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Clinical and Imaging Characteristics of SARS-CoV-2 Breakthrough Infection in Hospitalized Immunocompromised Patients

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Objective: To evaluate the clinical and imaging characteristics of SARS-CoV-2 breakthrough infection in hospitalized immunocompromised patients in comparison with immunocompetent patients.

Materials and Methods: This retrospective study analyzed consecutive adult patients hospitalized for COVID-19 who received at least one dose of the SARS-CoV-2 vaccine at two academic medical centers between June 2021 and December 2022. Immunocompromised patients (with active solid organ cancer, active hematologic cancer, active immune-mediated inflammatory disease, status post solid organ transplantation, or acquired immune deficiency syndrome) were compared with immunocompetent patients. Multivariable logistic regression analysis was performed to evaluate the effect of immune status on severe clinical outcomes (in-hospital death, mechanical ventilation, or intensive care unit admission), severe radiologic pneumonia (≥ 25% of lung involvement), and typical CT pneumonia.

Results: Of 2218 patients (mean age, 69.5 ± 16.1 years), 274 (12.4%), and 1944 (87.6%) were immunocompromised an immunocompetent, respectively. Patients with active solid organ cancer and patients status post solid organ transplantation had significantly higher risks for severe clinical outcomes (adjusted odds ratio = 1.58 [95% confidence interval {CI}, 1.01–2.47], $P = 0.042$; and 3.12 [95% CI, 1.47–6.60], $P = 0.003$, respectively). Patient status post solid organ transplantation and patients with active hematologic cancer were associated with increased risks for severe pneumonia based on chest radiographs (2.96 [95% CI, 1.54–5.67], $P = 0.001$; and 2.87 [95% CI, 1.50–5.49], $P = 0.001$, respectively) and for typical CT pneumonia (9.03 [95% CI, 2.49–32.66], $P < 0.001$; and 4.18 [95% CI, 1.70–10.25], $P = 0.002$, respectively).

Conclusion: Immunocompromised patients with COVID-19 breakthrough infection showed an increased risk of severe clinical outcome, severe pneumonia based on chest radiographs, and typical CT pneumonia. In particular, patients status post solid organ transplantation was specifically found to be associated with a higher risk of all three outcomes than hospitalized immunocompetent patients.

Keywords: COVID-19; Breakthrough infections; Immunocompromised host; Computed tomography; Treatment outcome

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INTRODUCTION

Immunocompromised patients have been shown to be at a greater risk of severe illness and death from COVID-19 than immunocompetent patients [1]. This heightened vulnerability can be rationalized by the hypothesis that SARS-CoV-2 infection progresses through three distinct pathophysiological stages: early infection involving viral invasion and replication; a pulmonary phase characterized by a host inflammatory response; and finally, a hyperinflammatory phase associated with immune response dysregulation [2,3]. After the virus infiltrates the host cells, its antigens stimulate humoral and cellular immunity in the host, triggering inflammatory reactions. Consequently, the initial immunocompromised state of these patients facilitates viral replication and exacerbates disease severity. Vaccination is the most effective method to prevent serious outcomes and death due to SARS-CoV-2 infection, even in immunocompromised patients [4-6]. However, the immune response to vaccination may be blunted in immunocompromised patients; thus, they may be at an increased risk of severe illness, regardless of their vaccination status [7].

Immunocompromised patients encompasses a heterogeneous population of patients, including individuals with various conditions, such as acquired immune deficiency syndrome (AIDS), active cancer, inflammatory or autoimmune disorders, and transplant recipients. Although each of these conditions is related to more severe COVID-19 outcomes, it is important to note that the severity of the outcome varies substantially within each of these immunocompromised conditions [8-13]. However, our understanding of the effects of an immunocompromised status on the clinical outcomes and radiological features of SARS-CoV-2 infection after vaccination is limited. In this study, we evaluated the clinical and imaging characteristics of immunocompromised patients hospitalized for SARS-CoV-2 breakthrough infections and compared them with those of immunocompetent patients.

MATERIALS AND METHODS

This study was approved by the Institutional Review Boards of the two participating institutions (IRB Nos. CNUH-2023-095 and 2305-004-126), which waived the requirement for informed consent owing to the retrospective nature of the study.

Study Design

This multicenter, retrospective cohort study was conducted at two academic medical centers registered in the Korean Imaging Cohort of COVID-19 (KICC-19) database, a nationwide open data repository [14]. All consecutive adult (≥ 18 years) patients hospitalized or isolated for COVID-19, as confirmed by real-time reverse transcriptase polymerase chain reaction per national guidelines, who underwent diagnostic full inspiratory chest imaging by radiography or CT were included in this repository.

Vaccination records were available from June 2021 owing to the introduction of a large-scale vaccination program in May 2021 in the Republic of Korea. Patients with SARS-CoV-2 infection who received at least one dose of the SARS-CoV-2 vaccine between June 2021 and December 2022 were enrolled. Only patients hospitalized for COVID-19 were eligible for the analysis, whereas those diagnosed with COVID-19 during hospitalization for other medical conditions, or whose clinical records were missing, were excluded (Fig. 1). Of the 2218 patients enrolled, 654 were included in our previous studies [5,6] that investigated the clinical and radiological severities of different SARS-CoV-2 variants and the clinical and imaging features of COVID-19 breakthrough infections. In the current study, we examined and compared the clinical and imaging characteristics of both immunocompromised and immunocompetent patients with SARS-CoV-2 breakthrough infection.

To adjust for the outcomes of breakthrough infections caused by variants, we attributed cases registered from June to December 2021 to the Delta variant, and those registered from January to December 2022 to the Omicron variant based on known periods of viral strain predominance [15]. These periods were defined based on a detection rate of > 50% among nationally circulating SARS-CoV-2 variants in infected individuals [16].

