

Original Article
Infectious Diseases,
Microbiology & Parasitology



Breakthrough COVID-19 Infection During the Delta Variant Dominant Period: Individualized Care Based on Vaccination Status Is Needed

Chan Mi Lee ^{1,2} Eunyoung Lee ^{1,2} Wan Beom Park ¹ Pyoeng Gyun Choe ¹
Kyoung-Ho Song ^{1,3} Eu Suk Kim ^{1,3} and Sang-Won Park ^{1,2}

¹Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

²Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

³Division of Infectious Diseases, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

 OPEN ACCESS

Received: May 27, 2022

Accepted: Jul 11, 2022

Published online: Aug 8, 2022

Address for Correspondence:

Sang-Won Park, MD

Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea.

Email: hswon1@snu.ac.kr


© 2022 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.


ORCID iDs

Chan Mi Lee 


<https://orcid.org/0000-0001-7907-0412>

Eunyoung Lee 

<https://orcid.org/0000-0001-8280-3605>

Wan Beom Park 

<https://orcid.org/0000-0003-0022-9625>

Pyoeng Gyun Choe 

<https://orcid.org/0000-0001-6794-7918>

ABSTRACT


Background: The clinical features of coronavirus disease 2019 (COVID-19) patients in the COVID-19 vaccination era need to be clarified because breakthrough infection after vaccination is not uncommon.

Methods: We retrospectively analyzed hospitalized COVID-19 patients during a delta variant-dominant period 6 months after the national COVID-19 vaccination rollout. The clinical characteristics and risk factors for severe progression were assessed and subclassified according to vaccination status.


Results: A total of 438 COVID-19 patients were included; the numbers of patients in the unvaccinated, partially vaccinated and fully vaccinated groups were 188 (42.9%), 117 (26.7%) and 133 (30.4%), respectively. The vaccinated group was older, less symptomatic and had a higher Charlson comorbidity index at presentation. The proportions of patients who experienced severe progression in the unvaccinated and fully vaccinated groups were 20.3% (31/153) and 10.8% (13/120), respectively. Older age, diabetes mellitus, solid cancer, elevated levels of lactate dehydrogenase and chest X-ray abnormalities were associated with severe progression, and the vaccination at least once was the only protective factor for severe progression. Chest X-ray abnormalities at presentation were the only predictor for severe progression among fully vaccinated patients.

Conclusion: In the hospitalized setting, vaccinated and unvaccinated COVID-19 patients showed different clinical features and risk of oxygen demand despite a relatively high proportion of patients in the two groups. Vaccination needs to be assessed as an initial checkpoint, and chest X-ray may be helpful for predicting severe progression in vaccinated patients.

Keywords: Breakthrough Infection; SARS-CoV-2; COVID-19; Severe Progression; Oxygen Therapy

Kyoung-Ho Song 

<https://orcid.org/0000-0002-4517-3840>

Eu Suk Kim 

<https://orcid.org/0000-0001-7132-0157>

Sang-Won Park 

<https://orcid.org/0000-0002-0550-1897>

Funding

This work was supported by a focused clinical research grant-in-aid from the Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (04-2022-0007).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Park SW. Data curation: Lee CM. Formal analysis: Lee CM, Lee E, Park WB, Choe PG, Song KH, Kim ES, Park SW. Investigation: Lee CM, Lee E, Park SW. Methodology: Lee CM, Park SW. Writing - original draft: Lee CM. Writing - review & editing: Lee CM, Lee E, Park WB, Choe PG, Song KH, Kim ES, Park SW.

INTRODUCTION

Vaccination has been one of the key ways in which the 2-year long coronavirus disease 2019 (COVID-19) pandemic has been addressed. Several types of COVID-19 vaccines were rapidly rolled out and have shown efficacy ranging from 74% to 95% in preventing COVID-19 depending on the vaccine platform.¹⁻³

Severe aggravation was also shown to be significantly prevented by the available vaccines.^{2,3} The imperfect efficacy of vaccination has resulted in breakthrough COVID-19 infections and severe progression of COVID-19 regardless of vaccination status, and the factors related to those events are of both scientific and clinical interest. Although the worldwide pandemic situation is largely easing, there is regional imbalance in the severity of the pandemic and in the coverage by vaccines, especially in countries with poor resources. Even in high-income countries, the proportion of unvaccinated individuals is not low. As the world approaches a strategy of living with COVID-19, physicians will frequently find themselves caring for vaccinated and unvaccinated COVID-19 patients and need to be educated for the clinical features of those patients.

Since the first rollout of the AZD1222 (ChAdOx1 nCoV-19) vaccine on February 26, 2021, national vaccine coverage in Korea has been favorable, but patients with breakthrough infections have been reported.^{4,5} Although population-based studies estimating the effectiveness of COVID-19 vaccines have been reported,⁶⁻⁸ information about the clinical features and risk factors for aggravation of vaccinated and unvaccinated COVID-19 patients in a real-world setting would be very helpful to physicians. The Korean national COVID-19 policy provided an opportunity to investigate vaccinated and unvaccinated COVID-19 patients needing hospitalization.

In this study, we aimed to describe how the clinical manifestations of COVID-19 patients present in a real-world in-hospital care setting during the COVID-19 vaccination era and to determine the clinical implications of vaccination status in the individual patient care.

