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Comparative Analysis of Clinical Outcomes Using Propensity Score Matching: Coronavirus Disease 2019 vs. Seasonal Influenza in Korea

Jae Kyeom Sim [1*] **Hye Sun Lee** [2*] **Juyeon Yang** [2] **Jin Gwack** [3] **Bryan Inho Kim** [3] **Jeong-ok Cha** [3] **Kyung Hoon Min** [1] **Young Seok Lee** [1], **and on behalf of the Severe Acute Respiratory Infection (SARI) Investigators**

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea
[2]Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea
[3]Division of Infectious Disease Control, Bureau of Infectious Disease Policy, Korea Disease Control and Prevention Agency (KDCA), Cheongju, Korea

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Address for Correspondence:
Young Seok Lee, MD, PhD
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
Email: avonlea76@korea.ac.kr

*Jae Kyeom Sim and Hye Sun Lee contributed equally to this manuscript.

ORCID iDs
Jae Kyeom Sim
https://orcid.org/0000-0003-0873-2807
Hye Sun Lee
https://orcid.org/0000-0001-6328-6948
Juyeon Yang
https://orcid.org/0000-0002-7621-5150
Jin Gwack
https://orcid.org/0000-0003-0932-9542
Bryan Inho Kim
https://orcid.org/0000-0002-1798-5315

ABSTRACT

Background: The advent of the omicron variant and the formulation of diverse therapeutic strategies marked a new epoch in the realm of coronavirus disease 2019 (COVID-19). Studies have compared the clinical outcomes between COVID-19 and seasonal influenza, but such studies were conducted during the early stages of the pandemic when effective treatment strategies had not yet been developed, which limits the generalizability of the findings. Therefore, an updated evaluation of the comparative analysis of clinical outcomes between COVID-19 and seasonal influenza is requisite.
Methods: This study used data from the severe acute respiratory infection surveillance system of South Korea. We extracted data for influenza patients who were infected between 2018 and 2019 and COVID-19 patients who were infected in 2021 (pre-omicron period) and 2022 (omicron period). Comparisons of outcomes were conducted among the pre-omicron, omicron, and influenza cohorts utilizing propensity score matching. The adjusted covariates in the propensity score matching included age, sex, smoking, and comorbidities.
Results: The study incorporated 1,227 patients in the pre-omicron cohort, 1,948 patients in the omicron cohort, and 920 patients in the influenza cohort. Following propensity score matching, 491 patients were included in each respective group. Clinical presentations exhibited similarities between the pre-omicron and omicron cohorts; however, COVID-19 patients demonstrated a higher prevalence of dyspnea and pulmonary infiltrates compared to their influenza counterparts. Both COVID-19 groups exhibited higher in-hospital mortality and longer hospital length of stay than the influenza group. The omicron group showed no significant improvement in clinical outcomes compared to the pre-omicron group.
Conclusion: The omicron group did not demonstrate better clinical outcomes than the pre-omicron group, and exhibited significant disease severity compared to the influenza group. Considering the likely persistence of COVID-19 infections, it is imperative to sustain comprehensive studies and ongoing policy support for the virus to enhance the prognosis for individuals affected by COVID-19.

Keywords: COVID-19; Influenza; Omicron Variant; Clinical Outcomes

Jeong-ok Cha
https://orcid.org/0009-0004-3491-9709
Kyung Hoon Min
https://orcid.org/0000-0003-0610-2182
Young Seok Lee
https://orcid.org/0000-0002-0144-2033

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Sim JK, Lee HS, Lee YS. Data curation: Sim JK, Lee HS, Yang J, Lee YS. Formal analysis: Sim JK, Lee HS, Yang J, Lee YS. Funding acquisition: Lee YS. Investigation: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS. Methodology: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS. Project administration: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS. Resources: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS. Software: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS. Supervision: Sim JK, Lee HS, Lee YS. Validation: Sim JK, Lee HS, Yang J, Lee YS. Visualization: Sim JK, Lee HS, Yang J, Lee YS. Writing - original draft: Sim JK, Lee HS, Lee YS. Writing - review & editing: Sim JK, Lee HS, Yang J, Gwack J, Kim BI, Cha JO, Min KH, Lee YS.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, a global public health challenge for the past 3 years, has had wide-ranging implications on various aspects of society, including interpersonal relationships and education, socioeconomic, and healthcare systems.[1] Among these issues, the large number and severity of COVID-19 infections have placed a substantial burden on the healthcare system, leading to a high mortality rate; this was particularly true in the initial stages of the pandemic.[2,3] Over time, various treatment strategies have been developed to improve the prognosis of COVID-19, including antiviral medications, vaccines, steroids, immunomodulators, oxygen therapy via a high-flow nasal cannula, and prone positioning.[4-8] Additionally, although omicron, the most recent variant, exhibits increased transmissibility than previous variants, it tends to result in milder disease severity.[9,10] Consequently, the mortality rates have significantly decreased recently.[3]

Studies have compared the clinical outcomes between COVID-19 and seasonal influenza. Patients with COVID-19 tend to be younger, to have fewer comorbidities, to experience a more severe disease course, to experience prolonged morbidity, and to have higher rates of intensive care unit (ICU) admission, mechanical ventilation use, and mortality compared to patients with influenza. However, such studies were conducted during the early stages of the pandemic when effective treatment strategies had not yet been developed, which limits the generalizability of the findings.[11-16] Therefore, an updated evaluation of this topic is required.

This study compared the clinical features and prognosis of patients with COVID-19 (before and after the emergence of the omicron variant) and patients with influenza in South Korea.

