decreased to 66% when Delta became the dominant variant. According to that report, the effectiveness of the vaccine against the variants gradually decreased, although statistical uncertainty existed since the estimation was based on a relatively short study period [8]. Nonetheless, the report stressed that vaccination was of paramount importance, even at a 66% reduction in infection risk.

The fourth outbreak in the Republic of Korea occurred in week 45 (October 31–November 6) in educational institutions such as schools and after-school academies, and the average weekly number of confirmed cases in Honam increased in November and December to 1,249, which was 3 times higher than was reported during the third outbreak. The Omicron variant, first identified in week 50, was less likely to cause severe illness, but showed higher transmissibility than the Delta variant; thus, the number of cases increased rapidly [9,10].

In the analysis of 1,861 confirmed cases during week 52 (December 19–25), out of 611 specimens (32.8%) the Delta variant was identified in 73.3% (n = 488) of the cases and Omicron in 26.7% (n = 163). The latter had rapidly increased within 2 weeks, up from 13.9% in week 50.

The KDCA Division of Novel Pathogen Analysis investigated the risk of reinfection with a variant as well as vaccine effectiveness by performing a plaque reduction neutralization test [3]. The potency of neutralizing the G genotype virus and its variants (Alpha and Beta) was analyzed using the convalescent sera of persons with COVID-19 and those infected with the Alpha or Beta variant, as well as the sera of vaccinated persons. The antibodies in already infected or vaccinated persons maintained the potency for neutralizing the Alpha and Beta variants, although the potency was somewhat lower in the latter [11]. According to a study by the KDCA National Institute of Health in which neutralizing antibody levels were compared by variant, the effectiveness of preventing infection by the Omicron variant decreased over time following the second dose, although the effectiveness of preventing severe illness was maintained. After administration of the third dose, the level of neutralizing antibodies increased, indicating that the potency for neutralizing Omicron and Delta variants increased. In persons who were vaccinated with the C or A vaccine for the first 2 doses and received their third dose with the C vaccine, the level of neutralizing antibodies against Omicron increased 10.5 to 113.2 times within 2 to 4 weeks when compared with levels before receiving the third dose. This suggested the need for an additional dose.

The WHO (January 7, 2022) emphasized that the risk of Omicron infection was “very high,” since the scope of hazards could expand due to the rapid transmission and high likelihood of large-scale outbreaks within a short period of time. On January 27, 2022, the European Center for Disease Prevention and Control stressed the importance of vaccination by classifying countries with a high vaccine penetration as “high” risk and countries with a low vaccine penetration as “very high” risk.

The COVID-19 pandemic persists due to the emergence of new variants. However, throughout human history, vaccines have played a significant role in effectively suppressing many infectious diseases; the COVID-19 vaccine also suppressed the spread of infection and reduced the occurrence of severe cases. Nevertheless, high expectations and anxiety regarding vaccines coexist. The complete safety and efficacy of vaccines for all individuals cannot be guaranteed, and the COVID-19 vaccine is not an exception. Moreover, vaccine effectiveness does not remain constant, as antibody levels decrease over time following each vaccination. However, an analysis of vaccinated persons found that in the Republic of Korea, the incidence of infection was lower in vaccinated persons and the effectiveness of the vaccine was >95%. Although the vaccine effectiveness changed as antibody levels decreased over time, a booster dose could restore the neutralizing antibody levels.

In this study, the prevention effectiveness of the vaccines was evaluated based on data in the Honam region, which has complex geographical characteristics (a mix of urban and rural areas) and a high proportion of older adults. The dominant variants were examined in each of the outbreaks in which the number of confirmed cases increased despite the high vaccine rate. This study had some limitations. The confirmed cases after vaccination were not classified according to severity and the number of deaths was not identified. This analysis did not cover the longer duration of the Omicron outbreak; thus, the estimation of the vaccine’s prevention effectiveness was likely affected. In addition,
although it was plausible for the level of viral exposure to vary in different outbreak situations, the analysis was conducted assuming a constant exposure level. This assumption may have impacted the results of our evaluation of the various vaccines.

Further studies should be conducted in the Republic of Korea to examine the effectiveness of vaccines according to the severity of COVID-19, the death and survival rates, and the variant type. The immunological characteristics of the specific variants involved should also be investigated. The current study reflects the epidemiological features of COVID-19 in the Republic of Korea and can serve as baseline data to promptly respond during future outbreaks of a rapidly evolving virus.

Notes

Ethics Approval
This study was approved by the IRB (IRB No: 2022-11-06-PE-A; 2022-11-28) of the KDCA for bioethics examination. The 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: ISS, JHP; Data curation: SHL, YPL; Formal analysis: ISS, JYL; Investigation: ISS; Methodology: ISS, SHL, YPL; Project administration: YSC, ISS; Validation: ISS, SHL, YPL, JYL; Visualization: ISS; Writing—original draft: ISS; Writing—review & editing: all authors. All authors read and approved the final manuscript.

References

Risk factors for COVID-19 outbreaks in livestock slaughtering and processing facilities in Republic of Korea

Seongju Choi¹, Tae Jong Son¹, Yeon-Kyung Lee²

¹Division of Infectious Disease Response, Gyeongbuk Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency, Daegu, Republic of Korea
²Division of Healthcare Associated Infection Control, Bureau of Healthcare Safety and Immunization, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea

ABSTRACT

Objectives: The goal of this study was to help prevent and control the spread of coronavirus disease 2019 (COVID-19) by identifying transmission routes and risk factors in livestock slaughtering and processing facilities (SPFs) and establishing an optimal intervention strategy for outbreaks.

Methods: This case series study was a demographic analysis of patients with confirmed COVID-19 associated with 5 SPFs in Korea between January and June 2021. Additionally, in a retrospective cohort study, the association between COVID-19 infection and risk factors was analyzed for SPFs at which outbreaks occurred.

Results: The COVID-19 attack rates were 11.2%, 24.5%, and 6.8% at 3 poultry SPFs (PSPFs) and 15.5% and 25.2% at 2 mammal SPFs (MSPFs). Regarding spatial risk factors, the COVID-19 risk levels were 12.1-, 5.2-, and 5.0-fold higher in the refrigeration/freezing, by-product processing, and carcass cutting areas, respectively, than in the office area. The risk of COVID-19 infection was 2.1 times higher among employees of subcontractors than among employees of contractors. The COVID-19 risk levels were 5.3- and 3.0-fold higher in foreign workers than in native Korean workers in the PSPFs and MSPFs, respectively.

Conclusion: As the COVID-19 pandemic continues, a detailed policy for infectious disease prevention and control intervention is needed, without interrupting economic activities. Thus, we propose an ideal intervention plan to prevent COVID-19 through disinfection and preemptive testing and to block its transmission through effective contact management during outbreaks at SPFs.

Keywords: Abattoirs; COVID-19; Disease outbreaks
Introduction

In late December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed in Wuhan City, Hubei Province, China [1]. Since then, SARS-CoV-2 has spread rapidly throughout Asian countries, such as Japan and Korea, and developed into an international pandemic. The World Health Organization declared a public health emergency and named the disease caused by SARS-CoV-2 coronavirus disease 2019 (COVID-19) [2]. SARS-CoV-2 is transmitted among humans through contact with patients, inhalation of virus-laden droplets, contact with virus-contaminated surfaces, and exposure to aerosols in enclosed spaces [3].

Identifying the transmission routes, characteristics, and risk factors of the highly contagious SARS-CoV-2 is critical in preventing and controlling its spread. Classifying and managing cluster outbreaks effectively blocks SARS-CoV-2 transmission and prevents infection. Accordingly, it is crucial to understand the transmission route and epidemiological characteristics of SARS-CoV-2 within the cluster and to establish testing and isolation strategies [4,5]. In 2020, during the early COVID-19 pandemic, livestock slaughtering and processing facilities (SPFs) in the United States (US) and Europe were hotspots for COVID-19 outbreaks and were a primary cause of community transmission [6]. Work environments at SPFs are conducive to the spread of respiratory viruses among employees. Potential risk factors include proximity to colleagues during long working hours, increased breathing rates due to physically strenuous work, and difficulty complying with infectious disease prevention and control rules because of the need to shout to communicate with colleagues amid ambient noise, thus increasing the risk of droplet transmission. Moreover, the indoor temperature is maintained at 10 to 15 °C when processing livestock products, and since the survival period of SARS-CoV-2 is longer in lower-temperature environments, this increases the risk of viral spread through contact with contaminated surfaces. The jobs at SPFs are difficult, and most of the work is subcontracted. Subcontractors perform the core activities of SPFs, including receiving, slaughtering, and deboning livestock as well as storing in cold temperatures, cutting, packaging, and distributing meat. Subcontractors work with human resources offices to hire foreign workers, who live in dormitories and form communities to rest and eat together. Failures in physical distancing and personal hygiene (for instance, not wearing the correct personal protective gear, such as masks) are major risk factors for viral transmission [7]. Many reports have emerged of COVID-19 outbreaks in Korea in 2020 from various facilities. Regarding hotspots of community outbreaks, epidemiological studies and reports have been conducted on fitness centers, a call center, nursing facilities, and a taekwondo gym (Tables S1, S2) [8–11]. In the first half of 2021, outbreaks of COVID-19 occurred at 8 domestic SPFs, greatly impacting the community spread; however, epidemiological studies and reports on COVID-19 outbreaks in domestic SPFs are lacking.

The prolonged COVID-19 pandemic has created a conflict between the economy and public healthcare. Although continuous social distancing suppresses the spread of infectious diseases, it imposes economic damage and burdens the medical system [12]. In particular, local economies and national food supplies can be adversely impacted by COVID-19 control measures affecting SPFs. However, proper distancing in daily life and preemptive vaccination can reduce the possibility of infection and prevent outbreaks [13]. Therefore, this study was conducted to identify the COVID-19 risk factors associated with SPFs and suggest an optimal intervention to limit the spread of COVID-19 through efficient infectious disease prevention and control measures in the event of an outbreak.

Materials and Methods

Study Design

In a case series study, demographic characteristics of patients with confirmed COVID-19 infection were examined to investigate the association with SPFs in Korea between January and June 2021. Additionally, a retrospective cohort study was conducted to analyze the correlation between COVID-19 infection and risk factors among all employees of the SPFs at which COVID-19 outbreaks occurred.
Study Population
As of March 2021, 87 mammal SPFs (MSPFs) and 56 poultry SPFs (PSPFs) existed in Korea. Between January and June 2021, among the 8 facilities at which at least 10 confirmed COVID-19 cases were reported, 5 facilities (2 MSPFs and 3 PSPFs) with COVID-19 test results of all employees were examined. A total of 2,125 individuals were surveyed, including 2,007 employees across 5 facilities; of the 402 confirmed cases, 280 people were infected in the facilities and 122 were cases of secondary transmission related to these facilities (i.e., among employees’ families, acquaintances, etc.).

Setting
Spatially, an SPF comprises subsidiary support facilities including a lairage area, a slaughterhouse or harvest area, space for chilling/refrigeration/freezing, a meat processing area, and an office and other auxiliary areas [14]. The lairage area, located outside the SPF, serves as a temporary holding space for livestock before slaughter. To mitigate heat stress for the animals during the summer, a spray device is installed in the lairage area. The slaughterhouse or harvest area should be kept at a temperature of 15 °C or lower and should utilize an air conditioning system that circulates air. Stainless steel is recommended for the machinery and equipment. The mammalian slaughter process includes the following stages: live animal entry and lairage, stunning, bleeding, head and hoof removal, scalding/dehairing, evisceration, carcass preparation, chilling/freezing, and meat processing. The slaughter space tends to be hot and humid, with depilation occurring in a hot water tank at 58 °C and cleaning done with hot water or steam. In contrast, chilling is typically conducted at around 2 °C to stabilize the meat temperature, while freezing is done at temperatures below −40 °C. As such, the harvest area is a high-temperature, high-humidity, and noisy environment, while the refrigeration/freezing area is a low-temperature environment [15,16].