METHODS

Patients and study setting

All hospitalized COVID-19 patients ≥ 19 years of age in whom COVID-19 infection was confirmed by real-time reverse transcription polymerase chain reaction were enrolled from September to October 2021 at Boramae Medical Center, a university affiliated hospital designated for the care of hospitalized COVID-19 patients. Patients for whom information on documented vaccination status was not available were excluded (**Fig. 1**). During the study period, COVID-19 patients classified as belonging to a high-risk group or a symptomatic low-risk group were allowed to be admitted to the hospital. Most other stable COVID-19 patients were isolated in residential treatment centers. The patients were grouped into vaccinated and unvaccinated groups, and their presenting clinical features and the overall risk factors at admission for severe progression were characterized. In the subgroup analysis, clinical predictors for severe progression were assessed in the fully vaccinated group.

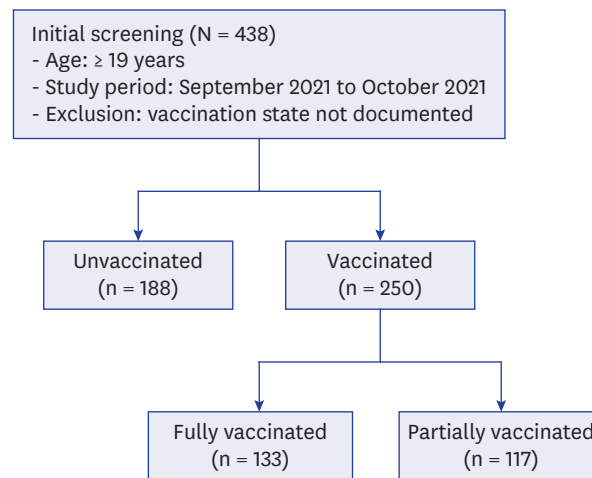


Fig. 1. Study setting. A total of 438 patients were enrolled, 188 of whom were unvaccinated and 250 of whom were vaccinated. The vaccinated group was divided into the fully vaccinated group and the partially vaccinated group.

Data collection and definitions

Data were retrospectively collected on demographics, vaccination status, clinical variables at presentation (clinical severity, symptoms and signs, laboratory findings and chest radiography), specific treatments, and clinical outcomes. COVID-19-specific treatments, including the use of remdesivir, monoclonal antibodies, or corticosteroids, and the use of antibacterial agents for periods ≥ 3 days were recorded. The level of oxygen supplementation, the in-hospital mortality, and the duration of hospitalization were used to assess the clinical outcomes.

Initial clinical severity was assessed based on the National Early Warning Score (NEWS)-2 and the Sequential Organ Failure Assessment (SOFA) score,⁹ and the severity of underlying comorbidity was estimated according to the Charlson comorbidity index (CCI).¹⁰ Patients with COVID-19 who had received full vaccination were defined as those who developed symptoms or were diagnosed with COVID-19 more than 14 days after completion the recommended vaccine regimen. Those who were vaccinated at least once but did not meet the criteria for full vaccination were defined as partially vaccinated.

The use of immunosuppressants was defined as having received any anticancer chemotherapy or any immunosuppressive agents, including steroids, within 30 days. The worst results of body temperature on the day of admission and laboratory findings within 24 hours after admission were used. Severe progression was defined as the occurrence of new oxygen demand during the clinical course of the disease, and oxygen demand was defined as needing oxygen for a period of more than 24 consecutive hours. Chest X-ray abnormalities were defined as the presence of lung infiltration suggestive of pneumonia on simple chest X-ray according to the independent formal report of the reviewing radiologists.

Statistical analysis

Student's *t*-test or the Mann-Whitney *U* test was used to compare continuous variables, and the χ^2 test or Fisher's exact test was used to compare categorical variables. To determine the risk factors for severe progression, multivariable logistic regression was performed using variables for which $P < 0.10$ in the univariate analysis. To avoid multicollinearity, the CCI, variable of no underlying disease and no initial symptoms were not included in the multivariable model. The SOFA score was excluded from the multivariable model to avoid

multicollinearity with the NEWS-2 and thrombocytopenia. To determine the goodness of fit for logistic regression models, the Hosmer-Lemeshow test was used. P values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Boramae Medical Center (No. 20-2021-54). The requirement for informed consent was waived by the IRB owing to the retrospective nature of the study. This study was conducted in compliance with the Declaration of Helsinki.

RESULTS

Clinical features of unvaccinated and vaccinated COVID-19 patients

A total of 438 patients were included in the analysis; 188 (42.9%) and 250 (57.1%) patients were included in the unvaccinated and vaccinated groups, respectively. Of the 250 vaccinated patients, 133 (53.2%) were fully vaccinated, and 117 (46.8%) were partially vaccinated (**Fig. 1**).

Analysis of the baseline characteristics of the patients showed that the vaccinated group was older, had a shorter time lag from diagnosis to admission or from onset of illness to admission, and had a lower initial NEWS-2 than the unvaccinated group (**Table 1**). The vaccinated group also had a higher CCI (median 2.0 vs. 0.0, $P < 0.001$) and a higher incidence of other underlying diseases (hypertension, diabetes mellitus, and chronic kidney disease) than the unvaccinated group. Patients without any underlying diseases were more frequent in the unvaccinated group. At admission, dyspnea and fever exceeding 38.0°C were more frequent, and white blood cell and platelet counts were lower, but lactate dehydrogenase (LDH) level and the proportion of chest X-ray abnormalities was higher (70.7% vs. 47.2%, $P < 0.001$) in the unvaccinated group than in the vaccinated group (**Table 1**).