METHODS

Study design

This retrospective study used data from the severe acute respiratory infection (SARI) surveillance system, which maintains a prospective nationwide database of patients with respiratory virus infections, atypical bacterial infections, and pneumococcal infections based on the World Health Organization operational guidelines for sentinel SARI surveillance. The Korea Disease Control and Prevention Agency (KDCA) manages this database and publishes weekly reports from sentinel sites regarding the occurrence of various infections along with the relevant clinical information. The SARI surveillance system includes data from patients with an acute respiratory illness characterized by a history of fever or documented fever ≥ 38°C accompanied by cough, symptom onset within the prior 10 days, and need for hospitalization.[17,18] The system was operational at 13 university-affiliated hospitals from 2017 to 2019 and was subsequently expanded to 42 such hospitals in 2020, inclusive of the initial 13 (**Supplementary Table 1**). The primary outcome of the present study was in-hospital mortality, whereas the secondary outcomes were hospital length of stay, ICU admission, ICU length of stay, and ICU mortality.

Study population and data collection

Using the SARI surveillance system, we extracted data for influenza patients who were infected between 2018 and 2019 and COVID-19 patients who were infected in 2021 (pre-omicron period) and 2022 (omicron period). The omicron variant became prevalent in 2022 following its first case reported from South Korea on November 25, 2021.[19,20] Data for influenza patients

were extracted from 2018–2019. Ideally, patients from the same year would be compared, but during the COVID-19 pandemic (2021–2022), only 71 adult patients with influenza were registered in the SARI system. Therefore, data from 2018 and 2019 were used to minimize differences related to changes in medical knowledge, technology, policies, and other variables by comparing patients from similar time periods.

Although the SARI system collects data for patients of all ages, we focused on adult patients aged ≥ 18 years. We excluded patients who had coinfections of both influenza and COVID-19.

Data were collected on baseline characteristics, including demographic information and comorbidities, clinical presentation, antibiotic use, and clinical outcomes. A detailed description of comorbidities is presented in **Supplementary Table 2**.

Statistical analysis

We compared patients with COVID-19 in 2021 (pre-omicron group), those with COVID-19 in 2022 (omicron group), and those with influenza (influenza group). Patients were included in the groups using propensity score matching and 1:1 nearest neighbor method based on logistic regression analysis. The adjusted covariates in the propensity score matching included sex, age, smoking, and comorbidities. The pre-omicron and omicron groups were matched with the influenza group. Balancing of absolute standardized differences between groups was achieved using conditioning on the propensity score, with differences below 0.1 (**Supplementary Tables 3-5**). Categorical variables are presented as numbers (percentages), whereas continuous variables are presented as medians (interquartile ranges). To compare the three groups, we used the chi-square test or Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables based on the results of a normality test. To account for multiple comparisons in the post hoc test, Bonferroni correction was applied.

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA). Two-sided *P* values < 0.05 were considered indicative of statistical significance.

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board of Korea University Guro Hospital (approval No. K2022-1592-002). The study was conducted in accordance with the Declaration of Helsinki. We ensured patient privacy and anonymity during the study. The need for written informed consent was waived.

RESULTS

Of the 1,353 patients who developed COVID-19 in 2021, 126 aged < 18 years were excluded, and 1,227 adult patients were included in the pre-omicron group. In 2022, 2,408 patients were diagnosed with COVID-19, of whom 460 were excluded due to age < 18 years or coinfection with influenza, whereas 1,948 were included in the omicron group. Between 2018 and 2019, 2,168 patients were infected with influenza, of whom 920 adults were included in the influenza group. Following propensity score matching, 491 patients were included in each group (**Fig. 1** and **Supplementary Fig. 1**).

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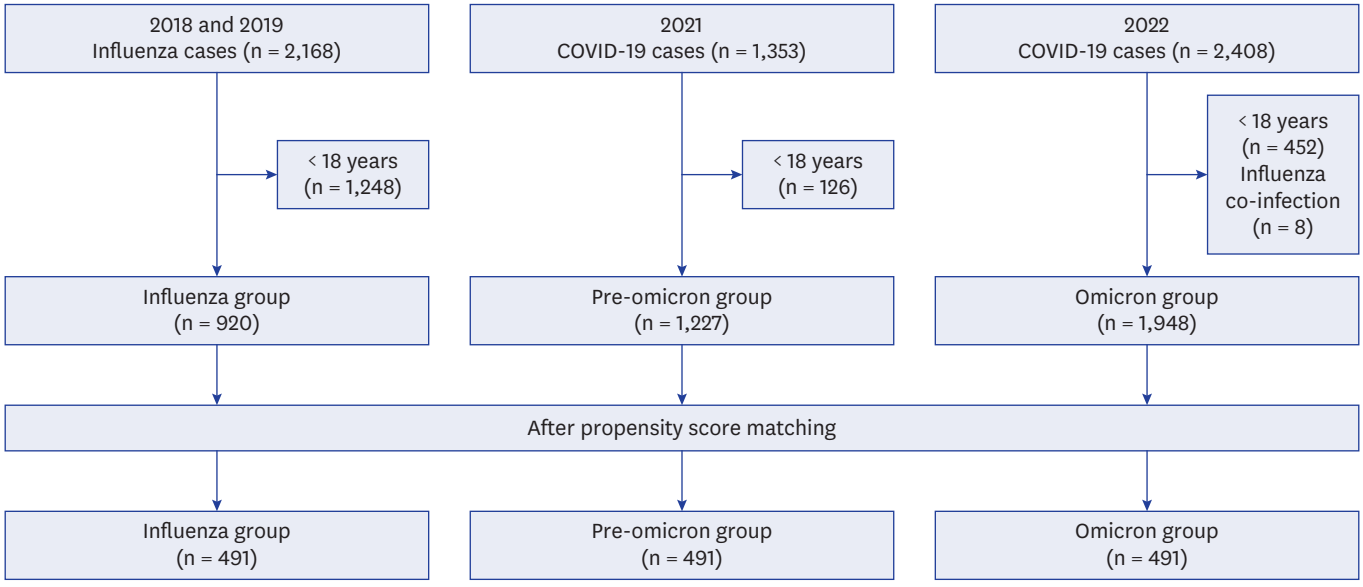

Fig. 1. Flowchart of patient selection.
COVID-19 = coronavirus disease 2019.

