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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

How we will reach a safer community

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At the end of last year, the Republic of Korea, China, and Japan responded to concerns about the increase in new coronavirus disease 2019 (COVID-19) patients and the emergence of new variants by strengthening their surveillance and quarantine measures. However, contrary to these concerns, the number of new cases and deaths decreased globally, and some have expressed the opinion that the World Health Organization (WHO) should reevaluate the declaration of a global public health crisis. However, the decision has been made to maintain the crisis status for the time being [1]. Nevertheless, in the first week of January, when the Rt value dropped below 1, the Republic of Korea implemented an exit strategy and has enforced it since January 30 [2]. The use of masks in public health facilities where a large number of people gather is now at individuals' discretion, while their use is mandatory in public transportation. And, it is necessary to transition to a long-term strategy based on the endemicity of COVID-19. In the United States, the BXX. 1.5 variant has become predominant, but it is expected to be resolved by May 11th [3]. Therefore, the search for an exit strategy should consider which measures should be prioritized to prepare for the next pandemic.

Building public trust in the safety and efficacy of currently available COVID-19 vaccines is of the utmost importance. Nationwide vaccination and booster programs have been initiated to curb the ongoing pandemic. During the vaccination campaign over the past 3 years, reports of vaccine adverse events have led to the need for research on the epidemiological relationship between vaccination and serious illnesses. To ensure scientific and objective judgments regarding this issue, the government has entrusted research on the adverse effects of COVID-19 vaccinations to the National Academy of Medicine of Korea. The study by Jeong et al. [4] published in this issue summarizes the methods used to research important adverse events following immunization; the ultimate goal of this research program is to increase the reliability of vaccines and combat vaccine hesitancy among medical professionals and the public.

The second measure that must be prioritized is the improvement of governance by amending laws and regulations related to infectious diseases. After the Middle East respiratory syndrome outbreak in 2015, the government introduced a legal system that classifies reporting and quarantine methods for disease management based on the severity of each disease group. However, the severity of COVID-19 can change depending on vaccination or mutations in the virus. Thus, the government has changed the classification of COVID-19 from a level 1 disease, which requires immediate reporting, isolation, and treatment cost support, to a level 4 disease, which requires self-payment of treatment and surveillance. This adjustment of the severity level has created confusion in its management and procedural problems related to changing legal measures. Therefore, the disease grouping according to management strategies should

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be discarded; instead, diseases should simply be listed in 'Korean alphabetical' reduce the confusion in the law, with lower-level laws such as presidential decrees and Ministry of Health and Welfare regulations governing the definition, diagnosis and treatment, public health measures, reporting methods, and international measures for each disease. An advantage of this approach would be that diseases requiring restrictions of individual freedom and rights would be strictly regulated by higher-level laws under the supervision of the National Assembly. This would ensure the ongoing stability of legal operations. In addition, delegating the details of disease management strategies to lower-level laws would allow more flexible management options depending on the epidemiological situation of each disease.

However, when amending laws and regulations, trends in international infectious disease management reform must be considered. The WHO recently announced a proposed revision of the International Health Regulations (IHR) and is currently seeking opinions [5]. The previous IHR focused on prevention and response in the public health sector based on traffic and trade following the international spread of diseases, whereas the recently proposed revision expands the scope of risks and emphasizes expanding the management of preparedness and social resilience in the healthcare system, as well as international cooperation and responsibilities. The government is also currently negotiating the Pandemic Prevention Treaty [6], which aims to overcome catastrophic infectious diseases through transparently communicating information about disease occurrence, strengthening the binding force of international law, ensuring equity in access to vaccines and treatments, easing the use of intellectual property rights, preparing the healthcare systems of low- and middle-income countries, addressing human rights issues related to discrimination and coercion, and addressing issues related to animals, humans, the environment, and health (One Health).

It is difficult to address pandemic diseases solely with the current legal system for infectious disease prevention and management. In other words, for managing all disaster-prone diseases, a new legal system that includes prevention, response, and resilience is necessary. This new legal system should encompass crisis declaration and mitigation, medical system preparation, education and training, personnel recruitment and retention, production and supply of materials, medical and non-medical measures, research and development, protection of vulnerable groups, and exemptions, among other things [7].

Thirdly, to improve our response to COVID-19, we should focus on what we did well and what we missed due to various difficulties. We must continue to learn from the past, and we will move forward to change the future through Health For All (epitope of Late LEE Director General of WHO Jong-wook, 2006). The importance of collaboration between a strong public health network and a treatment system centered around private medical institutions was emphasized during the COVID-19 pandemic. Collaborative mechanisms of this type are needed for the efficient use of limited healthcare resources and continued efforts to eradicate diseases.

When nationwide medical insurance for universal health coverage was implemented in 1988, the national organization for managing tuberculosis (TB) was eliminated from health centers as many TB patients sought treatment at private medical institutions, resulting in inaccurate reporting and statistics for almost 10 years. Therefore, a new model of public-private collaboration was developed and implemented, which enabled proper TB management. Thanks to this, the goal of eradicating TB by 2030 is achievable. Therefore, even in the absence of a national TB management system centered around health centers, as we approach the eradication stage, the public health program for disease prevention and contact tracing must never be separated from the treatment program for patients. This approach will also be applicable to the strategy for eradicating acute infectious diseases, such as measles and COVID-19.

In the beginning of the COVID-19 pandemic, public health measures such as isolation and contact tracing were effective in blocking its transmission and reducing the number of patients. However, as local community transmission without epidemiological associations progressed, the severity of the disease decreased, and the vaccine uptake rate increased, infection prevention and management were abandoned altogether. The trade-off between preventing economic stagnation, achieving a high vaccination rate, and maintaining public health policies has been difficult, but well executed [8]. Nonetheless, the Republic of Korea has seen a globally unprecedented number of new cases. Therefore, ongoing efforts are needed to follow the principles of infection prevention and management even in a surge situation, in order to minimize the occurrence of cluster cases patients and collateral damage.

It is now increasingly believed that the COVID-19 pandemic will soon end; therefore, related budgets and programs are gradually decreasing, which raises concerns that programs may be terminated before the disease is eradicated [9]. We need to create alternatives to avoid making these concerns a reality, such as establishing a self-sufficient healthcare system at the district or regional level that can withstand surges, including tracing and quarantine for close contacts of infected patients at the local level, epidemiological investigations of cluster outbreaks, home-based medical care, primary care, the management of high-risk groups

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and critically ill patients, comprehensive medical care delivery systems, linkage between patient and public health information, collaboration between public health and private laboratories, government call centers, and social care. A comprehensive payment system, such as bundled payment or, capitation, needs to be created to make such a system work, in other word the health insurance payment system needs to be changed. A new model for district health systems should be developed to establish a collaborative system between the public health programs of health centers, metropolitan governments, and the central government and private medical institutions to prevent and treat various diseases. Pilot projects are needed to create this system, taking into account cases of establishing self-sufficient district healthcare systems through cooperation between the public and private sectors, such as the Accountable Care Organization model in the United States and the primary care network in Australia.

Finally, rapid diagnosis, treatment, as well as the scaling-up and roll-out of vaccines, are crucial for preparedness against diseases that pose public health crises. Latecomers to vaccine development have failed to dominate the market. In the future, mRNA vaccines can be used not only for preventing infectious diseases, such as malaria and measles, but also as therapeutic vaccines for chronic diseases; therefore, the market for them will continue to grow. However, although vaccines are a global public good, countries have had to pay significant costs to pharmaceutical companies to obtain additional vaccines beyond their allocated amounts in order to protect their own populations during this pandemic. As a result, low-income countries have failed to obtain enough vaccines to protect their citizens. While Moderna and Pfizer in the United States devoted all their resources to vaccine development and succeeded at "warp" or "light" speed, many countries with insufficient technology, human resources, and production capacity had to rely on imports and global aid, making it difficult to develop alternatives. They will face the same difficulties in the event of a new pandemic (Disease X). The news that the WHO is building regional spoke-hub centers [10] to solve these problems is undoubtedly welcome. Despite the creation of tools such as the COVAX facility, which is one of collaborative initiative between international organizations to respond to COVID-19, access to infectious disease management strategies such as PPE, diagnostics, therapeutics, and vaccines was difficult due to export controls. The importance of research and development cannot be overemphasized. At this point, we must confirm where our country stands in terms of developing and securing strategic resources for the next pandemic and prepare countermeasure. Concrete strategies are being discussed, such as governance reform for inter-ministerial collaboration and coordination, rapid research and development and scaling-up of vaccine production against circulating variants, the revision of regulations related to approval for emergency use, securing budgets for bio-related research and development and market formation, nurturing and developing related human resources, and improving incentives and entry barriers to promote corporate participation. However, there remains a significant gap in the world market for vaccine and therapeutic development.

Notes

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

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References

1. World Health Organization (WHO). Statement on the fourteenth meeting of the International Health Regulations (2005) Emergency Committee regarding the coronavirus disease (COVID-19) pandemic. [Internet]. WHO; 2023 [cited 2023 Feb 22]. Available from: https://www.who.int/news/item/30-01-2023-statement-on-the-fourteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic.
2. Korea Disease Control and Prevention Agency (KDCA). February 22, 2023 news briefing. COVID-19 weekly report [Internet]. KDCA; 2023 [cited 2023 Feb 22]. Available from: https://www.kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=721844&cg_code=&act=view&nPage=2. Korean.
3. U.S. plans to end public health emergency for COVID in May. The New York Times [Internet]. 2023 Feb 3 [cited 2023 Feb 22]. Available from:https://www.nytimes.com/2023/01/30/us/politics/biden-covid-public-health-emergency.html.
4. Jeong NY, Park H, Oh S, et al. A framework for nationwide COVID-19 vaccine safety research in the Republic of Korea: the COVID-19 Vaccine Safety Research Committee. Osong Public Health Res Perspect 2023; 14:5–14.
5. World Health Organization (WHO). Article-by-article compilation of proposed amendments to the International Health Regulations (2005) submitted in accordance with decision WHA75(9) (2022) [Internet]. WHO; 2022 Nov [cited 2023 Feb 23]. Available from: https://apps.who.int/gb/wgihr/pdf_files/wgihr1/WGIHR_Compilation-en.pdf.
6. World Health Organization (WHO). Zero draft of the WHO CA+ for the consideration of the Intergovernmental Negotiating Body at its fourth meeting [Internet]. WHO; 2023 [cited 2023 Feb 23]. Available from: https://apps.who.int/gb/inb/pdf_files/inb4/A_INB4_3-en.pdf.

7. Lee JK, Shin SD, Park MJ. Building a legislative model responding to public health emergencies and disaster. Legislative response to pandemic. Korean Parliamentarian Forum on Global Health; 2020.
8. Cho J, Cho Y, Han C, et al. Pandemic response strategies: lessons from Asia-Pacific and European economies for healthcare sectors in the EBRD regions, October 2022. European Bank for Reconstruction and Development; 2022.
9. Castro KG, LoBue P. Bridging implementation, knowledge, and ambition gaps to eliminate tuberculosis in the United States and globally. Emerg Infect Dis 2011;17:337–42.
10. World Health Organization (WHO). The mRNA vaccine technology transfer hub [Internet]. WHO; 2021 Jun 21 [cited 2023 Feb 23]. Available from: https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub.

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Special Article

A framework for nationwide COVID-19 vaccine safety research in the Republic of Korea: the COVID-19 Vaccine Safety Research Committee

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ABSTRACT

With the introduction of coronavirus disease 2019 (COVID-19) vaccines, the Korea Disease Control and Prevention Agency (KDCA) commissioned the National Academy of Medicine of Korea to gather experts to independently assess post-vaccination adverse events. Accordingly, the COVID-19 Vaccine Safety Research Committee (CoVaSC) was launched in November 2021 to perform safety studies and establish evidence for policy guidance. The CoVaSC established 3 committees for epidemiology, clinical research, and communication. The CoVaSC mainly utilizes pseudonymized data linking KDCA's COVID-19 vaccination data and the National Health Insurance Service's claims data. The CoVaSC's 5-step research process involves defining the target diseases and organizing *ad-hoc* committees, developing research protocols, performing analyses, assessing causal relationships, and announcing research findings and utilizing them to guide compensation policies. As of 2022, the CoVaSC completed this research process for 15 adverse events. The CoVaSC launched the COVID-19 Vaccine Safety Research Center in September 2022 and has been reorganized into 4 divisions to promote research including international collaborative studies, long-/short-term follow-up studies, and education programs. Through these enhancements, the CoVaSC will continue to swiftly provide scientific evidence for COVID-19 vaccine research and compensation and may serve as a model for preparing for future epidemics of new diseases.

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

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Introduction

With the protracted coronavirus disease 2019 (COVID-19) crisis that began in December 2019, vaccines were hailed as a key to emerging from the pandemic and returning to normalcy. Through enormous efforts, vaccines were developed and approved in record time and quickly rolled out to the global population. However, the unprecedented speed of development and emergency use authorization, as well as the fact that some of the newly developed COVID-19 vaccines were based on innovative and unfamiliar platforms, raised safety concerns among experts and the general public. In Korea, COVID-19 vaccines were first introduced in late February 2021. Currently, Korea has one of the highest vaccination rates in the world, with 87.1% of the entire population being fully vaccinated (as of November 18, 2022).

Korea carries out vaccine safety monitoring through passive and active surveillance. For passive surveillance, safety data based on vaccine adverse events (AEs) reported by healthcare professionals, vaccinated individuals, and vaccine manufacturers are collected and analyzed, whereas active surveillance utilizes big data such as the vaccination registry, health insurance claims, and electronic medical records (EMRs) to proactively investigate selected population groups for the pre-emptive monitoring of AE cases [1,2].

In the United States (US), the Vaccine Adverse Event Report System serves as a passive vaccine surveillance system that is jointly operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [3]. For active surveillance, V-Safe, a mobile phone-based system that collects individual AE reports, is operated by the CDC [4]. Once cases are collected, an EMR-based monitoring system called Vaccine Safety Datalink enables each participating site to prepare computerized data files by utilizing a standardized data dictionary for active monitoring [5,6]. The US FDA also established an active surveillance system called the Biologics Effectiveness and Safety System under the umbrella of the Center for Biologics Evaluation and Research. The FDA has used large-scale health insurance claims data and electronic health records to build a protocol for assessing the safety and effectiveness of COVID-19 vaccines [7,8].

The European Medicines Agency has a passive surveillance system called EudraVigilance [9], which collects and analyzes individual cases of suspected AEs after vaccination. For active surveillance, it relies on the Vaccine Monitoring Collaboration for Europe (VAC4EU) [10]. The United Kingdom operates its own existing program, called the Yellow Card Scheme, to collect suspected AEs in relation to drugs, vaccines, and medical devices. For COVID-19 vaccine monitoring, they have added the Coronavirus Yellow Card, a dedicated system for reporting only COVID-19-related vaccine side effects [11,12].

In Korea, since the rollout of the COVID-19 vaccine program, the Korea Disease Control and Prevention Agency (KDCA) has classified AEs into non-serious and serious cases for analysis based on patients' status at the time of reporting. The results are disclosed on its website every week. In addition, Korea operates the national COVID-19 Vaccine Injury Compensation System for AEs that occur after vaccination. While reviewing requests for compensation, the KDCA saw a growing need to establish safety evidence, focusing on the domestic population. As the demand to generate evidence for vaccine surveillance intensified, the KDCA commissioned the National Academy of Medicine of Korea (NAMOK) to gather experts from medical, pharmaceutical, and healthcare sectors and independently assess the relationship between AEs and COVID-19 vaccines. As a result, the COVID-19 Vaccine Safety Research Committee (CoVaSC) was launched on November 12, 2021 to perform a wide range of COVID-19 vaccine safety studies assessing the relationship between AEs and vaccines in order to establish evidence for policy guidance.

Against the backdrop, this paper intends to provide a brief explanation of the CoVaSC, including its organizational structure, activities, major research processes, and findings.

Materials and Methods

Establishment of Committees

Under the leadership of committee president and assistant administrator, the CoVaSC established 3 committees for epidemiology, clinical research, and communication, as well as 13 sub-committees (Figure 1). The Epidemiology Committee uses COVID-19 vaccine AE reports to monitor and detect safety signals. It also utilizes linked KDCA–National Health Insurance Service (NHIS) data to establish research plans, conduct statistical analyses of the association between COVID-19 vaccines and AEs, and perform observed-to-expected ratio analysis for each target disease. The Clinical Research Committee is in charge of developing operational definitions, creating research protocols together with the Epidemiology Committee, and conducting literature reviews on target diseases and causality assessments based on the results of relationship analyses. The Clinical Research Committee has brought clinical experts on board to form *ad-hoc* committees for diverse diseases and take the lead in research activities. The Communication Committee develops strategies for communication with healthcare professionals and the public. It also creates press releases and organizes forums to release CoVaSC research findings. A total of 22 members have contributed to CoVaSC research, together

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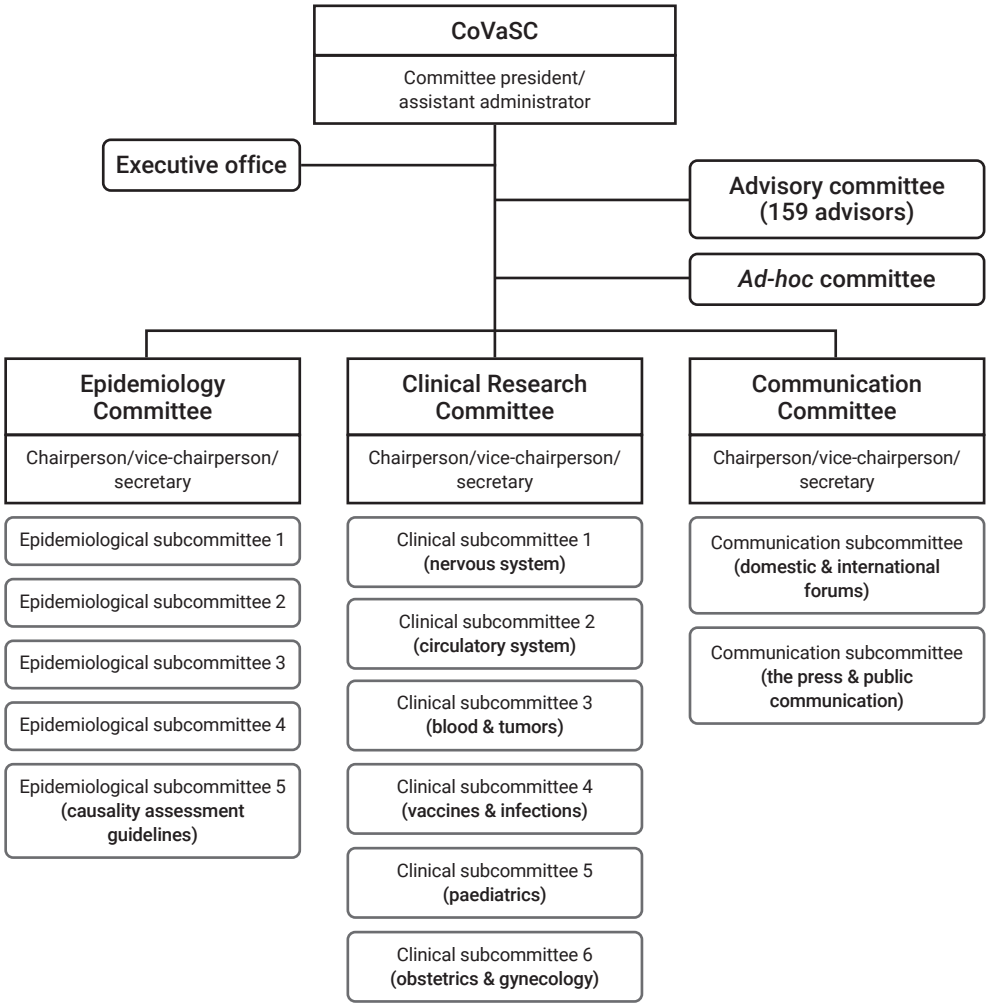

Figure 1. Organizational chart of the COVID-19 Vaccine Safety Research Committee (CoVaSC).

with 159 experts in advisory groups.

Scopes and Topics of Research

The CoVaSC has a broad set of roles, including basic surveys, research plan development, data analysis, and reporting (Figure 2). To ensure the transparent sharing of research outcomes with healthcare professionals and the general public, it organizes forums and briefings. The major contents of CoVaSC research include (1) domestic and international trends in causality assessment and the results of literature reviews, (2) monitoring of AE reports and signal detection, (3) statistical analysis of domestic data related to COVID-19 vaccines, (4) causality assessment between COVID-19 vaccination and AEs, and (5) communication with healthcare professionals and the public through regular forums. Promoting close cooperation with the KDCA and NHIS is crucial for the success of CoVaSC research since those 2 organizations are major resources for research data. The KDCA, for example, provides access to its vaccination database, which encompasses healthcare personnel's reports on AEs in relation to COVID-19 vaccines and COVID-19 vaccination records of the entire population in Korea. The NHIS has an enormous database of health insurance claims, which are generated when healthcare facilities claim insurance reimbursements for medical services that they provide to patients, which covers the entire Korean population of about 51 million. The NHIS links its database with that of the KDCA and provides a data analysis room for researchers to use. The CoVaSC, KDCA, and NHIS hold regular monthly meetings to share their research findings and foster collaboration.

Sources of Research Data

KDCA vaccination data and AE reports

Since the launch of the COVID-19 vaccine program in Korea on February 26, 2021, the KDCA has collected vaccination

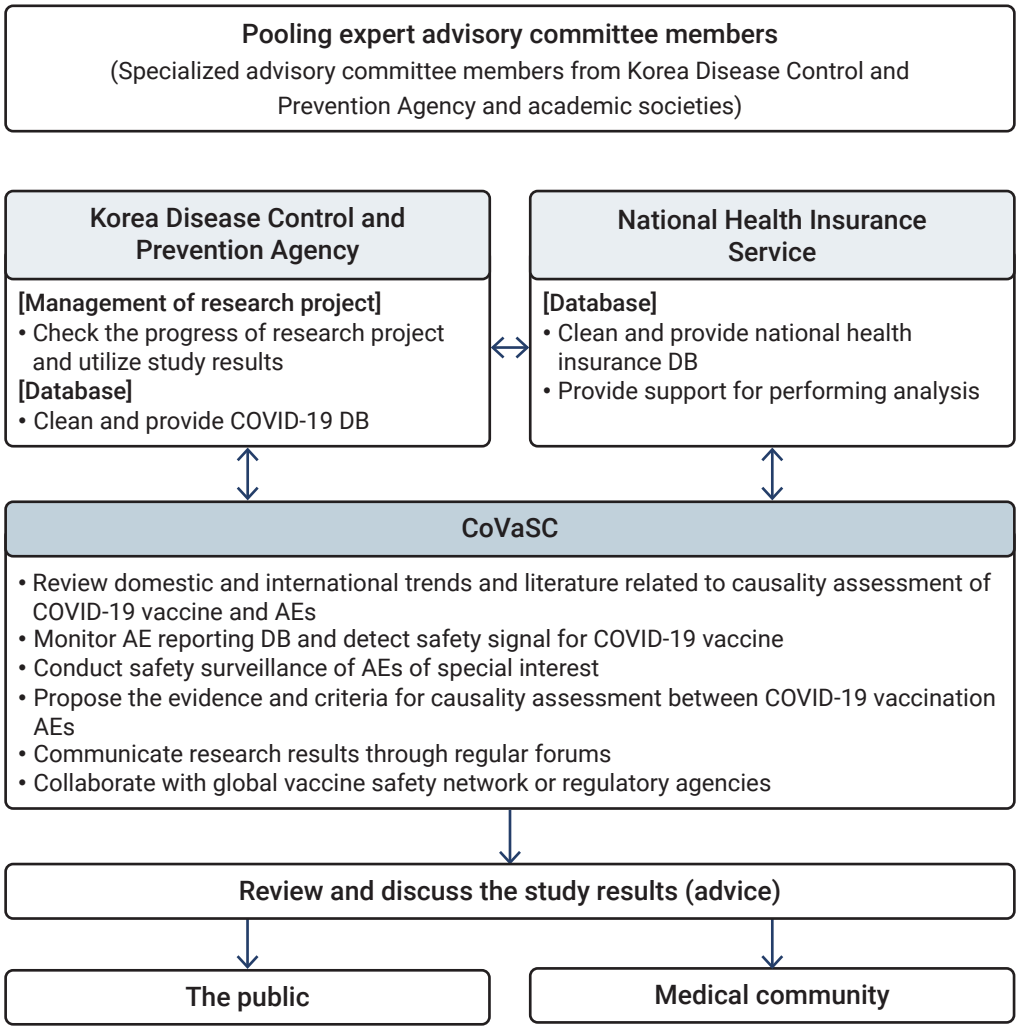

Figure 2. Roles of participating agencies and summary of research topics.
DB, database; CoVaSC, COVID-19 Vaccine Safety Research Committee; AE, adverse event.

data from the entire population, and details of adverse reactions have been reported by healthcare clinics and medical institutions in accordance with the Infectious Disease Control and Prevention Act. In addition, in June 2000, Korea started to register immunization records electronically under the National Immunization Program (NIP), and since 2002, all the immunization records at local healthcare centers and private clinics have been kept in the KDCA's electronic system [13]. The records of COVID-19 vaccines are managed separately from the NIP, and various information, including the vaccination date, vaccine dose, and type of vaccine, is electronically stored. Regarding AE reports, information on the types of AEs, date of onset, and diagnosis and prognosis are collected. These data enable potential safety signals to be detected early and cost-efficiently through AE monitoring.

NHIS claims data

Since Korea has a health insurance system with universal coverage, all medical services provided to the public are linked with insurance claims data. After providing medical services, healthcare institutions make claims for service fees to the NHIS (the insurer), and insurance claims data are generated in the process. As NHIS manages enrolled and insured individuals and pays costs based on the billing records, its database has accumulated a vast array of data, including insurance eligibility, medical services and prescription records, details of health screening, and information on healthcare institutions [14]. The NHIS claims database provides information on the medical services that have been offered due to AEs after COVID-19 vaccination.

The CoVaSC received pseudonymized data that connected KDCA's COVID-19 vaccination data and NHIS's database. The CoVaSC researchers could access the database to perform

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analyses at NHIS's data analysis center. The data were periodically updated during the research period to keep abreast with the latest trends.

Research Process

Figure 3 shows a general overview of CoVaSC's research process.

Defining target diseases and forming an *ad-hoc* committee for each disease

In consultation with the KDCA, the CoVaSC first created a list of adverse events of special interest (AESIs), for which safety issues have been raised in relation to COVID-19 vaccines. In order to set priorities for causality analysis, the CoVaSC conducted a survey in December 2021 to weigh epidemiological and clinical significance and public interest among different research candidates. For hematologic disorders, the incidence rate per 100,000 was first calculated for each disease to identify disorders with an observed occurrence that is significantly higher than expected. Table 1 shows the final priority list of diseases for causality assessment.

After defining the target diseases, an *ad-hoc* committee was established for each target disease, which comprised clinical and epidemiological specialists in the target disease. After finalizing the target diseases, a kick-off meeting of each relevant *ad-hoc* committee was held to discuss research plans for causality evaluation between the vaccine and the target disease.

Developing study protocols

Prior to the official start of the research, protocols were written, revised, and reviewed for each target disease. These research protocols described the purpose, duration, and subjects of research, exposure information, the operational definition of the target disease, study design, and statistical analysis methods. Clinicians from each *ad-hoc* committee devised an operational definition of the related disease by applying diagnosis codes based on the International Classification of Diseases, 10th Revision, procedure/surgery codes, and criteria to exclude underlying diseases. The protocols were first drafted by epidemiologists and then reviewed by the clinicians in the relevant *ad-hoc* committees for revision and finalization.

Performing data analysis

Since the CoVaSC relies on a huge amount of data, such as COVID-19 vaccination records, insurance claims data, and AE reports of the entire Korean population, all the missing values and outliers have to be dealt with to extract clean data for the analysis dataset. For example, there were cases where 1 of the 2 vaccination records was missing for fully vaccinated people, or the same vaccination was recorded redundantly, which should have been excluded. Once the data mining process was completed, demographics and vaccination status were reviewed for a technical analysis, and the associations between AEs and COVID-19 vaccines were investigated.

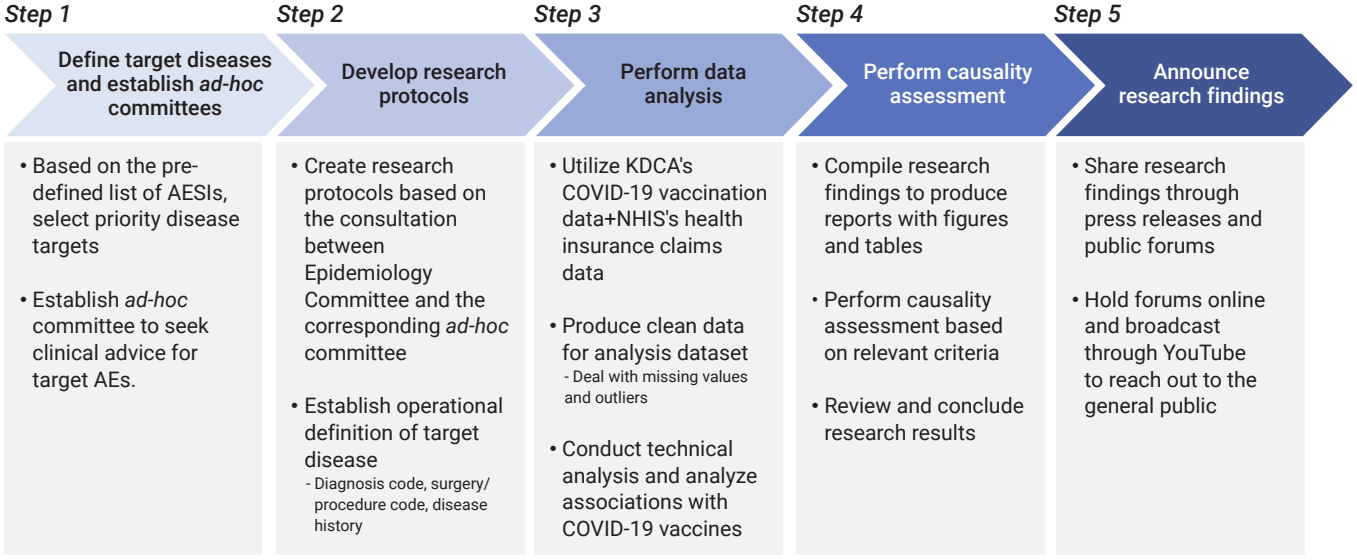

Figure 3. Overview of the COVID-19 Vaccine Safety Research Committee research process.
AESI, adverse event of special interest; AE, adverse event; KDCA, Korea Disease Control and Prevention Agency; NHIS, National Health Insurance Service.