The fully vaccinated group was older and had a shorter time lag from diagnosis to admission or onset of illness to admission than the partially vaccinated group. In the partially vaccinated group, 70.9% of patients had been vaccinated with BNT162b2 (**Table 2**). The fully vaccinated group had higher median CCI (3.0 vs. 1.0, $P < 0.001$) and higher proportion of individuals with hypertension and chronic kidney disease than the partially vaccinated group. At presentation, cough was more frequent and the level of LDH was higher in the partially vaccinated group than in the fully vaccinated group (**Table 2**).

The unvaccinated group required more oxygen therapy during the clinical course of the disease than the vaccinated group (nasal prong, 30.8% vs. 16.8%; facial mask, 0.0% vs. 0.4%; high flow, 2.7% vs. 2.8%; intubation, 1.6% vs. 1.2%; $P = 0.008$) (**Table 3**). Thirty-five patients in the unvaccinated group required oxygen therapy on the day of admission; of the 153 patients in that group without initial oxygen demand, 31 (20.3%) experienced clinical progression to severe disease. Thirteen patients in the fully vaccinated group required oxygen therapy initially; of the 120 patients in that group without initial oxygen demand, 13 (10.8%) required oxygen therapy later (**Fig. 2**). Consistent with their greater need for oxygen therapy, the unvaccinated group received more remdesivir and corticosteroids. Antibacterial agents were used more frequently in the unvaccinated group than in the vaccinated group (38.3% vs. 21.2%, $P < 0.001$) (**Table 3**). The fully vaccinated group remained in the hospital longer

Table 1. Presenting characteristics of coronavirus disease 2019 patients according to vaccination status at admission

Variables	Unvaccinated (n = 188)	Vaccinated (n = 250)	P
Age, yr	44 (36–56)	61 (45–71)	< 0.001
Male	90 (47.9)	116 (46.4)	0.760
BMI	23.5 (21.0–26.0)	24.2 (21.5–26.8)	0.014
Diagnosis to admission, day	3.0 (0.0–5.0)	1.0 (0.0–2.0)	< 0.001
Symptom onset to admission, day	5.5 (3.0–7.0)	4.0 (2.0–7.0)	0.007
Initial NIH classification			
Asymptomatic, mild	52 (27.7)	129 (51.6)	
Moderate	101 (53.7)	92 (36.8)	
Severe, critical	35 (54.5)	29 (11.6)	
Initial severity			
NEWS-2	2.0 (1.0–3.0)	1.0 (0.0–2.0)	0.002
SOFA score	1.0 (0.0–1.0)	0.0 (0.0–1.0)	0.123
Underlying comorbidity			
CCI	0.0 (0.0–1.5)	2.0 (0.0–3.0)	< 0.001
Hypertension	33 (17.6)	84 (33.6)	< 0.001
Diabetes mellitus	23 (12.2)	52 (20.8)	0.018
Chronic heart disease	1 (0.5)	8 (3.2)	0.085
Cerebrovascular disease	3 (1.6)	10 (4.0)	0.142
COPD	1 (0.5)	3 (1.2)	0.638
Asthma	11 (5.9)	7 (2.8)	0.111
Chronic liver disease	3 (1.6)	9 (3.6)	0.203
Chronic kidney disease	3 (1.6)	15 (6.0)	0.022
Renal replacement therapy	0 (0.0)	3 (1.2)	0.263
Solid cancer	13 (6.9)	25 (10.0)	0.256
Hematologic malignancy	2 (1.1)	2 (0.8)	> 0.999
Immunosuppressant use	12 (6.4)	11 (4.4)	0.357
None	99 (52.7)	80 (32.0)	< 0.001
Initial symptoms			
Loss of smell	12 (6.4)	11 (4.4)	0.357
Loss of taste	13 (6.9)	11 (4.4)	0.252
Cough	107 (56.9)	121 (48.4)	0.077
Dyspnea	20 (10.6)	10 (4.0)	0.006
None	16 (8.5)	34 (13.6)	0.097
Initial body temperature \geq 38.0°C	47 (25.0)	31 (12.4)	0.001
Initial laboratory findings			
White blood cells, /mm ³	4,175 (3,138–5,285)	4,990 (3,730–6,250)	0.002
Lymphocytes, %	28.0 (19.0–36.4)	25.5 (17.6–34.5)	0.110
Hemoglobin, g/dL	13.6 (12.8–14.6)	13.3 (12.4–14.3)	0.120
Platelets, $\times 10^3$ /mm ³	172 (140–233)	200 (144–245)	0.021
Bilirubin, total, mg/dL	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.010
Lactate dehydrogenase, U/L	251 (197–328)	210 (173–270)	< 0.001
Creatinine kinase, U/L	77 (55–138)	72 (53–110)	0.630
CRP, mg/dL	2.28 (0.61–4.94)	1.53 (0.34–4.97)	0.996
Creatinine, mg/dL	0.72 (0.58–0.91)	0.77 (0.63–0.91)	0.063
Ct value (RdRp gene)	18.6 (14.7–23.8)	18.5 (14.8–23.6)	0.862
Chest X-ray abnormality	133 (70.7)	118 (47.2)	< 0.001

Values are presented as number (%) or median (interquartile range).

BMI = body mass index, NIH = National Institutes of Health, NEWS = National Early Warning Score, SOFA = Sequential Organ Failure Assessment, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, Ct = cyclic threshold, RdRp = RNA dependent RNA polymerase.

(median 10.0 days vs. 8.0 days, $P < 0.001$) than did the partially vaccinated group, but the proportion of patients needing oxygen therapy did not differ between the fully and partially vaccinated groups (**Supplementary Table 1**).