Baseline characteristics

The comparison among the three groups revealed significant differences in terms of the baseline characteristics, with differences observed between each pair of groups. In particular, the pre-omicron group exhibited significant differences compared to the other groups (**Table 1**). The median age for the pre-omicron group was 56 years, significantly lower than that for the omicron and influenza groups (70 and 70 years, respectively). The

Table 1. Baseline characteristics before propensity score matching

Variables	Pre-omicron (n = 1,227)	Omicron (n = 1,948)	Influenza (n = 920)	*P* value[a]	*P* value[b]		
					Pre-omicron vs. omicron	Pre-omicron vs. influenza	Omicron vs. influenza
Age, yr	56 (40–68)	70 (58–81)	70 (57–80)	< 0.001	< 0.001	< 0.001	> 0.999
Sex, male	676 (55.1)	1,118 (57.4)	467 (50.8)	0.004	0.610	0.139	0.003
Smoking	87 (7.1)	53 (2.7)	54 (5.9)	< 0.001	< 0.001	0.775	< 0.001
Comorbidity							
Cardiac disease	100 (8.1)	355 (18.2)	141 (15.3)	< 0.001	< 0.001	< 0.001	0.166
Respiratory disease	24 (2.0)	201 (10.3)	165 (17.9)	< 0.001	< 0.001	< 0.001	< 0.001
Hepatic disease	22 (1.8)	59 (3.0)	32 (3.5)	0.037	0.095	0.041	> 0.999
Renal disease	50 (4.1)	229 (11.8)	98 (10.6)	< 0.001	< 0.001	< 0.001	> 0.999
Diabetes	234 (19.1)	561 (28.8)	230 (25.0)	< 0.001	< 0.001	0.003	0.101
Neurological disease	63 (5.1)	274 (14.1)	94 (10.2)	< 0.001	< 0.001	< 0.001	0.012
Hematological disease	21 (1.7)	97 (5.0)	5 (0.5)	< 0.001	< 0.001	0.043	< 0.001
Immunocompromised	22 (1.8)	147 (7.5)	76 (8.3)	< 0.001	< 0.001	< 0.001	> 0.999
Asthma	22 (1.8)	68 (3.5)	78 (8.5)	< 0.001	0.015	< 0.001	< 0.001
HIV/AIDS	1 (0.1)	4 (0.2)	2 (0.2)	0.698	> 0.999	> 0.999	> 0.999
Tuberculosis	0 (0)	8 (0.4)	9 (1.0)	0.002	0.080	0.001	0.194
Antibiotics use[c]							
Beta-lactam	434 (35.4)	1,194 (61.3)	241 (61.3)	< 0.001	< 0.001	< 0.001	> 0.999
Fluoroquinolone	221 (18.0)	582 (29.9)	134 (34.1)	< 0.001	< 0.001	< 0.001	0.293
Macrolide	85 (6.9)	256 (13.1)	101 (25.7)	< 0.001	< 0.001	< 0.001	< 0.001
Others	252 (20.5)	495 (25.4)	110 (28.0)	0.001	0.005	0.006	0.860

Data are presented with number (%) or median (interquartile range).
HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome.
[a]*P* value in Kruskal-Wallis test; [b]*P* value in post hoc analysis (Bonferroni correction); [c]Data on antibiotic use were available in 393 patients in influenza group.

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Table 2. Baseline characteristics after propensity score matching

Variables	Pre-omicron (n = 491)	Omicron (n = 491)	Influenza (n = 491)	*P* value[a]	*P* value[b]		
					Pre-omicron vs. omicron	Pre-omicron vs. influenza	Omicron vs. influenza
Age, yr	64 (49–74)	65 (52–77)	65 (49–77)	0.304	0.369	> 0.999	> 0.999
Sex, male	235 (47.9)	248 (50.5)	237 (48.3)	0.671	> 0.999	> 0.999	> 0.999
Smoking	20 (4.1)	19 (3.9)	19 (3.9)	0.982	> 0.999	> 0.999	> 0.999
Comorbidity							
Cardiac	48 (9.8)	56 (11.4)	62 (12.6)	0.366	> 0.999	0.470	> 0.999
Respiratory	16 (3.3)	19 (3.9)	14 (2.8)	0.670	> 0.999	> 0.999	> 0.999
Hepatic	10 (2.0)	12 (2.4)	13 (2.6)	0.815	> 0.999	> 0.999	> 0.999
Renal	30 (6.1)	38 (7.7)	26 (5.3)	0.280	0.944	> 0.999	0.362
Diabetes	107 (21.8)	105 (21.4)	108 (22.0)	0.972	> 0.999	> 0.999	> 0.999
Neurological	37 (7.5)	35 (7.1)	30 (6.1)	0.663	> 0.999	> 0.999	> 0.999
Hematological	4 (0.8)	2 (0.4)	2 (0.4)	0.743	> 0.999	> 0.999	> 0.999
Immunocompromised	10 (2.0)	17 (3.5)	12 (2.4)	0.358	0.516	> 0.999	> 0.999
Asthma	12 (2.4)	8 (1.6)	8 (1.6)	0.558	> 0.999	> 0.999	> 0.999
HIV/AIDS	0 (0)	0 (0)	0 (0)	> 0.999	> 0.999	> 0.999	> 0.999
Tuberculosis	0 (0)	0 (0)	0 (0)	> 0.999	> 0.999	> 0.999	> 0.999
Antibiotics use[c]							
Beta-lactam	187 (38.1)	262 (53.4)	135 (61.4)	< 0.001	< 0.001	< 0.001	0.141
Fluoroquinolone	85 (17.3)	118 (24.0)	71 (32.27)	< 0.001	0.028	< 0.001	0.064
Macrolide	24 (4.9)	74 (15.1)	50 (22.73)	< 0.001	< 0.001	< 0.001	0.039
Other	120 (24.4)	134 (27.3)	53 (24.09)	0.510	0.923	> 0.999	> 0.999

