Radiology

SARS-CoV-2 Variants Infection in Relationship to Imaging-based Pneumonia and Clinical Outcomes

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Abbreviations: ICU (intensive care unit), OR (odds ratio)

Summary statement:

Periods of SARS-CoV-2 Omicron versus the Delta variant prevalence and vaccination status were associated with better clinical outcomes and less severe pneumonia at CT in hospitalized patients with COVID-19.

Key Results:

1. In 2180 adults hospitalized with confirmed COVID-19, initial chest x-rays (75% vs. 68%, $P < .001$) and CT (71% vs. 35%, $P < .001$) were more likely to be negative for pneumonia during periods of Omicron versus Delta variant prevalence, respectively.

2. Periods of Omicron variant prevalence had a lower risk of CT pneumonia severity (OR, 0.71; $P = .04$) and clinical severity (ICU admission or in-hospital death, OR 0.43; $P = .004$) than Delta variant prevalence.

Abstract

Background: Few reports have evaluated the effect of the SARS-CoV-2 variant and vaccination on the clinical and imaging features of COVID-19.

Purpose: To evaluate and compare the effect of vaccination and variant prevalence on the clinical and imaging features of infections by the SARS-CoV-2.

Materials and Methods: Consecutive adults hospitalized for confirmed COVID-19 at three centers (two academic medical centers and one community hospital) and registered in a nationwide open data repository for COVID-19 between August 2021 and March 2022 were retrospectively included. All patients had available chest radiographs or CT. Patients were divided into two groups according to predominant variant type over the study period. Differences between clinical and imaging features were analyzed using Pearson $\chi 2$ test, Fisher exact test, or the independent t-test. Multivariable logistic regression analyses were used to evaluate the effect of variant predominance and vaccination status on imaging features of pneumonia and clinical severity.

Results: Of the 2180 patients (mean age, 57 years ± 21, 1171 women), 1022 patients (46%) were treated during the Delta variant predominant period and 1158 (54%) during the Omicron period. The Omicron variant prevalence was associated with lower pneumonia severity based on CT scores (OR, 0.71 [95% CI: 0.51, 0.99; $P = .04$]) and lower clinical severity based on ICU admission or in-hospital death (OR 0.43, 95% CI: 0.24, 0.77, $P = .004$) than the Delta variant prevalence. Vaccination was associated with the lowest odds of severe pneumonia based on CT scores (OR 0.05, 95% CI:0.03, 0.13, $P < .001$) and clinical severity based on ICU admission or in-hospital death (OR 0.15, 95% CI: 0.07, 0.31, $P < .001$) relative to no vaccination.

Conclusion: The SARS-CoV-2 Omicron variant prevalence and vaccination were associated with better clinical outcomes and lower severe pneumonia risk relative to Delta variant prevalence.

Introduction

The first case of COVID-19 was detected toward the end of 2019, and in August 2022 over 587 million confirmed cases and six million deaths were reported (1). The overall mortality rate has declined from an initial 2 % to 1.2 %, probably due to vaccination or the emergence of clinically milder strains. COVID-19 vaccines have proven to be effective and critical tools for controlling the pandemic. Globally, as of August, 2022, a total of 12 billion vaccine doses had been administered and 4.8 billion persons were fully vaccinated (2).

According to the Korea Disease Control and Prevention Agency (KDCA) data, the number of confirmed cases of COVID-19 per 100,000 of the Korean population was 16.6 in the unvaccinated group and 3.1 in the fully vaccinated group, and non-vaccinated individuals were at 5.2-fold higher risk of COVID-19 than the fully vaccinated (3). Although COVID-19 vaccines are highly effective, breakthrough infections have been reported with varying incidence rates (4). Recently, the numbers of those infected or vaccinated have increased, but so has the number of breakthrough infections (4). In our previous study (5), we found that the clinical and imaging characteristics of COVID-19 breakthrough infections in fully vaccinated patients tended to be milder than those of unvaccinated patients. In addition, several recently published studies revealed that clinical course and pneumonia severity are somewhat different according to the viral variants (6-9). However, few reports have evaluated the effect of both vaccination and viral variant prevalence on clinical and imaging severity of COVID-19. Therefore, the purpose of this study was to evaluate the clinical and imaging features of COVID-19 according to viral variant prevalence and vaccination statuses, to analyze their relationships with clinical severity and vaccination status.

Materials and Methods

The study was approved by the institutional review board (2207–002–116), which waived the requirement for informed consent due to the retrospective nature of the study.

Study Design and Patients

The Korea Disease Control and Prevention Agency (KDCA) monitors COVID-19 variant types by analyzing 10 to 30% of daily confirmed cases in Korea through random sampling (10). According to a KDCA report, the detection rate of the Delta variant exceeded 90% from August to November 2021 (10-12), but the Omicron variant gradually replaced the Delta variant from December 2021 to January 2022, and the detection rate of the Omicron variant exceeded 90% from February 2022 (10-12). In this study, we included patients with a COVID-19 registered from August 2021 to March 2022 (Fig. 1). Periods in which the detection rate of each variant exceeded 90% were defined as *periods of variant predominance*. Accordingly, August to November 2021 was defined as the Delta variant predominant period (the Delta period), and February to March 2022 as the Omicron variant predominant period (the Omicron period).

This multicenter study was conducted at three centers (one community hospital [center 1, n = 1144] and two academic medical centers [center 2, n = 617; center 3, n = 419]) registered in the Korean Imaging Cohort of COVID-19 (KICC) database (a nationwide open data repository) (13). The patients were ≥ 18 years-old consecutive patients hospitalized for COVID-19 (as confirmed by real-time reverse transcriptase polymerase chain reaction [RT-PCR] per national guidelines) with available chest radiographs (posteroanterior or anteroposterior view) or CT images. The indications of hospitalization were determined based on the patient`s risk and severity of symptom, and also applied differently according to periods of variant predominance and level of center. All confirmed patients were eligible for hospitalization and isolation in the Delta period, whereas high-risk patients or patients with severe symptoms were eligible for hospitalization in the Omicron period.