Risk factors for severe progression in COVID-19 patients and vaccination status

The risk factors for severe progression during the clinical course among patients who did not initially require oxygen therapy were identified by multivariable analysis. Older age (adjusted

Table 2. Presenting characteristics of partially and fully vaccinated coronavirus disease 2019 patients at admission

Variables	Partially vaccinated (n = 117)	Fully vaccinated (n = 133)	P
Age, yr	53 (42–60)	69 (58–76)	< 0.001
Male	54 (46.2)	62 (46.6)	0.942
BMI	23.8 (21.1–26.6)	24.4 (22.0–27.2)	0.412
Diagnosis to admission, day	1.0 (0.0–5.0)	0.0 (0.0–1.0)	< 0.001
Symptom onset to admission, day	5.0 (3.0–8.0)	3.0 (1.0–5.0)	< 0.001
Initial NIH classification			
Asymptomatic, mild	53 (45.3)	76 (57.1)	
Moderate	48 (41.0)	44 (33.1)	
Severe, critical	16 (13.7)	13 (9.8)	
Initial severity			
NEWS-2	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.300
SOFA score	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.462
Vaccination status			
BNT162b2	83 (70.9)	52 (39.1)	
AZD1222	25 (21.4)	66 (49.6)	
Ad26.COV2.S	2 (1.7)	8 (6.0)	
mRNA-1273	7 (6.0)	2 (1.5)	
Cross-vaccination, others	0 (0.0)	5 (3.8)	
Underlying comorbidity			
CCI	1.0 (0.0–2.0)	3.0 (2.0–4.0)	< 0.001
Hypertension	26 (22.2)	58 (43.6)	< 0.001
Diabetes mellitus	21 (17.9)	31 (23.3)	0.298
Chronic heart disease	3 (2.6)	5 (3.8)	0.727
Cerebrovascular disease	2 (1.7)	8 (6.0)	0.110
COPD	1 (0.9)	2 (1.5)	> 0.999
Asthma	2 (1.7)	5 (3.8)	0.453
Chronic liver disease	6 (5.1)	3 (2.3)	0.312
Chronic kidney disease	1 (0.9)	14 (10.5)	0.001
Renal replacement therapy	0 (0.0)	3 (2.3)	0.250
Solid cancer	11 (9.4)	14 (10.5)	0.835
Hematologic malignancy	0 (0.0)	2 (1.5)	0.500
Immunosuppressant use	3 (2.6)	8 (6.0)	0.184
None	51 (43.6)	29 (21.8)	< 0.001
Initial symptoms			
Loss of smell	6 (5.1)	5 (3.8)	0.599
Loss of taste	5 (4.3)	6 (4.5)	0.927
Cough	66 (56.4)	55 (41.4)	0.017
Dyspnea	6 (5.1)	4 (3.0)	0.522
None	11 (9.4)	23 (17.3)	0.069
Initial body temperature $\geq 38^{\circ}\text{C}$	17 (14.5)	14 (10.5)	0.338
Initial laboratory findings			
White blood cells, /mm ³	4,650 (3,480–6,075)	5,180 (4,110–6,618)	0.066
Lymphocytes, %	24.4 (17.5–34.5)	25.7 (17.7–35.1)	0.994
Hemoglobin, g/dL	13.3 (12.5–14.2)	13.3 (12.2–14.2)	0.197
Platelets, $\times 10^3/\text{mm}^3$	203 (148–253)	197 (157–245)	0.967
Bilirubin, total, mg/dL	0.4 (0.3–0.6)	0.5 (0.3–0.6)	0.252
Lactate dehydrogenase, U/L	219 (171–309)	204 (178–240)	0.004
Creatinine kinase, U/L	71 (53–110)	74 (55–110)	0.274
CRP, mg/dL	1.84 (0.33–5.70)	1.24 (0.35–4.08)	0.076
Creatinine, mg/dL	0.70 (0.60–0.86)	0.81 (0.68–0.97)	0.016
Ct value (RdRp gene)	19.3 (14.7–24.7)	18.3 (15.0–23.2)	0.257
Chest X-ray abnormality	61 (52.1)	57 (42.9)	0.143

Values are presented as number (%) or median (interquartile range).

BMI = body mass index, NIH = National Institutes of Health, NEWS = National Early Warning Score, SOFA = Sequential Organ Failure Assessment, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, Ct = cyclic threshold, RdRp = RNA dependent RNA polymerase.

odds ratio [aOR], 1.04; 95% confidence interval [CI], 1.02–1.07; $P = 0.003$), diabetes mellitus (aOR, 2.31; 95% CI, 1.00–5.33; $P = 0.049$), solid cancer (aOR, 3.18; 95% CI, 1.14–8.85; $P = 0.027$), elevated level of LDH (aOR, 2.99; 95% CI, 1.34–6.65; $P = 0.007$), and chest X-ray

Table 3. Treatments and clinical outcomes of unvaccinated and vaccinated coronavirus disease 2019 patients

Variables	Unvaccinated (n = 188)	Vaccinated (n = 250)	P
Specific treatments			
Remdesivir	66 (35.1)	54 (21.6)	0.002
Dexamethasone	76 (40.4)	58 (23.2)	< 0.001
Monoclonal antibody	20 (10.6)	16 (6.4)	0.110
Antibacterial agents	72 (38.3)	53 (21.2)	< 0.001
Clinical outcomes (maximum oxygen therapy)			
No oxygen therapy	122 (64.9)	197 (78.8)	0.008
Nasal prong	58 (30.8)	42 (16.8)	
Facial mask	0 (0.0)	1 (0.4)	
High flow	5 (2.7)	7 (2.8)	
Intubation	3 (1.6)	3 (1.2)	
In-hospital mortality	0 (0.0)	1 (0.4)	> 0.999
Admission to discharge, day	8.0 (7.0–10.0)	9.0 (7.0–11.0)	0.676

Values are presented as number (%) or median (interquartile range). Monoclonal antibody: only regdanvimab (CT-P59; Celltrion Inc., Incheon, Korea) was used in Korea.