Immune Status Definition

Immunocompromised status was defined as active cancer in a solid organ, active hematological cancer, active immune-mediated inflammatory disorder (IMID), AIDS, or status post organ transplantation [4].

Active solid organ cancer was defined as remaining localized or metastatic cancer in patients with or without oncological treatment at the time of viral infection [17]. Patients with a previous history of treated cancer or those in remission with adjuvant cytotoxic chemotherapy or hormonal treatment were not considered to have active

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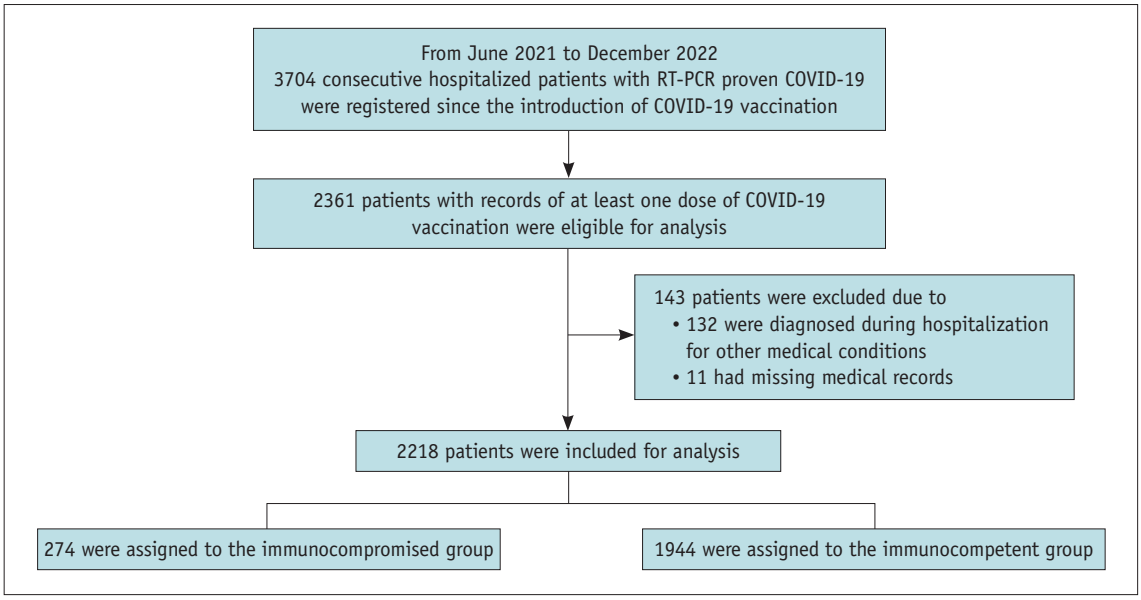

Fig. 1. Flow diagram of the study. RT-PCR = real time polymerase chain reaction

cancer [18,19]. Active hematological cancer was defined as ongoing treatment or post-allogeneic stem cell transplant immunosuppression [20], and active IMID included rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, or inflammatory bowel disease in patients receiving immunosuppressive or immunomodulatory drugs [21].

Clinical Data Collection and Assessment

Clinical factors, such as demographic characteristics, smoking history, vaccination status, history of prior SARS-CoV-2 infection, body mass index at admission, comorbidities, and clinical outcomes, were evaluated using the electronic medical records. Vaccination states were defined as the receipt of one or two vaccine doses ≥ 14 days before diagnosis [22], or more than 3 doses ≥ 7 days before diagnosis [23]. A history of prior SARS-CoV-2 infection was defined as a positive test result for the virus 45 days after recovery from a previous infection caused by the same or different viral strains. Severe clinical outcomes were defined as in-hospital death, the requirement for mechanical ventilation, and intensive care unit (ICU) admission. In-hospital death was defined as death that occurred during hospitalization due to a COVID-19 breakthrough infection.

Radiologic Data Collection and Assessment

The chest radiographs and CT images obtained from the KICC cloud-based data storage platform were reviewed. All 2218 patients underwent chest radiography at admission or during hospitalization; however, only 711 patients (center 1 [n = 460] and center 2 [n = 251]) underwent initial chest CT at admission or during hospitalization < 1 week after symptom onset.

All images were independently reviewed by two thoracic radiologists (J.E.L. and Y.J.J., with 9 and 20 years of experience, respectively) who were blinded to all clinical information. Any disagreements were resolved by consensus. Image interpretation was conducted after consensus session training using KICC cloud-based data not included in the current study to reduce inter-reader discrepancies [6]. Pneumonia extent on initial and follow-up chest radiographs and pneumonia extents and patterns on CT images were analyzed using a modified 3-point visual scoring system based on the percentage of any opacity on chest radiographs and CT images (negative = no evidence of pneumonia, non-severe pneumonia < 25% involvement, and severe pneumonia ≥ 25% involvement) [5,6,24]. Radiological outcomes were classified using a 3-point scale by assessing the most severe extent of pneumonia observed on both chest radiographs and CT images during hospitalization. Pneumonia patterns on CT images were categorized as typical, indeterminate, atypical, or negative, according to the Radiological Society of North America (RSNA) Expert Consensus Statement [25]. Typical patterns included peripheral ground-glass opacities (GGOs) or multifocal rounded GGOs, which may or may not be combined with consolidation, lines within the lobules, or reverse halo. An indeterminate pattern was defined as the presence of GGOs with or without consolidation, but lacking

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typical pattern features. An atypical pattern was defined as the presence of lobar and/or segmental consolidation without GGOs, discrete centrilobular nodules, lung cavitation, or smooth interlobular septal thickening with pleural effusion, but lacking typical or indeterminate pattern features. Emphysema and interstitial lung disease were also evaluated during CT assessment.