Data are presented with number (%) or median (interquartile range).
HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome.
[a]*P* value in Kruskal-Wallis test; [b]*P* value in post hoc analysis (Bonferroni correction); [c]Data on antibiotic use were available in 220 patients in influenza group.

pre-omicron group had fewer comorbidities such as cardiac (8.1%, 18.2%, and 15.3%, respectively), respiratory (2.0%, 10.3%, and 17.9%), renal (4.1%, 11.8%, and 10.6%), and neurological diseases (5.1%, 14.1%, and 10.2%), immunocompromised condition (1.8%, 7.5%, and 8.3%), and asthma (1.8%, 3.5%, and 8.5%). Furthermore, antibiotics were used less frequently in the pre-omicron group than the other groups.

The omicron group exhibited greater similarity to the influenza group than to the pre-omicron group in terms of the baseline characteristics. Compared to the pre-omicron and influenza groups, the omicron group had a lower proportion of smokers (7.1%, 5.9%, and 2.7%, respectively) and higher proportions of neurological (5.1%, 10.2%, and 14.1%) and hematological (1.7%, 0.5%, and 5.0%) diseases. Compared to the influenza group, asthma (3.5% vs. 8.5%) and respiratory diseases (10.3% vs. 17.9%) were less common in the omicron group.

Following propensity score matching, the baseline characteristics showed no statistically significant differences among the groups, except for antibiotic use, which was less common in the pre-omicron group than the other groups (**Table 2**).

Clinical manifestations

In all groups, fever and cough were the most common symptoms, with more than 90% of patients experiencing these symptoms. The body temperature was higher in the influenza group than the COVID-19 groups, whereas it was not significantly different between the pre-omicron and omicron groups (38.1°C, 37.7°C, and 37.8°C, respectively, in the matched cohort). Sputum production was more common in the influenza group, affecting approximately two-third of patients, whereas it affected more than 40% of patients in the pre-omicron and omicron groups (65.2%, 42.2%, and 47.3% in the matched cohort). There were no significant differences in the prevalence of dyspnea between the two COVID-19 groups, affecting approximately one-third of patients in each. Conversely, almost one-fifth of patients in the influenza group experienced

Table 3. Clinical manifestations after propensity score matching

Variables	Pre-omicron (n = 491)	Omicron (n = 491)	Influenza (n = 491)	*P* value[a]	*P* value[b]		
					Pre-omicron vs. omicron	Pre-omicron vs. influenza	Omicron vs. influenza
Body temperature	37.7 (36.9–38.2)	37.8 (36.9–38.4)	38.1 (37.5–38.6)	< 0.001	0.185	< 0.001	< 0.001
Fever, ≥ 38°C	460 (93.7)	477 (97.1)	461 (93.9)	0.022	0.028	> 0.999	0.041
Chill	60 (12.2)	65 (13.2)	84 (17.1)	0.068	> 0.999	0.091	0.273
Myalgia	89 (18.1)	43 (8.8)	55 (11.2)	< 0.001	< 0.001	0.006	0.604
Cough	473 (96.3)	478 (97.3)	454 (92.5)	0.001	> 0.999	0.025	0.001
Sputum	207 (42.2)	232 (47.3)	320 (65.2)	< 0.001	0.326	< 0.001	< 0.001
Dyspnea	170 (34.6)	178 (36.3)	102 (20.8)	< 0.001	> 0.999	< 0.001	< 0.001
Rhinorrhea[c]	32 (6.5)	37 (7.5)	30 (13.6)	0.005	> 0.999	0.006	0.030
Sore throat[c]	87 (17.7)	66 (13.4)	12 (5.5)	< 0.001	0.194	< 0.001	0.005
Diarrhea	16 (3.3)	11 (2.2)	15 (3.1)	0.598	0.988	> 0.999	> 0.999
Vomiting[c]	7 (1.4)	19 (3.9)	14 (6.4)	0.002	0.051	0.001	0.432
Infiltrates on chest X-ray[d]	339 (69.3)	304 (63.3)	279 (56.8)	< 0.001	0.145	< 0.001	0.115

Data are presented with number (%) or median (interquartile range).
[a]*P* value in Kruskal-Wallis test; [b]*P* value in post hoc analysis (Bonferroni correction); [c]Data on rhinorrhea, sore throat, vomiting were available in 220 patients in influenza group; [d]Data on infiltrates on chest X-ray were available in 489 and 480 patients in pre-omicron and omicron groups, respectively.

dyspnea, which was significantly less common compared to the pre-omicron and omicron groups (20.8%, 34.6%, and 36.3% in the matched cohort). Pulmonary infiltrates, as detected in chest X-rays, were most common in the pre-omicron group, followed by the omicron and influenza groups, with incremental differences of 6% between each group (69.3%, 63.3%, and 56.8%, respectively, in the matched cohort). However, a statistically significant difference was observed only between the pre-omicron and influenza groups.