Processing can take place either in the same facility or at a dedicated processing facility. The poultry slaughter process involves live animal entry and lairage, electrical stunning, bleeding, scalding/dehairing, head and foot removal, evisceration, chilling, segmentation, processing, packaging, and cooling. Scalding/dehairing is performed by immersing the poultry in hot water treated with sodium carbonate. Evisceration is automated, and chilling for 1 hour is necessary to lower the meat temperature. The meat is either packaged immediately after segmentation or processed prior to packaging. Cooling should be maintained below −2 °C. The processing part of the facility consists of a meat processing area and a by-product processing area; to maintain freshness, the temperature there should be maintained at approximately 4 °C. Processing tables and equipment should be made of stainless steel. Finally, auxiliary supporting facilities include offices, laboratories, dressing/locker rooms, staff lounges, and cafeterias (Figure 1).

SFP field workers include employees of the contractor that manages the facility, employees of subcontractors related to livestock product processing and distribution, and external workers such as inspectors (e.g., veterinarians), cafeteria staff, and environmental service and security workers.

Case Definition
For the 5 SPFs with COVID-19 outbreaks between January and June 2021, employees who tested positive on a polymerase chain reaction (PCR) test, as well as their family members and acquaintances who tested positive through community transmission due to contact with the employees, were evaluated.

Data and Statistical Analysis
Information on confirmed cases of SPF-related COVID-19 outbreaks was provided through the COVID-19 information management system and COVID-19 outbreak database of the Korea Disease Control and Prevention Agency. Epidemiological investigation reports from the local public health center regarding the employees of the 5 SPFs were used to collect data on the type of employment (contractor, subcontractor, or external company), workspace, type of residence (private home or dormitory), and COVID-19 test results.

For statistical analysis, logistic regression analysis was performed using IBM SPSS ver. 22.0 (IBM Corp.). Orange software ver. 3.32.0 (Bioinformatics Laboratory, Faculty of Computer and Information Science, University of Ljubljana) was used to conduct the Fisher exact test and independent samples t-test. The demographic characteristics of the confirmed cases were categorized by sex, age, symptoms, nationality, and type of transmission, and numbers and ratios were described for each variable. To understand whether the employment type, workspace, and/or residence type affected COVID-19 transmission, the attack rate was calculated, and multivariate logistic regression analysis was performed to calculate the odds ratio (OR), 95% confidence interval, and p-value. Statistical significance was considered to be indicated by p-values < 0.05. To determine whether the risk of COVID-19 and presence of symptoms differed depending on nationality, the t-test and chi-square test were conducted to characterize any differences in the
Figure 1. (A) Working area, process diagram, and COVID-19 risk factors in a poultry slaughtering and processing facility (PSPF). (B) Working area, process diagram, and COVID-19 risk factors in a mammal slaughtering and processing facility (MSPF). (C) Floor plan of a PSPF. (D) Floor plan of a MSPF.
average reverse transcription real-time PCR (RT-PCR) cycle threshold (Ct) values and asymptomatic percentages of the patients with confirmed COVID-19.

**Ethics Statement**

This study was approved by the Korea Disease Control and Prevention Agency Institutional Review Board (IRB No: 2022-10-2-PE-A).

**Results**

**Outbreak Description**

Among the COVID-19 outbreaks at SPFs across Korea between January and June 2021, 3 PSPFs (facilities A, B, and C) and 2 MSPFs (facilities D and E) were investigated after all of their employees were tested for COVID-19. The slaughtering capacities were 150,000, 42,985, and 300,000 heads/day at facilities A, B, and C, respectively. Daily slaughters of 80 cows and 1,800 pigs at facility D and 400 cows and 3,000 pigs at facility E were reported. The COVID-19 attack rates during the outbreaks were 11.2%, 24.5%, 6.8%, 15.5%, and 25.2% at facilities A, B, C, D, and E, respectively. For both PSPFs and MSPFs, high slaughtering capacity was associated with a low COVID-19 attack rate.

The index patient at facility A was a female foreign worker who lived in a dormitory and worked in carcass processing as an employee of a subcontractor. She had symptoms of cough and fever starting on January 20, 2021, and COVID-19 was confirmed on January 26, 2021. When all employees working at facility A and their 572 family members were tested for COVID-19, infection was confirmed in 27 employees and 3 family members. By February 10, when the outbreak ended, COVID-19 was confirmed in 44 of 392 employees at facility A (attack rate, 11.2%). Including the 22 family and community contacts confirmed to have COVID-19, a total of 66 patients were infected. The median age was 45.5 years, with more female patients (n = 37, 56.1%) than male patients. The majority of those with COVID-19 were asymptomatic (n = 40, 61.5%). The number of foreign patients (n = 36, 54.5%) was greater than that of native Korean patients.

The index patient at facility B was a native Korean man in charge of inspecting livestock products. He was tested for COVID-19 on January 29, 2021 due to symptoms of runny nose, headache, muscle pain, and cough, and COVID-19 was confirmed on February 1, 2021. An outbreak was suspected, and 33 additional cases were confirmed after COVID-19 testing of all 147 employees of facility B. By February 17, when the outbreak ended, 37 employees were confirmed to have COVID-19 (attack rate, 24.5%). The additional confirmation of 22 family and community contacts yielded a total of 59 confirmed cases. The median age was 44 years, with more male patients (n = 33, 55.9%) than female patients. The majority of those with COVID-19 were asymptomatic (n = 42, 71.2%). The number of native Korean patients (n = 36, 61.0%) was greater than that of foreign patients.

The index patient at facility C was a female foreign worker who lived in a dormitory and worked in carcass processing as an employee of a subcontractor. She was tested for COVID-19 on February 25, 2021 for symptoms of fever, chills, and muscle pain, and COVID-19 was confirmed on February 28, 2021. When all 736 employees of facility C and their family members were tested, COVID-19 was confirmed for 14 employees and 1 family member. By March 20, when the outbreak ended, 41 of 606 employees had been confirmed to have COVID-19 (attack rate, 6.8%). The additional confirmation of 4 family contacts yielded a total of 45 confirmed cases. The median age was 32 years, with more male patients (n = 28, 62.2%) than female patients. Most patients were asymptomatic (n = 28, 62.2%). Foreign workers accounted for the majority of the confirmed cases (n = 41, 91.1%).

The index patient at facility D was a native Korean female family member of an employee at the facility. She was tested on March 2, 2021 for symptoms of loss of taste, loss of smell, and runny nose, and COVID-19 was confirmed on March 6, 2021. An epidemiological survey of confirmed COVID-19 cases in the community revealed 2 facility D employees and 1 family member. When the coworkers and family contacts of the confirmed patients associated with facility D were tested, 11 employees and 3 family contacts were found to have COVID-19. An outbreak was suspected, and all employees of facility D as well as their family and community contacts were tested on March 7, 2021. Overall, 66 employees and 11 family and community contacts were confirmed to have COVID-19. On March 8, 2021, part of facility D was closed for 2 weeks, and preemptive COVID-19 testing was conducted among foreign community residents. By March 24, when the outbreak ended, 93 of 600 employees had been confirmed to have COVID-19 (attack rate, 15.5%). Including an additional 51 family members and community contacts, a total of 144 confirmed COVID-19 cases were recorded. The median age was 51 years, with more male patients (n = 99, 68.8%) than female patients. More patients had mild symptoms (n = 82, 56.9%) than were asymptomatic, and 4 patients (2.8%) died. The number of native Korean patients (n = 105, 72.9%) was greater than that of foreign patients.

The index patient in facility E was a native Korean woman. As an employee of the contractor, she worked in carcass processing. She was tested for COVID-19 on May 7, 2021.
for symptoms of cough and sore throat, and COVID-19 was confirmed on May 11, 2021. On May 12, 2021, all employees of facility E were tested for COVID-19, which was confirmed in 37 people. By May 31, when the outbreak ended, 65 of 258 employees were confirmed positive for COVID-19 (attack rate, 25.2%). Including 20 family members and community contacts, 85 COVID-19 cases were confirmed in total. The median age was 47 years, with more men (n = 61, 69.3%) than women. The number of asymptomatic patients (n = 46, 52.3%) was greater than that of symptomatic patients, and 2 patients (2.3%) died. The number of foreign patients (n = 47, 53.4%) was greater than that of native Korean patients (Table 1; Figure 2).

Analysis of Risk Factors

Logistic regression analysis was conducted to examine the effects of the type of employment, work area, and type of residence on the risk of COVID-19. For the PSPFs, multivariate analysis revealed that subcontractor employees (OR, 2.09; p = 0.018), external worker status (OR, 0.04; p < 0.001), work in the refrigeration/freezing area (OR, 12.09; p < 0.001), work in the inspection area (OR, 34.38; p = 0.002), work area other than harvest and livestock product processing (OR, 0.46, p = 0.011), and dormitory living (OR, 4.54; p < 0.001) were significant risk factors for COVID-19. The infection risk was 2.09 times higher among employees of subcontractors than among contractor employees. Moreover, the external workers had a 96% lower COVID-19 risk than the contractor employees. The COVID-19 risk was 12.09-fold higher among those working in the refrigeration/freezing area than among the office area employees, and workers in the inspection area were also at a higher risk of infection relative to the office area employees. Employees performing tasks other than harvest and livestock product processing had a 54% lower COVID-19 risk relative to the office area employees. The risk of COVID-19 was 4.54-fold higher among employees living in dormitories than among those living in private homes.

For the MSPFs, multivariate analysis revealed that external worker status (OR, 0.17; p = 0.013), work in the by-product processing area (OR, 5.21; p = 0.011), work in the carcass area (OR, 0.17; p = 0.013) were significant risk factors for COVID-19. The infection risk was 5.21 times higher among employees working in the by-product processing area than among the office area employees. Moreover, employees working in the carcass area had a 4.54% higher COVID-19 risk than those working in the office area employees.

Table 1. Demographic characteristics of confirmed COVID-19 cases among SPF employees and their contacts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Facility</th>
<th>n</th>
<th>n (%)</th>
<th>n</th>
<th>n (%)</th>
<th>n</th>
<th>n (%)</th>
<th>n</th>
<th>n (%)</th>
<th>n</th>
<th>n (%)</th>
<th>n</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A (n = 66)</td>
<td>B (n = 59)</td>
<td>C (n = 45)</td>
<td>D (n = 144)</td>
<td>E (n = 88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td>Chungcheongbuk-do</td>
<td>Chungcheongnam-do</td>
<td>Chungcheongbuk-do</td>
<td>Gyeonggi-do (south)</td>
<td>Gyeonggi-do (north)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of facility</td>
<td></td>
<td>Poultry</td>
<td>Poultry</td>
<td>Poultry</td>
<td>Beef/pork</td>
<td>Beef/pork</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily slaughter capacity</td>
<td></td>
<td>150,000</td>
<td>42,985</td>
<td>300,000</td>
<td>400/3,000</td>
<td>80/1,800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workers in facility</td>
<td></td>
<td>392</td>
<td>151</td>
<td>606</td>
<td>600</td>
<td>258</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed COVID-19 cases among</td>
<td></td>
<td>44/392 (11.2)</td>
<td>37/151 (24.5)</td>
<td>41/606 (6.8)</td>
<td>93/600 (15.5)</td>
<td>65/258 (25.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>workers/total workers (attack rate, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age (y), median (IQR)</td>
<td></td>
<td>46 (4–77)</td>
<td>37 (56.1)</td>
<td>44 (38–83)</td>
<td>32 (24–62)</td>
<td>51 (0–90)</td>
<td>47 (1–85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (y)</td>
<td></td>
<td>&lt; 19</td>
<td>3 (4.5)</td>
<td>3 (5.1)</td>
<td>0 (0)</td>
<td>6 (4.2)</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–39</td>
<td>25 (37.9)</td>
<td>19 (32.2)</td>
<td>31 (68.9)</td>
<td>38 (26.4)</td>
<td>25 (28.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40–59</td>
<td>25 (37.9)</td>
<td>32 (54.2)</td>
<td>12 (26.7)</td>
<td>62 (43.1)</td>
<td>46 (52.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 60</td>
<td>13 (19.7)</td>
<td>5 (8.5)</td>
<td>2 (4.4)</td>
<td>38 (26.4)</td>
<td>16 (18.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td>Asymptomatic</td>
<td>40 (60.6)</td>
<td>42 (71.2)</td>
<td>28 (62.2)</td>
<td>57 (39.6)</td>
<td>46 (52.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>25 (37.9)</td>
<td>16 (27.1)</td>
<td>17 (37.8)</td>
<td>82 (56.9)</td>
<td>40 (45.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
<td>1 (1.5)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (2.8)</td>
<td>2 (2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td>Native</td>
<td>30 (45.5)</td>
<td>36 (61.0)</td>
<td>4 (8.9)</td>
<td>105 (72.9)</td>
<td>41 (46.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foreign</td>
<td>36 (54.5)</td>
<td>23 (39.0)</td>
<td>41 (91.1)</td>
<td>39 (27.1)</td>
<td>47 (53.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission</td>
<td></td>
<td>Family contacts</td>
<td>17 (77.3)</td>
<td>16 (72.7)</td>
<td>4 (100.0)</td>
<td>17 (33.3)</td>
<td>11 (47.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Community resident contacts</td>
<td>5 (22.7)</td>
<td>6 (27.3)</td>
<td>0 (0)</td>
<td>34 (66.7)</td>
<td>12 (52.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise specified.

