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

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Editorial

To become a more stronger and safer country

Jong-Koo Lee

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In March 2023, various indicators suggest that we are progressively emerging from the coronavirus disease 2019 (COVID-19) crisis. A crucial aspect of the post-COVID plan that must not be neglected is the government's vaccination strategy. On March 22, the government issued vaccination guidelines for the upcoming fall season to prepare for the post-COVID era [1]. To date, we have maintained a high level of population immunity. However, the uptake of the fourth dose stands at 44.3%, and the rate of winter preventive vaccinations is a mere 35.4%, reflecting a general vaccine fatigue. The assessment of the current situation is based on the low incidence and mortality rates in children, adolescents, and middle-aged adults, taking into account the cost-effectiveness of preventing disease and death. Specifically, increasing the age group eligible for last year's fourth dose and winter preventive booster from 60 to 65 years old this year seems highly sensible. This is a rational decision because the cumulative fatality rate for those under 65 years old in Korea is 0.08%, which is half of the 0.16% fatality rate for those aged 65 to 69 years old and lower than the national average of 0.11%. Our approach aligns with the World Health Organization (WHO) SAGE recommendations [2]. Most importantly, to ensure the success of these policy changes, it is essential to provide transparent information, enabling people to make informed vaccination decisions. Reassessing the vaccination program, along with data on vaccine adverse reactions and safety, is anticipated to reduce hesitancy among vaccine recipients and improve vaccination rates. In particular, a paper published last month, titled "A framework for nationwide COVID-19 vaccine safety research in the Republic of Korea: the COVID-19 Vaccine Safety Research Committee," addressed the challenge of analyzing vaccine adverse events by exploring fundamental concepts of research methodology [3]. This month's study on the incidence of heart disease following vaccination [4], although limited to the adolescent cohort, is consistent with the population-based risk assessment report from the National Academy of Medicine of Korea, using health insurance data. The findings align with those of reports from other countries, earning positive evaluations.

The Korea Disease Control and Prevention Agency offers compensation for damages based on the causality classification system (WHO-Uppsala Monitoring Centre causal assessment system) in cases where adverse reactions to vaccines are reported. As of the end of last month, a total of 135,716,807 COVID-19 vaccine doses had been administered, with a reported general adverse event rate of 3.42 cases per 1,000 doses, a major adverse event rate of 0.13 cases per 1,000 doses, and a mortality rate of 0.01 cases per 1,000 doses administered [5].

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For a report to be acknowledged as vaccine-related damage, it must satisfy the causality assessment criteria, with recognized cases classified as "definitely related," "probably related," or "possibly related." However, stringent criteria apply to category 4 adverse reactions (probably not related, unlikely). There have been 15 disease categories in subcategory 4–1 (where the timing of the adverse reaction after vaccination is plausible, but there are insufficient data about the adverse reaction), and 30 disease categories in subcategory 4–2 (where other causes are more probable than the vaccine). This has resulted in public dissatisfaction due to the strict criteria employed for causality assessment and corresponding compensation, which are constrained by the current limitations in scientific knowledge and methodological challenges. To address this issue, the government is concurrently focusing on statistical plausibility and mechanistic validity. Overcoming vaccine hesitancy is vital to ensuring a safer society as we prepare for future epidemics. Notably, the compensation program was established in response to vaccine adverse reactions during the 1994 Japanese encephalitis vaccination campaign and has primarily focused on pediatric vaccination to achieve herd immunity despite known adverse effects. Consequently, for vaccinations targeting adults with underlying conditions such as hypertension, diabetes, and heart disease, further research on factors contributing to or triggering these conditions, along with appropriate compensation, should be considered.

Despite a high vaccination rate against COVID-19, more than 70% of the population in Korea has been infected or re-infected with COVID-19, as evidenced by national survey results for N antibodies. It is essential to establish a cohort study infrastructure to assess the short-term, medium-term, and long-term health effects of hybrid or natural infection on these individuals. This includes evaluating the effects and side effects of vaccination, assessing the impact of COVID-19 infection on chronic diseases, and obtaining vital insights for restructuring the future healthcare system. Examples of important issues include delays in early cancer detection through screening and postponed treatment of diagnosed patients. The Korean Bio-Bank of the Korea National Institute of Health will play a significant role in this research.

As the COVID-19 situation stabilizes, frontline healthcare workers are transitioning back to their original duties from emergency tasks. While various chronic disease management programs have been suspended or delayed, frontline workers have resumed ongoing education and on-the-job training to enhance their work performance. The pandemic has underscored the challenges faced by frontline health workers in adapting to new job skills and responsibilities and has revealed their reluctance to work on the front lines. It has also demonstrated that personality, competence, and teamwork are more crucial than technical skills and education level. Furthermore, the education of frontline public health workers should incorporate competency-based methods using advanced IT, rather than traditional face-to-face education. However, the educational system for frontline public health workers is struggling to adapt to these changes. Innovative and transformative changes are necessary in the educational system for public health workers to cultivate versatile workers who can function in any situation and improve their ability to adapt to new technologies. In the process of overcoming the pandemic, we have learned the importance of collaborating with various professionals beyond the field of healthcare, including those in social welfare, general administration, crisis management, and community participation [6]. Therefore, the educational system for public health workers needs to be reformed to become more resilient in the face of the next pandemic.

Notes

Ethics Approval
Not applicable.

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Review Article

Points to consider when developing drugs for dry eye syndrome

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ABSTRACT

Changes in both the social environment (e.g., the increased use of electronic media) and the atmospheric environment (e.g., air pollution and dust) have contributed to an increasing incidence of eye disease and an increased need for eye care. Notably, the signs and symptoms of dry eye syndrome can impact the daily quality of life for various age groups, including the elderly, and usually requires active treatment. The symptoms of dry eye syndrome include tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities. As treatments for dry eye are being developed, a standardized guideline is needed to increase the efficiency of drug development and improve the quality of clinical trial data. In this paper, we present general considerations for the pharmaceutical industry and clinical trial investigators designing clinical trials focused on the development of drugs to treat dry eye syndrome.

Keywords: Clinical trial; Dry eye syndrome; Efficacy; Ophthalmic solutions; Safety

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Introduction

Eye diseases have been increasing in all age groups due to recent changes in the social environment such as the increased use of electronic devices (e.g., computers and cellular phones). In addition, the worsening air environment including fine particulates (e.g., dust) contributes to increases in eye disease. The need for eye care has increased because of these 2 factors. According to the Korea Pharmaceutical and Bio-Pharma Manufacturers Association, the production of ophthalmic agents (eye drops, eye ointments) has increased by approximately 10% every year over the past 3 years [1,2]. The domestic production of ophthalmic agents from 2018 to 2021 is presented in Table 1 [1,2]. In October 2020, the National Health Insurance Service took measures to reduce the price of ophthalmic agents because of the rapid increase in prescriptions for disposable eye drops [3] and because the marketing and usage of eye drops are expected to remain high.

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Table 1. Production of ophthalmic agents in Korea

	2018	2019	2020	2021	Average rate of increase (%)
Production amount (unit: 100 million won)	4,261	4,965	5,584	5,764	10.7

Source: Korea Pharmaceutical and Bio-Pharma Manufacturers Association [1,2].

Ophthalmic solutions are preparations administered to the eye, including liquid aseptic preparations applied to eye tissues such as the conjunctival sacs and solid aseptic preparations used in dissolution or suspension form. These preparations are usually made by adding excipients to the active ingredient and dissolving or suspending them in a solvent or by filling a container with excipients and the active ingredient to create a solid aseptic preparation [4]. Ophthalmic solutions include antihistamine-containing eye drops, used to alleviate symptoms such as allergic conjunctivitis, and artificial tears, used to alleviate dry eye symptoms.

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis in the tear film, resulting in tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities [5]. The eyes become sore and sensitive, with a feeling of foreign matter like grains of sand in the eye, which can lead to shooting pain and dryness. In severe cases, patients may complain of headaches, the eyes may be bloodshot, or the surface of the eye can be damaged. If it is clear that the dry eye symptoms are caused by disease, treatment of the disease improves it. Otherwise, the most common treatment is an "artificial tears" eye drop [6–9]. The signs and symptoms of dry eye syndrome are not only inconvenient but can also lower the quality of life for all age groups. As shown in Figure 1, the age groups affected by dry eye are evenly distributed from teenagers to adults in their 70s [10]. Active treatment is usually needed.

Since new treatments for dry eye continue to be developed, a standardized guideline is needed to support the efficiency of dry eye drug development and improve the quality of clinical trial data. The National Institute of Food and Drug Safety Evaluation (NIFDS) in the Ministry of Food and Drug Safety has published a relevant guideline [11]. Therefore, we suggest the general consideration when designing clinical trials, specifically for the pharmaceutical industry and clinical trial investigators who want to develop drugs for dry eye syndrome.

HIGHLIGHTS

This paper offers general considerations for designing clinical trials to develop drugs that treat dry eye syndrome, including the protocol design, study population, comparator, and efficacy endpoints. This information is intended to help the pharmaceutical industry and clinical trial investigators.

General Considerations for Clinical Trials

To conduct a clinical trial for the development of drugs to treat dry eye syndrome, the investigator should prepare a clinical trial protocol and submit the appropriate dossier according to the Pharmaceutical Affairs Act, Article 34 [12], the Regulation on Safety of Pharmaceuticals, etc, Article 24 [13], and the Regulation on Approval for Investigational New Drug Application of Drug [14]. Approval must be obtained from the Minister of Food and Drug Safety.

The design of clinical trials to develop dry eye syndrome drugs should follow the NIFDS general guidelines for clinical trials. However, special consideration must be given to the selection of the comparator, the target population, efficacy, safety, and clinical evaluation parameters.

Clinical Pharmacological Study

A clinical pharmacological study is a first-in-human trial to administer an investigational product (IP). It is necessary to conduct a clinical trial in healthy adults who can confirm the safety/tolerability and pharmacokinetics (systemic exposure) of the IP during a stepwise dose increase in single and repeated administration. Reasonable evidence for selection of the initial clinical dose and the stepwise dose increases should be provided by referring to nonclinical study data.

When the IP is applied to the eye for the first time, monocular administration is recommended for the single and subsequent administrations. If 2 drops are required at a time, an appropriate interval should be set because the tissue characteristics of the eye limit the amount that can be held in the eye (approximately 20–30 μL). When performing pharmacokinetic analysis to confirm the degree of systemic exposure after administration, parent drug (unchanged substance) and active metabolite analyses should be performed, considering the characteristics of the IP. If the IP binds to red blood cells and requires whole

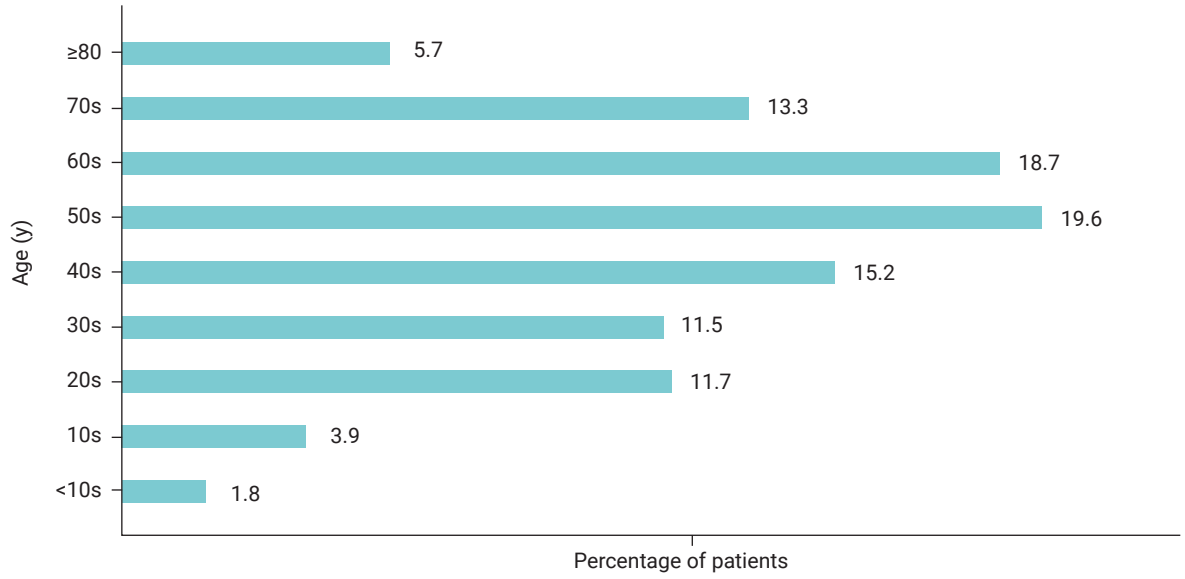

Figure 1. Distribution of patients with dry eye syndrome across age groups in 2020.
Source: Health Insurance Review and Assessment Service [10].

blood analysis, both whole blood and plasma should be analyzed. It is necessary to establish the inclusion/exclusion criteria as they relate to ophthalmology, and a safety evaluation including an ophthalmological examination and local tolerability evaluation should be conducted by an ophthalmologist.

Exploratory Clinical Study

An exploratory clinical study is first conducted to explore the IP and determine the dosing, study design, evaluation items, and evaluation methods for the subsequent confirmatory clinical study. It is necessary to verify the appropriate concentration, administration method, and dose to confirm the validity of the indication results for patients with dry eye syndrome. In addition, a dose-response study is needed to assess the safety of the IP.

Confirmatory Clinical Study

A confirmatory clinical study is conducted to confirm the safety and efficacy of the IP. In general, it is recommended to verify the safety and efficacy under conditions involving traditional environmental exposures (e.g., seasonal). However, a challenge model study using a control chamber in which temperature, airflow, humidity, and other factors are controlled may also be considered. Add-on treatment in which the IP is added to a standardized treatment regimen is also acceptable.

Comparator

In a comparative clinical study for the development of drugs to treat dry eye syndrome, the comparator may be a placebo (i.e., a vehicle including excipients but excluding the active ingredient) or an existing treatment. It is recommended that the IP demonstrates statistical and clinical superiority over the comparator in a randomized, double-blind, and parallel-design trial. Therefore, since water is commonly used in drugs to treat dry eye syndrome and is known as an effective ingredient in itself, a vehicle control should be used as a comparator in the comparative clinical study. Since there are currently no known effective treatments for dry eye syndrome, equivalence or non-inferiority trials are not recommended without good analytical validation (sensitivity) methods (including both positive and negative controls).

Study Population

Patients with eye discomfort consistent with dry eye syndrome should be enrolled. The inclusion criteria should include both objective signs and subjective symptoms. The signs of dry eye are determined by objective viewing of the eye surface through corneal staining, conjunctival staining, measuring tear break-up time, and Schirmer tear test scoring, and others. The symptoms of dry eye are subjective experiences of eye discomfort, such as blurred vision, light sensitivity, a feeling of sand-like grit in the eye, and others. It is important that studies include large populations with

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demographic subgroups, including different sex, age, race/ethnicity, and eye color groups.

Dry eye secondary to scarring (e.g., from irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or the destruction of conjunctival goblet cells (as with vitamin A deficiency) are considered severe and patients with these conditions should be studied separately from routine dry eye syndrome. Severe blepharitis or obvious inflammation at the eyelid margin can interfere with the interpretation of study results, and patients with these conditions should also be studied separately from routine dry eye syndrome.

In studies aimed at developing drugs to treat dry eye syndrome, exclusion criteria for the study population should be established, considering criteria such as vision parameters, ophthalmic diseases, surgical history, prior medications/ concomitant drugs, and history of wearing contact lenses.

Recommended exclusions: (1) a maximum corrected vision; (2) ophthalmic diseases, such as ocular hypertension, glaucoma, allergy, active eye inflammation (uveitis, iritis, blepharitis, etc), autoimmune disease (Sjögren's syndrome, etc), retinal disease, and other clinically significant eye diseases that are not caused by dry eye syndrome (e.g., corneal surface disease, abnormal corneal sensitivity, excessive secretion of tears, etc); (3) ophthalmic surgery such as vision correction surgery (refractive correction such as LASIK, etc), or cataract surgery where a sufficient recovery period has not elapsed since punctal occlusion, etc; (4) current drugs that may affect the evaluation of safety and efficacy: (a) preparations for dry eye syndrome (e.g., eye drops, anti-inflammatory drugs such as cyclosporin, hyaluronic acid preparations, tetracycline preparations); (b) preparations known to cause dry eye syndrome or drugs that may affect the evaluation of safety and efficacy (e.g., oral contraceptives, anticholinergic drugs, tricyclic antidepressants, antihistamines, hypnotics, diuretics, antimuscarinic drugs, β-blockers, oral aspirin, corticosteroids, mast cell stabilizers); and (5) if contact lenses have been worn recently or contact lenses are required during clinical trials.

Efficacy

In general, safety and efficacy should be demonstrated in appropriate and well-controlled multicenter studies. Dry eye syndrome is a disease sensitive to the surrounding environment, and it can be difficult to objectively prove the efficacy of drugs through the subjective reaction of patients. It is recommended that efficacy be demonstrated in a natural exposure study with repeated administrations over a sufficient period of time, considering the mechanism of action of the IP and the purpose of treatment. It is recommended that one of the following are demonstrated: (1) a statistically significant difference between the IP and the vehicle for at least 1 objective predefined sign of dry eye (mean group score of the IP versus the vehicle) and at least 1 subjective predefined symptom of dry eye (mean group score); (2) a statistically significant difference between the percentage of patients who have reached complete recovery of corneal staining; or (3) a statistically significant difference between the percentage of patients who increased ≥10 mm in their Schirmer tear test scores.

If signs and symptoms are used to demonstrate efficacy, several different endpoints for the objective sign or the subjective symptom are recommended: (1) signs of dry eye include, but are not limited to corneal staining results, conjunctival staining results, decreased tear break-up time, and decreased Schirmer tear test scores (with or without anesthesia); (2) symptoms of dry eye include, but are not limited to, blurred vision, light sensitivity, a feeling of sand in the eye, ocular irritation, ocular pain or discomfort, and ocular itching.

Subjective symptom improvement can also be demonstrated by showing statistically significant differences in the percentage of patients who have reached complete recovery of symptoms. The regulatory agency should be consulted if cases are to be included where complete recovery (complete clearing of signs or symptoms) has not been achieved in the responder analysis. In other words, responders should be defined in advance.

Efficacy for a sign and efficacy for a symptom need not be demonstrated in the same clinical trial, but should be demonstrated in one or more clinical trials. The sponsor should describe all the scoring methods or scales used to measure the efficacy variables and submit the scoring methods or scales with the clinical trial protocol. The scoring methods or scales should be verified methods.

Pivotal clinical trials should be conducted using the formulation that is proposed for marketing. If only the efficacy for a sign is demonstrated in a pivotal clinical trial, the drug indications may be limited according to the results. Thus, the efficacy for a certain symptom should be confirmed based on a secondary endpoint.

Safety

The study should include a sufficient number of patients to identify adverse drug events. To achieve this, a sufficient number of patients using the IP should complete treatment

with a concentration and frequency of use at least as high as is proposed for marketing.

Before submitting an application dossier for marketing authorization, it is necessary to ensure that follow-up observations were completed over a sufficient period following administration. Evaluations should be conducted over a sufficiently long period of time (e.g., 12 months) [15].

For reformulations of drug substances that have already been approved in the same dosage form, the same route of administration, and the same or lower concentration, a shorter period of treatment may be considered when safety information is included from a sufficient number of patients.

It is recommended to demonstrate safety in a natural exposure study using repeated administrations over a sufficient period of time. If the efficacy study period is shorter, it is recommended that the safety study be conducted for at least 6 weeks.

Other Considerations

Excipients may be certified in Korea and abroad and their purpose in the drug combination should be pharmaceutically reasonable. The excipient should have no direct pharmacological effect and should not decrease the efficacy of the drugs or interfere with quality control. If there is no previous experience with the excipient in Korea, data to confirm its safety (e.g., nonclinical data) are needed. For nonclinical study data, one should refer to the NIFDS guideline on the nonclinical evaluation of pharmaceuticals [16].

Conclusion

According to the Health Insurance Review & Assessment Service, the number of patients with dry eye in Korea was approximately 2.45 million in 2020 and the condition was evenly distributed across age groups (teenagers to older adults in their 70s) [10]. Most of the drugs to treat dry eye syndrome in domestic and foreign markets are dominated by products from global pharmaceutical companies. Most of the domestic market is also dominated by drugs that originated in the United States (US), Japan, and Switzerland. The global market for dry eye syndrome treatments was approximately 6.5 trillion won (5,465 million US dollars) in 2021 and is expected to grow at an annual rate of 4.8% from 2022 to 2027 [17]. The domestic market for drugs to treat dry eye syndrome reached 300 billion won in 2020 [18] and the market is expected to continue growing as the number of patients with dry eye increases every year. Furthermore, with the expiration of patents in 2021 for the current drugs used to treat dry eye syndrome, generic drugs have been released, and a number of domestic pharmaceutical and biopharmaceutical companies have begun developing new drugs to treat dry eye syndrome, as well as launching the generic drugs.

A draft guideline for developing drugs to treat dry eye syndrome was published by the US Food and Drug Administration in 2020 [19], and has not yet been finalized. In Korea, a guideline has been published [11] to support the development of effective drugs to treat dry eye syndrome by increasing the efficiency of drug development and improving the quality of clinical trial data. We hope that this paper, based on the Korean guideline [11], will help the domestic pharmaceutical industry and investigators who want to design clinical trial protocols for developing drugs to treat dry eye syndrome.

Notes

Ethics Approval
Not applicable.

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

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Availability of Data
All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

Authors' Contributions
Conceptualization: SB, HS, HJO; Writing–original draft: SB, HS; Writing–review & editing: HS, HJO. All authors read and approved the final manuscript.

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Original Article

The incidence and clinical characteristics of myocarditis and pericarditis following mRNA-based COVID-19 vaccination in Republic of Korea adolescents from July 2021 to September 2022

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ABSTRACT

Objectives: Age-specific information regarding myocarditis/pericarditis in adolescents following mRNA-based coronavirus disease 2019 (COVID-19) vaccination in Asia remains insufficient. This study investigated the incidence and clinical characteristics of myocarditis/pericarditis in Republic of Korea adolescents after mRNA-based COVID-19 vaccination.

Methods: This retrospective descriptive study utilized patient data from the Korea Immunization Management System. Incidence rates were calculated according to age and sex. Clinical characteristics (symptoms/signs, laboratory values, and imaging results) were compared between mild and severe cases.

Results: Between July 19, 2021 and September 30, 2022, 3,728,224 individuals aged 12 to 19 years received 6,484,165 mRNA-based COVID-19 vaccines, and 173 cases met the case definition for myocarditis/pericarditis: 151 mild (87.3%) and 22 severe (12.7%). The incidence was 3.8-fold higher in males than in females. Troponin I/ troponin T was elevated in 96% of myocarditis cases, demonstrating higher sensitivity than creatine kinase-myocardial band (67.6%) or C-reactive protein (75.2%). ST-segment or Twave on electrography abnormalities were found in 60.3% (85/141). Paroxysmal/sustained atrial/ventricular arrhythmias were more common in severe than in mild cases (45.5% vs. 16.8%, $p = 0.008$). Edema on T2-weighted magnetic imaging occurred in 21.6% (8/37) and 62.5% (5/8) of mild and severe cases, respectively ($p = 0.03$). Abnormal pericardial fluid collection or pericardial inflammation was found in 75.4% of pericarditis cases (49/65).

Conclusion: Myocarditis/pericarditis occurred in rare cases following mRNA-based COVID-19 vaccination. Most cases were mild, but the incidence was higher in adolescent males and after the second dose. As bivalent severe acute respiratory syndrome coronavirus 2 mRNA vaccination started in Republic of Korea in October 2022, the post-vaccination incidence of myocarditis/pericarditis should be closely monitored, considering clinical characteristics.

Keywords: Adverse event following immunization; COVID-19 vaccines; Myocarditis; Pericarditis

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Introduction

Coronavirus disease 2019 (COVID-19) symptoms in children are generally mild. However, serious complications, including multisystem inflammatory syndrome in children, can occur [1,2]. To prevent COVID-19 infection and minimize the occurrence of serious complications, vaccination has been introduced alongside non-pharmacological approaches, such as enforcing mask policies, social distancing, and school closures [3]. By reducing the requirement for quarantine and the number of hospital admissions due to COVID-19, vaccination has had additional sociopsychological benefits, such as decreasing school absences and limiting the mental health issues associated with temporary shutdowns [4].

In Republic of Korea, the mRNA-based BNT162b2-BioNTech COVID-19 vaccine was first made available to high school seniors and high school employees on July 19, 2021. Vaccination was then extended to adolescents aged 16 to 17 years on October 18, 2021, and to those aged 12 to 15 years on November 1, 2021 [5–7].

Although the COVID-19 vaccines are effective in preventing the development of severe symptoms and death from COVID-19 infection [8–10], they have also been reported to cause myocarditis and pericarditis in rare cases [11–15]. In a review of the relationship between mRNA-based COVID-19 vaccines and myocarditis, the Advisory Committee on Immunization Practices reported that myocarditis or pericarditis occurred more frequently in male adolescents and young adults after the second dose [15]. In addition, several reports related to the occurrence and characteristics of myocarditis and pericarditis following mRNA-based COVID-19 vaccination have been published in multiple countries [14,16–19]. One systematic review analyzed the clinical presentation and outcomes of 74 patients who developed myocarditis after administration of mRNA vaccines [20]. Meanwhile, in Republic of Korea, after the COVID-19 vaccination plan for high school seniors was announced, a study was conducted to examine the epidemiology and clinical characteristics of myocarditis and pericarditis in patients aged 17 years and younger prior to the introduction of COVID-19 vaccines [21].

However, age-specific information regarding the occurrence and characteristics of myocarditis and pericarditis in adolescents following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in Asia remains insufficient [22]. Accordingly, this study aimed to investigate the incidence and clinical characteristics of myocarditis and pericarditis in adolescents (aged 12– 19 years) in Republic of Korea following mRNA-based COVID-19 vaccination from July 19, 2021 (when COVID-19 vaccination was initiated in adolescents of the study age range) to September 30, 2022. We also analyzed the differences in clinical characteristics according to the level of severity.

HIGHLIGHTS

- The age-specific information regarding myocarditis and pericarditis in adolescents following mRNA-based COVID-19 vaccination in Asia remains insufficient. This study aimed to investigate the incidence and clinical characteristics of myocarditis and pericarditis in adolescents in Republic of Korea following mRNA-based COVID-19 vaccination.
- Following mRNA-based COVID-19 vaccination, myocarditis and pericarditis has been reported as a rare, most cases were mild, but the incidence rate was particularly higher in men, and after the second dose.
- As bivalent SARS-CoV-2 mRNA vaccination started in Republic of Korea from October 2022, development of myocarditis and pericarditis after vaccination should be monitored closely considering clinical characteristic.

Materials and Methods

Detection, Reporting, and Assessment of Adverse Events of Myocarditis and Pericarditis

In Korea, physicians, medical doctors, and dentists are required to report events of diagnosed adverse reactions following vaccination through the Korea Immunization Management System (KIMS); they can also be reported by the affected vaccinated person, or by their parents or guardians [23]. The reported cases were then investigated by city or provincial government epidemiologists in order to collect additional data (e.g., clinical records, underlying diseases, lab test results, and treatment approach and outcomes), and the results were reviewed by a rapid response team [24]. Based on these results, the diagnostic certainty and causality assessment of myocarditis and pericarditis cases were finally reviewed and determined by the Adverse Event Following Immunization (AEFI) Expert Advisory Committee operated by the Korea Disease Control and Prevention Agency [24,25]. The level of diagnostic certainty was assessed using a slightly modified version of the diagnostic criteria as defined by the Brighton Collaboration case definition of myocarditis and pericarditis (Tables 1, 2) [25,26].

Table 1. Case definition for myocarditis

	Definite case	Probable case	Possible case
Criteria for case definition	• Confirm through histopathologic examination and reject other causes (①+③) • Confirm abnormal test findings (must include an elevated troponin level) and reject other causes (②+③)	• Should be symptomatic and meet the testing criteria; reject other causes (①+②+③)	• Should be symptomatic and meet the testing criteria; reject other causes (①+②+③)
① Histopathologic examination or symptoms	Evidence of myocarditis in histopathologic examination (endomyocardial biopsy or autopsy)	≥1 Specific cardiac symptoms or ≥2 Nonspecific myocarditis symptoms	≥1 Specific cardiac symptoms or ≥2 Nonspecific myocarditis symptoms
② Tests	Two or more out of the 3 tests below. Must include an elevated troponin level: ≥1 Elevated myocardial biomarker (limited to troponin T and troponin I) and ≥1 Abnormalities on cMRI or ≥1 Abnormalities on echocardiogram	One or more out of the 4 tests below: ≥1 Abnormalities on cMRI or ≥1 Elevated myocardial biomarker (troponin I, troponin T, CK-MB) or ≥1 Abnormalities on echocardiogram or ≥1 New or recovered specific abnormalities on ECG	Both tests below: ≥1 Elevated myocardial biomarker and ≥1 New or recovered nonspecific abnormalities on ECG
③ Rejection of other causes	Reject other probable causes/diagnoses	Reject other probable causes/diagnoses	Reject other probable causes/diagnoses

Based on Korea Disease Control and Prevention Agency [25].
These criteria for diagnostic comparability were used for the purposes of early assessment and case collection. Final decisions regarding diagnostic compatibility and causality followed the decisions of experts and the vaccine adverse event evaluation team.
cMRI, cardiac magnetic resonance imaging; CK-MB, creatine kinase-myocardial band; ECG, electrocardiography.

Table 2. Case definition for pericarditis

	Definite cases	Probable cases
Criteria for case definition	• Confirm through histopathologic examination and reject other causes (①+③) • Meet the testing criteria and reject other causes (②+③)	• Should be symptomatic and meet the testing criteria; reject other causes (①+②+③)
① Histopathologic examination or symptoms	Evidence of pericarditis in histopathologic examination (biopsy or autopsy)	≥1 Specific cardiac symptoms
② Tests	Two or more out of the 3 tests below. Evidence of abnormal fluid collection or pericardial inflammation in imaging test (if the finding of pericardial inflammation is unclear in the presence of the evidence of pericardial effusion, it should be accompanied by the results of an elevated inflammation biomarker test) or New occurrence or recovery of all 3 specific ECG findings or ≥1 Physical exam suggesting pericardial effusion	One or more out of the 3 tests below: ≥1 New or recovered specific abnormalities in ECG or Evidence of abnormal fluid collection or pericardial inflammation on imaging tests (if the finding of pericardial inflammation is unclear in the presence of the evidence of pericardial effusion, it should be accompanied by the results of an elevated inflammation biomarker test) or ≥1 Physical exam suggesting pericardial effusion
③ Rejection of other causes	Reject other probable causes/diagnoses	Reject other probable causes/diagnoses

Based on Korea Disease Control and Prevention Agency [25].
These criteria for diagnostic comparability were used for the purposes of early assessment and case collection. Final decisions regarding diagnostic compatibility and causality followed the decisions of experts and the vaccine adverse event evaluation team.
ECG, electrocardiography.

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Study Population

Between July 19, 2021 and September 30, 2022, 3,728,224 individuals aged 12 to 19 years received a total of 6,484,165 mRNA-based COVID-19 vaccines, and 319 cases were reported through the KIMS as suspected myocarditis or pericarditis following vaccination. Of these 319 reported cases, 186 cases met the case definition (myocarditis: definite, possible, or probable; pericarditis: definite or probable). Of the 186 cases, we excluded 13 cases in which (1) the adverse reactions occurred more than 42 days after vaccination [27]; (2) the events were determined to have causes other than COVID-19 vaccination after review by the AEFI Expert Advisory Committee [24,25]; or (3) more information was required for causality assessment. Finally, 173 cases were selected for use in this study (Figure 1).

Data Collection

This retrospective descriptive study was conducted using patient data from the KIMS. We collected the following types of data: age, sex, type of vaccine, number of the vaccine, vaccination date, symptom onset dates, symptoms and signs, laboratory values (troponin I or T, creatine kinase-myocardial band [CK-MB], C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]), imaging results (electrocardiography [ECG], echocardiography, and cardiac magnetic resonance imaging [cMRI]), and other test results.