Data Collection

Demographic characteristics (age and sex), smoking history, vaccination status, body-mass index (BMI) at time of admission, comorbidities (hypertension, diabetes, cardiovascular disease, cancer, chronic kidney disease, and immunocompromised state), clinical symptoms (fever, cough, sputum, dyspnea, myalgia, sore throat, and sensory loss), initial laboratory findings, and clinical outcomes were

evaluated using the Korean Imaging Cohort of COVID-19 (KICC) cloud-based data storage platform. Vaccination status was classified as unvaccinated, partially vaccinated, fully vaccinated, or booster dose administered (Table E1). Initial laboratory findings included white blood cell (WBC), lymphocyte, platelet counts, lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels. Leukocytosis was defined as a WBC count of > 10 000/μL, lymphocytopenia as a lymphocyte count of < 1500/μL, and thrombocytopenia as a platelet count of < 150 000/μL. The predefined clinical thresholds for LDH and CRP elevation were 50 mg/L and 250 U/L, respectively. Clinical outcomes were receipt of supplemental oxygen, mechanical ventilation, intensive care unit (ICU) admission, and in-hospital death.

Chest radiographs and CT images obtained during hospitalization were acquired from the Korean Imaging Cohort of COVID-19 (KICC) cloud-based data storage platform. The initial chest radiograph images were obtained in all patients at admission and followed up every 2-3 days until discharge. The chest CT images were obtained differently depending on patients' condition and the situation of centers, the CT images obtained at admission or during hospitalization, but within a week of symptom onset were regarded as the initial CT images. An initial chest radiograph was obtained for all 2180 patients, and an initial chest CT scan was obtained for 1413 patients (center 1 [n = 1144], center 2 [n = 82], and 3 [n = 187] (Fig. 1).

Image Analysis

Two thoracic radiologists (M.H. and J.E.L., with 3 and 8 years of experience), unaware of patient clinical information, reviewed all images independently. Inter-reader discrepancies were resolved by consensus agreements. Pneumonia extent on initial and all follow-up chest radiographs and pneumonia extent and patterns on CT images were analyzed. We used a modified visual scoring system with a 3-point scale based on percentage of any opacification on chest radiographs and CT images (score 0 = no evidence of pneumonia, score 1 = 1%–25% involvement, and score 2 = >25% involvement) (5, 14, 15). Pneumonia patterns on CT images were categorized as typical, indeterminate, atypical, or negative as per the RSNA Expert Consensus Statement (16).

Statistical Analysis

Statistical analysis was performed using SPSS version 28.0 (IBM). Categorical variables are presented as numbers and percentages and continuous variables as means and SDs. The 2180 patients were divided into two groups according to variant predominance. Significances of intergroup were determined using Pearson $\chi 2$ test or Fisher exact test for categorical variables (sex, smoking history, comorbidities, symptoms, initial laboratory findings, three-point chest radiography and CT scores, CT pneumonia pattern, and clinical outcomes), and the significances of differences between continuous variables (age and hospital length of stay) were determined using the independent t-test. Post hoc analysis was performed using the Bonferroni method. Bonferroni-adjusted *P* values were determined by multiplying raw *P* values by numbers of comparisons. Kappa statistics were used to estimate inter-reader agreements for chest radiography and CT scores and CT pneumonia pattern. Cohen's kappa coefficient values of < 0.40 indicated poor agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and 0.81-1 as almost perfect agreement. Multivariable ordinal logistic regression analyses were used to evaluate the association of pneumonia severity with variant predominance and vaccination status, and multivariable binary logistic regression analyses were used to evaluate the association of clinical severity with variant predominance and vaccination status. The unadjusted models included each of predominant variant and vaccination status, and the adjusted multivariable models included predominant variant and vaccination status with additional covariates of age, sex, smoking history, hypertension, diabetes, cardiovascular disease, history of cancer, chronic kidney disease, immunocompromised state, obesity, and laboratory measures above or below predefined clinical thresholds (WBC, lymphocyte, and platelet counts and LDH and CRP levels) as covariates. Statistical significance was accepted for *P* values < .05.

Results

Clinical characteristics and outcomes of patients according to variant predominance

Of the 2849 patients, 662 patients registered from inconclusive variant predominance period and 7 patients with missing imaging evaluation were excluded (Fig. 1). Baseline clinical characteristics and outcomes of the 2180 patients included in the analysis according to variant predominance and vaccination status are presented in (Fig. 1, Table 1) and Table E2. Mean age was higher in the Omicron variant prevalence group (the Omicron group) (63 years ± 20) than in the Delta variant prevalence group (the Delta group) (49 years ± 19) ($P < .001$). The percentage of women was higher in the Omicron group (56%, 649 of 1158 patients vs. 51%, 522 of 1022 patients) ($P = .02$), and the percentage of unvaccinated individuals was higher in the Delta group (61%, 625 of 1022 vs. 21%, 239 of 1158). Only the Omicron group included individuals who received a booster vaccine dose.

The mean time between final vaccination and diagnosis was greater in the Omicron than the Delta group (86 days ± 52 vs. 61 days ± 45) ($P < .001$). Percentages of patients with comorbidities including hypertension, diabetes, cardiovascular disease, history of cancer, chronic kidney disease were higher in the Omicron group ($P < .001$), but the percentage of obese patients was higher in the Delta group ($P = .008$). Percentages of patients with leukocytosis, or an elevated CRP level were higher than in the Omicron group ($P < .001$), and the percentage of patients with thrombocytopenia was also higher in the Omicron group ($P = .03$). Mean hospital stay was shorter in the Omicron group (9.5 days ± 17 vs. 12 days ± 7.9) ($P < .001$) and proportions of patients received supplemental oxygen or mechanical ventilation and in-hospital deaths were higher in the Omicron group.

Vaccination Status and Breakthrough Infections

864 (40%) of the 2180 patients had not been vaccinated at time of diagnosis, 172 (8%) were partially vaccinated, 512 (23%) were fully vaccinated, and 632 (29%) had received a booster dose. Mean time between last vaccination and diagnosis was 79 days ± 51. Of the 1316 vaccinated patients, 1258 (96%)

received a vaccination within 6 months of diagnosis, and 58 (4%) more than 6 months at diagnosis (Table E3).