SPF, livestock slaughtering and processing facility; IQR, interquartile range.
cutting area (OR, 4.95; \( p = 0.017 \)), and dormitory living (OR, 3.34; \( p < 0.001 \)) were significant risk factors for COVID-19. External workers had an 83% lower COVID-19 risk relative to contractor employees. Employees working in the by-product processing area and carcass cutting area had 5.21-fold and 4.95-fold higher risks of infection, respectively, relative to those working in the office area. Additionally, those living in dormitories had a 3.34-fold higher risk of COVID-19 than those living in private homes (Table 2).

**Comparison Between Native Korean and Foreign Employees**

A contingency table was prepared to verify the difference in the proportion of symptomatic and asymptomatic patients by nationality among the employees confirmed to have COVID-19. Among the foreign workers at PSPFs, 61 (66.3%) were asymptomatic and 31 (33.7%) were symptomatic, whereas among the native Korean workers, 12 (40.0%) were asymptomatic and 18 (60.0%) were symptomatic. Among the foreign workers at MSPFs, 42 (60.0%) were asymptomatic and 28 (40.0%) were symptomatic, whereas among the native Korean workers, 36 (40.9%) were asymptomatic and 52 (59.1%) were symptomatic. The chi-square test was conducted to determine the statistical significance of the association of symptoms with nationality. The presence of symptoms differed significantly by nationality for both PSPFs and MSPFs (\( p < 0.05 \)). The proportion of asymptomatic cases was higher among the foreign than the native Korean employees (Table 3).

To examine whether the high proportion of asymptomatic patients among foreign employees influenced the delay in COVID-19 testing, an independent samples t-test was conducted on the RT-PCR Ct values to verify whether the viral load differed significantly according to nationality. The
average Ct values of the foreign employees in the PSPFs and MSPFs were 3.0 points and 2.7 points higher than those of the native Korean employees, respectively, constituting a significant difference ($p < 0.05$) (Figure 3).

**Discussion**

Comparing the daily slaughter processing capacity and attack rate of COVID-19 at 5 SPFs with outbreaks between January and June 2021 revealed that higher slaughter processing capacity was associated with a lower COVID-19 attack rate. In Korea, the Slaughterhouse Restructuring Act was implemented in 2009 to modernize, automate, and expand SPFs. However, smaller SPFs still face problems, such as outdated facilities and low sanitation levels [17]. Thus, the relatively low COVID-19 attack rates in higher-capacity SPFs were attributed to the lower density of employees due to automation as well as the improved working conditions associated with a modernized facility, such as better ventilation and sanitation. In contrast, in a study by Taylor et al. [7] of outbreaks in abattoirs in the US, greater processing capacity was associated with a higher COVID-19 attack rate. Larger abattoirs in the US employ more people and involve more activities than smaller operations. Moreover, because such facilities require a larger physical space, employees must shout louder to communicate, leading to increased droplet generation. Therefore, according to that US study, employees in larger facilities are particularly vulnerable to respiratory virus transmission. Furthermore, in outbreaks in Irish slaughterhouses, 0.5% of small slaughterhouses managed by local governments and 15.3% of large slaughterhouses managed by the central government had COVID-19 outbreaks, demonstrating that larger facilities

---

**Table 2. Multivariate analysis of risk factors for COVID-19 in PSPFs and MSPFs**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PSPFs</th>
<th>MSPFs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of workers</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Type of employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractor(^a) employee</td>
<td>375 26</td>
<td></td>
</tr>
<tr>
<td>Subcontractor(^b) employee</td>
<td>517 91</td>
<td>2.09 (1.14–3.85)</td>
</tr>
<tr>
<td>External worker(^c)</td>
<td>257 5</td>
<td>0.04 (0.01–0.18)</td>
</tr>
<tr>
<td>Working area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>86 7</td>
<td></td>
</tr>
<tr>
<td>Harvest</td>
<td>45 18</td>
<td>1.82 (0.60–5.54)</td>
</tr>
<tr>
<td>By-product processing</td>
<td>44 7</td>
<td>0.41 (0.12–1.45)</td>
</tr>
<tr>
<td>Refrigeration/freezing</td>
<td>95 12</td>
<td>12.09 (3.47–42.16)</td>
</tr>
<tr>
<td>Carcass cutting</td>
<td>115 15</td>
<td>0.41 (0.14–1.21)</td>
</tr>
<tr>
<td>Meat processing</td>
<td>420 58</td>
<td>0.48 (0.19–1.25)</td>
</tr>
<tr>
<td>Inspection</td>
<td>19 2</td>
<td>34.38 (3.63–325.40)</td>
</tr>
<tr>
<td>Others(^d)</td>
<td>325 3</td>
<td>0.46 (0.14–0.65)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private home</td>
<td>726 30</td>
<td></td>
</tr>
<tr>
<td>Dormitory</td>
<td>423 92</td>
<td>4.54 (2.56–8.04)</td>
</tr>
</tbody>
</table>

Data were adjusted for several variables (type of employment, working area, and residence) using logistic regression analysis. PSPF, poultry slaughtering and processing facility; MSPF, mammal slaughtering and processing facility; OR, odds ratio; CI, confidence interval; Ref. reference.

\(^a\)A company that performs work on a contract basis and arranges to supply materials.

\(^b\)A company that signs a contract to perform some or all of the obligations of the contractor.

\(^c\)Inspectors (e.g., veterinarians), cafeteria staff, environmental service workers, security workers, etc.

\(^d\)Workers performing tasks other than slaughtering livestock and processing livestock products.

\(*p<0.05, **p<0.01, ***p<0.001.

---

**Table 3. Comparison of asymptomatic patients between native Korean and foreign employees working in SPFs with confirmed COVID-19**

<table>
<thead>
<tr>
<th>Facility type</th>
<th>Symptoms</th>
<th>Nationality</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Foreign</td>
<td>Native</td>
</tr>
<tr>
<td>PSPF</td>
<td>Total</td>
<td>92 (100.0)</td>
<td>30 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>61 (66.3)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>31 (33.7)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>MSPF</td>
<td>Total</td>
<td>70 (100.0)</td>
<td>88 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>42 (60.0)</td>
<td>36 (40.9)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td>28 (40.0)</td>
<td>52 (59.1)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). Data were analyzed using the chi-square test to assess differences in the percentage values.

SPF, slaughtering and processing facility; PSPF, poultry SPF; MSPF, mammal SPF.

\(*p<0.05.

---

https://doi.org/10.24171/j.phrp.2023.0035
Multivariate logistic regression analysis showed that the high-risk areas for COVID-19 transmission in the SPFs were the refrigeration/freezing area, the by-product processing area, and the carcass cutting area, with 12.1-fold, 5.2-fold, and 5.0-fold higher risks of COVID-19, respectively, than the office area. Potential contributors to the risk of respiratory viral outbreaks in these areas include a low-temperature environment, a low ventilation rate and continuous air recirculation, stainless steel machinery and equipment, proximity between workers, and intense physical labor [19]. Studies have reported that SARS-CoV-2 survives longer in environments with higher relative humidity and lower temperature, as well as on stainless steel surfaces, resulting in an increased risk of COVID-19 [20,21]. Moreover, complying with infectious disease prevention and control measures is difficult when working in proximity to coworkers, as is wearing masks due to the intense physical work required [22]. Furthermore, Iulietto et al. [22] found that the noise level of machines in the workplace was 85 to 100 dB, and workers had to shout at 85 dB or louder to communicate. This reportedly increases the risk of COVID-19 by promoting droplet production [23]. In a German slaughterhouse, similar to our study, the infection risk was 2.4 times and 2.3 times greater for carcass cutting and slaughter workers, respectively, compared with their counterparts working in the office [24]. Additionally, in a mass outbreak in a slaughterhouse in the US, the incidence of COVID-19 was higher among employees cutting carcasses, processing livestock products, and slaughtering than in those who worked in other departments; this was attributed to the difficulty keeping a safe distance from coworkers [25]. Overall, these results indicate that the working environment is a major risk factor for infection transmission. Employees in charge of inspection have limited exposure to COVID-19 because they rarely enter the slaughtering area, as their role involves inspecting the pathological conditions of the slaughtered livestock. In overseas cases, the inspection staff who rarely entered the slaughtering area were not infected [26]. However, in the present study, infection was confirmed in 2 inspection staff members in facility B among the 5 SPFs. During breaks and at lunchtime, employees leave their work areas and gather in cafeterias and break rooms to remove their masks and eat. These common areas are conducive to the spread of viruses among employees [27]. Therefore, the inspection staff were assumed to have been infected with COVID-19 in this public area.

The risk of COVID-19 was 21 times higher among employees of subcontractors than among contractor employees. The contractor provides the slaughterhouse facilities and offers tasks to subcontractors according to consumer demand. Subcontractors manage contracting with producers, slaughtering, and processing. Therefore, the core activities of an SPF, such as receiving livestock, slaughtering, deboning, refrigeration/freezing, cutting, processing, and packaging, are primarily performed by subcontractors. These activities are conducted in work environments with a high risk of COVID-19, and because they require intense labor, they provide a constant risk of occupational diseases such as musculoskeletal disorders. Therefore, it is difficult to distinguish between symptoms of COVID-19 and those of occupational diseases, hindering the early-stage detection of COVID-19 and resulting in a high risk of outbreak [27]. According to a study by Mallet et al. [27], the risk of COVID-19 among subcontractor employees was 3 times higher than that among contractor employees in a French abattoir facility. In a German slaughterhouse in the study by Finci et al. [23], the risk of COVID-19 among the employees of subcontractors was 14 times higher than that among employees of the contractor. A study in the US showed that the cumulative incidence of COVID-19 was 1.8 times higher in non-regular workers at a slaughterhouse facility.

### Table: Comparison of Reverse Transcription RT-PCR Ct Values by Nationality and Facility Type

<table>
<thead>
<tr>
<th>Facility type</th>
<th>Nationality</th>
<th>Mean</th>
<th>Student t</th>
<th>p</th>
<th>RT-PCR Ct value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSPFs (n=122)</td>
<td>Native</td>
<td>18.3</td>
<td>3.047</td>
<td>0.003**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foreign</td>
<td>22.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSPFs (n=158)</td>
<td>Native</td>
<td>20.3</td>
<td>2.675</td>
<td>0.008**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foreign</td>
<td>22.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Severe acute respiratory syndrome coronavirus 2 viral loads by nationality among employees with confirmed COVID-19 working at PSPFs and MSPFs. Data, consisting of n samples with Ct values, were analyzed using the Student t-test to examine differences in the average reverse transcription RT-PCR Ct values of patients with confirmed COVID-19 by nationality. **p < 0.01.