Statistical Analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Categorical variables were reported as numbers and percentages, while continuous variables were expressed as means and standard deviations. Pearson's χ^2 test or Fisher's exact test were applied to assess the significance of differences between study groups for categorical variables, such as sex, smoking history, comorbidities, dominant variant, vaccination status, time after last vaccination, history of prior SARS-CoV-2 infection, clinical outcomes, three-point chest radiography and CT scores, and CT pneumonia patterns. An independent *t*-test was applied for continuous variables (age and time since the last vaccination). Multivariable logistic regression analysis was conducted to evaluate the association between immune status and severe clinical outcomes (in-hospital death, mechanical ventilation, or ICU admission), severe radiologic pneumonia (≥ 25% lung involvement), and typical CT pneumonia. Two models were employed: one with immune status as a binary variable (immunocompetent vs. immunocompromised), and the other with individual categories for immunocompromised states compared to immunocompetent patients as the reference. Covariates, including age, sex, smoking history, hypertension, diabetes, cardiovascular disease, chronic kidney disease, obesity, dominant variants, vaccination status, time after the last vaccination, and history of prior SARS-CoV-2 infection, were included to account for confounding factors. Differences were considered statistically significant at *P*-values less than 0.05.

RESULTS

Baseline Clinical Characteristics and Outcomes

Of the 2361 patients, 132 diagnosed with COVID-19 but hospitalized for other medical conditions, and 11 with missing medical records were excluded (Fig. 1). Of the 2218 patients included, 274 (12.4%) were categorized into the immunocompromised group and 1944 (87.6%) into the immunocompetent group. The baseline clinical characteristics of the 2218 study patients are summarized in Table 1.

The mean age of the entire patient cohort was 69.5 ± 16.1 years and among them, 50.7% (1124/2218) were male. The immunocompromised group had a lower mean age of 66.7 ± 13.2 years compared to 69.9 ± 16.4 years in the immunocompetent group ($P = 0.002$). The immunocompromised group had a higher percentage of males (65.7% vs. 48.6%, $P < 0.001$), smokers (27.4% vs. 18.8%, $P < 0.001$), and chronic kidney disease patient (18.6% vs. 11.6%, $P = 0.001$), but a lower incidence of cardiovascular disease (15.0% vs. 24.5%, $P < 0.001$) than the immunocompetent group. The immunocompromised group had a higher prevalence of the Omicron variant (78.5% vs. 63.8%), and a lower prevalence of the Delta variant (21.5% vs. 36.2%) than the immunocompetent group ($P < 0.001$). The immunocompromised group had a higher percentage of patients who received more than three doses of vaccination (61.0% vs. 52.2%, $P = 0.016$) and patients who had been vaccinated more than 6 months prior (41.2% vs. 19.8%, $P < 0.001$) than the immunocompetent group.

The immunocompromised group was further subdivided into five subtypes: active solid organ cancer (53.3%, 146/274), status post solid organ transplantation (17.9%, 49/274), active hematologic cancer (15.3%, 42/274), active IMID (11.7%, 32/274), and AIDS (1.8%, 5/274). The detailed patient composition by immunocompromised subtype is summarized in Supplementary Table 1.

Clinical Outcomes of COVID-19 Breakthrough Infection According to Immune Status

The immunocompromised group had higher rates of in-hospital death (14.2% vs. 7.7%, $P < 0.001$), mechanical ventilation requirements (12.4% vs. 6.5%, $P < 0.001$), ICU admission requirements (13.9% vs. 8.6%, $P = 0.005$), and severe clinical outcomes (21.9% vs. 13.2%, $P < 0.001$) (Table 2). Notably, the crude proportion of patients with severe clinical outcomes was significantly higher in those with active solid organ cancer (21.2%, 31/146), status post solid organ transplantation (24.5%, 12/49), and active hematological cancer (23.8%, 10/42) than in immunocompetent patients (13.2%, 257/1944) (Fig. 2A).

The adjusted odds ratios (ORs) for severe clinical outcomes are summarized in Table 3 and Supplementary Table 2. The adjusted ORs for a severe clinical outcome was significantly higher in the immunocompromised group (OR, 1.88 [95%

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Table 1. Baseline characteristics of patients with SARS-CoV-2 vaccination

Variables	Immunocompromised (n = 274)	Immunocompetent (n = 1944)	*P*
Age, yr	66.7 ± 13.2	69.9 ± 16.4	0.002
Sex			< 0.001
Male	180 (65.7)	944 (48.6)	
Female	94 (34.3)	1000 (51.4)	
Smoking history			< 0.001
Smoker	75 (27.4)	365 (18.8)	
Never-smoker	199 (72.6)	1579 (81.2)	
Comorbidities			
Hypertension	133 (48.5)	1032 (53.1)	0.158
Diabetes	86 (31.4)	628 (32.3)	0.761
Cardiovascular disease	41 (15.0)	476 (24.5)	< 0.001
Chronic kidney disease	51 (18.6)	225 (11.6)	0.001
Obesity	11 (4.0)	81 (4.1)	0.937
Emphysema or ILD*	5 (3.6)	35 (6.1)	0.247
Variant			< 0.001
Delta	59 (21.5)	704 (36.2)	
Omicron	215 (78.5)	1240 (63.8)	
Vaccination status			0.016
1 dose	22 (8.0)	234 (12.0)	
2 doses	85 (31.0)	695 (35.8)	
More than 3 doses	167 (61.0)	1015 (52.2)	
Time after last vaccination			< 0.001
Vaccinated more than 6 months ago	113 (41.2)	384 (19.8)	
Vaccinated within the last 6 months	161 (58.8)	1560 (80.2)	
History of prior SARS-CoV-2 infection			< 0.001
Yes	9 (3.3)	14 (0.7)	
No	265 (96.7)	1930 (99.3)	
Immunocompromised types			N/A
Active solid organ cancer	146 (53.3)	N/A	
Status post solid organ transplantation	49 (17.9)	N/A	
Active hematologic cancer	42 (15.3)	N/A	
Active IMID	32 (11.7)	N/A	
AIDS	5 (1.8)	N/A	