Troponin I, troponin T, CK-MB, and CRP levels were deemed elevated if they were higher than the laboratory's reference levels. The ESR was determined to be elevated if it exceeded 20 mm/h [28,29]. Imaging test results were classified based on the Adverse Events of Special Interest Case Definition Companion Guide of the Safety Platform for Emergency Vaccines [26]. The cases were divided into mild and severe. Severe cases were defined as death, admission to the intensive care unit (ICU), or life-threatening conditions [24]. In addition, when examining the clinical characteristics of myocarditis and pericarditis, myopericarditis cases were included in both myocarditis and pericarditis cases for analysis.

Statistical Analysis

For all demographic and clinical characteristics, categorical variables were presented as frequencies and percentages. The mean and standard deviation were used to present normally distributed continuous variables, while the median and interquartile range (IQR) were applied to present skewed variables. The normality of distributions was assessed with the Shapiro-Wilk test. The chi-square and Fisher exact tests were performed to compare categorical variables, and the Mann-Whitney U-test was

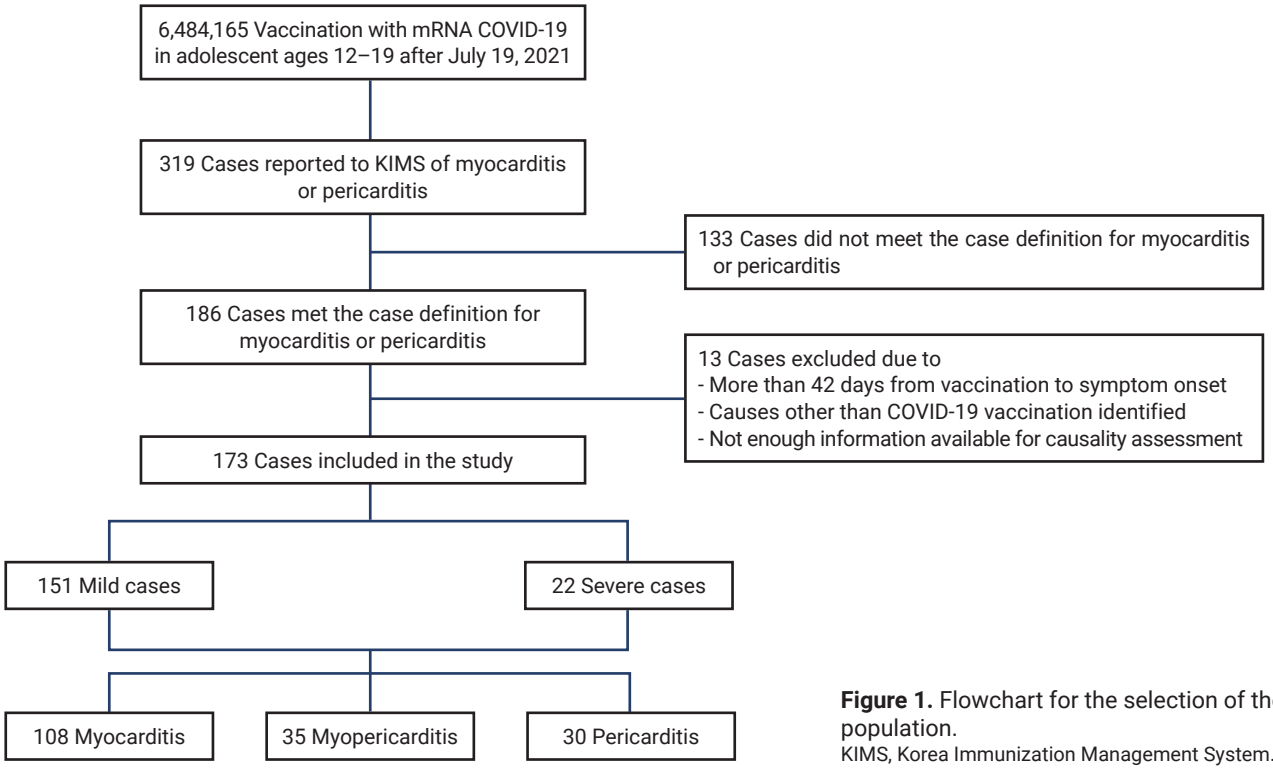

Figure 1. Flowchart for the selection of the study population.
KIMS, Korea Immunization Management System.

performed to compare continuous variables. The incidence rates of myocarditis and pericarditis were estimated as the ratio between the number of outcomes and the number of person-days that occurred during the period of interest per 1,000,000 person-days, and 95% confidence intervals (CIs) were calculated. All data were analyzed using the R software ver. 4.1.2 (The R Foundation). A p-value <0.05 was considered to indicate statistical significance.

Ethics Statement

This study protocol was reviewed and approved by the Public Institutional Review Board (IRB) designated by the Ministry of Health and Welfare (IRB No: P01-202212-01-00). The requirement for informed consent was waived by the IRB.

Results

General Characteristics of 12- to 19-Year-Olds with Myocarditis and Pericarditis

The median age of the 173 cases was 16 years (IQR, 15–18 years). Those aged 12 to 17 years comprised 66.5% ($n=115$) of the cases, while those aged 18 to 19 years made up the remaining 33.5% ($n=58$). The frequency of the 12 to 17 year age group was about twice as high as that of the 18 to 19 year age group. In terms of sex, 924,165 adolescent males received a total of 3,342,994 vaccinations, from which 139 cases of myocarditis or pericarditis occurred; while 1,804,059 adolescent females received a total of 3,141,172 vaccinations, from which 34 cases of myocarditis or pericarditis occurred. The incidence of myocarditis or pericarditis was approximately 4 times greater in adolescent males (80.3%, $n=139$) than in females (19.7%, $n=34$). Most patients had received 2 vaccine doses (56.6%, $n=98$), followed by 1 dose (27.2%, $n=47$) and 3 doses (16.2%, $n=28$). Myocarditis was diagnosed in 62.4% of cases ($n=108$), myopericarditis in 20.2% ($n=35$), and pericarditis in 17.3% ($n=30$). Almost all of the adolescents (96.0%, $n=166$) received the BNT162b2 vaccine, while 4.0% ($n=7$) received the mRNA-1273 vaccine. The median time from vaccination to symptom onset was 2 days (IQR, 1–3 days). Most cases (87.3%, $n=151$) were mild, while 12.7% ($n=22$) were severe. No deaths were reported (Table 3).

The incidence rate of myocarditis/pericarditis was approximately 3.8 times higher in males (0.99 per 100,000 person-days; 95% CI, 0.83–1.17 per 100,000 person-days) than in females (0.26 per 100,000 person-days; 95% CI, 0.18–0.36 per 100,000 person-days), regardless of the number of doses received. The highest rate was observed in males aged 12 to 17 years after the second dose (1.64 per 100,000 person-days; 95% CI, 1.27–2.09 per 100,000 person-days) (Table 4).

The proportion of severe cases in females was 23.5%,

Table 3. Demographic characteristics of myocarditis or pericarditis that met the case definition within 42 days after mRNA-based COVID-19 vaccination among 12- to 19-year-olds by dose number, July 2021–September 2022

Characteristic	Total	Dose 1	Dose 2	Dose 3
No. of vaccination doses administered	6,484,165	2,826,964	2,746,110	910,282
No. of cases that met the case definition for myocarditis or pericarditis	173 (100.0)	47 (27.2)	98 (56.6)	28 (16.2)
Age group (y)				
12–17	115 (66.5)	33 (28.7)	74 (64.3)	8 (7.0)
18–19	58 (33.5)	14 (24.1)	24 (41.4)	20 (34.5)
Sex				
Male	139 (80.3)	34 (24.5)	82 (59.0)	23 (16.5)
Female	34 (19.7)	13 (38.2)	16 (47.1)	5 (14.7)
Adjudication diagnosis				
Myocarditis	108 (62.4)	30 (27.8)	65 (60.2)	13 (12.0)
Myopericarditis	35 (20.2)	9 (25.7)	17 (48.6)	9 (25.7)
Pericarditis	30 (17.3)	8 (26.7)	16 (53.3)	6 (20.0)
Type of vaccine				
BNT162b2	166 (96.0)	45 (27.1)	94 (56.6)	27 (16.3)
mRNA-1273	7 (4.0)	2 (28.6)	4 (57.1)	1 (14.3)
Time from vaccination to symptom onset (d)	2 (1–3)	3 (1–9.5)	2 (1–3)	2 (1–3)
Severity				
Mild case	151 (87.3)	40 (26.5)	85 (56.3)	26 (17.2)
Severe case[a)]	22 (12.7)	7 (31.8)	13 (59.1)	2 (9.1)
Death	0 (0)	0 (0)	0 (0)	0 (0)

Data are presented as n (%) or median (interquartile range).
[a)]Intensive care unit admission or life-threatening condition.

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Table 4. Incidence rates of myocarditis or pericarditis cases that met the case definition within 42 days of mRNA-based COVID-19 vaccination among 12- to 19-year-olds, July 2021–September 2022 (per 100,000 person-days)

Sex/age group (y)	Total	Dose 1	Dose 2	Dose 3
All	0.64 (0.54–0.74)	0.40 (0.29–0.53)	0.85 (0.69–1.04)	0.73 (0.49–1.06)
Male	0.99 (0.83–1.17)	0.56 (0.39–0.78)	1.38 (1.10–1.72)	1.15 (0.73–1.73)
12–17	1.08 (0.87–1.32)	0.56 (0.35–0.84)	1.64 (1.27–2.09)	0.98 (0.39–2.02)
18–19	0.84 (0.61–1.13)	0.55 (0.28–0.99)	0.86 (0.50–1.38)	1.25 (0.71–2.03)
Female	0.26 (0.18–0.36)	0.23 (0.12–0.39)	0.29 (0.16–0.46)	0.27 (0.09–0.64)
12–17	0.24 (0.15–0.38)	0.26 (0.12–0.47)	0.24 (0.11–0.46)	0.17 (0.00–0.95)
18–19	0.28 (0.15–0.47)	0.16 (0.03–0.47)	0.38 (0.15–0.78)	0.32 (0.09–0.82)

Data are presented as odds ratio (95% confidence interval).

Table 5. Demographics characteristics of myocarditis and pericarditis cases that met the case definition within 42 days of mRNA-based COVID-19 vaccination among 12- to 19-year-olds by severity, July 2021–September 2022

Characteristic	Total (n = 173)	Mild case (n = 151)	Severe case (n = 22)[a]	p-value
Age group (y)				
12–17	115 (66.5)	98 (85.2)	17 (14.8)	0.36
18–19	58 (33.5)	53 (91.4)	5 (8.6)	
Sex				
Male	139 (79.8)	125 (89.9)	14 (10.1)	0.06
Female	34 (19.7)	26 (76.5)	8 (23.5)	
Adjudication of the diagnosis				
Myocarditis	108 (62.4)	92 (85.2)	16 (14.8)	0.07
Myopericarditis	35 (20.2)	29 (82.9)	6 (17.1)	
Pericarditis	30 (17.3)	30 (100.0)	0 (0)	
Type of vaccine				
BNT162b2	166 (96.0)	144 (86.7)	22 (13.3)	0.59
mRNA-1273	7 (4.0)	7 (100.0)	0 (0)	
Dose				
1	47 (27.2)	40 (85.1)	7 (14.9)	0.58
2	98 (56.6)	85 (86.7)	13 (13.3)	
3	28 (16.2)	26 (92.9)	2 (7.1)	
Time from vaccination to symptom onset (d)	2 (1–3)	2 (1–3)	3 (2–4.75)	0.003**

Data are presented as n (%) or median (interquartile range).
[a]Intensive care unit admission, or life-threatening condition.
**p < 0.01.

which was higher, although not significantly, than that reported in males (10.1%). The proportion of severe cases was the highest in myopericarditis patients (17.1%), followed by patients diagnosed with myocarditis (14.8%). All diagnosed cases of pericarditis were mild. The median time from vaccination to symptom onset was 2 days (IQR, 1–3 days) (Table 5) in mild cases and 3 days (IQR, 2–4.75 days) in severe cases (p = 0.003) (Table 5, Figure 2).

Clinical Characteristics of 12- to 19-Year-Olds with Myocarditis and Pericarditis

Myocarditis

The most common clinical symptom was chest pain or pressure (93.7%, 134/143) followed by dyspnea (30.1%, 43/143) and heart palpitations (16.1%, 23/143).

Troponin I or T was elevated in 95.8% of the tested cases (137/143), CK-MB was elevated in 67.6% (94/139), and CRP was elevated in 75.2% (100/133). Additionally, the ESR was ≥20 mm/h in 16.7% of the tested cases (14/84). The proportion of cases with elevated troponin I or T was 95.9% in mild cases (116/121) and 95.5% in severe cases (21/22), whereas the proportions of cases with elevated CK-MB (65.8% vs. 77.3%), CRP (73.9% vs. 83.3%), and ESR (10.7% vs. 66.7%, p = 0.001) were higher in severe cases.

On ECG, ST-segment or T-wave abnormalities (elevation or inversion) were found in 60.3% of cases (85/141), paroxysmal or sustained atrial or ventricular arrhythmias in 21.3% (30/141), and atrioventricular (AV) nodal conduction delays or intraventricular conduction defects in 6.4% (9/141). Paroxysmal or sustained atrial or ventricular arrhythmias were more common in severe cases than in mild cases (45.5%

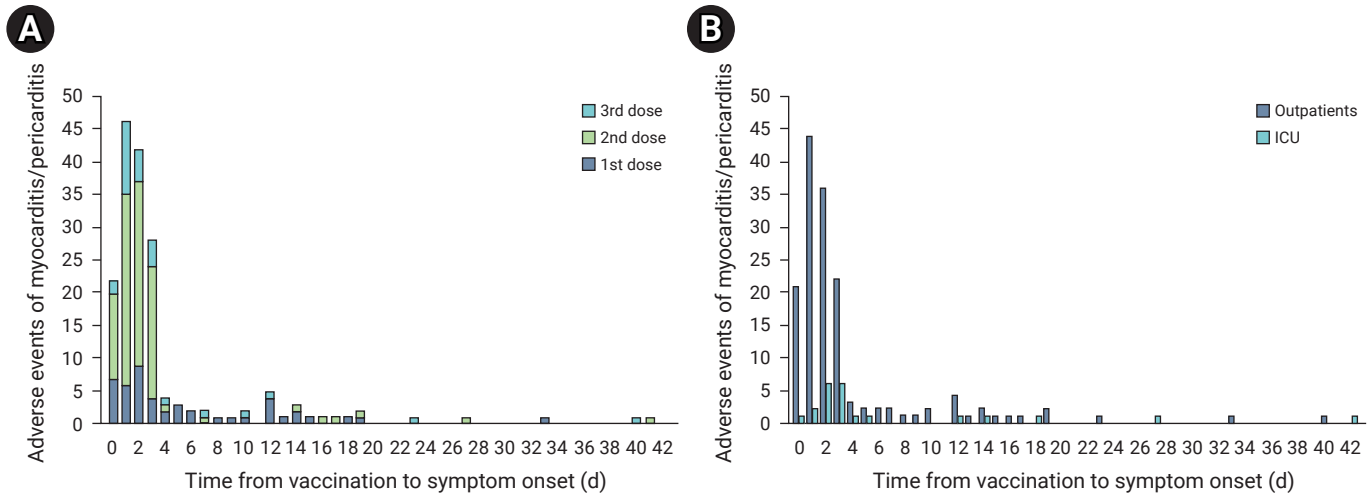

Figure 2. Time from vaccination to symptom onset in days. (A) Time from vaccination to symptom onset by number of doses. Blue, orange, and gray bars represent the number of cases after the first, second, and third doses, respectively. See Table 3 for detailed figures. (B) Time from vaccination to symptom onset by severity. Blue, orange, and gray bars represent outpatients (mild cases) and intensive care unit (ICU) (severe cases), respectively.

vs. 16.8%, $p = 0.008$). Additionally, the proportion of cases with the finding of AV nodal conduction delays or intraventricular conduction defects was higher in severe cases than in mild cases (18.2% vs. 4.2%, $p = 0.034$).

On echocardiography, the proportion of patients with a left ventricular ejection fraction (LVEF) < 55% was 10.6% in mild cases (12/113) and 35.3% in severe cases (6/17). Among the severe cases, 1 patient with moderate dysfunction (LVEF, 35%–44%) and 1 patient with severe dysfunction (LVEF, < 35%) were identified.

Edema on T2-weighted MRI occurred in 28.9% (13/45) of all tested cases, 21.6% of mild cases (8/37), and 62.5% of severe cases (5/8; $p = 0.03$). Additionally, late gadolinium enhancement on T1-weighted MRI was reported in 48.9% of all tested cases (22/45), 43.2% of mild cases (16/37), and 75.0% of severe cases (6/8) (Table 6).

Pericarditis

Chest pain or pressure were the most common symptoms (98.5%, 64/65), followed by dyspnea (15.4%, 10/65) and heart palpitations (29.2%, 19/65). CRP was elevated in 76.3% of cases (45/59), and ESR was ≥ 20 mm/h in 25.0% (8/32). The proportions of elevated CRP (74.1% vs. 100.0%) and ESR (24.1% vs. 33.3%) were higher in severe cases than in mild cases, but with no statistically significant difference.

ST-segment or T-wave abnormalities (elevation or inversion) were reported on ECG in most cases (77.8%, 49/63). Meanwhile, an ST-segment depression in augmented vector right was detected in 6.3% (4/63) of cases and PR-depression throughout the leads (best shown on leads II and V3) without reciprocal ST-segment changes (depressions) in 6.3% (4/63).

On echocardiography findings, the proportion of patients with an LVEF < 55% was 12.8% in mild cases (6/47) and 16.7% in severe cases (1/6), whereas mild dysfunction (LVEF, 45%–54%) was observed in 10.6% of mild cases (5/47) and 16.7% of severe cases (1/6), respectively.

Imaging test results (echocardiogram, MRI, cMRI, or computed tomography) further revealed that abnormal pericardial fluid collection or pericardial inflammation occurred in 75.4% of all tested cases (49/65), 76.3% of mild cases (45/59), and 66.7% of severe cases (4/6) (Table 7).

Discussion

In the current study, the occurrence and clinical characteristics of myocarditis and pericarditis in adolescents aged 12 to 19 years after mRNA-based COVID-19 vaccination in Republic of Korea from July 2021 to September 2022 were examined. Myocarditis and pericarditis were identified as rare occurrences, and though most cases (87%) were mild, the incidence rate was higher in adolescent males and following the second dose.

This finding is consistent with several previous study findings. For example, Truong et al. [30] analyzed cases of suspected myocarditis after COVID-19 vaccination in individuals under the age of 20 years from 26 pediatric medical centers in the United States and Canada. They found that 90.6% of the reported cases were in males, and 91.4% were in those who had received a second vaccine dose. These patterns were also observed before the introduction

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Table 6. Symptoms and laboratory, ECG, and imaging results of myocarditis cases

Characteristic	Total (*n* = 143)	Mild case (*n* = 121)	Severe case (*n* = 22)[a]	*p*-value
Symptoms (*n* = 143)				
Acute chest pain or pressure	134/143 (93.7)	114/121 (94.2)	20/22 (90.9)	0.91
Dyspnea after exercise, at rest, or lying down	43/143 (30.1)	35/121 (28.9)	8/22 (36.4)	0.65
Palpitation	23/143 (16.1)	20/121 (16.5)	3/22 (13.6)	< 0.999
Diaphoresis	2/143 (1.4)	2/121 (1.7)	0/22 (0)	< 0.999
Nonspecific symptom (fever, mental change, abdominal pain, nausea, vomiting)	2/143 (1.4)	0/121 (0)	2/22 (9.1)	< 0.999
Laboratory values				
Myocardial biomarker				
Elevated troponin I or T (*n* = 143)	137/143 (95.8)	116/121 (95.9)	21/22 (95.5)	< 0.999
Elevated CK-MB (*n* = 139)	94/139 (67.6)	77/117 (65.8)	17/22 (77.3)	0.42
Inflammation biomarker				
Elevated CRP (*n* = 133)	100/133 (75.2)	85/115 (73.9)	15/18 (83.3)	0.56
Elevated ESR (*n* = 84)	14/84 (16.7)	8/75 (10.7)	6/9 (66.7)	< 0.001***
Testing/imaging				
ECG (*n* = 141)				
ST-segment or T-wave abnormalities (elevation or inversion)	85/141 (60.3)	70/119 (58.8)	15/22 (68.2)	0.56
Paroxysmal or sustained atrial or ventricular arrhythmias	30/141 (21.3)	20/119 (16.8)	10/22 (45.5)	0.008*
AV nodal conduction delays or intraventricular conduction defects	9/141 (6.4)	5/119 (4.2)	4/22 (18.2)	0.034*
Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy	0/141 (0)	0/119 (0)	0/22 (0)	-
Echocardiogram, LVEF (*n* = 130)				
Normal (≥ 55%)	112/130 (86.1)	101/113 (89.4)	11/17 (64.7)	0.004**
Mild dysfunction (45%–54%)	16/130 (12.3)	12/113 (10.6)	4/17 (23.5)	
Moderate dysfunction (35%–44%)	1/130 (0.8)	0/113 (0)	1/17 (5.9)	
Severe dysfunction (< 35%)	1/130 (0.8)	0/113 (0)	1/17 (5.9)	
Cardiac MRI (*n* = 45)				
Edema on T2-weighted study, typically patchy in nature	13/45 (28.9)	8/37 (21.6)	5/8 (62.5)	0.03
Late gadolinium enhancement on T1-weighted study with an increased enhancement ratio between myocardial and skeletal muscle, typically involving at least one non-ischemic regional distribution with recovery (myocyte injury)	22/45 (48.9)	16/37 (43.2)	6/8 (75.0)	0.13

Data are presented as *n* (%). Abnormality was defined per the reference range of the hospital or laboratory where the test was performed.
ECG, electrocardiography; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AV, atrioventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.
[a]Intensive care unit admission or life-threatening condition.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

of COVID-19 vaccines. That is, Kim and Cho [31] examined the nationwide incidence, treatment, and outcomes of acute myocarditis in Korean children between 2007 and 2016 using the database of the Korea Health Insurance Review & Assessment Service (HIRA). They found that the incidence of acute myocarditis was significantly higher in boys greater than 13 years of age. Although the specific causes of these sex-based differences are unclear, high testosterone levels in boys can directly facilitate immune responses, which lead to an increased likelihood of inflammation, fibrosis, dilated cardiomyopathy, and heart failure [32].

The median time from vaccination to symptom onset was 2 days (IQR, 1–3 days), and in most cases, symptoms occurred within 7 days. More specifically, the median time to symptom onset after the first dose was 3 days (IQR, 1–9.5 days), and that after the second dose was 2 days (IQR, 1–3 days). A similar finding was reported by Oster et al. [33], who indicated that the median time until symptom onset was 3 days (IQR, 1–8 days) and 2 days (IQR, 1–3 days) after the first and second doses, respectively. Hence, in individuals vaccinated with mRNA-based vaccines, a diagnosis of myocarditis is generally made within 2 to 3 days of vaccination [13], whereas in typical cases of viral myocarditis, symptoms often manifest within a few weeks to a few months [34].

The current study also found that 12.7% of the cases were considered severe, with no deaths reported. Meanwhile,

Table 7. Symptoms and laboratory, ECG, and imaging results of pericarditis cases

Characteristic	Total (*n* = 65)	Mild case (*n* = 59)	Severe case (*n* = 6)[a]	*p*-value
Symptoms (*n* = 65)				
Acute chest pain or pressure	64/65 (98.5)	58/59 (98.3)	6/6 (100.0)	< 0.999
Dyspnea after exercise, at rest, or lying down	19/65 (29.2)	18/59 (30.5)	1/6 (16.7)	0.66
Palpitation	10/65 (15.4)	9/59 (15.3)	1/6 (16.7)	< 0.999
Diaphoresis	0/65 (0)	0/59 (0)	0/6 (0)	-
Laboratory values				
Inflammation biomarker				
Elevated CRP (*n* = 59)	45/59 (76.3)	40/54 (74.1)	5/5 (100.0)	0.33
Elevated ESR (*n* = 32)	8/32 (25.0)	7/29 (24.1)	1/3 (33.3)	< 0.999
Testing/imaging				
ECG (*n* = 63)				
ST-segment or T-wave abnormalities (elevation or inversion)	49/63 (77.8)	43/57 (75.4)	6/6 (100.0)	0.32
ST-segment depression in aVR	4/63 (6.3)	3/57 (5.3)	1/6 (16.7)	0.34
PR-depression throughout the leads (best shown in leads II & V3) without reciprocal ST-segment changes (depressions)	4/63 (6.3)	3/57 (5.3)	1/6 (16.7)	0.34
Echocardiogram, LVEF (*n* = 53)				
Normal (≥ 55%)	46/53 (86.7)	41/47 (87.2)	5/6 (83.3)	0.54
Mild dysfunction (45%–54%)	6/53 (11.3)	5/47 (10.6)	1/6 (16.7)	
Moderate dysfunction (35%–44%)	0/53 (0)	0/47 (0)	0/6 (0)	
Severe dysfunction (< 35%)	0/53 (0)	0/47 (0)	0/6 (0)	
Cardiac imaging (echocardiogram, MRI, cardiac MRI, CT) (*n* = 65)				
Abnormal pericardial fluid collection or pericardial inflammation	49/65 (75.4)	45/59 (76.3)	4/6 (66.7)	0.62

Data are presented as *n* (%). Abnormality was defined per the reference range of the hospital or laboratory where the test was performed.
ECG, electrocardiography; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; aVR, augmented vector right; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; CT, computed tomography.
[a]Intensive care unit admission or life-threatening condition.

Kim and Cho [31] conducted a study on the nationwide incidence, treatment, and outcomes of acute myocarditis in Korean children based on the 2007–2016 HIRA database. They reported that 22.8% of acute myocarditis pediatric patients required extracorporeal membrane oxygenation, or ventilator support, and 6.9% died.

With respect to clinical symptoms, most cases manifested as chest pain or pressure, which agrees with the findings of previous studies [33]. Of note, severe cases reported manifestations of nonspecific symptoms, such as stomachache or vomiting, without specific symptoms, such as chest pain or pressure. Considering that nonspecific symptoms can be mistaken for gastrointestinal (GI) issues (e.g., viral gastroenteritis), misdiagnoses can occur if based solely on symptoms without suspecting myocarditis [35]. Furthermore, several studies have indicated that cases of myocarditis accompanied by GI symptoms in children were closely related to ICU admission and fatal outcomes [20,36,37], so it is clinically important to screen children presenting with GI symptoms for myocarditis [37]. Reportedly, myocarditis accompanied by GI symptoms may be caused by poor perfusion to the digestive system due to cardiac dysfunction, or by infection of the GI tract by the same virus causing myocarditis [38].

Troponin I or T was elevated in 96% of the tested cases. Similarly, elevated troponin I or T levels were previously reported in 98% of patients under the age of 30 years by Oster et al. [33], and in 100% of patients by Truong et al. [30]. Elevation of troponin I, which is expressed in cardiac muscles, has high sensitivity and high specificity for detecting damage to the myocardium [39,40]. CRP levels were elevated in 75.2% and 76.3% of the cases diagnosed with myocarditis and pericarditis, respectively, while the ESR was ≥20 mm/h in 16.7% and 25.0% of the cases. A similar degree of incongruence between CRP and ESR trends was reported by Marshall et al. [14], who reported 7 cases of acute myocarditis and myopericarditis in male adolescents who complained of chest pain within 4 days of vaccination with BNT162b2-BioNTech COVID-19 vaccines. In their study, CRP levels were elevated in 6/7 cases, while the mean ESR was 18.29 ± 14.95 mm/h, suggesting that CRP is a more sensitive marker of inflammation than ESR [41,42]. While CRP begins to increase 4–6 hours after inflammation begins, and peaks 2 to 3 days later, ESR levels tend to rise and fall more slowly, thus causing a disparity in the levels of these 2 factors [43].

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In patients with myocarditis, various abnormalities are detected via ECG, including ST-segment or T-wave, Q waves, AV block, and bundle branch blocks. In agreement with previous studies [21,22], the most common finding in this study was ST-segment or T-wave abnormalities (elevation or inversion). Similarly, Witberg et al. [44] reported abnormal ECG findings in 67% of adolescents diagnosed with myocarditis related to vaccination with BNT162b2. Additionally, Jain et al. [18] assessed patients aged ≤21 years and diagnosed with myocarditis related to COVID-19 vaccination across 16 hospitals in the US. They found that 70% of the patients exhibited abnormalities in ECG results, with ST-segment or T-wave abnormalities (elevation or inversion) determined to be the most common. In the current study, the occurrence of paroxysmal or sustained atrial or ventricular arrhythmias was more common in severe than in mild, cases (45.5% vs. 16.8%, $p=0.008$). This was also found in a previous study that reported that 25% of acute myocarditis cases exhibited cardiac arrhythmia, which was more frequently observed in severe myocarditis [45,46]. Furthermore, in the current study, AV nodal conduction delays or intraventricular conduction defects were more frequently observed in severe cases compared with mild cases (18.2% vs. 4.2%, $p=0.034$). Indeed, high-grade AV block is associated with higher morbidity and mortality rates in myocarditis patients [47].

On echocardiography, an LVEF <55% was observed in 13.9% and 13.3% of myocarditis and pericarditis cases, respectively. Meanwhile, in a meta-analysis of 24 studies on myocarditis related to BNT162b2 and mRNA-1273 COVID-19 vaccines, Woo et al. [20] reported that the median LVEF in myocarditis patients aged ≤20 years was 56.8% (43.7%–64.7%). Truong et al. [30] further reported that 62 cases (82.7%) with cMRI abnormalities had normal LVEF. In contrast, in the current study, of the cases with severe myocarditis, 1 case each was found to have moderate dysfunction (LVEF, 35%–44%) and severe dysfunction (LVEF, <35%). Importantly, a retrospective study conducted among 320 patients diagnosed with acute myocarditis reported a mean LVEF of 54%±9%, and found that, in comparison to patients with normal LVEF, those with decreased LVEF were more likely to receive steroid therapy during hospital stays and experience cardiovascular complications [48].

cMRI is a noninvasive diagnostic method that is highly effective in the diagnosis of myocarditis [49]. Schauer et al. [50] analyzed 16 patients aged 12 to 16 years who had been diagnosed with myopericarditis after receiving the BNT162b2 COVID-19 mRNA vaccine and received MRI within a median time of 2 days after symptom onset. All 16 patients presented with evidence of edema on T2-weighted imaging, and 93.8% (15/16) had late gadolinium enhancement in a patchy subpericardial to transmural pattern with a predilection for the inferior left ventricular free wall. However, no patient had pericardial effusion. Meanwhile, Truong et al. [30] reported that 55.7% of the patients for whom cMRI was conducted showed myocardial edema, and 76.3% had late gadolinium enhancement (median time from symptom onset to test, 5 days; IQR, 3–17 days). Meanwhile, in the current study, myocardial edema on T2-weighted MRI was observed in 28.9% of the cases, late gadolinium enhancement on T1-weighted MRI was detected in 48.9%, and 26.7% did not exhibit any abnormalities on their MRI scans. According to previous studies, in patients with acute myocarditis, cMRI markers of myocardial inflammation demonstrated a rapid and continuous decrease. Therefore, if myocarditis is suspected, cMRI scanning should be performed at an early stage of the disease [51], within 14 days [52].

Some studies have indicated that myocarditis caused by COVID-19 infection is more common than that induced following vaccination [53–55]. For instance, Fronza et al. [55] differentiated myocarditis occurring after COVID-19 vaccination from that occurring after COVID-19 or other viral infections and compared them with other causes of myocarditis. The pattern of cardiac damage observed on the MRI scans of patients diagnosed with myocarditis after COVID-19 vaccination was similar to that of patients with myocarditis due to other causes; however, the myocardial abnormalities were less severe in patients with vaccine-related myocarditis (e.g., less functional impairment, lower native T1, and less frequent involvement of the septum). Moreover, according to a recent study performed by the United States Center for Disease Control and Prevention, in adolescents aged 12 to 17 years (i.e., an age group considered to have high cardiac risk), myocarditis or pericarditis occurred in 50 people per 100,000 after COVID-19 infection, and in 22 people per 100,000 after the second vaccine dose. It was further reported that mRNA-based COVID-19 vaccines were associated with a risk for adverse reactions, including myocarditis; however, the absolute risk level was low, and the adverse reactions were largely mild, with patients recovering rapidly.