PSPFs, poultry slaughtering and processing facility; MSPFs, mammal slaughtering and processing facility; RT-PCR, real-time polymerase chain reaction; Ct, cycle threshold.
The findings of this study also showed that the risk of COVID-19 was higher among the employees of subcontractors than among contractor employees. Foreign workers had 5.3-fold and 3.0-fold higher risk of COVID-19 than native Korean workers in PSPFs and MSPFs, respectively. The proportions of asymptomatic cases were 66.3% and 60.0% among foreigners working in PSPFs and MSPFs, respectively; these were higher than those of their native Korean counterparts (40.0% and 40.1%, respectively). According to a study by He et al. [28], the proportion of asymptomatic cases among patients with COVID-19 was estimated to be 15% to 20%, and the present study reported a high proportion of asymptomatic cases in the SPFs. To verify whether the delay in COVID-19 detection impacted the proportion of asymptomatic cases, for both PSPFs and MSPFs, the viral loads of the employees confirmed to have COVID-19 were compared using RT-PCR. The results showed that the average Ct value was higher among foreign employees than native Korean employees. This suggests that COVID-19 confirmation took longer in foreign employees than in the native Korean workers. Thus, it was assumed that foreign employees had either had no symptoms, had mild symptoms in the past that went unrecognized, or had symptoms but did not report them, resulting in the spread of COVID-19. Additionally, the fact that many of the foreign employees lived in dormitories may have affected the viral spread. These results show that foreign workers are an important factor in COVID-19 transmission. The number of foreign employees in Korea is increasing due to the sharp drop in the working population following low birth rates in this rapidly aging society [29]. Foreign workers, who primarily hold non-regular positions, engage in physically demanding tasks and are susceptible to infectious diseases due to their communal living arrangements in dormitories [30]. These residences are often located on the outskirts of the city, inside the workplace, or in a factory, where access to hospitals or medical welfare facilities is difficult [31]. Furthermore, foreign workers’ use of medical institutions may be limited due to treatment costs, poor protection of rights, and communication difficulties. Those without a residence permit have limited access to medical services and often avoid treatment and consultations for infectious diseases out of fear of being deported [32].

This study had some limitations. First, only 5 SPFs that reported outbreaks between January and June 2021 had COVID-19 test records for all employees. Thus, the results may not be representative of all SPFs with an outbreak during that period in Korea. Second, the calculated risks of COVID-19 for contractors and subcontractors may have been underestimated. Foreign workers are often hired by main contractors through a human resource agency. In some cases, the foreign workers, who are non-regular workers, are classified as employees of the main contractor even though they are employees of subcontractors. Therefore, considering that slaughterhouse facilities have many confirmed foreign workers, the risk of subcontractors may have been underestimated; hence, caution is needed in future analysis. Third, data may have been omitted regarding confirmed cases of community transmission. A limit exists to tracking the people classified as close contacts after an SPF employee or visitor moves to another area, which may contribute to more cases of community spread and additional outbreaks. Therefore, the attack rate is likely an underestimate of the actual prevalence. Fourth, SARS-CoV-2 transmission can occur through multiple routes in SPFs. Identifying risk factors in facilities with many confirmed cases can be difficult due to the extensive transmission that has already occurred. Additionally, regression analysis may be insufficient to identify higher risk factors in situations where ventilation systems, workplace density, and housing arrangements for workers differ. Consequently, analyzing epidemiological data from each facility is necessary to identify high-risk work environments in a facility-specific manner. Fifth, Ct values exhibit notable variability, and in patients infected with SARS-CoV-2, they decrease gradually during the first week of infection and subsequently increase progressively over time [33]. Nevertheless, in this study, it was assumed that all patients with COVID-19 from 1 of the 5 facilities had contracted the virus through contact with other confirmed cases within the same facility, and that uniform sample amounts were collected from identical locations. Moreover, a higher Ct value was presumed to correspond to a longer infection period. Sixth, personal information collection for contacts was not explicitly stated in the Infectious Disease Control and Prevention Act, limiting the ability to adjust for demographic characteristics such as sex and age, which are recognized risk factors. Consequently, this study reports risk factor findings based on the social and spatial characteristics of SPF employees, including the type of employment, working area, and type of residence.

**Conclusion**

Between January and June 2021, 402 COVID-19 cases were reported at 5 domestic SPFs, with 280 people infected in the facilities and 122 infected by community transmission due to outbreaks. In contrast with overseas studies, the attack rate of COVID-19 in domestic SPFs was lower in larger facilities than in smaller facilities, and additional research is needed.
to determine the cause of this finding. SPFs are associated with many potential risk factors for COVID-19, including social and spatial factors. The risk levels of COVID-19 in the refrigeration/freezing, by-product processing, and carcass cutting areas were 12.1 times, 5.2 times, and 5.0 times higher than that in the office area, respectively. Therefore, to prevent a COVID-19 outbreak, it is important to conduct periodic preemptive testing and symptom monitoring of those working in spaces with a high risk of COVID-19 exposure and to continuously disinfect common spaces. Social risk factors include employer type and foreign worker status (nationality). At PSPFs, the COVID-19 risk was 21.0 times higher among the employees of subcontractors than the employees of contractors. Regarding nationality, foreign workers in PSPFs and MSPFs had 5.3-fold and 3.0-fold higher risk of COVID-19, respectively, than domestic workers. Therefore, in the event of a confirmed COVID-19 case, an outbreak can be prevented by isolating a wide range of contacts or by conducting preemptive COVID-19 testing of all employees in the facility. Foreign workers are an important part of domestic industrial activities as well as slaughterhouse facilities and will gradually become more relied upon in the future. However, in the context of infection control, they face difficulties in daily life, including challenges receiving treatment at domestic medical institutions and communication issues. Therefore, to manage infectious diseases efficiently in domestic SPFs, continuous efforts to improve the infection control system and environmental risk factors within each facility are warranted, as well as a better understanding of the effects of viral transmission, especially for foreign workers.

Supplementary Material

Table S1. COVID-19 outbreak cases in Republic of Korea;
Table S2. Univariate analysis of risk factors for COVID-19 in PSPFs and MSPFs. Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0035.

Notes

Ethics Approval
This study was approved by the Korea Disease Control and Prevention Agency Institutional Review Board (IRB No: 2022-10-2-PE-A).

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

Funding
None.

Availability of Data
The data used in this study are protected under the Personal Information Protection Act.

Authors’ Contributions
Conceptualization: all authors; Date curation: all authors; Formal analysis: all authors; Investigation: SC, Methodology: all authors; Project administration: YKL, TJS; Resources: all authors; Software: all authors; Supervision: TJS; Validation: all authors; Visualization: all authors; Writing—original draft: SC; Writing—review & editing: YKL, TJS. All authors read and approved the final manuscript.

Additional Contributions
We thank the relevant ministries, including those at local and provincial levels, for their effort in responding to COVID-19 outbreaks.

References


Correlations between regional characteristics of counties and the ratio of intracounty to extracounty sources of COVID-19 in Gangwon Province, Republic of Korea

Seungmin Jeong1,2, Chaeyun Lim1, Sunhak Bae3, Youngju Nam1, Eunmi Kim1, Myeonggi Kim1, Saerom Kim1, Yeojin Kim1

1Gangwon Centre for Infectious Diseases, Gangwon, Republic of Korea
2Department of Preventive Medicine, Kangwon National University Hospital, Chuncheon, Republic of Korea
3Department of Geography Education, College of Education, Kangwon National University, Chuncheon, Republic of Korea

ABSTRACT

Objectives: This study aimed to examine the correlations between the regional characteristics of counties in Gangwon Province, Republic of Korea and the ratio of intracounty to extracounty sources of coronavirus disease 2019 (COVID-19) infection.

Methods: The region of the infectious contact was analysed for each COVID-19 case reported in Gangwon Province between February 22, 2020 and February 7, 2022. The population, population density, area, the proportion of urban residents, the proportion of older adults (>65 years), financial independence, and the number of adjacent counties were assessed for each of the 18 counties in Gangwon Province. Correlation coefficients between regional characteristics and the ratio of intracounty to extracounty infections were calculated.

Results: In total, 19,645 cases were included in this study. The population, population density, proportion of older adults, and proportion of urban residents were significantly correlated with the ratio of intracounty to extracounty infections. A stratified analysis with an age cut-point of 65 years showed that the proportion of older adults had a significant negative correlation with the ratio of intracounty to extracounty infections. In other words, the proportions of extracounty infections were higher in counties with higher proportions of older adults.

Conclusion: Regions with ageing populations should carefully observe trends in infectious disease outbreaks in other regions to prevent possible transmission.

Keywords: COVID-19; Infection control; Local government

Introduction

In Republic of Korea, county authorities are responsible for managing many infectious
diseases, including coronavirus disease 2019 (COVID-19) [1]. The statistics of outbreaks of infectious diseases, including COVID-19, are aggregated by county. In addition, epidemiological investigations on COVID-19 patients are conducted by county-level health authorities (public health centres) in the county where each case is confirmed. The county's public health centre is obligated to disinfect places visited by patients with confirmed infection and has the authority to order isolation of contacts of patients with confirmed infection. Infection transmission across county boundaries necessitates collaboration with public health centres in other counties, which can be complicated. If the incidence of extracounty infections is high, more attention needs to be paid to outbreaks in surrounding counties, which requires collaborative work with health authorities in other counties. If the source of infection crosses county borders, the responsibility for infection control is unclear, leading to an increased risk of poor infectious disease management [2]. Therefore, it is important to review the ratio of intracounty to extracounty transmission in each county. Furthermore, identifying characteristics associated with a low ratio of intracounty to extracounty transmission—implying a high level of extracounty transmission—could help health authorities in counties with similar characteristics manage the spread of infectious diseases.

This study investigated the correlations between the ratio of intracounty to extracounty transmissions and county characteristics, including the population size, population density, and proportion of older residents.

Materials and Methods

We used a database containing information on cases of COVID-19 in Gangwon Province confirmed using polymerase chain reaction tests. The database included findings from basic and in-depth epidemiological investigations, comprising demographic information (sex, age, and occupation, region in which the COVID-19 test was performed, and region of residence), epidemiological information (date of diagnosis, date of onset of COVID-19 symptoms, presence of symptoms, and the cycle threshold value), and information from the infection schematic created based on in-depth epidemiological investigations (relationship between the person who transmitted the infection and the infected person, suspected place in which transmission occurred, and suspected date and time of transmission). The database was managed and accessed by the Gangwon Provincial Office.

The region of the infectious contact was analysed for each COVID-19 case reported in Gangwon Province from February 22, 2020, when the first case occurred, to February 7, 2022. Cases of infections from overseas arrivals and those in detention centres, military units, and nursing homes were excluded. The region of the person who transmitted the infection (transmitter) was classified into (1) the same county/city (intracounty), (2) a different county/city (extracounty), and (3) cases with no information on the transmitter. The region of the person who transmitted the infection (transmitter) was classified into (1) the same county/city (intracounty), (2) a different county/city (extracounty), and (3) cases with no information on the transmitter. The transmission rate of intracounty to extracounty infections was calculated. The population, population density, area (size of the jurisdictional area), proportion of urban residents in the county, proportion of older adults (>65 years) in the county, financial independence, and the number of adjacent counties were assessed for all 18 counties in Gangwon Province. The correlation coefficient (CC) between each regional characteristic and the ratio of intracounty to extracounty infections was calculated, and p-values were used to test for statistical significance. A sensitivity analysis based on age was conducted to calculate the CCs between the county characteristics and the proportion of extracounty transmission. The analysis was performed using SAS ver. 9.4 (SAS Institute Inc.).

The study was approved by the Institutional Review Board (IRB) of Kangwon National University Hospital (IRB No: KNUH-2021-02-001).

