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Early pulmonary fibrosis-like changes between delta and pre-delta periods in patients with severe COVID-19 pneumonia on mechanical ventilation

Jung-Wan Yoo[1], Won-Young Kim[2], Chi Ryang Chung[3], Young-Jae Cho[4], Jinwoo Lee[5], Yangjin Jegal[6], Junghyun Kim[7], Joon-Sung Joh[8], Tae Yun Park[9], Ae-Rin Baek[10], Joo Hun Park[11], Ganghee Chae[6], Jung Hwa Hwang[12] & Jin Woo Song[13]✉

It remains unclear whether pulmonary fibrosis-like changes differ in patients with different SARS-CoV-2 variants. This study aimed to compare pulmonary fibrotic changes between two SARS-CoV-2 variant periods (delta vs. pre-delta) in critically ill patients with SARS-CoV-2 pneumonia. Clinical data and chest CT images of patients with SARS-CoV-2 pneumonia receiving mechanical ventilation were collected from 10 hospitals in South Korea over two periods: delta (July-December, 2021; $n=64$) and pre-delta (February, 2020-June, 2021; $n=120$). Fibrotic changes on chest CT were evaluated through visual assessment. Of 184 patients, the mean age was 64.6 years, and 60.5% were ale. Fibrosis-like changes on chest CT (median 51 days from enrollment to follow up CT scan, interquartile range 27–76 days) were identified in 75.3%. Delta group showed more fibrosis-like changes (≥ 2) (69.8% vs. 43.1%, $P=0.001$) and more frequent reticulation and architectural distortion+/-parenchymal band than pre-delta group. Even after propensity score matching with clinical variables, delta group had more severe (≥ 2) fibrosis-like changes (71.4% vs. 38.8%, $P=0.001$), and more frequent reticulation and architectural distortion+/-parenchymal band than pre-delta group. Our data suggest that critically ill patients with SARS-CoV-2 in delta period had more severe pulmonary fibrosis-like changes than those in pre-delta period.

Keywords SARS-CoV-2, Mechanical ventilation, Pulmonary fibrosis-like change

[1]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea. [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chung Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea. [3]Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea. [4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea. [5]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea. [6]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea. [7]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea. [8]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, National Medical Center, Seoul, Republic of Korea. [9]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government, Seoul National University Boramae Medical Center, Seoul, Republic of Korea. [10]Division of Allergy and Pulmonology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea. [11]Department of Pulmonary and Critical Care Medicine, Ajou University School of Medicine, Suwon, Republic of Korea. [12]Department of Radiology, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea. [13]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu 05505, Seoul, Republic of Korea. ✉email: jwsongasan@gmail.com

The COVID-19 pandemic following the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has swept the globe imposing substantial health burden across the world[1–4]. Pulmonary manifestations of infection with SARS-CoV-2 are diverse, ranging from mild upper respiratory tract illness to critical conditions such as severe pneumonia and/or acute respiratory distress syndrome (ARDS)[5,6]. Those critical conditions have been known to be associated with substantially increased mortality[7–13]. Patients recovering from acute phase of COVID-19 pneumonia present a wide spectrum of clinical and radiological courses from nearly complete resolution to substantial sequelae[14,15,16]. Pulmonary fibrosis-like changes are respiratory sequelae in patients with COVID-19 pneumonia[17,18]. These changes is one of long COVID syndrome affecting multiple organs leading to poor short- and long-term outcomes of substantial impact, such as persistent respiratory symptoms[19]. Several studies reported that severity of COVID-19 pneumonia was associated with the degree and extent of pulmonary fibrosis-like changes as well as clinical status of patients[20–25].

SARS-CoV-2, known causative virus responsible for COVID-19, has mutated genetically and developed diverse variants[26,27]. Several variants have predominantly spread worldwide from their original place[28,29]. These dominant variants have caused certain waves in the pandemic, having major impact on human health around the world. All types of variant may have the potentials to induce severe pneumonia during COVID-19 infection and pulmonary fibrosis-like changes after acute phase of pneumonia[30]. Although clinical outcomes of patients infected with variants at different outbreak periods have been reported[31–34], it remains unclear whether pulmonary fibrosis-like changes differ between outbreak periods of SARS-CoV-2 variants in patients with severe COVID-19 pneumonia. This multicenter study aimed to evaluate pulmonary fibrosis-like changes in patients with severe COVID-19 pneumonia receiving mechanical ventilation (MV) and compare them between pre-delta and delta periods.