Pneumonia severity and patterns by variant predominance

Kappa agreements for initial and follow-up chest radiographs and CT scores between two readers were as follows: initial chest radiographs, 0.76; follow-up chest radiographs, 0.90; initial CT images, 0.89. Kappa agreements for CT patterns between two readers were almost perfect (0.85). Pneumonia severities and patterns by variant predominance are presented in Table 2. 1744 patients (80%) of the 2180 patients underwent at least one follow-up chest radiography during hospitalization. According to initial chest radiography assessments, 68% (695 of 1022) of patients in the Delta group, and 75% (866 of 1158) of those in the Omicron group had negative chest radiographs (score of 0), and the proportion of patients with an initially negative chest radiograph was higher in the Omicron group (Bonferroni adjusted $P < .001$). Additionally, 15% (149 of 1022) of patients in the Delta group and 12% (136 of 1158) of patients in the Omicron group had a chest radiograph score of 2. The proportion of patients with severe pneumonia (a chest radiograph score of 2) was similar in the Omicron and Delta groups (Bonferroni adjusted $P = .10$).

According to worst chest radiography assessments during hospitalization, 66% (671 of 1022) of patients in the Delta group and 73% (843 of 1158) of patients in the Omicron group were negative for pneumonia on chest radiographs. The proportion of patients with negative chest radiograph findings during follow-up was higher in the Omicron group (Bonferroni adjusted $P < .001$). Additionally, 16% (164 of 1022) of patients in the Delta group and 16% (182 of 1158) of patients in the Omicron group had a chest radiograph score of 2. The proportion of patients with severe pneumonia in worst chest radiographs (score of 2) was similar in the Omicron and Delta groups (Bonferroni adjusted $P = .83$).

Overall, 1413 of the 2180 patients (65%) underwent chest CT during hospitalization; of these, 35% (209 of 601) of patients in the Delta group and 71% (573 of 812) of patients in the Omicron group were

negative CT findings for pneumonia. The proportion of negative CT scans (score 0) was higher in the Omicron group (Bonferroni adjusted $P < .001$). Additionally, 19% (114 of 601) of patients in the Delta group and 12% (100 of 812) of patients in the Omicron group had a CT score of 2. The proportion of patients with a CT score of 2 was lower in the Omicron group (Bonferroni adjusted $P < .001$). Of the 1413 patients that underwent chest CT, 631 (45%) were positive for pneumonia, and the most common CT patterns observed were "typical" (76% [298 of 392] in the Delta group, and 42% [101 of 239] in the Omicron group). The proportion with a "typical" CT pattern was lower in the Omicron group (Bonferroni adjusted $P < .001$) and the proportion with an "atypical" CT pattern was higher in the Omicron group (Bonferroni adjusted $P < .001$).

Factors associated with pneumonia severity

The unadjusted and adjusted odds ratios (ORs) of pneumonia severity are summarized in Table 3. Adjusted multivariable analysis showed that the Omicron variant prevalence had a lower OR for pneumonia severity based on CT scores (OR, 0.71 [95% CI: 0.51, 0.99; $P = .04$]). Adjusted multivariable analysis showed that all vaccinated statuses except ≥ 6 months from partial vaccination had lower ORs for pneumonia severity based on chest radiograph and CT scores than the unvaccinated (all *Ps* < .001) (Figs. 2 & 3). The ORs of pneumonia severity based on chest radiograph and CT scores were the lowest for patients that had been administered a booster dose (OR, 0.07 [95% CI: 0.05, 0.10, $P < .001$] and 0.05 [95% CI: 0.03, 0.13, $P <. 001$], respectively).

Factors associated with clinical severity

The unadjusted and adjusted ORs of clinical severity are summarized in Table 4. Adjusted multivariable analysis showed that the Omicron variant prevalence had lower ORs for clinical severity based on ICU admission or in-hospital death (OR, 0.43 [95% CI: 0.24, 0.77; $P = .004$]). Adjusted multivariable analysis showed that booster dose administered patients and fully vaccinated patients

within 6 months prior to admission had lower ORs for clinical severity based on receipt of supplemental oxygen than the unvaccinated ($P < .001$). Fully vaccinated patients above 6 months and partially vaccinated patients within 6 months prior to admission also had lower ORs for clinical severity based on receipt of supplemental oxygen than the unvaccinated ($P = .01$ and .003, respectively). Adjusted multivariable analysis showed that booster dose administered patients and fully vaccinated patients within 6 months prior to admission had lower ORs for clinical severity based on ICU admission or in-hospital death than the unvaccinated ($P < .001$). Partially vaccinated patients within 6 months prior to admission also had lower OR for clinical severity based on ICU admission or in-hospital death than the unvaccinated ($P = .01$). The ORs for clinical severity based on receipt of supplemental oxygen and ICU admission or in-hospital death were the lowest for patients that had received a booster dose (OR, 0.10 [95% CI: 0.07, 0.16, $P < .001$] and 0.15 [95% CI: 0.07, 0.31, $P <. 001$], respectively).

Discussion

The effect of the SARS-CoV-2 variant and vaccination on the clinical and imaging features of COVID-19 remain lacking. In this study, we evaluated the clinical and imaging features of COVID-19 according to viral variants prevalence and vaccination status and analyzed their relationships with clinical severity. Summarizing our findings were as follows: 1) The clinical characteristics of the Delta and Omicron prevalence groups were quite different, and the proportions of patients requiring supplemental oxygen (26% vs. 21%, $P = .008$) or mechanical ventilation (5% vs. 3%, $P = .003$) and in-hospital deaths (4% vs. 2%, $P < .001$) were higher in the Omicron group. 2) The proportions of patients with an initially negative chest radiographic (75% vs. 68%, $P < .001$) or CT findings (71% vs. 35%, $P < .001$) were also higher in the Omicron group. 3) The most common CT pattern was typical (RSNA classification (10)), but the proportion of an atypical CT pattern (28% vs. 3%) was higher in the Omicron group ($P < .001$). 4) Adjusted multivariable analysis also showed that all vaccinated statuses except > 6 months from partial vaccination, had lower ORs for pneumonia severity based on chest radiograph and CT scores than the unvaccinated (all $P < .001$). In addition, Omicron variant prevalence

had significantly lower ORs for clinical severity based on ICU admission or in-hospital death (OR, 0.43 [95% CI: 0.24, 0.77; *P* = .004]).