Table 1. Summary of COVID-19 Vaccine Safety Research Committee adverse events of special interest and schedule of announcements of research results

Category	Adverse events of special interest	Schedule for announcement of results
Death	All-cause death	2nd Forum (March 4, 2022)
Cardio-cerebrovascular diseases	Myocarditis	2nd Forum (March 4, 2022)
	Pericarditis	2nd Forum (March 4, 2022), 3rd Forum (May 21, 2022)
	Stroke	2nd Forum (March 4, 2022)
	Acute myocardial infarction	2nd Forum (March 4, 2022)
	Heart failure	3rd Forum (May 21, 2022)
	Aortic dissection	3rd Forum (May 21, 2022)
Neurological diseases	Acute transverse myelitis	3rd Forum (May 21, 2022)
	Acute disseminated encephalomyelitis	3rd Forum (May 21, 2022)
	Guillain-Barré syndrome	3rd Forum (May 21, 2022)
	Miller-Fisher syndrome	3rd Forum (May 21, 2022)
Obstetric diseases	Abnormal uterine bleeding	4th Forum (August 11, 2022)
Hematologic diseases	Deep vein thrombosis	4th Forum (August 11, 2022)
	Pulmonary embolism	4th Forum (August 11, 2022)
	Cerebral venous sinus thrombosis	4th Forum (August 11, 2022)

Discussing study results and assessing causal relationships

After analyses were completed, study reports were created, including tables and figures to reveal any associations that were found. To perform causality assessments between COVID-19 vaccines and AEs, CoVaSC referred to the Committee of US Surgeon General Criteria [15] and the Bradford-Hill Criteria [16], the 2 globally recognized criteria for causality investigations. The *ad-hoc* committee of the relevant disease then compiled the analysis results, as well as evidence from Korea and abroad, for a comprehensive review. After a discussion among the *ad-hoc* committee members, the final decision was made on whether the case fulfilled the causality criteria.

Announcing research findings

The CoVaSC created press releases and held forums to share its research outcomes with healthcare professionals and the general public. Epidemiologists on the Epidemiology Committee announced the results of epidemiological studies, and clinicians on the Clinical Research Committee shared the results of causality assessments. The CoVaSC held 4 forums by the end of 2022. The first forum briefly explained the purpose and methodology of its research, and the other 3 were held to share research findings. The first forum was held on November 26, 2021 to introduce the CoVaSC, its methodology for epidemiological research, and the criteria that would be used for causality assessment. During the second forum on March 4, 2022, the results of safety monitoring and causality assessments between COVID-19 vaccination and AEs were announced, focusing on death, myocarditis/pericarditis, acute myocardial infarction, and stroke. In the subsequent third forum on May 12, the study findings regarding Guillain-Barré Syndrome, Miller-Fisher Syndrome, heart failure, aortic dissection, acute transverse myelitis (ATM), and acute disseminated encephalomyelitis were released. The fourth and final forum on August 11 showed the results of causality assessments for thrombosis-related diseases, such as deep vein thrombosis, cerebral venous sinus thrombosis and abnormal uterine bleeding (AUB), and presented the causality assessment guidelines for COVID-19 vaccine safety studies. The forums were conducted online and broadcast through YouTube to reach the broader public.

Major Research Methodologies

Detecting signals from AE reports

To detect signals of vaccine-related adverse reactions based on the monitoring of AE reports, the research used 2 well-known disproportionality analysis indices for data mining: (1) the proportional reporting ratio (PRR) and (2) reporting odds ratio (ROR). The PRR is calculated by dividing the percentage of a specific AE of a specific COVID-19 vaccine versus the percentage of the same AE from a different COVID-19 vaccine, whereas the ROR is calculated by dividing the odds of AE caused by a specific COVID-19 vaccine by the odds of AE from a different vaccine. Using these 2 indices, the committee explored different combinations of vaccines and AEs to identify adverse reactions that were more frequent than the pre-defined values. Then they observed them as signals to identify statistical associations between a particular AE and a particular COVID-19 vaccine.

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Observed-to-expected ratio analysis

For the diseases selected for the association analysis, an observed-to-expected ratio analysis was performed that referred to the pre-COVID occurrence rate to predict the expected occurrence rate after the vaccination against COVID-19. On this basis, the difference between the expected and the observed incidence rates was evaluated. For this study, the monthly incidence rate of each target disease was calculated for 10 years before the COVID-19 vaccination program. The prediction model was produced based on the observed incidence rate using an auto-regressive integrated moving average (ARIMA) model. A seasonal ARIMA model was applied in order to reflect changes in demographics and medical behaviors over time. If the observed value deviated beyond the 95% confidence interval of the predicted value, Poisson regression was conducted.

Cohort study

A cohort study was designed to compare the incidence rate of relevant AEs between the groups with and without vaccine exposure. The incidence rate and the relative and absolute risk rates of relevant AEs were assessed within the follow-up period in the exposed and the non-exposed groups. Although selecting the most appropriate comparator is critically important for cohort studies, it was a herculean task to define the non-exposure group for COVID-19 vaccines due to the overwhelmingly high vaccination rate. Therefore, the research used people who had received influenza shots, for example, as an active control group or people with the same demographic profile and comorbidity index score as a historical control group to analyze outcome variables, particularly death.

Self-controlled study

If the process of selecting subjects is likely to trigger high selection bias, a self-controlled study design can be applied, which sets an individual patient as a control against himself or herself to address time-invariant confounders. In vaccine safety research, self-controlled case series (SCCS) and self-controlled risk interval (SCRI) designs are mainly used as self-controlled studies. An SCCS is an epidemiological study design that uses patients who experienced the outcome variables during the observation period to specify the risk window during which each individual is potentially at a higher risk of developing AEs. The remaining non-risk period is set as the control window to compare the AE incidence rate between the risk window and the control window [17,18], whereas an SCRI investigates people who have been vaccinated to compare the AE incidence rate between the pre-defined risk period and the control period before or after vaccination [19]. A major difference between the 2 research designs is that an SCCS defines research subjects based on the occurrence of the outcome variables. After specifying the risk window, it defines the rest of the entire research period as the control window. However, an SCRI analyzes people who have been vaccinated and sets a certain period as the control window; therefore, the observation span of an SCRI is shorter than that of an SCCS.

Results

The CoVaSC analyzed the association of AEs likely to occur after COVID-19 vaccination based on the monitoring of AE reports. For AE report monitoring, the committee studied various subgroups defined according to age, sex, and vaccine to describe the status and trend of reporting. It also explored AE signals for different types of COVID-19 vaccines. The CoVaSC conducted diverse analyses on 15 different AEs to estimate their relationship with COVID-19 vaccines (Table 2).

Among the diseases where statistical associations were found, myocarditis, pericarditis, and AUB furnished evidence to guide policies. On March 4, 2022, myocarditis was announced to have an association with COVID-19 vaccines. Accordingly, the COVID-19 Vaccine Injury Compensation Committee acknowledged a causal relationship between myocarditis and the mRNA vaccine and applied the decision retroactively. This decision opened the door for those whose previous compensation requests were rejected on the ground of insufficient evidence to receive compensation with no strings attached. For pericarditis not accompanied by myocarditis, based on the finding released on May 12, 2022, the decision was reverted from "inadequate" to "adequate" evidence for its causality with COVID-19 vaccines. This decision also applied retroactively, but with the condition that those who had yet to apply for compensation should submit an application. As of August 16, 2022, AUB was added to the list of diseases with a suspected association (but with insufficient evidence for causality) after releasing relevant research results.

Discussion

Since Korea introduced the COVID-19 vaccination program without having a monitoring and surveillance system in place, the CoVaSC was established in 2021 to conduct scientific safety assessments of adverse reactions to COVID-19 vaccines based on the available domestic data. As such, the CoVaSC has carried out a diverse range of research, and its research findings have contributed to policy-making and scientific studies. Fifteen diseases were investigated for

Table 2. Summary of COVID-19 Vaccine Safety Research Committee COVID-19 vaccine safety studies

Adverse events	Study results (statistical significance)	Utilization of research findings
All-cause death	Not significant	Not applicable
Myocarditis	Significantly increased risk (only mRNA vaccines)	Acknowledged the causality of myocarditis that occurred after mRNA vaccination
Pericarditis	Significantly increased risk (only mRNA vaccines)	Acknowledged the causality of pericarditis that occurred after mRNA vaccination
Stroke	Not significant	Not applicable
Acute myocardial infarction	Not significant	Not applicable
Acute transverse myelitis	Significantly increased risk	Decided to perform a reanalysis
Acute disseminated encephalomyelitis	Not significant	Decided to perform a reanalysis
Heart failure	Not significant	Not applicable
Aortic dissection	Not significant	Not applicable
Abnormal uterine bleeding	Significantly increased risk	Added to the list of reportable adverse events following COVID-19 vaccination
Deep vein thrombosis	Significantly increased risk (only BNT162b2 mRNA vaccines)	Decided to perform a reanalysis
Pulmonary embolism	Significantly increased risk (only BNT162b2 mRNA vaccines)	Decided to perform a reanalysis
Cerebral venous sinus thrombosis	Significantly increased risk	Identified the need to ensure the validity of diagnosis through electronic medical records research
Guillain-Barré syndrome	Not significant	Decided to perform a reanalysis
Miller-Fisher syndrome	Not significant	Decided to perform a reanalysis

their associations with COVID-19 vaccines. Victims of AEs for which the CoVaSC suggested potential causality received compensation, and some AEs were added to the list of diseases with a potential association with COVID-19 vaccines. However, due to the limitations of the available data at the time of the initial research, the analyses of some diseases, such as ATM and deep vein thrombosis, were postponed.

Various factors have enabled such large-scale, comprehensive research. First, databases played a significant role. The availability of population-wide data, including vaccination records and medical use data, provided a significant boost to the CoVaSC. The KDCA-NHIS linked data offered a rich source of information to conduct association studies. The data have been constantly updated to stay relevant and up-to-date, thanks to well-established governance and close collaboration between the KDCA and the NHIS.

Second, the participation of experts from various fields warrants mention. AESIs are very diverse, requiring input from clinical experts in various specialties along with experts in epidemiology, healthcare, and statistics. Therefore, the CoVaSC established Epidemiology, Clinical Research, and Communication Committees and efficiently assigned them different roles. In addition, professional advisory groups and *ad-hoc* committees for different target diseases were formed in order to ensure efficient and highly coordinated research. By assigning experts to the right place while promoting collaboration, the CoVaSC was able to produce solid research results in a relatively short period of time.

Still, there is room for improvement. It is undeniably true that AE reports, vaccination data, and health insurance claims data provide a valuable source of information, yet they have the potential to trigger bias. AE reports are about suspected, not confirmed cases; therefore, they must be linked with clinical data such as EMRs to cross-check whether the diagnosis is correct and appropriate. For insurance claims data, clinical experts devised operational definitions to estimate statistical associations, but often without a full understanding of the actual patients who experienced these conditions. For example, a large number of victims complaining of chest pain were diagnosed with pericarditis, but this diagnosis later turned out to be incorrect, which exaggerated the number of pericarditis occurrences and caused difficulty in accurately estimating the rate.

Furthermore, the process of submitting, reviewing, and paying out of health insurance claims caused a time lag in the data, which may compromise the accuracy of real-time analysis. In order to overcome these issues, the CoVaSC plans to develop methods of improving diagnostic accuracy, such as conducting EMR reviews for diseases with extremely low occurrence rates or with low diagnostic accuracy. In addition, for diseases with high clinical significance but low incidence, it plans to establish a network of hospitals to promote joint, collaborative research.

The CoVaSC launched COVID-19 Vaccine Safety Research

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Center in September 2022 and reshuffled the organization from the previous 3-committee system to a 4-division structure, which includes the following divisions: (1) Epidemiological Research, (2) Clinical Research, (3) Communication and Education, and (4) International Cooperation. Under these 4 divisions, there are 7 teams for epidemiological research, 7 teams for clinical research, 1 team each for communication and education, and 1 international cooperation team. Building on existing AE monitoring and causality assessment, the CoVaSC plans to carry out diverse research with the newly established COVID-19 Vaccine Safety Research Center, including international studies, long-/short-term follow-up studies, the construction of a nationwide hospital research network, and educational programs. In particular, with the enactment of the Public Notice on the Designation of the Assigned Agencies to Perform COVID-19 Vaccine Safety Researches & Investigations on November 4, 2022, the commissioner of the KDCA requested the NAMOK to engage in COVID-19 vaccine safety studies and surveillance research, which provides a solid foundation to operate the COVID-19 Vaccine Safety Research Center.

To further improvement of the causality assessment, the CoVaSC applied reports and frameworks from the National Academy of Medicine of the US. Based on this experience, it decided to use both epidemiological and mechanistic approaches for future studies to draw conclusions on the associations between AEs and COVID-19 vaccines. To promote international research, the CoVaSC has arranged several international conferences and webinars with the US CDC, the National Center for Immunization Research and Surveillance from Australia, and the World Health Organization to have concrete discussions on study designs and statistical analysis methods. Starting from its collaboration with the Global Vaccine Data Network, the CoVaSC has pursued broader opportunities to work together with other international institutions to perform joint research on the safety assessment of COVID-19 vaccines. In addition, for diseases difficult to analyze with insurance claims data (for instance, if a disease is not reimbursable or patients rarely visit hospitals for the disease), the CoVaSC plans to develop tools to conduct surveys for short- and long-term follow-up. It will also launch an educational training program for clinicians and the general public to deepen their understanding of terminology and causality assessment methodologies in order to lay the groundwork for effective communication to share research results in the future.

Conclusion

The CoVaSC will continue to serve as an organization that swiftly provides scientific evidence for COVID-19 vaccine surveillance. As time passes, its safety database and evidence will constitute essential sources of information to guide policies and help us tackle public healthcare crises in the future. The CoVaSC's governance and research processes can also serve as a reference for future research projects.

Notes

Ethics Approval

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

Conflicts of Interest

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

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Availability of Data

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

Authors' Contributions

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

References

1. Choi NK, Lee J, Park BJ. Recent international initiatives of drug safety management. J Korean Med Assoc 2012;55:819–26. Korean.
2. World Health Organization (WHO). COVID-19 vaccines: safety surveillance manual, 2nd ed [Internet]. WHO; 2021 [cited 2022 Nov 15]. Available from: https://apps.who.int/iris/handle/10665/345178.
3. Shimabukuro TT, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2015; 33:4398–405.
4. Centers for Disease Control and Prevention (CDC). V-safe after vaccination health checker for COVID-19 vaccine [Internet]. CDC; 2022 [cited 2022 Nov 15]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html.
5. Chen RT, Glasser JW, Rhodes PH, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. The Vaccine Safety Datalink Team. Pediatrics 1997;99:765–73.
6. Centers for Disease Control and Prevention (CDC). Vaccine safety datalink (VSD) [Internet]. CDC; 2022 [cited 2022 Nov 15]. Available from: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/

vsd/index.html.
7. U. S. Food and Drug Administration. CBER biologics effectiveness and safety (BEST) system [Internet]. U. S. Food and Drug Administration; 2022 [cited 2022 Nov 15]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
8. U. S. Food and Drug Administration. COVID-19 vaccine safety surveillance [Internet]. U. S. Food and Drug Administration; 2021 [cited 2022 Nov 15]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance.
9. European Medicines Agency. EudraVigilance: European database of suspected adverse drug reaction reports [Internet]. European Medicines Agency; 2022 [cited 2022 Nov 15]. Available from: http://www.adrreports.eu/en/background.html.
10. VAccine monitoring Collaboration for Europe. About VAC4EU [Internet]. Vaccine monitoring Collaboration for Europe; 2022 [cited 2022 Nov 15]. Available from: https://vac4eu.org/about/.
11. GOV.UK. Research and analysis: report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance [Internet]. GOV.UK; 2021 [cited 2022 Nov 15]. Available from: https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance.
12. Medicines and Healthcare products Regulatory Agency. Coronavirus Yellow Card reporting site [Internet]. Medicines and Healthcare products Regulatory Agency; 2022 [cited 2022 Nov 15]. Available from: https://coronavirus-yellowcard.mhra.gov.uk/.
13. Kim CS, Park O, Kim MY, et al. A study on registration data analysis of national immunization registry information system. J Korea Inst Inf Commun Eng 2015;19:1151–6. Korean.
14. Seong SC, Kim YY, Khang YH, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799–800.
15. United States Surgeon General's Advisory Committee on Smoking and Health. Smoking and health: report of the advisory committee to the surgeon general of the public health service. U. S. Department of Health, Education, and Welfare; 1964.
16. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
17. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;25:1768–97.
18. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ 2016;354:i4515.
19. Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. Am J Epidemiol 2015;181:608–18.

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Original Article

The first reported hepatitis E outbreak in a food manufacturing factory: Korea, 2022

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ABSTRACT

Objectives: On February 16, 2022, 12 cases of hepatitis E virus (HEV) infection were reported in a food manufacturing factory in Korea. The aim of this study was to identify additional cases and to determine the source of this HEV outbreak.

Methods: This study was an in-depth investigation of 12 HEV immunoglobulin M (IgM)-positive cases and their demographic, clinical, and epidemiological characteristics. On-site specimens were collected from the environment and from humans, and a follow-up investigation was conducted 2 to 3 months after the outbreak.

Results: Among 80 production workers in the factory, 12 (15.0%) had acute HEV infection, all of whom were asymptomatic. The follow-up investigation showed that 3 cases were HEV IgM-positive, while 6 were HEV IgG-positive. HEV genes were not detected in the HEV IgM-positive specimens. HEV genes were not detected in the food products or environmental specimens collected on-site. HEV was presumed to be the causative pathogen. However, it could not be confirmed that the source of infection was common consumption inside the factory.

Conclusion: This was the first domestic case of an HEV infection outbreak in a food manufacturing factory in Korea. Our results provide information for the future control of outbreaks and for the preparation of measures to prevent domestic outbreaks of HEV infection.

Keywords: Asymptomatic infections; Diseases outbreaks; Hepatitis E; Korea

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Introduction

Hepatitis E is an acute viral infection caused by the hepatitis E virus (HEV) [1]. According to the World Health Organization, 20 million cases of hepatitis E are reported annually, of which 3.3 million (16.5%) are symptomatic. In 2015, 44,000 people died from hepatitis E [2].

The incubation period of hepatitis E is 15 to 64 days (average, 40 days) [3]. Hepatitis E is a waterborne and foodborne disease orally transmitted through the consumption of contaminated water or food. The signs and symptoms include fever, fatigue, vomiting, stomachache, jaundice, and dark brown urine. Although these symptoms are like those of hepatitis A, most cases of hepatitis E are asymptomatic. Hepatitis E can progress to chronic infection in immunocompromised patients [1,4].

HEV has 8 genotypes, 4 (1–4) of which are reported in humans [5]. HEV genotypes 1 and 2 are mostly found in Asian and African countries with poor sanitation and are transmitted through the fecal-to-oral route, often in large-scale waterborne outbreaks. HEV genotypes 3 and 4 cause zoonotic infection between humans and animals, mainly boars, pigs, and deer. Sporadic cases of infection through the consumption of contaminated foods have been reported in Europe, North America, parts of Asia (Japan, Taiwan), Australia, and New Zealand [4,6]. HEV genotype 7 has been reported in people who consume meat and milk derived from camels [7].

Sporadic outbreaks of hepatitis E from the consumption of undercooked meat and processed meat products have been reported in the developed countries of Europe and Japan [4,8]. Domestic cases of hepatitis E have been reported from the consumption of boar bile and raw roe deer meat [9–11]. As a result, interest in hepatitis E has expanded, and hepatitis E was designated a class 2 notifiable infectious disease with commencement of a mandatory surveillance system on July 1, 2020. According to statistics on infectious diseases by the Korea Disease Control and Prevention Agency (KDCA), approximately 500 cases a year are reported. However, when compared to hepatitis A, B, and C, awareness of hepatitis E is relatively low among healthcare workers and the public in Korea. Studies on hepatitis E are lacking in Korea, which is a non-epidemic area of acute hepatitis E [12].

On February 16, 2022, an outbreak of hepatitis E was reported in a food manufacturing factory in Korea during a routine health examination of workers. As this was the first reported domestic outbreak of hepatitis E, the KDCA examined the incidence and cause of the outbreak in the factory and initiated an epidemiological investigation to establish preventive measures.

Materials and Methods

Study Background and Settings

The site of the outbreak was a food manufacturing factory that produced food by mixing, charging, drying, and packing. Among the 162 employees, 80 were production workers. The processing system in the factory was automated and all operations were sealed. There was no process in which employees had direct contact with the raw materials and products. The production workers worked in 3 shifts (day, evening, and night), and there was a cafeteria used by all employees in the factory. According to the requirements of importing countries, the production workers underwent annual health examinations with a surveillance checklist that included bacillary dysentery, hepatitis A, and hepatitis E. On February 16, 2022, the routine on-site health examination of 80 production workers showed 12 cases of hepatitis E infection.

Considering that the cases were clustered in one factory during a single time period, and that the number of cases was higher than the usual occurrence reported in the province where the factory was located (4 cases annually), we identified this cluster as an HEV outbreak within the factory.

Epidemiological Investigation

Case definition

According to the diagnostic criteria for hepatitis E, we defined cases as those who tested positive for HEV immunoglobulin M (IgM) among the production workers who worked and underwent routine health examinations in the factory from December 14, 2021 to February 16, 2022. As all cases were asymptomatic, diagnostic test results were substituted for symptoms.

Study design

The cases were detected through routine health examinations and not based on the manifestation of symptoms after consumption of a particular food item. Therefore, the source of common exposure was unclear. The long incubation period of acute hepatitis E (15–64 days) hindered the application of cohort or case-control studies. Therefore, a case series study was conducted involving the production workers who met the case definition.

Case investigation

Basic case information was obtained using an epidemiologic report form. An in-depth epidemiological investigation was conducted through phone calls. Demographic information

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was collected including sex, age, and residence, as well as epidemiological characteristics including signs and symptoms; history of underlying disease; history of HEV infection; travel history; history of animal contact; history of contact with HEV-infected patients; history of blood donation, blood transfusion, or organ donation; and history of food consumption during the risk exposure period (15–64 days) and the incubation period for index patients (December 14, 2021 to February 1, 2022). Clinical characteristics were obtained, including HEV test results and alanine transaminase and aspartate transaminase measurements. The history of hospital visits during the estimated exposure period was obtained from the drug utilization review (DUR) data of the Health Insurance Review & Assessment Service. Record reviews were used, since all HEV-positive cases were reportedly asymptomatic.

Environmental Investigation

Investigation of the cafeteria and food items

Considering that more than 1 month had passed since the diagnosis of the cases, and that all the cases used the same cafeteria in the factory, the investigation focused more on the cafeteria and food items than on the worksite or environment. The Food Sanitation Act mandates the preservation of food for 144 hours after provision. Since the preserved foods from the risk exposure period were not available, the most recent preserved foods were collected.

The consumption history of meat and processed meat products from the list of food items provided at the cafeteria was analyzed in addition to the in-depth epidemiological investigation. The consumption history of raw meat, processed meat products, animal liver/intestine, and frozen fruits was examined. Furthermore, the kitchen and cooking environment, method of food preservation and distribution, and supply of food ingredients were investigated by interviewing kitchen employees. Since the IgM-positive HEV infection had occurred in the past, recent changes in suppliers of food ingredients, kitchen workers, and the cooking environment were also investigated.

Investigation of the worksite and environment

Environmental specimens were collected from workroom handles, manufactured products, and water that the cases could have been in contact with while working.

Laboratory Testing

Anti-HEV IgM was tested in the positive plasma samples using an abia HEV IgM enzyme linked immunosorbent assay kit (AB Diagnostic Systems GmbH) according to the manufacturer's manual. Anti-HEV IgM-positive samples were tested for HEV RNA using the PowerChek HEV virus qRT-PCR kit (KogeneBiotech Co.). Primers and probes were designed based on multiple sequence alignment of the HEV genome sequences in the open reading frame 2/3 region. Environmental samples were taken from within the facility, and HEV RNA quantitative reverse transcription polymerase chain reaction (qRT-PCR) tests were performed. Environmental tests were conducted on water purifiers, doorknobs, telephones, manufactured products in the workplace, kitchen tools in the cafeteria, and preserved foods.

Follow-up Investigation

To monitor the onset of additional cases and determine the continuation of the outbreak, a follow-up was conducted in April 2022, 2 to 3 months after the outbreak was detected, by screening for HEV IgM, HEV IgG, and HEV genes.

Data Analysis

Descriptive statistics (presented as frequencies and percentages) were used to analyze differences in the demographic, clinical, and epidemiological characteristics of the cases collected during the epidemiological investigation. Microsoft Excel 2013 (Microsoft Corp.) was used for the analysis.

Ethics Approval

The study protocol was approved by the Institutional Review Board of the KDCA (IRB-2022-08-03-PE-A).

Results

Descriptive Epidemiology

On February 16, 2022, 12 of 80 production workers in the factory tested positive for HEV in their routine on-site health examinations.

Demographic and clinical characteristics showed that all 12 cases were men and the median age was 50 years (range, 43–59 years). The attack rate of acute hepatitis E among production workers was 15.0% (12/80). Regarding age, 18.2% of production workers (8/44) were in their 50s and 12.9% (4/31) were in their 40s. The attack rate according to work division was 23.5% (4/17) in department B and 18.8% (3/16) in department E (Table 1).

All cases were asymptomatic (HEV carriers), and most (10/12) showed normal liver function, based on alanine transaminase and aspartate transaminase levels. A history of chronic diseases (e.g., hypertension) was found in 8 cases, and cases no. 1, no. 3, and no. 8 tested anti-HEV IgM-positive since their previous health examination in 2020. Although all cases reported being asymptomatic during the investigation, the

Table 1. Hepatitis E attack rate by age, sex, and work department among the factory production workers ($n = 80$)

Variable	Total	Hepatitis E cases (n)	Attack rate (%)
Total	80	12	15.0
Age (y), median (range)	50 (27–60)	50 (43–59)	
20–29	1	0	0.0
30–39	3	0	0.0
40–49	31	4	12.9
50–59	44	8	18.2
≥ 60	1	0	0.0
Sex			
Male	80	12	15.0
Female	0	0	0.0
Department			
A	6	1	16.7
B	17	4	23.5
C	7	1	14.3
D	10	1	10.0
E	16	3	18.8
F	4	1	25.0
G	13	0	0.0
H	7	1	14.3

DUR of the Health Insurance Review & Assessment Service revealed that 1 case (no. 8) had presented with digestive symptoms (i.e., gastroenteritis and colitis) during the estimated HEV exposure period (December 2021 to February 2022) (Table 2).

The analysis of the epidemiological characteristics of the production workers revealed that, within the estimated HEV exposure period, there was no history of overseas travel (including to acute hepatitis E epidemic regions), blood donation, blood transfusion, organ donation, or contact with a hepatitis E-infected patient. As zoonotic infection is possible in acute hepatitis E, any history of animal contact while hunting or while in a barn or farm near the factory or home was examined. The results showed that case no. 12 had a small barn containing 6 hens and 2 dogs. Any history of consuming undercooked meat, animal liver or bile, shellfish, processed meat products (e.g., unheated sausage), or frozen fruits was investigated. Cases no. 4 and no. 10 had consumed cow liver or raw meat but did not develop symptoms (Table 3).

Environmental Investigation

During the on-site epidemiological investigation, we collected and tested 3 human specimens from the kitchen employees; 19 environmental specimens from handles in the worksite, kitchen knives, cutting boards, washcloths, preserved food products, and water; and 4 specimens from manufactured products. However, no pathogens were isolated from these specimens, and the source of infection could not

Table 2. Demographic and clinical characteristics of the HEV-infected factory production workers ($n = 12$)

Characteristic	Case no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Age (y)	45	52	59	50	53	57	50	49	50	52	48	43
Symptoms	None	None	None	None	None	None	None	None	None	None	None	None
ALT/AST levels (U/L)	39/29	13/24	26/26	32/20	31/33	21/34	20/34	20/18	81/58	100/82	24/29	45/49
Underlying disease	HTN	HTN	None	HTN	HTN, CKD	HTN, gout	None	None	Gout, DM, AMI	HTN	None	HTN, dyslipidemia
History of HEV	Yes	No	Yes	No	No	No	No	Yes	No	No	No	No
Results of DUR	None	None	None	None	Kidney disease (2018–present)	None	None	Gastroenteritis, colitis (Dec 2021)	None	None	None	None

HEV, hepatitis E virus; ALT, alanine transaminase; AST, aspartate transaminase; HTN, hypertension; CKD, chronic kidney disease; DM, diabetes mellitus; AMI, acute myocardial infarction; DUR, drug utilization review.