Methods

Study population

This was a post-hoc analysis of a Korean multicenter registry consisting of two independent cohorts. Ten hospitals in South Korea participated in this study. All included patients met the following criteria: (1) ≥ 18 years; (2) confirmation of SARS-CoV-2 infection using a real-time reverse transcription polymerase chain reaction assay in upper or lower respiratory tract samples; (3) diagnosis of pneumonia radiologically; (4) severe or critical conditions based on criteria described by the WHO's COVID-19 clinical classification;[35] and (5) receiving mechanical ventilation (MV) admitted to the intensive care unit. Patients with pre-existing interstitial lung disease were excluded.

We enrolled two cohorts over two separate periods: July–December 2021 (prospective cohort) and February 2020–June 2021 (retrospective cohort). In South Korea, the outbreak mainly attributed to the delta variant occurred from July 2021 to January 2022. In this study, the delta period was defined as the period from July to December 2021, while pre-delta period was defined as the period before the delta variant outbreak (from February 2020 to June 2021). Of the 190 patients with severe COVID-19 pneumonia enrolled during the study, six were excluded from clinical data analysis: one due to inadequate images for computed tomography (CT) analysis in the prospective cohort, and five due to patients in the delta period being included in the pre-delta period of the retrospective cohort. Finally, 184 patients (64 in the delta period and 120 in the pre-delta period) were included in this study (Fig. 1). Figure 2 shows the number of enrolled patients by month. The number of enrolled patients were highest in December of 2020 during the pre-delta period and August of 2021 during the delta period.

The local institutional review board (IRB) of each hospital approved the study protocol (IRB of Asan Medical Center, No. 2021 – 0769 and 2021 – 1353). The study was registered with the Korea Clinical Research Informative Service (No. KCT0006312). Written informed consent was obtained from all participants or their next of kin in the prospective cohort but was waived in the retrospective cohort. All consecutive patients prospectively or retrospectively registered in the dataset up to December 24, 2021, were analyzed.

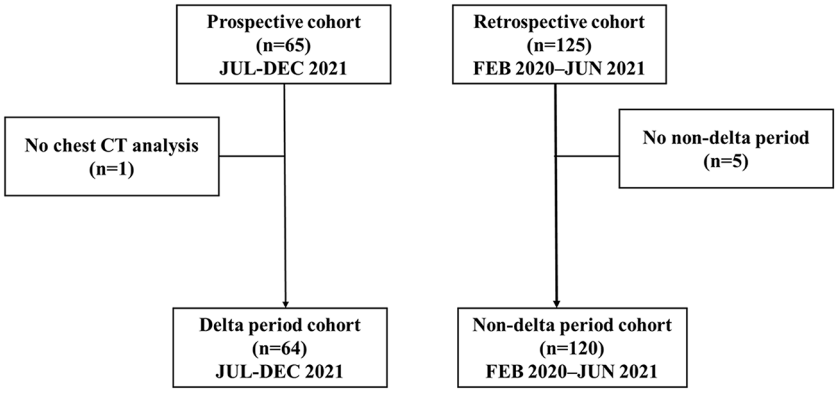

Fig. 1. The enrollment of patients in study. CT, chest tomography.