Our study has several limitations. First, the quantity and quality of information, which was collected from medical charts or interviews, may have varied depending on the collected data and the healthcare environment in the region. There may also have been unobserved clinical findings. Considering these points, overgeneralization should be avoided when interpreting the results of this study. Second, the criteria for defining myocarditis or pericarditis after vaccination in each country may be slightly different, but

this study did not consider these details in the comparison.

Conclusion

This study investigated the incidence and clinical characteristics of myocarditis and pericarditis in adolescents aged 12 to 19 years in Republic of Korea following mRNA-based COVID-19 vaccination using patient data from the KIMS from July 2021 to September 2022. Myocarditis and pericarditis have been reported as rare occurrences following mRNA-based COVID-19 vaccination. Most cases were mild, but the incidence rate was particularly higher in adolescent males and after the second dose. As bivalent severe acute respiratory syndrome coronavirus 2 mRNA vaccination against the Omicron variants started in Republic of Korea in October 2022, the development of myocarditis and pericarditis after vaccination should be monitored closely considering clinical characteristics [23]. Further comprehensive research, including studies of the incidence and pathophysiology of myocarditis and pericarditis in Korean adolescents after vaccination with COVID-19, as well as the treatment and prognosis of these conditions, should be conducted in the future.

Notes

Ethics Approval
This study was reviewed and approved by the Public Institutional Review Board designated by the Ministry of Health and Welfare (IRB No: P01-202212-01-00) and performed in accordance with the principles of the Declaration of Helsinki.

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

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

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

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Original Article

Risk factors for deaths associated with COVID-19 according to the cause of death classification in Republic of Korea

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ABSTRACT

Objectives: This study aimed to classify coronavirus disease 2019 (COVID-19)-related deaths according to whether COVID-19 was listed as the cause of death, and to investigate the differences in demographic characteristics and risk factors for COVID-19 death classifications.
Methods: A total of 5,625 deaths in South Korea among patients with confirmed COVID-19 from January 20, 2020 to December 31, 2021 were selected. Excluding false reports and unnatural deaths, 5,597 deaths were analyzed. Based on death report data, deaths were classified according to whether the cause of death was listed as COVID-19 (CD) or not (NCD). The epidemiological characteristics and causes of deaths were investigated using descriptive, univariate, and multivariate statistical analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to analyze the risk factors.
Results: The case fatality ratio was 0.89% and increased with age. Additionally, 96.4% of the subjects had an underlying disease, and 53.4% died in winter. The proportion of NCDs was 9.3%, of whom 19.1% died at home and 39.0% were confirmed to have COVID-19 after death. Malignant neoplasms (102/416 vs. 637/4,442; OR, 1.71; 95% CI, 1.36–2.16; $p < 0.001$) were significantly associated with NCD.
Conclusion: This is the first study to analyze risk factors by cause of death using COVID-19 death report data in South Korea. These results are expected to be used as evidence for establishing a death monitoring system that can collect timely information in a new infectious disease pandemic.

Keywords: COVID-19; Death; Republic of Korea; Risk factors

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Introduction

Since the first case of coronavirus disease 2019 (COVID-19) was confirmed in December

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2019, 627 million confirmed cases of COVID-19 have been reported and 6.5 million deaths have occurred worldwide as of October 30, 2022 [1]. In South Korea, 25,538,799 cases have been confirmed and 29,158 deaths have been reported [2].

Numerous studies have demonstrated that age and underlying diseases are major risk factors for death from COVID-19 [3–5]. In the United States (US), 80% of COVID-19 deaths at the beginning of the COVID-19 pandemic in 2020 occurred in people aged 65 years or older [5]. In Brazil, 75% of COVID-19 deaths in 2020 were among people aged 60 years or older [6]. In Italy, one of the countries with the highest COVID-19-related mortality since the beginning of the COVID-19 pandemic, more than 94% of COVID-19 deaths from February to September 2020 occurred in elderly people aged 60 years or older, and at least 70% had an underlying disease [7]. In South Korea, more than 90% of COVID-19 deaths took place in elderly people in their 60s or older [2].

The higher proportions of confirmed cases and deaths among elderly people with underlying diseases can lead to another problem—namely, the capacity of national health systems could be temporarily exceeded. In addition, because it is difficult to accurately determine whether the direct cause of death is COVID-19 infection or the aggravation of underlying diseases due to COVID-19 [8–10], some countries have suggested that caution should be taken when interpreting COVID-19-related deaths [8,11].

Epidemiological studies regarding the exact number of deaths are key measures that are widely used as surrogate variables to accurately identify the most vulnerable groups in a country and assess the severity of diseases [12]. In particular, mortality data play an essential role in public health decision-making or policy-making regarding the magnitude and duration of necessary interventions [13,14]. As proper reporting on deaths during the COVID-19 pandemic is very useful for effectively planning public health control measures [15,16], various countries have counted COVID-19 deaths for the purpose of infectious disease surveillance.

The World Health Organization (WHO) recommends that a death in a probable or confirmed COVID-19 case be reported as a death due to COVID-19, unless there is a clear alternative cause of death that cannot be related to COVID-19 (e.g., unnatural deaths) [17]. According to the US Centers for Disease Control and Prevention, a death should be reported as related to COVID-19 when a confirmed COVID-19 infection results in death, or when a death in a suspected or presumed COVID-19 case without laboratory results is recorded as a death due to COVID-19 on the death certificate by a medical professional [18]. In the UK, deaths within 28 days of the confirmation of COVID-19 infection are counted as COVID-19-related deaths, and cases where the cause of death is clearly determined to be COVID-19 by a medical professional are also recommended to be counted as deaths due to COVID-19 [10]. The official global number of COVID-19 deaths (i.e., daily mortality) is provided by the WHO COVID-19 dashboard. However, it is not clear whether cases of COVID-19 that are confirmed after death are included in the count of COVID-19 deaths. In South Korea, the COVID-19 death counting criteria are generally similar to the WHO criteria, but COVID-19 cases confirmed through postmortem testing and cases where COVID-19 testing was performed before death but COVID-19 was confirmed after death are also included in the number of deaths due to COVID-19 [19].

Despite the establishment of these death counting systems or criteria in each country, specific aspects of the COVID-19 pandemic have acted as a significant obstacle to accurately counting COVID-19 deaths [20]. Some deaths associated with COVID-19 in the US have not been classified as COVID-19 deaths [20]. In Brazil, it was difficult to accurately determine the number of deaths associated with COVID-19 due to the limited availability of diagnostic tests in the early stages of the pandemic [21,22]. In addition, issues related to the classification of deaths have been raised, as India lacks complete death certificates [23], and Indonesia is known to have under-reported deaths due to incomplete certification of deaths [24]. A study also identified many errors related to causes of death on death certificates in Iran [25]. Therefore, research emphasizing the importance of accurate death reporting according to an analysis of the underlying or direct cause of death is needed.

This study aimed to classify deaths in individuals with

HIGHLIGHTS

- The number of deaths associated COVID-19 increased with age in South Korea. Therefore, it is necessary to prepare the public health response for elderly people who are at a high risk of death.
- The group whose cause of death was not listed as COVID-19 in the reports had more deaths at home than in hospitals. And underlying diseases related to malignant neoplasms were frequent.
- It is necessary for public health agencies to make accurate and timely death statistics and analysis through unified standards by quickly establishing a death counting system or guideline in the early stage of the pandemic.

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COVID-19 according to whether COVID-19 was listed as the cause of death, using COVID-19-related death reporting data and epidemiological information in South Korea, and to analyze differences in the demographic characteristics of COVID-19 deaths and risk factors for whether a death was classified as being caused by COVID-19.

Materials and Methods

Subjects and Case Definition

Among patients with confirmed COVID-19 between January 20, 2020 and December 31, 2021, a total of 5,625 deaths that were registered in the Korea Disease Control and Prevention Agency (KDCA) COVID-19 information management system were selected as the subjects of this study. In South Korea, the data of COVID-19 cases and deaths reported by healthcare institutions or local public health centers are registered in the KDCA COVID-19 information management system according to Article 11 of the Infectious Disease Control and Prevention Act.

A patient with confirmed COVID-19 was defined as a person in whom, during the investigation period, severe acute respiratory syndrome coronavirus 2 viral genes in a specimen collected from the upper respiratory tract were detected using reverse-transcription polymerase chain reaction in accordance with the laboratory diagnostic criteria, regardless of clinical symptoms [19]. "Deceased" referred to people who had no alternative cause of death related to COVID-19, such as unnatural deaths, (1) people who were confirmed to be infected with COVID-19 and died during the isolation period, (2) people who were confirmed to be infected with COVID-19 after death, or (3) people who died after release from COVID-19-related isolation for whom a medical opinion was available regarding whether the death was related to COVID-19, and then confirmed the fact of death with the respective local government. Critically ill patients referred to those who were treated in isolation with respiratory support, such as non-invasive ventilation, high-flow oxygen therapy, invasive ventilation, extracorporeal membrane oxygenation, or continuous renal replacement therapy.

The variables used in this study included epidemiological information (sex, age group, region, the presence or absence and type of underlying diseases, vaccination history, respiratory support history, place of death, date of COVID-19 confirmation, and date of death), and items regarding the cause of death (a) the direct cause of death, (b) causes of (a), (c) causes of (b), (d) causes of (c), and other physical conditions except for causes of death (a)–(d).

The reported deaths were classified as those listed as being caused by COVID-19 (CD) and those not listed as being caused by COVID-19 in the death reports (NCD). A single author carried out the classification of deaths as CD or NCD.

Age was categorized as under or older than 60 years, and regions were divided into metropolitan cities and provinces. Metropolitan cities included Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, Sejong, and Jeju, and the provinces included Gyeonggi-do, Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, and Gyeongsangnam-do.

All analyses were performed based on the regions where COVID-19 tests were performed and cases were confirmed. Cases where a death report was requested to be withdrawn due to a false report by the local authority responsible for reporting deaths and cases that were confirmed as unnatural deaths were excluded from the analysis.

Classification of the Cause of Death

From the 5,625 reported deaths, 5,597 were finally selected for analysis, excluding 12 false reports and 16 confirmed unnatural deaths.

Deaths were categorized into 2 groups based on the information in the death reporting data according to the algorithm presented in Figure 1: CD (if the cause of death was listed as COVID-19 in the respective death report) or NCD (if the cause of death was not listed as COVID-19). The NCD group included cases with unknown and missing causes of death in the COVID-19 death reporting data.

Statistical Analysis

A descriptive statistical analysis was performed to investigate the epidemiological characteristics and causes of death of the deceased people, and the distribution of deaths according to sex, age group, area, and underlying diseases was analyzed. Univariate analysis of the relationships between each epidemiological variable and the CD and NCD groups was conducted. Multivariate logistic regression analysis was carried out using statistically significant variables from the univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to analyze risk factors for the classification of the causes of death (significance level: $p < 0.05$). All analyses were performed using Microsoft Excel 2018 and IBM SPSS ver. 23.0 for Windows (IBM Corp.).

Ethics Statement

This study was approved by the Institutional Review Board of KDCA (IRB No: 2022-11-05-PE-A).

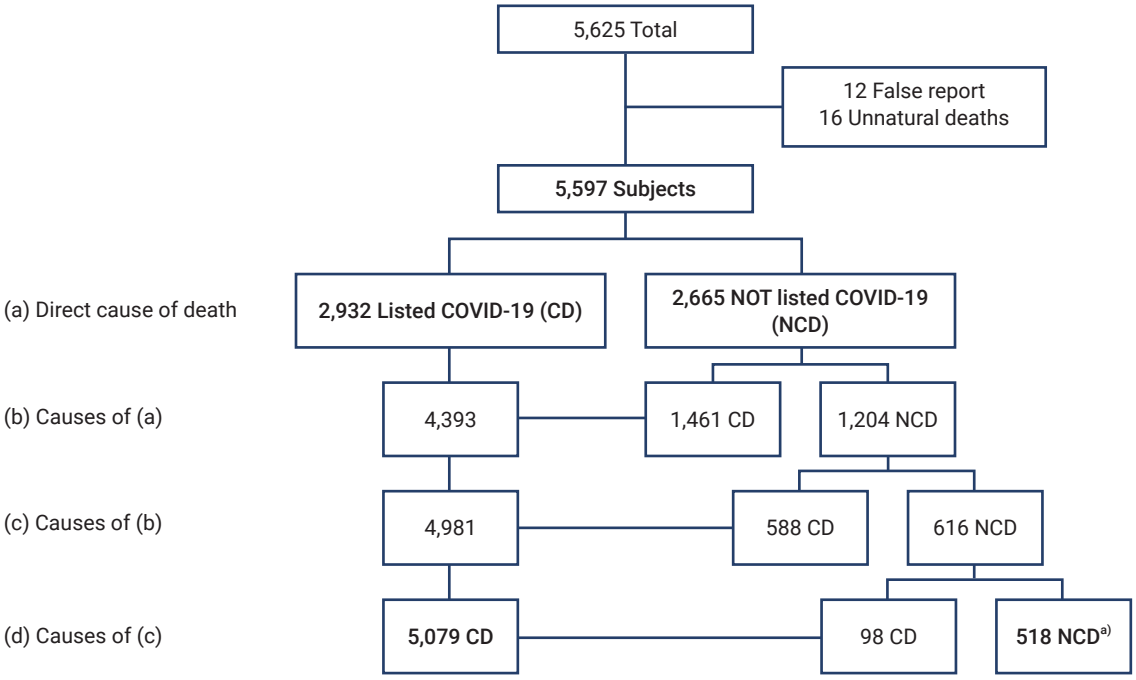

Figure 1. A classification algorithm of the subjects.
CD, cause of death listed as COVID-19 on death report; NCD, cause of death not listed as COVID-19 on death report.
[a)]Included cases with unknown (*n*=122) and missing (*n*=8) causes of death.

Results

Epidemiological Characteristics

The total number of confirmed cases during the investigation period was 635,253, from which 5,625 deaths were reported. The case fatality ratio (CFR) was 0.89%. Individuals in their 60s or older accounted for 5,202 of the 5,597 deaths (92.9%) investigated, and the proportion of those in their 80s was the highest (*n*=2,019, 36.1%). The CFR increased with age, and the mortality rates of those in their 60s, 70s, 80s, and 90s or older were 0.94%, 3.93%, 11.95%, and 21.81%, respectively (Table 1, Figure 2).

In addition, 96.4% of deaths (*n*=5,395) occurred in people with an underlying disease, the most common of which was cardiovascular disease (*n*=3,739, 69.3%). Furthermore, 95.6% of deaths (*n*=5,351) took place in medical institutions. There were 367 cases (6.6%) in which COVID-19 was confirmed after death, 2,971 patients received critical care before death (53.1%) (Table 1), and 53.4% (*n*=2,987) died in the winter, between December and February (Figure 3).

Characteristics of COVID-19 Deaths According to the Classification

The number of those whose cause of death was listed as COVID-19 (i.e., the CD group) was 5,079 (90.7%), whereas the number of those whose cause of death was not listed as COVID-19 (i.e., the NCD group) was 518 (9.3%). In the NCD group, 122 people (2.2%) had an unknown cause of death and the cause of death was left blank, with no details related to the cause of death, for 8 people (0.1%) (Table 1, Figure 1).

The number of men was higher than women in both groups (51.3% vs. 54.1%), and there was no significant difference in age between the groups (median, 80 vs. 80 years; mean, 77.9 vs. 76.9 years; interquartile range [IQR], 71–86 years vs. 69 –86 years), and the number of those in their 80s was the highest. By region, the number of deaths was highest in Seoul and Gyeonggi-do (32.2% vs. 31.7% and 33.5% vs. 24.1% in the CD and NCD groups, respectively). At least 1 underlying disease was recorded in 5,395 deaths, and the proportion of those with 4 or more underlying diseases was 19.2% in the CD group and 16.6% in the NCD group. The most common underlying disease was cardiovascular disease, as 67.7% of people in the CD group and 58.5% of those in the NCD group had this condition. The proportion of those who had received no vaccination or only 1 dose of vaccination was 74.6% in the CD group and 74.5% in the NCD group, with no significant difference between the groups. The most common place of death was medical institutions (97.3% in the CD group and 78.6% in the NCD group).

Of the deceased, 53.1% received critical care (56.3% in the CD group and 21.6% in the NCD group). Meanwhile, 367 individuals (6.6%) were confirmed to have COVID-19 after

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Table 1. Characteristics of the subjects according to the classification of the cause of death

Variable	Total (*n* = 5,597)	CD (*n* = 5,079)	NCD (*N* = 518)
Sex			
Male	2,883	2,603 (51.3)	280 (54.1)
Female	2,714	2,476 (48.7)	238 (45.9)
Age group (y)			
0–19	3	3 (0.1)	0 (0)
20–59	392	346 (6.8)	46 (8.9)
60–69	854	762 (15.0)	92 (17.8)
70–79	1,516	1,401 (27.6)	115 (22.2)
80–89	2,019	1,825 (35.9)	194 (37.5)
≥90	813	742 (14.6)	71 (13.7)
Region			
Seoul	1,801	1,637 (32.2)	164 (31.7)
Busan	277	239 (4.7)	38 (7.3)
Daegu	366	339 (6.7)	27 (5.2)
Incheon	263	228 (4.5)	35 (6.8)
Gwangju	45	44 (0.9)	1 (0.2)
Daejeon	168	132 (2.6)	36 (6.9)
Ulsan	62	55 (1.1)	7 (1.4)
Sejong	4	4 (0.1)	0 (0)
Gyeonggi-do	1,828	1,703 (33.5)	125 (24.1)
Gangwon-do	102	92 (1.8)	10 (1.9)
Chungcheongbuk-do	109	92 (1.8)	17 (3.3)
Chungcheongnam-do	146	134 (2.6)	12 (2.3)
Jeollabuk-do	105	94 (1.9)	11 (2.1)
Jeollanam-do	38	36 (0.7)	2 (0.4)
Gyeongsangbuk-do	163	149 (2.9)	14 (2.7)
Gyeongsangnam-do	91	81 (1.6)	10 (1.9)
Jeju	13	7 (0.1)	6 (1.2)
Unspecified	16	13 (0.3)	3 (0.6)
No. of underlying diseases			
No	202	178 (3.5)	24 (4.6)
Yes	5,395	4,901 (96.5)	494 (95.4)
1	1,436	1,280 (25.2)	156 (30.1)
2	1,643	1,489 (29.3)	154 (29.7)
3	1,255	1,157 (22.8)	98 (18.9)
≥4	1,061	975 (19.2)	86 (16.6)
Underlying disease			
Cardiovascular	3,739	3,436 (67.7)	303 (58.5)
Endocrine	2,284	2,100 (41.3)	184 (35.5)
Respiratory	478	432 (8.5)	46 (8.9)
Gastrointestinal	195	178 (3.5)	17 (3.3)
Urinary	811	740 (14.6)	71 (13.7)
Psychologic	317	286 (5.6)	31 (6.0)
Malignant neoplasms (cancer)	739	637 (12.5)	102 (19.7)
Hematological	121	109 (2.1)	12 (2.3)
Neurological	1,958	1,796 (35.4)	162 (31.3)
Musculoskeletal	391	355 (7.0)	36 (6.9)
Others	166	158 (3.1)	8 (1.5)
Vaccination status (dose)			
Unvaccinated	3,907	3,540 (69.7)	367 (70.8)
1	267	248 (4.9)	19 (3.7)
2	1,297	1,175 (23.1)	122 (23.6)
3	126	116 (2.3)	10 (1.9)
Place of death			
Hospital	5,351	4,944 (97.3)	407 (78.6)
Home	221	122 (2.4)	99 (19.1)
Others	25	13 (0.3)	12 (2.3)
Respiratory support	2,971	2,859 (56.3)	112 (21.6)
Infection confirmed after death	367	165 (3.2)	202 (39.0)
Interval between infection confirmation and death (d)	16.2	16.5	11.9

CD, cause of death listed as COVID-19 on death report; NCD, cause of death not listed as COVID-19 on death report.

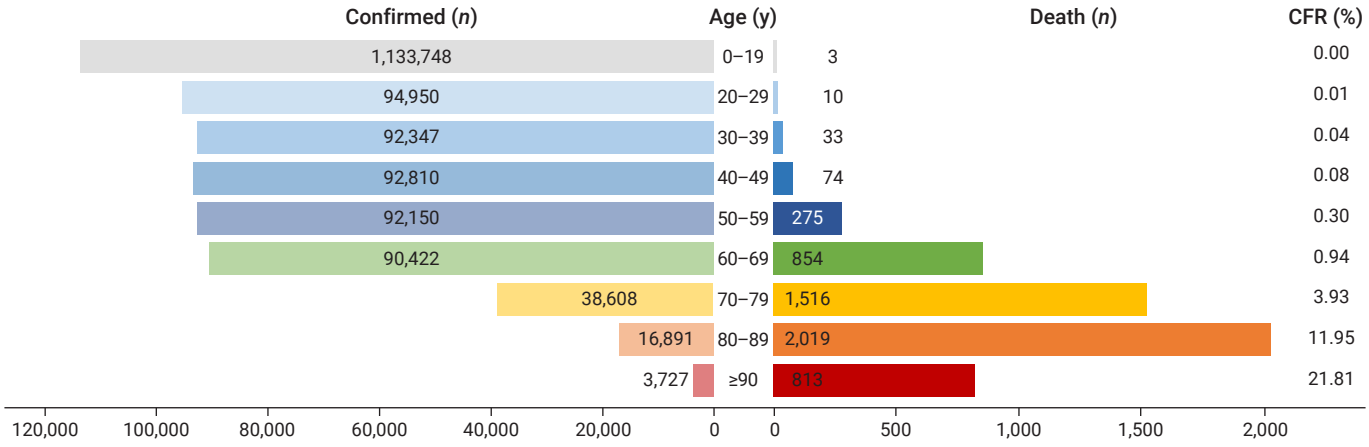

Figure 2. Number of confirmed patients, deaths, and case fatality ratio (CFR) by age group.

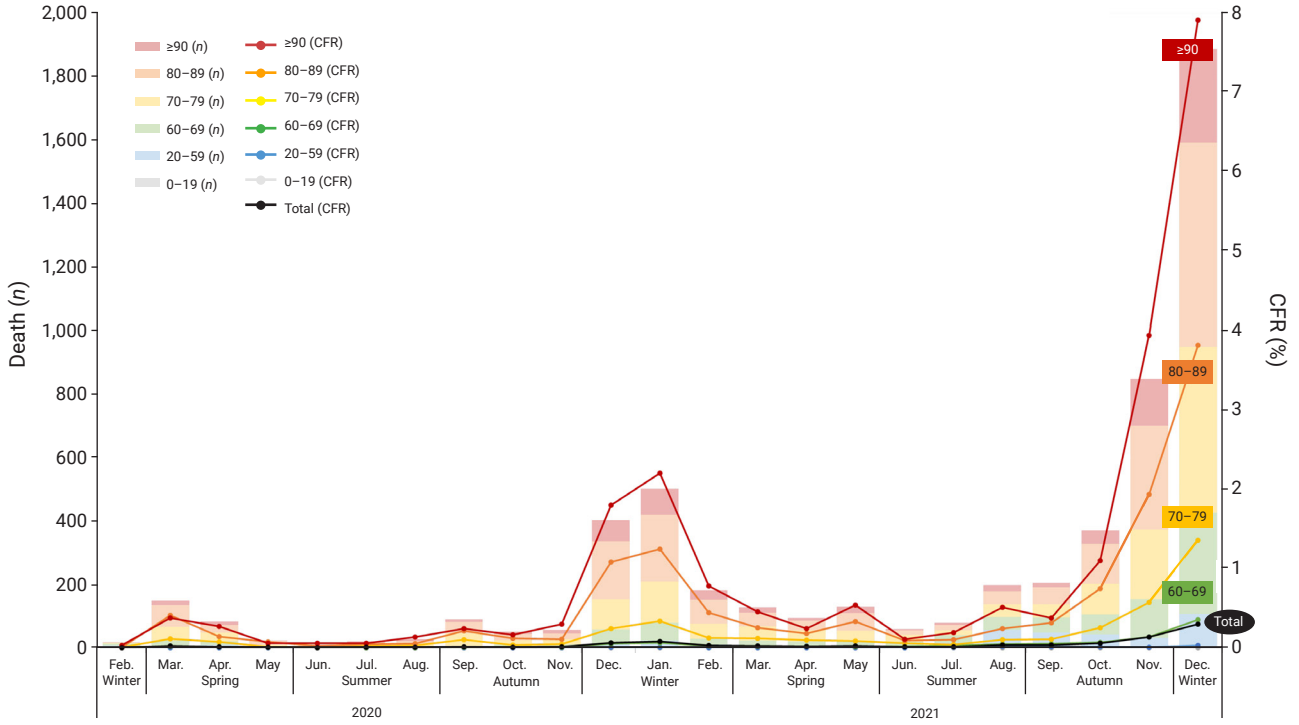

Figure 3. Case fatality ratio (CFR) by age and month of the year.

death. Of those cases, 165 (3.2%) were in the CD group and 202 (39.0%) were in the NCD group, indicating that a postmortem diagnosis of death was more common in the NCD group than in the CD group.

The average time interval from the date of COVID-19 confirmation to the date of death in 5,230 deaths, excluding the 367 deaths where COVID-19 infection was confirmed after death, was 16.2 days, with 16.5 days in the CD group and 11.9 days in the NCD group (median, 13 days vs. 8 days; IQR, 7–21 vs. 2 –16 days).

Comparison of Epidemiological Variables for COVID-19-Related Deaths

Univariate and multivariate analyses were conducted to evaluate the relationships between epidemiological variables and COVID-19-related deaths. Statistically significant relationships were found for region, place of death, respiratory support, and COVID-19 confirmation after death. In terms of

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region, Busan (OR, 1.59; 95% CI, 1.09–2.32; $p=0.021$), Incheon (OR, 1.53; 95% CI, 1.04–2.26; $p=0.041$), Daejeon (OR, 2.72; 95% CI, 1.82–4.07; $p<0.001$), Chungcheongbuk-do (OR, 1.84; 95% CI, 1.07–3.17; $p=0.038$), and Jeju (OR, 8.56; 95% CI, 2.84–25.76; $p<0.001$) showed significant relationships with the NCD group. Gyeonggi-do (OR, 0.73; 95% CI, 0.57–0.93; $p=0.014$) was significantly associated with the CD group. NCD cases were more likely to die at home (OR, 9.85; 95% CI, 7.42–13.09; $p<0.001$) but less likely to receive respiratory support (OR, 0.21; 95% CI, 0.17–0.27; $p<0.001$) than CD cases. COVID-19 confirmation after death was also more common in the NCD group (OR, 19.0; 95% CI, 15.05–24.08; $p<0.001$) (Table 2).

Multivariate analysis was performed using the variables that were statistically significant in the univariate analysis. The NCD group showed a significantly higher risk of death at home (OR, 2.11; 95% CI, 1.49–3.00; $p<0.001$) and COVID-19 confirmation after death (OR, 9.45; 95% CI, 7.20–12.40; $p<0.001$) than the CD group. Residence in the provinces (OR, 0.80; 95%

Table 2. Univariate analysis of epidemiological variables related to COVID-19 deaths according to the classification of the causes of death

Variable	Univariate odds ratio (95% confidence interval)	*p*-value
Sex		
Male	Reference	
Female	0.89 (0.75–1.07)	0.224
Age group (y)		
<60	Reference	
≥60	0.76 (0.55–1.04)	0.090
Region		
Seoul	Reference	
Busan	1.59 (1.09–2.32)	0.021
Daegu	0.80 (0.52–1.21)	0.336
Incheon	1.53 (1.04–2.26)	0.041
Gwangju	0.23 (0.03–1.66)	0.182
Daejeon	2.72 (1.82–4.07)	<0.001
Ulsan	1.27 (0.57–2.84)	0.717
Sejong	-	
Gyeonggi-do	0.73 (0.57–0.93)	0.014
Gangwon-do	1.08 (0.55–2.12)	0.951
Chungcheongbuk-do	1.84 (1.07–3.17)	0.038
Chungcheongnam-do	0.89 (0.48–1.65)	0.834
Jeollabuk-do	1.17 (0.61–2.23)	0.765
Jeollanam-do	0.55 (0.13–2.32)	0.595
Gyeongsangbuk-do	0.94 (0.53–1.66)	0.938
Gyeongsangnam-do	1.23 (0.63–2.42)	0.674
Jeju	8.56 (2.84–25.76)	<0.001
Unspecified	2.30 (0.65–8.17)	0.371
Underlying disease		
No	Reference	
Yes	0.75 (0.48–1.16)	0.191
Vaccination status		
Unvaccinated	Reference	
Vaccinated (1–3 doses)	0.95 (0.76–1.15)	0.622
Place of death		
Hospital	Reference	
Home	9.85 (7.42–13.09)	<0.001
Others	11.21 (5.08–24.73)	<0.001
Respiratory support		
No	Reference	
Yes	0.21 (0.17–0.27)	<0.001
Infection confirmed after death		
No	Reference	
Yes	19.0 (15.05–24.08)	<0.001

CI, 0.65–0.98; $p=0.029$) and the use of respiratory support (OR, 0.40; 95% CI, 0.32–0.51; $p<0.001$) were significantly less common in NCD cases than in CD cases (Table 3).

Comparison of Underlying Diseases as Risk Factors for the Classification of COVID-19 Deaths

In a further analysis, cardiovascular disease (303/215 vs. 3,436/1,643; OR, 0.67; 95% CI, 0.56–0.81; $p<0.001$) and endocrine disease (184/334 vs. 2,100/2,979; OR, 0.78; 95% CI, 0.65–0.94; $p=0.012$) were more common in the CD group than in the NCD group, while malignant neoplasms (102/416 vs. 637/4,442; OR, 1.71; 95% CI, 1.36–2.16; $p<0.001$) showed a significant association with the NCD group (Table 4).

Discussion

Since the WHO declared the COVID-19 outbreak as a public health emergency of international concern in January 2020 [26] and a pandemic in March 2020, COVID-19 has spread around the world. COVID-19 is a life-threatening infectious disease that has had major effects on people's lives [27]. In 2020, when the COVID-19 outbreak began, COVID-19 was the top cause of death in Brazil [6], and it was the third leading cause of death in the US [28]. Although COVID-19 did not rank high as a cause of death in South Korea, it was announced that the number of deaths due to COVID-19 increased by 429.5% from 2020 to 2021 [29].

Studies regarding deaths due to COVID-19 have focused mainly on hospitalized patients, and several risk factors for death due to COVID-19 have been identified [6,30–32]. However, the presence of at least 1 risk factor did not meaningfully distinguish between the CD and NCD groups. The major risk factors for COVID-19-related death are age and underlying diseases, which is why the CD group predominantly contained elderly patients with underlying diseases. In Germany, more than 40% of those who died from COVID-19 had at least 1 underlying disease, and there was no significant difference in risk factors between the CD and NCD groups [8].

In South Korea, 96.4% of COVID-19 deaths occurred in those who had an underlying disease. However, no previous studies have investigated the causes of death in deceased COVID-19 patients in South Korea. To address that knowledge gap, this study analyzed the epidemiological characteristics of COVID-19-related deaths and explored underlying diseases as risk factors by classifying all COVID-19-related deaths between 2020 and 2021 according to whether or not the cause of death was listed as COVID-19. The CFR in COVID-19 cases increased with age in Europe and the US [5,7,8]. Similarly, the number of deaths among elderly people with COVID-19 was high in South Korea, and the CFR also increased with age.