The pre-omicron and omicron groups had no significant differences in terms of clinical manifestations, except for fever (93.7% and 97.1%, respectively, in the matched cohort) and myalgia (18.1% and 8.8% in the matched cohort). The clinical manifestations of patients are presented in **Table 3** and **Supplementary Table 6**.

Clinical outcomes

Both before and after matching, the pre-omicron and omicron groups exhibited a higher in-hospital mortality than the influenza group (13.0%, 10.0%, and 3.0%, respectively, in the matched cohort); however, there were no significant differences between the pre-omicron and omicron groups. The hospital length of stay was longer in the pre-omicron group, followed by the omicron and influenza groups, with significant differences between each group pairs (12, 8, and 6 days, respectively, in the matched cohort). The ICU admission rate was higher in the pre-omicron group than the omicron group; however, no significant differences were observed between each COVID-19 group and the influenza group (15.7%, 9.6%, and 12.4% in the pre-omicron, omicron, and influenza groups, respectively, in the matched cohort). The ICU mortality rate was not significantly different among the groups (29.9%, 25.5%, and 19.7% in the matched cohort). The ICU length of stay was longer in the pre-omicron group than the omicron and influenza groups (17, 9, and 8 days, respectively), whereas there were no significant differences between the omicron and influenza groups. The clinical outcomes of patients are presented in **Table 4** and **Supplementary Table 7**.

DICUSSION

Following propensity score matching, we compared patients in the pre-omicron, omicron, and influenza groups in terms of their clinical features and prognosis. Although the in-

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Table 4. Clinical outcomes after propensity score matching

Variables	Pre-omicron (n = 491)	Omicron (n = 491)	Influenza (n = 491)	*P* value[a]	*P* value[b]		
					Pre-omicron vs. omicron	Pre-omicron vs. influenza	Omicron vs. influenza
In-hospital mortality	64 (13.0)	49 (10.0)	15 (3.0)	< 0.001	0.401	< 0.001	< 0.001
Hospital LOS, days	12 (10–19)	8 (7–15)	6 (4–11)	< 0.001	< 0.001	< 0.001	< 0.001
ICU admission	77 (15.7)	47 (9.6)	61 (12.4)	0.015	0.012	0.425	0.456
ICU mortality	23 (29.9)	12 (25.5)	12 (19.7)	0.393	> 0.999	0.515	> 0.999
ICU LOS, days	17 (9–31)	9 (6–14)	8 (4–14)	< 0.001	0.001	< 0.001	> 0.999

Data are presented with number (%) or median (interquartile range).
LOS = length of stay, ICU = intensive care unit.
[a]*P* value in Kruskal-Wallis test; [b]*P* value in post hoc analysis (Bonferroni correction).

hospital mortality rate was lower and the hospital length of stay was shorter in the omicron group than the pre-omicron group, the in-hospital mortality rate was higher and the hospital length of stay was longer than the influenza group. Despite the development of multiple effective treatments and the less severe disease caused by the omicron variant than the other variants, the prognosis for omicron variants was still worse than that for seasonal influenza.

Patients in the pre-omicron group were younger and had fewer comorbidities than those in the remaining groups, consistent with the results of studies conducted during the initial stages of the pandemic.[11-16] Conversely, the baseline characteristics were similar between the omicron and influenza groups, with almost half of the patients aged ≥ 70 years and a high prevalence of comorbidities. The age distribution and prevalence of comorbidities varied among patients with the omicron variant and those with previous COVID-19 variants.[21,22] However, it is unclear whether these differences are attributable to the microbiological characteristics of the omicron variant (e.g., low virulence)[9] or waning immunity among older individuals and those with multiple comorbidities.[23]

Antibiotics were used less frequently in the pre-omicron group. Throughout the ongoing COVID-19 pandemic, there may have been changes in diagnostic and hospitalization thresholds. The SARI surveillance system does not include data on laboratory tests or vital signs. However, if such thresholds have changed, then laboratory tests or vital signs in the omicron group may have been less favorable, possibly leading to more frequent antibiotic use in this group. A study conducted in Korea on the use of antibiotics in COVID-19 patients revealed that advanced age and comorbidities were associated with frequent antibiotic prescription.[24] In our study, both the omicron and influenza groups, which are characterized by older age and a higher prevalence of comorbidities compared to the pre-omicron group, may have experienced increased antibiotic usage. Additionally, baseline characteristics and antibiotic use patterns were similar in the omicron and influenza groups. Although we used baseline characteristics for propensity score matching, there may be other unadjusted factors.

The clinical manifestations were similar between the pre-omicron and omicron groups. Conversely, there were significant differences between the COVID-19 and influenza groups in terms of the clinical manifestations, particularly dyspnea and pulmonary infiltrates, which were more common in patients with COVID-19. Notably, the frequency of dyspnea varied across studies. The prevalence of dyspnea among hospitalized patients with COVID-19 and influenza varied across studies, ranging from 60% to 90%. Furthermore, these studies showed conflicting results, with some indicating a higher prevalence of dyspnea in COVID-19 or influenza and other demonstrating no significant differences.[15,25,26] A Korean study found that dyspnea affected 10.6% and 23.4% of patients with pneumonia caused by COVID-19

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and influenza, respectively. However, the study only investigated dyspnea of New York Heart Association class 2 or higher.[27]