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Table 3. Epidemiological characteristics of the HEV-infected factory production workers (n = 12)

Characteristic	Case no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Travel history	No	No	No	No	No	No	No	No	No	No	No	No
History of blood donation/ transfusion	No	No	No	No	No	No	No	No	No	No	No	No
Contact with HEV-infected patient	No	No	No	No	No	No	No	No	No	No	No	No
Contact with animals	No	No	No	No	No	No	No	No	No	No	No	Yes[a]
Ingestion of HEV risk-related foods	No	No	No	Yes[b]	No	No	No	No	No	Yes[c]	No	No

HEV, hepatitis E virus.
[a]Small stock (6 chickens, 2 dogs). [b]Raw cattle liver. [c]Raw beef.

be determined. The factory operated its own self-service cafeteria, and no specific problems were identified in the sanitary conditions of the cooking environment, the cooking staff, or the food suppliers. All processes within the workshop were automated and contained within a closed workspace. Therefore, there was no contact between the workers and the products, and the likelihood of contamination of the manufactured food by workers was assessed to be low.

Follow-up Investigation

The follow-up tests revealed 3 HEV IgM-positive results (3 previously HEV IgM-positive cases) and 6 HEV IgG-positive results (2 previously HEV IgM-positive cases and 4 previously negative cases). Viral genes were not isolated in the IgM-positive specimens (Table 4). Based on the results of the follow-up investigation, the 3 HEV IgM-positive workers were among those who had first been reported in February 2022, and no new cases had developed among the HEV IgM-negative workers.

Discussion

Hepatitis E infection was designated a class 2 notifiable infectious disease in July 2020 in Korea. According to the Health Insurance Review and Assessment Service, the annual number of reported cases of acute hepatitis E was fewer than 100 between 2010 and 2018. Reported cases reached a peak of 219 in 2019, dropped to 169 in 2020, then increased again to 235 in 2021.

Hepatitis E infection presents a wide range of clinical symptoms, from no or mild symptoms to fulminant hepatitis. Unlike previous reports outside Korea, all cases diagnosed in the current outbreak were asymptomatic [6,13]. However, the predominantly high infection rate in men aged 50 years or older in the present outbreak was in line with previous studies [2,6,14]. This epidemiological investigation showed that all 12 cases of acute hepatitis E from the factory were asymptomatic, but did show HEV IgM-positive results. Therefore, the causative pathogen was presumed to be HEV. Since the virus detected in the human specimens was not detected in the environmental specimens, it could not be determined that the source of infection was through common consumption inside the factory. Furthermore, the epidemiological investigation did not reveal common sources of exposure outside the workplace, such as the use of a common restaurant or other common activities. Acute hepatitis E occurred in 12 of 80 production workers in the factory, accounting for an attack rate of 15.0%. Considering an incubation period of 40 days (range, 15–64 days) from February 2022 when the cases were detected, the infections inside the factory could have occurred between December 2021 and February 2022. Although all cases reported being asymptomatic during the investigation, the DUR of the Health Insurance Review & Assessment Service revealed that 1 case (no. 8) had symptoms of gastroenteritis and colitis and a history of hepatitis E in the past, so the possibility of an index case could not be ruled out. Despite the possibility of co-exposure among all cases, and insufficient evidence for an external environmental route of infection, it was difficult to determine the source of infection.

To prevent the spread of HEV, we monitored for additional cases and anyone presenting with symptoms for the maximum incubation period of 64 days. In addition, follow-ups were conducted with the production workers 2 to 3 months after the outbreak (April 2022). The local public health center collected blood samples from the production workers between April 18 and 19, 2022, and the Department of Virus Analysis at the KDCA analyzed the specimens. *In vitro* diagnostic agents approved by the Ministry of Food and Drug Safety were used for antibody testing, and the HEV IgM-positive specimens were subjected to additional viral gene detection tests. Three HEV IgM-positive cases (all

Table 4. Results of the F/U investigation of the factory production workers ($n = 76$)

	Case no.	Routine health examination		F/U investigation (April 18–19, 2022)		
		IgM (February 16, 2022	PCR (March 5 and 7, 2022)	IgM	IgG	PCR
Anti-HEV IgM(+) ($n = 12$)	1	Positive	Negative	Negative	Positive	Negative
	2	Positive	Negative	Negative	Negative	Negative
	3	Positive	Negative	Positive	Positive	Negative
	4	Positive	Negative	Positive	Negative	Negative
	5	Positive	Negative	Negative	Negative	Negative
	6	Positive	Negative	Negative	Negative	Negative
	7	Positive	Negative	Positive	Negative	Negative
	8	Positive	Negative	Negative	Negative	Negative
	9	Positive	Negative	Negative	Negative	Negative
	10	Positive	Negative	Negative	Negative	Negative
	11	Positive	Negative	Negative	Negative	Negative
	12	Positive	Negative	Negative	Negative	Negative
Anti-HEV IgM(−) ($n = 64$)	4 Cases of the HEV-IgM(−)	Negative	None	Negative	Positive	Negative
		Negative	None	Negative	Positive	Negative
		Negative	None	Negative	Positive	Negative
		Negative	None	Negative	Positive	Negative
	60 Cases of the HEV-IgM(−)	Negative	None	Negative	Negative	Negative

F/U, follow-up; IgM, immunoglobulin M; PCR, polymerase chain reaction; IgG, immunoglobulin G; HEV, hepatitis E virus.

previously HEV IgM-positive) and 6 HEV IgG-positive cases (2 previously HEV IgM-positive and 4 previously negative) were found. Among them, 1 case was both HEV IgM- and IgG-positive, and no viral genes were detected in the HEV IgM-positive specimens. The 3 HEV IgM-positive cases had previously tested positive for HEV IgM on February 16, 2022. No new positive cases were detected among the previously HEV IgM-negative workers in the follow-up testing. Although HEV can be detected in blood for 3 to 6 weeks after infection, its detection has also been reported after several months. As all cases showed normal liver function and no symptoms, no further interventions were performed, and the monitoring of the hepatitis E outbreak in the factory ended on April 25, 2022 (Figure S1).

This outbreak investigation had a few limitations. First, because 19 days passed between the time that a diagnosis of hepatitis E was made and the beginning of the on-site epidemiological investigation and collection of specimens, the timeliness of the investigation, the design, and the selection of subjects were not sufficient. Considering the long incubation time of hepatitis E (15–64 days) and the time when the outbreak was first recognized, the on-site epidemiological investigation was conducted at least 1 month after the onset of infections. Therefore, there were no preserved foods on-site that had been consumed by the HEV IgM-positive cases. It was also difficult to obtain cooperation for the investigation from the factory staff. For this reason, we were only able to investigate HEV IgM-positive production workers and not all employees. Thus, the risk of infection from food consumption could not be determined in this case series study. Although the factory cafeteria was used by all employees, the investigation was only conducted among production workers who were subject to routine health examinations, limiting our assessment of the route and location of the infection in this outbreak. In the event of a future hepatitis E outbreak, an appropriate investigation design and selection of subjects is necessary to identify the source and route of infection and to take effective control measures.

Second, the factory had failed to take appropriate measures in the past when cases of hepatitis E were found during annual health examinations of the production workers because the cases had no specific symptoms, and the factory was not aware that hepatitis E was a notifiable infectious disease. According to previous studies [15–17], hepatitis E reinfections can occur despite immunization. HEV IgM-positive individuals convert to negative within 6 months on average, but HEV IgM positivity can last for 2 to 3 years. In this case, it was determined that 3 workers had been HEV IgM-positive in the past due to previous exposure to the virus, with antibodies remaining from the previous infection. In the event of an outbreak of hepatitis E, appropriate case management

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measures require timely notification of the disease.

Third, the HEV genotype that caused this outbreak could not be determined because qRT-PCR results from the 12 HEV IgM-positive cases did not show viral genes. In a previous study [18], only 1 of 6 cases with HEV IgM-positive results showed positive qRT-PCR results, indicating that HEV viremia had decreased significantly in the serum of cases with acute symptomatic hepatitis E and, therefore, could not be detected. Further efforts are needed to isolate HEV genes from cases.

Fourth, there is no internationally standardized diagnosis method for hepatitis E, and the possibility of false positives due to the low sensitivity of domestically approved hepatitis E antibody tests cannot be ruled out. According to the results of a previous study in Korea [19], the seroprevalence of HEV IgG in 147 study subjects was 23.1% when tested by Wantai kits (Wantai Biological Pharmacy Enterprise), while the GeneLab (GeneLabs Diagnostics) test for the same group showed 14.3%, indicating a high degree of reproducibility. Therefore, further research is needed on diagnostic methods, including a comparison of the sensitivity and specificity of various hepatitis E antibody test kits.

Despite these limitations in our investigation, this was the first epidemiological investigation and response to a domestic hepatitis E outbreak in Korea. The results of this study suggest the following strategies for domestic hepatitis E control:

First, we should raise awareness regarding hepatitis E and provide information and guidance to healthcare workers to enable an early diagnosis when symptoms manifest. Hepatitis E was designated a class 2 notifiable infectious disease in July 2020. However, because its incidence is low in Korea, and most cases are reportedly asymptomatic, awareness is low among healthcare workers. This leads to frequent omissions or delayed reporting, likely resulting from a low rate of diagnosis even when the infection presents with symptoms. To avoid delays in the reporting of hepatitis E, awareness must be raised.

Second, it is necessary to identify which groups are at risk of infection in Korea to establish effective HEV control strategies. The current outbreak was detected through routine health examinations of production workers required by other countries before exporting the products of the factory. Since hepatitis E is mostly asymptomatic or mildly symptomatic, it is possible to miss hepatitis E even when there is an outbreak. Therefore, it would be helpful to identify domestic risk groups by conducting seroprevalence surveys at the national or regional levels, targeting specific groups with known risk factors.

Third, since HEV can be transmitted zoonotically, hepatitis E needs to be monitored, prevented, and managed using a One Health approach to prevent the spread of HEV from animal hosts to humans [20]. According to recent studies from Europe, Japan, and Australia, HEV genotypes 3 and 4 can lead to zoonotic waterborne or foodborne infections in humans and animals, mainly pigs, boars, and deer [4,6]. It is necessary to establish a system of communication and collaboration among multiple authorities to prepare an integrated governmental response system for infectious diseases, with a focus on the risk factors among people, animals, food, and the environment.

Conclusion

This was the first domestic outbreak of HEV infection to occur in a food manufacturing factory in Korea. Our results may provide useful information for effective outbreak control and the preparation of preventive measures against future domestic outbreaks of HEV infection. Currently, no commercial vaccine has been developed for hepatitis E in Korea. Therefore, to reduce the prevalence of hepatitis E infection and prevent outbreaks, the importance of consuming foods prepared in sanitary settings and fully cooked at the appropriate temperature should be publicly promoted. Raising public awareness of hepatitis E and establishing supportive systems is vital.

Supplementary Material

Figure S1. Timeline of the HEV outbreak. Supplementary data are available at https://doi.org/10.24171/j.phrp.2022.0305.

Notes

Ethics Approval

The study protocol was approved by the Institutional Review Board of the KDCA (IRB-2022-08-03-PE-A). Obtaining informed consent was exempted by the IRB 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: JG; Data curation: YY, SS, JL, HY; Formal analysis: YY, JL, HY; Investigation: HY, MGH, DYL, SWP, SAP, JL; Methodology: JL, HY,

SHJ, JG; Project administration: HY; Resources: HY; Supervision: SS, JG; Visualization: YY, JL, HY; Writing–original draft: HY; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions
We are grateful to the investigation participants, the workers, and the managers of the food manufacturing factory for their cooperation. We also thank our colleagues in the related province and the public health center for their contribution to data and sample collection.

References

1. Dalton HR, Izopet J, Bendall R. Hepatitis E. In: Sanyal AJ, Boyer, TD, Lindor KD, et al, editors. Zakim and Boyer's hepatology: a textbook of liver disease. 7th ed. Elsevier; 2018. p. 522–34.
2. World Health Organization (WHO). Hepatitis E [Internet]. WHO; 2022 [cited 2023 Jan 3]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e.
3. Yapa CM, Furlong C, Rosewell A, et al. First reported outbreak of locally acquired hepatitis E virus infection in Australia. Med J Aust 2016;204:274.
4. Guillois Y, Abravanel F, Miura T, et al. High proportion of asymptomatic infections in an outbreak of hepatitis E associated with a spit-roasted piglet, France, 2013. Clin Infect Dis 2016;62:351–7.
5. Lampejo T, Curtis C, Ijaz S, et al. Nosocomial transmission of hepatitis E virus and development of chronic infection: the wider impact of COVID-19. J Clin Virol 2022;148:105083.
6. Zhang L, Yan B, Xu A. A hepatitis E outbreak by genotype 4 virus in Shandong province, China. Vaccine 2016;34:3715–8.
7. Lee GH, Tan BH, Teo EC, et al. Chronic infection with camelid hepatitis e virus in a liver transplant recipient who regularly consumes camel meat and milk. Gastroenterology 2016;150:355–7.
8. Mizuo H, Yazaki Y, Sugawara K, et al. Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido, Japan. J Med Virol 2005;76:341–9.
9. Kim YM, Jeong SH, Kim JY, et al. The first case of genotype 4 hepatitis E related to wild boar in South Korea. J Clin Virol 2011;50:253–6.
10. Choi JY, Lee JM, Jo YW, et al. Genotype-4 hepatitis E in a human after ingesting roe deer meat in South Korea. Clin Mol Hepatol 2013;19:309–14.
11. Yun H, Kim JS, Lee HJ, et al. The complete genome sequence and molecular analysis of human hepatitis E virus genotype IV identified from a Korean patient. Arch Virol 2010;155:1003–8.
12. Lim JW, Park CS, Ahn JM, et al. Nine cases of sporadic acute hepatitis E in Korea. Korean J Hepatol 2006;12:230–6. Korean.
13. Yin W, Han Y, Xin H, et al. Hepatitis E outbreak in a mechanical factory in Qingdao City, China. Int J Infect Dis 2019;86:191–6.
14. Yoon Y, Jeong HS, Yun H. et al. Hepatitis E virus (HEV) seroprevalence in the general population of the Republic of Korea in 2007-2009: a nationwide cross-sectional study. BMC Infect Dis 2014;14:517.
15. Choi Y, Zhang X, Skinner B. Analysis of IgG Anti-HEV antibody protective levels during hepatitis E virus reinfection in experimentally infected rhesus macaques. J Infect Dis 2019;219:916–24.
16. Riveiro-Barciela M, Rando-Segura A, Barreira-Díaz A, et al. Unexpected long-lasting anti-HEV IgM positivity: is HEV antigen a better serological marker for hepatitis E infection diagnosis? J Viral Hepat 2020;27:747–53.
17. Lu J, Huang Y, Wang P, et al. Dynamics of hepatitis E virus (HEV) antibodies and development of a multifactorial model to improve the diagnosis of HEV infection in resource-limited settings. J Clin Microbiol 2021;59:e02321–20.
18. Choi GH, Jeong SH, Hwang JH, et al. Causative role and clinico-epidemiological characteristics of hepatitis E virus in acute viral hepatitis. Public Health Wkly Rep 2021;14:2151–62. Korean.
19. Park HK, Jeong SH, Kim JW, et al. Seroprevalence of anti-hepatitis E virus (HEV) in a Korean population: comparison of two commercial anti-HEV assays. BMC Infect Dis 2012;12:142.
20. Velavan TP, Pallerla SR, Johne R, et al. Hepatitis E: an update on one health and clinical medicine. Liver Int 2021;41:1462–73.

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Original Article

Chronic kidney disease in Indonesia: evidence from a national health survey

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ABSTRACT

Objectives: Several previous studies have stated that consuming certain foods and beverages might increase the risk of chronic kidney disease (CKD). This study aimed to examine the relationships of food and beverage consumption with other risk factors for CKD.
Methods: Data sources included the 2018 Basic Health Research (Riskesdas) and the National Socio-Economic Survey (Susenas), which were analyzed using a cross-sectional design. The study samples were households from 34 provinces in Indonesia, and the analysis was performed with provincial aggregates. Data were analyzed using risk factor analysis followed by linear regression to identify relationships with CKD.
Results: The prevalence of CKD in Indonesia was 0.38%. The province with the highest prevalence was North Kalimantan (0.64%), while the lowest was found in West Sulawesi (0.18%). Five major groups were formed from 15 identified risk factors using factor analysis. A linear regression model presented 1 significant selected factor ($p = 0.006$, $R^2 = 31\%$). The final model of risk factors included water quality, consumption of fatty foods, and a history of diabetes.
Conclusion: Drinking water quality, fatty food consumption, and diabetes are associated with CKD. There is a need to monitor drinking water, as well as to promote health education and provide comprehensive services for people with diabetes, to prevent CKD.

Keywords: Chronic kidney diseases; Diabetes mellitus; Drinking water; Fatty food

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Introduction

Chronic kidney disease (CKD) significantly contributes to the morbidity and mortality caused by non-communicable diseases. Its prevalence has steadily increased worldwide. Although hemodialysis and kidney transplantation are essential modalities that can save the lives of patients with CKD, they are often very expensive. The number of patients who will undergo kidney transplantation is expected to reach 5.4 million by 2030. This condition is increasing most rapidly in low-and middle-income countries. Globally, there are also significant

inequalities in access to high-quality kidney disease treatment, and several low- and middle-income countries cannot meet the increasing need for dialysis [1].

According to the 2017 Global Burden of Disease study, CKD is the 12th leading cause of death. It directly causes about 1.23 million deaths, and 1.36 million additional deaths are associated with cardiovascular disease due to impaired kidney function [2].

During the coronavirus disease 2019 (COVID-19) pandemic, people with CKD were found to develop more severe symptoms of COVID-19 than patients without CKD [3]. Individuals with CKD also have a higher prevalence of hypertension and diabetes, which are associated with higher mortality due to COVID-19 [4,5].

When kidney activity has declined to the point that the kidneys no longer function, then a patient is considered to be in the chronic renal failure phase, which is the final and most severe stage of kidney disease. Medically, CKD is defined as a decrease in the renal filtration rate or the estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 for 3 months or more. Patients are deemed to have chronic renal failure when their kidney function decreases to 85% or lower of baseline [6,7].

According to a study conducted in Africa, several factors influence CKD, including a history of hypertension, anemia, a family history of kidney disease, and consumption of coconut oil [8]. Several studies have also reported that diet is related to the incidence of CKD [9–11]. This is reinforced by several other investigations examining the relationship between CKD and the consumption of food and beverages, including foods high in fat and sugar [12], acidic foods [13], cholesterol [14], and drinking water [15,16]. A study conducted in Sri Lanka stated that drinking water with concentrations of cadmium, lead, and fluoride exceeding the maximum limit was associated with chronic kidney damage [17]. Other studies also suggested that high water intake might be associated with slower CKD development [18,19].

Kidney disease has long been a public health problem in Indonesia, and in 2007, it was one of the top 10 causes of death in rural areas in the 5- to 14-year age group [20]. The prevalence of doctor-diagnosed CKD in 2013 was 0.2%, while that of kidney stones was 0.6% [21]. It is estimated that these numbers will continue to increase in the future. In addition, previous studies stated that age, economic status, history of hypertension, sex, history of diabetes mellitus, and obesity [22], consuming energy drinks along with soft drinks [6], and the presence of coronary heart disease, stroke, and comorbidities [23] have a relationship with the occurrence of CKD. However, it is important to note that those previous studies highlighted overall impairments in kidney function, were mostly health facility-based, and were primarily conducted in single sub-districts. Therefore, this study analyzed data from national community-based surveys, focusing on long-standing cases of CKD (i.e., for at least 3 consecutive months), and analyzing the relationships of CKD with dietary patterns, beverage consumption, and a history of comorbidities.

Materials and Methods

Study Design and Sample

This study used a cross-sectional design and secondary data from the 2018 Basic Health Research (Riskesdas) and the National Socio-Economic Survey (Susenas). Riskesdas is a national health survey conducted by the National Institute of Health Research and Development–Ministry of Health in 34 provinces in Indonesia. The target samples included 300,000 households from 30,000 census blocks Susenas is conducted by the Central Statistics Agency with probability proportional to size sampling derived using a linear systematic sampling method [24].

Dependent Variable

The dependent variable in this study was the prevalence of CKD, measured as a numeric outcome. The related survey question was "Has [NAME] ever been diagnosed by a doctor as suffering from chronic kidney failure? or at kidney disease for least 3 months consistently?" According to the Riskesdas questionnaire interview guideline, CKD is defined according to the Indonesian Nephrology Association as kidney damage both in structure and/or function that lasts for 3 months or more [25].

Independent Variables

This study focused on food intake, beverage consumption, and comorbid conditions that are related to CKD. The independent variables were defined as the percentage of respondents who reported consuming the listed food at least twice per day in the last month. The food consumption habits comprised salty, flavored, fatty, and grilled food, as well as foods with preservatives, instant food, sugary beverages, soft and energy drinks, alcohol, and plain drinking water. Smoking behavior and hygienic behavior (handwashing) were also investigated. In addition, participants' history of comorbid diseases (e.g., hypertension or diabetes mellitus) was also included as an independent variable.

The drinking water quality variable was defined referring to the guidelines from the Joint Monitoring Program (World Health Organization [WHO]/United Nations International

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Children's Emergency Fund [UNICEF]), which states that the time to obtain water should be less than 30 minutes, the physical quality of good drinking water is characterized by no color, no smell, no taste, and no turbidity or foam [26,27], and the distance from a waste disposal site must be more than 10 meters [28]. According to the WHO/UNICEF, the potential of water sources to produce safe water depends on their nature, design, and construction. The sources of improved drinking water commonly used by residents are piped water, drilled or tube wells, protected dug wells, protected springs, rainwater, and bottled water [29]. Additionally, hygienic behavior was defined as the habit of washing one's hands with soap and running water before preparing food, whenever one's, hands are dirty due to the process of handling money, interacting with animals or gardening, as well as after defecating, bathing babies/children, and using pesticides/insecticide, and before feeding a baby and eating [24].

Study Tools

The 2018 Riskesdas and Susenas reports were used as a tool in this study. From these 2 reports, the independent and dependent variables were obtained and recorded in Excel (Microsoft Corp.) as a new subset of data for further analysis.

Instrument reliability and validity

Cronbach's alpha is a measure of internal consistency, and its values range from 0 to 1. A value greater than 0.60 is considered to indicate that an instrument is reliable and acceptable. A high Cronbach's alpha shows that the items in an instrument are highly correlated [30].

Statistical Analysis

Since this study aimed to identify foods and beverages associated with the prevalence of CKD, it started by identifying several types of foods and beverages that were frequently consumed by survey participants, as well as their history of comorbid conditions. Fifteen variables were analyzed: salty, flavored, fatty, and grilled food; foods with preservatives; instant foods; sugary, soft, and energy drinks; alcohol; and plain drinking water. In addition, smoking behavior, personal hygiene, and comorbidities such as diabetes mellitus and hypertension were analyzed to determine their relationship with CKD.

First, a descriptive analysis was performed. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy, which has values ranging from 0 to 1, was used to test the feasibility of factor analysis. A KMO value > 0.5 indicates that factor analysis is feasible [31]. Bartlett test of sphericity is a statistical test to test whether variables are correlated. A significant value (< 0.05) indicates that there is a relationship among the variables [31].

Next, factor analysis was performed to reduce the number of the original variables by examining the covariance before conducting linear regression. The basic purpose of factor analysis is to identify relationships between variables by conducting a correlation test. It is useful to apply factor analysis to focus on only a few manageable factors rather than a large number of variables [31]. Meanwhile, linear regression was carried out to determine the relationship between CKD and the factors that were formed. All statistical analyses were performed with IBM SPSS ver. 21.0 (IBM Corp.).

Ethics Approval

Ethical approval and permission for conducting this study followed the Ethical Approval for RISKESDAS 2018 from Komisi Etik Penelitian Kesehatan, Badan Penelitian dan Pengembangan Kesehatan (Ethical Committee of Health Research, National Institute of Health Research and Development–Ministry of Health, Republic of Indonesia) No. LB.02.01/2/KE.267/2017.

Results

Overview of CKD Prevalence and Risk Factors

Data on CKD collected from 34 provinces in Indonesia in 2018 were analyzed. The average prevalence was 0.38%, meaning that 4 out of 1,000 people were diagnosed with CKD. The highest prevalence was found in North Kalimantan Province, while the lowest was in West Sulawesi, as shown in Figure 1.

Figure 2 shows several bars and points representing the conditions of each province. The blue bars represent the percentage of respondents with good water quality, while the percentages of food/beverage consumption, comorbidities, and handwashing behavior are represented by dots. A greater number of dots displayed at the top of the bar indicates a higher risk of CKD in the province. In general, the quality of drinking water in all provinces was moderate, with the highest percentage of good water quality occurring in Capital Region (Daerah Khusus Ibukota) Jakarta Province. Furthermore, the percentage of flavored food consumption was very high in almost all provinces. The highest percentage of fatty food consumption was found in Central Java Province, while the highest percentage of alcohol consumption was in North Sulawesi. Salty foods were most frequently consumed by residents in West Java Province, while sweet beverages were most frequently consumed in Yogyakarta Province, as shown in Figure 2.

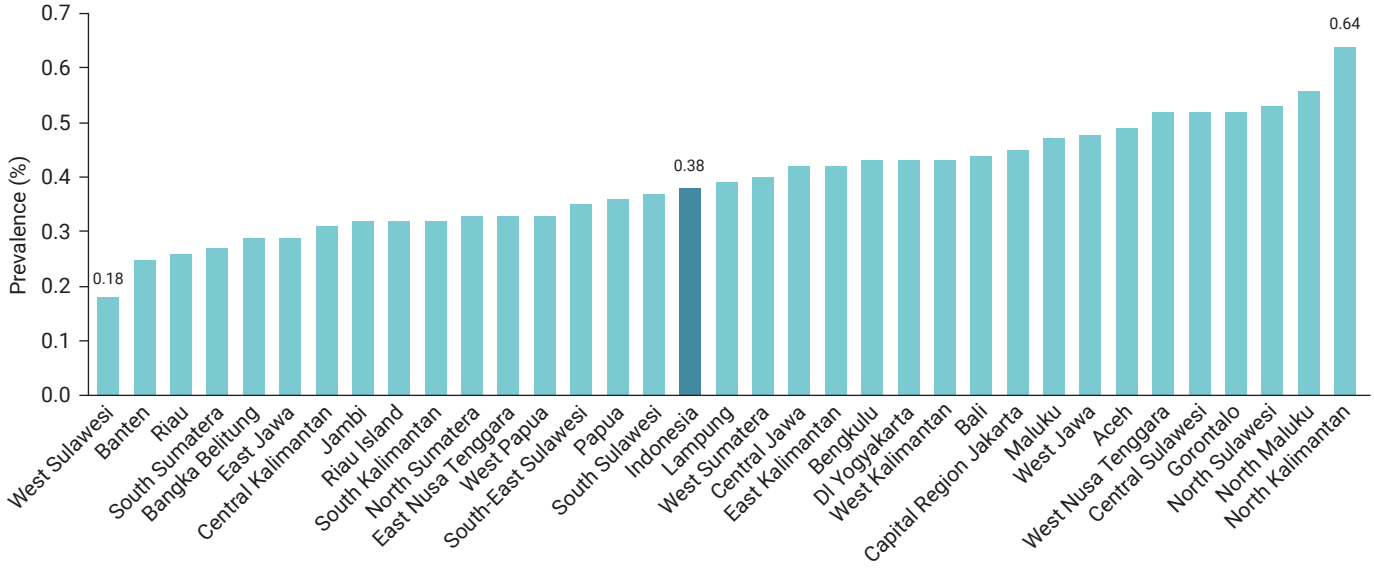

Figure 1. Prevalence of chronic kidney disease by province in Indonesia, 2018.

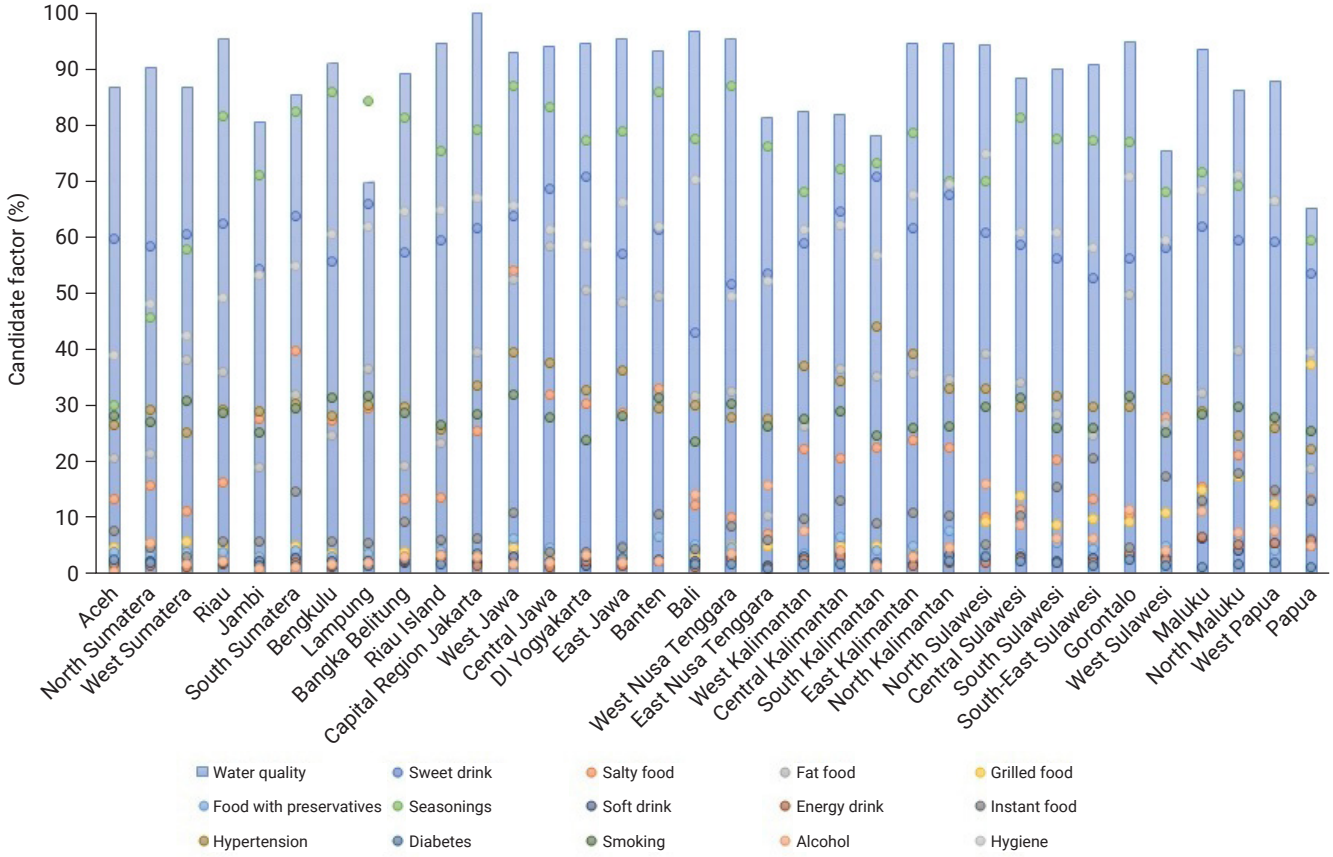

Figure 2. Candidate factors associated with chronic kidney disease by province in Indonesia, 2018.