Table 3. Multivariate analysis of epidemiological variables related to COVID-19 deaths according to the classification of the causes of death

Variable	Multivariate odds ratio (95% confidence interval)	*p*-value
Region		
Metropolitan city	Reference	
Province	0.80 (0.65–0.98)	0.029
Unspecified	3.82 (0.90–16.14)	0.068
Place of death		
Hospital	Reference	
Home	2.11 (1.49–3.00)	<0.001
Others	2.54 (0.99–6.49)	0.052
Respiratory support		
No	Reference	
Yes	0.40 (0.32–0.51)	<0.001
Confirmed after death		
No	Reference	
Yes	9.45 (7.20–12.40)	<0.001

Table 4. Underlying diseases as risk factors for the classification of the cause of deat

Underlying disease	Odds (yes/no) of NCD vs. CD	Odds ratio (95% confidence interval)	*p*-value
Cardiovascular	303/215 vs. 3,436/1,643	0.67 (0.56–0.81)	<0.001
Endocrine	184/334 vs. 2,100/2,979	0.78 (0.65–0.94)	0.012
Respiratory	46/472 vs. 432/4,647	1.05 (0.76–1.44)	0.835
Gastrointestinal	17/501 vs. 178/4,901	0.93 (0.56–1.55)	0.891
Urinary	71/447 vs. 740/4,339	0.93 (0.72–1.21)	0.641
Psychologic	31/487 vs. 286/4,793	1.07 (0.73–1.56)	0.817
Malignant neoplasms (cancer)	102/416 vs. 637/4,442	1.71 (1.36–2.16)	<0.001
Hematological	12/506 vs. 109/4,970	1.08 (0.59–1.98)	0.924
Neurological	162/356 vs. 1,796/3,283	0.83 (0.68–1.01)	0.070
Musculoskeletal	36/482 vs. 355/4,724	0.99 (0.70–1.42)	0.955
Others	8/510 vs. 158/4,921	0.49 (0.24–1.00)	0.062

NCD, cause of death not listed as COVID-19 on death report; CD, cause of death listed as COVID-19 on death report.

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Therefore, it is necessary to continue to implement COVID-19 prevention and control measures for elderly people who are more vulnerable to disease transmission and are at a high risk of death. In particular, it is necessary to prepare the public health response for the winter, when many deaths occur. According to previous studies, symptoms such as dyspnea, pneumonia, and cough at COVID-19 diagnosis were significantly associated with COVID-19 being reported as the cause of death, indicating that these symptoms served as predictors of disease severity and death [8]. Although information on the definite diagnosis of the deceased and the symptoms at the time of death could not be identified, pneumonia was listed as the case of death for 52.5% of the deceased. However, we could not confirm whether their symptoms were directly caused by COVID-19 infection or due to aggravation of other underlying diseases.

Through this study, we found that the NCD group had a higher likelihood of dying at home and having COVID-19 infection confirmed after death than the CD group. The information on the patients who died before COVID-19 results were available may not have been timely enough to determine the correct cause of death. Furthermore, malignant neoplasms as underlying diseases were more frequent in NCD cases than in CD cases, indicating that some of the NCD cases were likely due to the exacerbation of malignant neoplasms rather than COVID-19. In addition, we found that the CD cases were more likely to have received critical care and had a longer interval from the day of diagnosis to death. We suggest that underlying diseases such as neoplasms could aggravate COVID-19-related deaths, which was probably an important factor in NCD cases. COVID-19 testing may have been delayed in NCD patients because it was difficult to clinically distinguish between symptoms caused by aggravation of the underlying diseases and COVID-19. Furthermore, the NCD group was less likely than the CD group to show severe respiratory symptoms and might not have required treatment in a hospital, which could explain why they were more likely to die at home. However, it is likely that the results of this study were affected by limitations in reported death information; therefore, further research is needed to elucidate more information on this topic for COVID-19 decedents. Nevertheless, we suggest high risk groups with underlying diseases, such as cancer patients, should be promptly tested for COVID-19. Once COVID-19 is diagnosed, treatment should be administered at an early stage to reduce mortality.

In this study, 8 cases had no description for any of the death report items. Furthermore, COVID-19 was not included in the death report for about 9.3% of deaths, and for 25.1% of them, the cause of death was not known at all. The rapid increase in the number of deaths in the special circumstances of the COVID-19 pandemic made it difficult to determine the cause of death at the right time when writing a death certificate. The information contained in the death report data varied in quality and did not support a definitive attribution of cause of death in all cases. Therefore, further analysis is needed to determine the quality of death certificates or death registration data.

In many countries, death certificates are the main source of official death statistics [33]. Accurate death diagnosis and reporting are critical to maintaining accurate and reliable mortality data. Because the quality of death certificate data eventually determines the accuracy of public health mortality data [20], efforts to improve the quality of data regarding suspected causes of death (i.e., efforts to provide complete and logical causal relationships) should be made. In particular, it is necessary to thoroughly educate people (e.g., physicians) on the criteria or guidelines stating that people infected with COVID-19 can die from other underlying diseases or accidents, and such cases are not deaths due to COVID-19. Thus, they are not subject to reporting requirements for deaths related to COVID-19.

In general, it is difficult to obtain characteristics of infected patients and clinical observations of patients at the population level in the early stages of a pandemic [34]. Thus, determining the exact cause of death is essential for planning prevention and control measures, especially during a pandemic that requires rapid public action [24]. In addition, high-quality death certificates containing correct information enable national health authorities to collect timely and accurate information to assist in the assessment and management of infectious diseases [20]. Therefore, it is necessary for public health agencies to make additional efforts to mitigate the spread of disease by quickly establishing a death counting system and guideline in the early stage of a pandemic or outbreak, and unified standards should be implemented to ensure the accuracy of death statistics and support analyses of those records.

This study has several limitations. First, because our analysis was based on death report data, it might contain less information than was contained in the corresponding death certificates. Some of the data were incomplete because the information from death reports varied qualitatively and missing data sometimes existed. Second, underlying diseases and causes of death were not analyzed using Korean Classification of Diseases codes. We analyzed epidemic data and information on deaths from death reports in the KDCA COVID-19 information management system. Third,

we did not adjust for potential confounding factors, such as COVID-19 variants and vaccine effectiveness. Furthermore, our study cannot provide a definitive explanation of how deaths can be attributed to COVID-19 after infection.

This is the first study to analyze risk factors for the reported cause of death using COVID-19 death report data in South Korea. The results of this study reconfirm that domestic COVID-19 response strategies and COVID-19 patient management methods, such as COVID-19 diagnostic tests and bed allocations, monitoring of patients' clinical status, and the provision of COVID-19 treatment, have been formulated based on scientific evidence. As the COVID-19 pandemic has continued for 3 years, COVID-19 variants continue to emerge. Hence, it is necessary to monitor COVID-19 deaths during COVID-19 variant outbreaks. Monitoring COVID-19 deaths can be used as a basis for strengthening COVID-19 prevention and control policies, which can minimize the damage caused by the disease, such as progression to severe illness or death. This study is also expected to be used as evidence for establishing a death counting system or criteria that can collect timely and accurate information in the event of a new infectious disease pandemic or outbreak.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of KDCA (IRB No: 2022-11-05-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. The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: NYK, DK; Data curation: NYK; Formal analysis: NYK, HJL, DK; Investigation: NYK, DK; Methodology: all authors; Project administration: DK; Resources: all authors; Software: all authors; Supervision: DK, NYK; Validation: all authors; Visualization: BR, ES; Writing–original draft: NYK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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Original Article

Vaccine hesitancy in patients with COVID-19 who have back pain

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ABSTRACT

Objectives: Musculoskeletal pain is among the most common symptoms in patients diagnosed with coronavirus disease 2019 (COVID-19), and it has placed a significant burden on health worldwide during the pandemic. This study explored vaccine hesitancy and associated factors in patients with positive COVID-19 polymerase chain reaction test results who were hospitalized and had back pain.
Methods: A cross-sectional study was conducted among 170 hospitalized COVID-19 patients over 18 years of age. Data were analyzed using descriptive statistics with IBM SPSS ver. 25.0.
Results: COVID-19 patients who were married considered COVID-19 vaccinations riskier than unmarried COVID-19 patients. Patients who had not been vaccinated expressed higher levels of distrust towards COVID-19 vaccines than patients who had been vaccinated. Participants had relatively little hesitation toward the Sinovac vaccine. High vaccine confidence was found in all participants regardless of vaccination status. Those who had not received the COVID-19 vaccine reported higher risk perceptions than those who had received at least 1 dose of any COVID-19 vaccine.
Conclusion: Measurements of the hesitancy of vaccinated and non-vaccinated patients or members of society towards vaccines can be an important parameter for health authorities to find solutions.

Keywords: Back pain; Coronavirus; COVID-19; Turkey; Vaccination hesitancy

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Introduction

As an anatomical area, the back extends from the top of the neck to the tailbone (Figure 1). Back pain refers to pain in the tissues in this area caused by mechanical or non-mechanical causes such as infection, inflammation, and trauma [1,2]. It has been observed that patients with back pain have breathing problems and avoid some behaviors due to the pain they experience

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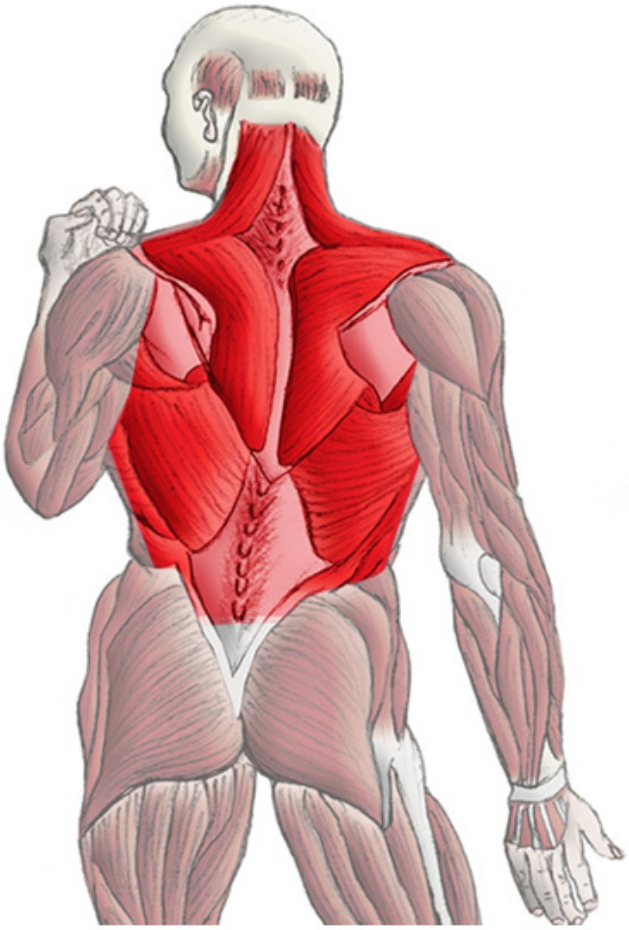

Figure 1. Muscle anatomy of areas affected by back pain. This drawing was drawn by the authors.

in coughing and physical movements [3]. The fact that back pain is one of the long-term effects of coronavirus disease 2019 (COVID-19) has made it even more important to research this issue [4].

Tissue damage has been reported to occur with the increased release of pro-inflammatory stimuli due to COVID-19 infection [4]. Accordingly, survivors of COVID-19 have shown some health problems such as widespread pain, weakness in the muscles, and increased sensitivity in the joints, which has prompted predictions that COVID-19 alone causes back pain and may place patients at risk for permanent pain and disability in the future [5]. The symptoms of infection have received substantial attention from researchers since the early days of COVID-19, and findings from recent studies have shown that musculoskeletal symptoms (of which back pain was the most common) were more common than respiratory symptoms [6,7]. Almost half (46.6%) of patients who contracted COVID-19 complained of

HIGHLIGHTS

- Patients who had not been vaccinated expressed higher levels of distrust towards COVID-19 vaccines than patients who had been vaccinated.
- Participants were less hesitant to get the Sinovac vaccine than other types of COVID 19 vaccines.
- All participants had high COVID-19 vaccine confidence.
- Those who did not have the COVID-19 vaccine were found to have a higher risk perception than those who had at least one dose of the COVID-19 vaccine.

pain, and 92.6% of patients diagnosed with COVID-19 who experienced musculoskeletal pain stated that they did not have pain before getting COVID-19. Pain in the thoracic region was experienced by 33.1% of these patients, and pain in the lumbar region by 25% [8].

Vaccination is a drug-free treatment that provides immunity, but the number of people who hesitate or refuse to be vaccinated has increased in recent years. This increase has attracted the attention of many institutions, including the World Health Organization (WHO). In 2019, the WHO recognized vaccine hesitancy and refusal as one of the top 10 threats to the world's health. According to the WHO, if vaccine hesitancy and refusal continue to spread among people at this rate, it will be a severe problem worldwide in the event of future pandemics such as COVID-19 [9].

One of the symptoms in patients with a positive COVID-19 polymerase chain reaction (PCR) test is back pain at various levels of severity [10]. In particular, back pain is one of the most significant symptoms of the spreading Omicron variant of COVID-19 [11]. However, back pain can be caused by many etiologies [12], making it essential to differentiate back pain caused by COVID-19 from back pain caused by other causes and not to confuse them. Thus, studies have attributed back pain to COVID-19 in patients who have never had back pain before and whose PCR test is positive [13]. In addition, it has been observed that people with chronic back pain experience more back pain when infected with COVID-19 [6]. Many studies have shown that back pain is often a long-term effect of COVID-19 that does not resolve quickly [5,6,8,10–12,14].

The long-term persistence of COVID-19-induced back pain is worth investigating both due to the resultant disease burden and because of treatment costs. In particular, clinicians and hospital administrators are trying to eliminate back pain caused by COVID-19, making plans and developing treatment protocols for this purpose. However, these efforts

are very costly. In addition, the quality of life of individuals with back pain caused by COVID-19 is diminished [15]. Therefore, vaccination, which is a much cheaper and more protective method [16], substantially increases the likelihood that infected individuals will have mild COVID-19 [17] and reduces treatment costs [18]. Health systems are currently experiencing problems in terms of financing resources, and waiting times for treatment have increased in many countries, especially due to the inadequacy of unaffordable health systems. Since back pain caused by COVID-19 creates a non-communicable disease burden, it may increase waiting times and accelerate the consumption of scarce financial resources. These reasons constitute the rationale for conducting this study only among patients with COVID-19 who experience back pain, rather than among patients with other conditions or patients with COVID-19 who do not experience back pain.

The fact that one of the symptoms of COVID-19, especially the Omicron variant, is back pain [19,20] may increase individuals' risk and necessitate long-term treatment.. Therefore, vaccination prior to contracting COVID-19 is important, since vaccines provide protection [21], alleviate the symptoms of COVID-19 [22,23], and reduce severe back pain [17]. Since vaccination is cheaper than treatment, it provides a less burdensome way of overcoming long-term COVID-19-induced back pain that would avoid the hospitalization of patients with long-term COVID-19-induced back pain, thereby ensuring that access to the hospital can be provided to those who really need it. These considerations made it necessary to conduct this study among COVID-19 patients with back pain. It is thought that this study will provide meaningful evidence to both clinicians and society.

The quality of life of those who experience back pain due to COVID-19 is diminished [15], and serious costs would be incurred to restore their quality of life. The motivation of this study was to draw attention to back pain as a symptom of COVID-19 in the context of vaccination, which is known to be very simple and cost-effective [16,18,22,23]. Specifically, this study investigated vaccine hesitancy and associated factors in patients with back pain who had PCR-confirmed COVID-19 tested and were hospitalized in a COVID-19 ward. It is hoped that this study will help resolve the problem of COVID-19 back pain without costly treatments, thereby alleviating the burden of disease.

Materials and Methods

Study Setting and Timing

This study was conducted in Diyarbakır, which is the largest city in southeastern Turkey. Patients hospitalized in the adult COVID-19 ward of Gazi Yaşar gil Education and Research Hospital, one of the largest hospitals in Diyarbakır, constituted the study population. The study was conducted in this hospital because one of the researchers was a medical doctor treating these patients. This study group exclusively comprised Turkish patients with positive COVID-19 PCR test results performed by the hospital's testing unit. The study was conducted as a face-to-face survey between September 3, 2021 and November 10, 2021, during the intense spread of the COVID-19.

Study Design

This descriptive cross-sectional study was based on the relational screening model, a causal comparison subtype of quantitative research methods. The physician-researcher administered the relevant questionnaire to patients who had a positive PCR test in the COVID-19 unit where the study was conducted, were hospitalized, and complained of back pain. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement's guidelines for reporting cross-sectional studies (Table S1).

Participants

The study participants were men and women over the age of 18 who were admitted to an adult ward for COVID-19 treatment and experienced back pain for the first time. Pediatric patients were not specifically excluded; instead, the inclusion of only adult patients reflects the inherent scope of practice of the adult COVID-19 ward. The participants were conscious and were admitted only to alleviate or eliminate symptoms such as back pain. The socio-demographic structure of the participants was similar to the socio-demographic structure of the people of Diyarbakır.

Sample Size and Sampling

According to the PCR test results performed by the hospital team, 700 people over the age of 18 were diagnosed with COVID-19 during the 2-month study. The study population consisted of 305 patients hospitalized in the COVID-19 ward who met the criteria for inclusion (Figure 2). The sample size from this population was calculated as 170 with a confidence interval of 95% and a margin of error of 5%. In order to avoid selection bias, every patient who met the selection criteria, was conscious and volunteered for the study was included in the study. Sample size calculation formula: If the number of individuals who make up the population of interest is known, the sample size can be calculated as follows [24]:

$$n = (N \cdot t^2 \cdot p \cdot q)/(d^2 \cdot (N-1) + t^2 \cdot p \cdot q),$$

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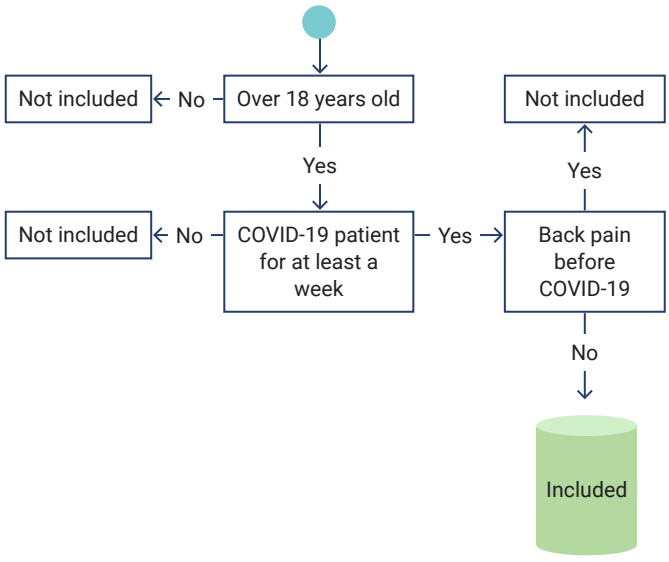

Figure 2. Sample selection diagram.

where N indicates the number of individuals in the study population, n is the number of individuals to be sampled, p is the frequency of occurrence (probability of occurrence) of the event under study, q is frequency of non-occurrence of the event under investigation (probability of non-occurrence), t is a theoretical value for a certain degree of freedom and the level of error determined, and d expresses the desired deviation (±) according to the frequency of occurrence of the event.

Figure 1 presents specific information about the anatomical area of back pain, and Figure 2 shows a sample selection diagram to facilitate a clearer understanding of the patient population within the study's scope.

Data Collection Tools

Data were collected using a demographic information form (prepared by the authors) and the Vaccination Hesitancy in Pandemics Scale. The scale used was developed by Larson et al. [25] and modified for COVID-19 vaccines by Çapar and Çınar [26].

The socio-demographic information form consisted of variables such as sex, age, marital status, education status, economic status, previous COVID-19 infection status, whether participants had lost a relative due to COVID-19, vaccination status against COVID-19 (including which vaccine and how many doses), how many days had passed since the last dose of vaccine was administered, the presence of chronic illness, and the severity of back pain.

The vaccine hesitancy scale in pandemics is a 5-point Likert-type instrument with 2 sub-dimension and 10 items, including 8 items about lack of confidence and 2 items about risk. The minimum score is 10, and the maximum score is 50. High scores indicate high vaccine hesitancy, while low scores indicate low vaccine hesitancy. The minimum score obtained from the lack of confidence sub-dimension is 8, and the maximum score is 40. The minimum score obtained from the risk sub-dimension is 2, and the maximum score is 10.

Data Analysis

Frequency and percentage values obtained from descriptive statistics were used to reveal and explain the socio-demographic characteristics of patients hospitalized in the COVID-19 ward. Frequency and percentage values were used for categorical variables related to vaccine hesitation, while mean and standard deviation values were used for continuous variables. Skewness and kurtosis values were also reported to evaluate the normality assumption for continuous variables. The independent-sample t-test for 2 groups and 1-way analysis of variance for more than 2 groups were used to determine the significance of differences in vaccine hesitancy scale in pandemics scores according to demographic data. In addition, the Pearson correlation coefficient (r) was used to evaluate the relationships between continuous variables [27]. A p-value <0.05 was considered to indicate statistical significance, and the results were analyzed at a 95% confidence level. All analyses were performed with IBM SPSS ver. 25.0 (IBM Corp.) [28].

Ethical Consideration

Ethical approval was received from the Diyarbakır Gazi Yaşargil Education and Research Hospital in Turkey (IRB-863-2021). The necessary permissions were obtained from the institution where the study was conducted. All patients included in the study voluntarily participated in the study, and oral consent was obtained from the participants. No ethical violations were committed during the study, and all processes were carried out while observing ethical rules. The necessary permits were also obtained from the Scientific Research Platform of the Ministry of Health for the study (permission code: 2021-09-03T10_03_52).

Results

Assumptions of Normality and Homogeneity of Variance

The skewness and kurtosis values of continuous variables were examined to evaluate the assumption of normality. The skewness and kurtosis values were between –1.5 and +1.5; therefore, the continuous variables (vaccine dose, vaccine

hesitancy scale total score, lack of confidence, risk, age, and the number of days since the last vaccination) were assumed to have a normal distribution and parametric tests could be used accordingly. The homogeneity of variance was also confirmed ($p > 0.05$) [29].

When the socio-demographic structure of the patients hospitalized in the COVID-19 ward was examined, it was seen that the distribution of men and women was almost even. The majority of the patients were in the middle and upper-income groups, while a minimal number of them were in the low-income group. However, 30.6% of the patients ($n = 52$) were illiterate, and 41.2% ($n = 70$) were primary school graduates. In addition, most of the patients were married, and 38.8% ($n = 66$) had at least 1 chronic disease. About a third of those included in the study had lost at least 1 relative due to COVID-19, and very few of them had been vaccinated against COVID-19. The most common vaccine that patients had received was Sinovac (11.2%; $n = 19$), followed by BioNTech (14.1%; $n = 24$) and Sinovac+BioNTech (4.7%; $n = 8$) (Table 1).

The mean number of COVID-19 vaccine doses was 1.38 ± 0.680, and the average time between the last COVID-19 vaccine and contracting COVID-19 was 21.17 ± 47,601 days. The average total vaccine hesitancy scale in pandemics score was 27.88 ± 6.044 (lack of confidence sub-dimension, 21.12 ± 5.392; risk sub-dimension, 6.75 ± 1.742) (Table 2).

A high level of positive correlation was found between the total score of the vaccine hesitancy scale and its sub-dimensions. Meanwhile, the vaccine dose showed moderate negative correlations with the total vaccine hesitancy score and its sub-dimensions. The number of days since the last dose showed weak negative correlations with the total score of patients' vaccine hesitancy and the score for the risk sub-dimension. The number of days since the last vaccine dose showed a strong positive correlation with the vaccine dose (Table 3).

Sex, income status, education status, chronic illness status, previous COVID-19 transmission status, loss of a relative due to COVID-19, and back pain severity did not show significant relationships with COVID-19 vaccine hesitancy ($p > 0.05$).

Married COVID-19 patients considered COVID-19 vaccines riskier than unmarried COVID-19 patients. This difference was statistically significant ($p < 0.05$). Patients who were not vaccinated had significantly higher levels of distrust of COVID-19 vaccines, higher scores for finding vaccines risky, and higher levels of vaccine hesitancy compared to those vaccinated ($p < 0.05$) (Table 4).

Differences were found between those who were not vaccinated and those who received any vaccine ($p < 0.05$).

Table 1. Information on patients' socio-demographic characteristics ($n = 170$)

Variable	Value
Age (y)	55.40 ± 14.283
Sex	
Female	80 (47.1)
Male	90 (52.9)
Income status	
Low	52 (30.6)
Middle	106 (2.4)
High	12 (7.1)
Educational status	
Illiterate	52 (30.6)
Primary-secondary school	70 (41.2)
High school	35 (20.6)
Associate's degree and above	13 (7.6)
Marital status	
Single	33 (19.4)
Married	137 (80.6)
Chronic disease status	
Yes	66 (38.8)
No	104 (61.2)
Previous COVID-19 infection	
Yes	11 (6.5)
No	159 (93.5)
Losing a relative due to COVID-19	
Yes	61 (35.9)
No	109 (64.1)
COVID-19 vaccination status	
Yes	51 (30.0)
No	119 (70.0)
COVID-19 vaccine type	
Not vaccinated	119 (70.0)
Sinovac	19 (11.2)
BioNTech	24 (14.1)
Sinovac+BioNTech	8 (4.7)
Severity of back pain	
Very little	18 (10.6)
A little more	38 (22.4)
Moderate	61 (35.9)
Too much	35 (20.6)
Unbelievable pain	18 (10.6)

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

Table 2. Patients' information on COVID-19 vaccines and vaccine hesitancy scores ($n = 170$)

Variable	Mean ± standard deviation
No. of vaccine doses	1.38 ± 0.680
Days since the last vaccine dose	21.17 ± 47.601
Total scale score	27.88 ± 6.044
Lack of confidence	21.12 ± 5.392
Risk	6.75 ± 1.742

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Table 3. Correlations between selected variables, the total vaccine uncertainty scale, and its sub-dimensions (n = 170)

Variable	Total scale score	Lack of confidence	Risk	Vaccine dose	Days since the last vaccine dose	Age
Total scale score	1					
Lack of confidence	0.960**	1				
Risk	0.498**	0.235**	1			
Vaccine dose	−0.253**	−0.217**	−0.206**	1		
Days since the last vaccine dose	−0.177*	−0.141	−0.180*	0.700**	1	
Age	−0.062	−0.048	−0.067	0.075	0.14	1

Pearson correlation coefficients (r) were used to quantify correlations between the variables.
*p < 0.05, **p < 0.01.

Post hoc test was performed to reveal between which groups this difference was. The variance of the groups was homogeneous, but the sample numbers were not equal, so the Scheffé *post hoc* test [30] was used. Those who were not vaccinated and those vaccinated with Sinovac from any brand of vaccine differed significantly in total vaccine hesitation score and risk sub-dimension score. In other words, those vaccinated with Sinovac had a much lower vaccination hesitancy than those who were not vaccinated and those who had been vaccinated from other brands (Supplementary Material 1). The unvaccinated and vaccinated groups of any brand all had high vaccine confidence. There was no difference between the groups in terms of this level of confidence (p > 0.05). The risk sub-dimension of the vaccine hesitancy scale in pandemics showed a significant difference only between those who were not vaccinated and those who received the Sinovac vaccine (p < 0.05), whereas the risk sub-dimension did not show a statistically significant difference according to the type of vaccine. Therefore, the high-risk perception of those who were not vaccinated showed a statistically significant difference from the low-risk perception of those who received the Sinovac vaccine (p < 0.05) (Table 4).

Discussion

Since this study was conducted in a population located in a city in the southeastern region of Turkey, its most significant limitation is that it cannot represent other regions of Turkey or other countries. Therefore, the results of this study should be evaluated within the framework of its population to avoid possible bias. Further studies, potentially using other methods to investigate different effects and relationships, should be conducted to supplement these findings.

Many other studies have investigated pain, pain management, pain perception, and COVID-19 vaccination [31]. However, the fact that this study was conducted specifically among COVID-19-positive patients with back pain in a COVID-19 ward constitutes the main novelty of this study.

The possibility of chronic back pain after COVID-19 has emerged as a major social issue. For instance, a study showed that musculoskeletal complaints were seen 27.1% more frequently in patients with diabetes and obesity after the COVID-19 pandemic than before. It has been observed that individuals with chronic diseases have worse COVID-19 prognoses [32,33]. As an explanation, it is highly likely that inflammatory changes develop in the organs of those who have had COVID-19. Meanwhile, several studies have documented that back pain increased after COVID-19 and turned into a long-term non-communicable disease [10,12,14–16]. These circumstances are likely to lead to an increase in the burden of disease and an increase in treatment costs.

Pain is a subjective element that is perceived by the human brain and related to a person's living experience, including psycho-social and cultural factors, as well as one's state of awareness [34]. Researchers have suggested that should be considered in a multifaceted way, and it has been proposed that pain can also trigger other conditions. In hospitalized patients, pain may have effects that will prolong the hospital stay, thereby increasing the likelihood of contracting certain infections, such as pneumonia [35]. It has been stated that back pain caused by COVID-19 requires long-term treatment [12]. Since most of these treatments are given in the hospital environment, prolonged treatment for back pain may also increase the likelihood of patients developing other infections.

In this study, back pain complaints were present in the majority in patients with musculoskeletal pain, who may be candidates for rehabilitation in the future. A study reported that 40% to 60% of COVID-19-positive patients experienced musculoskeletal pain [36]. Another study also stated that when back pain is not treated effectively on time, it may become chronic, leading to an increase in the incidence and costs of morbidity [1,2]. Meanwhile, a previous study showed that patients who received the COVID-19 vaccine experienced less musculoskeletal pain and more easily overcame the disease [37]. The findings of many similar

Table 4. Comparison of total scores on the vaccine hesitancy scale and its sub-dimensions of according to selected variables (n = 170)

Variable	Lack of confidence		Risk		Vaccine hesitancy score	
	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD
Sex						
Female	20.95	5.252	6.63	1.829	27.59	5.980
Male	21.27	5.538	6.87	1.663	28.13	6.122
t	0.381		0.855		0.587	
p	0.704		0.394		0.558	
Income status						
Low	20.42	5.210	6.92	1.666	27.35	5.607
Middle	21.31	5.598	6.69	1.769	28.00	6.378
High	22.42	4.144	6.67	1.922	29.08	4.907
F	0.846		0.331		0.459	
p	0.431		0.719		0.633	
Educational status						
Illiterate	20.98	5.304	6.56	1.564	27.53	5.885
Primary-secondary school	21.40	5.289	6.90	1.571	28.30	5.881
High school	19.91	5.293	6.51	2.020	26.42	5.751
Associate's degree and above	23.38	6.265	7.46	2.366	30.84	7.679
F	1.433		1.326		1.915	
p	0.235		0.268		0.129	
Marital status						
Single	21.39	5.755	6.09	1.843	27.48	6.647
Married	21.05	5.331	6.92	1.684	27.97	5.912
t	0.327		2.49		0.414	
p	0.744		0.014*		0.680	
Chronic disease status						
Yes	21.09	5.305	6.79	1.631	27.89	5.856
No	21.13	5.472	6.74	1.816	27.87	6.189
t	0.051		0.173		0.004	
p	0.959		0.863		0.997	
Previous COVID-19 infection						
Yes	20.73	3.901	5.82	1.601	26.55	4.967
No	21.14	5.488	6.82	1.737	27.97	6.114
t	0.248		1.865		0.754	
p	0.805		0.064		0.452	
Losing a relative due to COVID-19						
Yes	21.41	5.544	6.87	1.756	28.28	6.143
No	20.95	5.323	6.70	1.740	27.65	6.005
t	0.527		0.615		0.648	
p	0.599		0.540		0.518	
Vaccination status						
Yes	19.29	4.338	6.10	1.835	25.39	4.846
No	21.899	5.606	7.04	1.628	28.94	6.210
t	3.332		3.252		4.007	
p	0.001*		0.001*		0.000**	
Vaccine type						
Not vaccinated	21.9	5.606	7.04	1.628	28.94	6.210
Sinovac	18.42	5.388	5.68	1.827	24.1	5.586
BioNTech	20.21	3.821	6.17	1.970	26.38	4.480
Sinovac+BioNTech	18.63	3.068	6.88	1.246	25.5	3.703
F	3.349		4.679		4.922	
p	0.021*		0.004*		0.003*	
Severity of back pain						
Very little	20.83	4.190	6.89	2.026	27.72	5.431
A little more	20.79	5.468	6.55	1.719	27.34	6.334
Moderate	20.97	5.262	6.85	1.904	27.82	5.734
Too much	21.26	5.226	6.74	1.245	28.00	5.269
Unbelievable pain	22.33	7.211	6.78	1.896	29.11	8.512
F	0.200		0.289		0.265	
p	0.938		0.885		0.900	

SD, standard deviation.

*Difference is significant at the 0.05 level (2-tailed); **difference is significant at the 0.01 level (2-tailed).

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studies have also pointed to the same results [19,23–25]. Vaccination at the required dose to avoid an unfavorable clinical course will protect the population at risk [38].