Previous studies have found that dyspnea is less common among patients infected with the omicron variant than the delta variant.[22,28] In our study, the pre-omicron group included patients with both alpha and delta variants.[20] Differences in study populations between our study and these previous ones may explain this discrepancy. Dyspnea is a subjective symptom, and most previous studies have not used an objective scale to evaluate it. Consequently, the prevalence of dyspnea may have been affected by the characteristics of the study population. Therefore, it remains uncertain whether the prevalence of dyspnea differs across COVID-19 variants and influenza. Pulmonary infiltrates, as observed in chest X-rays, were more common in the COVID-19 groups than the influenza group, consistent with previous studies[15,25,27,29]; the same was true for the pre-omicron group versus the omicron group. Differences in the occurrence of pulmonary infiltrates can be attributable to tissue and cellular tropism of pathogens. Influenza virus primarily affects the upper respiratory tract, and in severe cases, the lower respiratory tract. Conversely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently involves the lower respiratory tract and lung parenchyma, leading to diffuse alveolar damage.[30] Compared to other COVID-19 variants, omicron preferentially replicates in the upper respiratory tract.[31] Due to differences in pathogen-related factors, clinical manifestations vary between COVID-19 and influenza, and among omicron and other variants.

In previous studies, the crude in-hospital mortality rate of COVID-19 patients was 2- to 3-fold higher than that of patients with influenza.[11,13,16] In the present study, the in-hospital mortality rate was approximately 3- to 4-fold higher in the COVID-19 groups than the influenza group, whereas there were no significant differences between the pre-omicron and omicron groups (13%, 10%, and 3% in the pre-omicron, omicron, and influenza groups, respectively, in the matched cohort). Initial clinical and translational studies demonstrated that the omicron variant is associated with mild disease and a good prognosis.[9,32] However, we did not find evidence to support these findings. Recent studies have demonstrated no significant differences in mortality rate among omicron and other COVID-19 variants.[21,22] Contrary to in-hospital mortality rates, ICU admission rates differed between the pre-omicron and omicron groups. During the COVID-19 pandemic, hospital policies changed in response to national quarantine guidelines. During the omicron period, the number of designated ICU beds for COVID-19 patients decreased, and mandatory quarantine guidelines and isolation periods were shorter than in the pre-omicron period. Consequently, indicators such as ICU admission rates and hospital lengths of stay may have been affected. However, as mortality is linked to disease severity rather than quarantine guidelines, no significant differences in mortality were observed. In the present study, the hospital and ICU lengths of stay were shorter in the omicron group than the other groups, which may be attributable to the less severe disease caused by omicron infection or changes in government policy regarding quarantine periods. Evolutionary changes in SARS-CoV-2 could lead to a reduction in its virulence and disease severity. However, caution should be exercised when interpreting data regarding changes in omicron disease severity,[33,34] because there is no biological basis for assuming that a specific pathogen will adapt to humans over time and reduce its virulence.[35] As quarantine was less effective in preventing the spread of omicron variants, South Korea shortened the isolation period, which may have influenced the duration of hospitalization.[36]

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This study had several strengths. First, we collected data for SARI patients hospitalized at several university-affiliated hospitals. Most of the included influenza patients had severe disease with comorbidities. Most patients with viral respiratory infections and no comorbidities do not require hospitalization because their symptoms are mild and they can be treated conservatively. To reduce the mortality associated with viral respiratory infections, efforts should focus on patients with severe infections or comorbidities who require hospitalization. Therefore, our results are particularly important because we focused on the prognosis of hospitalized patients with respiratory infections. Second, the SARI surveillance system involves standardized data collection, which prevents discrepancies due to variation in data collection and enhances the reliability of comparisons. Finally, we used propensity score matching to adjust for variation in the baseline characteristics among groups. As a result, there were no significant differences among the groups in terms of the baseline characteristics, thus allowing accurate comparison of the prognosis among the COVID-19 and influenza groups.

This study also had several limitations. First, this study carries inherent bias due to its retrospective observational design. The in-hospital mortality rate of the COVID-19 group was higher than that of the influenza group. However, it cannot be confirmed that there is a causal relationship between COVID-19 infection and high mortality rates. Further research is needed. Nevertheless, the data analyzed in this study were collected prospectively by the SARI surveillance system. We also adjusted for potential confounders using propensity score matching. Second, data for the COVID-19 and influenza groups were collected at different time periods, reflecting the significant reduction in influenza cases during the COVID-19 pandemic due to national social distancing strategies. [17,37,38] However, this time difference was not accounted for in our analysis, nor were changes in participating hospitals considered. However, hospitals active in 2018–2019 continued to participate in 2021–2022, and all were university-affiliated hospitals with ≤ 1,000 beds (**Supplementary Table 1**), suggesting a modest potential impact of site variation. Third, the SARI system does not collect information on influenza subtypes or specific COVID-19 variants. Some patients in the omicron group may have had infections with other COVID-19 variants, but a KDCA study reported that > 90% of COVID-19 cases since early February 2022 were omicron variant infections.[39] Therefore, it is reasonable to assume that the majority of patients in the omicron group were infected with this variant. As clinical characteristics and outcomes of influenza A and B are comparable in hospitalized patients,[40] and no significant association between influenza A subtype and clinical outcomes was found in a Korean study,[41] the lack of subtype analysis is unlikely to have substantially affected the overall findings. Fourth, our data lack details on laboratory tests, vital signs, or severity scores, restricting our ability to incorporate disease severity into propensity score matching, which may impact clinical outcomes. As mentioned earlier, diagnostic and admission thresholds may have changed, leading to potential variation in clinical indicators accordingly. However, similar results were observed in previous studies that also adjusted only for age and baseline characteristics.[11-13,16] Fifth, treatment details such as the use of steroids and antiviral agents for COVID-19 were not collected despite the significant impact of timely administration of these medications on prognosis. Finally, we did not evaluate factors related to immunity, such as previous infection or vaccination status. Vaccination is closely associated with disease severity and need for hospitalization in COVID-19.[42] Therefore, the immunity status of patients is an important factor when evaluating COVID-19 disease severity. Considering the increasing number of vaccinated individuals during the omicron era, further evidence is needed to determine the disease severity and prognosis of this variant.[20]