Data are presented as means ± standard deviations or number of patients (%).
*Emphysema and ILD were assessed in 139 and 572 immunocompromised and immunocompetent patients, respectively, who underwent CT evaluations.
ILD = interstitial lung disease, N/A = not applicable, IMID = immune-mediated inflammatory disorder, AIDS = acquired immune deficiency syndrome

confidence interval {CI}, 1.33–2.65], $P < 0.001$) than in the immunocompetent group. Regarding the different types of immunocompromised patients, the adjusted ORs for severe clinical outcomes were significantly higher in the active solid organ cancer subgroup (OR, 1.58 [95% CI, 1.01–2.47], $P = 0.042$) and the status post solid organ transplantation subgroup (OR, 3.12 [95% CI, 1.47–6.60], $P = 0.003$) (Fig. 3).

Radiologic Outcomes of COVID-19 Breakthrough Infection According to Immune Status

According to the pneumonia severities determined based on chest radiographs, which were performed in all patients, the crude proportions of patients with severe pneumonia were significantly higher in patients who had undergone solid organ transplantation (44.9%, 22/49) and patients with active hematologic cancer (52.4%, 22/42) than in immunocompetent patients (25.2%, 490/1944) (Fig. 2B). The adjusted ORs for severe pneumonia based on chest

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Table 2. Unadjusted crude comparison of outcomes of COVID-19 breakthrough infections according to immune status

Outcomes	Immunocompromised (n = 274)	Immunocompetent (n = 1944)	*P*
Clinical outcomes			
In-hospital death	39 (14.2)	149 (7.7)	< 0.001
Mechanical ventilation	34 (12.4)	126 (6.5)	< 0.001
ICU admission	38 (13.9)	168 (8.6)	0.005
Severe clinical outcomes*	60 (21.9)	257 (13.2)	< 0.001
Pneumonia based on chest radiograph†			< 0.001
Negative	131 (47.8)	1140 (58.6)	
Non-severe pneumonia (< 25%)	45 (16.4)	314 (16.2)	
Severe pneumonia (≥ 25%)	98 (35.8)	490 (25.2)	
Pneumonia based on chest CT‡			0.004
Negative	45 (32.4)	124 (21.7)	
Non-severe pneumonia (< 25%)	37 (26.6)	229 (40.0)	
Severe pneumonia (≥ 25%)	57 (41.0)	219 (38.3)	
RSNA CT pattern§			< 0.001
Typical	51 (54.3)	137 (30.6)	
Indeterminate	15 (16.0)	80 (17.9)	
Atypical	28 (29.7)	231 (51.5)	

Data are presented number of patients (%).
*Severe clinical outcomes are defined as any one of the following: in-hospital death, the need for mechanical ventilation, or ICU admission, †Chest radiograph was available for all 2218 patients, ‡CT images were available for 139 patients (50.7%) in the immunocompromised group and 572 patients (29.4%) in the immunocompetent group, §RSNA CT pattern analysis was available for 94 patients (34.3%) in the immunocompromised group and 448 patients (23.0%) in the immunocompetent group who had pneumonia findings on chest CT.
ICU = intensive care unit, RSNA = Radiological Society of North America