According to the findings obtained in this study, vaccine hesitancy differed depending on marital status, vaccination status, and the type of vaccine received. Previous studies have also found that vaccine hesitancy is affected by many factors; for instance, in a survey conducted with 13,426 people, 71.5% of participants were likely to have the COVID-19 vaccine, and 48.1% would comply with these recommendations if their employers advised them to receive the vaccination [39]. These findings show that especially in the process of conducting COVID-19 vaccination campaigns, it is necessary to take into account individuals' demographic characteristics and the statements of people who may influence them.

The findings obtained in the examinations align with observations that pain is felt differently on an individual basis depending on sociocultural characteristics, sex, environment, and psychosomatic factors [40,41]. Similarly, despite individual differences in perceptions, it was thought that vaccination hesitancy at the social level involved similar factors to those involved in feeling pain. A sense of responsibility towards society and a person's beliefs are the most critical predictors of getting vaccinated [34,42]; thus, examining the coexistence of these different perceptions constitutes a strength of the research. A study supporting this finding was conducted by the US Food and Drug Administration. That study observed an increased humoral response due to booster dose COVID-19 mRNA vaccines in immunocompromised rheumatic/musculoskeletal patients and vulnerable individuals. Based on that result, it was predicted that individuals would not hesitate to get vaccinated, and it was reported to be effective in protection [42].

Individuals have hesitated between the fear of contracting COVID-19 and anxiety about the vaccine's side effects. Successful results have been obtained in reducing hesitancy through efforts to address concerns about the vaccine in the simultaneous worldwide vaccine activities [43].

It is a fact that back pain caused by COVID-19 can be reduced by necessary, appropriately dosed, and reliable vaccines, as has been demonstrated by many studies. In particular, the importance of vaccination, which is a preventive measure instead of an expensive treatment, for reducing back pain caused by COVID-19 should be explained to society. While explaining to individuals that necessary precautions can be taken with simple vaccination, it is very important to understand the reasons for individuals' vaccine instability and vaccine refusal and to put scientific evidence-based management practices into effect.

Conclusion

It is predicted that COVID-19 will continue to affect people's lives worldwide with changing forms and variants. However, despite this trend, there are many casualties among people who have become complacent by ignoring the evolution of the virus. It is predicted that new COVID-19 waves may come, even if they are relatively small. In order to reduce the number of new cases, complications, and deaths, it is necessary to continue effective public health measures. An essential public health measure is ensuring society-wide immunity against pandemics. Protecting public health and overcoming the pandemic process with less damage is possible with national and international cooperation. In particular, the reasons for COVID-19 vaccine hesitancy should be identified, these reasons should be eliminated, and the vaccination rate should be increased. Otherwise, the illness burden of back pain caused by COVID-19 and the financial burden that this disease will bring to health finances will prevent the health system from fulfilling its goals, causing significant public health problems.

Supplementary Material

Table S1. STROBE Statement: checklist of items that should be included in reports of cross-sectional studies; **Supplementary Material 1.** Additional analysis. Supplementary data is available at https://doi.org/10.24171/j.phrp.2023.0003.

Notes

Ethics Approval

Ethical approval was received from the Diyarbakır Gazi Yaşargil Education and Research Hospital in Turkey (IRB-863-2021). The necessary permissions were obtained from the institution where the study was conducted.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

Data is available on request.

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Original Article

COVID-19 outbreak in a religious village community in Republic of Korea and risk factors for transmission

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ABSTRACT

Objectives: This study aimed to assess the scale and transmission patterns of coronavirus disease 2019 (COVID-19) in a religious village community in South Korea, to determine the risk factors of transmission, and to evaluate vaccine effectiveness.
Methods: An epidemiological survey was conducted, and data were collected and analyzed from 602 villagers in the religious village community. Multivariate logistic regression analysis was used to identify the risk factors for COVID-19 transmission and to evaluate vaccine effectiveness.
Results: The outbreak attack rate was 72.1% (434/602). The attack rate was high among women in their 60s, the unemployed, residents living near religious facility (< 500 m), and the unvaccinated. Age, the distance between religious facility and residences, and the absence of vaccination were identified as risk factors for transmission. Vaccine effectiveness was 49.0%, and the highest effectiveness was seen in the age group of 59 years or younger (65.8%).
Conclusion: This village community was isolated, with little communication with the outside world. However, the frequency of close contact between residents was relatively high, contributing to the spread of COVID-19 in the village even with relatively short exposure. Vaccination rates in the village community were also lower than those in the general public. Public health authorities should consider the potential impact of cultural factors, including religion, that could lead to the exponential spread of COVID-19 in closed village communities.

Keywords: COVID-19; Disease outbreaks; Religion; Vaccine effectiveness

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Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic in late December 2019, more than 24 million cumulative confirmed cases have been reported in South Korea between January 20, 2020, and September 25, 2022 [1]. South Korea has maintained the crisis alert

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level at "serious" and has made various efforts to prevent the spread of COVID-19 [2]. For instance, social distancing measures were implemented, such as working from home, school closures, and meeting restrictions, as well as other policies such as wearing masks, hand hygiene, and vaccination [3,4].

Since 2020, several variants of COVID-19 have been reported, raising concerns about the effectiveness of vaccination [5,6]. The Delta variant, first detected in India in 2020, accounted for 99% of cases in the United States by late 2021 and accelerated hospitalizations due to its high transmissibility [7]. In South Korea, the Delta variant was prevalent from July 2021 to the end of January 2022. Although there were some differences by age, the COVID-19 vaccination rate for the first dose by September 17, 2021 was approximately 70% [2]. The COVID-19 vaccine was found to be effective in reducing the risk of infection and mortality during the period when the Delta variant was prevalent [6,8].

COVID-19 is known to be transmitted through respiratory droplets, and outbreaks are particularly common in "3-C" environments (close contact, closed spaces, and crowded places) [9]. In particular, religious practices such as group prayers, religious education attendance, and sharing a meal may increasingly influence the spread of COVID-19 [9–11]. Approximately 48% of confirmed cases of COVID-19 in Malaysia were related to religious events [12]. In addition, the possibility of widespread transmission within religious groups has been demonstrated in the United States [11]. In 2020, South Korea experienced a rapid, large-scale outbreak of COVID-19 in the local community, triggered by the Shincheonji Church's religious activities and group outreach, mainly in Daegu [13]. Those who have experienced the COVID-19 outbreak are reported to experience mental health problems such as loneliness, anxiety, depression, as well as social problems such as stigma [14,15].

This study aimed to determine the extent and transmission pattern of the outbreak of COVID-19 in a religious village community in South Korea when the Delta variant was prevalent, to evaluate vaccine effectiveness, and to identify risk factors for transmission at the village level.

Materials and Methods

Outbreak Detection

On November 21, 2021, a religious member (a 77-year-old woman) living in a village of a religious community was confirmed positive for COVID-19. She was tested due to a chief complaint of muscle pain and chills that had lasted since November 19, 2021. After her contacts were traced and tested, 4 additional cases were confirmed, suggesting transmission.

HIGHLIGHTS

- COVID-19 outbreak in a religious village community attack rate was 72.1%. The distance between the religious facility and residences, vaccination status, age were identified as risk factors for the COVID-19 outbreak in village communities.
- The risk of COVID-19 transmission was relatively higher in residents who reside within 500 m from the religious facility, than residents who reside outside 1,000 m from the religious facility.
- This village community had a closed characteristic. The close contact between residents was frequent, contributing to the spread of COVID-19 in the village even with relatively short exposure.

Case Definition and Epidemiological Investigations

Regardless of clinical manifestations, positive cases were confirmed for COVID-19 using real-time polymerase chain reaction tests of specimens collected from the upper or lower respiratory tract. In accordance with the Infectious Disease Prevention and Control Act, basic epidemiological investigations were conducted on confirmed cases, including information on the individual, symptoms, and underlying diseases; the source of infection; religious group activities; and interpersonal contacts. Among the confirmed cases, the index case was determined to have the earliest confirmed date. Moreover, the suspected primary case was determined to have the earliest symptom onset by reviewing data, such as the date of symptom onset described in the basic epidemiological survey and details of medical institutions obtained through drug utilization review. The epidemiological investigation determined the management level by assessing the risk of exposure according to the COVID-19 response guidelines [16]. "Unvaccinated" referred to individuals that had not been vaccinated or were within 14 days of receiving the first dose. "Vaccinated" referred to individuals for whom 14 days had elapsed since the second dose.

COVID-19 Control Measures for the Religious Community

When the initial 5 cases were investigated, it was found that the village was populated by people from the same religious group, who formed a village revolving around religious facilities. The health authorities (the Korea Disease Control and Prevention Agency [KDCA] and the local health center) conducted a field epidemiological investigation and risk assessment of the village and discussed measures to manage

contacts with confirmed cases to prevent further transmission of the infection.

In the risk assessment, several religious activities were observed where droplets could spread in confined spaces. Additionally, there were frequent activities involving close physical contact between the religious leaders and members or between members themselves. As the exposure took place in November, the religious facilities were not adequately ventilated due to seasonally low temperatures, and no auxiliary ventilation systems were installed to compensate for this inadequate ventilation. Temperature controls and visitor lists, which were required by social distancing rules in religious facilities, were not properly implemented, and insufficient resources were provided, such as hand sanitizers for hand hygiene. Since an objective assessment of the circumstances of each religious activity was not possible due to the absence of surveillance cameras in the religious facilities, the overall situation was assessed through a field epidemiological investigation and in-depth interviews with confirmed cases and contacts in the village. Although the last in-person religious activity took place on November 14, 2021, a kimchi making event was conducted in the village for 2 days (November 15–16, 2021). Approximately 60 to 70 villagers who were also religious members participated in this event, and kimchi was delivered to many residents of the village community. After checking villagers' COVID-19 vaccination status, it was found that 76.1% were not vaccinated, and residents aged 60 years or older accounted for 38.2% of the study population. Therefore, a substantial risk of severe COVID-19 cases was expected. Based on the results of the risk assessment, 2 portable testing clinics were set up in the village where all residents of the village community could undergo rapid testing. Additional door-to-door testing was performed for those who had difficulty visiting the testing clinics. All residents of the village were exposed by close contact; they were instructed to maintain quarantine. They were also closely monitored and tested every 3 days; this interval was chosen considering village residents' cooperation, laboratory testing capacity, and local government resources. The local government implemented a strict quarantine with controlled access to the village. Further, the administration temporarily closed religious facilities and restricted gatherings. The local government organized and operated an extended care and monitoring team for treatment. In preparation for an emergency, hospital beds were secured and buses were prepared for rapid transfers.

Study Design and Data Collection and Analysis

This retrospective cohort study was conducted among residents of a religious village community during a COVID-19 outbreak.

Data were collected from 602 residents of the village community from epidemiological information registered in the COVID-19 information management system of the KDCA and from the COVID-19 vaccination system. Thirty-one of the confirmed cases resided in other regions and had visited local religious facilities in the past, and 18 cases of secondary infection with contacts from villagers in the religious community were excluded from this study.

The chi-square test was conducted after performing a descriptive statistical analysis of sex, age, occupation, place of residence (the distance from the location of religious facilities), and the COVID-19 vaccination status of infected and uninfected individuals. Multivariate logistic regression analysis was performed to identify risk factors for COVID-19. Vaccine effectiveness was assessed by analyzing the relevant effects in the unvaccinated and vaccinated subjects. All data were analyzed using IBM SPSS ver. 22.0 (IBM Corp.).

Ethics Statement

The study protocol was reviewed and approved by the KDCA Institutional Review Board (IRB No: 2022-11-08-PE-A). The requirement for informed consent was waived by the IRB.

Results

Epidemic Curve

The suspected primary case had experienced cough, phlegm, and headache since November 13, 2021, and the diagnosis date was November 23, 2021. The suspected primary case's residence was the same as that of the index case, who was diagnosed on November 21, 2021, after complaining of muscle pain and chills on November 19, 2021. Although the source of infection could not be identified in the suspected primary case, the outbreak in the village community was assumed to have begun on November 11, 2021. The COVID-19 outbreak, triggered by religious activities on November 14, 2021, and village events such as kimchi making on November 15 and 16, 2021, resulted in rapid transmission of the virus in the community. The outbreak lasted for 30 days, until December 21, 2021, when the last patient was diagnosed (Figure 1).

General Characteristics of the COVID-19 Outbreak in a Religious Community

Of the 602 residents in the village community, 434 were infected with COVID-19, with an attack rate of 72.1%. The attack rate was 64.6% in male (155/240) and 77.1% in female (279/362; $p < 0.001$). By age, 252 patients (67.7%) were aged

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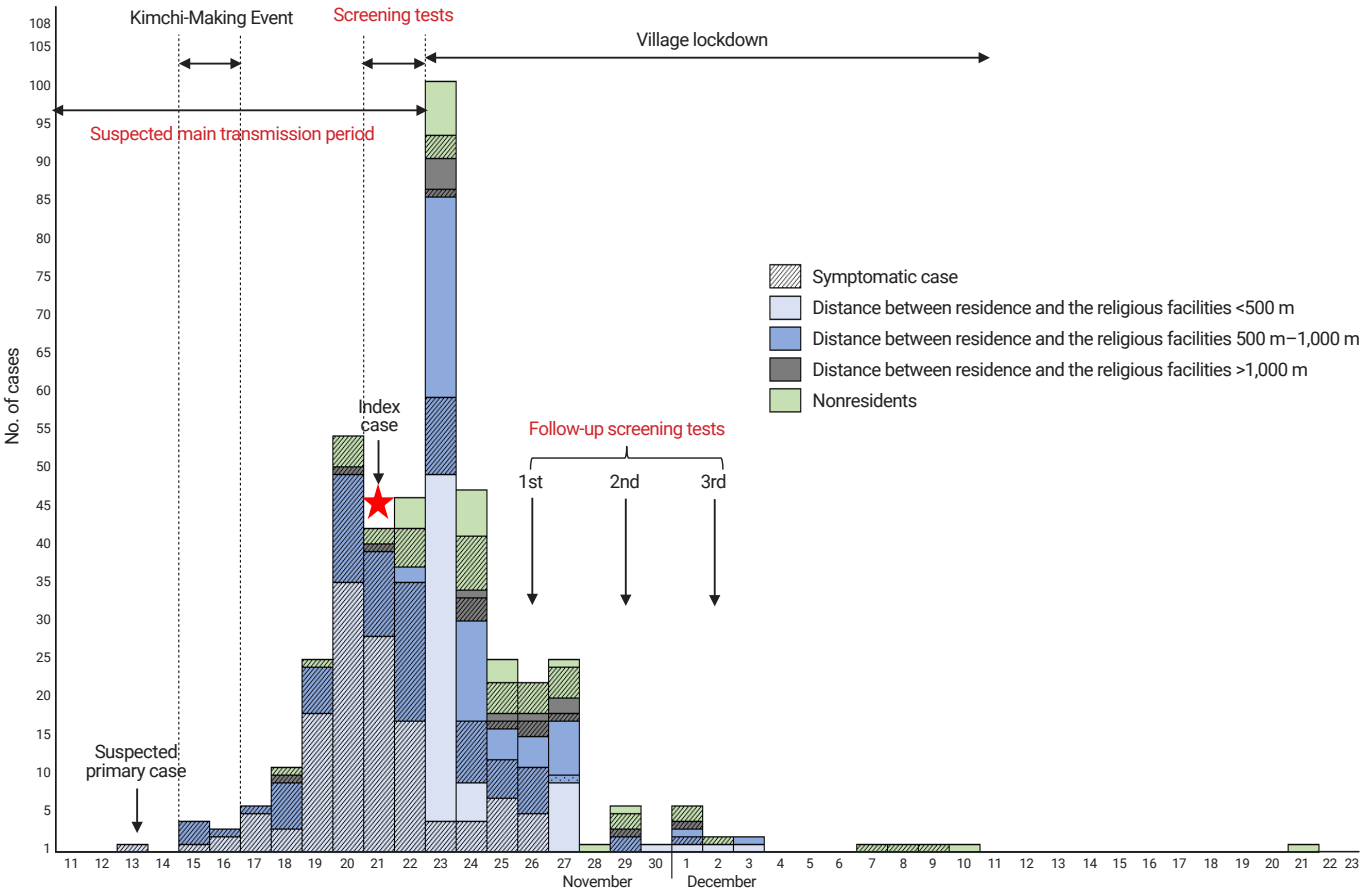

Figure 1. Epidemic curve of the COVID-19 outbreak in a religious village community and relevant risk factors for transmission.

59 years or younger, 108 (83.7%) were aged 60 to 69 years, and 74 (73.3%) were aged 70 years or older ($p = 0.002$). The COVID-19 patients included 266 unemployed people (100.0%), 138 employed people (84.7%), and 173 non-responders ($p < 0.001$). A total of 193 individuals infected with COVID-19 (87.7%) resided within 500 m of the religious facilities, 151 (72.6%) resided within 500 to 1,000 m, and 22 (57.9%) resided more than 1,000 m from the facilities ($p < 0.001$) (Figure 2). There were 374 confirmed cases (81.7%) that were unvaccinated for COVID-19, while 5 confirmed cases (55.6%) had completed the first dose of vaccination. Fifty-five confirmed cases (40.7%) had received the second vaccine dose ($p < 0.001$) (Table 1).

Risk Factors for COVID-19 Transmission in a Religious Community

The risk factors for COVID-19 transmission in the village community were identified as age, the distance between religious facility and residences, and vaccination status. Compared with the group aged 59 years or younger, the odds ratio for infection was 6.23 (95% confidence interval [CI], 2.66–14.59) in the group aged 60 to 69 years and 2.89 (95% CI, 1.36–6.16) in those aged 70 years or older. The relative risk of infection was 3.42 times (95% CI, 1.42–8.21) higher in those who lived within 500 m of the religious facilities than in those who lived at more than 1,000 m away. The relative risk of infection was 9.23 times (95% CI, 5.03–16.93) higher in the unvaccinated group than in those who had been vaccinated (Table 2).

Effectiveness of the COVID-19 Vaccine in the At-risk Population of a Religious Community

The overall vaccine effectiveness of COVID-19 vaccine was 49.0% after the completion of the second dose (43.9% in males and 51.8% in females). By age, the vaccine effectiveness was 65.8% among those 59 years or younger, 39.8% among those 60 to 69 years old, and 42.0% among those 70 years or older. Furthermore, it was 11.0% in those who lived within 500 m from the religious facilities, 61.2% in those who lived at a distance of 500 to 1,000 m, and 69.6% in those who lived more than 1,000 m from the religious facilities (Table 3).

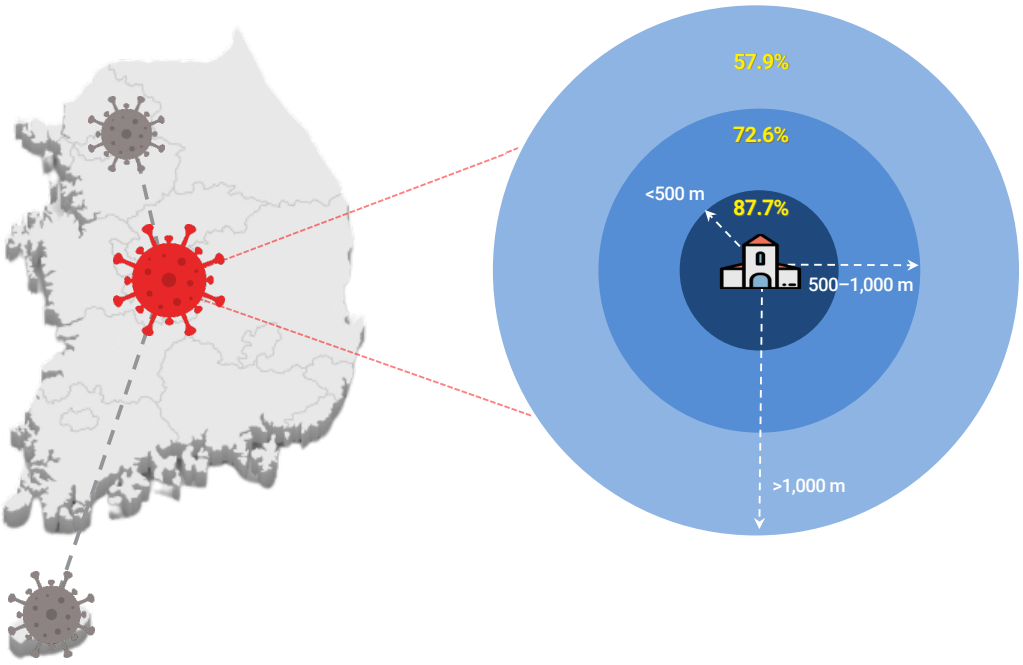

Figure 2. Transmission of COVID-19 in a religious community and attack rate based on the distance of residences from the religious facility.

Table 1. General characteristics of the COVID-19 outbreak in a religious village community in South Korea

Characteristic	Total	Infected	Uninfected	Attack rate (%)	*p*-value[a]
Total	602 (100.0)	434 (100.0)	168 (100.0)	72.1	
Sex					< 0.001
Male	240 (39.9)	155 (35.7)	85 (50.6)	64.6	
Female	362 (60.1)	279 (64.3)	83 (49.4)	77.1	
Age (y)					0.002
≤ 59	372 (61.8)	252 (58.1)	120 (71.4)	67.7	
60–69	129 (21.4)	108 (24.9)	21 (12.5)	83.7	
≥ 70	101 (16.8)	74 (17.1)	27 (16.1)	73.3	
Employed (n = 429)[b]					< 0.001
No	266 (62.0)	266 (65.8)	0 (0.0)	100.0	
Yes	163 (38.0)	138 (34.2)	25 (100.0)	84.7	
Distance (n = 466)[c]					< 0.001
< 500 m	220 (47.2)	193 (52.7)	27 (27.0)	87.7	
500–1,000 m	208 (44.6)	151 (41.3)	57 (57.0)	72.6	
> 1,000 m	38 (8.2)	22 (6.0)	16 (16.0)	57.9	
Vaccination status					< 0.001
Unvaccinated	458 (76.1)	374 (86.2)	84 (50.0)	81.7	
1 Dose	9 (1.5)	5 (1.2)	4 (2.4)	55.6	
2 Doses	135 (22.4)	55 (12.7)	80 (47.6)	40.7	

Data are presented as n (%).
[a]Determined using the chi-square test. [b]People whose occupation was not confirmed were excluded (n = 173). [c]Registered people in other regions were excluded based on their residence listed in the resident registration (n = 136). Distance: distance of the residence from the religious facility.

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Table 2. Multiple logistic regression results of risk factors in COVID-19 outbreak of a religious village community in South Korea

Characteristic	*n* (%)	aOR[b]	95% CI	*p*-value
Sex	434 (100.0)			
Male	155 (35.7)	Reference	0.78–2.18	0.308
Female	279 (64.3)	1.31		
Age (y)	434 (100.0)			
≤ 59	252 (58.1)	Reference		
60–69	108 (24.9)	6.23	2.66–14.59	< 0.001
≥ 70	74 (17.1)	2.89	1.36–6.16	0.006
Distance (*n* = 366)[a]	366 (100.0)			
< 500 m	193 (52.7)	3.42	1.42–8.21	0.006
500–1,000 m	151 (41.3)	1.47	0.64–3.38	0.364
> 1,000 m	22 (6.0)	Reference		
Vaccination status	434 (100.0)			
Unvaccinated	374 (86.2)	9.23	5.03–16.93	< 0.001
Vaccinated	60 (13.8)	Reference		

Data are presented as *n* (%).
aOR, adjusted odds ratio; CI, confidence interval.
[a]Registered people in other regions were excluded based on their residence listed in the resident registration (*n* = 68). Distance: distance of the residence from the religious facility. [b]Odds ratios were calculated by logistic regression after adjustment for sex, age, distance, and vaccination state.

Table 3. Effectiveness of the COVID-19 vaccine among the at-risk population of a religious village community in South Korea

Vaccination status	Total (*n* = 602)		Infected (*n* = 434)		VE (95% CI)
	Unvaccinated	Vaccinated[a]	Unvaccinated	Vaccinated	
Sex	458 (76.1)	144 (23.9)	374 (86.2)	60 (13.8)	49.0 (37.8–58.1)
Male	164 (68.3)	76 (31.7)	123 (79.4)	32 (20.6)	43.9 (25.9–57.5)
Female	294 (81.2)	68 (18.8)	251 (90.0)	28 (10.0)	51.8 (35.7–63.8)
Age (y)	458 (76.1)	144 (23.9)	374 (86.2)	60 (13.8)	49.0 (37.8–58.1)
≤ 59	307 (82.5)	65 (17.5)	235 (93.3)	17 (6.7)	65.8 (48.3–77.4)
60–69	86 (66.7)	43 (33.3)	83 (76.9)	25 (23.1)	39.8 (22.1–53.4)
≥ 70	65 (64.4)	36 (35.6)	56 (75.7)	18 (24.3)	42.0 (18.4–58.7)
Employed[b]	361 (84.1)	68 (15.9)	349 (86.4)	55 (13.6)	16.3 (5.9–25.6)
No	228 (85.7)	38 (14.3)	228 (85.7)	38 (14.3)	-
Yes	133 (81.6)	30 (18.4)	121 (87.7)	17 (12.3)	37.7 (14.4–54.7)
Distance[c]	373 (80.0)	93 (20.0)	321 (87.7)	45 (12.3)	43.8 (30.4–46.0)
< 500 m	186 (84.5)	34 (15.5)	166 (86.0)	27 (14.0)	11.0 (-63.0–25.5)
500–1,000 m	162 (77.9)	46 (22.1)	136 (90.1)	15 (9.9.)	61.2 (42.8–74.4)
> 1,000 m	25 (65.8)	13 (34.2)	19 (86.4)	3 (13.6)	69.6 (16.1–89.0)

Data are presented as *n* (%).
VE, vaccine effectiveness; CI, confidence interval; -, VE (95% CI) is not reported in the table because all of the unemployed people in the study were infected with COVID-19.
[a]Vaccinated: Those for whom 14 days had passed since receiving the second dose. [b]People whose employment was not confirmed were excluded (*n* = 173). [c]Registered people in other regions were excluded based on their residence listed in the resident registration (*n* = 136). Distance: distance of the residence from the religious facility.

Discussion

This is the first report of a COVID-19 outbreak in a closed religious village community in South Korea. The outbreak lasted for 30 days, from November 21, 2021, when the index case was confirmed, to December 21, 2021. Of the 602 residents in the village community, a total of 434 COVID-19 cases were confirmed. A genetic analysis revealed that this outbreak involved a Delta variant (B.1.167). A suspected cause of extensive transmission within the village was

interpersonal exchanges at religious and general village events.

There were 434 confirmed cases (attack rate, 72.1%); 77.1% of the village's female population and 64.6% of its male population were infected. The higher attack rate in female residents may have been due to their active participation in religious gatherings such as religious practices and social events such as kimchi making, as shown in previous studies [13]. The attack rate was 73.3% in those 70 years of age or older, 83.7% in those aged 60 to 69 years of age, and 67.7% in those were 59 years of age or younger. Although not shown in the table, the proportion of cases among unemployed individuals increased with age: 126 (49.0%) in those aged 59 years or younger, 75 (77.3%) in those aged 60 to 69 years, and 65 (86.7%) in those aged 70 years or older. Compared to employed individuals, it is reasonable to assume that unemployed residents engaged in village activities for considerably longer time periods and had more opportunities to participate in religious activities [17,18]. Among unemployed residents, the highest incidence was found in those aged 70 and older. However, healthy, unemployed individuals of 60 to 69 of age are presumed to have been most actively involved in religious and village activities, leading them to be exposed most frequently, because unhealthy and unemployed individuals have a limited ability to engage in outside activities [19,20]. Residents were divided into 3 groups according to the distance between their residence and the religious facilities, considering the household distribution and the walking distance. The attack rate was the highest (87.7%) among those who lived within 500 m from the religious facilities, while it was 72.6% in those who resided at a distance of 500 to 1,000 m, and 57.9% in those who lived more than 1,000 m from the facilities. Consistent with a previous study [21] reporting that those who lived closer to a religious facility attended religious services more frequently, the infection rate was higher among residents who lived closer to a religious facility due to frequent participation in religious activities. This was also reflected in the epidemic curve (Figure 2).

Age, the distance between the religious facility and residences, and vaccination status were identified as risk factors for COVID-19 transmission in the village community. In this village, social distancing and quarantine measures were not strictly observed due to the nature of religious activities and the prioritization of religious activities over personal activities, frequent social gatherings among the members, and close-contact religious activities. In addition, although the COVID-19 vaccination rate of the general population was close to 70% at the time of the mass outbreak, the vaccination rate in the village was only 24%, which is thought to be the result of misinformation and villagers' distrust of the vaccination, since they lived in a closed and isolated community.

The vaccine effectiveness after the completion of the second dose in this study was 49%, which was similar to the effectiveness in a high-risk group in the United Kingdom [22]. However, this finding is significantly lower than the reported vaccine effectiveness of 85% in the general population [23]. In addition, as the distance between religious facility and villagers' residences increased, vaccine effectiveness increased; this trend may have been influenced by not only the vaccination, but also the decreased likelihood of exposure to virus among those residing further from the facility.

COVID-19 vaccination is essential to control the pandemic by forming herd immunity [24]. According to studies on vaccine refusal behavior despite vaccine availability, major factors included fear of disease, concerns about vaccine safety, fear of side effects, distrust of vaccine effectiveness and the healthcare system, attitudes towards vaccination, and a history of influenza vaccination [24–27]. In addition, occupational status, income, health status, religion, and political orientation have been found to influence the decision to receive the vaccination [19,22]. Therefore, health authorities should provide accurate information on the safety and side effects of vaccines through various channels such as social media, and should actively manage fake news. It will also be necessary to foster positive attitudes toward vaccination and elicit vaccination intentions through planned communication to alleviate vaccine fears [9,17]. Because the attitudes of members of religious groups toward vaccines are shaped by their religious beliefs and responses to public health messages from religious leaders [20], religious leaders could positively or negatively influence the health behavior of their followers during an epidemic [9]. In contrast to general religious groups, where religious leaders generally play a positive role, in religious village communities that are closed and separated from the outside world may be more influenced by misbeliefs and misinformation, which could lead to vaccine refusal and uncooperative attitudes to epidemiological investigations [28]. Therefore, active countermeasures such as temporary lockdowns and periodic screening testing during the outbreak could be effective in preventing the transmission of COVID-19. Similar findings have been reported in Taiwan and China, where the spread of infection was prevented by lockdown and quarantine, rapid investigations, screening of villagers, and vaccination in villages with cluster outbreaks of COVID-19 caused by the Delta variant [29,30]. Although coercive and repressive containment measures could

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quickly stop the spread of infectious diseases, they could also cause humanitarian, psychological, and economic problems. Therefore, agreement and support for the need for containment measures among villagers, and public health authorities are needed [29].

This study has several limitations. Temporary buildings and religious facilities were renovated, and group shelters existed in the community under investigation. However, because of the rejection of the religious community an epidemiological investigation of on-site housing facilities was not allowed, and information collection was limited. In a situation where the number of confirmed cases was rapidly increasing, it was difficult to determine the date of individual exposures and sources of infection because most confirmed cases had participated in religious services and religious activities on multiple occasions.

Nonetheless, this study described the characteristics of an outbreak in a closed religious village community, identified risk factors for transmission, and found evidence of vaccine effectiveness. The findings suggest that religious beliefs and cultures may influence individual and group behaviors related to the spread of COVID-19. The results of this study may have significant implications for containing outbreaks through public health measures. These measures include temporary implementation of lockdown measures, early detection of asymptomatic cases through active screening testing, and the establishment of a treatment system for severe cases in a closed village community for religious reasons.

Notes

Ethics Approval

Obtaining informed consent was exempted by the IRB of Korea Disease Control and Prevention Agency (IRB No: 2021-11-08-PE-A) as there was no personal information 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: BIK; Data curation: JS; Formal analysis: JS; Methodology: EL, YC; Project administration: BIK; Resources: JS, GK; Visualization: JS, EK; Writing–original draft: JS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Information

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency or the institutions with which the authors are affiliated.

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Original Article

Quality of life in patients treated for COVID-19–associated mucormycosis at a tertiary care hospital

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19)–associated mucormycosis (CAM) has emerged as a formidable infection in patients with COVID-19. The aggressive management of CAM affects quality of life (QOL); thus, this study was designed to assess the QOL in patients with CAM at a tertiary healthcare institution.