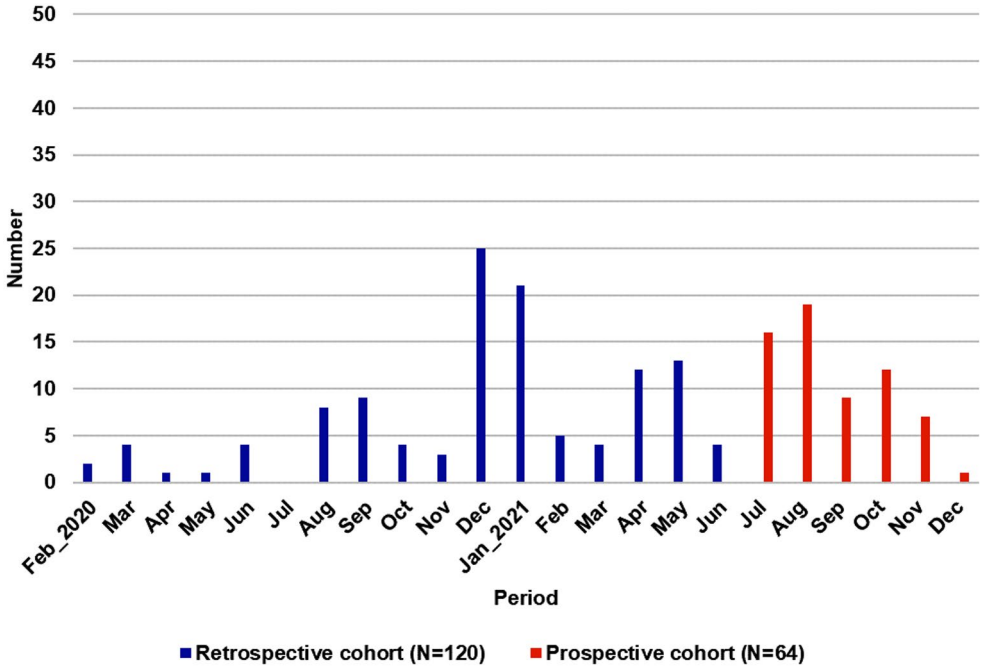

Fig. 2. Period of enrollment of patients.

Data collection

Clinical data such as age, sex, body mass index (BMI), and comorbidities were collected. Details on laboratory parameters, pharmacologic or non-pharmacologic treatments in ICU admission were also collected. These data were collected from electronic case report forms (https://icreat.nih.go.kr) filled up when patients were hospitalized or followed up in outpatient clinics after discharge, both in the prospective cohort (delta period) and in the retrospective cohort (pre-delta period).

Evaluation of pulmonary fibrosis-like changes

In the prospective cohort, survivors were followed in the outpatient clinic of each hospital where they underwent chest CT and pulmonary function test (PFT) one month post-discharge. For patients who died before discharge or were transferred to other hospitals, the last CT scan images performed during their hospitalization were retrieved. The same criteria used in the prospective cohort were also applied to the retrospective cohort. To assess early fibrotic-like changes, a minimum time interval of two weeks from COVID-19 diagnosis was considered.

In this multicenter study, imaging data collected included chest CT scans obtained with various types of CT equipment and techniques. All participants were scanned with a 16- or 64-detector CT scanner during breath-hold at full inspiration, with the patient in the supine position. Axial chest CT images were reconstructed with a slice thickness of 1.00–1.25 mm, at 5–10 mm intervals using a high spatial frequency reconstruction algorithm. Fibrosis-like changes on chest CT were evaluated through visual assessment by experienced thoracic radiologists (B.D.N and J.H.H with 7 and 30 years of experience in thoracic radiology, respectively [the prospective cohort]; S.L and J.W.L with 11 and 6 years of experience, respectively [the retrospective cohort]) by consensus, blinded to the clinical information.

To minimize inter-reader variability, a consensus meeting was held to set the standard for sample cases before conducting further analyses Fibrosis-like changes included: reticulation, architectural distortion ± parenchymal band, traction bronchiectasis and honeycombing change (Figure S1)[36,37]. Reticulation is defined by numerous small linear opacities that, when combined, produce a pattern resembling a net[36]. Architectural distortion is characterized by abnormal displacement of bronchi, vessels, fissures, or septa caused by interstitial fibrosis[36]. Parenchymal band is defined as stripes which run parallel or perpendicular to the pleura[36]. Traction bronchiectasis is defined as irregular bronchial dilatation caused by surrounding retractile pulmonary fibrosis[36]. Honeycombing features are numerous and of various sizes consisting of cystic airspaces with thick fibrous walls with complete loss of acinar architecture within them[36]. We used a categorical classification (present / not present) to assess the radiological change of each component of pulmonary fibrosis-like changes. We defined the number of fibrotic changes as the sum of the presence of each component of pulmonary fibrosis-like changes.

Statistical analysis

All values are presented as mean ± standard deviation for continuous variables or number (percentages) for categorical variables. The Student's t-test or the Mann-Whitney U test was used for continuous variables, and the chi-squared test or Fisher's exact test was used to compare categorical variables. Index date was defined as the date of admission to the ICU and follow-up period was defined as the time from admission to the ICU to discharge from hospital. Propensity score matching (PSM) was used to control for potential confounding

variables in the comparison of pulmonary fibrosis-like changes between the delta and pre-delta periods. Control variables included age, hypertension, hemoglobin concentration, platelet counts and treatment modalities including remdesivir, tocilizumab and prone positioning; they were significantly different between the two period groups at baseline characteristics. IBM SPSS software (version 21.0; IBM, Armonk, New York) was used for statistical analyses, and the "MatchIt" package of R was used for PSM analysis. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Clinical characteristics

Mean age of total patients was 64.9 years old and 62.5% were male. During time of follow-up (median: 43 days, interquartile range [IQR]: 27–79 days), overall mortality was 15.8%. Patients in the delta period were younger and had lesser comorbidities, especially hypertension, than those in the pre-delta period (Table 1). Hemoglobin concentration and platelet counts were significantly higher in patients in the delta period than those in the pre-delta period (Table 1). Patients in the delta period received significantly more remdesivir and tocilizumab, as well as prone positioning during MV, than those in the pre-delta period (Table 2).