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Descriptive Statistics and Factor Analysis

This study used factor analysis to extract a smaller set of variables from the large number of original variables to make linear regression more manageable. Fifteen independent variables were assumed to have a relationship with CKD. To analyze the associations of variables, the KMO method was used to measure the suitability of data for factor analysis. As shown in Table 1, the KMO statistic was 0.559. This value was >0.5, which indicates that sampling was adequate. The Bartlett test of sphericity value was 292.42, with a significance of <0.001, which met the requirements because the significance was below 0.05 (5%).

Table 2 shows the eigenvalues and total variance obtained from principal component analysis. Before extraction, 15 linear components were identified within the data set. After extraction and rotation, there were 5 distinct linear components within the data set with eigenvalues >1. These 5 factors accounted for a combined 78.3% of the total variance. This is supported by the KMO value of 0.559, which can be considered adequate and also indicates that factor analysis was useful for the variables.

Table 1. The Kaiser-Meyer-Olkin test and Bartlett test of sphericity

Test	Value
Kaiser-Meyer-Olkin measure of sampling adequacy	0.559
Bartlett test of sphericity	
Approximate chi-square	292.42
df	105
p	<0.001

df, degree of freedom.

The 5 factors formed were as follows. Factor 1 consisted of grilled food, food containing preservatives, instant food, soft drinks, and energy drinks. Factor 2 comprised sweet and salty foods, alcoholic beverages, and hypertension. Meanwhile, factor 3 consisted of the quality of drinking water, fatty foods, and diabetes, while the components in factor 4 included hygienic behavior and food flavorings, and factor 5 consisted of smoking behavior.

Reliability and Validity

Validity tests were carried out to determine the precision of the variables used, while reliability tests were performed to analyze the internal consistency through Cronbach's alpha. A validity value ≥0.5 is considered satisfactory, while the adequate threshold value for Cronbach's alpha is ≥0.6 [30]. In this analysis, the validity value was 91.9%, while Cronbach's alpha of the 15 variables was 0.622; thus, both thresholds were exceeded. This shows that the variables exhibited correlations with their component grouping, meaning that they were internally consistent.

Multivariable Linear Regression

To identify risk factors associated with CKD, multivariable analysis was performed on the 5 factors. Table 3 shows the multivariate model of linear regression analysis of the 5 factors in relation to CKD. The model showed an R^2 of 31% and a significant *p*-value, as demonstrated in Table 3. Factor 3, which comprised the quality of drinking water, fatty foods, and diabetes, showed a significant relationship with CKD. The final model, which contained water quality, fatty food, and diabetes, had a significant association with CKD

Table 2. Grouping of variables in the statistical test results of factor analysis

Component	Initial eigenvalues			Extraction sums of squared loadings			Rotation sums of squared loadings		
	Total	% of variance	Cumulative (%)	Total	% of variance	Cumulative (%)	Total	% of variance	Cumulative (%)
1	4.350	29.001	29.001	4.350	29.001	29.001	3.429	22.860	22.860
2	2.842	18.945	47.946	2.842	18.945	47.946	2.645	17.635	40.495
3	2.022	13.482	61.428	2.022	13.482	61.428	2.333	15.554	56.049
4	1.282	8.548	69.976	1.282	8.548	69.976	2.054	13.695	69.744
5	1.258	8.386	78.362	1.258	8.386	78.362	1.293	8.618	78.362
6	0.777	5.177	83.539						
7	0.559	3.724	87.264						
8	0.514	3.430	90.693						
9	0.386	2.573	93.266						
10	0.318	2.117	95.383						
11	0.247	1.644	97.027						
12	0.188	1.255	98.282						
13	0.151	1.007	99.289						
14	0.064	0.426	99.714						
15	0.043	0.286	100.000						

Extraction method: principal component analysis. Initial eigenvalues <1, then factor of extraction sum of squared loading cannot be formed.

Table 3. Multivariable linear regression test results

Variable	Unstandardized coefficients		t	*p*
	B	Standard error		
(Constant)	0.395	0.016	24.902	< 0.001
Factor 1: grilled food, preservatives, instant food, soft drinks, and energy drinks	0.022	0.016	1.336	0.192
Factor 2: sweet drinks, salty food, hypertension, alcohol	−0.015	0.016	−0.960	0.345
Factor 3: water quality, fatty food, diabetes	0.047	0.016	2.949	0.006*
Factor 4: hygiene, food flavoring	0.001	0.016	0.091	0.928
Factor 5: smoking behavior	0.019	0.016	1.155	0.258
$R^2 = 0.313$				

*$p < 0.05$.

Table 4. Final model

Model	Unstandardized coefficients		95% CI for B	Standardized coefficients	*p*
	B	Standard error			
(Constant)	0.395	0.016	0.362–0.427		< 0.001
Water quality, fatty food, diabetes	0.047	0.016	0.015–0.080	0.462	0.006

CI, confidence interval.

($p = 0.006$) (Table 4).

Discussion

Main Findings

The results showed that the risk of CKD was relatively high in people who often consumed fatty foods, drank unhealthy water, and had diabetes mellitus. The highest prevalence was found in North Kalimantan Province.

Factors Associated with CKD

Based on the results, people who drink unhealthy water are more likely to develop CKD than those who consume quality water. This is most likely due to the presence of chemical substances and minerals associated with impaired kidney function in poor-quality water. Arsenic exposure is associated with the risk of end-stage renal disease, and this effect is modified by comorbidities, which should be treated in the early stages [32]. Water from wells with higher levels of total dissolved solids and arsenic had a positive correlation with the occurrence of CKD [16]. Furthermore, consuming drinking water from dug wells contaminated with cadmium, lead, and fluoride can increase the prevalence of CKD [33,34]. Soil contamination with toxic metals and fluoride presumably comes from agricultural fertilizers in the long term, which continuously causes groundwater contamination [17]. Balanced levels of minerals in drinking water have a beneficial effect on kidney health [35]. There is also a need to strengthen the water quality surveillance system to reduce the risk of disease. This is important for achieving the Sustainable Development Goal targets for improving water quality and identifying populations at risk [36].

The results also showed that people who consumed more fatty foods were more likely to have CKD. This is consistent with a previous study that stated that consuming a high-fat diet was associated with a significant increase in the likelihood of developing CKD [12]. In contrast, the consumption of fruits and vegetables, along with a lower intake of red and processed meat, is associated with a reduced incidence of CKD [10]. Another study suggested that a low-acid diet slows the development of CKD [13].

The analysis also showed that comorbid diabetes mellitus might increase the occurrence of CKD. Subjects with diabetes mellitus are more likely to develop CKD than normal individuals. However, diabetes care has been found to be associated with a decreased risk of developing kidney disease [37]. Moreover, comprehensive care is recommended for the management of patients with diabetes and kidney disease to prevent cardiovascular disease. For example, moderate physical activity of at least 150 minutes per week is recommended, along with smoking cessation, reducing obesity, salt restriction, and a low-protein diet [38].

Based on the results, there is a need to increase the monitoring of drinking water for public consumption. In addition, it is important to increase public knowledge about the risks associated with excessive consumption of fatty foods, as well as comprehensive care for patients with

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diabetes, including a healthy lifestyle to prevent severe disease. It is assumed that the relationships of CKD with the quality of drinking water and fatty foods have great potential for further investigations using other methods and designs, such as cohort studies supported by comprehensive laboratory examinations.

Strengths and Limitations

The major strength of this analysis is that it used data from the results of a national public health survey. This implies that it can describe the prevalence of the disease nationally with a large sample, but there were also limitations. As a national health survey with a cross-sectional method, water quality and disease were evaluated based on interviewees' statements using a structured questionnaire, not based on the results of laboratory measurements.

Conclusion

This study found a relationship between CKD and unhealthy drinking water, excessive fatty food consumption, and a history of diabetes mellitus. Based on these results, there is a need to safely manage drinking water and increase public knowledge about the risks of consuming fatty foods to reduce the risk of CKD. Comprehensive care for patients with diabetes and a healthy lifestyle are also important to prevent disease progression.

Notes

Ethics Approval

Ethical approval and permission for conducting this study followed the Ethical Approval for RISKESDAS 2018 from Komisi Etik Penelitian Kesehatan, Badan Penelitian dan Pengembangan Kesehatan (Ethical Committee of Health Research, National Institute of Health Research and Development–Ministry of Health, Republic of Indonesia) No. LB.02.01/2/KE.267/2017.

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: PSH, DHT; Data curation: DHT, ID; Formal analysis: DHT, ID; Methodology: NEWS, NS; Supervision: PSH; Validation: PSH, NEWS, NS, FA; Visualization: FA; Writing-original draft: PSH, ID; Writing review & editing: PSH, DHT, NEWS, NS, ID, FA. All authors read and approved the final manuscript.

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References

1. International Society of Nephrology. The ISN framework for developing dialysis programs in low-resource settings. International Society of Nephrology; 2021.
2. Institute for Health Metric and Evaluation. Chronic kidney disease a 'global killer in plain sight' [Internet]. Institute for Health Metric and Evaluation; 2020 [cited 2022 Jun 3]. Available from: http://www.healthdata.org/news-release/new-study-chronic-kidney-disease-global-killer-ckd.
3. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol 2020;52:1193–4.
4. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648–55.
5. Schiffrin EL, Flack JM, Ito S, et al. Hypertension and COVID-19. Am J Hypertens 2020;33:373–4.
6. Delima D, Tjitra E, Tana L, et al. Risk factors for chronic kidney disease: a case control study in four hospitals in Jakarta in 2014. Bull Health Res 2017;45:17–26. Indonesian.
7. Vaidya SR, Aeddula NR. Chronic renal failure [Internet]. StatPearls Publishing; 2022 [cited 2023 Jan 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535404/.
8. Hussien FM, Hassen HY. Dietary habit and other risk factors of chronic kidney disease among patients attending dessie referral hospital, Northeast Ethiopia. Int J Nephrol Renovasc Dis 2020;13:119–27.
9. Silva Junior GB, Fraser SD, Néri AK, et al. Association between dietary patterns and renal function in a cross-sectional study using baseline data from the ELSA-Brasil cohort. Braz J Med Biol Res 2020;53:e10230.
10. Bach KE, Kelly JT, Palmer SC, et al. Healthy dietary patterns and incidence of CKD: a meta-analysis of cohort studies. Clin J Am Soc Nephrol 2019;14:1441–9.
11. Crews DC, Kuczmarski MF, Miller ER 3rd, et al. Dietary habits, poverty, and chronic kidney disease in an urban population. J Ren Nutr 2015;25:103–10.
12. Asghari G, Momenan M, Yuzbashian E, et al. Dietary pattern and incidence of chronic kidney disease among adults: a population-based study. Nutr Metab (Lond) 2018;15:88.
13. Banerjee T, Liu Y, Crews DC. Dietary patterns and CKD progression. Blood Purif 2016;41:117–22.
14. Arifa SI, Azam M, Handayani OW. Factors associated with chronic kidney disease incidence among patients with hypertension in Indonesia. Media Kesehatan Masyarakat Indonesia 2017;13:319–28.
15. Clark WF, Sontrop JM, Huang SH, et al. Effect of coaching to increase water intake on kidney function decline in adults with chronic

kidney disease: the CKD WIT randomized clinical trial. JAMA 2018; 319:1870–9.

16. Gobalarajah K, Subramaniam P, Jayawardena UA, et al. Impact of water quality on chronic kidney disease of unknown etiology (CKDu) in Thunukkai Division in Mullaitivu District, Sri Lanka. BMC Nephrol 2020;21:507.
17. Perera WP, Dayananda MD, Liyanage JA. Exploring the root cause for chronic kidney disease of unknown etiology (CKDu) via analysis of metal ion and counterion contaminants in drinking water: a study in Sri Lanka. J Chem 2020;8670974.
18. Choi HY, Park HC, Ha SK. High water intake and progression of chronic kidney diseases. Electrolyte Blood Press 2015;13:46–51.
19. Clark WF, Huang SH, Garg AX, et al. The chronic kidney disease water intake trial: protocol of a randomized controlled trial. Can J Kidney Health Dis 2017;4:2054358117725106.
20. Ministry of Health Republic of Indonesia. Basic Health Research 2007 [Internet]. National Institute of Health Research and Development; 2007 [cited 2022 Nov 4]. Available from: https://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2007/lap_rkd07.pdf.
21. Ministry of Health Republic of Indonesia. National Basic Health Research Report (RISKESDAS) 2013 [Internet]. National Institute of Health Research and Development; 2013 [cited 2022 May 4]. Available from: https://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2013/Laporan_riskesdas_2013_final.pdf.
22. Sulistiowati E, Idaiani S. Risk factors for chronic kidney disease based on cross-sectional analysis of preliminary data cohort study of non-communicable diseases, population age 25-65 years in Kebon Kalapa Village, Bogor City, 2011. Bull Health Res 2015;43:163–72. Indonesian.
23. Riyadina W, Rahajeng E, Driyah S. Profile of chronic kidney disease on new cases of diabetes mellitus, coronary heart dissease, and stroke patients of cohort study in Bogor, Indonesia. Media Health Res Dev 2020;30:295–304. Indonesian.
24. Ministry of Health Republic of Indonesia. Basic Health Research Report (Riskesdas) 2018 [Internet]. National Institute of Health Research and Development; 2018 [cited 2022 Jun 3]. Available from: http://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2018/Laporan_Nasional_RKD2020_FINAL.pdf.
25. Indonesian Renal Registry Team. 10th Report of Indonesian Renal Registry [Internet]. Indonesian Renal Registry Team; 2017 [cited 2023 Jan 25]. Available from: https://www.indonesianrenalregistry.org/data/IRR%202017%20.pdf. Indonesian.
26. Ministry of Health Republic of Indonesia. Environmental health quality standards and water health requirements for sanitation hygiene, swimming pools, solus per aqua, and public baths [Internet]. Ministry of Health Republic of Indonesia; 2017 [cited 2023 Jan 25]. Available from: http://hukor.kemkes.go.id/uploads/produk_hukum/PMK_No._32_ttg_Standar_Baku_Mutu_Kesehatan_Air_Keperluan_Sanitasi,_Kolam_Renang,_Solus_Per_Aqua_.pdf. Indonesian.
27. Ministry of Health Republic of Indonesia. Regulation of the Minister of Health of the Republic of Indonesia Number 492/Menkes/Per/IV/2010 concerning drinking water quality requirements [Internet]. Ministry of Health Republic of Indonesia; 2017 [cited 2023 Jan 25]. Available from: https://indok3ll.com/peraturan-menteri-kesehatan-republik-indonesia-nomor-492-menkes-per-iv-2010-tentang-persyaratan-kualitas-air-minum/. Indonesian.
28. Minister of Public Works and People's Housing. Regulation of the Minister of Public Works and People's Housing of the Republic of Indonesia number 29/prt/m/2018 concerning [Internet]. Minister of Public Works and People's Housing; 2018 [cited 2023 Feb 3]. Available from: https://peraturan.bpk.go.id/Home/Details/159743/permen-pupr-no-29prtm2018-tahun-2018.
29. United Nations Children's Fund (UNICEF); World Health Organization (WHO). Core questions on water, sanitation and hygiene for household surveys: 2018 update [Internet]. UNICEF and WHO; 2018 [cited 2023 Jan 25]. Available from: https://washdata.org/sites/default/files/documents/reports/2019-03/JMP-2018-core-questions-for-household-surveys.pdf.
30. Sujarweni VW. SPSS for research. Pustaka Baru Press; 2015.
31. Shrestha N. Factor analysis as a tool for survey analysis. Am J Appl Math Stat 2021;9:4–11.
32. Cheng YY, Chang YT, Cheng HL, et al. Associations between arsenic in drinking water and occurrence of end-stage renal disease with modifications by comorbidities: a nationwide population-based study in Taiwan. Sci Total Environ 2018;626:581–91.
33. Wasana HM, Aluthpatabendi D, Kularatne WM, et al. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. Environ Geochem Health 2016;38:157–68.
34. Dharmaratne RW. Fluoride in drinking water and diet: the causative factor of chronic kidney diseases in the North Central Province of Sri Lanka. Environ Health Prev Med 2015;20:237–42.
35. Jo SM, Nam J, Park SY, et al. Effect of mineral-balanced deep-sea water on kidney function and renal oxidative stress markers in rats fed a high-salt diet. Int J Mol Sci 2021;22:13415.
36. Bain R, Johnston R, Khan S, et al. Monitoring drinking water quality in nationally representative household surveys in low- and middle-income countries: cross-sectional analysis of 27 multiple indicator cluster surveys 2014-2020. Environ Health Perspect 2021;129:97010.
37. Hsu PC, Tsai YT, Lai JN, et al. Integrating traditional Chinese medicine healthcare into diabetes care by reducing the risk of developing kidney failure among type 2 diabetic patients: a population-based case control study. J Ethnopharmacol 2014;156:358–64.
38. Nordheim E, Geir Jenssen T. Chronic kidney disease in patients with diabetes mellitus. Endocr Connect 2021;10:R151–9.

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Original Article

Association between face covering policies and the incidence of coronavirus disease 2019 in European countries

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ABSTRACT

Objectives: This study was conducted to determine the impact of the strengthening or relaxation of face covering mandates on the subsequent national case incidence of coronavirus disease 2019 (COVID-19) in Europe as the full vaccination rate was increasing.

Methods: European countries in which case incidence increased for 3 consecutive weeks were monitored and analyzed using COVID-19 incidence data shared by the World Health Organization (WHO). The epidemic trend of COVID-19 in Europe was compared with that of countries elsewhere in the world based on WHO weekly epidemiological reports from June 20 to October 30, 2021. In addition, this study provided insight into the impact of government mask mandates on COVID-19 incidence in Europe by measuring the index scores of those facial covering policies before and after mandate relaxation or strengthening. The effects of the vaccination rate and the speed of vaccination on COVID-19 incidence were also analyzed.

Results: The incidence of COVID-19 after the relaxation of face covering mandates was significantly higher than before relaxation. However, no significant difference was observed in vaccination rate between countries with increased and decreased incidence. Instead, rapid vaccination delayed the resurgence in incidence.

Conclusion: The findings suggest that face covering policies in conjunction with rapid vaccination efforts are essential to help mitigate the spread of COVID-19.

Keywords: COVID-19; Europe; Incidence; Respirator; Vaccination

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Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19) first identified in Wuhan, China in December 2019, led to a global pandemic [1]. By October 2021, the COVID-19 pandemic was

in its second year in Europe, which had again become the center of the global epidemic. Although over 2.8 million COVID-19 cases were reported in the week of October 4–10, 2021, the weekly number of new cases reported globally had continued to decline since late August 2021 after increasing for nearly 2 months since mid-June 2021 [2]. While the incidence of COVID-19 cases was decreasing globally, Europe had experienced a plateau in incidence starting at the end of July 2021; then, in the third week of September, the number of new cases began to increase, with European countries accounting for most of those with increased incidence for the third consecutive week [2,3]. Over half of the European countries (42 of 61, 68.9%) exhibited an increase in the number of new cases during the week of October 18–24, accounting for more than half (57%) of the weekly new cases worldwide and making Europe the only world region reporting an increase in cases [4]. According to some studies, the spread of COVID-19 increased not only in Russia and eastern Europe, where vaccine coverage is significantly lower than elsewhere, but also in European countries with high vaccination rates that implemented "living with COVID-19" strategies (most notably, removing some requirements for facial coverings) [5,6].

Although vaccinated individuals appear to be well protected against serious symptoms [7], vaccination has little effect on the disruption of the infection chain necessary to restrain the epidemic [8]. Moreover, achieving high coverage is difficult given the complexity of large-scale vaccine production, distribution, and uptake [7]. This indicates a need to continue with non-pharmacological interventions (NPIs), such as physical distancing and wearing face coverings, as long as a substantial proportion of individuals remain unvaccinated [9,10]. As the emergence of variants and the weakening of immunity can also reduce vaccine effectiveness [7,8], the prevention of new infections is limited even in countries with high vaccination rates. One study on the resurgence of COVID-19 in a highly vaccinated healthcare workforce emphasized that the rapid reintroduction of NPIs, including the wearing of face coverings indoors, can counter the rapid spread of a new viral variant [11]. Moreover, many children have not yet been vaccinated, and young children are not required to wear face coverings in numerous countries [12]. This suggests that government countermeasures, such as the compulsory wearing of face coverings even for vaccinated adults, are required. Many countries have increased compliance with mask-wearing by strengthening mandates in various settings [13]. An analysis showed that these laws and regulations were effective in raising compliance with mask-wearing and delaying the spread of COVID-19 [14,15]. In many studies on the impact of face coverings on virus transmission, the period of mandatory masking has been used for analysis [16]. At the start of the 2021–2022 school year, in the 2 largest counties of the United States (US) state of Arizona, schools with a face covering mandate were 3.5 times less likely to experience a school-related COVID-19 outbreak than schools without one [17].

As vaccination rates improve, demand is increasing to relax COVID-19 guidelines, despite most of the populations in question remaining susceptible [18]. In 2021, the rate of mask-wearing declined significantly worldwide, including in countries with low vaccination rates [16]. However, due to the risk of another wave of infections, the appropriate time to lift quarantine restrictions remains uncertain [18]. Recent mathematical modeling indicates that if NPIs are relaxed too early—before immunity has been fully established—a large outbreak may occur, resulting in hospitalization and death [1]. Although an abrupt weakening of NPIs may result in a similar number of deaths as a prolonged infection wave under a gradual relaxation of NPIs, a more extended infection period with a smaller outbreak provides a much greater chance for future interventions to be effective and reduces stress on the health care system [1].

Given the ongoing epidemic, we must evaluate the effectiveness of mask-wearing after some immunization progress has been achieved [19]. Although evidence for the effective impact of face coverings on COVID-19 transmission has accumulated at the individual level, the additional benefit of national mandates is less certain. We focused on the impact of the legal requirement to wear a face covering on the national weekly case incidence of the disease by analyzing the strength of government masking policies in European countries. In this study, we aimed to analyze the association between the strength of face covering mandates and national COVID-19 case incidence by quantifying the government policy indicators of such mandates and the trend of vaccination rates in European countries. In addition, we attempted to assess whether the protective effect of vaccination and masking mandates could reduce COVID-19 case incidence at the national level.

Materials and Methods

The study targeted 25 European countries with an increase in COVID-19 cases for 3 consecutive weeks between September 19 and October 30, 2021 (Russia, Ukraine, Romania, Bulgaria, Republic of Moldova, Georgia, Belarus, Poland, Czech Republic, Austria, Denmark, Lithuania, Estonia, Latvia, the Netherlands, Belgium, Greece, France, Germany, Portugal, Azerbaijan, Norway, Turkey, Hungary, and Ireland) and

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10 countries with a decrease or no increase in cases for 3 consecutive weeks (Italy, Spain, Sweden, Switzerland, Slovenia, Albania, Serbia, Bosnia and Herzegovina, Croatia, and Cyprus). The number of weekly confirmed cases by country was calculated based on the new daily COVID-19 incidence data shared by the WHO, and countries in which the number of cases increased for 3 consecutive weeks were monitored. In addition, WHO weekly epidemiological reporting was used to compare the trend of the COVID-19 outbreak between Europe and other world regions. The data collection period was from June 20, 2021 (when the number of new cases and countries with increasing COVID-19 cases for 3 consecutive weeks began to increase simultaneously) to October 30, 2021, before the first case of the Omicron variant was reported in Europe.

The government response regarding mandatory masking was quantified using the facial coverings section corresponding to the health system among the 23 policy indicators of governmental COVID-19 response. These indicators were presented by the Oxford COVID-19 Government Response Tracker of the Blavatnik School of Government at Oxford University in the United Kingdom. Based on rules regarding the use of facial coverings outside the home, government policies were scored as 0 (no policy), 1 (recommended), 2 (required in some specified shared/public spaces outside the home with other people present or some situations in which social distancing was not possible), 3 (required in all shared/public spaces outside the home with other people present or all situations in which social distancing was not possible), or 4 (required outside the home at all times regardless of location or presence of other people). We calculated the average vaccination rate over 2 weeks to investigate any difference in incidence or case growth rate based on the rate of fully vaccinated people by country. A US Centers for Disease Control and Prevention (CDC) study indicated that about 2 weeks are required after vaccination for the body to produce antibodies that protect against infection. That study also showed that the risk of infection is reduced by 90% following the second dose of vaccine [20]. In the present study, national vaccination rates were classified as 0 (<40%), 1 (≥40% and <60%), or 2 (≥60%) based on the number of fully vaccinated people provided by Our World in Data. Incidence refers to the number of weekly new COVID-19 cases per 100,000 people in each country.

We analyzed the correlations among the incidence or growth rate in COVID-19 cases, the strengthening or relaxation of face covering policies, and the vaccination rate. Regarding face coverings, we investigated whether the mandates were relaxed at least once along with the index scores of those facial covering policies during the 7 weeks immediately prior to the start of the increase in cases. One study showed that new COVID-19 cases peaked 45 days after the lifting of masking mandates [21]. Thus, changes in face covering policies and the associated index scores were observed for 7 weeks. In addition, the t-test was conducted for the incidence and the case growth rate before and after the mandatory wearing of face coverings was eased or strengthened. The index scores of the facial covering policies and vaccination rates were also analyzed using t-testing for the 25 countries in which the incidence increased for 3 consecutive weeks and the 10 countries in which incidence decreased or did not increase during that period. In a further analysis, we examined the time for 26 countries to reach 40% fully vaccinated by October 30, 2021, along with the amount of time taken for the re-increase in COVID-19 incidence after the 40% vaccination threshold. The basis for the vaccination threshold of 40% was the global COVID-19 vaccination strategy and time-bound coverage target announced by the WHO [22]. The WHO warned that the risk of emergent vaccine-resistant variants may continue if the 40% vaccination target cannot be reached [23]. The International Monetary Fund staff also proposed that at least 40% of the population in all countries should be vaccinated by the end of 2021 to bring the pandemic under control [24]. Thirteen countries (Latvia, France, Portugal, Azerbaijan, Norway, Turkey, Italy, Spain, Sweden, Switzerland, Serbia, Croatia, and Cyprus) began to see a resurgence in incidence within 3 months of achieving 40% vaccination coverage. The other 13 countries, which displayed no increase in disease incidence within 3 months of achieving 40% vaccination coverage, were Poland, Czech Republic, Austria, Denmark, Lithuania, Estonia, Netherlands, Belgium, Greece, Germany, Hungary, Ireland, and Slovenia. Of the 13 countries in which 13 weeks or more elapsed before a re-increase in incidence after a vaccination rate of 40% was achieved, 11 countries (accounting for approximately 42% of the total countries) took 13 weeks, while the rest of the 13 countries took more than 13 weeks. Accordingly, the speed of vaccination was compared between countries reaching 40% before and after 3 months. For countries with 2 or more re-increase periods after achieving 40% vaccination coverage, the re-increase period was defined from the week of the interval including the week with the highest incidence. Analysis of variance was used to evaluate the significance of differences in the average incidence or the case growth rate in the 25 countries according to the average vaccination rate for 2 weeks immediately before the increase in cases for 3 consecutive weeks.

Statistical Analysis

All statistical analyses were conducted using Rex ver. 3.6.3 excel-based software (Rexsoft Co.; http://rexsoft.org).

Results

To identify trends in COVID-19 cases, we followed the CDC criteria to monitor weekly changes in the number of cases over a 4-week period by country. The CDC has provided a line graph on a monthly basis to visualize trends in the number of US COVID-19 cases [25]. The average incidence among the 25 countries where the COVID-19 case incidence increased for 3 consecutive weeks was significantly higher than that of the 10 countries where the number of cases decreased or did not increase during that period (Table 1). The correlation between the average incidence or weekly case growth rate per 100,000 population over 4 weeks for countries in which the incidence increased for 3 consecutive weeks and countries that relaxed the mandatory mask-wearing criteria at least once in the 7 weeks immediately before the increase was positive (r = 0.339, 0.388) (Tables 2, 3). However, negative correlations (r = −0.204, −0.260) were found between the average incidence during the 4 weeks of increase and the average vaccination rate for the 2 weeks immediately before the increase and during the 4 weeks of increase, respectively (Table 2). Negative correlations were also found individually (r = −0.165, −0.298) between the average case growth rate during the 4 weeks of increase and the average vaccination rate for the 2 weeks immediately before the increase and during the 4 weeks of increase, respectively (Table 3). In addition, the COVID-19 incidence during the 4 weeks after relaxation of mask mandates was significantly higher than that during the 4 weeks before relaxation (Table 4). This finding showed that the implementation of face covering mandates was necessary to prevent the spread of COVID-19 at the national level. The incidence rate in the 2 weeks after reinforcement

Table 2. Correlations among COVID-19 incidence, index score of facial covering policies, and vaccination rate in European countries

Variable	Average incidence per 100,000 population for 4 weeks[a]
Average incidence per 100,000 population for 4 weeks[a]	1
Relaxation of mandatory face covering policies at least once for 7 weeks[b]	0.339
Average index scores of facial covering policies	
For 7 weeks[b]	0.103
For 4 weeks[a]	0.309
Average vaccination rate	
For 2 weeks[b]	−0.204
For 4 weeks[a]	−0.260

[a]Three consecutive weeks of increasing incidence (between September 19 and October 30, 2021); [b]Shortly prior to 3 consecutive weeks of increasing incidence.