Results

During the analysis period, 20,658 COVID-19 cases were reported in Gangwon Province, of which 19,645 cases satisfied the criteria for inclusion in the analysis. No information on the transmitter was available in 2,956 cases (25.2% of all cases). Table 1 shows the intracounty to extracounty transmission ratio in each county. Wonju County had the highest ratio...
(4.13), and Goseong County had the lowest ratio (0.62). Table 2 shows the correlations between the county characteristics and the ratio of intracounty to extracounty transmission. Population (CC, 0.57; \( p = 0.01 \)), population density (CC, 0.57; \( p = 0.01 \)), the proportion of older adults (CC, −0.77; \( p < 0.01 \)), and the proportion of urban residents (CC, 0.56; \( p = 0.02 \)) were significantly correlated with the ratio of intracounty to extracounty transmissions. Of the county characteristics, the proportion of older adults was the most strongly and significantly correlated. Therefore, the cases were divided according to age (younger and older than 65 years) to examine this correlation in more detail (Table 3). Both the total population and the proportion of older adults were significantly negatively correlated with the ratio of intracounty to extracounty transmissions. A sensitivity analysis based on age was conducted to evaluate the correlations between each regional characteristic and the proportion of extracounty transmission. The proportion of older adults and the proportion of urban residents were significantly correlated with the ratio of intracounty to extracounty transmissions, with CCs of −0.64 and 0.54, respectively. Figure 1 shows a scatterplot of significant correlations between the ratio of intracounty to extracounty transmission and county characteristics. The ratio of intracounty to extracounty transmission showed a stronger linear relationship to the proportion of older adults than to any other county characteristics.

**Discussion**

The proportion of older adults was the county characteristic that showed the highest correlation with the ratio of intracounty to extracounty infections. In the age-stratified analysis, the negative correlation between the proportion

---

### Table 1. Ratio of intracounty to extracounty transmission in each county

<table>
<thead>
<tr>
<th>County</th>
<th>Total cases of COVID-19 (n)</th>
<th>Intracounty transmission</th>
<th>Extracounty transmission</th>
<th>No information on the transmitter</th>
<th>Ratio of intracounty to extracounty transmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wonju</td>
<td>5,250</td>
<td>3,300 (62.9)</td>
<td>799 (15.2)</td>
<td>1,151 (21.9)</td>
<td>4.13</td>
</tr>
<tr>
<td>Chunchon</td>
<td>3,483</td>
<td>1,795 (51.5)</td>
<td>672 (19.3)</td>
<td>1,016 (29.2)</td>
<td>2.67</td>
</tr>
<tr>
<td>Gangneung</td>
<td>2,604</td>
<td>1,396 (53.6)</td>
<td>479 (18.4)</td>
<td>729 (28.0)</td>
<td>2.91</td>
</tr>
<tr>
<td>Sokcho</td>
<td>1,656</td>
<td>903 (54.5)</td>
<td>348 (21.0)</td>
<td>405 (24.5)</td>
<td>2.59</td>
</tr>
<tr>
<td>Donghae</td>
<td>1,347</td>
<td>868 (64.4)</td>
<td>226 (16.8)</td>
<td>253 (18.8)</td>
<td>3.84</td>
</tr>
<tr>
<td>Hongcheon</td>
<td>1,042</td>
<td>594 (57.0)</td>
<td>294 (28.2)</td>
<td>154 (14.8)</td>
<td>2.02</td>
</tr>
<tr>
<td>Cheorwon</td>
<td>615</td>
<td>376 (61.1)</td>
<td>147 (23.9)</td>
<td>92 (15.0)</td>
<td>2.56</td>
</tr>
<tr>
<td>Taebaek</td>
<td>468</td>
<td>263 (56.2)</td>
<td>112 (23.9)</td>
<td>93 (19.9)</td>
<td>2.35</td>
</tr>
<tr>
<td>Pyeongchang</td>
<td>438</td>
<td>193 (44.1)</td>
<td>171 (39.0)</td>
<td>74 (16.9)</td>
<td>1.13</td>
</tr>
<tr>
<td>Samcheok</td>
<td>384</td>
<td>182 (47.4)</td>
<td>141 (36.7)</td>
<td>61 (15.9)</td>
<td>1.29</td>
</tr>
<tr>
<td>Yangyang</td>
<td>383</td>
<td>166 (43.3)</td>
<td>127 (33.2)</td>
<td>90 (23.5)</td>
<td>1.31</td>
</tr>
<tr>
<td>Yeongdeok</td>
<td>352</td>
<td>154 (43.8)</td>
<td>132 (37.5)</td>
<td>66 (18.8)</td>
<td>1.17</td>
</tr>
<tr>
<td>Hoengseong</td>
<td>351</td>
<td>111 (31.6)</td>
<td>161 (45.9)</td>
<td>79 (22.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Goseong</td>
<td>348</td>
<td>112 (32.2)</td>
<td>180 (51.7)</td>
<td>56 (16.1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Jeongseon</td>
<td>302</td>
<td>161 (53.3)</td>
<td>104 (34.4)</td>
<td>37 (12.3)</td>
<td>1.55</td>
</tr>
<tr>
<td>Yanggu</td>
<td>230</td>
<td>145 (63.0)</td>
<td>37 (16.1)</td>
<td>48 (20.9)</td>
<td>3.92</td>
</tr>
<tr>
<td>Hwacheon</td>
<td>201</td>
<td>101 (50.2)</td>
<td>62 (30.8)</td>
<td>38 (18.9)</td>
<td>1.63</td>
</tr>
<tr>
<td>Inje</td>
<td>191</td>
<td>80 (41.9)</td>
<td>79 (41.4)</td>
<td>32 (16.8)</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

---

### Table 2. Correlations between county characteristics and the ratio of intracounty to extracounty transmission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population</th>
<th>Sensitivity analysis&lt;sup&gt;a)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>( p )</td>
</tr>
<tr>
<td>Population (n)</td>
<td>0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Area (km&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>−0.42</td>
<td>0.09</td>
</tr>
<tr>
<td>Population density (/km&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Proportion of older adults (%)</td>
<td>−0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proportion of urban residents (%)</td>
<td>0.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Financial independence</td>
<td>0.46</td>
<td>0.05</td>
</tr>
<tr>
<td>No. of adjacent counties</td>
<td>−0.18</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<sup>a</sup>Correlation with extracounty transmission proportion.

---

https://doi.org/10.24171/j.phrp.2023.0014

221
of older adults in the county and the ratio of intracounty to extracounty transmissions was significant in all age groups. These findings suggest that population ageing in a region affects not only the characteristics of infections in older adults, but also the characteristics of infections in younger individuals living in the same region.

COVID-19 is a respiratory infectious disease closely related to social gatherings [3]. Counties with ageing populations could be expected to have fewer social gatherings with people from other counties than counties with younger populations.
Older adults tend to have smaller networks and travel shorter distances, and counties with ageing populations often have poor transportation options [4]. Therefore, we expected that counties with ageing populations would have less interaction with other counties and less disease transmission from individuals in other counties. However, the observed trend was contrary to our expectations. Therefore, in counties with ageing populations, it is necessary to carefully observe the trends in infectious disease outbreaks in other counties and prepare adequate measures to prevent transmission.

Our study has some limitations. First, we only investigated COVID-19 cases in Gangwon Province. Second, approximately 25.2% of cases did not have information on the transmitter, so the results may have been biased. Third, cases of transmission from Gangwon Province to regions outside Gangwon Province were not investigated.

Of the county characteristics assessed, population, population density, the proportion of older adults, and the proportion of urban residents were significantly related to the ratio of intracounty to extracounty transmission. Of these factors, the proportion of older adults was of particular importance. Based on the findings of this study, counties with ageing populations should carefully observe trends in infectious disease outbreaks in nearby counties to prevent possible transmission. Additional research is needed to determine how county characteristics, such as the proportion of older adults in the county population, affect the transmission of infectious diseases. In addition, a nationwide study should be conducted to enable an in-depth analysis of regional characteristics and the spread of infectious diseases between regions.

Notes

Ethics Approval
This study was approved by the Institutional Review Board of Kangwon National University Hospital (IRB No: KNUH-2021-02-001) and performed in accordance with the principles of the Declaration of Helsinki. 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
All data generated or analysed during this study are included in this published article. Other data may be requested through the corresponding author.

Authors’ Contributions
Conceptualization: SJ, SB; Data curation: CL, YN, EK, MK, SK, YK; Formal analysis: SJ, SB; Methodology: SJ, CL, SB; Validation: SJ, SB; Writing—original draft: SJ, CL; Writing—review & editing: all authors. All authors read and approved the final manuscript.

References

https://doi.org/10.24171/j.phrp.2023.0014
Temporal association between the age-specific incidence of Guillain-Barré syndrome and SARS-CoV-2 vaccination in Republic of Korea: a nationwide time-series correlation study

Hyunju Lee1, Donghyok Kwon1, Seoncheol Park2,3, Seung Ri Park4, Darda Chung5, Jongmok Ha4,6

1Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
2Department of Mathematics, Hanyang University, Seoul, Republic of Korea
3Research Institute for Natural Sciences, Hanyang University, Seoul, Republic of Korea
4Gyeonggi Infectious Disease Control Center, Gyeonggi Provincial Government, Suwon, Republic of Korea
5Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
6Department of Neurology, Yeoncheon Public Medical Center, Yeoncheon, Republic of Korea

ABSTRACT

Objectives: The incidence of Guillain-Barré syndrome (GBS) changed significantly during the coronavirus disease 2019 (COVID-19) pandemic. Emerging reports suggest that viral vector-based vaccines may be associated with an elevated risk of GBS.

Methods: In this nationwide time-series correlation study, we examined the age-specific incidence of GBS from January 2011 to August 2022, as well as data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations and infections from February 2021 to August 2022. We compared the forecasted estimates of age-specific GBS incidence, using the pre-SARS-CoV-2 period as a benchmark, with the actual incidence observed during the post-vaccination period of the pandemic. Furthermore, we assessed the temporal association between GBS, SARS-CoV-2 vaccinations, and COVID-19 for different age groups.

Results: In the age group of 60 and older, the rate ratio was significantly elevated during June-August and November 2021. A significant, strong positive association was observed between viral vector-based vaccines and GBS incidence trends in this age group ($r = 0.52$, $p = 0.022$). For the 30 to 59 years age group, the rate ratio was notably high in September 2021. A statistically significant, strong positive association was found between mRNA-based vaccines and GBS incidence in this age group ($r = 0.61$, $p = 0.006$).

Conclusion: Viral vector-based SARS-CoV-2 vaccines were found to be temporally associated with an increased risk of GBS, particularly in older adults. To minimize age-specific and biological mechanism-specific adverse events, future vaccination campaigns should adopt a more personalized approach, such as recommending homologous mRNA-based SARS-CoV-2 vaccines for older adults to reduce the heightened risk of GBS.

Keywords: COVID-19; COVID-19 vaccines; Guillain-Barré syndrome; SARS-CoV-2
Introduction

Since the World Health Organization declared a global pandemic in March 2020 [1], nationwide vaccination campaigns against coronavirus disease 2019 (COVID-19) have played a crucial role in achieving population-level immunity and preventing severe outcomes [2]. However, the consequences of widespread exposure to novel immune stimuli, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccines, are still being investigated [3].

As of August 2022, there are 3 primary vaccine mechanisms utilized in the Republic of Korea: viral vector-based ChAdOx1-S/nCoV-19 (Oxford-AstraZeneca) and Ad.26.COV2.S (Janssen); mRNA-based BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines; and the recombinant protein NVX-CoV2373 (Novavax) vaccine, which is the latest addition to the arsenal.

In our previous study, which explored the correlation between changes in the respiratory and gastrointestinal infectious disease landscape and Guillain-Barré syndrome (GBS) incidence, we hypothesized that the significant increase in GBS from June 2021 to November 2021 might be attributed to the introduction of SARS-CoV-2 vaccines, specifically viral vector-based vaccines [4]. This hypothesis has been supported by several large database-driven studies employing prospective surveillance, retrospective cohort, or self-controlled case series study designs [5–8]. However, these methodologies do not account for seasonal patterns or incorporate historical data that could serve as a comparative baseline or reference for forecasting. Consequently, there was a need for a more intuitive approach.

Building upon our previous research, our objectives were to (1) compare the projected age-specific GBS incidence rates with the actual incidence observed during the post-vaccination pandemic period (February 2021 to August 2022), and (2) assess the temporal relationship between GBS, SARS-CoV-2 vaccination, and COVID-19 across various age groups, as well as the biological mechanisms of the vaccines.