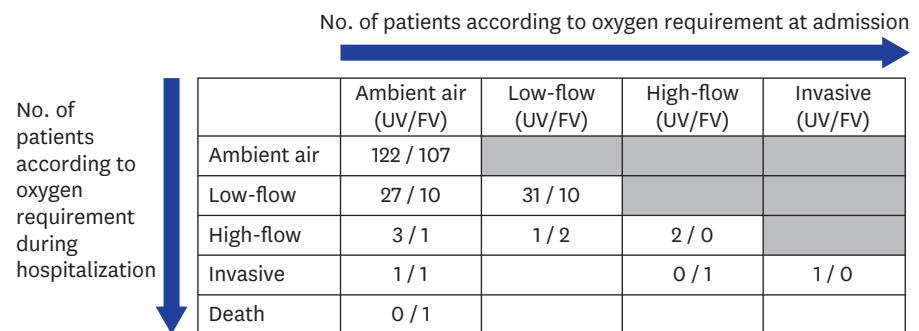


Fig. 2. Requirement for oxygen therapy at admission and during hospitalization among the unvaccinated (n = 188) and fully vaccinated groups (n = 133). The results are presented as the number of individuals in the UV group and the FV group. Among the 188 patients in UV group, 35 patients required oxygen at admission and 31 patients out of the other 153 patients (20.3%, 31/153) experienced clinical aggravation to need new oxygen requirement. Among the 133 patients in FV group, 13 patients required oxygen at admission and 13 patients out of the other 120 patients (10.8%, 13/120) experienced clinical aggravation to need new oxygen requirement. UV = unvaccinated, FV = fully vaccinated.

abnormality (aOR, 3.41; 95% CI, 1.31–8.89; $P = 0.012$) were significantly associated with severe progression. Vaccination at least once was associated with reduced risk of severe progression (aOR, 0.35; 95% CI, 0.15–0.79; $P = 0.011$) (Table 4). In the fully vaccinated patients without initial oxygen demand, chest X-ray abnormalities were the only risk factor for severe progression (aOR, 20.16; 95% CI, 2.43–167.66; $P = 0.005$) by multivariable analysis. Elevated level of C-reactive protein (CRP) was excluded from the multivariable model because the P value of the Hosmer-Lemeshow test was < 0.05 in the model including elevated level of CRP (Table 5).

DISCUSSION

During the study period, the national policy of Korea was to isolate most COVID-19 patients in residential treatment centers that mainly provided daily living support with minimum medical care for 10 days. Patients with high risk factors for severe progression or complication, or symptomatic patients who required further medical care were admitted or transferred to dedicated hospitals such as our study hospital. In addition, COVID-19 vaccination in Korea was first made available to the high-risk group, which included elderly individuals. Although

Table 4. Risk factors for severe progression among unvaccinated and vaccinated coronavirus disease 2019 patients at admission