From February to April 2022, the number of confirmed COVID-19 cases rose sharply due to the Omicron variant in Korea, and the number of confirmed cases accounted for 95% of all confirmed cases in Korea during the period (17). In February 2022, the Korean government announced a new treatment strategy based on the screening and treatment of high-risk populations at early as possible (18). Confirmed patients with no or mild symptoms were asked to isolate at home, and the isolation period at home or hospital was reduced from 10 to 7 days. Accordingly, the patients recruited in the Omicron period were of higher-risk than those recruited in the Delta period, and thus, clinical outcomes were poorer in the Omicron group than in the Delta group. However, multivariable analysis adjusted for baseline characteristic differences showed clinical outcomes were better in the Omicron group.

Although it is difficult to infer intrinsic severity of the Omicron variant due to the effect of difference in population immunity, the Omicron variant causes less severe pneumonia than the Alpha (15) or Delta variant (8, 9), which concurs with our findings. In particular, the multivariable analysis conducted in our current study, which was corrected for vaccination status and underlying disease, showed that the Omicron variant prevalence was an independent protective factor of pneumonia severity as compared with the Delta variant prevalence, which supports the results of previous studies. Notably, we found the "atypical" pattern of COVID-19 pneumonia was more prevalent in the Omicron group, which is also consistent with previous studies (8, 9). Although the exact pathogenesis of the "atypical" pattern of COVID-19 pneumonia was not determined, we believed it was probably the result of co-infection or secondary infections, rather than COVID-19 pneumonia (16, 19). When the Omicron variant become predominant, the severity of pneumonia decreased and the negative scan rate increased, but proportions of patients admitted with a co-infection or secondary infection increased in line with increased admissions of high-risk hospitalized patients, which may have influenced the pneumonia patterns.

As vaccination rates increased, the proportion of patients admitted with a COVID-19 breakthrough infection increased, and overall disease severity decreased (20, 21). The effectiveness of vaccination

for Delta and Omicron variants has been well demonstrated (22, 23). In an earlier study, we conducted during the early Delta period, vaccination was found to reduce disease severity and rate of pneumonia and improve clinical outcomes (5). In our current study, multivariable analysis showed vaccinated status was negatively associated with pneumonia severity and poor clinical outcomes, and that it was a stronger independent factor of lower risk than variant status. Therefore, the Delta to Omicron switch and a higher vaccination rate may been largely responsible for the observed reductions in clinical and pneumonia severities in patients with COVID-19.

Several limitations of this study warrant consideration. First, the study was conducted on patients hospitalized for COVID-19, which may have introduced selection bias. Second, we defined our study groups according to periods of variant predominance rather than by testing. Third, we used medical records to determine vaccination histories and thus, were unable to evaluate the effectiveness of different types of vaccine. Finally, there were several potential confounders (changes in treatment methods and number of vaccine doses between two variants prevalence) to impact on the results.

In summary, the SARS-COV-2 Omicron variant prevalence and vaccination were associated with better clinical outcomes and lower severe pneumonia risk. Vaccination was found to have the greatest protective effects on pneumonia and clinical severity in SARS-CoV-2 Omicron and Delta variant infections.

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Table 1. Clinical Characteristics and Outcomes of Patients with COVID-19 Patients by Predominant Variant

Variables	Delta group (N=1022)	Omicron group (N=1158)	*P* value
Age (years)	49 ± 19	63 ± 20	<.001*
Sex			
Female	522 (51)	649 (56)	.02*
Male	500 (49)	509 (44)	
Smoking history			
Smoker	139 (17)	72 (11)	<.001*
Never smoker	678 (83)	596 (89)	
Vaccination status			
Unvaccinated	625 (61)	239 (21)	<.001*
Any vaccinated	397 (39)	919 (79)	<.001*
Partially vaccinated	140 (14)	32 (2.8)	
Fully vaccinated	257 (25)	255 (22)	
Booster dose administered	0 (0)	632 (55)	
Symptoms			
Asymptomatic	123 (12)	125 (11)	.36
Symptomatic	899 (88)	1033 (89)	
Comorbidities			
Hypertension	279 (27)	535 (46)	<.001*
Diabetes	145 (14)	305 (26)	<.001*
Cardiovascular disease	93 (9.1)	251 (22)	<.001*
Obesity	85 (8.3)	63 (5.4)	.008*
History of cancer	60 (5.9)	129 (11)	<.001*
Chronic kidney disease	39 (3.8)	122 (11)	<.001*
Immunocompromised	14 (1.4)	24 (2.1)	.21
Initial laboratory findings			
WBC count >10,000/μl	31 (3.0)	106 (9.2)	<.001*
Lymphocyte count <1000/μl	260 (25)	270 (23)	.24
Platelet count <150,000/μl	170 (17)	233 (20)	.03*
LDH >250 U/L	313 (31)	397 (34)	.06
CRP >50 mg/L	131 (13)	247 (21)	<.001*
Clinical outcomes			
Length of hospital stay	12 ± 7.9	9.5 ± 17	<.001*
Requiring O_2 supply	214 (21)	298 (26)	.008*
ICU admission	50 (5)	63 (5)	.56
Mechanical ventilation	30 (3)	54 (5)	.003*
In-hospital death	19 (2)	49 (4)	<.001*

Note.- WBC = White blood cell, LDH = Lactate dehydrogenase, CRP = C-reactive protein, ICU = Intensive care unit. Values in parentheses are percentages. Values are presented as means ± standard deviations, where applicable. * Indicates statistical significance ($P < .05$).

Table 2. Pneumonia Chest Radiograph and CT Severity Scores and Patterns of Patients with COVID-19 Patients by Predominant Variant

Variables	Delta group (N=1022)	Omicron group (N=1158)	*P* value		
			All	0 (or typical) vs. others†	2 (or atypical) vs. others†
Radiograph score (initial)					
0	695 (68)	866 (75)	.002*	<.001*	.10
1	178 (17)	156 (14)			
2	149 (15)	136 (12)			
Radiograph score (worst)					
0	671 (66)	843 (73)	<.001*	<.001*	.83
1	187 (18)	133 (11)			
2	164 (16)	182 (16)			
CT score[a]					
0	209 (35)	573 (71)	<.001*	<.001*	<.001*
1	278 (46)	139 (17)			
2	114 (19)	100 (12)			
CT pattern[b]					
Typical	298 (76)	101 (42)	<.001*	<.001*	<.001*
Indeterminate	81 (21)	71 (30)			
Atypical	13 (3)	67 (28)			

Note.- Values in parentheses are percentages. Values are presented as means ± standard deviations, where applicable. * Indicates statistical significance ($P < .05$).