Pulmonary fibrosis-like changes on chest CT

The overall median time from ICU admission to chest CT scan was 51 days (IQR 27–76 days). This was significantly longer in the delta period than in the pre-delta period (62 days vs. 38 days, $P=0.005$). At least one pulmonary fibrotic-like changes on chest CT were found in 75% (138/184) of all patients (Table 3). There

Variables	Total	Delta period	Pre-delta period	*P*-value
Patents number	184	64	120	
Age, years	64.9 ± 13.8	58.2 ± 13.8	68.5 ± 12.4	< 0.001
Males	115 (62.5)	41 (64.1)	74 (61.7)	0.749
BMI, kg/m^2	25.4 ± 4.7	26.3 ± 5.4	25.0 ± 4.3	0.073
Smoking history				0.658
Never smoker	120 (75.9)	43 (75.4)	77 (76.2)	
Ex- or current smoker	38 (24.1)	14 (24.6)	24 (23.8)	
Unknown	26 (14.1)	7 (10.9)	19 (15.8)	
Comorbidities	141 (76.6)	42 (65.5)	99 (82.5)	0.001
Diabetes mellitus	72 (39.1)	21 (32.8)	51 (42.5)	0.200
Hypertension	104 (56.5)	25 (39.1)	79 (65.8)	< 0.001
Cardiovascular disease	24 (13)	8 (12.5)	16 (13.3)	0.873
Cerebrovascular disease	19 (10.3)	3 (4.7)	16 (13.3)	0.066
Liver disease	8 (4.3)	4 (6.3)	4 (3.3)	0.452
Kidney disease	10 (5.4)	1 (1.6)	9 (7.5)	0.169
Malignancy	16 (8.7)	4 (6.3)	12 (10)	0.390
Lung disease	12 (6.5)	3 (4.7)	9 (7.5)	0.547
SOFA score	4.9 ± 2.8	4.7 ± 2.9	4.9 ± 2.7	0.411
APACHE score	14.2 ± 8.3	13.6 ± 9.3	14.6 ± 7.8	0.248
WBC, x10^3/uL	10.2 ± 5.9	9.9 ± 4.5	10.4 ± 6.6	0.658
Hemoglobin, g/dL	12.8 ± 1.9	13.3 ± 1.9	12.5 ± 1.9	0.012
Platelet, x10^3/uL	213.6 ± 104	238.4 ± 106.9	200.7 ± 100.5	0.011
Total bilirubin, mg/dL	0.6 ± 0.4	0.6 ± 0.3	0.6 ± 0.4	0.677
Total protein, g/dL	6 ± 0.7	6.0 ± 0.7	5.9 ± 0.7	0.393
Albumin, g/dL	3.0 ± 0.5	3.1 ± 0.6	3.0 ± 0.4	0.581
BUN, mg/dL	23.8 ± 15.3	21.8 ± 10.9	24.8 ± 17.1	0.316
Creatinine, mg/dL	1 ± 0.8	0.8 ± 0.4	1.0 ± 0.9	0.154
LDH, IU/L	594.9 ± 254	601.9 ± 242.9	591.6 ± 271.4	0.541
CRP, mg/dL	11.2 ± 8.8	11.2 ± 10.2	11.1 ± 7.9	0.436
Procalcitonin, ng/mL	0.9 ± 3.7	1.3 ± 5.5	0.7 ± 1.9	0.390
Ferritin, ng/mL	1046 ± 1172	1330 ± 1576	865 ± 779	0.107
P/F ratio	108.4 ± 53.6	102.4 ± 50.7	112.3 ± 55.4	0.242

Table 1. Baseline characteristics of the study population at ICU admission. Data are expressed as mean ± standard deviation (SD) or number (%) unless otherwise indicated. BMI, body mass index; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; WBC, white blood cell; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; P/F, arterial oxygen partial pressure to fractional inspired oxygen.