Table 3. Correlation among COVID-19 case growth rate, index score of facial covering policies, and vaccination rate in European countries

Variable	Average growth rate of cases per 100,000 population for 4 weeks[a]
Average growth rate of cases per 100,000 population for 4 weeks[a]	1
Relaxation of mandatory face covering policies at least once for 7 weeks[b]	0.388
Average index scores of facial covering policies	
For 7 weeks[b]	−0.041
For 4 weeks[a]	0.121
Average vaccination rate	
For 2 weeks[b]	−0.165
For 4 weeks[a]	−0.298

[a]Three consecutive weeks of increasing incidence (between September 19 and October 30, 2021); [b]Shortly prior to 3 consecutive weeks of increasing incidence.

Table 1. COVID-19 incidence, index score of facial covering policies, and vaccination rate in European countries

Group	No. of countries	Incidence*	Index scores of facial covering policies	Vaccination rate
Total	35	219.8 ± 199.4 (23.1–898.5)	2.2 ± 0.8 (0.0–4.0)	1.2 ± 0.8 (0.0–2.0)
High incidence[a]	25	244.1 ± 211.6 (27.6–898.5)	2.2 ± 0.8 (0.0–4.0)	1.2 ± 0.8 (0.0–2.0)
Low incidence[b]	10	158.9 ± 150.7 (23.1–562.8)	2.2 ± 0.9 (0.0–3.0)	1.3 ± 0.8 (0.0–2.0)

Data are presented as mean ± standard deviation (range).
[a]Three consecutive weeks of increasing incidence (between September 19 and October 30, 2021); [b]Three consecutive weeks of decreasing or no increase in incidence (between September 19 and October 30, 2021).
*$p < 0.05$.

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of mandatory masking policies was higher than in the 2 weeks before reinforcement, while the case growth rate was lower in the 2 weeks after strengthening of masking policies; however, neither change was statistically significant (Table 5). In contrast, no significant difference in average vaccination rate was observed in the 2 weeks immediately before the increase or decrease in incidence between countries with increasing and decreasing incidence (Table 6).

In addition, countries with an average vaccination rate of 60% or higher for the 2 weeks immediately prior to the 4-week increase showed decreases in the average incidence and case growth rate during the increase compared to countries with vaccination rates at or above 40% and less than 60%, but this was not statistically significant (Figures 1, 2). Furthermore, by analyzing the time taken for the re-increase in incidence after reaching the 40% vaccination threshold and the time to reach a fully vaccinated rate of 40%, we concluded that countries in which the incidence began to increase again after 3 months took significantly less time to reach 40% vaccination than countries where the incidence began to re-increase within 3 months (Table 7).

Discussion

This study showed the impact of face covering mandates and vaccination coverage on the incidence of COVID-19 in 35 European countries from June 20 to October 30, 2021. The average COVID-19 case incidence in countries where incidence increased for 3 consecutive weeks was significantly higher than in countries where cases decreased or did not increase during that period (Table 1). Furthermore, relaxation of face covering mandates was associated with an increase in the incidence of COVID-19 (Tables 2–4). Six US states (North Dakota, Iowa, Montana, Texas, Wyoming, and Arkansas) lifted face covering mandates between January and March 2021. As indicated by an event study analysis, daily new cases began to increase within 9 to 15 days after the mandates were lifted, followed by the highest increase (12 cases per 100,000 people)

Table 4. Comparison of COVID-19 incidence for 4 and 2 weeks before and after relaxation of mandatory masking policies in European countries

Group	No. of countries	Mean ± SD		Mean difference (95% CI)
		Pre	Post	
4 Weeks*	11	97.0 ± 61.4	140.1 ± 132.3	−43.1 (−84.4 to −1.9)
2 Weeks	13	91.9 ± 59.4	129.5 ± 123.3	−37.6 (−93.7 to 18.4)

SD, standard deviation; CI, confidence interval.
*$p < 0.05$.

Table 5. Comparison of COVID-19 incidence and growth rate in cases for 2 weeks before and after reinforcement of mandatory masking policies in European countries

Variable	No. of countries	Mean ± SD		Mean difference (95% CI)
		Pre	Post	
Incidence	9	173.9 ± 225.1	263.1 ± 272.0	−89.2 (−187.1 to 8.7)
Growth rate of cases	9	53.4 ± 67.7	9.2 ± 91.6	44.3 (−70.3 to 158.8)

SD, standard deviation; CI, confidence interval.

Table 6. Comparison of index score of facial covering policies and vaccination rate between countries with increasing and decreasing incidence

Variable	High-incidence countries ($n = 25$)[a]	Low-incidence countries ($n = 10$)[b]
Average index scores of facial covering policies for 7 weeks[c]	2.5 ± 0.7	2.1 ± 0.8
Average vaccination rate for 2 weeks[c]	1.1 ± 0.9	1.2 ± 0.8

Data are presented as mean ± standard deviation.
[a]Three consecutive weeks of increasing incidence (between September 19 and October 30, 2021); [b]Three consecutive weeks of decreasing or no increase in incidence (between September 19 and October 30, 2021); [c]Shortly prior to 3 consecutive weeks of increasing or decreasing incidence.

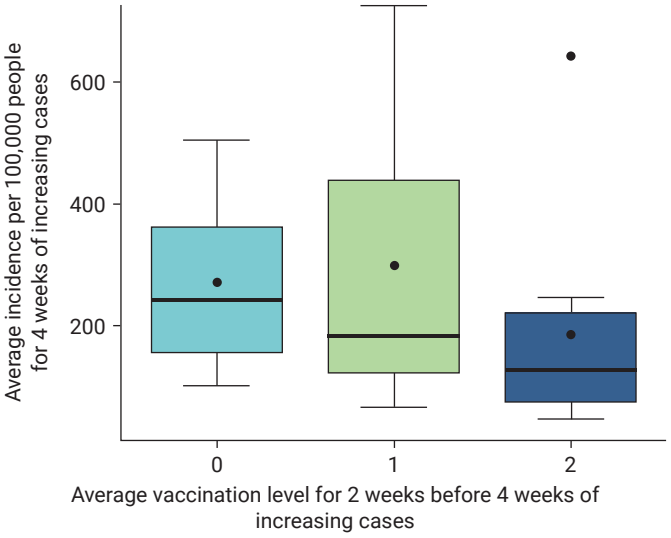

Figure 1. Incidence of COVID-19 in countries by level of vaccination.
The dot indicates the mean value.

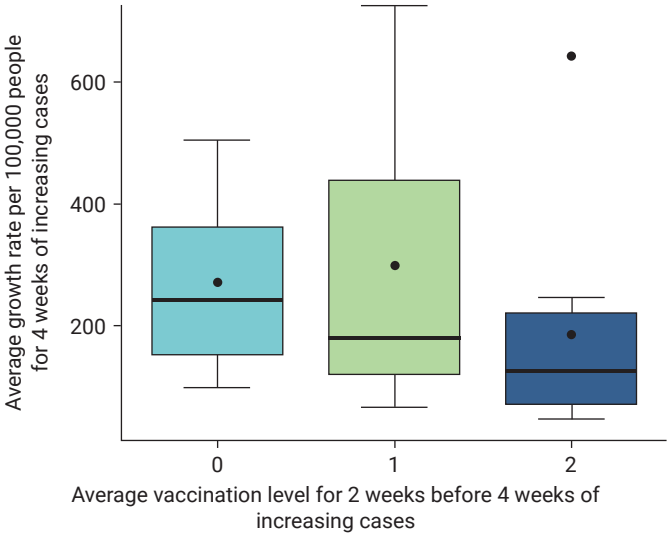

Figure 2. Growth rate of COVID-19 cases in countries by level of vaccination.
The dot indicates the mean value.

Table 7. Time to reach fully vaccinated coverage of 40% based on the time taken for re-increase in COVID-19 incidence after 40% vaccination

Variable	Before 3 mo (*n* = 13)	After 3 mo (*n* = 13)	*p*
Time to reach 40% fully vaccinated (wk)[a]	29.9 ± 3.7	26.9 ± 2.0	< 0.05

Data are presented as mean ± standard deviation.
[a]December 27, 2020 to October 9, 2021.

on day 45 [20]. This result implies that policies mandating mask-wearing in public needed to be strengthened, given that some states demanded or initiated the lifting of face covering obligations around that time [21]. We also found an increase in incidence and a decrease in the case growth rate after 2 weeks of reinforcement of face covering mandates, but neither finding was statistically significant (Table 5). The enforcement of mask-wearing may take longer than desired because behavior change reinforcement must disrupt current habits and simultaneously encourage a new and unfamiliar set of behaviors [26]. According to Layyy et al. [27], it takes 18 to 254 days for a person to form a new habit and an average of 66 days for a new behavior to become automatic. COVID-19 incidence may continue to increase in the early stages of strengthening of face covering mandates. Given the decrease in the case growth rate, however, the incidence could also decline over time. One study [28] showed that strengthening of face covering mandates in most or all shared or public places between August 2020 and January 2021 in 114 regions of 8 European countries reduced the reproduction number by 12% (95% confidence interval [CI], 7%–17%). Before the onset of the second wave of infection, these countries had implemented policies that mandated face coverings in only some public places. Thus, the advantage of wearing a face covering is expected to be realized when strengthened masking mandates are implemented [28]. Similarly, a 2% decrease in the growth rate of daily cases, constituting a significant difference, was observed at ≥21 days after masking became compulsory in a natural experiment including 15 US states [14]. In another study, the effectiveness of wearing a face covering was tested using mathematical modeling tools, with the results showing that public masking could considerably slow the spread of COVID-19 and prevent further outbreaks of the disease [29]. These findings demonstrate that face coverings are effective in protecting non-infected face-covering wearers from acquiring the disease and preventing infected wearers from transmitting the disease to others [13,16,30–32]. Therefore, governments must strongly encourage the use of face coverings in various public places using regulations [13].

In contrast, as seen in Table 6, no significant difference was present in vaccination rates between countries with increasing and decreasing incidence, which indicates that the increase or decrease in COVID-19 incidence may have little correlation with the level of vaccination. In fact, a national-level study revealed no perceptible relationship

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between the fully vaccinated percentage of the population and new COVID-19 cases across 68 countries [33]. Iceland and Portugal, where more than 75% of the population had been fully vaccinated, had more COVID-19 cases per 1 million people than countries such as Vietnam and South Africa, where about 10% of the population had been fully vaccinated. In the US, 2947 counties also showed no significant decline in COVID-19 cases as the percentage of fully vaccinated population increased [33]. The US CDC identified 4 of the 5 counties with the highest percentage of fully vaccinated population (84.3%–99.9%) as high-transmission counties [33]. Conversely, counties with less than 20% of the population fully vaccinated accounted for 26.3% of the 57 counties classified by the CDC as low-transmission counties. This suggests that NPIs, such as masking, should be implemented as vaccination rate increases [33]. From the end of June 2021, the number of European countries demanding or implementing the relaxation or lifting of face covering mandates has increased [6]. Perhaps people can wear less face coverings with the relief after COVID-19 vaccination [21]. However, a sizable proportion of Europe was vulnerable to infection in July 2021. At that time, just 35% of adults in the Europe and European Economies Area (including Iceland and Norway) were fully vaccinated, and Russia and other former Soviet Union countries had barely reached a 10% vaccination completion rate [6]. In addition, European civil officials appeared reluctant to adopt a culture of mask-wearing, which in Asian countries after the influenza epidemics of 1918, 1957, and 1968 and the SARS-CoV-1 outbreak in 2002 has been prevalent as an effective measure for epidemic containment [6]. The European Centers for Disease Control and Prevention has issued a risk assessment urging strict adherence to public health measures that have previously worked to control the effects of different variants [34]. The WHO has urged "extreme caution" for countries considering lifting COVID-19 restrictions, warning that high vaccination rates will not prevent the growing transmission of the virus [35]. Furthermore, the virus is still evolving and changing, and it is unclear to what extent vaccination provides protection against becoming infected or spreading the virus to others [35]. A recent study re-emphasized the difficulty of controlling the COVID-19 pandemic with vaccination alone [7]. This study also showed that the incidence of the disease increases again upon the cessation of masking when a certain range of vaccination rate has been achieved [7]. This is because reaching a certain vaccination level does not immediately stop the spread of the virus. Alternatively, wearing a face covering could prevent further COVID-19 cases until transmission finally begins to wane after 2 to 10 weeks [7]. Simulation outcomes of another study also suggested that eliminating NPIs (such as movement restriction and mask-wearing) while COVID-19 vaccines are being delivered may considerably increase infections, hospitalizations, and deaths compared to a situation in which NPIs are maintained [36]. These results emphasized that the 2 strategies of increasing the vaccination rate and adhering to sustainable NPIs (such as masking) should be combined to safely return to pre-COVID-19 pandemic conditions [36]. This combination is potentially synergistic because vaccination protects against the disease while face coverings interfere with virus transmission using a physical barrier to any coronavirus variant [8].

In addition, as shown in Figures 1 and 2, the number of new COVID-19 cases per 100,000 people increased until the countries achieved a vaccination rate of 60% of their total populations, but decreased after reaching 60% vaccination coverage. This result resembles that of a study in which the number of new cases per million people and the reproductive rate of COVID-19 slowly decreased as the vaccination rate increased, with a marked decrease when the vaccination rate exceeded 60% [37]. However, as of August 20, 2021, COVID-19 vaccination rates had not reached 60% on any continent, meaning that the vaccination rates were too low to prevent disease transmission [37]. In addition, this study showed that the faster a certain vaccination level was reached, the longer it took for the incidence to re-increase (Table 7). The results indicate that a rapid rise in the COVID-19 vaccination rate attenuates the intensity of the epidemic, extending the time to prepare for a resurgence. A scenario analysis by Wang et al. [38] in 2022 showed that accelerating the vaccination speed in the early stages of a vaccination campaign can reduce infections and increase vaccine effectiveness. In a scenario involving a doubled speed of vaccination, the vaccine effectiveness increased to 77.5% (95% CI, 29.2%–93.6%), averting an additional 1.71 million cases. By contrast, when the vaccination speed was halved, predicted vaccination effectiveness declined to 43.7% (95% CI, 9.34%–70.2%), with 2.55 million more infections. Therefore, the speed of vaccination from the beginning of the vaccination campaign is crucial, given the spread of new COVID-19 variants and the need for booster shots [38]. The simulation model of another study showed that reaching 80% vaccination while maintaining masking could avoid 7.66 million SARS-CoV-2 cases [7]. However, achieving this same range 2 months later could prevent 8.57 million cases. These results emphasize the need for continued adherence to masking in addition to the rapid implementation of vaccination.

This study has several limitations. During the re-spreading

of COVID-19 in Europe, a confirmed European case of the Omicron variant was reported, limiting the extension of the study period. Moreover, it was difficult to measure the independent impact of mandatory masking because European countries implemented multi-layered infection prevention and control measures, and this study examined COVID-19 incidence only at the national level. Lastly, of the 25 European countries selected for the study, Eastern European countries accounted for 44% (11 countries), or nearly half. This is due to limitations on the availability of the index scores of masking policies and vaccination rate. Thus, assessing the effectiveness of face covering mandates in Europe with more data from other European countries may help generalize our findings.

Conclusion

The hasty easing or lifting of face covering mandates along with increasing vaccination rates has resulted in a resurgence of COVID-19 infection in European countries. Not all countries on the same continent can vaccinate with equal speed, and the effects of masking at the national level may depend on government mandates. Hence, we strongly recommend policymakers proceed cautiously regarding the adjustment of face covering mandates to avoid a resurgence of COVID-19 incidence. Further control of the COVID-19 epidemic at the national level should allow for an effective vaccination campaign. It would also be wise to appropriately plan for effective and sustainable face covering mandates until the vaccination rate reaches a certain level.

Notes

Ethics Approval
Ethical approval was not required for this study on human participants because the data were accessed from the WHO, Our World in Data, and the Oxford COVID-19 Government Response Tracker (a publicly available database).

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

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None.

Availability of Data
The datasets are publicly available.

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

Additional Contributions
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References

1. Moore S, Hill EM, Tildesley MJ, et al. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. Lancet Infect Dis 2021;21:793–802.
2. World Health Organization (WHO). COVID-19 weekly epidemiological update, edition 61, 13 October 2021 [Internet]. WHO; 2021 [cited 2021 Dec 13]. Available from: https://apps.who.int/iris/handle/10665/346574.
3. World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard [Internet]. WHO; 2021 [cited 2021 Dec 17]. Available from: https://covid19.who.int/data.
4. World Health Organization (WHO). COVID-19 weekly epidemiological update, edition 63, 26 October 2021 [Internet]. WHO; 2021 [cited 2021 Dec 26]. Available from: https://apps.who.int/iris/handle/10665/347449.
5. Mathieu E, Ritchie H, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19) [Internet]. OurWorldInData.org; 2020 [cited 2023 Jan 11]. Available from: https://ourworldindata.org/covid-vaccinations.
6. Europe must open with extreme caution this summer. Lancet Reg Health Eur 2021;6:100176.
7. Bartsch SM, O'Shea KJ, Chin KL, et al. Maintaining face mask use before and after achieving different COVID-19 vaccination coverage levels: a modelling study. Lancet Public Health 2022;7:e356–65.
8. Brüssow H, Zuber S. Can a combination of vaccination and face mask wearing contain the COVID-19 pandemic? Microb Biotechnol 2022;15:721–37.
9. Paltiel AD, Schwartz JL, Zheng A, et al. Clinical outcomes of a COVID-19 vaccine: implementation over efficacy. Health Aff (Millwood) 2021;40:42–52.
10. Saad-Roy CM, Wagner CE, Baker RE, et al. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. Science 2020;370:811–8.
11. Keehner J, Horton LE, Binkin NJ, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med 2021;385:1330–2.
12. Joi P. Can we stop wearing masks after being vaccinated? [Internet]. GAVI Vaccines work; 2021 [cited 2021 Dec 10]. Available from: https://www.gavi.org/vaccineswork/can-we-stop-wearing-masks-after-being-vaccinated.
13. Howard J, Huang A, Li Z, et al. An evidence review of face masks against COVID-19. Proc Natl Acad Sci U S A 2020;118:e2014564118.
14. Lyu W, Wehby GL. Community use of face masks and COVID-19: evidence from a natural experiment of state mandates in the US.

https://doi.org/10.24171/j.phrp.2022.0287

Health Aff (Millwood) 2020;39:1419–25.
15. Hatzius J, Struyven D, Rosenbery I. Face masks and GDP [Internet]. Goldman Sachs; 2020 [cited 2021 Dec 15]. Available from: https://www.goldmansachs.com/insights/pages/face-masks-and-gdp.html.
16. Leech G, Rogers-Smith C, Monrad JT, et al. Mask wearing in community settings reduces SARS-CoV-2 transmission. Proc Natl Acad Sci U S A 2022;119:e2119266119.
17. Jehn M, McCullough JM, Dale AP, et al. Association between K-12 school mask policies and school-associated COVID-19 outbreaks: Maricopa and Pima Counties, Arizona, July-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1372–3.
18. Bauer S, Contreras S, Dehning J, et al. Relaxing restrictions at the pace of vaccination increases freedom and guards against further COVID-19 waves. PLoS Comput Biol 2021;17:e1009288.
19. Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ 2021;375:e068302.
20. Centers for Disease Control and Prevention (CDC). CDC real-world study confirms protective benefits of mRNA COVID-19 vaccines [Internet]. CDC; 2021 [cited 2021 Dec 11]. Available from: https://www.cdc.gov/media/releases/2021/p0329-COVID-19-Vaccines.html.
21. Adjodah D, Dinakar K, Chinazzi M, et al. Association between COVID-19 outcomes and mask mandates, adherence, and attitudes. PLoS One 2021;16:e0252315.
22. World Health Organization (WHO). Strategy to achieve global covid-19 vaccination by mid-2022 [Internet]. WHO; 2021 [cited 2022 Mar 28]. Available from: https://www.who.int/publications/m/item/strategy-to-achieve-global-covid-19-vaccination-by-mid-2022.
23. Besheer M. WHO launches strategy to vaccinate 40% of world against COVID by end of 2021 [Internet]. Voice of America; 2021 [cited 2022 Jan 11]. Available from: https://www.voanews.com/a/who-launches-strategy-to-vaccinate-40-of-world-by-end-of-2021-/6261489.html.
24. Agarwal R, Gopinath G. A proposal to end the COVID-19 pandemic [Internet]. International Monetary Fund; 2021 [cited 2023 Jan 11]. Available from: https://www.imf.org/en/Publications/Staff-Discussion-Notes/Issues/2021/05/19/A-Proposal-to-End-the-COVID-19-Pandemic-460263.
25. Centers for Disease Control and Prevention (CDC). COVID data tracker [Internet]. CDC; 2021 [cited 2021 Dec 15]. Available from: https://covid.cdc.gov/covid-data-tracker/#datatracker-home.
26. Call M. Why is behavior change so hard? [Internet]. Accelerate Learning Community; 2022 [cited 2022 Aug 15]. Available from: https://accelerate.uofuhealth.utah.edu/resilience/why-is-behavior-change-so-hard.
27. Layyy P, van Jaarsveld CH, Potts HW, et al. How are habits formed: modeling habit formation in the real world. Eur J Soc Psychol 2010;40:998–1009.
28. Sharma M, Mindermann S, Rogers-Smith C, et al. Understanding the effectiveness of government interventions against the resurgence of COVID-19 in Europe. Nat Commun 2021;12:5820.
29. Stutt RO, Retkute R, Bradley M, et al. A modelling framework to assess the likely effectiveness of facemasks in combination with 'lock-down' in managing the COVID-19 pandemic. Proc Math Phys Eng Sci 2020;476:20200376.
30. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet 2020;395:1973–87.
31. Peeples L. Face masks: what the data say. Nature 2020;586:186–9.
32. European Centre for Disease Prevention and Control (ECDC). Using face masks in the community: reducing COVID-19 transmission from potentially asymptomatic or pre-symptomatic people through the use of face masks [Internet]. ECDC; 2020 [cited 2021 Oct 28]. Available from: https://www.ecdc.europa.eu/en/publications-data/using-face-masks-community-reducing-covid-19-transmission.
33. Subramanian SV, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States. Eur J Epidemiol 2021;36:1237–40.
34. European Centre for Disease Prevention and Control (ECDC). Rapid Risk Assessment: Assessing SARS-CoV-2 circulation, variants of concern, non-pharmaceutical interventions and vaccine rollout in the EU/EEA, 16th update [Internet]. ECDC; 2021 [cited 2021 Oct 28]. Available from: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-assessing-sars-cov-2-circulation-variants-concern.
35. World Health Organization (2021). COVID-19 Virtual Press conference. 7 July 2021 [Internet]. WHO; 2021 [cited 2021 Sep 25]. Available from: https://www.who.int/publications/m/item/covid-19-virtual-press-conference-transcript---7-july-2021.
36. Patel MD, Rosenstrom E, Ivy JS, et al. Association of simulated COVID-19 vaccination and nonpharmaceutical interventions with infections, hospitalizations, and mortality. JAMA Netw Open 2021;4:e2110782.
37. Huang C, Yang L, Pan J, et al. Correlation between vaccine coverage and the COVID-19 pandemic throughout the world: based on real-world data. J Med Virol 2022;94:2181–7.
38. Wang R, Wang J, Hu T, et al. Population-level effectiveness of COVID-19 vaccination program in the United States: causal analysis based on structural nested mean model. Vaccines (Basel) 2022;10:726.

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Original Article

Evaluation and follow-up of pain, fatigue, and quality of life in COVID-19 patients

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ABSTRACT

Objectives: We evaluated pain, fatigue, anxiety, depression, and quality of life in patients hospitalized for coronavirus disease 2019 (COVID-19) and observed them over a period of 3 months. We also investigated the relationship of these symptoms to age, sex, disease severity, and levels of anxiety and depression.

Methods: The study included 100 confirmed COVID-19 patients (i.e., positive on a polymerase chain reaction test) between the ages of 18 and 75 years. Pain (visual analog scale [VAS]), fatigue (fatigue severity scale), anxiety, and depression (hospital anxiety and depression scales) were evaluated on the first day of hospitalization and at 1-month and 3-month follow-ups. The short form-12 questionnaire was used to measure quality of life at the 1-month and 3-month follow-ups.

Results: No differences were found in pain, fatigue, anxiety levels, depression levels, and quality of life according to disease severity. High VAS scores at hospital admission were related to continued pain at the 3-month follow-up (odds ratio [OR], 1.067; $p < 0.001$). High VAS (OR, 1.072; $p = 0.003$) and anxiety levels (OR, 1.360; $p = 0.007$) were related to severe fatigue at the 3-month evaluation.

Conclusion: Pain, fatigue, anxiety, and depression appear to be long-term sequelae of COVID-19 and can affect quality of life. High VAS and anxiety levels were found to be associated with long-term fatigue.

Keywords: COVID-19; Fatigue; Pain

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Introduction

On February 11, 2020, the World Health Organization (WHO) named a new disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), and declared the COVID-19 pandemic on March 11, 2020 [1]. Since then, the virus has spread rapidly around the world. As of June 2022, more than 535 million people had been

infected with COVID-19, and 6 million had died [2].

COVID-19 can affect all age groups, from infants to the elderly, and manifests as a viral disease with a wide range of clinical symptoms, of which fatigue, fever, and cough are the most common [3]. The most frequent musculoskeletal symptoms are myalgia, arthralgia, back pain, and fatigue, which can be seen from the onset of symptoms through the most severe stages of the disease [4–6]. Symptoms such as fatigue and dyspnea have been shown to persist beyond the acute stage to long after discharge from the hospital, emphasizing the importance of long-term follow-up and the rehabilitation therapy needs of COVID-19 patients [7]. References to long-term COVID or post-COVID syndrome have come to the fore. The National Institute for Health and Care Excellence defines post-COVID syndrome as "signs and symptoms that develop during or after an infection consistent with COVID-19 that last more than 12 weeks and cannot be explained by another diagnosis" [8].

The current literature supports the premise that pain in COVID-19 patients is due, at least in part, to the neurotropism of SARS-CoV-2. Pain can be caused by the interaction of the virus with the angiotensin-converting enzyme isoform 2 receptors in spinal neurons and microglia, by immune system-mediated inflammation, or by viral damage [9].

Pain and fatigue dramatically affect quality of life. In one study, the quality of life was found to be worse in COVID-19 patients with persistent pain [10], but the factors associated with these persistent symptoms were unclear. In this study, we evaluated musculoskeletal symptoms such as pain and fatigue, levels of anxiety and depression, and the quality of life in patients hospitalized for COVID-19 and followed them for 3 months. We also investigated how their symptoms were linked to age, sex, disease severity, and levels of anxiety and depression.

Materıals and Methods

Participants

This was a single-center cohort study that included confirmed COVID-19 (i.e., polymerase chain reaction positive) patients between ages 18 and 75 years who were hospitalized at the Afyonkarahisar Health Sciences University Hospital, Pandemic Service between February 15, 2021 and July 15, 2021 and voluntarily agreed to participate.

We excluded patients who were unwilling, illiterate, or pregnant and patients with a history of chronic pain or fatigue during the past 6 months (before COVID-19). We also excluded critically ill patients with respiratory failure requiring mechanical ventilation, shock, or organ failure requiring admission to the intensive care unit (ICU). Patients who were later taken to the ICU or who could not be reached during the follow-up period were excluded.

A total of 242 patients were hospitalized with a diagnosis of COVID-19 at the Afyonkarahisar Health Sciences University Hospital between February 1, 2021 and July 1, 2021. Forty-two patients were >75 years old, 19 did not want to participate, 26 had chronic fatigue and pain symptoms, 8 were illiterate, and 6 were pregnant. Thus, 141 patients were assessed for eligibility. Of the 141 patients, 21 could not be reached for follow-up by telephone, 5 had communication problems due to language differences, and 15 were transferred to the ICU. Therefore, the remaining 100 patients were contacted and completed the questionnaire (Figure 1).

Assessments

Pain

For the pain assessment, we used the visual analog scale (VAS), which is easy to understand, apply, and interpret. It provides valid and reliable data in a short time. Using a visual linear scale of 100 mm, the patient was told that point 0 represented no pain and point 100 represented the most severe pain they had ever felt in their life. The patient was asked to put a mark on the point corresponding to his/her pain. Patients who marked a VAS score of more than 4 mm were considered to have pain [11]. In addition, we determined the location of their pain (neck, back, low back, upper extremity, lower extremity).