Variables	Severe progression (n = 55)	Non-progression (n = 319)	Univariate		Multivariate	
			OR (95% CI)	P	aOR (95% CI)	P
Age, yr	61 (47–71)	50 (38–64)	1.03 (1.01–1.05)	0.002	1.04 (1.02–1.07)	0.003
Male	28 (50.9)	143 (44.8)	1.28 (0.72–2.26)	0.404		
BMI	23.9 (21.0–26.2)	24.0 (21.3–26.6)	0.98 (0.92–1.06)	0.655		
Diagnosis to admission, day	1.0 (0.0–4.0)	1.0 (0.0–4.0)	0.96 (0.86–1.08)	0.491		
Symptom onset to admission, day	4.0 (2.0–6.0)	4.0 (2.0–7.0)	0.97 (0.89–1.06)	0.520		
Initial severity						
NEWS-2	1.0 (1.0–2.0)	1.0 (0.0–2.0)	1.34 (1.09–1.63)	0.005	1.11 (0.86–1.43)	0.428
SOFA score	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.60 (1.18–2.19)	0.003		
Vaccination status						
Vaccination at least once	24 (43.6)	197 (61.8)	0.48 (0.27–0.86)	0.013	0.35 (0.15–0.79)	0.011
Fully vaccinated	13 (23.6)	107 (33.5)	0.61 (0.32–1.19)	0.149		
Underlying comorbidity						
CCI	2.0 (1.0–4.0)	1.0 (0.0–3.0)	1.26 (1.11–1.44)	< 0.001		
Hypertension	15 (27.3)	80 (25.1)	1.12 (0.59–2.14)	0.730		
Diabetes mellitus	14 (25.5)	42 (13.2)	2.25 (1.13–4.48)	0.021	2.31 (1.00–5.33)	0.049
Chronic heart disease	0 (0.0)	8 (2.5)	-	0.999		
Cerebrovascular disease	0 (0.0)	12 (3.8)	-	0.999		
COPD	1 (1.8)	3 (0.9)	1.95 (0.20–19.10)	0.566		
Asthma	3 (5.5)	13 (4.1)	1.36 (0.37–4.93)	0.642		
Chronic liver disease	3 (5.5)	7 (2.2)	2.57 (0.64–10.26)	0.181		
Chronic kidney disease	5 (9.1)	10 (3.1)	3.09 (1.01–9.42)	0.047	2.17 (0.51–9.24)	0.294
Renal replacement therapy	0 (0.0)	3 (0.9)	-	0.999		
Solid cancer	11 (20.0)	26 (8.2)	2.82 (1.30–6.10)	0.009	3.18 (1.14–8.85)	0.027
Hematologic malignancy	1 (1.8)	3 (0.9)	1.95 (0.20–19.10)	0.566		
Immunosuppressant use	6 (10.9)	15 (4.7)	2.48 (0.92–6.70)	0.073	0.75 (0.18–3.07)	0.688
None	16 (29.1)	140 (43.9)	0.53 (0.28–0.98)	0.042		
Initial symptoms						
Loss of smell	3 (5.5)	17 (5.3)	1.03 (0.29–3.62)	0.970		
Loss of taste	2 (3.6)	19 (6.0)	0.60 (0.14–2.63)	0.495		
Cough	35 (63.6)	153 (48.0)	1.90 (1.05–3.43)	0.034	1.60 (0.79–3.23)	0.188
Dyspnea	4 (7.3)	16 (5.0)	1.49 (0.48–4.62)	0.495		
None	2 (3.6)	45 (14.1)	0.23 (0.05–0.98)	0.046		
Initial body temperature \geq 38°C	15 (27.3)	45 (14.1)	2.28 (1.17–4.47)	0.016	2.10 (0.86–5.13)	0.103
Initial laboratory findings						
Leukocytosis (WBC > 10,000/mm ³)	2 (1.9)	6 (1.9)	1.97 (0.39–10.01)	0.414		
Thrombocytopenia (platelet < 130,000/mm ³)	13 (23.6)	37 (11.6)	2.36 (1.16–4.80)	0.018	1.08 (0.44–2.67)	0.864
Elevated LDH (> 300 U/L)	21 (38.2)	41 (12.9)	4.19 (2.22–7.90)	< 0.001	2.99 (1.34–6.65)	0.007
Elevated CRP (> 1 mg/dL)	47 (85.5)	167 (52.4)	5.35 (2.45–11.68)	< 0.001	2.07 (0.82–5.22)	0.123
Ct value (RdRp gene)	18.4 (14.2–21.4)	18.5 (14.7–23.6)	0.98 (0.93–1.02)	0.316		
Chest X-ray abnormality	48 (87.3)	141 (44.2)	8.66 (3.80–19.72)	< 0.001	3.41 (1.31–8.89)	0.012

OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, NEWS = National Early Warning Score, SOFA = Sequential Organ Failure Assessment, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, WBC = white blood cell, LDH = lactate dehydrogenase, CRP = C-reactive protein, Ct = cyclic threshold, RdRp = RNA dependent RNA polymerase.

the percentage of fully vaccinated individuals in the national population \geq 18 years of age was 54.2%, it differed markedly in different age groups. The percentages of fully vaccinated individuals over 80, 70–79, and 60–69 years of age were 79.8%, 89.6%, and 87.6%, respectively, but among individuals 50–59, 40–49, 30–39, and 18–29 years of age, the percentages were 58.4%, 32.2%, 36.1% and 32.5%, as of 28 September 2021.

Our results showed that the hospitalized COVID-19 patients in our study had characteristics in accordance with the national admission guidelines for COVID-19 patients. The vaccinated patients were older, had more comorbidities and were admitted to the hospital as early as possible in the fear that their condition might worsen. This might result in lower clinical severity at admission among these patients. In contrast, the unvaccinated patients were

Table 5. Risk factors for severe progression among fully vaccinated coronavirus disease 2019 patients at admission