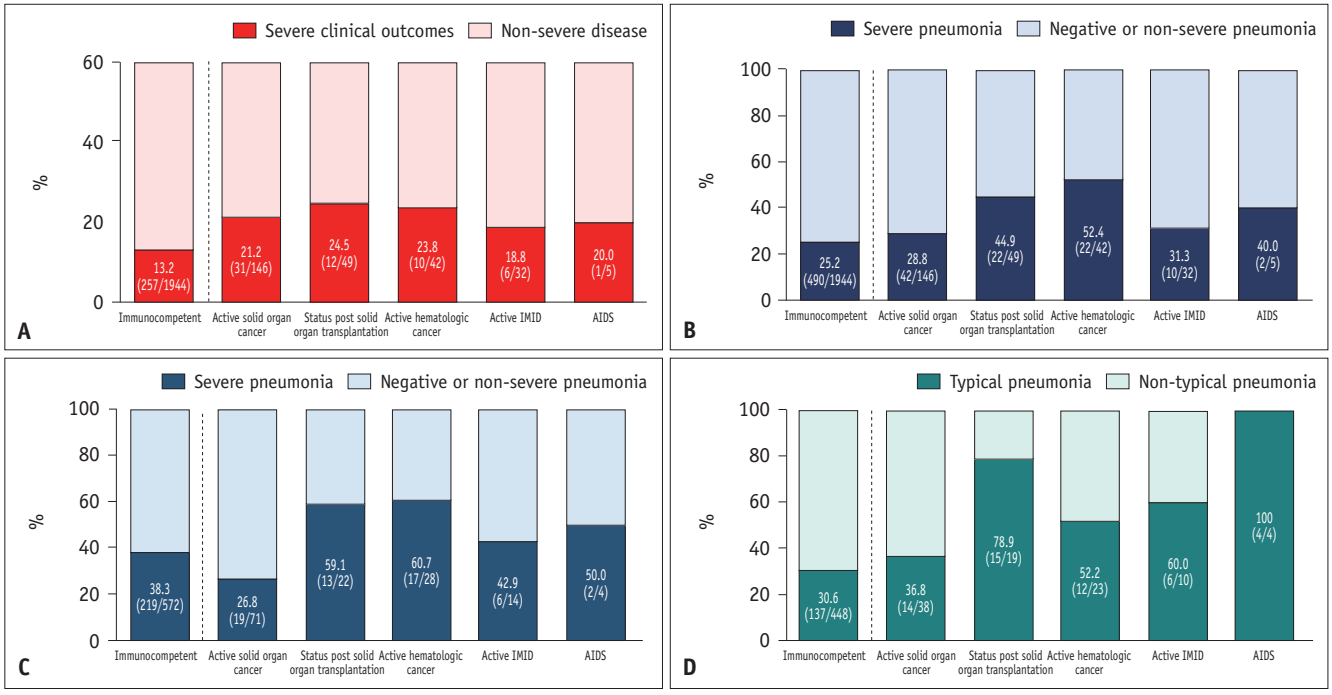

Fig. 2. Clinical and pneumonia severities and CT pneumonia patterns in patients with different immune statuses. **A:** Clinical outcomes according to immune status. **B:** Pneumonia severity according to immune status, as assessed on chest radiographs. **C:** Pneumonia severity according to immune status, as assessed on chest CT images. **D:** Radiologic pneumonia patterns as determined by chest CT images according to immune status. IMID = immune-mediated inflammatory disorder, AIDS = acquired immune deficiency syndrome

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Table 3. Multivariable-adjusted association between immune status and severe clinical outcomes for COVID-19 breakthrough infection

Variable	Model 1		Model 2	
	Adjusted OR	*P*	Adjusted OR	*P*
Severe clinical outcomes* (n = 317 vs. 1901)				
Immunocompetent	Reference		N/A	
Entire immunocompromised	1.88 (1.33–2.65)	< 0.001	N/A	N/A
Immunocompetent	N/A		Reference	
Active solid organ cancer	N/A	N/A	1.58 (1.01–2.47)	0.042
Status post solid organ transplantation	N/A	N/A	3.12 (1.47–6.60)	0.003
Active hematologic cancer	N/A	N/A	1.85 (0.87–3.92)	0.109
Active IMID	N/A	N/A	2.17 (0.84–5.61)	0.107
AIDS	N/A	N/A	2.06 (0.21–19.47)	0.525

The data in parentheses are 95% confidence intervals. Analysis was performed using a logistic regression model. Model 1 included the entire immunocompromised group, with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, chronic kidney disease, obesity, variants, vaccination status, time from last vaccination, and history of prior SARS-CoV-2 infection as covariates. Model 2 included each immunocompromised type with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, chronic kidney disease, obesity, variants, vaccination status, time from the last vaccination, and history of prior SARS-CoV-2 infection as covariates.
*Severe clinical outcomes are defined as any one of the following: in-hospital death, the need for mechanical ventilation, or intensive care unit admission.
OR = odds ratio, N/A = not applicable, IMID = immune-mediated inflammatory disorder, AIDS = acquired immune deficiency syndrome