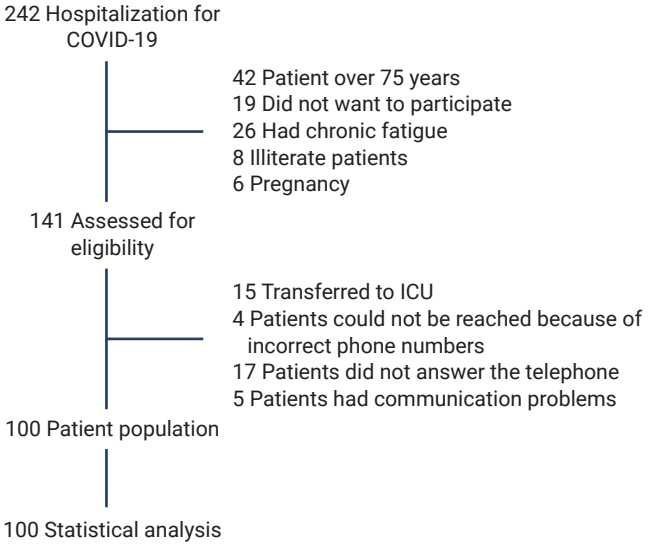

Figure 1. Diagram of patient sample selection and exclusions (boxes on the right).
COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Fatigue

Fatigue was evaluated using the Turkish version of the fatigue severity scale (FSS). The FSS consists of 9 items, and each item is scored on a 7-point scale from 1 to 7 (1, strongly disagree; 7, strongly agree). The total score is calculated by deriving the arithmetic mean. In our study, patients were considered to have severe fatigue if the total FSS score was ≥4 [12].

Anxiety and depression

We used the hospital anxiety and depression scale (HADS) to determine the risk of anxiety and depression in patients and to determine its level. The HADS consists of 2 subscales to evaluate anxiety and depression, and the cutoff scores in the Turkish version are 10 for the anxiety subscale and 7 for the depression subscale [13].

Quality of life

The short form-12 (SF-12) was used to evaluate patients' quality of life. The SF-12, a shortened and simplified version of the SF-36, is an easy-to-administer questionnaire. It assesses the 2 main components of general health, physical and mental health, and consists of 12 questions. High scores indicate good health.

Patients' demographic information was obtained including comorbidities, initial COVID-19 symptoms, vaccination status, and drugs used by the patient. Pain, fatigue, anxiety, and depression were evaluated on the first day of hospitalization (initial) and at the 1-month and 3-month follow-ups. The 1-month and 3-month patient evaluations were conducted over the telephone. In these phone interviews, answers to the SF-12 questionnaire were used to measure the patients' quality of life, pain, fatigue, anxiety, and depression.

A patient's COVID-19 illness was classified as mild, moderate, or severe according to the severity of their symptoms. Levels of pain, fatigue, anxiety, depression, and quality of life were compared according to disease severity. The disease severity classification was determined based on the clinical management guidelines for COVID-19 published by the WHO. Patients without evidence of pneumonia or hypoxia were classified as mild cases. Patients with clinical signs and symptoms of pneumonia but no signs of severe pneumonia and no need for oxygen were classified as moderate cases. Patients with signs and symptoms of pneumonia, a respiratory rate of more than 30 breaths per minute, severe respiratory distress, or a saturated oxygen level in room air of <90% were considered severe cases [14].

The correlations between symptoms and quality of life were investigated. In addition, the factors that could predict pain and fatigue at the 3-month follow-up were assessed.

Statistical Analysis

The statistical analysis was performed using IBM SPSS ver. 20.0 (IBM Corp.). The distribution of continuous variables was evaluated using the Shapiro-Wilk test. For descriptive statistics, the number of units, percent, and median (range) values were given. For comparisons of 2 independent groups using nonparametric data, the Mann-Whitney U-test was applied. For a comparison of 3 independent groups using nonparametric data, the Kruskal-Wallis test was used. A Spearman correlation analysis was used to evaluate the associations between quantitative variables. Prior to logistic regression analysis, we used the chi-square test, Student t-test, and analysis of variance to identify factors related to long-term pain and fatigue with $p < 0.1$. These factors were then analyzed using logistic regression analysis. A p-value less than 0.05 was considered to indicate statistical significance.

Ethical Approval and Ministry Permission

We received approval for this study from the Afyonkarahisar Health Sciences University, Clinical Research Ethics Committee (January 8, 2021; Protocol 2021/57), as well as permission from the Ministry of Health of the Republic of Turkey. The ClinicalTrials.gov identifier number for the study is NCT04454333. The study was conducted following the principles of the Declaration of Helsinki. Written informed consent for the study was obtained.

Results

The patients' demographic data, comorbidities, initial symptoms, pain sites, drugs used, and vaccination status are presented in Table 1. The frequencies of pain, severe fatigue, anxiety, and depression are shown in Figure 2.

The mean VAS, FSS, HADS-anxiety, HADS-depression, and SF-12 scores for female and male patients at their initial, 1-month, and 3-month follow-up evaluations are given in Table 2. The VAS score was higher in females than in males in both the 1-month and 3-month follow-ups ($p = 0.040$, $p = 0.007$, respectively). The mean VAS, FSS, HADS-anxiety, HADS-depression, and SF-12 scores showed statistically significant changes at 1 month and 3 months, respectively (Table 2).

There were no differences in pain severity, fatigue, anxiety, or depression according to disease severity ($p > 0.05$). When males and females were examined separately, the 3-month VAS value in the moderate disease category was significantly higher in females than in males ($p = 0.009$). In patients with severe disease, anxiety and depression scores were significantly higher in females than in males at the 3-month follow-up ($p = 0.038$, $p = 0.010$, respectively) (Table 3).

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Table 1. Demographic information, comorbidities, initial symptoms, pain sites, medications, and vaccination status of patients hospitalized for COVID-19

Variable	Value (n = 100)
Age (y), mean ± SD (range)	53.45 ± 12.76 (20–75)
Sex (male:female)	49:51
Education	
No formal education	3
Primary school	39
High school	33
University	25
Comorbidities	
None	31
Hypertension	5
Diabetes mellitus	10
Coronary artery disease	1
Chronic respiratory disease	1
Other	24
Multiple	28
Initial symptoms	
Fever	34
Cough	65
Sore throat	21
Headache	26
Musculoskeletal pain	46
Fatigue	63
Loss of taste and smell	8
Pain sites	
Cervical	66
Back	77
Low back	55
Upper extremity	64
Lower extremity	68
Analgesic	
NSAID	43
Paracetamol	35
Opioids	3
None	14
Drug	
Favipiravir	93
None	7
Corticosteroids	69
Vaccination status	
None	75
1 Dose Sinovac[a]	4
2 Doses Sinovac	15
1 Dose BioNTech[b]	1
2 Doses BioNTech	1
2 Doses Sinovac, 1 dose BioNTech	3
2 Doses Sinovac, 2 doses BioNTech	1

COVID-19, coronavirus disease 2019; *n*, number of patients; SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug.
[a]CoronaVac, [b]mRNA BNT162b2.

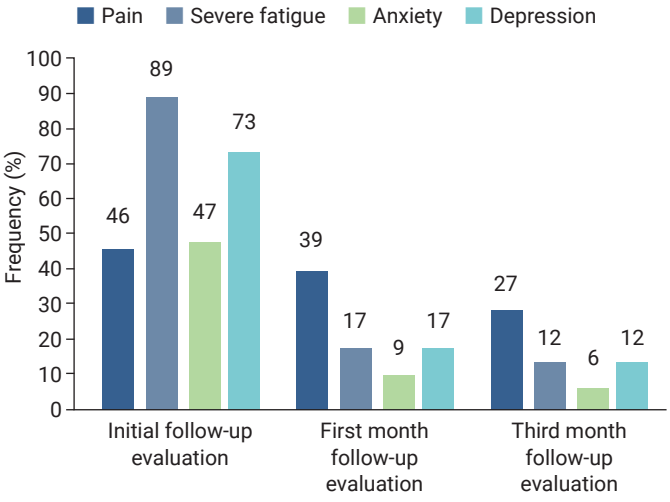

Figure 2. Frequency of symptoms at initial, 1-month, and 3-month follow-up evaluations.

In the initial evaluations, VAS values and fatigue levels showed a moderately positive correlation ($p < 0.001$, $r = 0.38$). In the long-term follow-up at 3 months, the correlation continued ($p < 0.001$, $r = 0.35$).

A weak correlation was found between the severity of depression symptoms and the VAS scores ($p = 0.007$, $r = 0.27$). In the long-term (3-month) follow-up, the correlation was not maintained ($p = 0.058$).

In the evaluations done at hospital admission and at 3 months, moderately positive correlations between fatigue and depression symptoms ($p < 0.001$; $r = 0.52$, $r = 0.35$, respectively) and between fatigue and anxiety symptoms ($p < 0.001$; $r = 0.61$, $r = 0.44$, respectively) were detected.

SF-12 scores were negatively and weakly correlated with VAS scores at 3 months ($p < 0.001$, $r = 0.261$). SF-12 scores showed moderately negative correlations with fatigue ($r = 0.607$), depression ($r = 0.538$), and anxiety ($r = 0.564$) at 3 months.

Comparisons of age; sex; presence of comorbidities; and VAS, FSS, HADS-anxiety, and HADS-depression scores in patients with and without pain in the third month are shown in Table 4. Sex ($p = 0.018$), initial VAS values ($p < 0.001$), HADS-depression scores at 3 months ($p = 0.002$), and FSS scores at 3 months) ($p < 0.001$) were statistically different between the patients with and without pain at 3 months (Table 4). Next, we analyzed sex, initial VAS values, HADS-depression scores (3-month), and FSS scores (3-month) using logistic regression analysis and found that high VAS values at hospital admission were predictive of pain in the 3-month follow-up (odds ratio [OR], 1.067; $p < 0.001$) (Table 5).

Comparisons of age, sex, and presence of comorbidities, as well as VAS, FSS, HADS-anxiety, and HADS-depression scores

Table 2. Mean VAS, FSS, HADS-anxiety, HADS-depression, and SF-12 scores at initial, 1-month, and 3-month follow-up evaluations in female and male COVID-19 patients

Evaluation time	Male ($n=49$)	Female ($n=51$)	p
Age (y)	54.49 ± 13.27	52.45 ± 12.31	0.42
VAS			
Initial	24.48 ± 32.58[a)]	37.64 ± 37.04[a)]	0.071
1 Month	11.22 ± 18.1	20.39 ± 23.36[b)]	0.040
3 Months	2.75 ± 8.35[b)]	8.33 ± 12.35[c)]	0.007
p*	< 0.001	< 0.001	
FSS			
Initial	4.99 ± 1.88[a)]	5.11 ± 1.55[a)]	0.825
1 Month	3.32 ± 1.83[b)]	3.54 ± 1.77[b)]	0.508
3 Months	2.38 ± 1.85[c)]	2.71 ± 1.63[c)]	0.229
p*	< 0.001	< 0.001	
HADS-anxiety			
Initial	9.93 ± 5.19[a)]	9.92 ± 5.29[a)]	0.975
1 Month	4.18 ± .08[b)]	4.76 ± 4.28[b)]	0.390
3 Months	2.42 ± 3.98[c)]	2.76 ± 3.78[c)]	0.409
p*	< 0.001	< 0.001	
HADS-depression			
Initial	10.28 ± 5.88[a)]	10.27 ± 5.83[a)]	0.981
1 Month	3.95 ± 4.43[b)]	4.29 ± 4.15[b)]	0.413
3 Months	2.87 ± 5.16[c)]	2.49 ± 3.67[c)]	0.243
p*	< 0.001	< 0.001	
SF-12			
1 Month	74.57 ± 15.71	75.31 ± 15.03	0.970
3 Months	86.83 ± 16.36	87.68 ± 15.58	0.869
p*	< 0.001	< 0.001	

Data are presented as mean ± standard deviation.
VAS, visual analog scale (for measuring pain); FSS, fatigue severity scale; HADS, hospital anxiety depression scale; SF-12, short form-12 (quality of life questionnaire); COVID-19, coronavirus disease 2019.
[a-c)]Different letters in the same column indicate within-group differences.
*Significance level of intragroup data; p-values < 0.05 indicate statistical significance.

in patients with and without pain in the third month are given in Table 6. VAS (3-month, $p=0.001$), HADS-anxiety (3-month, $p<0.001$), and HADS-depression (3-month, $p<0.001$) scores showed a statistically significant difference between patients with and without severe fatigue in the third month. We then analyzed VAS (3 months), HADS-anxiety (3 months), and HADS-depression (3 months) scores using logistic regression analysis and found that high VAS scores (OR, 1.072; $p=0.003$) and anxiety levels (OR, 1.360; $p=0.007$) were predictive of severe fatigue in the third month (Table 7).

Discussion

Arthralgia and myalgia are not unique to COVID-19 and are common symptoms of flu-like syndromes [15]. Myalgia is seen in up to 50% of COVID-19 patients [16]. We found the frequency of pain to be 46% in hospitalized COVID-19 patients. In a Turkish study, the most common pain symptoms were myalgia and arthralgia (69.2%) [17]. In another study, 159 patients reported at least 1 type of pain syndrome, with a prevalence of 71.6% [18]. Hoong et al. [19] reported that 30% of 294 hospitalized COVID-19 patients reported musculoskeletal symptoms. Of these, 88 patients (37.5%) had myalgia, 5.7% had arthralgia, 6.8% had new-onset back pain, and 50% had diffuse body pain. In our study, a detailed pain examination was conducted according to regions of the body, and back pain was found to be the most prevalent site (77%). This was followed by lower extremity pain (68%), neck pain (66%), upper extremity pain (64%), and low back pain (55%).

In a study of 379 patients in our hospital, the frequency of myalgia was found to be higher among patients in the ICU than on the ward [20]. Studies have reported that the frequency of pain increases as the severity of the disease increases. For example, in one study, low lymphocyte and high D-dimer levels, the presence of back pain, computed tomography findings of COVID-19, longer hospital stays, and chronic disease were associated with post-COVID-19 musculoskeletal symptoms [21]. Disser et al. [16] concluded that myalgia could be a predictive factor in determining overall disease severity in patients with abnormal chest computed tomography and radiography findings. Furthermore, Tuzun et al. [22] reported a higher incidence of arthralgia in patients with severe COVID-19, whereas Hoong et al. [19] concluded that the presence of musculoskeletal symptoms was not related to the risk of developing pneumonia. In our study, there were no significant differences in VAS scores according to disease severity. As far as we know, our study is the first to evaluate the presence and severity of pain in COVID-19 patients using the VAS. Unlike other studies, our study investigated whether the severity of pain, rather than the subjective presence of pain, changed according to the severity of the disease. Pain severity did not differ significantly between groups based on disease severity. Myalgia is a common symptom in COVID-19. Its presence may vary according to the severity of the disease. However, there is not enough evidence to conclude that the severity of myalgia increases according to the severity of the disease.

Studies have shown that symptoms such as myalgia, anxiety, and fatigue are more persistent in females than in males in long-term follow-ups [23,24]. More fatigue, pain,

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Table 3. Comparison of fatigue, anxiety, depression, and quality of life according to disease severity and sex

Variable	Evaluation time	Mild disease ($n=43$)		Moderate disease ($n=47$)		Severe disease ($n=10$)		p
		Male	Female	Male	Female	Male	Female	
Age (y)	Initial	49.8 ± 13.3	46.8 ± 12.0	56.4 ± 12.2	55.4 ± 10.7	63.8 ± 11.9	65.0 ± 9.8	0.001
	p[a]	0.458		0.864		0.914		0.041[b] 0.003[c] 0.188[d]
VAS	Initial	17.1 ± 28.9	26.6 ± 33.5	28.6 ± 33.7	44.2 ± 38.2	35.0 ± 40.7	57.5 ± 39.5	0.056
	p[a]	0.324		0.134		0.476		
	1 Month	8.8 ± 16.9	11.6 ± 18.2	12.7 ± 20.1	25.4 ± 23.8	14.2 ± 16.3	37.5 ± 33.0	0.074
	p[a]	0.591		0.067		0.257		
	3 Months	2.9 ± 7.8	3.9 ± 10.2	3.4 ± 9.9	11.0 ± 11.9	0.0 ± 0.0	16.3 ± 19.7	0.115
	p[a]	0.968		0.009		0.257		
FSS	Initial	4.2 ± 2.1	4.9 ± 1.5	5.7 ± 1.5	5.1 ± 1.7	5.3 ± 1.7	6.0 ± 1.0	0.129
	p[a]	0.285		0.55		> 0.999		
	1 Month	2.8 ± 1.7	3.2 ± 1.9	3.7 ± 1.8	3.6 ± 1.6	3.8 ± 2.0	5.1 ± 1.1	0.054
	p[a]	0.401		0.685		0.352		
	3 Months	2.8 ± 1.8	2.3 ± 1.6	2.6 ± 1.8	2.8 ± 1.5	2.9 ± 2.1	4.7 ± 1.1	0.035[e]
	p[a]	0.307		0.765		0.171		
HADS-anxiety	Initial	8.7 ± 5.2	9.1 ± 6.0	11.4 ± 4.9	10.2 ± 4.7	9.0 ± 5.9	12.8 ± 5.1	0.185
	p[a]	0.836		0.441		0.476		
	1 Month	3.7 ± 3.4	4.4 ± 5.2	4.6 ± 4.8	4.6 ± 3.4	4.3 ± 3.9	8.3 ± 2.2	0.149
	p[a]	0.941		0.499		0.114		
	3 Months	2.0 ± 2.6	2.4 ± 4.6	3.1 ± 5.2	2.6 ± 3.1	1.7 ± 2.7	5.8 ± 1.5	0.208
	p[a]	0.503		0.445		0.038		
HADS-depression	Initial	9.4 ± 5.2	9.2 ± 7.1	11.4 ± 6.2	10.6 ± 4.5	9.5 ± 7.4	13.8 ± 5.3	0.197
	p[a]	0.51		0.732		0.476		
	1 Month	3.2 ± 3.5	3.9 ± 4.5	4.9 ± 5.2	4.0 ± 3.8	3.3 ± 4.5	8.0 ± 2.8	0.171
	p[a]	0.795		0.966		0.067		
	3 Months	2.8 ± 5.4	2.3 ± 4.3	3.6 ± 5.5	2.3 ± 3.3	0.5 ± 1.2	5.0 ± 1.2	0.243
	p[a]	0.826		0.991		0.010		
SF-12	1 Month	78.6 ± 14.7	79.2 ± 17.4	71.5 ± 16.6	73.9 ± 12.7	71.6 ± 15.2	62.5 ± 3.6	0.035[e]
	p[a]	0.894		0.685		0.476		
	3 Months	90.0 ± 15.1	88.5 ± 19.0	84.7 ± 18.3	88.5 ± 12.6	83.4 ± 13.3	78.4 ± 10.9	0.168
	p[a]	0.903		0.654		0.762		

Data are presented as mean ± standard deviation.

VAS, visual analog scale for measuring pain; FSS, fatigue severity scale; HADS, hospital anxiety depression scale; SF-12, short form-12; p, significance level of data between mild, moderate and severe disease groups without distinction between male and female.

[a]Significance level of the comparison of the mean of male and female within the group; [b]significance value of the difference between the mean age of patients with mild and moderate disease; [c]significance value of the difference between the mean age of patients with mild and severe disease; [d]significance value of the difference between the mean age of patients with moderate and severe disease; [e]There was no difference between groups in *post hoc* analyses.

anxiety, and depression were reported in female patients [25]. In our study, we also found that the severity of pain was higher in females, although anxiety and fatigue were similar in both sexes. Understanding why pain is more common and more severe in females requires further research.

Although we found that pain persisted, it decreased from an initial rate of 46% to 27% at the 3-month follow-up. It has been reported in the literature that symptoms of COVID-19 can persist for up to 35 days and that approximately 10% of those infected with COVID-19 will suffer from musculoskeletal symptoms for some time within the first year [26,27]. The study by Karaarslan et al. [23] showed that approximately 2 out of 5 patients had at least 1 musculoskeletal symptom at 6 months. Fatigue, arthralgia, and myalgia are the most common musculoskeletal symptoms, both acutely and long-term.

Table 4. Factors associated with the presence of pain at the 3-month evaluation of COVID-19 patients

Variable	Patients with pain in the third month		Patients without pain in the third month		*p*[a]
	Male	Female	Male	Female	
Age (y)	53.4 ± 12.7	53.1 ± 9.5	54.7 ± 13.5	52.1 ± 13.8	0.727
p	0.897		0.443		
Comorbidity					
Yes	0.238	0.762	0.521	0.479	0.248
No	0.5	0.5	0.64	0.36	
p	0.215		0.330		
VAS (initial)	69.3 ± 12.9	72.8 ± 12.7	15.7 ± 27.6	16.7 ± 30.1	< 0.001
p	0.938		0.966		
FSS (3 mo)	3.9 ± 1.4	3.5 ± 1.7	2.0 ± 1.7	2.2 ± 1.3	< 0.001
p	0.559		0.376		
HADS-anxiety (3 mo)	4.1 ± 4.8	2.6 ± 2.4	2.1 ± 3.7	2.8 ± 4.4	0.034
p	0.658		0.596		
HADS-depression (3 mo)	6.8 ± 8.2	2.6 ± 1.9	2.1 ± 4.4	2.3 ± 4.4	0.002
p	0.585		0.753		

Data are presented as mean ± standard deviation.
COVID-19, coronavirus disease 2019; VAS, visual analog scale for measuring pain; FSS, fatigue severity scale; HADS, hospital anxiety depression scale.
[a]Significance value of the parameters compared without male-female grouping between patients with and without pain at the third month.

Table 5. Multivariate logistic regression model for variables associated with pain at the 3-month follow-up

Variable	OR (95% CI)	*p*
Sex	1.243 (0.869–16.943)	0.076
VAS (initial)	1.067 (1.032–1.102)	< 0.001
FSS (3 mo)	1.377 (0.854–2.222)	0.190
HADS-anxiety (3 mo)	0.792 (0.562–1.116)	0.182
HADS-depression (3 mo)	1.243 (0.923–1.673)	0.152

OR, odds ratio; CI, confidence interval; VAS, visual analog scale for measuring pain; FSS, fatigue severity scale; HADS, hospital anxiety depression scale.

Fatigue, muscle weakness, shortness of breath, pain and discomfort, anxiety and depression, and impaired concentration have been shown to persist in more than 20% of patients with post-COVID syndrome, up to 47% in some studies [28]. In one systematic review the prevalence of post-COVID syndrome reached 80% and symptoms, particularly fatigue, persisted for up to 24 weeks [29]. According to a large Chinese longitudinal cohort study, most COVID-19 survivors had a significant improvement at the 1-year follow-up. Although improved, these patients still had more problems with movement, pain, anxiety, or depression than the control group [30].

Research to optimize the management of post-COVID syndrome, the long-lasting symptoms of COVID-19 and their influencing factors, is ongoing. In the current literature, post-COVID syndrome is independent of the acute disease severity and the humoral response [31,32]. However, there are also studies showing that severe acute COVID-19, hospitalization, and comorbidities affect the persistence of symptoms [28], and that myalgia in the initial phase is associated with musculoskeletal pain as a post-COVID sequela [27]. Supporting this hypothesis, we found that high initial VAS scores were associated with pain at the 3-month follow-up. However, post-COVID syndrome is still poorly understood, and more research is needed [32].

There are studies showing that muscle weakness and decreased physical performance after COVID-19 infection [33] and chronic fatigue syndrome are common with COVID-19 [34,35]. In our study, we determined the frequency of severe fatigue, as evaluated with the FSS, to be 89% in hospitalized COVID-19 patients. Similarly, fatigue was reported in 85% of cases in a case series of 7 acute-phase patients [36]. In the study by Tuzun et al. [22], the most common musculoskeletal symptom was fatigue (85.3%). The overall prevalence of fatigue symptoms in one review was 25.6% (range, 4%–100%) [5]. Goertz et al. [37] found that 92.9% and 93.5% of hospitalized and non-hospitalized COVID-19 patients, respectively, reported continued fatigue up to 79 days after disease onset. In a group of 120 hospitalized COVID-19 patients studied by Garrigues et al. [7], symptoms such as fatigue and shortness of breath were still present 110 days after the patients were sent home [7].

Because fatigue is a common and persistent symptom of COVID-19, it is important to analyze the associated factors. In a study by Townsend et al. [38], there was no relationship between the severity of the disease (hospital admission,

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Table 6. Factors associated with the presence of severe fatigue at the 3-month evaluation of COVID-19 patients

Variable	Patients with severe fatigue in the third month		Patients without severe fatigue in the third month		p[a]
	Male	Female	Male	Female	
Age (y)	53.2 ± 11.8	51.6 ± 12.7	55.2 ± 14.1	53.2 ± 12.2	0.381
p	0.753		0.5		
Comorbidity					
Yes (%)	39.3	60.7	46.3	53.7	0.860
No (%)	50.0	50.0	68.4	31.6	
p	0.530		0.111		
VAS (3 mo)	5 ± 11.2	13.7 ± 14.7	1.6 ± 6.3	3.9 ± 7.9	0.001
p	0.051		0.108		
HADS-anxiety (3 mo)	4.4 ± 5.5	4.3 ± 4.4	1.4 ± 2.4	1.5 ± 2.7	< 0.001
p	0.761		0.653		
HADS-depression (3 mo)	4.6 ± 5.7	4 ± 4.5	1.9 ± 4.7	1.3 ± 2.3	< 0.001
p	> 0.999		0.343		

Data are presented as mean ± standard deviation.
VAS, visual analog scale for measuring pain; HADS, hospital anxiety depression scale.
[a]Significance value of the parameters compared without male-female grouping between patients with and without severe fatigue at the third month.

Table 7. Multivariate logistic regression model for variables associated with severe fatigue at the 3-month follow-up evaluation of COVID-19 patients

Variable	OR (95% CI)	*p*
VAS (3 mo)	1.072 (1.024–1.123)	0.003
HADS-anxiety (3 mo)	1.360 (1.088–1.701)	0.007
HAD-depression (3 mo)	0.918 (0.767–1.098)	0.349

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; VAS, visual analog scale for measuring pain; HADS, hospital anxiety depression scale.

supplemental oxygen, or intensive care needs) and the severity of fatigue. This is supported by our study, which found that the severity of fatigue did not differ according to disease severity. Townsend et al. [38] also reported more fatigue in females than in males and in those previously diagnosed with depression and anxiety. A relationship between fatigue and anxiety has also been shown in different diseases, such as stroke [39]. We found that fatigue was correlated with pain, depression, and anxiety. The current literature suggests that pain and anxiety may be associated with fatigue in COVID-19 disease. Therefore, although fatigue was a persistent symptom in COVID-19 regardless of disease severity, it may be associated with female sex, anxiety, depression, and pain.

Depression, anxiety, and post-traumatic stress syndrome are all long-term sequelae of COVID-19 [34]. Ma et al. [40] reported a 43.1% prevalence of depression in COVID-19 patients, and that having a family member infected with COVID-19, having a severe COVID-19 infection, being male, and frequently using social media to obtain information about COVID-19 may be independently associated with depression. Cohorts with >20% of patients admitted to the ICU during acute COVID-19 outbreaks reported a higher prevalence of fatigue, anxiety, depression, and sleep disturbance than cohorts with ICU admissions <20% [41]. The reported risk factors for mental health symptoms include female sex and being a healthcare worker. While pain can be a risk factor for mental health symptoms, some studies have also reported no relationship between pain and anxiety or depression [10,42]. Initially, 47% of our patients had symptoms of anxiety and 73% had symptoms of depression. The proportion of patients with anxiety decreased to 9% at the 1-month follow-up and to 6% at the 3-month follow-up. Patients with symptoms of depression decreased to 17% and 12% at the 1-month and 3-month follow-ups, respectively. In our study, no significant differences were observed in the symptoms of anxiety or depression according to disease severity and sex. Only fatigue and symptoms of anxiety or depression were correlated. Although various risk factors for anxiety and depression after COVID-19 have been reported, studies with larger samples are needed on this subject.

Pain, fatigue, anxiety, and depression can significantly affect quality of life. Patients with COVID-19 have been reported to have a poor quality of life and suffer from significant physical and psychological impairments. Therefore, we need to follow up with patients to fully understand the long-term impact of COVID-19 and establish prompt and efficient interventions to mitigate its consequences [43]. In our study, we evaluated the quality

of life at 1 month and 3 months after discharge from the hospital and found a significant improvement in the quality of life at 3 months. It was an expected result that the quality of life would improve as the disease improved. Although significant improvements were reported in patients' quality of life, based on the patients' degree of dyspnea at rest and during daily activities for 15 days after discharge from the hospital, the quality of life in COVID-19 patients was worse than the normal population at 4-week and 6-week follow-ups [43–45]. Longer follow-up studies have also shown an overall lower quality of life for up to 3 months [25]. One study reported that people with severe COVID-19 demonstrated a low quality of life at their 6-month follow-ups [46].

Studies have shown that decreased muscle performance, functional capacity, and dyspnea after COVID-19 infection can lead to increased disability and decreased quality of life [47]. In an analysis of 420 patients, it was reported that sex, age, education level, employment status, diabetes, heart failure, and ICU admission were important independent predictors of quality of life [48]. In another study, a relationship was found between age, sex, the severity of clinical subtypes, length of hospital stay, lung function parameters, and some subscales of the SF-36 quality of life questionnaire [43]. In a cohort study of 251 patients followed for 3 months, female sex and the need for intensive care were independently associated with worsening quality of life [49]. It has also been reported that the incidence of low quality of life is higher among patients with a history of ICU admission and fatigue [50]. Quality of life was also worse in patients with persistent pain [10]. In our study, although there was no significant difference in quality of life based on disease severity and sex, quality of life was found to be negatively correlated with the severity of fatigue, anxiety, and depression symptoms. Therefore, it is important that rehabilitation be implemented to ease pain and fatigue so that patients can live better lives.

Conclusion

Pain, fatigue, anxiety, and depression appear to be long-term sequelae of COVID-19 and can significantly affect patients' quality of life. Regardless of disease severity, a high initial VAS level may be a risk factor for long-term pain. High VAS and anxiety levels were also found to be associated with long-term fatigue.

At the time of our study, the pandemic was waning due to effective vaccines. However, the problems of patients with long-term COVID-19 should not be ignored. To improve the quality of life for people who have had COVID-19, further studies are needed that focus on treatment and rehabilitation.