Variables	Severe progression (n = 13)	Non-progression (n = 107)	Univariate		Multivariate	
			OR (95% CI)	P	aOR (95% CI)	P
Age, yr	74 (72–80)	67 (51–75)	1.07 (1.01–1.14)	0.015	1.05 (0.98–1.11)	0.163
Male	8 (61.5)	45 (42.1)	2.20 (0.68–7.18)	0.190		
BMI	23.1 (22.6–25.5)	24.5 (22.0–27.2)	0.90 (0.76–1.07)	0.236		
Diagnosis to admission, day	1.0 (0.0–1.5)	0.0 (0.0–1.0)	0.98 (0.67–1.43)	0.925		
Symptom onset to admission, day	2.0 (1.0–5.0)	2.0 (1.0–4.0)	0.99 (0.81–1.23)	0.954		
Initial severity						
NEWS-2	1.0 (0.5–2.0)	1.0 (0.0–1.0)	1.25 (0.84–1.87)	0.272		
SOFA score	0.0 (0.0–2.0)	0.0 (0.0–1.0)	1.50 (0.93–2.42)	0.100		
Vaccination status						
Vaccination date to symptom onset, day	71 (62–122)	66 (43–119)	1.01 (0.99–1.02)	0.416		
Underlying comorbidity						
CCI	4.0 (3.0–5.0)	3.0 (1.0–4.0)	1.34 (1.00–1.81)	0.051		
Hypertension	7 (53.8)	44 (41.1)	1.67 (0.53–5.31)	0.385		
Diabetes mellitus	4 (30.8)	24 (22.4)	1.54 (0.44–5.43)	0.505		
Chronic heart disease	0 (0.0)	5 (4.7)	-	0.999		
Cerebrovascular disease	0 (0.0)	8 (7.5)	-	0.999		
COPD	1 (7.7)	1 (0.9)	8.83 (0.52–150.49)	0.132		
Asthma	0 (0.0)	4 (3.7)	-	0.999		
Chronic liver disease	0 (0.0)	2 (1.9)	-	0.999		
Chronic kidney disease	3 (23.1)	9 (8.4)	3.27 (0.76–14.06)	0.112		
Renal replacement therapy	0 (0.0)	3 (2.8)	-	0.999		
Solid cancer	2 (15.4)	12 (11.2)	1.44 (0.28–7.29)	0.660		
Hematologic malignancy	0 (0.0)	2 (1.9)	-	0.999		
Immunosuppressant use	1 (7.7)	7 (6.5)	1.19 (0.14–10.52)	0.875		
None	1 (7.7)	25 (23.4)	0.27 (0.03–2.21)	0.224		
Initial symptoms						
Loss of smell	0 (0.0)	5 (4.7)	-	0.999		
Loss of taste	0 (0.0)	6 (5.6)	-	0.999		
Cough	8 (61.5)	41 (38.3)	2.58 (0.79–8.41)	0.117		
Dyspnea	0 (0.0)	2 (1.9)	-	0.999		
None	1 (7.7)	2 (19.6)	0.34 (0.04–2.77)	0.315		
Initial body temperature $\geq 38^{\circ}\text{C}$	2 (15.4)	9 (8.4)	1.98 (0.38–10.35)	0.418		
Initial laboratory findings						
Leukocytosis (WBC $> 10,000/\text{mm}^3$)	1 (7.7)	6 (5.6)	1.40 (0.16–12.66)	0.763		
Thrombocytopenia (platelet $< 130,000/\text{mm}^3$)	3 (23.1)	6 (5.6)	5.05 (1.09–23.34)	0.038	3.34 (0.54–20.75)	0.195
Elevated LDH ($> 300 \text{ U/L}$)	2 (15.4)	5 (4.7)	3.71 (0.64–21.43)	0.143		
Elevated CRP ($> 1 \text{ mg/dL}$)	12 (92.3)	52 (48.6)	12.69 (1.59–101.08)	0.016		
Ct value (RdRp gene)	18.4 (13.2–21.1)	18.3 (15.0–23.4)	0.96 (0.87–1.06)	0.422		
Chest X-ray abnormality	12 (92.3)	32 (29.9)	28.13 (3.51–225.48)	0.002	20.16 (2.43–167.66)	0.005

OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio, BMI = body mass index, NEWS = National Early Warning Score, SOFA = Sequential Organ Failure Assessment, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, WBC = white blood cell, LDH = lactate dehydrogenase, CRP = C-reactive protein, Ct = cyclic threshold, RdRp = RNA dependent RNA polymerase.

largely younger, had fewer comorbidities and were admitted to the hospital later in the clinical course of the disease due to severe manifestations that were not prevented by vaccination. We did not intend to compare the individual study subjects, vaccinated and unvaccinated directly; instead, we wanted to describe the type of COVID-19 patients we would expect to see in the hospital after the peak of the pandemic eased down. Although the composition of study subjects can be directly attributed to the national policy for allocation of COVID-19 patients, the scenario may be similar in real-world practice in the near future or might exist in other regions of the globe due to the existence of different policies for pandemic control in different countries.

The proportion of patients who required supplemental oxygen was higher in the unvaccinated group than in the vaccinated group. Considering the older age of the vaccinated group

and the higher proportion of comorbidities in that group, the fact that a lower proportion of patients in the vaccinated group needed oxygen therapy might be due to the effect of vaccination. Among unvaccinated and fully vaccinated patients without initial oxygen demand, the proportions of patients with severe progression were 20.3% (31/153) and 10.8% (13/120), respectively. One study conducted in Korea during the early COVID-19 pandemic showed that 11.7% (16/136) of unvaccinated patients experienced clinical aggravation with a need for oxygen treatment during the clinical course of the disease.¹¹ As the delta variant was the predominant strain at the time of our study (September–October 2021),^{12,13} the higher rate of progression observed in our study might be partially due to the virulence of the delta variant. Compared to the fully vaccinated patients, the proportion of unvaccinated patients who experienced severe progression was higher. Previous studies have shown that COVID-19 vaccination significantly prevents severe outcomes and reduces the length of hospitalization in high-risk groups.^{14,15} The results of our study suggest that a considerable proportion of younger COVID-19 patients with few comorbidities experience high degree of clinical severity and have a need for oxygen therapy in real practice. Fortunately, the oxygen therapy rarely requires invasive ventilation. However, in resource limited settings, even the failure of simple oxygen therapy may lead to a fatal outcome.

Treatment with remdesivir or dexamethasone was associated with severe cases of the disease. Interestingly, the use of antibacterial agents was also higher in the unvaccinated group, despite the assumption that the older group with multiple comorbidities might require more antibiotics to cope with complications of the disease. This somewhat unexpected result might be due to the higher clinical severity of the unvaccinated group and may indirectly reflect the tendency to inappropriately prescribe antibiotics for patients with COVID-19 who show severe symptoms, such as high fever, dyspnea, chest X-ray abnormalities and hypoxemia, not exactly based on the bacterial complications.^{16,17}

Regarding the laboratory findings, an elevated level of LDH at presentation was a predictor of severe progression. One previous study showed that elevated LDH levels during 6–10 days after the onset of illness were associated with clinical aggravation.¹¹ Abnormal baseline chest X-ray finding was also reported to be a risk factor for oxygen requirement.¹⁸ In this study, chest X-ray abnormalities at the initial presentation were a risk factor for severe progression among unvaccinated and vaccinated patients, and also in fully vaccinated patients. Therefore, several important predictors of severe progression that were identified in unvaccinated patients during the early part of the COVID-19 pandemic still appear to be risk factors for severe progression, even under the influence of vaccination and change of dominant variant strain.