Materials and Methods

Study Design

We carried out a nationwide longitudinal, time-series correlation study spanning from 2011 to 2022. We compared the real-world age-specific incidence of GBS during the pandemic post-vaccination period (February 2021 to August 2022) to the forecasted estimates based on the pre-vaccination period reference (January 2011 to January 2021). Furthermore, we assessed the temporal association between the incidence of GBS and either SARS-CoV-2 vaccination or COVID-19 during the post-vaccination period. The results were detailed by stratifying relevant age groups and vaccine mechanisms.

Designation of Age Groups

The designation of age groups was based on 2 references: vaccine rollout policy and the results from our previous study on the pandemic incidence of GBS. First, regarding vaccination policy, The Republic of Korea’s vaccine rollout during the first 2 quarters of 2021 (February to June) was primarily age-specific. The first quarter targeted patients and workers in nursing homes and facilities (age <65 years), primary medical responders in the field, and hospital personnel. The second quarter included patients and workers in nursing homes and facilities (age <65 years), residents of COVID-vulnerable facilities (homeless shelters and elder homes), and adults aged ≥60 years (initially age ≥75 years from April and age 60 to 75 years from June). Moreover, after reports of thrombosis with thrombocytopenia syndrome in younger populations, viral vector-based vaccines were contraindicated for those aged <30 years. Secondly, in relation to our previous study’s results, we observed a significant increase in GBS incidence for age groups over 60. Consequently, we trichotomized the age groups as follows: 0 to 29, 30 to 59, and ≥60 years.

Data Collection

The National Health Insurance Service (NHIS) database was used to obtain nationwide incidence and demographic data on patients newly diagnosed with GBS, who were either hospitalized or received outpatient treatment from January
2021 to August 2022.

In comparison to our prior research [4], we have expanded our reference timeframe from 2017–2019 to 2011–2020 to enhance the accuracy of our forecasts. Additionally, we have lengthened the vaccination periods from under one year to one and a half years to bolster our analysis.

In patients with a primary diagnosis of GBS (International Classification of Diseases, 10th Revision: G61.0, n = 12,433), there were 10,577 cases during the pre-vaccination period (January 2011 to January 2021) and 1,856 cases in the post-vaccination period (February 2021 to August 2022).

The data on SARS-CoV-2 vaccination, such as manufacturer, dose number, and age distribution, obtained during the post-vaccination period of the pandemic, were also extracted from the NHIS database.

The Korea Disease Control and Prevention Agency (KDCA) database was utilized to obtain nationwide SARS-CoV-2 infection data from January 2020 to August 2022 for comparison with SARS-CoV-2 vaccines. This data included all variant types and reinfection statuses.

Statistical Analysis
For the time-series analysis, a Gaussian regression model was chosen to predict the number of GBS patients, taking into account both the general trend and seasonality. This model was used to forecast the expected incidence and 95% prediction intervals of GBS based on the pre-vaccination reference period from January 2011 to January 2021.

The cumulative frequency of new-onset GBS and rate ratios (RRs) between observed and expected values during the post-vaccination period of the pandemic were calculated for the total population and for specific age groups (0 to 29, 30 to 59, and ≥ 60 years). The RR was determined by comparing the expected value (predicted using a regression model) to the observed value (the actual number of reported GBS cases). An RR not equal to 1.0 at the 5% level was deemed clinically significant.

We determined the temporal association between GBS and SARS-CoV-2 vaccination, stratified by biological mechanism (viral vector-based, mRNA-based, and protein recombinant vaccines), using Pearson correlation analysis. The correlation coefficient (r) was calculated to assess the trends in the absolute difference in cumulative frequency between the expected and observed cases of GBS, SARS-CoV-2 vaccination, and COVID-19. The degree of association adhered to a conventional paradigm: weak (0.10 ≤ r < 0.30), moderate (0.30 ≤ r < 0.50), and strong (r ≥ 0.50) [9].

Data analysis was conducted using R statistical software ver. 4.1.2 (The R Foundation). The R forecast package includes optimal values for level, trend, and seasonality parameters, which were employed in the statistical analysis of this study [10].

Ethics Approval
The Institutional Review Board of the KDCA exempted this study from ethical approval (2022-01-03-PE-A) because of the retrospective analysis of de-identified data that were already obtained through epidemiological investigation, presented minimal privacy or confidentiality risk to participants, and met the current public health interest requirements. All study procedures have been reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The requirement for consent was waived because we retrospectively collected de-identified data.

Results
Real-World GBS Incidence during the Pandemic Post-Vaccination Period versus Forecasted Estimates
Overall, there was no significant difference between the observed and predicted cumulative frequency of GBS for all age groups combined. However, when examined on a monthly basis, the RR was significantly elevated in September 2021 for the 30 to 59 years age group (RR, 1.57; 95% confidence interval [CI], 1.00–3.89).

For individuals aged 60 years and older, the RR was significantly elevated in June 2021 (RR, 1.41; 95% CI, 1.08–2.03), July 2021 (RR, 1.47; 95% CI, 1.16–1.99), August 2021 (RR, 1.30; 95% CI, 1.01–1.82), and November 2021 (RR, 1.44; 95% CI, 1.07–2.19). For individuals under 30 years of age, the RR was significantly lower in April and August 2021, with RR values of 0.40 (95% CI, 0.27–0.81) and 0.44 (95% CI, 0.32–0.74), respectively. In 2022, no statistically significant differences in RR were observed across all age groups on a monthly basis (Table 1, Figure 1).

Time-Series Correlation Analysis during the Pandemic Post-Vaccination Period
We performed Pearson correlation analysis to analyze the time-series relationships of GBS with SARS-CoV-2 vaccination and COVID-19 incidence during the post-vaccination phase of the pandemic (February 2021 to August 2022).

For individuals under 30 years of age, no significant temporal association was found between GBS and either SARS-CoV-2 vaccination or COVID-19 infection. In the 30 to 59 age group, a statistically significant and strong positive temporal association was observed between the incidence of GBS and mRNA-based vaccines (r = 0.61,
Table 1. The age-specific cumulative frequency and RRs of incident Guillain-Barré syndrome during the post-vaccination period of the pandemic (February 2021 to August 2022)

<table>
<thead>
<tr>
<th>Date</th>
<th>Age &lt;30 y</th>
<th>Age 30–59 y</th>
<th>Age 60 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs.</td>
<td>Exp.</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>291</td>
<td>344</td>
<td>0.85 (0.54–1.89)</td>
</tr>
<tr>
<td>2021</td>
<td>135</td>
<td>199</td>
<td>0.68 (0.44–1.51)</td>
</tr>
<tr>
<td>February</td>
<td>12</td>
<td>14</td>
<td>0.84 (0.50–2.83)</td>
</tr>
<tr>
<td>March</td>
<td>10</td>
<td>14</td>
<td>0.70 (0.41–2.36)</td>
</tr>
<tr>
<td>April</td>
<td>8</td>
<td>20</td>
<td>0.40 (0.27–0.81)*</td>
</tr>
<tr>
<td>May</td>
<td>11</td>
<td>17</td>
<td>0.67 (0.42–1.68)</td>
</tr>
<tr>
<td>June</td>
<td>15</td>
<td>20</td>
<td>0.75 (0.50–1.51)</td>
</tr>
<tr>
<td>July</td>
<td>13</td>
<td>21</td>
<td>0.62 (0.42–1.17)</td>
</tr>
<tr>
<td>August</td>
<td>11</td>
<td>25</td>
<td>0.44 (0.32–0.74)*</td>
</tr>
<tr>
<td>September</td>
<td>16</td>
<td>17</td>
<td>0.96 (0.60–2.41)</td>
</tr>
<tr>
<td>October</td>
<td>11</td>
<td>17</td>
<td>0.64 (0.41–1.54)</td>
</tr>
<tr>
<td>November</td>
<td>13</td>
<td>16</td>
<td>0.80 (0.50–2.08)</td>
</tr>
<tr>
<td>December</td>
<td>15</td>
<td>18</td>
<td>0.82 (0.53–1.80)</td>
</tr>
<tr>
<td>2022</td>
<td>156</td>
<td>145</td>
<td>1.07 (0.69–2.39)</td>
</tr>
<tr>
<td>January</td>
<td>13</td>
<td>15</td>
<td>0.88 (0.53–2.73)</td>
</tr>
<tr>
<td>February</td>
<td>19</td>
<td>14</td>
<td>1.34 (0.78–4.56)</td>
</tr>
<tr>
<td>March</td>
<td>16</td>
<td>14</td>
<td>1.13 (0.66–3.84)</td>
</tr>
<tr>
<td>April</td>
<td>19</td>
<td>20</td>
<td>0.96 (0.64–1.95)</td>
</tr>
<tr>
<td>May</td>
<td>23</td>
<td>17</td>
<td>1.39 (0.87–3.56)</td>
</tr>
<tr>
<td>June</td>
<td>26</td>
<td>20</td>
<td>1.31 (0.87–2.63)</td>
</tr>
<tr>
<td>July</td>
<td>20</td>
<td>21</td>
<td>0.95 (0.64–1.61)</td>
</tr>
<tr>
<td>August</td>
<td>20</td>
<td>25</td>
<td>0.80 (0.57–1.35)</td>
</tr>
</tbody>
</table>

Obs., observed value; Exp., expected value; RR, rate ratio; CI, confidence interval.
*RR was calculated as Obs./Exp. p<0.05 was considered statistically significant.

No significant associations were found for other vaccine mechanisms or COVID-19 infections. In older adults (≥60 years), viral vector-based vaccines demonstrated a significant and strong positive temporal association with the incidence of GBS (r = 0.52; p = 0.022). However, no significant temporal association was observed between GBS incidence and mRNA-based vaccines (r = 0.06; p = 0.797), recombinant protein vaccines (r = −0.36; p = 0.126), or COVID-19 infection (r = −0.36; p = 0.127) (Figure 2).

Discussion

We conducted a nationwide time-series correlation study involving 1,856 cases of GBS during the pandemic following the vaccine rollout. We compared the real-world age-specific incidence of GBS with forecasted values based on pre-pandemic incidence data. Additionally, we assessed the temporal association between the time-series trends of GBS and mRNA-based vaccines (r = 0.896), while a smaller percentage received viral vector-based vaccines (10.1%). For those aged 60 and older, mRNA-based vaccines remained the predominant choice (59.4%); however, this group had the highest proportion of individuals receiving viral-vector vaccines (39.6%) (Table S1).

Our results reveal varying findings in GBS incidence among different age groups, with a particular focus on older
adults. Although age is a recognized risk factor for GBS [11,12], our estimates indicate that even after accounting for age and comparing it to the projected 2021 incidence based on historical baselines, this result remained valid. Furthermore, despite the influx of new vaccine recipients in 2022, GBS incidence aligned with the predicted outcomes. This implies that the 2021 increase in GBS incidence among older adults cannot be solely attributed to age, but was also influenced by other factors closely related to age. Considering the results of the mechanism-stratified time-series correlation analyses in conjunction with this finding, we can infer that viral vector-based vaccines may have a temporal association with increased GBS incidence. This observation supports previous studies that suggested a potential link between viral vector-based vaccines [5,6]. Additionally, while COVID-19 remains a relevant factor during the pandemic era that has a temporal association with GBS [13], the results of the correlation analysis were statistically insignificant, which is consistent with the findings from our previous study.