In conclusion, the omicron group did not demonstrate better clinical outcomes than the pre-omicron group, and exhibited significant disease severity compared to the influenza group. Considering the likely persistence of COVID-19 infections, it is imperative to sustain comprehensive studies and ongoing policy support for the virus to enhance the prognosis for individuals affected by COVID-19.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Hospitals participating in the severe acute respiratory infection surveillance system

Supplementary Table 2
Description of comorbidities

Supplementary Table 3
Absolute standardized difference between pre-omicron and influenza groups after propensity score matching

Supplementary Table 4
Absolute standardized difference between omicron and influenza groups after propensity score matching

Supplementary Table 5
Absolute standardized difference between pre-omicron and omicron groups after propensity score matching

Supplementary Table 6
Clinical manifestations before propensity score matching

Supplementary Table 7
Clinical outcomes before propensity score matching

Supplementary Fig. 1
The number of study population and total population in the SARI cohort according to each year.

REFERENCES

1. Onyeaka H, Anumudu CK, Al-Sharify ZT, Egele-Godswill E, Mbaegbu P. COVID-19 pandemic: a review of the global lockdown and its far-reaching effects. *Sci Prog* 2021;104(2):368504211019854. PUBMED | CROSSREF
2. Rennert-May E, Leal J, Thanh NX, Lang E, Dowling S, Manns B, et al. The impact of COVID-19 on hospital admissions and emergency department visits: a population-based study. *PLoS One* 2021;16(6):e0252441. PUBMED | CROSSREF

3. Horita N, Fukumoto T. Global case fatality rate from COVID-19 has decreased by 96.8% during 2.5 years of the pandemic. *J Med Virol* 2023;95(1):e28231. PUBMED | CROSSREF
4. Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VCC, Edwards KM, et al. Infectious diseases society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis* 2022;ciac724. PUBMED | CROSSREF
5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020;383(27):2603-15. PUBMED | CROSSREF
6. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(5):403-16. PUBMED | CROSSREF
7. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA* 2020;324(1):57-67. PUBMED | CROSSREF
8. Ehrmann S, Li J, Ibarra-Estrada M, Perez Y, Pavlov I, McNicholas B, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021;9(12):1387-95. PUBMED | CROSSREF
9. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022;399(10332):1303-12. PUBMED | CROSSREF
10. Perez-Guzman PN, Knock E, Imai N, Rawson T, Elmaci Y, Alcada J, et al. Epidemiological drivers of transmissibility and severity of SARS-CoV-2 in England. *Nat Commun* 2023;14(1):4279. PUBMED | CROSSREF
11. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021;9(3):251-9. PUBMED | CROSSREF
12. Brehm TT, van der Meirschen M, Hennigs A, Roedl K, Jarczak D, Wichmann D, et al. Comparison of clinical characteristics and disease outcome of COVID-19 and seasonal influenza. *Sci Rep* 2021;11(1):5803. PUBMED | CROSSREF
13. Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for influenza or COVID-19 in Germany. *Int J Infect Dis* 2021;103:316-22. PUBMED | CROSSREF
14. de Marignan D, Vacheron CH, Ader F, Lecocq M, Richard JC, Frobert E, et al. A retrospective comparison of COVID-19 and seasonal influenza mortality and outcomes in the ICUs of a French university hospital. *Eur J Anaesthesiol* 2022;39(5):427-35. PUBMED | CROSSREF
15. López Montesinos I, Arrieta-Aldea I, Dicastillo A, Zuccarino F, Sorli L, Guerri-Fernández R, et al. Comparison of hospitalized coronavirus disease 2019 and influenza patients requiring supplemental oxygen in a cohort study: clinical impact and resource consumption. *Clin Infect Dis* 2022;75(12):2225-38. PUBMED | CROSSREF
16. Fröhlich GM, De Kraker MEA, Abbas M, Keiser O, Thiabaud A, Roelens M, et al. Hospital outcomes of community-acquired COVID-19 versus influenza: insights from the Swiss hospital-based surveillance of influenza and COVID-19. *Euro Surveill* 2022;27(1):2001848. PUBMED | CROSSREF
17. Lee YS, Kang M, Cho J, Kang D, Min KH, Suh GY, et al. Nationwide social distancing and the epidemiology of severe acute respiratory infections. *Yonsei Med J* 2021;62(10):954-7. PUBMED | CROSSREF
18. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ* 2018;96(2):122-8. PUBMED | CROSSREF
19. Lee JJ, Choe YJ, Jeong H, Kim M, Kim S, Yoo H, et al. Importation and transmission of SARS-CoV-2 B.1.1.529 (Omicron) variant of concern in Korea, November 2021. *J Korean Med Sci* 2021;36(50):e346. PUBMED | CROSSREF
20. Ryu B, Shin E, Kim NY, Kim DH, Lee H, Kim A, et al. Severity of COVID-19 associated with SARS-CoV-2 variants circulating in the Republic of Korea. *Public Health Wkly Rep* 2022;15(47):2873-95. CROSSREF
21. Heydarifard Z, Shafiei-Jandaghi NZ, Safaei M, Tavakoli F, Shatizadeh Malekshahi S. Comparison of clinical outcomes, demographic, and laboratory characteristics of hospitalized COVID-19 patients during major three waves driven by alpha, delta, and omicron variants in Tehran, Iran. *Influenza Other Respi Viruses* 2023;17(8):e13184. PUBMED | CROSSREF
22. Mondi A, Mastrorosa I, Piselli P, Cimaglia C, Matusali G, Carletti F, et al. Evolution of SARS-CoV-2 variants of concern over a period of delta and omicron cocirculation, among patients hospitalized for COVID-19 in an Italian reference hospital: impact on clinical outcomes. *J Med Virol* 2023;95(6):e28831. PUBMED | CROSSREF