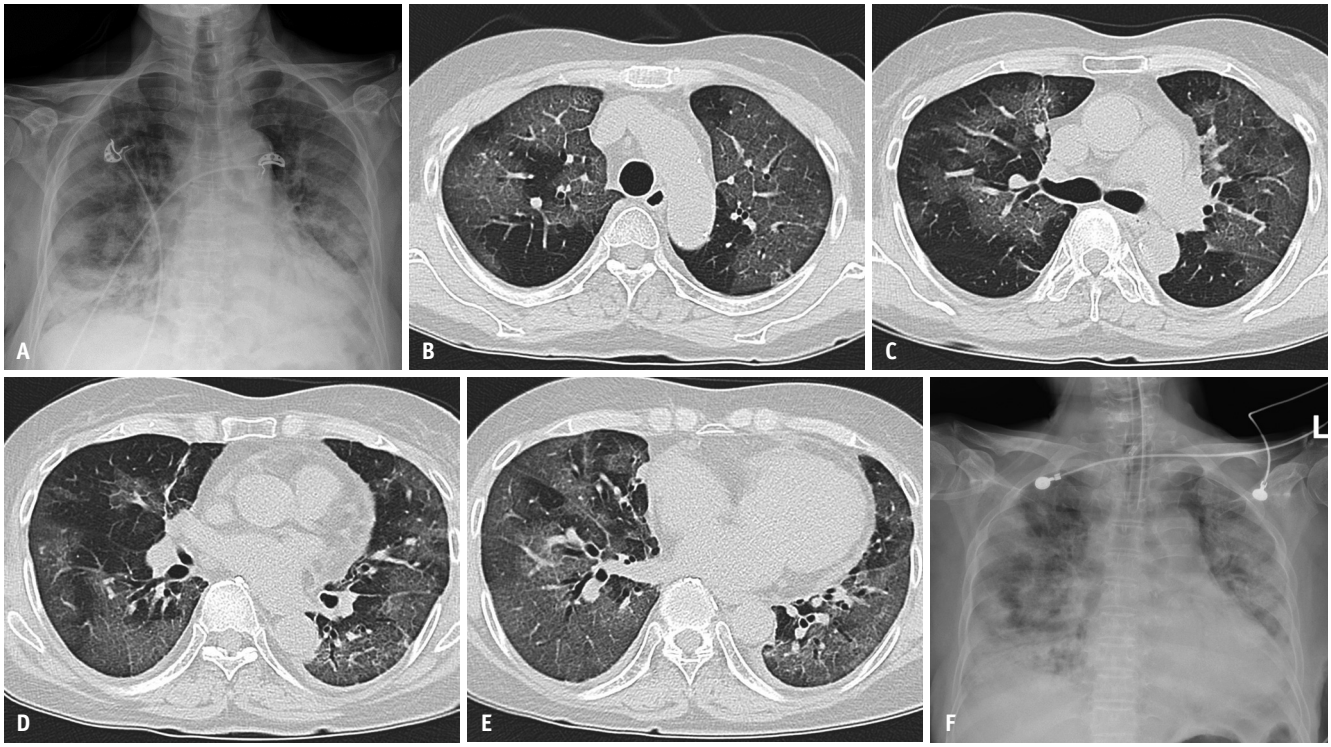

Fig. 3. COVID-19 pneumonia during the Omicron variant-dominant period in a 69-year-old female patient with a history of kidney transplantation. **A:** Initial chest radiograph showing a multifocal area of GGO in the bilateral lungs. The case was classified as 'severe pneumonia' (≥ 25% lung involvement) based on the modified 3-point visual scoring system. **B-E:** Lung window images of a transverse non-enhanced chest CT scan obtained at admission showing diffuse and extensive areas of GGO with intralobular interstitial thickening (crazy-paving pattern) involving bilateral lungs. CT findings were classified as "typical" according to the Radiological Society of North America chest CT classification system. **F:** Follow-up chest radiograph taken 1 day later demonstrating extensive GGO and consolidation in bilateral lungs. The patient was placed on mechanical ventilation the same day due to worsening of dyspnea, but progressed to acute respiratory distress syndrome, and finally succumbed to the disease. GGO = ground-glass opacity

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radiographs are summarized in Table 4 and Supplementary Table 3. The adjusted OR for severe pneumonia based on chest radiography was significantly higher in the immunocompromised group (OR, 1.56 [95% CI, 1.16–2.09], $P = 0.003$]) than in the immunocompetent group. For different types of immunocompromised status, the adjusted OR for severe pneumonia was significantly higher in the status post solid organ transplantation subgroup (OR, 2.96 [95% CI, 1.54–5.67], $P = 0.001$) and the active hematologic cancer subgroup (OR, 2.87 [95% CI, 1.50–5.49], $P = 0.001$) than in the immunocompetent group (Table 4, Figs. 3, 4).

According to pneumonia severity determined based on chest CT scans, which were available for 711 patients (32.1%) who underwent chest CT, the crude proportion of patients with severe pneumonia was significantly higher in patients with active hematologic cancer (60.7%, 17/28) than in immunocompetent patients (38.3%, 219/572) (Fig. 2C). The adjusted ORs for severe pneumonia based on chest CT findings are summarized in Table 4 and Supplementary Table 4. The adjusted OR for severe pneumonia based on chest CT was also significantly higher in the active hematologic cancer subgroup (OR, 2.56 [95% CI, 1.08–6.09], $P = 0.032$) than in the immunocompetent group (Table 4).

Of the 711 patients who underwent chest CT, 542 (76.2%) developed pneumonia. These patients were available for assessment of the RSNA CT pneumonia pattern. The

Table 4. Multivariable-adjusted association between immune status and severe pneumonia for COVID-19 breakthrough infection

Variable	Model 1		Model 2	
	Adjusted OR	*P*	Adjusted OR	*P*
Severe pneumonia based on chest radiograph (≥ 25% lung involvement) (n = 588 vs. 1630)				
Immunocompetent	Reference		N/A	
Entire immunocompromised	1.56 (1.16–2.09)	0.003	N/A	N/A
Immunocompetent	N/A		Reference	
Active solid organ cancer	N/A	N/A	0.97 (0.65–1.46)	0.920
Status post solid organ transplantation	N/A	N/A	2.96 (1.54–5.67)	0.001
Active hematologic cancer	N/A	N/A	2.87 (1.50–5.49)	0.001
Active IMID	N/A	N/A	2.03 (0.90–4.55)	0.084
AIDS	N/A	N/A	2.11 (0.33–13.32)	0.426
Severe pneumonia based on chest CT (≥ 25% lung involvement) (n = 276 vs. 435)*				
Immunocompetent	Reference		N/A	
Entire immunocompromised	1.00 (0.67–1.51)	0.979	N/A	N/A
Immunocompetent	N/A		Reference	
Active solid organ cancer	N/A	N/A	0.67 (0.33–1.33)	0.252
Status post solid organ transplantation	N/A	N/A	1.90 (0.74–4.88)	0.179
Active hematologic cancer	N/A	N/A	2.56 (1.08–6.09)	0.032
Active IMID	N/A	N/A	1.18 (0.39–3.54)	0.767
AIDS	N/A	N/A	1.38 (0.18–10.30)	0.753
Typical pneumonia based on chest CT (n = 188 vs. 354)*				
Immunocompetent	Reference		N/A	
Entire immunocompromised	3.59 (1.10–6.14)	< 0.001	N/A	N/A
Immunocompetent	N/A		Reference	
Active solid organ cancer	N/A	N/A	1.54 (0.68–3.46)	0.294
Status post solid organ transplantation	N/A	N/A	9.03 (2.49–32.66)	< 0.001
Active hematologic cancer	N/A	N/A	4.18 (1.70–10.25)	0.002
Active IMID	N/A	N/A	6.09 (1.49–24.87)	0.012
AIDS	N/A	N/A	N/A	N/A