†*P* values were adjusted for post hoc analysis using the Bonferroni method by multiplying raw *P* values by 2 (the number of comparisons).

[a]Available in 1413 patients.

[b]Available in 631 patients.

Table 3. Odds Ratios for Pneumonia Severity by Predominant Variant and Vaccination Status

Variable	Model 1		Model 2	
	Unadjusted OR	*P* value	Adjusted OR	*P* value
Chest Radiograph				
Predominant variant				
Delta	Reference		Reference	
Omicron	0.76 (0.63–0.91)*	.002*	0.92 (0.68-1.23)	.56
Last vaccination status				
Unvaccinated	Reference		Reference	
< 6 months after partially vaccinated	0.35 (0.24–0.51)*	<.001*	0.38 (0.24-0.57)*	<.001*
≥ 6 months after partially vaccinated	0.83 (0.28–2.32)	.73	0.30 (0.08-1.04)	.06
< 6 months after fully vaccinated	0.22 (0.17–0.29)*	<.001*	0.14 (0.10-0.20)*	<.001*
≥ 6 months after fully vaccinated	0.50 (0.26–0.94)*	.03*	0.15 (0.07-0.33)*	<.001*
Booster dose administered	0.17 (0.13–0.21)*	<.001*	0.07 (0.05-0.10)*	<.001*
CT				
Predominant variant				
Delta	Reference		Reference	
Omicron	0.28 (0.23–0.35)*	<.001*	0.71 (0.51-0.99)*	.04*
Last vaccination status				
Unvaccinated	Reference		Reference	
< 6 months after partially vaccinated	0.43 (0.28-0.67)*	<.001*	0.42 (0.26-0.68)*	<.001*
≥ 6 months after partially vaccinated	0.42 (0.10-1.68)	.22	0.33 (0.07-1.52)	.15
< 6 months after fully vaccinated	0.13 (0.09-0.18)*	<.001*	0.11 (0.08-0.17)*	<.001*
≥ 6 months after fully vaccinated	0.26 (0.13-0.52)*	<.001*	0.16 (0.07-0.33)*	<.001*
Booster dose administered	0.07 (0.05-0.09)*	<.001*	0.05 (0.03-0.13)*	<.001*

Note.- OR = Odds ratio. Data in parentheses are 95% confidence intervals. The analysis was performed using an ordinal logistic regression model. Model 1 was the unadjusted model. Model 2 included predominant variant and vaccination status with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, history of cancer, chronic kidney disease, immunocompromised state, obesity, and laboratory measures above or below predefined clinical thresholds (WBC, lymphocyte, and platelet counts and lactate dehydrogenase [LDH] and C-reactive protein [CRP] levels) as covariates. * Indicates statistical significance ($P < .05$).

Table 4. Odds Ratios for Clinical Severity by Predominant Variant and Vaccination Status

Variable	Model 1		Model 2	
	Unadjusted OR	*P* value	Adjusted OR	*P* value
Requirement for supplemental oxygen (N=512)				
Predominant variant				
Delta	Reference		Reference	
Omicron	1.31 (1.07–1.60)*	.008*	1.10 (0.75–1.59)	.63
Last vaccination status				
Unvaccinated	Reference		Reference	
< 6 months after partially vaccinated	0.37 (0.24–0.58)*	<.001*	0.41 (0.22–0.74)*	.003*
≥ 6 months after partially vaccinated	2.22 (0.80–6.17)	.12	0.46 (0.10–2.15)	.32
< 6 months after fully vaccinated	0.36 (0.27–0.48)*	<.001*	0.18 (0.12–0.28)*	<.001*
≥ 6 months after fully vaccinated	1.11 (0.59–2.08)	.75	0.27 (0.10–0.73)*	.01*
Booster dose administered	0.34 (0.27–0.45)*	<.001*	0.10 (0.07–0.16)*	<.001*
ICU admission or in-hospital death (N=135)				
Predominant variant				
Delta	Reference		Reference	
Omicron	1.13 (0.79–1.60)	.49	0.43 (0.24–0.77)*	.004*
Vaccination status				
Unvaccinated	Reference		Reference	
< 6 months after partially vaccinated	0.16 (0.05–0.51)*	.002*	0.17 (0.04–0.65)*	.01*
≥ 6 months after partially vaccinated	0.63 (0.08–4.87)	.63	0.16 (0.01–1.65)	.12
< 6 months after fully vaccinated	0.33 (0.20–0.55)*	<.001*	0.27 (0.14–0.53)*	<.001*
≥ 6 months after fully vaccinated	1.05 (0.40–2.73)	.92	0.31 (0.09–1.05)	.06
Booster dose administered	0.19 (0.11–0.33)	<.001	0.15 (0.07–0.31)*	<.001*

Note.- OR = Odds ratio. Data in parentheses are 95% confidence intervals. The analysis was performed using a logistic regression model. * Indicates statistical significance ($P < .05$). Model 1 was the unadjusted model. Model 2 included predominant variant and vaccination status with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, history of cancer, chronic kidney disease, immunocompromised state, obesity, and laboratory measures above or below predefined clinical thresholds (WBC, lymphocyte, and platelet counts and lactate dehydrogenase [LDH] and C-reactive protein [CRP] levels) as covariates.