Variables	Total	Delta period	Pre-delta period	*P*-value
Patents number	184	64	120	
Use of remdesivir	136 (73.9)	57 (89.1)	79 (65.8)	0.001
Use of steroid	177 (96.2)	64 (100)	113 (94.2)	0.098
Steroid duration, days	7.1 ± 6.5	6.0 ± 3.2	7.7 ± 7.8	0.271
Use of tocilizumab	20 (10.9)	17 (26.6)	3 (2.5)	<0.001
Use of NMB	147 (82.6)	47 (78.3)	100 (84.7)	0.286
Duration of MV, days	27.8 ± 28.4	23.9 ± 27.8	29.9 ± 28.6	0.071
Prone position	79 (42.9)	34 (53.1)	45 (37.5)	0.041
CRRT	27 (14.7)	6 (9.4)	21 (17.5)	0.138
ECMO	26 (14.1)	11 (17.2)	15 (12.5)	0.385
Overall mortality	29 (15.8)	8 (12.5)	21 (17.5)	0.375

Table 2. Treatment of the study population during ICU care[a]. Data are expressed as mean ± standard deviation (SD) or number (%) unless otherwise indicated. NMB, neuromuscular blocker; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation. [a]All patients received mechanical ventilation.

Variables	Total	Delta period	Pre-delta period	*P*-value
Patents number	184	64	120	
Proportion of at least one fibrosis-like changes	138 (75)	49 (76.6)	89 (74.2)	0.721
Fibrotic changes ≥ 2	100 (54.3)	48 (75)	52 (43.3)	< 0.001
Fibrotic changes ≥ 3	42 (22.8)	35 (54.7)	7 (5.8)	< 0.001
Mean number of fibrosis-like changes	1.6 ± 1.2	2.2 ± 1.4	1.2 ± 0.9	< 0.001
Fibrotic patterns on CT scan				
Reticulation	63 (34.2)	40 (62.5)	23 (19.2)	< 0.001
Architectural distortion +/- parenchymal band	96 (52.2)	44 (68.8)	52 (43.3)	0.001
Traction bronchiectasis /bronchiolectasis	120 (65.2)	47 (73.4)	73 (60.8)	0.087
Honeycombing change	12 (6.5)	11 (17.2)	1 (0.8)	< 0.001
Duration from ICU admission to chest CT scan, days	51 (27–76)	62 (43.2–79.7)	38 (24–70)	0.005

Table 3. Comparison of pulmonary fibrosis-like changes between delta and pre-delta period groups. Data are expressed as mean ± standard deviation (SD) or number (%) unless otherwise indicated. CT, computed tomography.

was no significant difference in the proportion of at least one fibrosis-like changes between the delta period ($n = 49$, 76.6%) and pre-delta period ($n = 74.2$, 89%). However, the mean number of pulmonary fibrosis-like changes was approximately twice as high in patients in the delta period (2.2 ± 1.4 vs. 1.2 ± 0.9, $P < 0.001$) than those in the pre-delta period, and the proportion of three or more fibrosis-like changes was shown to be 10 times higher in patients in the delta period (54.7% vs. 5.8%, $P < 0.001$). For features of pulmonary fibrosis-like changes, reticulation (62.5% vs. 19.2%, $P < 0.001$), architectural distortion (68.8% vs. 43.3%, $P < 0.001$), and honeycombing change (17.2% vs. 0.8%, $P < 0.001$) were significantly more prevalent in patients in the delta period compared to those in pre-delta period (Figure S2).

Pulmonary fibrosis-like changes after matching

To balance confounding variables, 41 patients in the delta period and 65 patients in the pre-delta period were matched (Figure S3). Table S1 summarizes comparison of characteristics after PSM. Mean ages tended to be lower in patients in the delta period than pre-delta period (63.4 ± 10.9 years vs. 66.5 ± 12.4 years, $P = 0.055$), but other characteristics were not significantly different.

Comparison of pulmonary fibrosis-like changes after PSM is presented in Table 4. Although the proportion of patients with at least one pulmonary fibrosis-like changes did not differ between the two periods (82.9% in the delta period vs. 73.8% in the pre-delta period, $P = 0.277$), the mean numbers of pulmonary fibrosis-like changes (2.5 ± 1.3 vs. 1.2 ± 0.9, $P < 0.001$) and the frequency of each feature (reticulation, 68.3% vs. 23.1%, $P < 0.001$; architectural distortion, 75.6% vs. 40%, $P < 0.001$; traction bronchiectasis/bronchiolectasis, 80.5% vs. 60%, $P = 0.028$; honeycombing change, 24.4% vs. 1.5%, $P < 0.001$) were significantly higher in patients in the delta period after PSM compared to those in the pre-delta period.