Limitations

A limitation of our study is that COVID-19 patients who were not hospitalized were not examined.

Notes

Ethics Approval

This study was approved by the Research Ethics Commission of the Afyonkarahisar Health Sciences University (2021/57) and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent, which was confirmed by the Research Ethics Commission of the Afyonkarahisar Health Sciences University.

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: all authors; Data curation: AİA; Formal analysis: SA; Investigation: SA, PŞK; Methodology: SA, ÜD, ND; Project administration: SA, PŞK, AİA; Resources: all authors; Software: AİA; Supervision: ÜD, ND; Validation: SA, ÜD, ND; Visualization: SA, AİA; Writing–original draft: SA; Writing–review and editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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References

1. Ochani R, Asad A, Yasmin F, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med 2021;29:20–36.
2. World Health Organization (WHO). Weekly epidemiological update on COVID-19-17-06 2022 [Internet]. WHO; 2022 [cited 2022 Oct 12]. Available at: https://covid19.who.int/?mapFilter=cases.
3. Baj J, Karakula-Juchnowicz H, Teresinski G, et al. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med 2020;9:1753.
4. Cipollaro L, Giordano L, Padulo J, et al. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. J Orthop Surg Res 2020;15:178.
5. Abdullahi A, Candan SA, Abba MA, et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front

https://doi.org/10.24171/j.phrp.2022.0275

Neurol 2020;11:687.
6. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol 2021;93:1013–22.
7. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020;81:e4–6.
8. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ 2021;372:n693.
9. Choi JI. Transition of COVID-19 to endemic phase and emergence of COVID-19 related neuropathic pain. Korean J Pain 2022;35:237–9.
10. Sahin T, Ayyildiz A, Gencer-Atalay K, et al. Pain symptoms in COVID-19. Am J Phys Med Rehabil 2021;100:307–12.
11. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240–52.
12. Gencay-Can A, Can SS. Validation of the Turkish version of the fatigue severity scale in patients with fibromyalgia. Rheumatol Int 2012;32:27–31.
13. Aydemir O, Küey L. Reliability and validity of the Turkish version of hospital anxiety and depression scale. Turkish J Psychiatry 1997; 8:280–7.
14. World Health Organization (WHO). Clinical management of COVID-19 [Internet]. WHO; 2020 [cited 2022 Jun 17]. Available at: https://apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5eng.pdf?sequence=1&isAllowed=y.
15. Vacchiano V, Riguzzi P, Volpi L, et al. Early neurological manifestations of hospitalized COVID-19 patients. Neurol Sci 2020;41:2029–31.
16. Disser NP, De Micheli AJ, Schonk MM, et al. Musculoskeletal consequences of COVID-19. J Bone Joint Surg Am 2020;102:1197–204.
17. Murat S, Dogruoz Karatekin B, Icagasioglu A, et al. Clinical presentations of pain in patients with COVID-19 infection. Ir J Med Sci 2021;190:913–7.
18. Oguz-Akarsu E, Gullu G, Kilic E, et al. Insight into pain syndromes in acute phase of mild-to-moderate COVID-19: frequency, clinical characteristics, and associated factors. Eur J Pain 2022;26:492–504.
19. Hoong CW, Amin MN, Tan TC, et al. Viral arthralgia a new manifestation of COVID-19 infection? A cohort study of COVID-19 -associated musculoskeletal symptoms. Int J Infect Dis 2021;104: 363–9.
20. Koseoglu Toksoy C, Yavuz T, Orhan S, et al. Neurological symptoms and findings in COVID-19: a prospective clinical study. Neurol Res 2022;44:1–6.
21. Bakilan F, Gokmen IG, Ortanca B, et al. Musculoskeletal symptoms and related factors in postacute COVID-19 patients. Int J Clin Pract 2021;75:e14734.
22. Tuzun S, Keles A, Okutan D, et al. Assessment of musculoskeletal pain, fatigue and grip strength in hospitalized patients with COVID-19. Eur J Phys Rehabil Med 2021;57:653–62.
23. Karaarslan F, Guneri FD, Kardes S. Long COVID: rheumatologic/musculoskeletal symptoms in hospitalized COVID-19 survivors at 3 and 6 months. Clin Rheumatol 2022;41:289–96.
24. Sykes DL, Holdsworth L, Jawad N, et al. Post-COVID-19 symptom burden: what is long-COVID and how should we manage it? Lung 2021;199:113–9.
25. Shanbehzadeh S, Tavahomi M, Zanjari N, et al. Physical and mental health complications post-COVID-19: scoping review. J Psychosom Res 2021;147:110525.
26. Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, et al. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PLoS One 2020;15:e0243882.
27. Fernandez-de-Las-Penas C, Rodriguez-Jimenez J, Fuensalida-Novo S, et al. Myalgia as a symptom at hospital admission by severe acute respiratory syndrome coronavirus 2 infection is associated with persistent musculoskeletal pain as long-term post-COVID sequelae: a case-control study. Pain 2021;162:2832–40.
28. Kayaaslan B, Eser F, Kalem AK, et al. Post-COVID syndrome: a single-center questionnaire study on 1007 participants recovered from COVID-19. J Med Virol 2021;93:6566–74.
29. Cabrera Martimbianco AL, Pacheco RL, Bagattini AM, et al. Frequency, signs and symptoms, and criteria adopted for long COVID-19: a systematic review. Int J Clin Pract 2021;75:e14357.
30. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021;398:747–58.
31. Anaya JM, Rojas M, Salinas ML, et al. Post-COVID syndrome: a case series and comprehensive review. Autoimmun Rev 2021;20:102947.
32. Eccles JA, Davies KA. The challenges of chronic pain and fatigue. Clin Med (Lond) 2021;21:19–27.
33. Paneroni M, Simonelli C, Saleri M, et al. Muscle strength and physical performance in patients without previous disabilities recovering from COVID-19 pneumonia. Am J Phys Med Rehabil 2021;100:105–9.
34. O'Connor CM. COVID-19 fatigue: not so fast. JACC Heart Fail 2020;8: 592–4.
35. Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. BMJ 2021;374:n1648.
36. Ferraro F, Calafiore D, Dambruoso F, et al. COVID-19 related fatigue: which role for rehabilitation in post-COVID-19 patients? A case series. J Med Virol 2021;93:1896–9.
37. Goertz YM, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 2020;6:00542–2020.
38. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One 2020;15:e0240784.
39. Galligan NG, Hevey D, Coen RF, et al. Clarifying the associations

between anxiety, depression and fatigue following stroke. J Health Psychol 2016;21:2863–71.
40. Ma YF, Li W, Deng HB, et al. Prevalence of depression and its association with quality of life in clinically stable patients with COVID-19. J Affect Disord 2020;275:145–8.
41. Premraj L, Kannapadi NV, Briggs J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. J Neurol Sci 2022;434:120162.
42. de Sousa Moreira JL, Barbosa SM, Vieira JG, et al. The psychiatric and neuropsychiatric repercussions associated with severe infections of COVID-19 and other coronaviruses. Prog Neuropsychopharmacol Biol Psychiatry 2021;106:110159.
43. Chen KY, Li T, Gong FH, et al. Predictors of health-related quality of life and influencing factors for COVID-19 patients, a follow-up at one month. Front Psychiatry 2020;11:668.
44. Santus P, Tursi F, Croce G, et al. Changes in quality of life and dyspnoea after hospitalization in COVID-19 patients discharged at home. Multidiscip Respir Med 2020;15:713.
45. van der Sar-van der Brugge S, Talman S, Boonman-de Winter L, et al. Pulmonary function and health-related quality of life after COVID-19 pneumonia. Respir Med 2021;176:106272.
46. Carenzo L, Protti A, Dalla Corte F, et al. Short-term health-related quality of life, physical function and psychological consequences of severe COVID-19. Ann Intensive Care 2021;11:91.
47. Akbarialiabad H, Taghrir MH, Abdollahi A, et al. Long COVID, a comprehensive systematic scoping review. Infection 2021;49: 1163–86.
48. Arab-Zozani M, Hashemi F, Safari H, et al. Health-related quality of life and its associated factors in COVID-19 patients. Osong Public Health Res Perspect 2020;11:296–302.
49. Todt BC, Szlejf C, Duim E, et al. Clinical outcomes and quality of life of COVID-19 survivors: a follow-up of 3 months post hospital discharge. Respir Med 2021;184:106453.
50. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL): a systematic review and meta-analysis. J Med Virol 2022;94:253–62.

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Original Article

Association between the empirical dietary inflammatory index and musculoskeletal pain in community-dwelling older adults: a cross-sectional study

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ABSTRACT

Objectives: Inflammation has been proposed to be one of the main causes of musculoskeletal pain. Diet is a lifestyle factor that plays an important role in managing inflammation; thus, we assessed the inflammatory potential of diets using the empirical dietary inflammatory index (EDII) to investigate the relationship between diet and musculoskeletal pain.

Methods: This cross-sectional study included 212 elderly individuals who were selected from health centers in Tehran, Iran. Dietary intake was evaluated using a valid and reliable 147-item food frequency questionnaire. To measure the intensity of pain, a visual analogue scale was used. Multiple linear regression was applied to assess the association between the EDII and musculoskeletal pain.

Results: In total, 62.7% and 37.3% of participants had mild and severe pain, respectively. The EDII values were 0.97 ± 0.72 and 1.10 ± 0.66, respectively, in those with mild and severe pain. A higher EDII score was associated with more intense musculoskeletal pain after adjusting for age and sex (β = 0.20; 95% confidence interval [CI], 0.06–0.26; $p < 0.001$), but not after adjustment for other confounders (β = −0.13; 95% CI, −1.54 to 0.60; $p = 0.39$).

Conclusion: Our findings indicated that higher dietary inflammation might not be associated with musculoskeletal pain in older adults. However, further investigations are required to confirm these findings.

Keywords: Aged; Empirical dietary inflammatory index; Inflammation; Musculoskeletal pain

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Introduction

Musculoskeletal conditions affect the soft tissues, joints, and bones, are common in the elderly

[1,2], and could lead to pain, a weakened locomotor system, and disability [3,4]. These conditions could also impose a heavy economic burden on society [5]. Although the exact mechanism is still not fully understood, evidence abounds associating these conditions with inflammatory diseases such as rheumatoid arthritis and osteoarthritis [6]. It has also been shown that an excessive amount of reactive oxygen species is present in individuals experiencing musculoskeletal conditions [7], along with other inflammatory markers such as tumor necrosis factor-alpha and interleukin-6 [8]. Therefore, it is reasonable to assume that managing inflammation could be an important step in mitigating musculoskeletal conditions [9]. Chronic inflammation can be significantly tackled by making lifestyle changes such as dietary interventions [10,11].

Some dietary components such as fruits, vegetables, whole grains, and spices, have been shown to demonstrate anti-inflammatory effects due to their high antioxidant and polyphenol content [12]. Conversely, high consumption of animal proteins and fats has been indicated to induce inflammation [13,14]. However, due to the synergistic or antagonistic effects that foods have on each other, evaluating the overall dietary pattern could provide more comprehensive insights into the diet-disease association [15]. The empirical dietary inflammatory index (EDII) can be used for this purpose [16]. The EDII is a hypothesis-driven index that has been recently proposed to assess the potential pro- or anti-inflammatory effect of the diet based on the intake of various food groups [17]. Several studies have investigated associations between the EDII and chronic diseases and have shown that a higher EDII was associated with an increased risk of diabetes, metabolic syndrome, and fatty liver disease [18,19]. However, to our knowledge, the association of this dietary index with musculoskeletal pain has not been investigated yet. Given the importance of improving the quality of life in the elderly, we conducted this study to determine whether there is an association between musculoskeletal pain and the EDII in the elderly.

Materials and Methods

Study Design

This cross-sectional study was conducted among a total of 213 elderly individuals who were enrolled in our study from September 2019 to August 2020 at health centers in Tehran, Iran. We divided the city of Tehran into 5 regions (north, south, east, west, and center). Then, 20 health centers that individuals attended routinely for check-ups were selected. We tried to enroll a certain amount of people from each region to attenuate the likelihood of financial gaps among our participants. The sample size was determined employing the following formula: $N = [(Z1-\alpha/2)^2 P(1-P)]/d^2$, using $P = 29$, $d = 4.06$, and $\alpha = 0.05$ [20]. The main inclusion criterion was being elderly (≥60 years old). The remaining inclusion criteria were as follows: having a history of musculoskeletal pain for at least 2 months, having no change in the usual dietary pattern over the previous year, being able to ambulate, not having a history of trauma or injury-related accidents, and not having cancer, acute diseases, and cognitive impairment. Participants following a special diet or those whose energy intake fell outside the normal range of 800 to 4,200 kcal were excluded from our study.

Participants' Characteristics

After the first screening, some participants did not meet our inclusion criteria, missed the first interview, or declined to participate; eventually, 212 older adults were enrolled in the study. Socio-demographic data, including age, sex, marital status, economic status (very bad, bad, average, good, and very good) [21], educational level (up to diploma and upper diploma), exercise, sleep duration, supplement intake, history of diseases (cardiovascular diseases, diabetes, digestive diseases, psychological diseases, and skeletal disorders) and medication use, were gathered by trained researchers.

Dietary Assessment

Participants' usual dietary intake was evaluated using a validated and reliable 147-item semi-quantitative food frequency questionnaire (FFQ) that elicited information on diet during the past 12 months on a daily, weekly, and monthly basis [22]. An expert nutritionist gathered dietary data through face-to-face interviews and converted portion sizes to intake (in grams) of each food item and nutrient. The Nutritionist IV software (First Databank Division, the Hearst Corporation; modified for Iranian foods) was used.

EDII scores were calculated based on dietary data derived from the FFQ, which has been used in previous studies [17,23]. The EDII includes 18 food groups. However, due to religious considerations, beer and wine were not included in the dietary score. Moreover, high- and low-energy beverages were considered a single food item in the FFQ. Therefore, we calculated the EDII score based on 15 food groups and 2 categorizations of inflammatory potential. The anti-inflammatory food group consisted of tea, coffee, dark yellow vegetables, leafy green vegetables, snacks, fruit juice, and pizza. Meanwhile, the pro-inflammatory group includes processed meat, red meat, organ meat, other fish (fish, or canned tuna), other vegetables (mixed vegetables, cooked mushrooms, green peppers, zucchini, eggplant, or cucumbers), refined grains, high-energy and low-energy

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drinks, and tomatoes. Regression coefficients were used to weigh the mean daily intake of the food groups. The obtained values were then summed and divided by 1,000. Positive scores of the EDII are an index of pro-inflammatory diets, while negative scores correspond to anti-inflammatory diets.

Pain Evaluation

A visual analogue scale, a valid, reliable, and responsive tool [24] with 0 to 10-cm lines, was used to measure the pain intensity of participants during the previous 3 months. Its score ranges from 0 to 10, with 0 indicating no pain, < 3 denoting mild pain, and ≥ 3 corresponding to severe pain [25]. Participants were asked to draw a vertical mark on the lines to indicate their pain level.

Assessment of Other Variables

Anthropometric measurements (height, body weight, body mass index [BMI], waist circumference [WC], and hip circumference) were assessed for all participants. Height was measured in the standing shoeless position by a standard stadiometer to the nearest 0.1 cm. Body weight was assessed by a digital scale (SECA) to the nearest 0.1 kg while participants wore light clothing. BMI was calculated as weight divided by height squared (kg/m^2) [26]. WC was assessed with an accuracy of 0.1 cm, at the level of the iliac crest [27], and hip circumference was recorded at the anterior superior iliac spine level [26]. Physical activity was evaluated by asking participants about their daily average time spent jogging, exercising, or engaging in other sports. The activity level was ranked into 4 categories (light, moderate, strong, and intense). Participants' physical activity level was calculated as metabolic equivalent-hours/day [28].

Statistical Analysis

The characteristics of the study population are expressed as mean ± standard deviation (for normally distributed data) or median (for data with a skewed distribution). The normality of the distribution of variables was assessed using the Kolmogorov-Smirnov test. The independent sample t-test and the chi-square test were used to evaluate the qualitative and quantitative variables, respectively.

The dietary intake of study participants across animal and plant protein tertiles was compared using analysis of covariance. All values were adjusted for energy intake. We used multiple linear regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for musculoskeletal pain across EDII tertiles in crude and multivariable-adjusted models. Age, sex, education, economic status, physical activity, BMI, energy intake, and economic status were adjusted in the control model. IBM SPSS ver. 24.0 (IBM Corp.) was used to perform the statistical analysis. A p-value < 0.05 was considered to indicate statistical significance.

Ethics Statement

All patients were informed about the characteristics of the study and signed a written informed consent form. The study protocol was reviewed and approved by the local ethical committee of Islamic Azad University, Tehran, Iran (Code: 1397.174.IR.IAU.SRB.REC).

Results

The demographics, lifestyle, work-related, and health characteristics of the participants are described in Tables 1 and 2, according to the intensity of pain. We evaluated 212 participants, of whom 48 were men (22.6%) and 164 were women (77.4%), with an average age of 66 years. The pain assessment showed that 62.7% and 37.3% of the participants experienced mild and severe pain, respectively. The BMI was 28.43 ± 3.76 kg/m^2 and 29.15 ± 4.22 kg/m^2 in those with mild and severe pain, respectively. The EDII values were 0.97 ± 0.72 and 1.10 ± 0.66 in participants with mild and severe pain, respectively; this difference was not statistically significant. Furthermore, 67.5% and 32.5% of participants with mild and severe pain were married. A comparison between the 2 pain groups indicated remarkable differences between them in terms of the head of the family, educational level, economic status, and psychological disorders (p = 0.01, p = 0.01, p = 0.001, p = 0.004, and p = 0.003, respectively). Additionally, gastrointestinal, cardiovascular, and psychological medication intake, and vitamin D supplement usage were significantly different between the mild and severe pain groups (p = 0.01, p = 0.02, p = 0.002, and p = 0.03, respectively).

The dietary intake of participants by tertile of EDII scores is presented in Table 3. People in the third tertile of the EDII consumed higher amounts of total energy, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, fiber, processed meat, red meat, other fish, other vegetables, refined grains, and tomatoes (p < 0.05). The intake of other dietary components such as carbohydrates, tea, coffee, dark yellow vegetables, leafy green vegetables, snacks, fruit juice, pizza, organ meat, and beverages did not differ according to the tertile of the EDII score.

Table 4 demonstrates the association between the EDII and musculoskeletal pain shown by multiple linear regression (Table 5). In the crude model, the EDII did not have a significant association with musculoskeletal pain (β = 0.07; 95% CI, –1.40 to 4.17; p = 0.32). After adjusting for covariates including age and sex, the association became significant (β = 0.20; 95% CI, 0.06–0.26; p < 0.001). However, the fully

Table 1. Demographic, lifestyle, work-related, and health characteristics of the study's participants

Variable	Mild pain (*n* = 133, 62.7%)	Severe pain (*n* = 79, 37.3%)	*p*
Age (y)	66.57 ± 5.74	66.11 ± 5.63	0.55
No. of family members	4.77 ± 1.28	5.44 ± 1.78	0.05*
No. of household members	2.42 ± 1.20	2.76 ± 1.15	0.13
Postmenopausal age (y)	47.12 ± 5.51	47.58 ± 5.51	0.75
Physical activity (min)	39.63 ± 28.25	34.76 ± 41.15	0.52
Sleep duration (min)	431.14 ± 86.39	415.03 ± 114.36	0.44
Study duration (min)	61.59 ± 85.16	51.92 ± 65.50	0.46
Weight (kg)	74.67 ± 8.71	73.02 ± 11.65	0.45
Height (cm)	162.46 ± 9.25	158.26 ± 8.08	0.01*
WC (cm)	96.57 ± 8.06	97.90 ± 11.12	0.52
WHR (cm)	0.86 ± 0.07	0.88 ± 0.07	0.17
WHtR (cm)	0.59 ± 0.06	0.61 ± 0.07	0.09
BMI (kg/m^2)	0.36 ± 4.22	29.15 ± 3.76	28.43
EDII	0.15 ± 0.66	1.10 ± 0.72	0.97
Sex			0.01*
Male	37 (77.1)	11 (22.9)	
Female	96 (58.5)	68 (41.5)	
Marital status			0.02*
Married	104 (67.5)	50 (32.5)	
Other	29 (50.0)	29 (50.0)	
Head of the family			0.01*
Father	23 (47.9)	25 (52.1)	
Mother	105 (66.9)	52 (33.1)	
Education			0.01*
Diploma or lower	87 (57.6)	64 (42.4)	
Upper diploma	46 (75.4)	15 (24.6)	
Spouse education			0.001*
Diploma or lower	74 (54.8)	61 (45.2)	
Upper diploma	57 (77.0)	17 (23.0)	
Economic status			0.004*
Very bad	4 (44.4)	5 (55.6)	
Bad	14 (45.2)	17 (54.8)	
Average	45 (55.6)	36 (44.4)	
Good	12 (66.7)	6 (33.3)	
Very good	57 (79.2)	15 (20.8)	

Data are presented as mean ± standard deviation or *n* (%).
WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; BMI, body mass index; EDII, empirical dietary inflammatory index.
*Considered significant. $p < 0.05$, the Student t-test was used to compare mean differences of quantitative variables, and the chi-square test was used for qualitative variables.

adjusted model did not show statistical significance (β = −0.13; 95% CI, −1.54 to 0.60; $p = 0.39$).

Discussion

The present study investigated the association between the EDII and musculoskeletal pain in older adults. A higher EDII was significantly associated with differences in nutrient and food intake Furthermore, there was a significant positive association between EDII and musculoskeletal pain after adjusting for age and sex.

Our study showed a significant association between the EDII and intake of total energy, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, fiber, processed meat, red meat, other fish and vegetables, refined grains, and tomatoes. As Phillips et al. [29] indicated in their study, the consumption of red and processed meats and refined cereals/ grains was higher and the intake of whole grains, fish,

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Table 2. Association of subjects characteristics, by pain severity

Variable	Severe pain (*n* = 79, 37.3%)	Mild pain (*n* = 133, 62.7%)	*p*
Medication			
Gastrointestinal	27 (60.0)	18 (40.0)	0.01*
Diabetes	54 (54.5)	45 (45.5)	0.40
Cardiovascular	10 (35.7)	18 (64.3)	0.02*
Psychological	26 (48.1)	28 (51.9)	0.002*
Supplements			
Vitamin D	86 (58.5)	61 (41.5)	0.03*
Multivitamins	50 (62.5)	30 (37.5)	0.54
Minerals	64 (60.4)	62 (39.6)	0.32
BMI status			0.71
Underweight	8 (72.7)	3 (27.3)	
Normal	86 (63.2)	50 (36.8)	
Overweight	39 (60.0)	26 (40.0)	
WC status			0.37
Normal	22 (66.7)	11 (33.3)	
Abdominal obesity	110 (61.8)	68 (38.2)	
WHR status			0.27
Normal	71 (65.1)	38 (34.9)	
Abdominal obesity	62 (60.2)	41 (39.8)	
WHtR status			0.36
Normal	57 (64.8)	31 (35.2)	
Abdominal obesity	76 (61.3)	48 (38.7)	

Data are presented as *n* (%).
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
*Considered significant. $p < 0.05$, the Student t-test was used to compare mean differences of quantitative variables, and the chi-square test was used for qualitative variables.

and low-fat dairy products was lower in participants with higher pro-inflammatory scores. Similarly, Bagheri et al. [30] reported that there was a significant association between the food-based inflammatory potential of the diet and greater consumption of refined grains, red meats, high-fat dairy, soft drinks, and potatoes. In addition, different fatty acids can stimulate inflammatory processes, or anti-inflammatory cell function through various mechanisms [31]. For instance, although monounsaturated and polyunsaturated fatty acids have anti-inflammatory properties, the n-6/n-3 ratio has been shown to be associated with the inflammatory response and coagulation [32]. Since the relationship between chronic conditions and inflammation is widely recognized, it is important to pay attention to the content and the inflammation score of individuals' diets.

Our findings showed no direct association between the EDII and musculoskeletal pain. Although studies on this topic are limited, Enrico [33] examined the relationship between the DII and chronic pain in adults, and the results showed that dietary inflammatory index (DII) scores were significantly related to the presence of neck and back pain. In addition, DII scores have been associated with pain lasting longer than 24 hours and 3 months. Similarly, Toopchizadeh et al. [34] revealed that the DII score was directly linked to pain intensity in knee osteoarthritis patients, and a higher DII score was associated with higher odds of having severe pain. In contrast, Correa-Rodriguez et al. [35] reported no association between the DII score and clinical symptoms in women with fibromyalgia. Nevertheless, they found that the DII score was associated with lower pressure pain thresholds.

Various studies have emphasized the anti-inflammatory properties of foods, which have been reported to reduce chronic pain, osteoarthritis-related pain, and neurogenic pain [36–38]. Anti-inflammatory diets can reduce pain via several putative mechanisms. Anti-inflammatory components such as flavonoids, curcuminoids, omega-3 polyunsaturated fatty acids, trombone, and taurine could have analgesic effects by preventing inflammatory signaling, regulating cyclooxygenase 2 activity, interacting with neuromodulator pathways (including the opiate receptors and the gamma-aminobutyric acid receptor signaling), targeting L-arginine/nitric oxide signaling, and reducing the production of prostaglandin E2 [37,39–41].

Although the present study was relatively novel and could further expand our knowledge of the detrimental effects of

Table 3. Nutrients and food group intake of the study population across tertiles of the EDII score

Nutrients and food group T	*p*	EDII score		
		T3 (*n* = 68)	T2 (*n* = 68)	T1 (*n* = 65)
Total energy (kcal/day)	0.01*	2,623.42 ± 1,525.00	1,972.34 ± 193.98	2,074.55 ± 1,435.33
Carbohydrate (% of energy)	0.09	91.03 ± 57.32	70.91 ± 35.48	78.34 ± 58.61
Protein (% of energy)	0.04*	408.37 ± 286.76	303.49 ± 130.84	320.08 ± 272.28
Total fat (% of energy)	0.001*	78.86 ± 31.90	60.81 ± 22.10	64.19 ± 28.72
Saturated fat (% of energy)	0.01*	23.58 ± 10.27	19.46 ± 7.96	19.13 ± 8.19
Monounsaturated fat (% of energy)	0.04*	24.53 ± 10.57	20.20 ± 8.01	20.96 ± 10.59
Polyunsaturated fat (% of energy)	0.01*	15.81 ± 7.93	12.17 ± 5.26	13.21 ± 7.65
Fiber (g/1,000 kcal)	0.01*	64.29 ± 74.53	37.42 ± 18.71	40.54 ± 42.79
Food groups (serving/day)				
Tea	0.30	2.15 ± 1.58	2.23 ± 2.01	2.71 ± 3.00
Coffee	0.41	0.07 ± 0.19	0.05 ± 0.13	0.11 ± 0.41
Dark yellow vegetables	0.85	0.22 ± 0.20	0.20 ± 0.22	0.20 ± 0.28
Leafy green vegetables	0.26	0.49 ± 0.87	0.47 ± 0.40	0.34 ± 0.25
Snacks	0.43	0.15 ± 0.95	0.05 ± 0.13	0.02 ± 0.08
Fruit juice	0.24	0.09 ± 0.27	0.04 ± 0.09	0.14 ± 0.50
Pizza	0.10	0.02 ± 0.04	0.02 ± 0.03	0.04 ± 0.08
Processed meat	0.03*	0.09 ± 0.17	0.03 ± 0.08	0.05 ± 0.10
Red meat	0.01*	0.60 ± 0.54	0.57 ± 0.46	0.38 ± 0.36
Organ meat	0.36	0.01 ± 0.04	0.02 ± 0.04	0.01 ± 0.02
Other fish	0.03*	0.21 ± 0.26	0.13 ± 0.15	0.12 ± 0.20
Other vegetables	0.001*	2.14 ± 1.35	1.15 ± 0.64	0.83 ± 0.52
Refined grains	0.001*	5.65 ± 5.69	2.42 ± 1.57	1.63 ± 1.37
Tomatoes	0.001*	1.39 ± 0.99	0.93 ± 0.66	0.52 ± 0.37
Beverages	0.24	2.22 ± 1.58	2.28 ± 2.01	2.83 ± 3.03

Data are presented as mean ± standard deviation.
EDII, empirical dietary inflammatory index; T, tertile.
*Considered significant.

Table 4. Association between pain intensity and tertiles of the EDII

Variable	Severe pain (32.3%)	Mild pain (62.7%)	*p*
EDII			0.01* (2-sided tail: 0.006)*
1st tertile (*n* = 71) (≤ 0.69)	47 (66.2)	24 (33.8)	
2nd tertile (*n* = 72) (0.70–1.14)	49 (68.1)	23 (31.9)	
3rd tertile (*n* = 69) (≥ 1.15)	37 (53.6)	32 (46.4)	
EDII			0.28
1st tertile	47 (66.2)	24 (33.8)	
Other tertiles	86 (61.0)	55 (39.0)	
EDII			0.04*
Other tertiles	96 (67.1)	47 (32.9)	
3rd tertile	37 (53.6)	32 (46.4)	
EDII			0.09
1st tertile	47 (66.2)	24 (33.8)	
3rd tertile	37 (53.6)	32 (46.4)	

Data are presented as *n* (%).
EDII, empirical dietary inflammatory index.
*$p < 0.05$, chi-square test.