The data in parentheses are 95% confidence intervals. Analysis was performed using a logistic regression model. Model 1 included the entire immunocompromised group, with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, chronic kidney disease, obesity, variants, vaccination status, time from last vaccination, and history of prior SARS-CoV-2 infection as covariates. Model 2 included each immunocompromised type with age, sex, smoking history, hypertension, diabetes, cardiovascular disease, chronic kidney disease, obesity, variants, vaccination status, time from the last vaccination, and history of prior SARS-CoV-2 infection as covariates.
*Models for severe and typical pneumonia based on CT included emphysema or interstitial lung disease as additional covariates.
OR = odds ratio, N/A = not applicable, IMID = immune-mediated inflammatory disorder, AIDS = acquired immune deficiency syndrome

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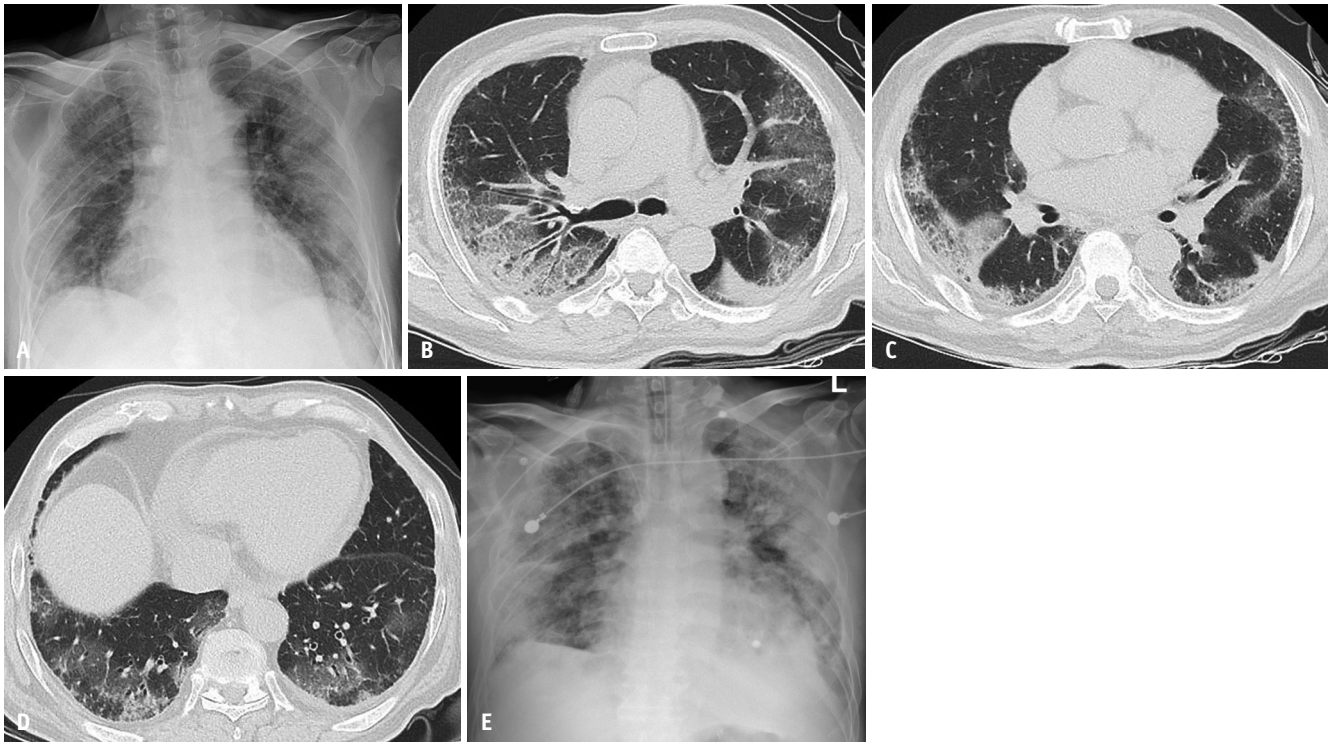

Fig. 4. A case of COVID-19 pneumonia during the Delta variant-dominant period in a 67-year-old male patient with malignant lymphoma. **A:** Initial chest radiograph showing a multifocal area of GGO at the peripheries of the bilateral lungs. The case was classified as 'severe pneumonia' (≥ 25% lung involvement) based on the modified 3-point visual scoring system. **B-D:** Lung window images of a transverse non-enhanced chest CT scan obtained at admission showing multifocal areas of GGO and consolidation with intralobular interstitial thickening (crazy-paving pattern) involving the bilateral lungs with subpleural predominance. CT findings were classified as "typical" according to the Radiological Society of North America chest CT classification system. **E:** Follow-up chest radiographs obtained on hospital day 10 demonstrating GGO progression in the bilateral lungs. The patient underwent mechanical ventilation 2 days later, but died of acute respiratory distress syndrome. GGO = ground-glass opacity

crude proportion of patients with typical CT pneumonia was significantly higher among those who had undergone solid organ transplantation (78.9%, 15/19), those with active hematologic cancer (52.2%, 12/23), and those with AIDS (100%, 4/4) than among immunocompetent patients (30.6%, 137/448) (Fig. 2D). The adjusted OR for typical CT pneumonia was significantly higher in the immunocompromised group (OR, 3.59 [95% CI, 1.10–6.14], $P < 0.001$) than in the immunocompetent group. Adjusted ORs for typical CT pneumonia are summarized in Table 4 and Supplementary Table 5. Analysis of the adjusted ORs for typical CT pneumonia for different types of immunocompromised status were significantly higher in the status post solid organ transplantation subgroup (OR, 9.03 [95% CI, 2.49–32.66], $P < 0.001$), the active hematologic cancer subgroup (OR, 4.18 [95% CI, 1.70–10.25], $P = 0.002$), and the active IMID subgroup (OR 6.09 [95% CI, 1.49–24.87], $P = 0.012$) than in the immunocompetent group (Table 4).