Methods: This cross-sectional study of 57 patients with CAM was conducted over 6 months using a semi-structured standard questionnaire (the abbreviated World Health Organization Quality of Life questionnaire [WHO-BREF]) and a self-rated improvement (SRI) scale ranging from 0 to 9. Cut-off values of ≤52 and <7 were considered to indicate poor QOL and poor improvement, respectively. The correlations of QOL and SRI scores were evaluated using Spearman rho values.

Results: In total, 27 patients (47.4%; 95% confidence interval [CI], 34.9%–60.1%) and 26 patients (45.6%; 95% CI, 33.4%–58.4%) had poor QOL and poor SRI scores, respectively. The overall median (interquartile range) QOL score was 52 (41–63). Headache (adjusted B, −12.3), localized facial puffiness (adjusted B , −16.4), facial discoloration (adjusted B, −23.4), loosening of teeth (adjusted B, −18.7), and facial palsy (adjusted B, −38.5) wer e significantly associated with the QOL score in patients with CAM.

Conclusion: Approximately 1 in 2 patients with CAM had poor QOL and poor improvement. Various CAM symptoms were associated with QOL in these patients. Early recognition is the key to optimal treatment, improved outcomes, and improved QOL in patients with CAM.

Keywords: Comorbidity; Mucormycosis; Pandemics; Quality of life; Vaccination

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Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, many fungal infections such as aspergillosis, invasive candidiasis, and mucormycosis have been reported, especially among

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patients with severe COVID-19 and those recovering from the disease [1]. Mucormycosis, also known as black fungus, is a rare angioinvasive fungal infection caused by a group of fungi termed mucoromycetes [1,2]. The incidence of mucormycosis has increased so dramatically that it has become a notifiable disease, increasing the overall disease burden. COVID-19–associated mucormycosis (CAM) has been reported in many countries, including Austria, Brazil, Egypt, France, India, Iran, Italy, and the United States [3,4]. A systematic review indicated that CAM constitutes 0.3% of COVID-19 coinfections [5]. The prevalence of mucormycosis in India has been estimated at approximately 140 per 1,000,000 population, which is nearly 80 times greater than the rate in developed countries [2,6]. Humans acquire the infection mainly via inhalation, ingestion, and traumatic inoculation, and generally only susceptible populations are infected.

India is one of the countries that have been most heavily impacted by COVID-19, with multiple waves of COVID-19 resulting in more than 100,000 deaths following the second wave in March 2021 [7,8]. This has been accompanied by an unanticipated increase in CAM cases. As a result, the Indian government has classified CAM as a notifiable illness, and numerous state governments have classified it as an epidemic [9].

Mucormycosis is not a new disease, and it primarily affects immunocompromised patients. With the second wave of COVID-19, the incidence of mucormycosis has increased following the injudicious use of steroids and monoclonal antibodies [10,11]. Leukopenia has also been observed in patients with COVID-19; this ultimately lowers the immune response, affecting multiple systems and increasing the risk of opportunistic infections including pulmonary (rhino-orbital-cerebral mucormycosis), gastrointestinal, integumentary, and disseminated diseases [12,13]. Globally, diabetes continues to be the primary risk factor for mucormycosis, which has a death rate of 46% [14]. The COVID-19 pandemic has increased the incidence of diabetes following the excessive use of steroids, further contributing to immune system impairment. The burden of diabetes in the Indian population is high, and diabetes increases people's susceptibility to opportunistic infections, which disturb normal body parameters [15,16].

All of these factors increase the disease burden, leading to morbidity along with physical, social, and psychological consequences. Both the clinical manifestations of an invasive disease process and the treatments available for the management of mucormycosis (primarily surgical) can affect individuals' psychological state; additionally, disability following extensive surgical procedures can impact social relations. These changes may impact the overall quality of life (QOL) [17]. CAM is associated with high mortality and morbidity, and its diagnosis is frequently missed in India [18].

HIGHLIGHTS

- Mucormycosis and COVID-19–associated mucormycosis (CAM) are relatively rare worldwide. The COVID-19 pandemic has led to high morbidity and mortality due to the nature of the disease and has compromised the quality of life (QOL) of patients who have recovered from CAM.
- This study documents the QOL of patients with CAM at a 6-month follow-up after interventions.
- The use of the validated abbreviated World Health Organization Quality of Life questionnaire (WHOQOL BREF) is an important highlight of this study.
- Approximately 1 in 2 patients with CAM showed poor QOL. The importance of rehabilitation for such recovered patients is highlighted in this study.

The World Health Organization (WHO) defines health as not merely the absence of disease or infirmity, but rather a state of complete psychological, mental, and social well-being [19]. Patrick and Erickson [20] defined health-related QOL as the value assigned to the duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy. Most chronic illnesses can degrade overall health by impairing the ability to live comfortably, as well as limiting functional status, productivity, and QOL, and are significant drivers of medical expenses [21].

Several Indian studies [22–24] have assessed the clinical and epidemiological features of CAM, but none have examined the QOL of recovered patients. Thus, we planned to determine the overall QOL among patients with CAM at a 6-month follow-up and assess the improvement among these patients at a tertiary health care institution.

Materials and Methods

Study Design and Duration

This was a hospital-based cross-sectional study performed over 6 months (November 2021 to April 2022).

Study Setting

This study was conducted at the All India Institute of

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Medical Sciences (AIIMS) Patna, an institute of national importance under the Ministry of Health and Family Welfare Government of India. AIIMS Patna provides comprehensive health care to the people of Bihar. This institute was declared a dedicated COVID-19 hospital and a center of excellence for the treatment of CAM in Bihar [25]. A total of 200 confirmed cases of CAM were admitted through the Flu Clinic of the Department of Community and Family Medicine and were treated jointly by the departments of otorhinolaryngology, ophthalmology, neurology, and neurosurgery.

Study Participants

All patients with laboratory-/image-confirmed mucormycosis who were admitted, treated, and presented during the 6-month follow-up period at the otorhinolaryngology department were included in the study. Patients who did not consent to participate in the study and those who self-reported being under psychiatric care prior to infection were excluded from the study.

Sample Size and Sampling Technique

Previous studies reported diminished QOL in approximately 50% to 60% of patients who underwent oromaxillofacial interventions involving oral maxillofacial and eye surgery [26–29]. Thus, assuming that 55% of patients with CAM have compromised QOL, a minimum sample size of 71 would be required to reveal the outcome at a 95% confidence level, 20% relative precision, 20% refusal rate, and a population adjustment of 200, as determined using Statulator [30]. We included all patients with CAM who met the inclusion criteria and presented for follow-up at the otorhinolaryngology outpatient department (OPD) or the ophthalmology OPD of the institution during the study period. A designated clinic for follow-up with these patients was run by the otorhinolaryngology and ophthalmology OPD on 1 designated day per week (Wednesday). We used consecutive sampling to collect information from the patients.

Study Tools and Procedure

A predesigned, semi-structured, standard questionnaire was created to collect the details of the patients with CAM. The questionnaire consisted of multiple sections. Section A included sociodemographic details, such as the age, sex, occupation, education, and residential address of the patients. Section B included details of the clinical profile and course of hospital stay of the patients, such as COVID-19 vaccination status, comorbidity profile, persistent symptoms, disease severity based on symptoms (early, moderately advanced, or very advanced), mode of treatment (medical, surgical, or both), duration of hospital stay, and whether intensive care unit (ICU) admission was required. Section C included a self-rated improvement (SRI) score on a scale of 0 to 9, where 0 represents no improvement and 9 represents full improvement. Section D comprised questions about the QOL of the patients at 6-month follow-up using the WHOQOL BREF questionnaire [31]. The WHOQOL BREF tool contains 26 items on a 5-point Likert scale, and the score ranges from 0 to 100 after conversion. Higher scores represent better QOL. The scale measures physical, psychological, social, and environmental domains of QOL. The scale has been validated in an Indian setting with good internal consistency (0.86) [32].

The study tool was developed using Epicollect5 (Centre for Genomic Pathogen Surveillance) in the English language, and the CAM patients or the attendants accompanying them were interviewed face-to-face when they presented at the OPD for follow-up using the study tool in their local language (Hindi). After obtaining informed written consent, responses were collected and back-translated according to the WHO standards for translation. The WHOQOL-BREF questionnaire is available in Hindi and was used to collect information from the patients.

The data were collected by junior residents of the Department of Community and Family Medicine after training by the principal investigator regarding the administration of the study tool. Quality assurance of data was maintained with regular data entry checks and interim analysis by the principal investigator and co-investigators.

Biostatistical Analysis

The information collected was downloaded from Epicollect5 in Google Sheets and analyzed using jamovi (The jamovi project) [33]. Descriptive analyses were performed regarding the demographic and clinical profiles of CAM patients. Categorical variables such as sex, residence, education, occupation, vaccination status, and ICU requirement were expressed as proportions and percentages. Continuous variables such as age, QOL score, and improvement score were expressed as mean ± standard deviation or median (interquartile range [IQR]) depending on the normality of the data. Continuous variables such as the SRI score were divided into 2 categories (good and poor) based on median score. A score of ≤7 was considered to indicate poor improvement. QOL was also categorized as good or poor based on the median score. A score of ≤52 was considered to indicate poor QOL. The median differences in the QOL score and SRI score across sociodemographic variables were assessed using the Mann-Whitney U-test. The associations between CAM severity, QOL category, and the clinical profile of CAM patients were assessed with the chi-square test. The

mean differences between various domains of QOL and the clinical profile of CAM patients were assessed with the Student *t*-test. Multiple linear regression analysis was used to identify significant predictors of the QOL score of the patients with CAM, and an adjusted beta coefficient with a 95% confidence interval (CI) was determined. The QOL score, individual domains, and SRI score were correlated using Spearman correlation, and the correlation coefficient rho was calculated. Statistical significance was considered to be indicated by a p-value < 0.05.

Ethics Statement

This study was approved by the institutional ethical committee of AIIMS Patna (No: AIIMS/Pat/IRC/2021/805). Ethical principles were adhered to throughout the study. Informed written consent was obtained for participation in the study.

Results

Of 120 patients who were admitted for treatment for CAM during the study period, 57 patients (47.5%) underwent follow-up, 20 (16.7%) did not consent to participate, 25 (20.8%) did not return for follow-up, and 18 (15.0%) died.

Sociodemographic Characteristics of CAM Patients

The mean ± standard deviation age of the participants was 49.1 ± 12.4 years. Approximately half (32, 52.5%), of the patients were 45 to 65 years old. Of the 61 total patients, the majority (41, 67.2%) were male, while only 10 of the patients (16.4%) were illiterate. Almost 70% of the patients (n = 39) were employed, and 38 (63.3%) resided in rural areas (Table 1).

Clinical Details of CAM Patients

Among the 57 patients, 26 (45.6%) had at least one comorbidity. More than half of the total patients (36, 59.0%), had received both doses of the COVID-19 vaccine, while 13 (21.3%) had received no dose of any available COVID-19 vaccine.

Approximately two-thirds of the patients, 38 (66.7%), were in moderate to advanced stages of the disease process. Around 89.5% patients (n = 51) received both medical and surgical treatment, and 28 patients (54.9%) who received both modes of treatment had good QOL, compared to 4 patients (66.7%) who received only medical treatment.

The median (IQR) duration of hospital stay for the CAM patients was approximately 25 days (3.0–35.0). Approximately 4 in 10 patients (23, 41.8%) were admitted to the ICU (Table 2) [34,35].

Association of Mucormycosis Stage with Sociodemographic Variables

Approximately 75% of the patients (21 patients) between 45 and 65 years of age had moderate to advanced disease. Around 57.9% of the men (22 patients) and 84.2% of the

Table 1. Associations of the SRI score and QOL score with the sociodemographic characteristics of patients with CAM (n = 61)

Variable	Category	*n* (%)	SRI score (out of 9)	QOL score (out of 100)
Age (y)	18–45	20 (32.8)	6 (5.0–8.0)	49.0 (40.5–58.3)
	45–65	32 (52.5)	7 (6.0–8.0)	56.5 (45.0–64.3)
	≥65	9 (14.8)	7 (5.0–8.0)	51.0 (36.0–63.0)
Sex	Male	41 (67.2)	7 (5.0–8.0)	51.5 (41.8–62.8)
	Female	20 (32.8)	7 (6.0–8.0)	52.0 (38.0–63.5)
Education	Illiterate	10 (16.4)	6 (4.3–7.0)	40.5 (32.5–55.3)
	Primary school	12 (19.7)	6 (6.0–7.2)	46.5 (31.0–62.5)
	Middle school	12 (19.7)	6 (6.0–7.5)	52.0 (43.0–62.0)
	High school	12 (19.7)	7 (6.5–8.5)	54.0 (47.0–67.0)
	Intermediate	3 (4.9)	9 (6.5–9.0)	53.0 (51.0–56.0)
	Graduate	10 (16.4)	7 (6.2–7.7)	58.5 (52.0–70.5)
	Professional	2 (3.3)	4 (2.5–5.5)	56.0 (50.5–61.5)
Occupation	Unemployed	22 (36.1)	7 (6.0–8.2)	52.0 (45.8–64.3)
	Employed	39 (63.9)	7 (5.0–7.0)	52.0 (36.0–63.0)
Residence (n = 60)[a]	Urban	22 (36.7)	7 (7.0–9.0)	59.0 (50.0–67.0)
	Rural	38 (63.3)	6 (6.0–7.0)	51.0 (35.0–62.5)

Data are presented as median (interquartile range) unless otherwise indicated.
SRI, self-rated improvement; QOL, quality of life; CAM, COVID-19–associated mucormycosis.
[a]Statistically significant difference in SRI score and QOL score by residence.

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Table 2. Clinical details of patients with CAM across QOL categories ($n = 57$)

Variable	Category	n (%)	QOL score category		p-value[a]
			Poor (27, 47.4%)	Good (30, 52.6%)	
COVID-19 vaccination status ($n = 61$)	No vaccine	10 (17.5)	4 (40.0)	6 (60.0)	0.846
	First dose	11 (19.3)	5 (45.5)	6 (54.5)	
	Second dose	36 (59.0)	18 (50.0)	18 (50.0)	
Comorbidity[b]	No	31 (54.4)	21 (67.7)	10 (32.3)	< 0.001
	Yes	26 (45.6)	6 (23.1)	20 (76.9)	
Stage[c]	Early	19 (33.3)	8 (42.1)	11 (57.9)	0.454
	Moderate to very advanced	38 (66.7)	20 (52.6)	18 (47.4)	
Mode of treatment	Medical	6 (10.5)	4 (66.7)	2 (33.3)	0.317
	Medical and surgical	51 (89.5)	23 (45.1)	28 (54.9)	
ICU requirement ($n = 55$)	No	32 (58.2)	14 (43.8)	18 (56.3)	0.350
	Yes	23 (41.8)	13 (56.5)	10 (43.5)	
Duration of stay (d)	Median (IQR)	25 (3.0–35.0)	30 (22.3–35.8)	20 (2.3–30.0)	
Self-rated improvement score	Poor	40 (70.2)	20 (50.0)	20 (50.0)	0.841
	Good	17 (29.8)	9 (52.9)	8 (47.1)	

Data are presented as n (%) unless otherwise indicated. Based on [35].
CAM, COVID-19–associated mucormycosis; QOL, quality of life; ICU, intensive care unit; IQR, interquartile range.
[a]Chi-square test. [b]Statistically significant. [c]Based on All India Institute of Medical Sciences Delhi classification of treatment organization and guidance for COVID-associated mucormycosis.

women (16 patients) had moderate to advanced CAM, and this sex difference in CAM stage was statistically significant ($p = 0.047$). Additionally, 17 patients (54.8%) with good SRI and 21 patients (80.8%) with poor SRI had moderate to advanced disease. The difference in CAM stage according to improvement was also statistically significant ($p = 0.039$) (Table 3).

SRI Scores of CAM Patients

The SRI scores of the patients are provided in Tables 1 and 3. Of a maximum total score of 9, the median (IQR) SRI score was 7 (6.0–8.0). The male patients had a median (IQR) score of 7 (6.0–8.0). Patients who had received intermediate-level education had a median score of 9 (6.5–9.0), while those with professional-level education had a median score of 4 (2.5–5.5). Statistically significant differences in scores were present between patients residing in urban and rural areas (7 [7.0–9.0] vs. 6 [6.0–7.0], respectively; $p = 0.039$) (Table 1). Approximately 54.4% of the patients ($n = 31$) had good SRI. A statistically significant difference ($p = 0.039$) was noted in the improvement score between the 2 stages of the disease, as almost three-fourths of the patients (14, 73.7%) with relatively early-stage disease showed good improvement, while more than half of the patients (21, 55.3%) with moderate to very advanced disease showed poor improvement (Table 3).

QOL of the Patients with CAM

The median (IQR) overall QOL score, of a total maximum score of 100, was 52 (41–63). The median (IQR) score was 50 (43– 61) for the physical domain, 55 (35–65) for the psychological domain, 58 (42–67) for the social domain, and 50 (34–66) for the environmental domain (Figure 1).

A statistically significant difference in patient QOL score was noted by occupation ($p < 0.001$) and place of residence ($p = 0.015$) (Table 1). Overall, 27 (47.4%; 95% CI, 34.9%–60.1%) of the 57 patients reported poor QOL. The difference in QOL categories across vaccination status, stages, modes of treatment, and ICU requirement are presented in Table 2. A statistically significant difference in QOL was found based on the presence or absence of any comorbidity ($p < 0.001$). Despite having comorbidities, 20 affected patients (76.9%) had good QOL, while only 10 (32.3%; approximately one-third) patients with no comorbidity exhibited good improvement. Almost 56.3% of patients who did not require ICU admission and 43.5% of patients who required ICU admission had good QOL, but this difference was not significant (Table 2). Approximately half of patients (20, 50.0%) with poor SRI had relatively poor QOL. This difference was not significant (Table 2).

Clinical Profile of CAM Patients across QOL Domains and SRI Score

The domain-wise scores for QOL across various variables are given in Table 4.

Physical Domain

Relatively high physical domain scores were observed among CAM patients who had received the vaccine, who had comorbidities, who did not require ICU admission, who received surgical treatment, and who were in the early

Table 3. Associations of mucormycosis stage with sociodemographic variables ($n = 57$)

Variable	Category	Stage of disease		Chi-square value (p-value)
		Early	Moderate–very advanced	
Age (y)	18–45 ($n = 20$)	9 (45.0)	11 (55.0)	2.103 (0.305)
	45–65 ($n = 28$)	7 (25.0)	21 (75.0)	
	≥65 ($n = 9$)	3 (33.3)	6 (66.7)	
Sex	Male ($n = 38$)	16 (42.1)	22 (57.9)	3.951 (0.047)
	Female ($n = 19$)	3 (15.8)	16 (84.2)	
Education	No formal education ($n = 8$)	4 (50.0)	4 (50.0)	1.163 (0.281)
	Formal education ($n = 49$)	15 (30.6)	34 (69.4)	
Occupation	Unemployed ($n = 20$)	6 (30.0)	14 (70.0)	0.154 (0.695)
	Employed ($n = 37$)	13 (35.1)	24 (64.9)	
Residence	Urban ($n = 21$)	10 (47.6)	11 (52.4)	3.692 (0.055)
	Rural ($n = 36$)	9 (25.0)	27 (75.0)	
Vaccination status	Received ($n = 47$)	19 (40.4)	28 (59.6)	
	Not received ($n = 10$)	0 (0)	10 (100)	
Improvement score	Good ($n = 31$)	14 (45.2)	17 (54.8)	4.283 (0.039)
	Poor ($n = 26$)	5 (19.2)	21 (80.8)	
Quality of life	Good ($n = 29$)	11 (37.9)	18 (62.1)	0.562 (0.454)
	Poor ($n = 28$)	8 (28.6)	20 (71.4)	

Data are presented as *n* (%).

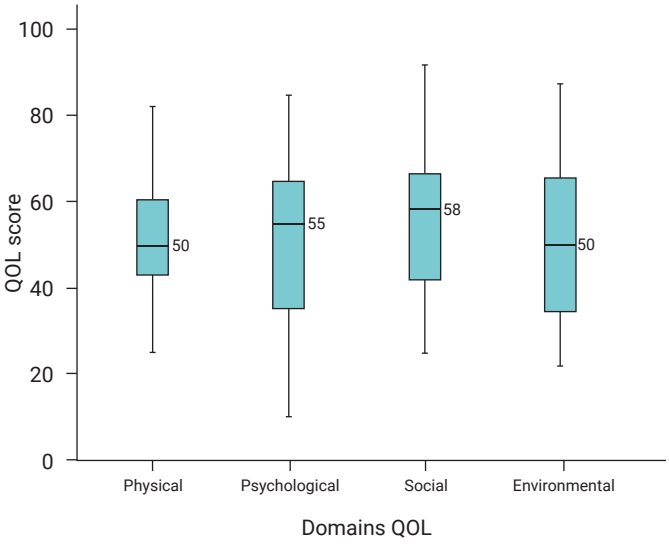

Figure 1. Box-and-whisker plot showing median (interquartile range) quality of life (QOL) domain scores among patients with COVID-19–associated mucormycosis.

stage of the disease, but these differences lacked statistical significance (Table 4).

Psychological Domain

CAM patients with comorbidities had better psychological domain scores than those without, and this difference was statistically significant ($p = 0.023$). Also, the psychological domain score was better among patients who had received COVID-19 vaccination, patients who did not require ICU admission, and patients with early-stage disease, although these differences were not statistically significant (Table 4).

Social Domain

CAM patients with comorbidities and those who had not received COVID-19 vaccination had relatively high social domain scores, and this difference was statistically significant ($p < 0.001$). Social domain scores were also relatively high in patients who did not require ICU admission and patients in the early stage of the disease process, but these differences were not statistically significant (Table 4).

Environmental Domain

CAM patients with comorbidities exhibited better environmental domain scores than those without, and this difference was statistically significant ($p < 0.001$). Environmental domain scores were relatively high in patients who had received the COVID-19 vaccination, who did not require ICU admission, and who were in the early stage of the disease process, but these differences were not statistically significant (Table 4).

Improvement Score

Relatively high SRI scores were observed among the patients with CAM who had received the vaccine and those who did not require ICU admission, and this difference was statistically significant ($p = 0.041$ and $p = 0.016$, respectively). SRI scores were also relatively high in patients with comorbidities and patients in the early stage of the disease, but these differences were not statistically significant (Table 4).

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Table 4. Clinical profile of patients with CAM across each domain of QOL and SRI score

Variable	Category	Physical	Psychological	Social	Environmental	Improvement score
Vaccination[a,b]	Taken	52.3 (12.4)	54.1 (17.9)	52.1 (18.3)	48.1 (16.8)	6.7 (1.9)
	Not taken	44.9 (11.3)	44.8 (23.9)	67.5 (20.1)	58.2 (22.0)	5.0 (2.9)
Comorbidities[a,c,d]	Present	54.2 (12.5)	59.2 (17.4)	65.4 (14.7)	59.2 (15.5)	6.4 (2.4)
	Absent	48.3 (11.9)	47.9 (18.9)	46.0 (18.5)	42 (16.3)	6.3 (2.1)
ICU requirement[a,b]	Needed	49.3 (12.3)	49.8 (20.5)	48.9 (23.4)	47.5 (21.1)	5.7 (2.1)
	Did not need	52.1 (12.6)	54.2 (17.8)	58.1 (15.4)	50.7 (16.0)	6.8 (2.3)
Staging of disease	Early	55.26±11.66	55.53±18.85	57.84±14.06	53.7±18.58	6.8 (2.6)
	Moderate to very advanced	48.87±12.39	51.82±19.16	53.32±21.56	47.9±17.68	6.1 (2.1)

All the data in the table represent mean±standard deviation unless and otherwise specified.
CAM, COVID-19–associated mucormycosis; QOL, quality of life; SRI, self-rated improvement; ICU, intensive care unit.
Statistically significant difference in [a]the social domain score, [b]the SRI score, [c]the psychological domain score, and [d]the environmental domain score.

Associations of the QOL Score with Symptomology

Bivariate linear regression showed that facial pain (B, −8.19; 95% CI, −15.9 to −0.4), localized facial puffiness (B, 13.3; 95% CI, 2.74 to 23.9), and eye redness (B, −10.5; 95% CI, −17.8 to −3.5) were significantly associated with the QOL score (Table 5). On multiple linear regression adjustment, regarding other symptoms, we found that headache (adjusted B, −12.3; 95% CI, −19.1 to −5.4), localized facial puffiness (adjusted B, −16.4; 95% CI, −26.6 to −6.3), facial discoloration (adjusted B, −23.4; 95% CI, −37.4 to −9.4), loosening of teeth (adjusted B, −18.7; 95% CI, −31.5 to −5.9), and facial palsy (adjusted B, −38.5; 95% CI, −65.8 to −11.2) wer e independently associated with the QOL score in patients with CAM (Table 5).

Correlations between the SRI Score and QOL Score Domains

We observed significant positive correlations between the physical ($r = 0.262$, $p = 0.04$) and psychological domains ($r = 0.447$, $p < 0.001$) of QOL and the SRI score. Regarding other domains of QOL, the social domain was negatively correlated and the environmental domain was positively correlated with the improvement score, but both correlations were statistically insignificant.

Discussion

With the onset of the COVID-19 pandemic, clinicians have seen an alarming increase in the number of CAM cases, reaching a level many times greater than the pre-COVID reported incidence of the disease [1]. The dual burden has impacted the health-related QOL. Although the prevalence of fungal coinfections in patients with COVID-19 has been reported in many studies [24,34,36,37], our knowledge of the impact of mucormycosis on the QOL of these patients is very limited.

In this cross-sectional study, we surveyed 57 patients with CAM who underwent operation and engaged in follow-up during the study period. Approximately 15% of patients died before the 6-month follow-up. Another study in India reported around 50% 90-day mortality [38].

In this study, overall, nearly half of the patients (48%) with CAM had poor QOL. Some studies have shown that the impact of COVID-19 is itself a reason for poor QOL [39–41]. A separate study of patients with head and neck cancer who underwent treatment similar to CAM treatment also indicated poor QOL at the beginning of the therapy that persisted until the end of therapy, revealing the course of such debilitating diseases [42]. A study from Brazil showed poor QOL in patients with facial deformities relative to others [28].

In a study conducted by Pisulkar et al. [43], the mean global QOL after maxillectomy and rehabilitation was reported to be 54±22.9. In the present study, the median QOL was approximately 52, with a minimum of 41 and a maximum of 63.

An editorial by Ghosh et al. [36] comparing CAM presentation between India and other countries found that rhino-orbito-cerebral CAM presentation is most common in India, while pulmonary and disseminated CAM predominate in other countries. In the present study, we found that headache, loosening of teeth, localized facial puffiness, facial discoloration, and facial palsy independently predicted the QOL score of patients with CAM. Nonspecific clinical signs and symptoms, such as unilateral headaches and facial pain, fever, numbness, and nasal discharge, characterize the early phases of rhino-orbito-cerebral CAM [44]. In advanced cases, facial paralysis occurs [45]. Tooth loosening in the upper jaw and toothache are prompt signs for the early diagnosis of rhino-orbito-cerebral CAM [34].

The present study showed that 54.9% of patients with CAM who received both medical and surgical interventions had good QOL at follow-up. Combined medical and surgical

Table 5. Multiple linear regression showing associations of the QOL score among patients with CAM ($n = 57$)

Variable (present)	Unadjusted B	95% CI	Adjusted B	95% CI
Headache[a)]	−6.9	−14.5 to 0.6	−12.3	−19.1 to −5.4
Facial pain	−8.2	−15.9 to −0.4	-	-
Localized facial puffiness[a)]	−13.3	−23.9 to −2.7	−16.4	−26.6 to −6.3
Discoloration and ulceration of face[a)]	−0.3	−11.5 to 10.8	−23.4	−37.4 to −9.4
Eye swelling	0.5	−7.6 to 8.6	-	-
Eye redness	−10.5	−17.8 to −3.5	-	-
Loosening of teeth[a)]	6.7	−2.8 to 16.4	−18.7	−31.5 to −5.9
Loss of vision	5.1	−6.1 to 16.1	-	-
Facial palsy[a)]	−16.5	−45.7 to 12.8	−38.5	−65.8 to −11.2
Drooping of eyelids	10	−19.4 to 39.4	-	-
$R^2 = 0.383$, $F(9, 47) = 6.33$, $p < 0.001$				

QOL, quality of life; CAM, COVID-19–associated mucormycosis; CI, confidence interval; -, There is decrease in the QOL scores in presence of respective symptoms.
[a)]Considered for adjustment in multivariable linear regression model.

treatment yields favorable outcomes [38]. A comparative study of India and other countries showed a similar result [46]. A study from Brazil, however, concluded no significant change in domain scores across treatment procedures [47].

In the present study, almost half of the CAM patients had at least one comorbidity; among them, nearly one-fourth had poor QOL. A study from Ranchi (Jharkhand, India) also showed poor QOL among those with comorbidities [48].

A study from North India [49] showed that morbidity and mortality rates were high among patients with post-tubercular mucormycosis, supporting our finding that the physical and environmental domains of QOL are affected more than other domains. These findings also align with a Turkish study on the QOL of patients with facial prostheses, a condition that is similarly debilitating to post-surgical mucormycosis. This explains the debilitating sequelae of mucormycosis that mainly affect these domains.

In our study, those who had been vaccinated for COVID-19 had better QOL than those who had not, indicating the effectiveness of the vaccine in decreasing COVID-19 severity [50–52] and the subsequent risk of CAM. Early recognition is the key to optimal treatment, improved outcomes, and improved QOL in patients with CAM [53].

Conclusion and Recommendations

Approximately 1 in 2 patients with CAM had poor QOL and poor SRI scores. The physical and environmental domains of QOL were most strongly affected.

Patients with comorbidities had relatively poor psychological, social, and environmental QOL domain scores, while patients who were not admitted to the ICU had relatively high improvement scores. Headache, localized puffiness of the face, loosening of the teeth, facial discoloration, and facial palsy were significantly associated with QOL score. We also observed weak positive correlations of the physical and psychological domains of QOL with the SRI score.

The highly invasive pathogenesis of mucormycosis often requires extensive surgical resection. Since the pandemic is not over and mucormycosis is not a preventable disease, it is imperative to rehabilitate these patients and reverse these effects. Both occupational and vocational rehabilitation (tertiary prevention) must be provided to ensure that patients who survive mucormycosis infection can continue to be functioning members of society.

Strengths and Limitations

Cases of mucormycosis, especially COVID-19–associated mucormycosis, are very rare, and the presence of a CAM epidemic during another pandemic (of COVID-19) is highly unusual. This study is one of the few studies in India and elsewhere to examine the QOL in mucormycosis-affected patients. The use of the validated WHO-BREF scale for assessing QOL is another strength of the study. We assessed the contribution of each symptom to overall QOL in patients with CAM.

This study is not without limitations. First, a mixed-methods approach would have provided better insight into QOL but was not feasible, as many patients were in a debilitating condition. Second, the sample size used was relatively small, but since this is a rare condition and the study was performed under epidemic conditions, we consider the sample size to be reasonable in context. Third, we could not capture the baseline QOL and thus could not compare it with the follow-up value.

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Notes

Ethics Approval
This study was approved by the Institute Ethics Committee of AIIMS, Patna (No: AIIMS/Pat/IEC/2021/805). We adhered to the principles of ethics throughout the study and thereafter and performed the study in accordance with the principles of the Declaration of Helsinki. Only those who provided written informed consent were included.

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

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None.

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

Authors' Contributions
Conceptualization: PK, SA, KB; Data curation: RRUR, NR, DA; Data analysis: RRUR, NR, DA; Methodology: PK, SA, RRUR; Supervision: PK, SA, KB; Writing-original draft: RRUR, NR; Writing-review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Analysis of pregnant women with critically severe COVID-19 in Republic of Korea from February 2020 and December 2021

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ABSTRACT

Objectives: This study aimed to describe the characteristics and risk factors for severe disease in pregnant women infected with coronavirus disease 2019 (COVID-19) from the early days of the COVID-19 epidemic in Korea to the predominant period of the Delta variant.
Methods: A retrospective cohort study was conducted among pregnant women diagnosed with COVID-19 between February 2020 and December 2021. Logistic regression analysis was performed to compare severe and mild cases after adjusting for pregnant women's age, nationality, infection route, outbreak area, infection period, symptoms, underlying disease, smoking status, trimester, and COVID-19 vaccination status.
Results: In total, 2,233 pregnant women were diagnosed with COVID-19 by December 2021. Among these, 96.7% had mild symptoms, 3.3% had severe symptoms, and 0.04% died. The risk factors for severe disease in pregnant women with confirmed COVID-19 were being in the age group of 35 to 45 years, having hyperlipidemia, being in the second or third trimester of pregnancy at the time of COVID-19 diagnosis, being infected during the Delta-predominant period, and having a fever (≥38 °C) at diagnosis. Furthermore, 47.1% of patients in the mild group and 84.9% of patients in the severe group had 3 or more risk factors.
Conclusion: Pregnant women with COVID-19 mainly experienced mild symptoms, but those with risk factors were at a higher risk of developing severe symptoms. Therefore, treatment and follow-up management should be thoroughly implemented.