Although a previous study reported the occurrence of breakthrough infections in fully vaccinated patients,¹⁹ the clinical characteristics and outcomes of vaccine breakthrough infections have not been systematically compared with those of infections in unvaccinated patients. Breakthrough COVID-19 infection in vaccinated people is also important from both the clinical and the pathophysiological perspectives. As expected based on studies that showed vaccine efficacy in preventing severe COVID-19,^{2,3} vaccination was the only protective factor for severe progression among patients with breakthrough infection and unvaccinated patients. As this study was conducted among hospitalized patients, the results may help clinicians manage patients with the potential of severe progression in hospital settings. As the chest X-ray abnormality was the only risk factor for clinical progression among fully vaccinated patients, it would be necessary to check the chest X-rays early during the patient's hospitalization and monitor clinical progression more carefully for the patients with initial chest X-ray abnormalities.

This study has several limitations. First, because it was conducted retrospectively at a single center, the generalization of the results may be limited. Second, the number of fully vaccinated patients with severe progression was relatively small. Third, we did not perform virologic analysis of concurrent SARS-CoV-2 variants. However, the likelihood of bias due to the variants may be minimal because most of the study patients were believed to be infected with the delta variant, considering the fact that the dominant viral population in Korea during the study period was the delta variant. Although our results may not be precisely applicable to other variants, the clinical framework could be extrapolated similarly.

In conclusion, we described the clinical features of unvaccinated and vaccinated COVID-19 patients in a hospitalized setting. The only protective factor for severe progression was the vaccination at least once. Among fully vaccinated patients, the chest X-ray abnormality was a predictor for severe progression. In a COVID-19 practice of hospitalized setting, vaccination should be an initial checkpoint for triage and chest X-ray may be helpful in predicting progression.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Treatments and clinical outcomes of partially and fully vaccinated coronavirus disease 2019 patients

[Click here to view](#)

REFERENCES

1. 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](#)
2. 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](#)
3. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 vaccine. *N Engl J Med* 2021;385(25):2348-60.
[PUBMED](#) | [CROSSREF](#)
4. Yi S, Kim JM, Choe YJ, Hong S, Choi S, Ahn SB, et al. SARS-CoV-2 delta variant breakthrough infection and onward secondary transmission in household. *J Korean Med Sci* 2022;37(1):e12.
[PUBMED](#) | [CROSSREF](#)
5. Wi YM, Kim SH, Peck KR. An outbreak of breakthrough infections by the SARS-CoV-2 delta variant in a psychiatric closed ward. *J Korean Med Sci* 2022;37(4):e28.
[PUBMED](#) | [CROSSREF](#)
6. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 delta variant in Qatar. *Nat Med* 2021;27(12):2136-43.
[PUBMED](#) | [CROSSREF](#)
7. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021;385(7):585-94.
[PUBMED](#) | [CROSSREF](#)
8. Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina. *N Engl J Med* 2022;386(10):933-41.
[PUBMED](#) | [CROSSREF](#)

9. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. *Crit Care* 2019;23(1):374.
[PUBMED](#) | [CROSSREF](#)
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
[PUBMED](#) | [CROSSREF](#)
11. Suh HJ, Kim DH, Heo EY, Lee HW, Lee JK, Lee CS, et al. Clinical characteristics of COVID-19: clinical dynamics of mild severe acute respiratory syndrome coronavirus 2 infection detected by early active surveillance. *J Korean Med Sci* 2020;35(32):e297.
[PUBMED](#) | [CROSSREF](#)
12. Korea Disease Control and Prevention Agency. Global trends and characteristics of the SARS-CoV-2 delta variant. *Public Health Wkly Rep* 2021;14(33):2363-5.
13. Korea Disease Control and Prevention Agency. July 2021 status and characteristics of the COVID-19 variant virus outbreak in the Republic of Korea. *Public Health Wkly Rep* 2021;14(48):3388-96.
14. Sun J, Zheng Q, Madhira V, Olex AL, Anzalone AJ, Vinson A, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. *JAMA Intern Med* 2022;182(2):153-62.
[PUBMED](#) | [CROSSREF](#)
15. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* 2021;326(20):2043-54.
[PUBMED](#) | [CROSSREF](#)
16. Sieswerda E, de Boer MG, Bonten MM, Boersma WG, Jonkers RE, Aleva RM, et al. Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. *Clin Microbiol Infect* 2021;27(1):61-6.
[PUBMED](#) | [CROSSREF](#)
17. Shin DH, Kang M, Song KH, Jung J, Kim ES, Kim HB. A call for antimicrobial stewardship in patients with COVID-19: a nationwide cohort study in Korea. *Clin Microbiol Infect* 2021;27(4):653-5.
[PUBMED](#) | [CROSSREF](#)
18. Ong SW, Hui TC, Lee YS, Haja Mohideen SM, Young BE, Tan CH, et al. High-risk chest radiographic features associated with COVID-19 disease severity. *PLoS One* 2021;16(1):e0245518.
[PUBMED](#) | [CROSSREF](#)
19. Jung J, Lee J, Park H, Lim YJ, Kim EO, Park MS, et al. Nosocomial outbreak by delta variant from a fully vaccinated patient. *J Korean Med Sci* 2022;37(17):e133.
[PUBMED](#) | [CROSSREF](#)