FIGUES

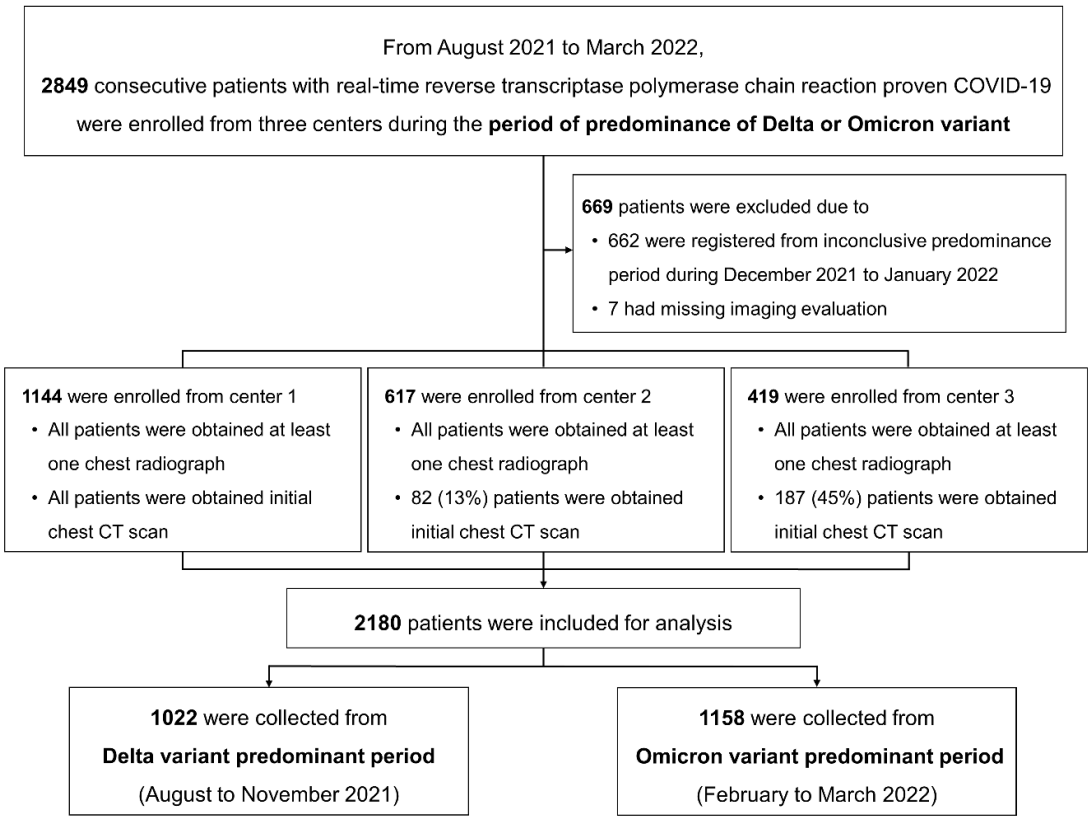

Figure 1. Flow diagram.

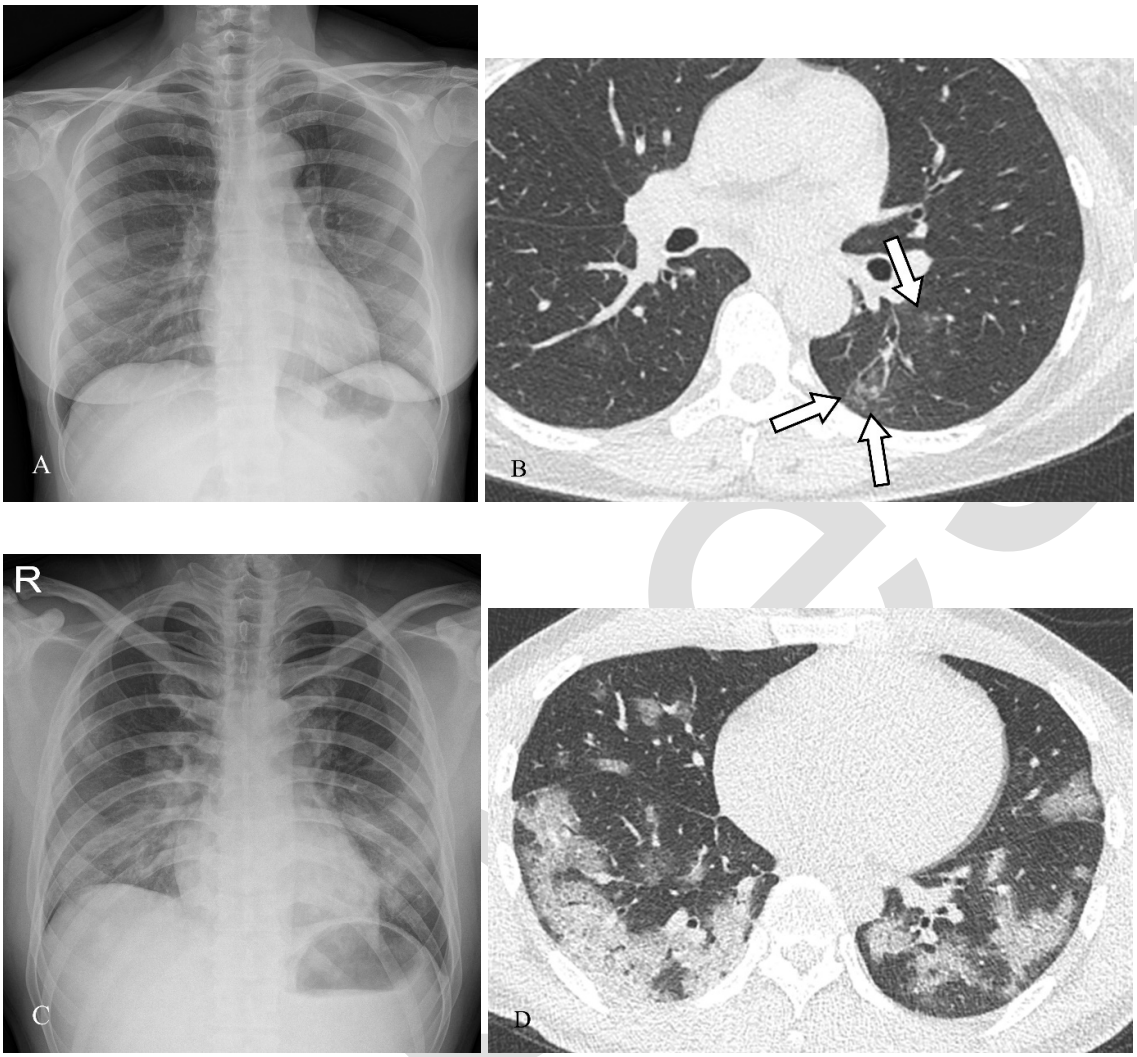

Figure 2. Representative cases showing pneumonia extents and patterns on chest radiographs and CT images during the Omicron period. **(A, B)** Images in a 52-year-old woman with a breakthrough COVID-19 infection 4 months after a second dose of the mRNA-1273 vaccine (fully vaccinated) in the Omicron period. The patient had no history of comorbidity. **(A)** Chest radiograph obtained at admission shows no abnormality in both lungs. The chest radiograph extent of pneumonia was scored as 0 (no evidence of pneumonia). **(B)** Axial chest CT image obtained on the same day shows poorly defined centrilobular nodules in the left lower lobe (arrows). The extent of pneumonia by CT was scored as 1 (1%–25% involvement). This case was classified as an "atypical" for COVID-19 pneumonia as per the RSNA