In September 2021, there was a notable increase in the incidence of GBS among individuals aged 30 to 59 years compared to predicted values. Moreover, a strong positive correlation was observed between mRNA-based vaccines and GBS incidence in this age group. Although this finding has not been replicated in other studies, we hypothesize that it may be due to the impact of heterologous vaccination in the 30 to 59 age group, which elicits greater immunogenicity and reactogenicity compared to homologous vaccination methods [14]. In Korea, most recipients of heterologous vaccines were initially vaccinated with viral vector-based vaccines and later received mRNA-based vaccines. Consequently, individuals aged 30 to 59 who were vaccinated with viral vector-based vaccines (primarily ChAdOx1-S/nCoV-19) in June were subsequently given mRNA-based vaccines (predominantly BNT162b2) from August to September 2021 [15]. In contrast, the vaccination rate for those aged 0 to 29 was lower than in other age groups, and the majority received mRNA-based vaccines, resulting in an insignificant temporal association between GBS and vaccination in this younger
GBS

Viral-vector based

mRNA-based

Protein recombinant

COVID-19

(Continued to the next page)
Figure 2. Summary of time-series correlation analyses (February 2021 to August 2022). The 3 variables—differential value between observed and expected Guillain-Barré syndrome (GBS) incidence; the number of severe acute respiratory syndrome coronavirus 2 vaccination stratified by biological mechanism; and the number of COVID-19 diagnosed during this period underwent Pearson correlation analyses. A scatter plot matrix is drawn in the graphic window. The lower off-diagonal presents scatter plots, the diagonal shows histograms, and the upper off-diagonal reports the Pearson correlation coefficients (with pairwise deletion). (A) Age < 30 years. (B) Age 30 to 59 years. (C) Age ≥ 60 years.

*p < 0.05, **p < 0.001 was considered statistically significant.

population. Overall, we hypothesize that the age-stratified incidence of GBS reflects a dose-response relationship with vector-based vaccines. However, additional research is needed to confirm this relationship and better understand the underlying mechanism.

Our study has several notable limitations: first, as an observational study, it does not establish causation. However, a potential dose-response relationship and the reproducibility of findings from different study designs may support causality. Nonetheless, GBS remains a rare disease, and the risk-to-benefit ratio should always be considered. Second, our study collected data on a per-dose basis, without gathering individual vaccination information. Consequently, we did not account for homologous or heterologous vaccination, which may have varying immunogenicity and reactogenicity [16,17]. Future studies addressing the cumulative effects of immune exposure should be conducted to address this issue. Third, we did not consider changes in vaccination policies throughout the study period. This may have led to minor fluctuations in vaccination patterns across age groups, but the overall impact is unclear. Relatedly, our age group structure may not accurately reflect vaccination policies, as our age groups were reconstituted from the 10-year interval data used in our previous study. To improve accuracy, future studies employing 5-year age gaps may be beneficial. Finally, our study focuses on a single ethnicity. However, the Asian population has been underrepresented in phase III trials of SARS-CoV-2 vaccines, making it crucial to collect specific adverse event data from this demographic.

In conclusion, we hypothesize that a synergistic effect between age and the viral vector-based SARS-CoV-2 vaccine mechanism may contribute to an increased risk of GBS. We propose that future vaccination campaigns adopt a more personalized approach, or “safest pathway,” to minimize age-specific and biological mechanism-specific adverse events.
For example, recommending mRNA-based vaccines instead of viral vector-based platforms and performing homologous vaccination whenever possible in older adults aged 60 years and above could be considered, until proven otherwise by other population-based studies, to avoid an increased risk of post-vaccination GBS.

Supplementary Material

Table S1. Summary of SARS-CoV-2 vaccination stratified by age groups in the post-vaccination period of the pandemic (February 2021 to August 2022). Supplementary data are available at https://doi.org/10.24171/j.phrp.2023.0050.

Notes

Ethics Approval
The Institutional Review Board of the KDCA exempted this study from ethical approval (2022-01-03-PE-A) because of the retrospective analysis of de-identified data that were already obtained through epidemiological investigation, presented minimal privacy or confidentiality risk to participants, and met the current public health interest requirements. The requirement for consent was waived because we retrospectively collected de-identified data.

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

Funding
None.

Availability of Data
The datasets are not publicly available. Any inquiries regarding the study should be directed to the corresponding authors.

Authors’ Contributions
Conceptualization: HL, SRP, DC; Data curation: HL, DK; Formal analysis: HL, SP; Methodology: HL, SRP, JH; Validation: DK; Visualization: HL, SP; Writing–original draft: HL, JH; Writing–review & editing: DC, JH. All authors read and approved the final manuscript.

Acknowledgements
The authors acknowledge the assistance of all their colleagues at the Korea Disease Control and Prevention Agency and Gyeonggi Infectious Disease Control Center for their dedication to public health and overall support for this project.

References

**Instruction for authors**

Enacted January 1, 2010
Last revised April 1, 2022

*Osong Public Health and Research Perspectives* (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health. PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials and correspondence, 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.

Before submitting a manuscript, authors should carefully read and follow the instructions for writing an article for PHRP. For issues not addressed in these instructions, authors should refer to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/recommendations/) from the International Committee of Medical Journal Editors (ICMJE). Manuscripts submitted to PHRP that do not follow these instructions will be returned to the authors without further review.

**Contact Us**

**Editorial Office:** Korea Disease Control and Prevention Agency National Center for Medical Information and Knowledge, 202 Osongsengmyung 2nd street, Osong-eup, Heungdeok-gu, Cheongju 28159, Korea
E-mail: ophrp@korea.kr

**Table of Contents**

ARTICLE PROCESSING CHARGES  
RESEARCH AND PUBLICATION ETHICS  
EDITORIAL POLICY  
SUBMISSION & PEER REVIEW PROCESS  
MANUSCRIPT PREPARATION  
FINAL PREPARATION FOR PUBLICATION

**ARTICLE PROCESSING CHARGES**

The author does not have pay publication charges for open access. The KDCA will pay to make the article open access.

**RESEARCH AND PUBLICATION ETHICS**

The journal adheres to the guidelines and best practices published by professional organizations, including the ICMJE Recommendations and the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by the Committee on Publication Ethics [COPE], Directory of Open Access Journals [DOAJ], World Association of Medical Editors [WAME], and Open Access Scholarly Publishers Association [OASPA]; https://doaj.org/bestpractice). Furthermore, all processes of handling research and publication misconduct shall follow the applicable COPE flowchart (https://publicationethics.org/resources/flowcharts).

**Human and Animal Rights**

Clinical research should be conducted in accordance with the World Medical Association’s Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Animal experiments should also be reviewed by an appropriate committee (Institutional Animal Care and Use Committee [IACUC]) for the care and use of animals. Studies involving pathogens requiring a high degree of biosafety should pass review of a relevant committee (Institutional Biosafety Committee [IBC]). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication.

**Statement of Informed Consent and Institutional Approval**

The editor of PHRP may request submission of copies of informed consent forms from human subjects in all studies and IRB approval documents. Articles where human subjects can be identified in descriptions, photographs, or pedigrees must be accompanied by a signed statement of informed consent to publish (in print and online) the descriptions, photographs, and pedigrees of each subject who can be identified. Articles describing the use of human samples in research and human experiments must be approved by the relevant review committee. Articles describing the use of animals in experiments must be approved by the relevant authorities.
Originality

Manuscripts are considered with the understanding that no part of the work has been published previously in print or electronic format and the paper is not under consideration by another publication or electronic medium.

Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication as described in the ICMJE Recommendations (http://www.icmje.org/icmje-recommendations.pdf).

Plagiarism and Duplicate Publication

Attempting to publish substantially similar work more than once without attribution of the original source(s) is considered a redundant publication. The definition of “substantially similar” is as follows: (1) at least one of the authors is common to all reports (it is likely to be plagiarism if there are no common authors); (2) the subject or study populations are the same or similar; (3) the methodology is typically identical or nearly so and; (4) the results and interpretation vary little or not at all.

If all or part of the subject population has been reported previously, it should be declared in the Materials and Methods and must be appropriately referenced. In cases where authors are concerned with any potential overlap with published manuscripts or manuscripts being reviewed, the authors must include a letter explaining how the manuscript submitted to PHRP significantly differs from other materials. For more information, please refer to ICMJE Recommendation (available at: http://www.icmje.org/recommendations/).

Authorship and the Author’s Responsibilities

Authorship credit must be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately in vestigated and resolved. The authors should meet these 4 conditions. If the number of authors exceeds 3, the specific role(s) of authors should be described at the end of the main text.

- Correction of authorship: Any requests for changes in authorship (adding author(s), removing author(s), or re-arranging the order of authors) after the initial manuscript submission and before publication should be explained in writing to the editor in a letter or e-mail from all authors. This letter must be signed by all authors of the paper. A copyright assignment must be completed by every author.
- Role of the corresponding author: The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all of the journal’s administrative requirements, such as providing the details of authorship, ethics committee approval, clinical trial registration documentation, and conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely manner, and after publication, should be available to respond to critiques of the work and cooperate with any requests from the journal for data or additional information or questions about the article.
- Contributors: Any researcher who does not meet all 4 ICMJE criteria for authorship discussed above but contributes substantively to the study in terms of idea development, manuscript writing, conducting research, data analysis, and financial support should have their contributions listed in the Notes section of the article.
- Recommendations for working with people with personal connections: Authors who intend to include minors (under the age of 19) or their family members (such as spouse, children, and relatives) in their research, including when publishing or presenting papers jointly with them, should clearly indicate this in the cover letter. For further information, please refer to the “Guidelines for Preventing Illegitimate Authorship” by the National Research Foundation of Korea (https://www.cre.re.kr/).

Conflict of Interest Statement

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.
Role of the Funding Source

The author is requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, then this should be stated.

Process for Managing Research and Publication Misconduct

When the journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the COPE (http://publicationethics.org/resources/flowcharts). The editorial boards of PHRP will carry out the discussion and decision for suspected cases. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

Complaints and Appeals Policy

The policies of PHRP are principally intended to protect the authors, reviewers, editors, and the publisher of the journal. The process of handling complaints and appeals follows the guidelines of the COPE (https://publicationethics.org/guidance/Guidelines).

Editorial Responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics, including guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.

EDITORIAL POLICY

Copyright

The Korea Disease Control and Prevention Agency (publisher) holds the copyright on all submitted materials and the right to publish, transmit, sell, and distribute them in the journal or other media. The publisher applies the Creative Commons Attribution license to works it publishes. Under this license, although the publisher retains ownership of the copyright for content, it allows anyone to download, reuse, reprint, distribute, and/or copy the content for non-commercial purposes.

Open Access License

Every article appearing in this journal will be published as open-access. Articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derives (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Author(s) do not need to permission to use tables or figures published in PHRP in other journals, books, or media for scholarly and educational purposes.

Article Sharing (Author Self-Archiving) Policy

PHRP is an open access journal, and authors who submit manuscripts to PHRP can share their research in several ways, including on preprint servers, social media platforms, at conferences, and in educational materials, in accordance with our open access policy. However, it should be noted that submitting the same manuscript to multiple journals is strictly prohibited.

Data Sharing Policy

To foster transparency, we encourage authors to state the availability of their data in your submission. This may be a requirement of your funding body or institution. If the data are unavailable to access or unsuitable to post, authors will have the opportunity to indicate why during the submission process, for example by stating that the research data are confidential.

Archiving Policy

The full text of PHRP has been archived in PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/journals/2151/) from the first volume, 2010. According to the deposit policy (self-archiving policy) of Sherpa/Romeo (http://www.sherpa.ac.uk/), authors cannot archive pre-prints (i.e., pre-refereeing), but they can archive post-print (i.e., final drafts post-refereeing). Authors can archive the publisher’s version/PDF. PHRP provides electronic backup and preservation of access to the journal content in the event the journal is no longer published by archiving the journal content in PubMed Central and the National Library of Korea.

Preprint Policy

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. PHRP allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. PHRP recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program—Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in PHRP, including DOI at PHRP. It is strongly recommended that authors cite the article in PHRP instead of the preprint at their next submission to journals.

Peer Review Policy

All papers, including those invited by the editor, are subject to peer review. PHRP has adopted a double-blind peer review policy, where the author identities remain anonymous to the reviewers, and vice versa, and the identities of the reviewers and authors are visible to (decision-making) the editor throughout the peer review process. The Editorial Board selects reviewers based on expertise, publication history, and past reviews. During the peer review process, reviewers can interact directly or exchange information (e.g., via submission systems or email) with only an editor, which is known as “independent review.” An initial decision will normally be made within 4–6 weeks after the reviewers agree to review a manuscript. No information about the review process or editorial decision process is published on the article page.