Keywords: COVID-19; Pregnancy; SARS-CoV-2; Severity

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Introduction

The first case of coronavirus disease 2019 (COVID-19) was confirmed in Hubei Province, China,

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in December 2019. By December 31, 2021, more than 286 million people worldwide had been infected with COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and more than 5.4 million deaths due to COVID-19 had been recorded [1]. In the early stages of the COVID-19 pandemic, few studies were conducted to elucidate the incidence and fatality rates of COVID-19 in pregnant women, but those studies indicated that pregnant women are vulnerable to COVID-19 infection [2]. According to the United States Centers for Disease Control and Prevention, 31.5% of pregnant women and 5.8% of non-pregnant women with COVID-19 were hospitalized in June 2020. The hospitalization rate for pregnant women was 5.4 times higher than that of non-pregnant women, the rate of intensive care unit (ICU) treatment 1.6 times higher, and the rate of ventilation treatment was 1.9 times higher [3]. The immune system is affected by the physiological changes associated with pregnancy. In particular, the number of immune cells decreases in the second and third trimesters [4,5]. These immunological changes result in a higher susceptibility to infectious diseases during pregnancy due to an increased heart rate and cardiac output, increased oxygen consumption, and decreased lung volume subsequent to anatomical changes [4]. Due to these characteristic changes in pregnancy and the possibility that an infection might cause a cytokine storm, pregnant women may have a higher risk of death and complications than the general population during outbreaks of certain infectious diseases, such as influenza [6–8]. However, in a study that compared non-pregnant and pregnant women of the same age at the beginning of the COVID-19 pandemic, no differences were found in the clinical symptoms and incidence of pneumonia caused by COVID-19 [9]. Furthermore, compared to pregnant women infected with SARS-CoV-2 in the early stage of the pandemic, higher risks for ICU treatment, premature birth, and neonatal hospitalization were identified in pregnant women infected with the Alpha and Delta variants [10]. However, a study comparing pregnant women with confirmed COVID-19 to non-pregnant women in Korea from January 2020 to February 2021 found that the incidence of COVID-19 in pregnant women (0.02%) was lower than the incidence in non-pregnant women of the same age group (0.14%) and non-pregnant women of all age groups (0.15%) [11]. Furthermore, until April 2021, all pregnant women with COVID-19 in Korea were treated in general wards, while 0.87% of non-pregnant women of the same age were treated in the ICU [12]. Previous studies related to COVID-19 in pregnant women in Korea were limited to data retrieved before the period when the Delta variant predominated. Consequently, data on critically severe symptoms in pregnant women with COVID-19 are lacking. Therefore, we described the characteristics of pregnant women diagnosed with COVID-19 in Korea from the early days of the COVID-19 epidemic to the Delta-predominant period and explored the risk factors for severe COVID-19 in pregnant women. This study aimed to present a basis for establishing careful management guidelines for pregnant women, who are considered vulnerable.

HIGHLIGHTS

- This study examined the characteristics and risk factors of pregnant women with COVID-19 in Korea.
- Out of 2,233 pregnant women with COVID-19 had 96.7% mild symptoms, 3.3% severe, and 0.04% death.
- Results suggest the importance of closely monitoring and treating pregnant women with COVID-19.

Materials and Methods

Study Design and Data Sources

This was a retrospective cohort study of pregnant women with confirmed COVID-19 in Korea. Data on pregnant women diagnosed with COVID-19 between February 2020 and December 2021 were obtained from the COVID-19 Basic Epidemiological Survey System of the Korea Disease Control and Prevention Agency (KDCA). Information on underlying diseases was obtained from the National Health Insurance Service database of the National Health Insurance Corporation from January 2016 to November 2021. Data on COVID-19 vaccination status were obtained from the KDCA COVID-19 vaccination system. The study cohort consisted of pregnant women with confirmed COVID-19 in Korea. The cohort was further divided into severe and mild groups. Pregnant women (i.e., Korean and foreign women who were 20 to 45 years of age) with COVID-19 were defined as those whose COVID-19 report details were confirmed using their resident registration number and name, and who checked the pregnancy status item in the COVID-19 Basic Epidemiological Survey. All COVID-19 cases confirmed during the study period were diagnosed using real-time reverse-transcription polymerase chain reaction. Mild and severe cases were classified according to the 11th edition (February 10, 2022) of the COVID-19 response guidelines. The mild group included patients who experienced no interference with daily life activities during the isolation period (no limitation of activity), had difficulties in daily life but did not require oxygen treatment (limitation of activity but no O_2),

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received oxygen therapy with a nasal prong (O_2 with a nasal prong), or received oxygen therapy with an oxygen mask (O_2 with a facial mask). The severe group included patients who required non-invasive ventilation/high-flow oxygen therapy, invasive ventilation, extracorporeal membrane oxygenation, or continuous renal replacement therapy. COVID-19 patients who died during pregnancy were defined as those who died within 28 days of infection with SARS-CoV-2 [13].

Study Population

A total of 2,235 pregnant women (i.e., Korean and foreign women who were 20 to 45 years of age) with confirmed COVID-19 based on their resident registration number or alien registration number and name who checked the pregnancy status item in the COVID-19 Basic Epidemiological Survey were selected as the study population. Among them, 2,160 patients had mild symptoms and 73 had critically severe symptoms.

Data Collection

Information on age, nationality, route of infection, period of SARS-CoV-2 infection, reported region, underlying disease, smoking status, trimester during SARS-CoV-2 infection, status of COVID-19 vaccination at the time of SARS-CoV-2 infection, symptoms at the time of diagnosis, and death were collected. Age was categorized into 2 groups: 20 to 34 years and 35 to 45 years. Nationality was classified as Korean and foreign, and infection routes were categorized as domestic outbreaks and foreign inflows. The standard infection period was based on week 31 of 2021, after the Delta variant had begun to spread in Korea and the detection rate of the Delta variant exceeded 50% based on a genetic analysis of confirmed COVID-19 patients in Korea [14]. The period up to week 30 of 2021 was defined as the period preceding the predominance of the Delta variant, and the period from week 31 to week 53 of 2021 was defined as the Delta-predominant period. The regions included Seoul, Busan, Incheon, Gyeonggi Province, and 13 other regions (Daegu, Gwangju, Daejeon, Ulsan, Sejong, Gangwon, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, and Jeju Provinces). The underlying diseases included diabetes, hypertension, hyperlipidemia, cardiovascular disease, cerebrovascular disease, cancer, chronic lung disease, pneumonia, renal disease, liver disease, tuberculosis, and asthma. Smoking status was categorized as smoking or nonsmoking. The pregnancy stage was classified as the first trimester if the gestational age was less than 14 weeks at the time of COVID-19 confirmation, the second trimester if the gestational age was 14 to 27 weeks, and the third trimester if the gestational age was 28 weeks or more. Symptoms included fever (≥38 °C), cough, sputum, sore throat, runny nose, myalgia, dyspnea, headache, nausea or vomiting, and diarrhea.

Statistical Analysis

The frequencies (%) of all categorical variables were calculated to describe the general characteristics of the patients.

Logistic regression analysis was performed to compare severe and mild cases. The pregnant women's age, nationality, infection route, outbreak area, infection period, symptoms, underlying disease, smoking status, gestation period at the time of diagnosis, and COVID-19 vaccination status at the time of diagnosis were all adjusted. The adjusted odds ratio (aOR) for each variable is presented with a 95% confidence interval (CI). The analysis was performed after excluding missing values. A p-value < 0.05 was considered to indicate statistical significance. All analyses were performed using the R software ver. 4.2.1 (The R Foundation).

Ethics Statement

Data collection was performed in accordance with Article 76-2 of the Infectious Disease Control and Prevention Act and was approved by the Institutional Review Board (IRB) of the KDCA (IRB No: 2022-11-10-PE-A).

Results

General Characteristics

This study analyzed 2,233 pregnant women aged 20 to 45 years who were diagnosed with COVID-19 between February 2020 (when the first confirmed case of COVID-19 in a pregnant woman was recorded) and December 2021. Among these patients, 2,160 (96.7%) had mild symptoms, 73 (3.3%) had severe symptoms, and 1 (0.04%) died. In total, 1,224 patients (54.8%) were aged 20 to 34 years, and 1,009 (45.2%) were aged 35 to 45 years. Furthermore, 1,933 patients (86.6%) were of Korean nationality, while 300 (13.4%) were foreign nationals. A total of 2,189 patients (98.0%) had domestic-acquired infections, and 44 (2.0%) were infected in another country. Additionally, 530 cases (23.7%) were confirmed before the Delta-predominant period, and 1,703 cases (76.3%) were confirmed during the Delta-predominant period. Seoul had the highest number of cases (n=771, 34.5%) among the 17 cities and provinces, followed by Gyeonggi Province (n=751, 33.6%), Incheon (n=135, 6.0%), and Busan (n=79, 3.5%). The remaining 13 regions had 497 cases (22.3%).

A total of 308 patients (13.8%) had at least 1 underlying disease. Among the underlying diseases of pregnant women

with confirmed COVID-19, chronic obstructive pulmonary disease was the most common (*n*=185, 8.3%), followed by asthma (*n*=83, 3.7%), hyperlipidemia (*n*=51, 2.3%), and liver disease (*n*=44, 2.0%). Furthermore, 49 patients (2.2%) were smokers and 2,149 (96.2%) were nonsmokers. At the time of diagnosis, 497 patients (22.3%) were in their first trimester (<14 weeks), 909 (40.7%) were in their second trimester (14 to 27 weeks), and 767 (34.3%) were in their third trimester (>28 weeks). At the time of diagnosis, 1,921 patients (86.0%) had not been vaccinated. Moreover, 101 patients (4.5%) had received a single vaccine dose and 158 (7.1%) had received 2 vaccine doses. Among pregnant women with confirmed COVID-19, 1 death (0.04%) occurred during the Delta-predominant period. The deceased pregnant woman was started on high-flow oxygen therapy on the eighth day after being diagnosed with COVID-19, but she died 13 days later of pneumonia and respiratory failure (Table 1).

Distribution of Symptoms

Among the pregnant women with COVID-19, 321 (14.4%) were asymptomatic. At the time of diagnosis, cough (*n*=1,064, 47.6%) was the most common symptom, followed by fever (≥38 °C; *n*=969, 43.4%). Respiratory symptoms included sputum (*n*=462, 20.7%), runny nose (*n*=444, 19.9%), and dyspnea (*n*=75, 3.4%). Other than respiratory symptoms, sore throat (*n*=865, 38.7%) was the most common symptom, followed by headache (*n*=558, 25.0%), myalgia (*n*=507, 22.7%), nausea or vomiting (*n*=19, 0.9%), and diarrhea (*n*=16, 0.7%). More than half of the patients with critically severe disease had fever (≥38 °C; *n*=47, 64.4%) and cough (*n*=46, 63.0%). No gastrointestinal symptoms such as nausea, vomiting, or diarrhea were reported (Figure 1).

Risk Factors

Based on a multivariate analysis, 5 risk factors were identified for severe symptoms in pregnant women with confirmed COVID-19: being 35 to 45 years of age (aOR, 2.0; 95% CI, 1.19–3.42), hyperlipidemia (aOR, 4.82; 95% CI, 1.04–17.66), being in the second or third trimester at the time of diagnosis (aOR, 11.28; 95% CI, 2.32–203.28 and aOR, 25.09; 95% CI, 5.30–449.29, respectively), being infected during the Delta-predominant period (aOR 3.37; 95% CI, 1.42–9.99), and having fever at diagnosis (≥38 °C; aOR, 2.78; 95% CI, 1.61–4.89). In contrast, myalgia (aOR, 0.34; 95% CI, 0.15–0.69) was identified as a protective factor against severe COVID-19. These significant results were obtained after adjusting for pregnant women's age, nationality, route of infection, region of infection, period of infection, symptoms, underlying disease, smoking status, trimester at the time of diagnosis, and COVID-19 vaccination status at the time of diagnosis (Table 2).

Discussion

This study sought to describe the characteristics of all pregnant women with confirmed SARS-CoV-2 infection from the beginning of the COVID-19 epidemic in Korea through the entire period of the Delta variant predominance. After exploring the risk factors for COVID-19 in pregnant women and dividing them into severe and mild cases, the distribution of risk factors was quantitatively evaluated. The identified risk factors for severe COVID-19 in pregnant women in Korea were older maternal age (35 to 45 years), underlying hyperlipidemia, diagnosis of SARS-CoV-2 infection in the second or third trimester, diagnosis of COVID-19 during the period of Delta variant predominance, and fever symptoms at diagnosis. Patients with critically severe symptoms were likely to have at least 2 of the 5 risk factors. Specifically, the proportion of patients with 3 or more of these risk factors was 47.1% (1,018/2,160) in the mild group and 84.9% (62/73) in the severe group (Figure 2). The odds ratio of critically severe illness in pregnant women with 3 or more of the 5 risk factors for severe COVID-19 (age ≥35 years, hyperlipidemia, diagnosis in the second or third trimester of pregnancy, infection during the Delta-predominant period, and fever symptoms at the time of diagnosis) was higher than that of the group with 2 or fewer risk factors. This result highlights the risk of critically severe symptoms associated with each combination of risk factors. Since the number of cases was low, the 95% CIs were relatively wide around the estimates for certain risk factors (e.g., age ≥35 years, hyperlipidemia, and diagnosis in the second or third trimester) (Table 3).

This study has some limitations. First, pregnant women with confirmed COVID-19 were identified through interviews during COVID-19 epidemiological investigations. Therefore, women who checked the pregnancy status item in the COVID-19 Basic Epidemiological Survey may have been omitted or incorrectly categorized, and the total number of pregnant women with COVID-19 may have been inaccurate. Second, risk factors according to the type of treatment for each stage of severe symptoms could not be identified because it was not possible to obtain clinical information related to the treatments administered to patients with critically severe symptoms. Third, it was not possible to distinguish between the effects of underlying diseases that existed before pregnancy and those that were caused by pregnancy and perinatal complications due to a lack of relevant information.

According to a recent study of pregnant women infected with COVID-19 at 15 hospitals located in the Republic of

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Table 1. General characteristics of women with SARS-CoV-2 infection during pregnancy in Korea between February 1, 2020, and December 31, 2021

Characteristic	Total pregnant women (*n* = 2,233)	Non-severe (*n* = 2,160)	Severe (*n* = 73)	*p*-value
Age group (y)				0.01[a]
20–34	1,224 (54.8)	1,195 (55.3)	29 (39.7)	
35–45	1,009 (45.2)	965 (44.7)	44 (60.3)	
Ethnic group				0.65[a]
Korean	1,933 (86.6)	1,868 (86.5)	65 (89.0)	
Foreign national	300 (13.4)	292 (13.5)	8 (11.0)	
Infection route				0.40[b]
Domestic	2,189 (98.0)	2,116 (98.0)	73 (100)	
Abroad	44 (2.0)	44 (2.0)	0 (0)	
Period of variant predominance				0.002[a]
Pre-Delta	530 (23.7)	524 (24.3)	6 (8.2)	
Delta	1,703 (76.3)	1,636 (75.7)	67 (91.8)	
Region				< 0.05[a]
Seoul	771 (34.5)	745 (34.5)	26 (35.6)	
Busan	79 (3.5)	74 (3.4)	5 (6.8)	
Incheon	135 (6.0)	125 (5.8)	10 (13.7)	
Gyeonggi Province	751 (33.6)	729 (33.8)	22 (30.1)	
Other areas	497 (22.3)	487 (22.5)	10 (13.7)	
Underlying diseases				
Diabetes mellitus	26 (1.2)	22 (1.0)	4 (5.5)	0.009[b]
Hypertension	29 (1.3)	29 (1.3)	0 (0)	1.00[b]
Hyperlipidemia	51 (2.3)	46 (2.1)	5 (6.8)	0.02[b]
Cardiovascular disease	5 (0.2)	5 (0.2)	0 (0)	1.00[b]
Cerebrovascular disease	3 (0.1)	3 (0.1)	0 (0)	1.00[b]
Malignancy	20 (0.9)	20 (0.9)	0 (0)	1.00[b]
COPD	185 (8.3)	182 (8.4)	3 (4.1)	0.28[b]
Renal disease	2 (0.1)	2 (0.1)	0 (0)	1.00[b]
Liver disease	44 (2.0)	41 (1.9)	3 (4.1)	0.17[b]
Tuberculosis	14 (0.6)	14 (0.6)	0 (0)	1.00[b]
Asthma	83 (3.7)	82 (3.8)	1 (1.4)	0.52[b]
Smoking				0.41[b]
Yes	49 (2.2)	49 (2.3)	0 (0)	
No	2,149 (96.2)	2,076 (96.1)	73 (100)	
Unknown	35 (1.6)	35 (1.6)	0 (0)	
Trimester of SARS-CoV-2 infection				< 0.001[a]
First (< 14 wk)	497 (22.3)	496 (23.0)	1 (1.4)	
Second (14–27 wk)	909 (40.7)	885 (41.0)	24 (32.9)	
Third (≥ 28 wk)	767 (34.3)	720 (33.3)	47 (64.4)	
Unknown	60 (2.7)	59 (2.7)	1 (1.4)	
Vaccination status				0.01[b]
Unvaccinated	1,921 (86.0)	1,849 (85.6)	72 (98.6)	
One dose	101 (4.5)	101 (4.7)	0 (0)	
Two doses	158 (7.1)	157 (7.3)	1 (1.4)	
Unknown	53 (2.37)	53 (2.5)	0 (0)	
Symptoms				0.09[a]
Asymptomatic infection	321 (14.4)	316 (14.6)	5 (6.8)	
Symptomatic infection	1,912 (85.6)	1,844 (85.4)	68 (93.2)	
Mortality				0.03[b]
Yes	1 (0.04)	0 (0)	1 (1.4)	
No	2,232 (99.96)	2,160 (100)	72 (98.6)	

Data are presented as *n* (%).
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COPD, chronic obstructive pulmonary disease.
[a]*p*-value by the chi-square test for the severe group; [b]*p*-value by the Fisher exact test for the severe group.

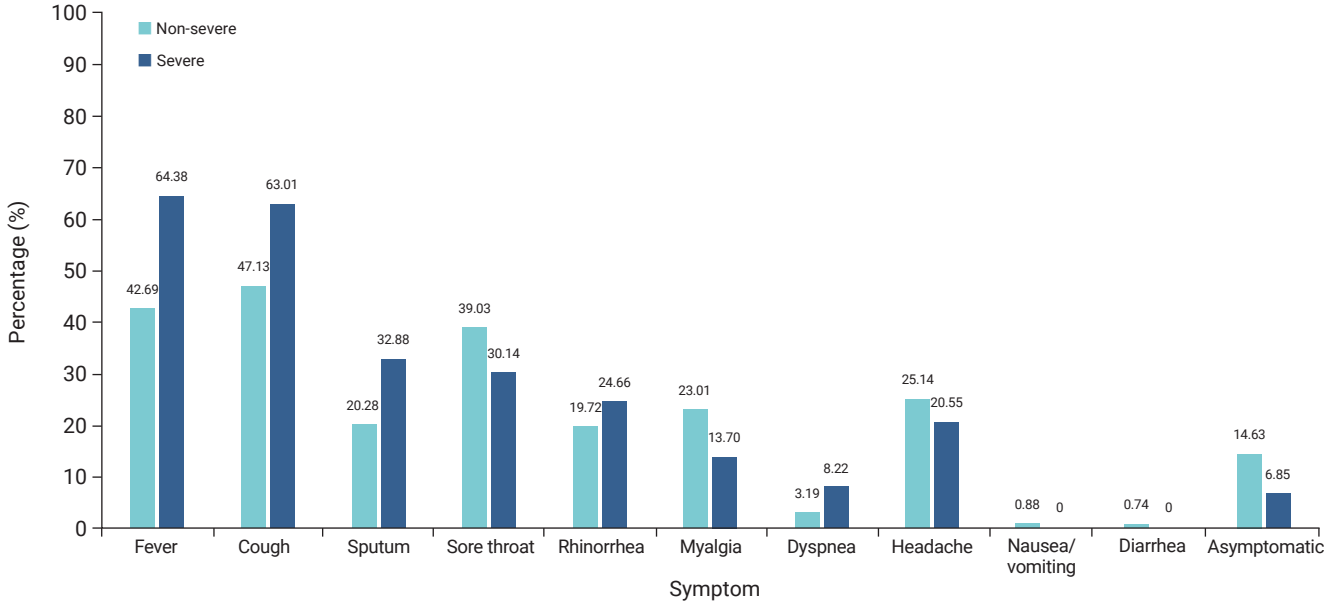

Figure 1. Distribution of the clinical symptoms reported by women with severe acute respiratory syndrome coronavirus 2 infection during pregnancy in Korea between February 1, 2020, and December 31, 2021.

Korea between January 2020 and December 2021, the ICU admission rate was 3.5% (9/257 people) [15], which was similar to the proportion of critically severe cases confirmed in the present study. In Korea, the rate of critically severe cases among all ages was 2.98% before the predominance of the Delta variant and 2.14% during the Delta-predominant period. During the same period, the rate of critically severe COVID-19 cases among patients aged 20 to 40 years was less than 1%, whereas pregnant women had a higher rate of critically severe COVID-19 cases [16]. However, the total fatality rate for all age groups was 0.89% (5,625/635,253 people) [17,18], while that for pregnant women was 0.04% (1/2,233 people), which was 22.3 times lower than the total fatality rate. In Scotland, 2% (114/5,653 people) of pregnant women diagnosed with COVID-19 between March 2020 and October 2021 received critical care [19]. Furthermore, early in the pandemic, the risk of ICU treatment for pregnant women in the United States was higher than that for non-pregnant women of the same age; however, the fatality rate was low [3].

According to a study conducted in the United Kingdom from March 2020 to March 2021 among COVID-19 inpatients aged 18 years or older, hyperlipidemia was associated with death (adjusted risk ratio [aRR], 1.07; 95% CI, 1.05–1.09), use of a ventilator (aRR, 1.13; 95% CI, 1.11–1.16), and ICU admission (aRR, 1.07; 95% CI, 1.05–1.09) due to COVID-19 [20]. In the present study, the risk of severe symptoms in pregnant women with hyperlipidemia was approximately 4.8 times higher than that in pregnant women without hyperlipidemia. In the future, comparative studies between the general population with hyperlipidemia and pregnant women are needed to clarify the degree to which various underlying diseases, including hyperlipidemia, increase the risk of severe COVID-19.

Regarding risk factors based on the stage of pregnancy, a study found that SARS-CoV-2 infection in the second and third trimesters may lead to abnormal circulation, placental infection, and negative perinatal outcomes [21]. The risk of critically severe disease was reported to be high in patients diagnosed after 21.5 weeks of pregnancy [15]. As pregnant women diagnosed with COVID-19 in the second or third trimester are at high risk of developing critically severe symptoms, it is necessary to implement careful prevention, promotion, and treatment interventions for pregnant women diagnosed with COVID-19 in the second trimester or beyond.

As the COVID-19 pandemic progressed, the number of confirmed cases increased. As a result, the authorities actively conducted COVID-19 testing during the Delta-predominant period compared to before the spread of the Delta variant. In June 2021, the World Health Organization recommended that women who are planning to become pregnant, are currently pregnant, or are breastfeeding be vaccinated against COVID-19 [22]. In Korea, COVID-19 vaccination for pregnant women began on October 18, 2021 [23]. Therefore, 1,921 (86.0%) pregnant women with confirmed COVID-19 in this survey

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Table 2. Crude and adjusted ORs for severe symptoms in pregnant women with confirmed COVID-19

Characteristic	Severe disease (*n* = 73)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Age group (y)		
20–34	Ref.	Ref.
35–45	1.88 (1.17–3.05)	2.00 (1.19–3.42)
Underlying diseases		
Diabetes mellitus[a)]	5.63 (1.62–15.21)	1.97 (0.32–9.36)
Hyperlipidemia[b)]	3.38 (1.14–8.03)	4.82 (1.04–17.66)
COPD[c)]	0.47 (0.11–1.27)	0.31 (0.04–1.19)
Liver disease[d)]	2.21 (0.53–6.28)	0.83(0.15–3.24)
Asthma[e)]	0.35 (0.02–1.62)	0.72 (0.03–9.35)
Trimester of SARS-CoV-2 infection		
First (< 14 wk)	Ref.	Ref.
Second (14–27 wk)	13.45 (2.83–240.85)	11.28 (2.32–203.28)
Third (≥ 28 wk)	32.38 (7.06–574.38)	25.09 (5.30–449.29)
Period of variant predominance		
Pre-Delta (until week 30 of 2021)	Ref.	Ref.
Delta (weeks 31–53 of 2021)	3.58 (1.68–9.28)	3.37 (1.42–9.99)
Vaccination status		
Unvaccinated	Ref.	Ref.
One dose	NA	NA
Two doses	0.16 (0.01–0.75)	0.25 (0.01-1.23)
Symptoms		
Fever[f)]	2.43 (1.50–4.00)	2.78 (1.61–4.89)
Cough[g)]	1.91 (1.19–3.13)	1.24 (0.72–2.15)
Sputum[h)]	1.93 (1.15–3.14)	1.57 (0.86–2.79)
Sore throat[i)]	0.67 (0.40–1.10)	0.59 (0.33–1.01)
Rhinorrhea[j)]	1.33 (0.75–2.25)	1.19 (0.64–2.13)
Myalgia[k)]	0.53 (0.25–1.00)	0.34 (0.15–0.69)
Dyspnea[l)]	2.71 (1.02–6.00)	1.39 (0.47–3.55)
Headache[m)]	0.77 (0.42–1.33)	0.78 (0.40–1.46)

OR, odds ratio; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COPD, chronic obstructive pulmonary disease; NA, not available.

Reference refers to the group that did not have [a)]diabetes mellitus, [b)]hyperlipidemia, [c)]COPD, [d)]liver disease, and [e)]asthma. Reference refers to the absence of [f)]fever, [g)]cough, [h)]sputum, [i)]sore throat, [j)]rhinorrhea, [k)]myalgia, [l)]dyspnea, and [m)]headache.

were unvaccinated, and only 1 person in the severe group had received 2 doses of the vaccine. In previous studies that compared the period when the Delta variant was predominant to the period before its predominance after adjusting for vaccination history, the risk of severe COVID-19 was found to increase during the period of Delta variant predominance (OR, 2.93; 95% CI, 1.18–7.69) [21]. Thus, based on the results of that previous study [21] and the relatively short period during which pregnant women in Korea could be vaccinated during the period covered by this study, it is reasonable to interpret the increase in the number of pregnant women with severe disease during the Delta-predominant period as being associated with the Delta variant itself.

Fever (31% to 41%) and cough (31% to 41%) were the main symptoms of SARS-CoV-2 infection in pregnant women, whereas myalgia (12% to 22%) and diarrhea (4% to 6%) are relatively rare [8]. In this study, the risk of critically severe disease in pregnant women with fever was higher than that in pregnant women without fever. Physiological responses such as temperature control during infection have long-term effects on pregnant women diagnosed with COVID-19 [6], and fever during pregnancy can increase the risk of neurological disorders in the fetus [24]. Therefore, fever symptoms must be closely monitored and treated in pregnant women diagnosed with COVID-19. In the present study, myalgia was identified as a factor inversely associated with severe COVID-19; however, this result may have been due to the small number of critically severe patients who experienced myalgia. Further studies are warranted to clarify this relationship.

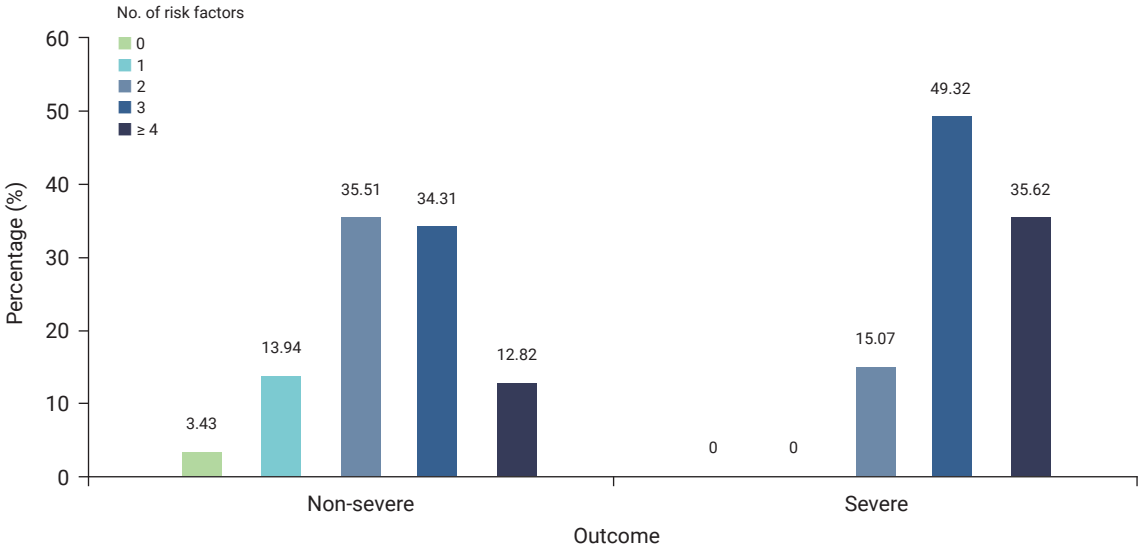

Figure 2. Frequency distribution based on the number of risk factors for women infected with severe acute respiratory syndrome coronavirus 2 during pregnancy in Korea.

Table 3. Risk of critically severe symptoms by risk factor combinations in women infected with SARS-CoV-2 during pregnancy

Characteristic	Severe disease (*n* = 73)	
	n (%)	OR (95% CI)[a]
Combinations of 3 factors		
Age, hyperlipidemia, trimester (*n* = 2)	1 (1.4)	97.09 (3.69–2,564.1)
Age, trimester, fever (*n* = 49)	2 (2.7)	4.13 (0.63–15.95)
Age, trimester, Delta (*n* = 307)	15 (20.5)	4.99 (2.28–11.25)
Trimester, Delta, fever (*n* = 337)	18 (24.7)	5.48 (2.60–12.09)
Combination of 4 factors		
Age, Delta, trimester, hyperlipidemia (*n* = 10)	1 (1.4)	10.78 (0.56–65.24)
Age, Delta, trimester, fever (*n* = 275)	23 (31.5)	8.86 (4.35–19.12)
Delta, trimester, hyperlipidemia, fever (*n* = 7)	2 (2.7)	38.84 (5.18–203.48)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; CI, confidence interval; age, older than 35 years; Delta, infection during the Delta-predominant period; trimester, infection in the second or third trimester; hyperlipidemia, pregnant women with hyperlipidemia; fever, fever at diagnosis (≥ 38 °C); combinations of 2 (*n* = 11), combination of 5 factors (*n* = 0).
[a]Reference refers to combinations of 2 factors (*n* = 11).

Conclusion

In conclusion, most pregnant women with SARS-CoV-2 infection were mildly symptomatic. However, pregnant women older than 35 years of age, those with hyperlipidemia, and those infected in the second or third trimester were significantly more likely to develop severe symptoms. Thus, treatment and follow-up management should be thoroughly implemented, and fever symptoms should be closely monitored and treated. Furthermore, pregnant women should be actively educated about these risk factors through guidelines to prevent infection. To further clarify changing patterns in infection risk as the distribution of variants changed throughout the COVID-19 pandemic, future research should investigate the overall epidemiological characteristics of pregnant women with COVID-19 during the Omicron-predominant period (i.e., in 2022 and beyond).