chest CT classification system. **(C, D)** Images of a 30-year-old man with no history of COVID-19 vaccination and no history of comorbidity in the Omicron period. **(C)** Chest radiograph taken at admission shows patchy ground-glass opacities in the middle to lower zones of both lungs. The chest radiograph extent of pneumonia was scored as 2 (>25% involvement). **(D)** Axial chest CT image obtained on the same day shows multifocal ground-glass opacities with a crazy-paving appearance in bilateral lungs. The extent of pneumonia at CT was scored as 2 (>25% involvement), and the appearance of COVID-19 pneumonia was classified as "typical" according to the RSNA chest CT classification system. RT-PCR, Reverse transcription polymerase chain reaction.

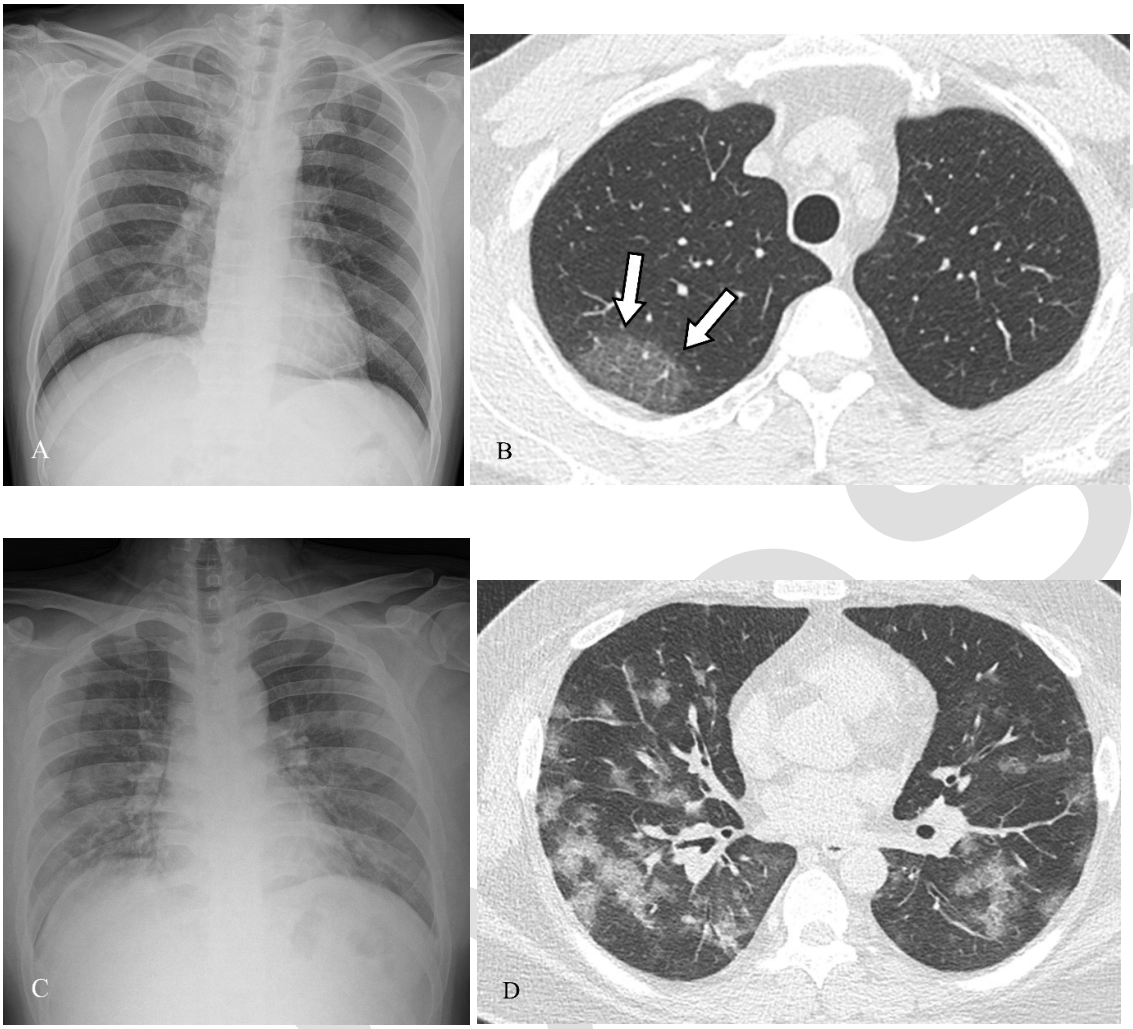

Figure 3. Representative cases showing pneumonia extents and patterns on chest radiographs and CT images during the Delta period. **(A, B)** Images in a 54-year-old man 1 month after a first dose of BNT162b2 vaccine (partially vaccinated) in the Delta period. The patient had no history of comorbidity. **(A)** Chest radiograph obtained at admission shows no abnormality in both lungs. The chest radiograph extent of pneumonia was scored as 0 (no evidence of pneumonia). **(B)** Axial chest CT image obtained on the same day shows unilateral focal ground-glass opacity in the right upper lobe (arrows). The extent of pneumonia by CT was scored as 1 (1%–25% involvement), and this case was classified as an "indeterminate" for COVID-19 pneumonia according to the RSNA chest CT classification system. **(C, D)** Images of a 32-year-old man with no history of COVID-19 vaccination and no history of comorbidity in the Delta period. **(C)** Chest radiograph at admission shows patchy ground-glass opacities in the

middle to lower zones of both lungs. The chest radiograph extent of pneumonia was scored as 2 (>25% involvement). Axial chest CT image obtained on the same day shows multifocal ground-glass opacities with a crazy-paving appearance in bilateral lungs. The extent of pneumonia by CT was scored as 2 (>25% involvement) and this case was classified as “typical” for COVID-19 pneumonia as per the RSNA chest CT classification system.