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Table 5. Multiple linear regression for the association of the pain score with the EDII

Variable	R	R^2	AR^2	B	Beta	95% CI	*p*
Crude	0.07	0.01	0.00	1.39 (1.41)	0.07	−1.40 to 4.17	0.32
Model 1	0.38	0.15	0.14	2.94 (1.59)	0.20	0.06 to 0.26	< 0.001*
Model 2	0.43	0.19	0.17	3.25 (1.59)	−0.13	−2.09 to −0.03	0.05
Model 3	0.39	0.15	0.11	−0.47 (0.54)	−0.06	−1.54 to 0.60	0.39

EDII, empirical dietary inflammatory index; model 1, adjusted for age and sex; model 2, adjusted for age, sex, education, and economic status; model 3, adjusted for age, sex, education, economic status, physical activity, body mass index, energy intake, and economic status.
*Considered significant.

a pro-inflammatory diet, there are some limitations that should be considered. Firstly, because of the cross-sectional nature of the study, we could not infer causality. Another limitation was the small sample size. Moreover, when using an FFQ, the risk of recall bias is substantial. Additionally, since our study population only included the elderly, our results cannot be extended to other populations. Finally, due to financial constraints, we were unable to assess inflammatory blood markers, although doing so could have provided better insights into this topic.

Conclusion

In conclusion, our findings indicated no association between a higher EDII and musculoskeletal pain in older adults. However, further investigations with a larger sample size, longitudinal and interventional design, and different populations are required to deepen our knowledge of the association between dietary indices and musculoskeletal pain.

Notes

Ethics Approval
All patients were informed about the characteristics of the study and signed a written informed consent form. The study protocol was reviewed and approved by the local ethical committee of Islamic Azad University, Tehran, Iran (Code: 1397.174.IR.IAU.SRB.REC).

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

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None.

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

Authors' Contributions
Conceptualization: MaR, ADM, AD; Formal Analysis: MaR, ZT; Investigation: MaR, ZT, ZE, SD, AE, MMD, MoR; Methodology: MaR, ADM, AD; Resources: MaR, ZT, ZE, SD, AE; Project administration: ADM, AD; Supervision: ADM, AD; Writing–original draft: MaR; Writing–review & editing: all authors. All authors read and approved the final manuscript.

References

1. Macfarlane GJ, Beasley M, Jones EA, et al. The prevalence and management of low back pain across adulthood: results from a population-based cross-sectional study (the MUSICIAN study). Pain 2012;153:27–32.
2. Blyth FM, Briggs AM, Schneider CH, et al. The global burden of musculoskeletal pain: where to from here? Am J Public Health 2019; 109:35–40.
3. Tuzun EH. Quality of life in chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:567–79.
4. van Schaardenburg D, Van den Brande KJ, Ligthart GJ, et al. Musculoskeletal disorders and disability in persons aged 85 and over: a community survey. Ann Rheum Dis 1994;53:807–11.
5. Cote P, van der Velde G, Cassidy JD, et al. The burden and determinants of neck pain in workers: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976) 2008;33(4 Suppl):S60–74.
6. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81:646–56.
7. Richards RS, Roberts TK, McGregor NR, et al. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. Redox Rep 2000;5:35–41.
8. Generaal E, Vogelzangs N, Macfarlane GJ, et al. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. Pain 2014;155:1605–12.
9. Kirsch Micheletti J, Blafoss R, Sundstrup E, et al. Association between lifestyle and musculoskeletal pain: cross-sectional study among 10,000 adults from the general working population. BMC Musculoskelet Disord 2019;20:609.
10. Galland L. Diet and inflammation. Nutr Clin Pract 2010;25:634–40.
11. Dai J, Jones DP, Goldberg J, et al. Association between adherence to the Mediterranean diet and oxidative stress. Am J Clin Nutr 2008; 88:1364–70.
12. Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Curr Opin Food Sci 2016;8:33–42.
13. Macphail K. C-reactive protein, chronic low back pain and, diet and lifestyle. Int Musculoskelet Med 2015;37:29–32.
14. Sutliffe JT, Wilson LD, de Heer HD, et al. C-reactive protein response

to a vegan lifestyle intervention. Complement Ther Med 2015;23:32–7.
15. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
16. Kanauchi M, Shibata M, Iwamura M. A novel dietary inflammatory index reflecting for inflammatory ageing: technical note. Ann Med Surg (Lond) 2019;47:44–6.
17. Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and validation of an empirical dietary inflammatory index. J Nutr 2016;146:1560–70.
18. Lee DH, Li J, Li Y, et al. Dietary inflammatory and insulinemic potential and risk of type 2 diabetes: results from three prospective U.S. cohort studies. Diabetes Care 2020;43:2675–83.
19. Farhadnejad H, Tehrani AN, Jahromi MK, et al. The association between dietary inflammation scores and non-alcoholic fatty liver diseases in Iranian adults. BMC Gastroenterol 2022;22:267.
20. Valipour G, Esmaillzadeh A, Azadbakht L, et al. Adherence to the DASH diet in relation to psychological profile of Iranian adults. Eur J Nutr 2017;56:309–20.
21. Safarpour M, Dorosty Motlagh A, Hosseini SM, et al. Prevalence and outcomes of food insecurity and its relationship with some socioeconomic factors. Knowl Health 2014;8:193–8.
22. Farhangi MA, Jahangiry L. Dietary diversity score is associated with cardiovascular risk factors and serum adiponectin concentrations in patients with metabolic syndrome. BMC Cardiovasc Disord 2018; 18:68.
23. Shakeri Z, Mirmiran P, Khalili-Moghadam S, et al. Empirical dietary inflammatory pattern and risk of metabolic syndrome and its components: Tehran Lipid and Glucose Study. Diabetol Metab Syndr 2019;11:16.
24. Alghadir AH, Anwer S, Iqbal A, et al. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. J Pain Res 2018;11:851–6.
25. Idvall E, Brudin L. Do health care professionals underestimate severe pain more often than mild pain? Statistical pitfalls using a data simulation model. J Eval Clin Pract 2005;11:438–43.
26. Wang Z, Hoy WE. Waist circumference, body mass index, hip circumference and waist-to-hip ratio as predictors of cardiovascular disease in Aboriginal people. Eur J Clin Nutr 2004;58:888–93.
27. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004; 79:379–84.
28. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9 Suppl):S498–504.
29. Phillips CM, Shivappa N, Hebert JR, et al. Dietary inflammatory index and biomarkers of lipoprotein metabolism, inflammation and glucose homeostasis in adults. Nutrients 2018;10:1033.
30. Bagheri A, Hashemi R, Soltani S, et al. The relationship between food-based pro-inflammatory diet and sarcopenia: findings from a cross-sectional study in Iranian elderly people. Front Med (Lausanne) 2021; 8:649907.
31. Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. Eur J Pharmacol 2011;668 Suppl 1:S50–8.
32. Kalogeropoulos N, Panagiotakos DB, Pitsavos C, et al. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. Clin Chim Acta 2010;411:584–91.
33. Enrico VT. Dietary inflammatory index and chronic pain in an adult, non-institutionalized civilian population of the US. Memorial University of Newfoundland; 2017.
34. Toopchizadeh V, Dolatkhah N, Aghamohammadi D, et al. Dietary inflammatory index is associated with pain intensity and some components of quality of life in patients with knee osteoarthritis. BMC Res Notes 2020;13:448.
35. Correa-Rodriguez M, Casas-Barragan A, Gonzalez-Jimenez E, et al. Dietary inflammatory index scores are associated with pressure pain hypersensitivity in women with fibromyalgia. Pain Med 2020;21: 586–94.
36. Lakhan SE, Ford CT, Tepper D. Zingiberaceae extracts for pain: a systematic review and meta-analysis. Nutr J 2015;14:50.
37. Xu Q, Zhang ZF, Sun WX. Effect of naringin on monosodium iodoacetate-induced osteoarthritis pain in rats. Med Sci Monit 2017; 23:3746–51.
38. Filho AW, Filho VC, Olinger L, et al. Quercetin: further investigation of its antinociceptive properties and mechanisms of action. Arch Pharm Res 2008;31:713–21.
39. Wang W, Chen J, Mao J, et al. Genistein ameliorates non-alcoholic fatty liver disease by targeting the thromboxane A2 pathway. J Agric Food Chem 2018;66:5853–9.
40. Al-Sayed E, Abdel-Daim MM. Analgesic and anti-inflammatory activities of epicatechin gallate from Bauhinia hookeri. Drug Dev Res 2018;79:157–64.
41. Bjorklund G, Aaseth J, Dosa MD, et al. Does diet play a role in reducing nociception related to inflammation and chronic pain? Nutrition 2019;66:153–65.

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Brief Report

Early countermeasures to COVID-19 at long-term care facilities in Gwangju Metropolitan City, Republic of Korea

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ABSTRACT

Objectives: The coronavirus disease 2019 (COVID-19) pandemic has continued since its first detection in the Republic of Korea on January 20, 2020. This study describes the early countermeasures used to minimize the risk of COVID-19 outbreaks during cohort quarantine and compares the epidemiological characteristics of 2 outbreaks in long-term care facilities (LTCFs) in Gwangju Metropolitan City in summer 2020.
Methods: An epidemiological investigation was conducted via direct visits. We investigated epidemiological characteristics, including incidence, morbidity, and mortality rates, for all residents and staff members. Demographic characteristics were analyzed using a statistical program. Additionally, the method of managing infection in LTCFs is described.
Results: Residents and caregivers had high incidence rates in LTCF-A and LTCF-B, respectively. LTCF-B had a longer quarantine period than LTCF-A. The attack rate was 20.02% in LTCF-A and 27.9% in LTCF-B. The mortality rate was 2.3% (1/43) in LTCF-B, the only facility in which a COVID-19 death occurred.
Conclusion: Extensive management requires contact minimization, which involves testing all contacts to mitigate further transmission in the early stages of LTCF outbreaks. The findings of this study can help inform and prepare public health authorities for COVID-19 outbreaks, particularly for early control in vulnerable facilities.

Keywords: Cohort isolation; COVID-19; Long-term care facility

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Introduction

Since the first case of coronavirus disease 2019 (COVID-19), which is caused by severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2), was confirmed in the Republic of Korea (ROK) on January 20, 2020, the disease has been identified in diverse sites in cluster patterns. Moreover, SARS-CoV-2 infection can manifest as a respiratory disease with severe pneumonia-like symptoms that require critical care [1]. The elderly population is generally susceptible, with a high incidence of severe disease and mortality. Those who attend gatherings face a high risk of infection and risk of complications. Deaths related to COVID-19 have been reported in other countries [2–4]. Eighty percent of deaths associated with COVID-19 were among adults aged ≥65 years, with the highest percentage of severe outcomes among persons aged ≥85 years [5]. Mortality was reported most commonly among individuals aged ≥80 years [6].

According to the Korea Disease Control and Prevention Agency (KDCA), as of July 1, 2020, deaths in the ROK due to COVID-19 totaled 282 cases of 1,285,231 individuals tested, with a mortality rate of 2.1%. The total number of cases in Gwangju Metropolitan City was 56 [7]. COVID-19 outbreaks have resulted from a variety of gatherings, including in churches and temples. The first long-term care facility (LTCF) outbreak and resident death occurred in Gwangju Metropolitan City. There have been no prior reports on early countermeasures for cluster LTCF outbreaks. This study describes the epidemiological characteristics and efforts to mitigate the spread of COVID-19 in LTCFs. It compares 2 LTCFs' extensive public health responses to COVID-19 outbreaks in order to assess similarities and differences in disease spread and individuals affected.

Materials and Methods

Epidemiological Investigation

Based on the Infectious Disease Control and Prevention Act, we identified and investigated patients as relevant who had worked at and been infected at LTCF-A and LTCF-B, and their contacts between June 26, 2020 and July 30, 2020 [8]. A confirmed person was defined as someone with laboratory-confirmed COVID-19 infection, regardless of clinical signs and symptoms [9,10], and the index case was defined as the first confirmed case of SARS-CoV-2 infection within a cluster outbreak. After epidemiological investigation to confirm the route of transmission, origin, and exposure environment, patients with COVID-19 were given appropriate medical care. We obtained information on demographic characteristics from interviews using standardized epidemiological investigation forms. For supplemental measures to trace contacts, we obtained additional personal epidemiological information using the global positioning system (GPS), credit card transactions, drug utilization review, and closed-circuit television.

Outbreak Recognition and Response Measures

We were alerted to the index cases of COVID-19 as caregivers who worked in LTCF-A and LTCF-B. The first confirmed case included another cluster associated with suspected acute respiratory illness.

The KDCA's immediate response team was sent to the spot for epidemiological investigation with contact tracing. Countermeasure response teams were launched immediately, namely the Gwangju Center for Infectious Disease Control and Prevention, Gwangju Infectious Disease Response Team, and Gwangju Buk-gu Public Health Center. The investigative response identified an outbreak during the cohort isolation group's quarantine period in LTCF-A and LTCF-B in Gwangju Metropolitan City, during a COVID-19 mass screening of residents (n=52) and staff members (n=31).

After the index case was identified, movement within LTCF-A and LTCF-B was limited. Visitors were prohibited from entering the facilities in order to limit exposure, since interaction had the potential for disease transmission. Each resident was assigned to a single room or a room with divided partitions, and no group activities were allowed. To prevent additional transmission, personal protective equipment (PPE) for staff members was always worn when caring for residents. Fever and symptoms such as cough, myalgia, and headaches were monitored and recorded daily. Nasopharyngeal swab specimens from all residents and staff, including caregivers, were screened using real-time reverse-transcription polymerase chain reaction (RT-PCR). All residents and staff were isolated for testing every 3 days and quarantined for 14 days after a positive result was confirmed. Those who were confirmed positive were transferred to other hospitals or treatment centers in the community. A person who had a negative test result after contact with a confirmed case was mandated to remain quarantined at the facility for 14 days.

Enhanced hygiene measures were implemented, including disinfection of surfaces and periodic natural ventilation through windows. In addition, after the contaminated room or area was cleaned, environmental sampling was performed. Environmental testing for SARS-CoV-2 at LTCF-A and LTCF-B was performed on July 1, 2020 and July 9, 2020, respectively.

Ethics Statement

Ethics approval was waived for this study because it was considered part of a response to a public health crisis.

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Results

LTCF-A is a 2-story structure located near a residential area. Twenty-six residents were managed by 14 staff members between June 26, 2020 and July 30, 2020. Resident space was located on the first and second floors of the building. The space was utilized by placing 2 persons per room. An elevator was used to move food and supplies, but not people, between floors. Ventilation was possible only by opening the window.

LTCF-B is a 4-story structure located in a rural area. Twenty-six residents were managed by 17 staff members. The space was utilized by placing 2 to 4 persons per room. Resident space was located on the first and second floors, and staff space was located on the third floor and the first basement floor of the building. Air conditioning and open windows were used for ventilation.

LTCF-A was quarantined immediately on July 1, 2020, after a caregiver on staff was identified on June 30 as the index case, and RT-PCR testing was performed on all personnel. As a result, 3 residents were confirmed to be positive and were transferred immediately to a hospital. As a complementary measure, all remaining personnel were quarantined for cohort isolation. On July 3, 3 asymptomatic residents were confirmed positive, after which no further positive results occurred until July 17, due to the 14-day quarantine.

Among the 26 residents of LTCF-A, all 6 positive cases were >70 years old (mean age, 81.5), and the 2 positive staff had a mean age of 43.5 years (Table 1). In LTCF-B, the average age of positive cases among residents was 87.6 years, and among staff was 56.4 years. More than 80% of the positive staff members showed initial symptoms such as fever, muscle pain, and fatigue. However, 100% (6/6) of the residents in LTCF-A and 71.4% (5/7) in LTCF-B were asymptomatic. Only 28.6% (2/7) of residents in LTCF-B showed symptoms, such as fever, muscle pain, sore throat, cough, and lethargy. Among the positive residents, 1 person died on July 16 from lethargy. The positive residents had comorbidities, including 11 with dementia (55%), 7 with hypertension (35%), 5 with diabetes (25%), and 3 with hyperlipidemia ($n=3$). Five residents were able to ambulate in a wheelchair, and 1 had difficulty in communication and movement (data not shown).

As illustrated in Figure 1, the index case at LTCF-B (symptomatic date: June 29), confirmed subsequently as positive for SARS-CoV-2, was already a patient under investigation on July 1. The index case at LTCF-B met the index case of LTCF-A on June 27 based on GPS tracking (data not shown). All LTCF-B personnel were evaluated and tested using RT-PCR

Table 1. Demographic characteristics of COVID-19 patients at facilities A and B

Characteristic	Overall	Facility A			Facility B		
		Total	Resident	Worker	Total	Resident	Worker
Total		40	26	14	43	26	17
Mean age (y)		74.4	87.1	50.9	72.3	87.2	49.5
Sex							
Male	5	2	1	1	3	1	2
Female	78	38	25	13	40	25	15
Confirmed cases	20	8	6	2	12	7	5
Mean age (y)		72.0	81.5	43.5	74.6	87.6	56.4
Sex							
Male	1	1	1	0	0	0	0
Female	19	7	5	2	12	7	5
Symptoms before diagnosis							
Symptomatic	8	2	0	2	6	2	4
Asymptomatic	12	6	6	0	6	5	1
Sign							
Fever	5	1	0	1	4	1	3
Headache	1	1	0	1	0	0	0
Muscle pain, fatigue	2	1	0	1	1	0	1
Sore throat, cough	2	0	0	0	2	0	2
Lethargy	1	0	0	0	1	1	0
Underlying disease							
Dementia	11	6	6	0	5	5	0
Hypertension	7	3	3	0	4	4	0
Diabetes	5	1	1	0	4	3	1
Hyperlipidemia	3	0	0	0	3	1	2

Figure 1. Epidemic curve of coronavirus disease 2019 outbreaks in long-term care facilities (LCTFs) by date of symptom onset. (A) LTCF-A, (B) LTCF-B. The index cases (*) of A and B facilities met.

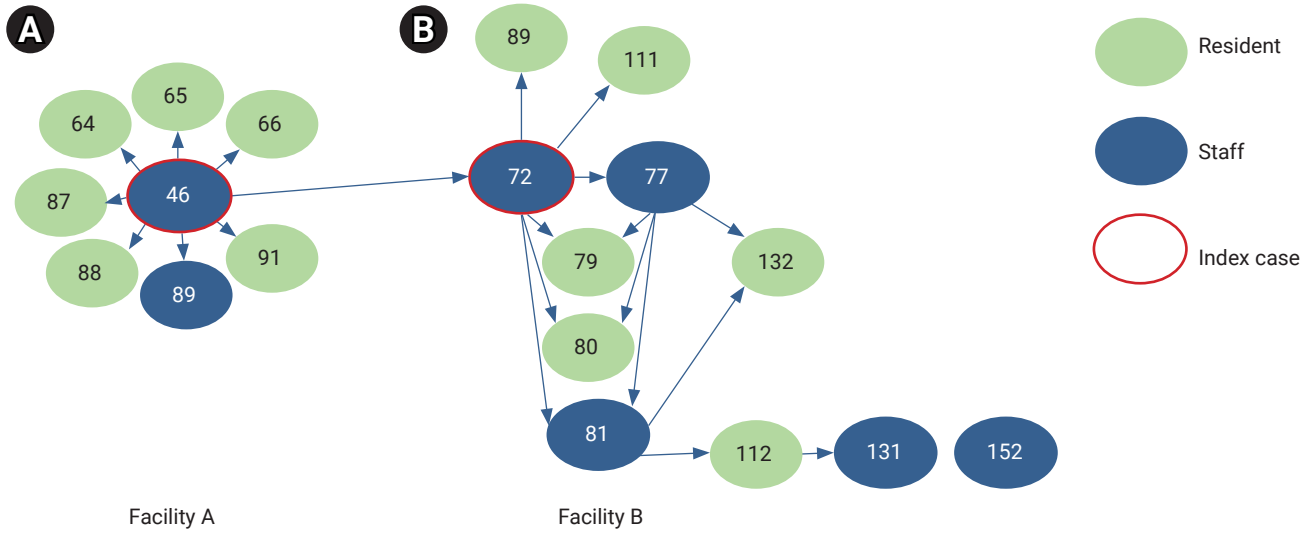

Figure 2. Identification of transmission route according to contact tracing in long-term care facilities (LCTFs). (A) LTCF-A, (B) LTCF-B.

as well. As a result of cumulative testing, on July 2, 2020, 4 people were confirmed positive for SARS-CoV-2, and the remaining personnel were isolated in single rooms on the second and third floors as a follow-up measure. Two people tested positive on July 5, 8, and July 10.

Cohort isolation was sustained for 14 days after the last confirmed case. After the start of quarantine on July 1 in LTCF-B, staff in the basement oversaw floor 1 residents, and staff on floor 3 oversaw floor 2 residents.

To prevent infection, staff members were required to wear

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protective suits when entering the room. Movement between floors outside of each person's living area was prohibited for disease control. The secondary attack rate was 8.3% (1/12), as close contacts with the first index case mingled among household members associated with LTCF-A.

For environmental evaluation, on July 1, LTCF-A collected 31 samples from patients' contact places (door handles, toilet handles, toilet bowls, etc.). As indicated by RT-PCR, only the handle of the front door was confirmed to be positive for SARS-CoV-2. The exposure site was sterilized 1 hour before sampling; however, the entrance door handle was not sterilized because the front door was open. Cycle threshold values for the E gene and RdRp gene of the door handle were 33.25 and 35.07, respectively. On July 9, 25 samples were collected from major contact places, including air purifiers and ventilation systems in LTCF-B. All of these RT-PCR test results were negative.

As a result of the epidemiological investigation associated with contact tracing, the expected transmission is shown in Figure 2. The first transmission was initiated by a meeting between the index cases of LTCF-A and LTCF-B. Transmission within LTCF-A was caused by only 1 staff member, transmission in LTCF-B started from the staff of LTCF-A, and additional transmission was caused by each facility's workers.

Discussion

This report has shown that countermeasures to COVID-19 outbreaks among the elderly who have greater risk of developing a more severe form of the disease. Strategy measures for COVID-19 among the elderly were followed by comprehensive tracing of all identified contacts. The extensive public health response to support LTCF residents included active testing to ascertain a mass screening for case detection and mitigate the risk of SARS-CoV-2 infection, quarantine of all contacts, and treatment of confirmed cases.

A previous study indicated that most elderly people residing in LTCFs have a significantly higher risk of severe disease and death [11]. Numerous deaths due to SARS-CoV-2 in LTCFs have been reported in other countries [12–14]. Previous studies have reported that most facilities requiring nursing had a significantly higher risk of severe disease and death, and it was estimated that approximately 42% of deaths were associated with COVID-19 [12]. In this study, the mortality rate was 8.33% (1/12) in LTCF-B. We found that the mortality rate was lower than previous findings, which ranged between 20.8% and 28.0% in similar populations [15,16]. This result indicates that the attack rate (incidence rate) was 20.02% and 27.9% in LTCF-A and LTCF-B, respectively. The morbidity rates were 5.0% (2/40) in LTCF-A and 14.0% (6/43) in LTCF-B. The mortality rate may be higher among those with pre-existing comorbidities, particularly cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer [17].

This study showed a high prevalence of asymptomatic infections among infected older residents, and of those who tested positive, only staff members exhibited symptoms. Viral shedding may peak in the pre-symptomatic phase within the primary stage of infection [18]. Most residents had a high risk due to the presence of multiple comorbidities, such as diabetes, high blood pressure, and dementia. Almost all the residents who tested positive had underlying chronic medical conditions. Among the positive residents in both facilities, all from LTCF-A and 71.4% from LTCF-B had dementia, which was in accordance with the asymptomatic state. Furthermore, none of the staff members of LTCF-A and 20% of those in LTCF-B were asymptomatic.

This result differs from a report wherein 75% of nursing home staff were asymptomatic [19]. The quarantine periods were 20 days for LTCF-A and 32 days for LTCF-B. The countermeasures were the same; however, the quarantine periods were different. It is estimated that the asymptomatic rate among caregivers is high. Contagious symptomatic or asymptomatic carriers of SAR-CoV-2 could represent the leading cause of increased COVID-19 transmission [20].

Social gatherings may pose an increased risk of infection. Residents and workers share space and materials in nursing facilities. Residents had a high incidence rate in LTCF-A while caregivers had a higher incidence rate in LTCF-B. The total quarantine period was extended (17 days at LTCF-A and 29 days at LTCF-B) after confirming the last positive case. There was no additional transmission by positive residents in LTCF-A, whereas more transmission occurred among caregivers in LTCF-B. Physical interactions with personnel may result in an increase in infectious diseases [21]. Therefore, staff must be educated to mitigate transmission during the quarantine period.

There were concerns about worsening of symptoms due to inherent characteristics of the elderly, such as the presence of underlying diseases like dementia, that required management. More effort was required to mitigate the risk of SARS-CoV-2 infection among these vulnerable groups. Therefore, RT-PCR diagnostic testing was conducted every 3 days as a countermeasure for the possibility of worsening asymptomatic cases. This method focused on rapidly identifying and relocating confirmed cases from the cohort environment to decrease the frequency of SARS-CoV-2 infection in the facility. To reduce contact and exposure, each resident was assigned to a single or double room. It has been reported that the incidence and mortality doubled

as density increased [22]. Team-based approaches, such as space separation, routine symptom monitoring of staff and residents, allocation of sufficient PPE, community support, and testing capacity, have been implemented to reduce additional infections. Similarly, other reports have shown reductions in incidence and mortality through preventive isolation (self-confinement) [23,24].

The current study has some limitations. Analysis of exposure risk was not possible because research, such as surveys on individual behavioral characteristics, could not be conducted. Although it is a report on the early countermeasures of an LTCF group outbreak in the early stages of the COVID-19 pandemic, the findings of this study can help inform and prepare public health authorities for COVID-19 outbreaks or other infectious disease outbreaks, particularly in setting up quarantine in vulnerable facilities. We hope that our records can be effectively utilized to mitigate SARS-CoV-2 transmission and protect vulnerable populations in LTCFs.

Notes

Ethics Approval

Ethics approval was waived for this study because it was considered part of a response to a public health crisis.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

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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

Investigation: HJK, JK, YSJ, HP, JMK, SYR, JHC, SYP; Project administration: YJP; Supervision: SEL; Writing–original draft: HJK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

References

1. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Euro Surveill 2020;25:2000058.
2. D'Adamo H, Yoshikawa T, Ouslander JG. Coronavirus disease 2019 in geriatrics and long-term care: the ABCDs of COVID-19. J Am Geriatr Soc 2020;68:912–7.
3. Ouslander JG. Coronavirus disease19 in geriatrics and long-term care: an update. J Am Geriatr Soc 2020;68:918–21.
4. ECDC Public Health Emergency Team; Danis K, Fonteneau L, Georges S, et al. High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA, May 2020. Euro Surveill 2020;25:2000956.
5. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343–6.
6. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:759–65.
7. Korea Disease Control and Prevention Agency (KDCA). COVID-19 occurrence status in Republic of Korea (July 1, 2020, regular briefing) [Internet]. KDCA; 2020 [cited 2023 Jan 11]. Available from: http://www.cdc.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=367669&cg_code=&act=view&nPage=195. Korean.
8. Korean Law Information Center. Infectious Disease Control and Prevention Act. Enforcement Date 07. Jan, 2016 [Internet]. Korean Law Information Center; 2016 [cited 2023 Jan 11]. Available from: https://www.law.go.kr/LSW/lsInfoP.do?lsiSeq=172762&viewCls=engLsInfoR&urlMode=engLsInfoR&chrClsCd=010203#0000. Korean.
9. Korea Centers for Disease Control and Prevention. COVID-19 response and management guidelines, 9-5th ed. Korea Centers for Disease Control and Prevention; 2020. Korean.
10. World Health Organization (WHO). Country and technical guidance: coronavirus disease (COVID-19) [Internet]. WHO; 2019 [cited 2023 Jan 11]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance.
11. Thompson DC, Barbu MG, Beiu C, et al. The impact of COVID-19 pandemic on long-term care facilities worldwide: an overview on international issues. Biomed Res Int 2020;2020:8870249.
12. Abrams HR, Loomer L, Gandhi A, et al. Characteristics of U.S. nursing homes with COVID-19 cases. J Am Geriatr Soc 2020;68:1653–6.
13. Comas-Herrera A, Patel D, Arling G, et al. International data on deaths attributed to COVID-19 among people living in care homes [Internet]. LTCcovid, Care Policy & Evaluation Centre, London School of Economics and Political Science; 2022 [cited 2023 Jan 11]. Available from: http://ltccovid.org/2022/02/22/international-data-on-deaths-attributed-to-covid-19-among-people-living-in-care-homes/.
14. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775–6.
15. Ly TDA, Zanini D, Laforge V, et al. Pattern of SARS-CoV-2 infection among dependant elderly residents living in long-term care facilities in Marseille, France, March-June 2020. Int J Antimicrob Agents 2020;56:106219.
16. Shimotsu ST, Johnson ARL, Berke EM, et al. COVID-19 infection control measures in long-term care facility, Pennsylvania, USA. Emerg Infect Dis 2021;27:644–5.
17. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.

https://doi.org/10.24171/j.phrp.2022.0293

18. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672–5.
19. Bayle C, Cantin D, Vidal JS, et al. Asymptomatic SARS COV-2 carriers among nursing home staff: A source of contamination for residents? Infect Dis Now 2021;51:197–200.
20. Furukawa NW, Brooks JT, Sobel J. Evidence supporting transmission of severe acute respiratory syndrome coronavirus 2 while presymptomatic or asymptomatic. Emerg Infect Dis 2020;26:e201595.
21. Strausbaugh LJ, Sukumar SR, Joseph CL. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. Clin Infect Dis 2003;36:870–6.
22. Brown KA, Jones A, Daneman N, et al. Association between nursing home crowding and COVID-19 infection and mortality in Ontario, Canada. JAMA Intern Med 2021;181:229–36.
23. Belmin J, Um-Din N, Donadio C, et al. Coronavirus disease 2019 outcomes in French nursing homes that implemented staff confinement with residents. JAMA Netw Open 2020;3:e2017533.
24. Krone M, Noffz A, Richter E, et al. Control of a COVID-19 outbreak in a nursing home by general screening and cohort isolation in Germany, March to May 2020. Euro Surveill 2021;26:2001365.

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Instruction for authors

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- **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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  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.
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