Notes

Ethics Approval

The collection of data in accordance with Article 76-2 of the infectious Disease Control and Prevention Act was approved by the Institutional Review Board of the KDCA (IRB No: 2022-11-10-PE-A).

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

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None.

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

Authors' Contributions
Conceptualization: all authors; Data curation: JJL; Formal analysis: JJL; Investigation: JJL; Methodology: SEL, YK, YJP; Project administration: YJP; Resources: JJL; Software: JJL; Supervision: YJP; Validation: SEL, YJP; Visualization: JJL; Writing–original draft: JJL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Estimated impact of the national hepatitis B immunization program on acute viral hepatitis B among adolescents in Republic of Korea

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ABSTRACT

Objectives: We aimed to estimate the impact of the national hepatitis B immunization program on the incidence of acute hepatitis B infection among adolescents in South Korea.
Methods: We estimated the counterfactual incidence rate of reported acute hepatitis B among adolescents from 2016 to 2020 compared to the assumption that the national hepatitis B immunization program for children had not been implemented since 1995. The impact of the national hepatitis B immunization program for adolescents was measured by estimating the absolute risk reduction and averted acute hepatitis B infections among adolescents from 2016 to 2020 attributed to the national immunization program.
Results: The relative risk reduction of acute hepatitis B among adolescents was estimated to be 83.5% after implementing the national hepatitis B immunization program. The incidence rate of reported acute hepatitis B infections among adolescents decreased from 0.39 to 0.06 per 100,000 person-years, and 43 acute hepatitis B infections, including 17 symptomatic cases, were averted annually from 2016 to 2020 by the national hepatitis B immunization program.
Conclusion: The national hepatitis B immunization program for children was effective in preventing acute hepatitis B infection among adolescents in South Korea.

Keywords: Adolescent; Hepatitis B; Immunization programs; Republic of Korea

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Introduction

Globally, 296 million people were living with chronic hepatitis B infection in 2019, with 2.5 million new infections every year [1]. In 2016, the member states of the World Health Organization committed to eliminating viral hepatitis as a major public health threat by 2030. The World Health Organization established a global health sector strategy on viral hepatitis and set global targets of achieving a 90% reduction in new chronic viral hepatitis B and C infections

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and a 65% reduction in deaths because of viral hepatitis B and C infections [2].

In South Korea, hepatitis B is the main cause of chronic liver disease, accounting for 60% to 70% of all cases of chronic liver disease [3]. The hepatitis B surface antigen (HBsAg) positivity rates were 2.7% among people over 20 years and 0.2% among adolescents aged 10 to 18 years in 2020 [4]. The hepatitis B surveillance system was initially operated as a sentinel monitoring system starting in 2000, and it was changed to a mandatory surveillance system in 2010 [5]. The focus of surveillance was limited to acute hepatitis B infections in January 2016 [6]. The national immunization program (NIP) for hepatitis B in infants was introduced in South Korea in 1995, and coverage of the 3 doses of hepatitis B vaccination among newborns increased from 82% in 1998 to 98% in 2018 [3,7]. According to a previous study, hepatitis B vaccination coverage was 37% among adults in 1994, although coverage in more recent years has not been determined [8].

Countries with low HBsAg positivity rates are likely to have horizontal transmission as the major mode of infection transmission, and data from the acute hepatitis B surveillance system indicate that around 400 cases of horizontally transmitted acute hepatitis B have occurred annually in South Korea [5,9]. The impact of vaccination on horizontal transmission as well as vertical transmission should be evaluated to estimate the impact of the hepatitis B NIP correctly. However, most studies in South Korea have investigated the impact of the hepatitis B NIP on vertical transmission based on the HBsAg positivity rate, and the impact of the hepatitis B NIP on horizontal transmission based on acute hepatitis B surveillance data has not yet been evaluated [9,10]. Hence, the aim of this study was to estimate the impact of the hepatitis B NIP on the incidence of acute hepatitis B infection among adolescents by estimating the absolute risk reduction (ARR) in South Korea from 2016 to 2020, with a focus on horizontal transmission.

HIGHLIGHTS

- The hepatitis B national immunization program (NIP) for children was effective in preventing acute hepatitis B infection among adolescents in South Korea.
- The relative risk reduction of acute hepatitis B among adolescents was estimated to be 83.5% after implementing the hepatitis B NIP.
- From 2016 to 2020, 43 acute hepatitis B infections including 17 symptomatic cases were estimated to be averted annually attributed to the hepatitis B NIP.

Materials and Methods

Descriptive Analysis

We conducted a descriptive analysis of acute hepatitis B cases reported from 2016 to 2020 and examined the distribution of cases by age group. Acute hepatitis B cases reported to the Korea Disease Control and Prevention Agency (KDCA) from January 2016 to December 2020 were collected from the integrated public healthcare information system. National population data were collected from the Korean Statistical Information Service [11]. The incidence rate (IR) per 100,000 person-years was estimated using the cumulative number of reported acute hepatitis B cases and person-years by age group for each year from 2016 to 2020.

Population

Members of the population aged 10 to 19 years and those aged 20 years and above in each year from 2016 to 2020 were defined as adolescents and adults, respectively. We did not define adolescents and adults based on birth cohorts in a specific year, because older adolescents drop out of the adolescent cohort as they become adults in later years, and the adolescent cohort is not affected by the different prevalence of risk exposures among adults, including the increased prevalence of sexual contacts and illicit drug use [12–14]. We conducted a sensitivity analysis to account for the effect of the hepatitis B NIP on the population that was defined as adults but born after the implementation of the hepatitis B NIP in each year from 2016 to 2020.

Study Design

We estimated the relative risk reduction (RRR) and the ARR of the hepatitis B NIP by comparing the reported IR of acute hepatitis B among adolescents from 2016 to 2020 (status with the hepatitis B NIP) with the estimated IR assuming that the NIP had not been implemented (status without the hepatitis B NIP). To estimate the IR among adolescents from 2016 to 2020 without the hepatitis B NIP, we used the ratio of adolescents to adults among acute hepatitis B patients in a previous study conducted by Yim et al. [15]. That study investigated acute hepatitis B patients at 3 tertiary general hospitals from February 1999 to February 2002.

We assumed that the ratio of adults to adolescents among acute hepatitis B patients reported from 2016 to 2020 without the hepatitis B NIP would be the same as the ratio from 1999 to 2002 if the population ratios in the 2 periods were identical. The number of reported acute hepatitis B cases among adults from 2016 to 2020 was multiplied by

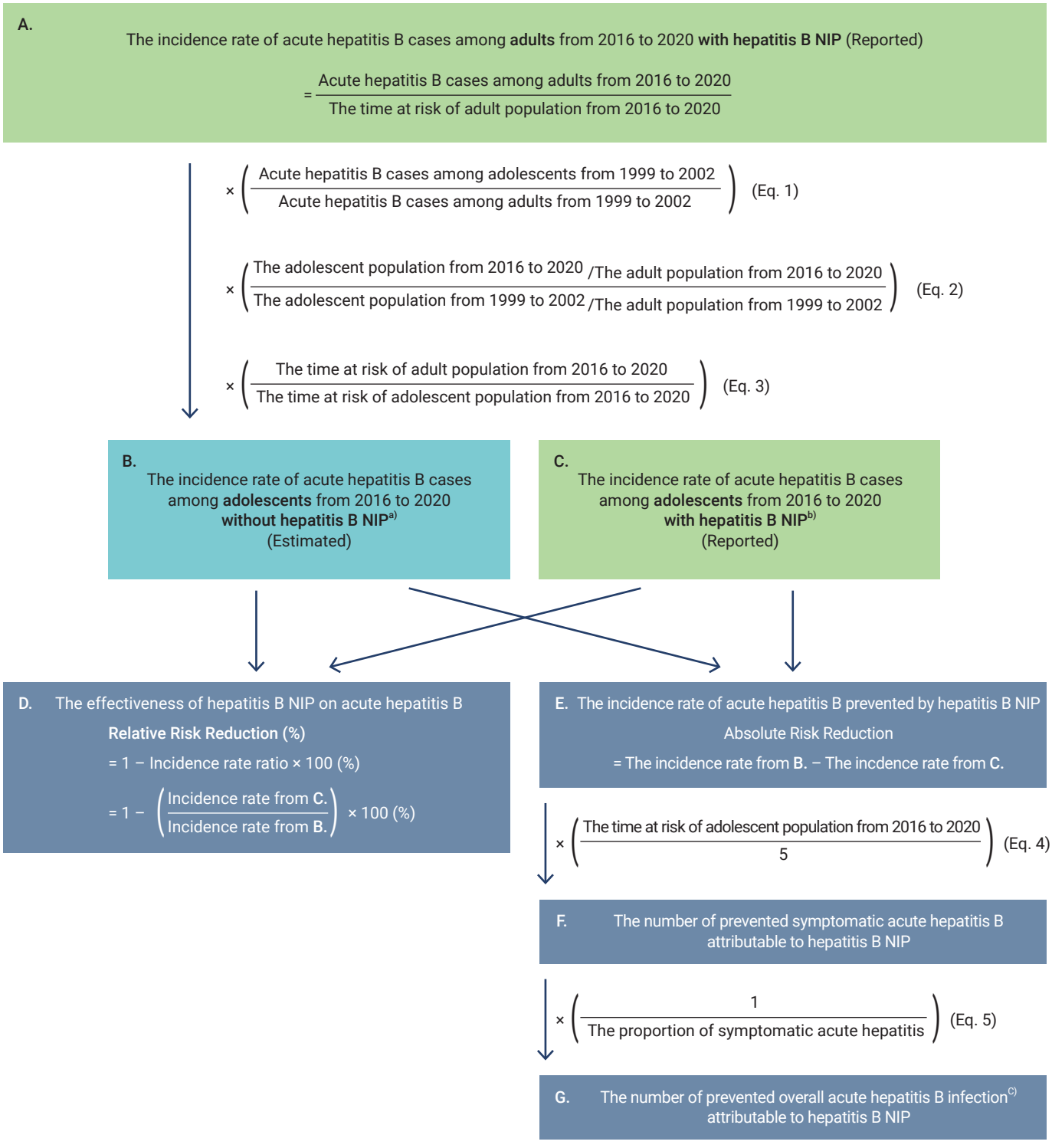

Figure 1. The process of estimating the impact of the national immunization program (NIP) for hepatitis B on the incidence of acute hepatitis B infection among adolescents.
[a)]The status if the hepatitis B NIP had not been implemented in 1995. [b)]The status when the hepatitis B NIP was implemented in 1995.
[c)]Overall acute hepatitis B infections, including both symptomatic and asymptomatic cases.

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the ratio of adolescents to adults among acute hepatitis B cases from the previous study (Figure 1A, Eq. 1). Since the ratio of adolescents to adults changed from 1999 to 2020, the average ratio of adolescents to adults from 2016 to 2020 was divided by the average ratio of that from 1999 to 2002, and the result was multiplied by the previously estimated number (Figure 1, Eq. 2). We conducted a sensitivity analysis to account for the change in the ratio of adolescents to adults among acute hepatitis B patients. The denominator for calculating the IR was changed from the time at risk of the adult population to the time at risk of the adolescent population (Figure 1, Eq. 3).

We assumed that the trends in hepatitis B vaccination coverage among adults subject to the hepatitis B NIP would be the same as those of hepatitis B vaccination coverage among the overall population not subject to the hepatitis B NIP during the overall study period. We divided the estimated IR of acute hepatitis B among adolescents without the hepatitis B NIP from 2016 to 2020 (Figure 1B) by the reported IR with the hepatitis B NIP (Figure 1C) to estimate the incidence rate ratio (IRR), and we subtracted the IRR from 1 to estimate the RRR attributed to the hepatitis B NIP (Figure 1D).

We estimated the ARR of acute hepatitis B by subtracting the reported IR of acute hepatitis B among adolescents from 2016 to 2020 with the hepatitis B NIP from the estimated IR without the hepatitis B NIP (Figure 1E). Since clinical symptoms and laboratory confirmation are essential for reporting acute hepatitis B, we assumed that all reported acute hepatitis B cases were symptomatic [5]. We multiplied the ARR by the average annual time at risk of the adolescent population from 2016 to 2020 to estimate the annual reduction of symptomatic acute hepatitis B cases from 2016 to 2020 (Figure 1F, Eq. 4). We also multiplied the reduction of symptomatic cases by the reciprocal proportion of symptomatic cases among all acute hepatitis B infections to estimate the overall reduction of acute hepatitis B infection, including symptomatic and asymptomatic cases (Figure 1G, Eq. 5) [16].

Parameters

The ratio of adolescents to adults among acute hepatitis B cases at 3 tertiary hospitals from 1999 to 2002 was 0.10 (95% confidence interval [CI], 0.02–0.21) [15]. The average ratio of the adolescent population to the adult population from 2016 to 2020 (0.13) was 0.61 times the average ratio of adolescents to adults from 1999 to 2002 (0.20). The average adolescent population from 2016 to 2020 was 5,214,595, which was equal to one-eighth of the adult population [11]. According to the estimate by Klevens et al. [16], 39.5% of overall acute hepatitis B infections were symptomatic (Table 1) [11,15,16].

Sensitivity Analysis

We conducted a 1-way deterministic sensitivity analysis to investigate the uncertainty originating from each parameter, and the results were presented in a tornado diagram to show the effect of variation in parameters on the outcome. We assumed that the ratio of adolescents to adults among patients was 0.10 without the hepatitis B NIP, using the same ratio of adolescents to adults as that from 1999 to 2002. However, the ratio of adolescents to adults was 0.12 (95% CI, 0.07–0.19) in a previous study investigating 185 acute hepatitis B patients from 1982 to 1986 [17]. The ratio decreased by 0.025 during approximately 15 years. The difference in the average ratios of adolescents to adults from 1982 to 1986 and from 1999 to 2002 was similar to the difference in the average ratios from 1999 to 2002 and from 2016 to 2020. Therefore, we conducted a sensitivity analysis to investigate how the outcomes changed when the ratio of adolescents to adults changed by 0.025.

There could have been uncaptured symptomatic acute hepatitis B cases in individuals who did not visit healthcare facilities. Klevens et al. [16] estimated that 88% of symptomatic hepatitis B patients visited healthcare facilities in the United States. Since most South Koreans (97%) are covered by the National Health Insurance Service, the proportion of symptomatic hepatitis B patients who visited healthcare facilities would likely be higher in South Korea [18]. Therefore, we investigated how the study outcomes changed

Table 1. The parameters of the process for estimating the protective effect of the national hepatitis B immunization program in South Korea

Description	Value	Reference
The ratio of adolescents to adults among acute hepatitis B cases from 1999 to 2002 (95% confidence interval)	0.10 (0.02–0.21)	[15]
The average ratio of the adolescent population to the adult population from 2016 to 2020 divided by the ratio of that from 1999 to 2002	0.61	[11]
The average ratio of the adult population to the adolescent population from 2016 to 2020	8.00	[11]
The average size of the adolescent population from 2016 to 2020	5,214,595	[11]
The proportion of symptomatic acute hepatitis among overall hepatitis B infections	0.395	[16]

when the proportion of symptomatic individuals visiting healthcare facilities changed from 88% to 100%.

Since the hepatitis B NIP was implemented in 1995, young adults from 2016 to 2020 would have been covered by the hepatitis B NIP. The time at risk of adults born after 1995 accounted for 6.5% of the overall observed time at risk of the adult cohort during the study period. Therefore, we conducted a sensitivity analysis to explore the impact of excluding adults who were born after 1995 from the adult cohort. We estimated the IR among adults born before 1994 under the assumption that the IR among adults born after 1995 was the same as the IR among the adolescent population.

Statistical Analysis

All statistical analyses were performed using R Statistical Software ver. 4.1.2 (R Foundation for Statistical Computing) and the "epiR" R package ver. 2.0.41, and the exact method based on the Poisson distribution was used to present CIs for the IRs. Wald CIs were presented for the RRR and the ARR.

Ethical Statement

The KDCA Institutional Review Board (IRB No: 2022-08-06-PE-A) determined that this study was exempt from ethics approval and informed consent because we used data without personal identifiers that were collected during legally mandated public health investigations under the authority of the Infectious Diseases Control and Prevention Act (No: 12444; No: 13392; No: 17067; No: 17642).

Results

Descriptive Analysis

In total, 1,741 acute hepatitis B cases were reported from 2016 to 2020. The overall IR was 0.68 (95% CI, 0.65–0.71) per 100,000 person-years. The IR among adolescents was significantly lower than the IR among adults. The IRs per 100,000 person-years were 0.06 (95% CI, 0.03–0.10) among adolescents and 0.83 (95% CI, 0.79–0.87) among adults. The cumulative number of reported acute hepatitis B cases among adolescents was only 17, while the cumulative number of reported acute hepatitis B cases among adults aged over 20 years was 1,719 from 2016 to 2020 (Table 2).

Impact of the Hepatitis B NIP

The IR of acute hepatitis B cases among adolescents from 2016 to 2020 without the hepatitis B NIP was estimated as 0.39 (95% CI, 0.37–0.41) cases per 100,000 person-years. The IR of acute hepatitis B among adolescents from 2016 to 2020 with the hepatitis B NIP was 0.06 (95% CI, 0.03–0.10) cases per 100,000 person-years. The RRR of acute hepatitis B attributed to the hepatitis B NIP was 83.5% (95% CI, 72.2–90.8) and the ARR was 0.33 (95% CI, 0.24–0.41) cases per 100,000 person-years. The annual number of averted hepatitis B infections among adolescents attributable to the NIP from 2016 to 2020 was 43.0 cases (95% CI, 32.2–53.9), including 17.0 (95% CI, 12.7–21.3) symptomatic cases (Table 3).

Sensitivity Analysis

If the ratio of adolescents to adults was 0.07, the estimated RRR was 77.7%, and the ARR per 100,000 person-years was 0.22. The number of overall averted acute hepatitis B infections was 30 cases including 12 symptomatic cases annually. In contrast, if the ratio of adolescents to adults was 0.12, the estimated RRR was 86.9% and the ARR per 100,000 person-years was 0.43. The overall number of averted acute hepatitis B infections increased to 56 cases, including 22 symptomatic cases every year. If the proportion of patients visiting healthcare facilities among symptomatic hepatitis B patients decreased from 100% to 88%, the yearly number of averted overall acute hepatitis B infections increased to

Table 2. The incidence rate[a] of acute hepatitis B infections by age group, and the cumulative number of reported acute hepatitis B infections and time at risk by sex and age from 2016 to 2020

Age group (y)	No. of cases among males	No. of cases among females	Total	Time at risk (person-year)	Incidence rate (95% CI)[a]	
0–9	2	3	5	21,744,242	0.02 (0.01–0.05)	
10–19	11	6	17	26,972,974	0.06 (0.03–0.10)	
20–39	392	203	595	70,008,079	0.84 (0.77–0.91)	0.83 (0.79–0.87)[b]
40–59	541	228	769	84,492,096	0.91 (0.84–0.97)	
≥ 60	188	167	355	54,013,848	0.68 (0.61–0.75)	
Overall	1,134	607	1,741	256,331,238	0.68 (0.65–0.71)	

CI, confidence interval.
[a]Per 100,000 person-years. The incidence rates in each age group were indirectly adjusted by sex, and the exact method based on the Poisson distribution was used to present confidence intervals. [b]Among the population aged over 20 years.

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Table 3. The estimated IR[a] of acute hepatitis B without the hepatitis B NIP[b] and the estimated impact of the hepatitis B NIP among adolescents in South Korea from 2016 to 2020

Description	Estimated value (95% CI)
The incidence rate[a] of acute hepatitis B cases among adolescents from 2016 to 2020 without the hepatitis B NIP[b]	0.39 (0.37–0.41)
The relative risk reduction (%) attributed to the hepatitis B NIP on acute hepatitis B infection	83.5 (72.2–90.8)
The absolute risk reduction[a] attributed to the hepatitis B NIP	0.33 (0.24–0.41)
The annual number of prevented symptomatic acute hepatitis B cases attributable to the hepatitis B NIP from 2016 to 2020	17.0 (12.7–21.3)
The annual number of prevented overall hepatitis B infections[c] attributed to the hepatitis B NIP from 2016 to 2020	43.0 (32.2–53.9)

IR, incidence rate; NIP, national immunization program; CI, confidence interval.
[a]Per 100,000 person-years. [b]The status if the hepatitis B NIP had not been implemented in 1995. [c]Overall acute hepatitis B infections, including both symptomatic and asymptomatic cases.

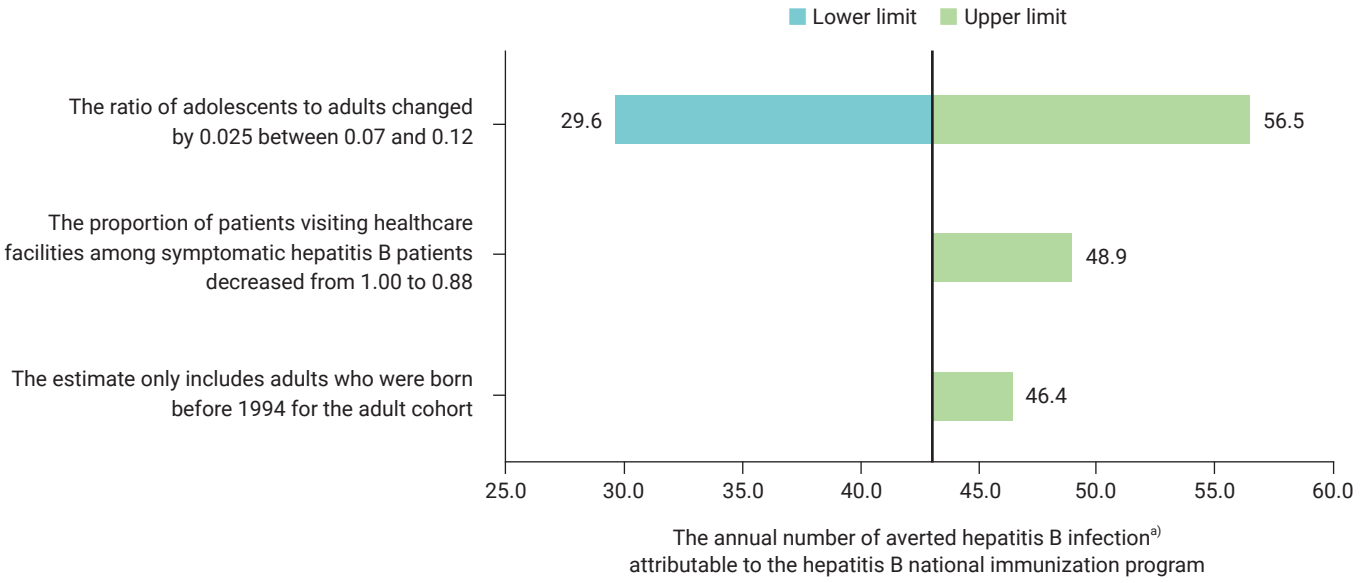

Figure 2. Sensitivity analysis of the annual number of acute hepatitis B cases[a] among adolescents averted due to the implementation of the hepatitis B national immunization program.
[a]Overall acute hepatitis B infections, including both symptomatic and asymptomatic cases.

49 cases, including 19 symptomatic cases. If the IR of acute hepatitis B among adults born after 1995 was the same as the IR among adolescents, the estimated RRR was 84.5% and the ARR was 0.35, and the annual number of averted overall hepatitis B infections was raised to 46, including 18 symptomatic cases (Figure 2).

Discussion

We found that the current IR of acute hepatitis B among adolescents is dramatically lower than that among adults in South Korea. The hepatitis B NIP for children appears to be an effective measure to prevent acute hepatitis B infections in adolescents. Our estimates suggest that approximately 83.5% of acute hepatitis B cases have been prevented by the hepatitis B NIP in South Korea, averting more than 40 cases of acute hepatitis B infection annually among adolescents. To the best of our knowledge, this is the first study to investigate the impact of the hepatitis B NIP in children on the incidence of acute hepatitis B in adolescents in South Korea.

We did not use an observational cohort design that would directly compare the IR between adults and adolescents because the risk exposure frequency among adolescents could be different from that of adults. Additionally, we did not compare different age cohorts in the same period or the same age cohort in different periods to estimate the effectiveness of the hepatitis B NIP. This is because hepatitis B surveillance focusing on acute hepatitis B infections was implemented in 2016 and has only been in operation for a limited period. Furthermore, the annual incidence of acute hepatitis B cases in adolescents is too small (fewer than 4 cases) to be divided into sub-cohorts.

We estimated the effectiveness of the hepatitis B NIP in South Korea under specific circumstances, rather than

the effectiveness of the hepatitis B vaccination program in general. This is because we were unable to identify parameters such as coverage of the hepatitis B NIP in each age group, even though the annual coverage of the hepatitis B NIP gradually increased from 90% in the early 2000s to 98% in 2019 [7]. Therefore, the estimated effectiveness of the hepatitis B NIP in South Korea cannot be directly compared to the effectiveness of hepatitis B vaccination programs in other countries.

The coverage of hepatitis B vaccination among adults in South Korea in recent years is unknown. However, the outcomes of our study already account for the effect of vaccination coverage among adults if the vaccination coverage among adults was the same as the coverage among the overall population without the hepatitis B NIP. This is because the estimated IR in the adolescent population (Figure 1B) was derived from the IR in the adult population (Figure 1A). However, even if the hepatitis B NIP had not been implemented, other vaccination programs for children may have raised awareness and coverage of the hepatitis B vaccine, especially among children. Therefore, the impact of the hepatitis B NIP implementation could have been smaller than the estimate in this study.

Several social, behavioral, and environmental changes can lead to changes in the risk pattern and incidence of hepatitis B infections. For example, the reuse of syringes was prohibited by law in 2016, and hepatitis B virus screening tests for transfusions have improved over the years [19,20]. However, the estimated RRR in this study was minimally affected by these changes when the risk of exposure to hepatitis B infection changed evenly among adolescents and adults. This is because both the estimated IR among adolescents without the hepatitis B NIP (Figure 1B) and the reported IR among adolescents with the hepatitis NIP (Figure 1C) were affected by these changes. However, these changes could affect the ARR and the number of averted cases by changing the scale of the IRs.

Changes in the frequency of risk exposure to hepatitis B infection in specific age cohorts could affect the RRR and ARR. For example, the HBsAg positivity rate among the population aged over 20 years decreased from 5.0% in 1998 to 2.7% in 2020, and the number of acute hepatitis B cases among adults could have been reduced by the decrease in positivity rate. Moreover, the introduction of oral antiviral therapy and positive externalities of the hepatitis B NIP, such as herd immunity, also could have reduced the incidence of acute hepatitis B among adults. The reduced incidence of acute hepatitis B among adults could have decreased the estimated IR among adolescents without the hepatitis B NIP (Figure 1B), as well as the estimated RRR (Figure 1D) and ARR (Figure 1E). Considering the positive externalities of the hepatitis B NIP to the adult population, our estimates of the RRR and ARR could have been underestimated.

Furthermore, the proportion of asymptomatic hepatitis B cases is generally higher among people who are infected at a younger age [21]. The estimated IR among adolescents without hepatitis B NIP (Figure 1B) could be overestimated compared with the reported IR among adolescents with hepatitis B NIP (Figure 1C) because the estimated IR was based on the reported numbers of symptomatic acute hepatitis B cases among adults, which may have a higher proportion of symptomatic cases than among adolescents. As a result, our estimates of RRR (Figure 1D) and ARR (Figure 1E) could also have been overestimated.

We estimated the overall protection provided by the hepatitis B NIP using population-level data, which cannot be directly compared to the effectiveness of hepatitis B vaccination programs in other countries. Therefore, it is necessary to conduct further studies that measure direct and indirect protection using individual-level infection records and vaccination histories. Moreover, the trends of risk factors for hepatitis B infection among adolescents, including sexual behavior, tattooing, and use of improperly sanitized equipment for cosmetic procedures, require more investigation. Given the substantial public health burden posed by hepatitis B infection, in-depth studies focusing on risk factors and the impact of exposure to these factors on the incidence of acute hepatitis B infection among adolescents should be conducted.

Conclusion

In many countries, acute hepatitis B infections have been consistently caused by horizontal transmission of the hepatitis B virus. However, the focus of most hepatitis B vaccination programs has been on preventing mother-to-child transmission. Our findings highlighted that the hepatitis B NIP for children, which is known to be effective in preventing mother-to-child transmission, has also been effective in preventing acute hepatitis B infections in adolescents. However, our study estimated the overall protection provided by hepatitis B NIP, and the trends of risk factors for hepatitis B infection among adolescents have not been fully investigated. Therefore, it is necessary to conduct further studies that measure the direct and indirect protection provided by the hepatitis B NIP, as well as studies focusing on risk factors for hepatitis B infection and its impact on the incidence of acute hepatitis B infection among adolescents.

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Notes

Ethics Approval

The KDCA Institutional Review Board (IRB No: 2022-08-06-PE-A) determined that this study was exempt from ethics approval and informed consent because we used data without personal identifiers that were collected during legally mandated public health investigations under the authority of the Infectious Diseases Control and Prevention Act (No: 12444; No: 13392; No: 17067; No: 17642).

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.

Acknowledgements

National acute hepatitis B cases reported to the KDCA collected from the integrated public healthcare information system were used for this analysis. The views expressed here are those of the authors, and not necessarily those of the KDCA.

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Correspondence

Comments on the article "Time-series comparison of COVID-19 case fatality rates across 21 countries with adjustment for multiple covariates"

To the Editor:
I read the recently published article by Kim et al. [1]. On page 424 [1], the authors state, referring to my paper [2], that "other research using time-series cross-sectional data appears to have underestimated the impact of autocorrelation and heteroscedasticity". However, this statement is incorrect and unfounded for 2 reasons. First, I used cross-sectional data rather than panel data, so there was no time component. The corollary is that residuals cannot be serially correlated. It makes no sense to consider autocorrelation in this case. Second, as shown in Section 5.1 of Perone [2], I safely considered heteroscedasticity in my paper: "Furthermore, since Breusch and Pagan (1979) and Shapiro and Wilk (1965) tests allowed to accept the null hypothesis of homoscedasticity and normality of residuals, models seemed well specified. However, due to the small sample, I preferred to adopt a conservative approach, by applying the HC2 correction proposed by MacKinnon and White (1985)" [3–5]. As a result, autocorrelation and heteroscedasticity issues have no bearing on the results of my paper.

Notes

Conflicts of Interest
The author has no conflicts of interest to declare.

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Response to the comment of Perone by the corresponding author Kim

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I agree with Prof. Perone's comment that his paper was referenced unproperly. His work should have been referenced in the next sentence, which is "or could not control for the effect of SARS-CoV-2 variants, especially during the emergence of the Delta and Omicron variants." Our intention was to point out that we should consider the effect of COVID-19 variants when comparing different countries' case fatality rates, complementing Perone's preceding work, which showed the effect of environmental factors on the case fatality rate [1]. This was a mistake that happened during the revision process, and I offer my apologies to Prof. Perone.

Notes

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

Reference

1. Perone G. The determinants of COVID-19 case fatality rate (CFR) in the Italian regions and provinces: an analysis of environmental, demographic, and healthcare factors. Sci Total Environ 2021;755(Pt 1):142523.

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Instruction for authors

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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.

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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/).

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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.

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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.

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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.

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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.

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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.

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SUBMISSION & PEER REVIEW PROCESS

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All manuscripts should be submitted online at https://mc04.manuscriptcentral.com/osongphrp (PHRP online submission system: ScholarOne). The entire process of manuscript submission, peer-review, and resubmission to PHRP is done through the online system.

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Any inquiry concerning manuscript submission should be directed to the editorial office at ophrp@korea.kr.

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- 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.
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MANUSCRIPT PREPARATION

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- 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).
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- 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).

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- **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.
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- **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.
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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.
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- **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.
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- 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**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  1. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. Academic Press; 2020.
  2. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. CRC Press; 2017. p. 627-80.
  3. Ministry of Employment and Labor. Statistics on occupational injuries and illnesses, 2008. Ministry of Employment and Labor; 2009.
- **Websites**
  1. World Health Organization (WHO). COVID-19 vaccines [Internet]. WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  1. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Springer; 2002. p. 182-91.
- **Dissertation**
  1. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Yonsei University; 2000.

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 ([a], [b], [c], [d]...), and notes on level of probability (*, **, *** for *p*).

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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.

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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

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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

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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.

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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.

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

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.

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- ▫ 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

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- ▫ All references listed in the reference section are cited in the text and vice versa.

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