Table E1. Definitions of Vaccination Statuses

Classification	Definition
Unvaccinated	No record of vaccination against COVID-19 or as being diagnosed with COVID-19 <14 days after receipt of the first vaccine dose
Partially vaccinated	≥ 14 days after receipt of a first vaccine dose and before receipt of the second dose with the ChAdOx1 nCoV-19 vaccine (AstraZeneca), the BNT162b2 vaccine (Pfizer–BioNTech), or the mRNA-1273 vaccine (Moderna)
Fully vaccinated	≥ 14 days after receipt of a second vaccine dose or ≥14 days after receipt of the first dose of Ad26.COV2.S vaccine (Johnson & Johnson–Janssen)
Booster dose administered	≥ 14 days after receipt of a third dose of BNT162b2 vaccine (Pfizer–BioNTech), mRNA-1273 vaccine (Moderna), or NVX-CoV2373 (Novavax) or ≥ 14 days after receipt of a second vaccine dose after receipt of a first dose of the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen)

Table E2. Clinical Characteristics and Outcomes of Patients in the Three Study Centers

Clinical characteristics	Center 1 (N=1144)	Center 2 (N=617)	Center 3 (N=419)	Entire cohort (N=2180)
Age (years)	55 ± 21	61 ± 22	56 ± 19	57 ± 21
Sex				
Female	612 (54)	330 (54)	229 (55)	1171 (54)
Male	532 (46)	287 (46)	190 (45)	1009 (46)
Smoking history				
Smoker	104 (9.1)	86 (14)	112 (27)	302 (14)
Never smoker	1040 (91)	531 (86)	307 (73)	1878 (86)
Vaccination status				
Unvaccinated	359 (31)	257 (42)	248 (59)	864 (40)
Any vaccinated	785 (69)	360 (58)	171 (41)	1316 (60)
Partially vaccinated	69 (6.0)	53 (8.6)	50 (12)	172 (7.9)
Fully vaccinated	258 (23)	147 (24)	107 (26)	512 (24)
Booster dose administered	458 (40)	160 (26)	14 (3.3)	632 (29)
Comorbidities [a]				
Any comorbidities	582 (51)	381 (62)	233 (56)	1196 (55)
No comorbidities	562 (49)	236 (38)	186 (44)	984 (45)
Symptoms				
Asymptomatic	128 (11)	74 (12)	46 (11)	248 (11)
Symptomatic	1016 (89)	543 (88)	373 (89)	1932 (89)
Initial laboratory findings				
WBC count >10,000/µl	42 (3.7)	69 (11)	26 (6.2)	137 (6.3)
Lymphocyte count <1000/µl	118 (10)	233 (38)	179 (43)	530 (24)
Platelet count <150,000/µl	172 (15)	152 (25)	79 (19)	403 (19)
LDH >250 U/L	181 (16)	382 (62)	147 (35)	710 (33)
CRP >50 mg/L	87 (7.6)	187 (30)	104 (25)	378 (17)
Clinical outcomes				
Length of hospital stay	8.2 ± 2.7	11 ± 22	15 ± 13	11 ± 14
Requiring O_2 supply	105 (9.2)	244 (40)	153 (39)	512 (24)
ICU admission	12 (1.0)	59 (9.6)	42 (10)	113 (5.2)
Mechanical ventilation	1 (0.1)	55 (8.9)	28 (6.7)	84 (3.9)
In-hospital death	8 (0.7)	40 (6.5)	20 (4.8)	68 (3.1)

Note.- WBC = White blood cell, LDH = Lactate dehydrogenase, CRP = C-reactive protein. ICU = Intensive care unit. Values in parentheses are percentages. Values are presented as means ± standard deviations, where applicable. * Indicates statistical significance ($P < .05$). [a] Comorbidities included HTN, DM, CVD, obesity, cancer, CKD, and immunocompromised state.

Table E3. Detailed Vaccination Statuses of Patients with COVID-19 Patients by Predominant Variant

Variables	Entire (N=2180)	Delta group (N=1022)	Omicron group (N=1158)	*P* value
Vaccination status				
Unvaccinated	864 (40)	625 (61)	239 (21)	<.001*
Any vaccinated	1316 (60)	397 (39)	919 (79)	<.001*
Partially vaccinated	172 (7.9)	140 (14)	32 (2.8)	
Fully vaccinated	512 (23)	257 (25)	255 (22)	
Booster dose administered	632 (29)	0 (0)	632 (55)	
Last vaccination type				
BNT162b2	836 (64)	167 (42)	669 (73)	<.001*
ChAdOx1 nCoV-19	237 (18)	176 (44)	61 (6.6)	
mRNA-1273	222 (17)	37 (9.3)	185 (20.1)	
Ad26.COV2.S	19 (1.4)	17 (4.3)	2 (0.2)	
NVX-CoV2373	2 (0.2)	0 (0.0)	2 (0.2)	
Time between last vaccination and diagnosis				
Mean days	79 ± 51	61 ± 45	86 ± 52	<.001*
Based on 6-month interval				
< 6 months	1258 (96)	385 (97)	873 (95)	.10
≥ 6 months	58 (4.4)	12 (3.0)	46 (5.0)	
Based on 6-month interval and vaccination status				<.001*
< 6 months after partially vaccinated	158 (12)	140 (35)	18 (2.0)	
≥ 6 months after partially vaccinated	14 (1.1)	0 (0.0)	14 (1.5)	
< 6 months after fully vaccinated	468 (36)	245 (62)	223 (24)	
≥ 6 months after fully vaccinated	44 (3.3)	12 (3.0)	32 (3.5)	
< 6 months after booster dose administered	632 (48)	0 (0.0)	632 (69)	
≥ 6 months after booster dose administered	0 (0.0)	0 (0.0)	0 (0.0)	

Note.- Values are presented as mean ± standard deviation, where applicable. * Indicates statistical significance (*P* < .05).