- The Editorial Office of PHRP receives and reviews all submitted manuscripts, and all submitted manuscripts are considered confidential. The submitted manuscripts are initially screened for formatting. Once the manuscript is provisionally accepted, it is sent to the 2 most relevant referees for review. The referees are selected by the editor from the Editorial Board’s database or the board members’ recommendation. The referees are then requested to evaluate the manuscript based on originality, validity, presentation, and importance and interest, and, when considered necessary, statistics.
- Acceptance of a manuscript depends on the evaluation, critiques, and recommended decision made by the referees. A referee may recommend “accept,” “minor revision,” “major revision,” and “reject.” If there are conflicting decisions between referees, or between the author and referee(s),
the Editor-in-Chief has the full right to decide whether the manuscript will be published in the journal. Three repeated decisions of "major revisions" are equivalent to rejection, and rejected papers will not be considered further.

- The reviewed manuscript with comments, recommendations, and revisions is returned to the corresponding author. The corresponding author is to submit the revised manuscript accompanied by point-to-point replies to the comments given by the editor and how the revisions have been made. There should be a reasonable explanation for any noncompliance with the recommendations. In cases where references, tables, or figures are moved, added, or deleted during the revision process, renumbering must be done so that all references, tables, and figures are cited in numeric order. If the revised paper is not received within 2 months of decision, the manuscript is considered to have been withdrawn.

- When the final decision on the acceptance of the manuscript is made, the Editorial Office notifies the corresponding author. The peer-review process takes approximately 8–12 weeks.

**MANUSCRIPT PREPARATION**

**General Requirements**

- All manuscripts must be in grammatically correct English and should be created using MS Word. The manuscript must be double-spaced and written in an A4 page format. Do not leave a space between paragraphs. Only a single font (preferably Times New Roman) should be used in 11 point with margins of 2.5 cm.
- All pages should be paginated consecutively.
- All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol. When indicating time, the 24-hour system is to be used.
- Math formulae: Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by "exp." Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

**Reporting Guidelines for Specific Study Designs**

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors are encouraged to consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

**Manuscript Types**

PHPR publishes editorials, original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews.

- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract, references, and tables and figure legends.
- **Review articles** provide concise reviews of subjects important to medical researchers, and can be written by an invited medical expert. These have the same format as original articles, but the details may be more flexible depending on the content. Manuscript limitations are 6,500 words from introduction to conclusion, 100 references, 10 figures and 10 tables. The abstract should
not exceed 200 words, and must be written as one unstructured paragraph.

- **Guidelines** are similar to original articles, but provide evidence-based recommendations expected to impact clinical research and practice. This category can include consensus-based statements of reporting standards or clinical practice guidelines.

- **Data Profiles (including Cohort Profiles)** present large data sets from specific populations that could be analyzed in epidemiological studies. Data Profiles should be structured with the following headings in the main text: Introduction, Collection, Data Resource Use, Strengths and Weaknesses, and Access. Cohort Profiles present up-to-date information about large population-based cohorts for which long-term data collection is planned. Data Profiles should be structured with the following headings in the main text: Introduction, Study Participants, Measurements, Key Findings, Strengths and Weaknesses, and Access. The main text of Data and Cohort Profiles is limited to 4,000 words, with an unstructured abstract of up to 200 words, a maximum of 7 tables and figures, and no more than 40 references.

- **Special Articles** deal with topics or issues that are relevant to public health, but without following a traditional study format. For example, articles in this category may address scientific methodology, wide-ranging ethical and social issues, scientific methodology, or other scholarly topics. Reports from consensus committees and working groups can be published as Special Articles. This category has a main text limit of 3,500 words, with an unstructured abstract of no more than 200 words, a maximum of 7 tables and figures, and no more than 40 references.

- **Brief reports** deal with issues of importance to biomedical researchers. The maximum length of the manuscript should be 2,000 words, including tables and figures.

- **Short communications** follow the general rules of the original article. The maximum length of the manuscript should be 3,000 words, including tables and figures.

- **Viewpoints** may deal with almost any topic deemed to be important in the fields of public health, ethics, health law, prevention, or health policy, and are not typically written in response to a specific article. Viewpoints should have a clear focus and present material in a well-organized and scholarly manner, but should not contain novel research findings or previously unpublished data. Although we welcome unsolicited viewpoint contributions, we request that authors contact the Editorial Office (ophrp@korea.kr) prior to submission to confirm that the proposed topic is suitable for the journal. The main text of Viewpoints is limited to 3,000 words, with an unstructured abstract of up to 150 words, a maximum of 4 tables and figures, and no more than 30 references.

- **Editorials** provide invited perspective on an area of PHRP, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required and a brief unstructured text should be prepared. Although editorials are normally invited or written by an editor, unsolicited editorials may be submitted. Manuscript limitations are 1,000 words and 20 references.

- **Commentaries** are brief articles with a narrow focus. The journal commissions most commentaries, but unsolicited commentaries will also be considered. Commentaries may undergo peer review. The length of commentaries should be limited to 1,000 words, 10 references, and 1 figure or small table.

- **Correspondence** is a comment from readers regarding a published article with a reply from the authors of the article. Manuscript limitations are 500 words, 2 tables/figures, and 5 references.

- **Book reviews** may be published. Please dispatch a book to the editorial office if you think the book is essential to public health personnel.

**Title Page**

Title page should include (1) the title of the article (less than 50 words); (2) name of the authors (first name, middle initial, last name in capitals) and institutional affiliation including the name of department(s) and institution(s) of each author; (3) name, full address (including the postal code) of the institutional affiliation, telephone and e-mail address of the corresponding author; (4) a running title of 50 characters or less including blank spaces; and (5) notes (disclaimers). Notes include ethics approval and consent to participate, conflict of interest, funding, availability of data, authors’ contributions, additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

**Abstract and Keywords**

An abstract and 3–6 relevant keywords (in alphabetical order)
are required. Abstracts should be no more than 250 words in length. Abstracts should be structured, with the following section headings: Objectives, Methods, Results, Conclusion. For selecting keywords, refer to the MeSH browser (http://www.ncbi.nlm.nih.gov/mesh).

**Highlights**

All papers must include 3–5 short sentences presenting short summary or findings in the next of title page. The highlight section should be no more than 100 words, including spaces.

**Main Body**

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name of the manufacturer. All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms “sex” (when reporting biological factors) and “gender” (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was confirmed (or waived) by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.
- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should not be repeated and the main conclusions of the study may be presented in the discussion.
- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

**References**

Authors are responsible for the accuracy and completeness of their references and for correct text citations.

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by “et al.”
- References cited in tables or figure legends should be included in sequence at the point where the table or figure is first mentioned in the main text.
- Do not cite abstracts unless they are the only available reference to an important concept.
- Uncompleted work or work that has not yet been accepted for publication (i.e., an “unpublished observation” or “personal communication” should not be cited as a reference). In the references list, references should be limited to those cited in the text and listed in the order in which they appear in the text. The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- Use of DOI is highly encouraged. Note that missing data will be highlighted at the proof stage for the author to correct.
• Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

• Journal articles

• Books

• Websites

• Conference papers

• Dissertation

Tables and Figures

Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order.

Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table (, , , ...), and notes on level of probability (*, **, *** for p).

Figures should be numbered with Arabic numerals consecutively in figure legends. The figures must not be interfered and must be clearly seen. The legend for each light microscopic image should include name of the stain and magnification. Electron microscopic images should contain an internal scale marker. All figures may be altered in size by the editor. The legends should briefly describe the data shown, explain abbreviations or reference points, and identify all units, mathematical expressions, abscissas, ordnates, and symbols.

Figures that are drawn or photographed professionally should be sent as JPG or PPT files. However, if an article receives approval for publication, files must be submitted as .tiff or .pdf. Each figure must have a caption explaining the figure. The preferred size of the images is 8 × 8 cm but 16.5 cm in width × 8 cm in length is also acceptable. It is authors’ full responsibility to submit images of sufficient quality for accurate reproduction and to approve the final color galley proof. All images must be correctly exposed, sharply focused, and prepared in files of 500 dpi or more.

When tables and figures are mentioned together in the text, they should be presented in parentheses as follows: (Table 1; Figure 1), (Tables 1, 2; Figures 1–3).

Appendix and Supplemental Data

If any materials are not enough to be included in the main text such as questionnaires, they can be listed in the Appendix. Any supplementary materials that help the understanding of readers or contain too great an amount of data to be included in the main text may be placed as supplementary data. Not only a recording of the abstract, text, audio or video files, but also data files should be added here.

FINAL PREPARATION FOR PUBLICATION

Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this
time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

**Manuscript Corrections**

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 48 hours when the manuscript editor contacts the corresponding author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

**Proofs and Reprints**

The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, the author(s) must notify the editorial office of any errors found in the file within 48 hours. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

**Errata and Corrigenda**

To correct errors in published articles, the corresponding author should contact the journal's editorial office with a detailed description of the proposed correction. Corrections that profoundly affect the interpretation or conclusions of the article will be reviewed by the editors. Corrections will be published as corrigenda (corrections of the author's errors) or errata (corrections of the publisher's errors) in a later issue of the journal.

**NOTICE:** These recently revised instructions for authors will be applied beginning with the February 2023 issue.
Author’s checklist

General Requirements

- The corresponding author (or the representative author of the co-corresponding authors) is the submitter of this manuscript.
- All manuscripts should be written in English.
- The main document with manuscript text and tables should be prepared in an MS Word (docx) or RTF file format.
- Manuscripts should be double-spaced in A4-size pages.
- Manuscripts should include line numbers.
- All pages should be numbered consecutively, starting with the abstract.

Title Page

- The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
- The title page is arranged in the following order: article title, authors’ full name(s), affiliation(s), and corresponding author’s information, running title (less than 50 characters), notes.
- The notes section including (1) ethics approval and consent to participate, (2) conflicts of interest, (3) funding, (4) availability of data, (5) author contributions, (6) additional contributions, and ORCID is in title page, not in the manuscript.

Abstract

- The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

Main Text

- The manuscript is organized according to following sequence: Title page, Abstract and keywords, Main text, References, Tables, and Figure legends.

Tables and Figures

- All tables and figures are numbered in the order of their appearance in a main text.
- Tables are included at the end of the manuscript as editable text and not as images.
- Figures are as separate files, in jpg, ppt, tiff, or pdf format.

References

- References are listed in proper format.
- All references listed in the reference section are cited in the text and vice versa.
Copyright Transfer and Conflict of Interest Disclosure Form

Title of the paper: ______________________________________________________

I. Copyright Transfer Form

The authors hereby transfer all copyrights in and to the manuscript named above in all forms and media, now or hereafter known, to the Korea Disease Control and Prevention Agency effective if and when the paper is accepted for publication in the Osong Public Health and Research Perspectives. The authors reserve all proprietary right other than copyright, such as patent rights.

Everyone who is listed as an author in this article should have made a substantial, direct, intellectual contribution to the work and should take public responsibility for it.

This paper contains works that have not previously published or not under consideration for publication in other journals.

II. Conflict of Interest Disclosure Form

All authors are responsible for recognizing any conflict of interest that could bias their work in the acknowledgments, disclosing all financial support and any other personal connections.

Please check the appropriate box below:

- □ No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

OR

- □ The authors certify that all conflicts of interest, as applicable to each author, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials are disclosed in the manuscript.
  (Please describe in detail about these interests.)

These interests may include one or more of the following: employment; consultancy within the past two years; ownership interests – including stock options – in a start-up company, the stock of which is not publicly traded; ownership interest - including stock options but excluding indirect investments through mutual funds and the like - in a publicly traded company; research funding; honoraria directly received from an entity; paid expert testimony within the past two years; any other financial relationship (e.g., receiving royalties); membership on another entity's Board of Directors or its advisory committees (whether for profit or not for profit).

- □ All authors certify that the work followed the research ethics and have approved the submission of the manuscript for publication.
Corresponding author: ___________________________ ____________________________ ________
Name                                          Signature         Date

Authors:                                      ___________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________
_________________________ ____________________________ ________

(This form must be signed by all authors in an order as appeared in the article, and should be returned to the editorial office.)