DISCUSSION

This study was conducted to improve the current understanding of the clinical and imaging characteristics of COVID-19 and its risk factors among immunocompromised patients in the vaccination era by comparing SARS-CoV-2 breakthrough infections in hospitalized immunocompromised and immunocompetent patients. We observed that the immunocompromised group showed increased risks for severe clinical outcomes (OR, 1.88 [95% CI, 1.33–2.65]), severe pneumonia based on chest radiographs (OR, 1.56 [95% CI, 1.16–2.09]), and typical CT pneumonia (OR, 3.59 [95% CI, 1.10–6.14]).

In a previous retrospective study conducted on a large national COVID-19 cohort of individuals who had received at least one dose of the SARS-CoV-2 vaccine, immunocompromised patients were observed to have a higher risk of COVID-19 breakthrough infection and severe outcomes [22], presumably because of their

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compromised immune systems, which is supported by significant reductions in seroconversion rates following COVID-19 vaccination in immunocompromised individuals [4]. Furthermore, immunocompromised patients have been reported to have a higher risk of breakthrough infection, even with the Omicron variant [26]. In line with these findings, the present study showed that COVID-19 breakthrough infection in immunocompromised patients was associated with a significantly greater risk of severe clinical outcomes and pneumonia, even after adjusting for several covariates, including age, sex, smoking history, comorbidities, viral mutations, vaccination status, and time after the last vaccination. The novelty of our study lies in the comprehensive evaluation of not only the clinical severity according to immune status, but also the radiological severity and pattern of COVID-19 pneumonia in hospitalized patients with breakthrough infection, encompassing both the Omicron and Delta variants.

Our study revealed that the status post solid organ transplantation had the highest increased risk of severe clinical outcomes, severe pneumonia, and typical COVID-19 pneumonia compared with immunocompetent patients. Following this group, patients with active hematologic cancer demonstrated an increased risk of severe pneumonia and typical COVID-19 pneumonia, but not severe clinical outcomes. According to previous meta-analyses, seroconversion rates after COVID-19 vaccination vary based on immunocompromised status, with patients status post solid organ transplantation exhibiting the lowest rates, followed by those with active hematological cancer, active solid cancer, and IMID [4,27]. A previous meta-analysis reported that status post solid organ transplantation and immunosuppressants, such as mycophenolic acid, belatacept, and tacrolimus, which are used to prevent transplant organ rejection, can contribute to poor vaccine response by reducing both cellular and humoral immunity [28]. Another meta-analysis indicated that patients with active hematological cancer exhibited impaired humoral and cellular immune responses after SARS-CoV-2 vaccination [29]. Notably, compared with patients with solid cancers, those with hematologic cancers demonstrated more pronounced B cell impairment and reduced SARS-CoV-2-specific antibody responses [30]. This compromised immune response may explain the increased risk of severe COVID-19 observed in immunocompromised populations, particularly among solid organ transplant recipients and patients with hematological cancers. Furthermore, our findings suggest a higher incidence of severe and typical CT pneumonia in recipients of solid organ transplantation and patients with active hematological cancer. These results indicate that lung injuries induced by SARS-CoV-2 could be more severe in immunocompromised patients owing to decreased vaccine efficacy. Severe lung injuries typically manifest as organizing pneumonia or diffuse alveolar damage patterns, which are radiologically classified as typical patterns of COVID-19 pneumonia. This severe lung damage correlates well with severe clinical outcomes in solid organ recipients, but not in patients with active hematological malignancies, potentially related to differential impacts on the immune response or variability in disease progression and treatment.

This study has several limitations. First, the number of patients with various immunocompromised conditions, particularly those related to the type and duration of immunosuppressive medications and specific immunosuppressive factors, was insufficient to allow for robust comparisons of breakthrough infection severity across various immunocompromised status categories. This limitation was particularly evident in the enrollment of patients. In our study, the number of patients with AIDS was limited and, because of the retrospective nature of the study, we were unable to evaluate the various immune statuses of these patients. In addition, we did not categorize patients with diabetes and chronic renal disease as immunocompromised individuals, and we were unable to investigate the medical history of other conditions that could potentially lead to immunosuppression, such as receiving anti-CD20 agents and B-cell-depleting therapies. Instead, we performed comparative analyses after adjusting for underlying diseases that could potentially affect immune status, such as diabetes and chronic renal disease, as covariates in the multivariable analysis. Second, a selection bias was possible as the study was performed on hospitalized patients, which may have increased the proportion of immunocompromised patients in the cohort. Third, our determination the cause of in-hospital death as an indicator of clinical severity was ambiguous. Although we defined in-hospital death as death occurring during the hospitalization period for COVID-19 breakthrough infection, ambiguity remains regarding whether the cause of death in immunocompromised patients was COVID-19 or their underlying diseases. Therefore, we did not use in-hospital mortality as an indicator of clinical severity. Instead, we assessed severe clinical outcomes by combining them with other severity indicators, such as ICU admission and

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mechanical ventilation. Finally, owing to the retrospective design of our study and the ongoing emergence of new variants, accurately reflecting the data based on the current variant of concern is challenging.

In conclusion, immunocompromised patients with COVID-19 breakthrough infection showed an increased risk of severe clinical outcomes, severe pneumonia based on chest radiographs, and typical CT pneumonia. In particular, patients status post solid organ transplantation was specifically found to be associated with a higher risk of all three outcomes than hospitalized immunocompetent patients.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.0992.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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