23. Menni C, May A, Polidori L, Louca P, Wolf J, Capdevila J, et al. COVID-19 vaccine waning and effectiveness and side-effects of boosters: a prospective community study from the ZOE COVID Study. *Lancet Infect Dis* 2022;22(7):1002-10. PUBMED | CROSSREF

24. Choi Y, Kang M, Shin DH, Jung J, Choi SJ, Kim NH, et al. Antibiotic prescription in patients with coronavirus disease 2019: analysis of national health insurance system data in the Republic of Korea. *J Korean Med Sci* 2023;38(25):e189. PUBMED | CROSSREF

25. Cobb NL, Sathe NA, Duan KI, Seitz KP, Thau MR, Sung CC, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza. *Ann Am Thorac Soc* 2021;18(4):632-40. PUBMED | CROSSREF

26. Auvinen R, Nohynek H, Syrjänen R, Ollgren J, Kerttula T, Mäntylä J, et al. Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients - a prospective observational study. *Infect Dis (Lond)* 2021;53(2):111-21. PUBMED | CROSSREF

27. Kim SH, Wi YM, Lim S, Han KT, Bae IG. Differences in clinical characteristics and chest images between coronavirus disease 2019 and influenza-associated pneumonia. *Diagnostics (Basel)* 2021;11(2):261. PUBMED | CROSSREF

28. Mella-Torres A, Escobar A, Barrera-Avalos C, Vargas-Salas S, Pirazzoli M, Gonzalez U, et al. Epidemiological characteristics of omicron and delta SARS-CoV-2 variant infection in Santiago, Chile. *Front Public Health* 2022;10:984433. PUBMED | CROSSREF

29. Lyons PG, Bhavani SV, Mody A, Bewley A, Dittman K, Doyle A, et al. Hospital trajectories and early predictors of clinical outcomes differ between SARS-CoV-2 and influenza pneumonia. *EBioMedicine* 2022;85:104295. PUBMED | CROSSREF

30. Flerlage T, Boyd DF, Meliopoulos V, Thomas PG, Schultz-Cherry S. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. *Nat Rev Microbiol* 2021;19(7):425-41. PUBMED | CROSSREF

31. Hui KPY, Ng KC, Ho JCW, Yeung HW, Ching RHH, Gu H, et al. Replication of SARS-CoV-2 omicron BA.2 variant in ex vivo cultures of the human upper and lower respiratory tract. *EBioMedicine* 2022;83:104232. PUBMED | CROSSREF

32. Hui KPY, Ho JCW, Cheung MC, Ng KC, Ching RHH, Lai KL, et al. SARS-CoV-2 omicron variant replication in human bronchus and lung ex vivo. *Nature* 2022;603(7902):715-20. PUBMED | CROSSREF

33. Bhattacharyya RP, Hanage WP. Challenges in inferring intrinsic severity of the SARS-CoV-2 omicron variant. *N Engl J Med* 2022;386(7):e14. PUBMED | CROSSREF

34. Meurisse M, Van Oyen H, Blot K, Catteau L, Serrien B, Klamer S, et al. Evaluating methodological approaches to assess the severity of infection with SARS-CoV-2 variants: scoping review and applications on Belgian COVID-19 data. *BMC Infect Dis* 2022;22(1):839. PUBMED | CROSSREF

35. Carabelli AM, Peacock TP, Thorne LG, Harvey WT, Hughes J, Peacock SJ, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nat Rev Microbiol* 2023;21(3):162-77. PUBMED | CROSSREF

36. Hong J, Park AK, Radnaabaatar M, Kim EJ, Kim DW, Jung J. The impact of entry restrictions on the spread of severe acute respiratory syndrome coronavirus variants between 2021 and 2022. *J Korean Med Sci* 2023;38(28):e223. PUBMED | CROSSREF

37. Kim S, Park JO, Lee HA, Park HA, Lee CA, Wang SJ, et al. Unintended beneficial effects of COVID-19 on influenza-associated emergency department use in Korea. *Am J Emerg Med* 2022;59:1-8. PUBMED | CROSSREF

38. Noh JY, Seong H, Yoon JG, Song JY, Cheong HJ, Kim WJ. Social distancing against COVID-19: implication for the control of influenza. *J Korean Med Sci* 2020;35(19):e182. PUBMED | CROSSREF

39. Park AK, Kim IH, Lee CY, Kim JA, Lee H, Kim HM, et al. Rapid emergence of the omicron variant of severe acute respiratory syndrome coronavirus 2 in Korea. *Ann Lab Med* 2023;43(2):211-3. PUBMED | CROSSREF

40. Su S, Chaves SS, Perez A, D'Mello T, Kirley PD, Yousey-Hindes K, et al. Comparing clinical characteristics between hospitalized adults with laboratory-confirmed influenza A and B virus infection. *Clin Infect Dis* 2014;59(2):252-5. PUBMED | CROSSREF

41. Yoon JG, Noh JY, Choi WS, Lee J, Lee JS, Wie SH, et al. A comparison of epidemiology and clinical outcomes between influenza A H1N1pdm09 and H3N2 based on multicenter surveillance from 2014 to 2018 in South Korea. *Influenza Other Respi Viruses* 2021;15(1):99-109. PUBMED | CROSSREF

42. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, et al. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ* 2022;376:e069761. PUBMED | CROSSREF