Discussion

This study showed that about two months after enrollment, at least one pulmonary fibrosis-like change developed in 73.5% of all patients with severe COVID-19 pneumonia receiving MV. Patients in the delta period

Variables	Total	Delta period	Pre-delta period	*P*-value
Patient numbers	106	41	65	
The proportion of at least one fibrosis-like changes	82 (77.4)	34 (82.9)	48 (73.8)	0.277
Fibrotic change ≥ 2	60 (56.6)	33 (80.5)	27 (41.5)	< 0.001
Fibrotic change ≥ 3	31 (29.2)	26 (63.4)	5 (7.7)	< 0.001
Mean number of fibrosis-like changes	1.7 ± 1.3	2.5 ± 1.3	1.2 ± 0.9	< 0.001
Fibrotic patterns on CT scan				
Reticulation	43 (40.6)	28 (68.3)	15 (23.1)	< 0.001
Architectural distortion +/- parenchymal band	57 (53.8)	31 (75.6)	26 (40)	< 0.001
Traction bronchiectasis /bronchiolectasis	72 (67.9)	33 (80.5)	39 (60)	0.028
Honeycomb change	11 (10.4)	10 (24.4)	1 (1.5)	< 0.001
Interval to chest CT scan, days	52.5 (28-85.5)	60 (49-79.5)	44 (21.5–98)	0.054

Table 4. Comparison of pulmonary fibrosis-like changes between delta and pre-delta period groups after propensity score matching. Data are expressed as mean ± standard deviation (SD) or number (%) unless otherwise indicated. CT, computed tomography. Propensity score matching variables: age, hypertension, hemoglobin concentration, platelet count, use of remdesivir, use of tocillizumab and prone position. CT, computed tomography.

had significantly more pulmonary fibrosis-like changes compared to those in the pre-delta period despite being younger, having fewer comorbidities and receiving more treatment. These findings suggest that pulmonary fibrosis-like changes in critically ill patients with severe COVID-19 pneumonia are determined by SARS-CoV-2 variants.

There are several reports showing severe COVID 19 pneumonia patients on MV been associated with more frequent pulmonary fibrosis-like changes. Gonzalez et al. evaluated pulmonary function and radiologic findings three months after hospital discharge (median 26 days of overall hospitalization) in 62 patents who survived from severe COVID-19 pneumonia (62.9% received MV)[21]. They found that 70.2% of patients had reticular lesions (49.1%) or fibrotic patterns (21.1%) on chest CT. Guler et al.., in their multicenter prospective cohort of 113 COVID-19 survivors (more than 70% who received MV) reported reticulations (59%), architectural distortion (52%), bronchiectasis (43%) and honeycombing change (11%) on chest CT at four months of follow-up. These radiologic findings were more frequent in patients with severe/critical COVID-19 than non-severe COVID-19 [22]. However, severe COVID-19 pneumonia with less use of MV was associated with less pulmonary fibrosis-like changes. Han et al.. in a study including 114 patients who survived severe COVID-19 pneumonia (13% received MV), also reported that pulmonary fibrosis-like change was revealed in 35% (40/114) at 6-month follow-up CT[23]. In prospective cohort study including 98 Korean patients with COVID-19 pneumonia (4.1% received MV), Lee et al.. reported that pulmonary fibrosis was observed in 43.9% on chest CT at 3 months after discharge[24], with the rate of pulmonary fibrosis-like change been half that of our findings.

Because our study included only patients receiving MV, which reflect a more severe forms of COVID-19 pneumonia, development of pulmonary fibrosis-like changes may be higher than otherwise reported[21–24]. The underlying mechanism of pulmonary fibrosis-like changes after acute phase of COVID-19 pneumonia has not been fully elucidated, but the impaired repair process and/or activation of pro-fibrotic pathways might be followed by multiple immune mechanisms like a cytokine storm at the post-acute phase of severe COVID-19 pneumonia[38–41].

The delta variant is characterized by greater respiratory transmission compared to the alpha variant, which developed before the omicron variant[34,42,43]. This feature also led to more frequent lower respiratory tract complications such as pneumonia. There have been a few reports about comparison of clinical features and outcomes between delta and alpha variants[33,44,45]. In a national study in the United Kingdom, individual-level data including 43,338 COVID-19-positive patients (8,682 with the delta variant, 34, 656 with the alpha variant) showed a significantly higher risk of hospitalization or emergency care visit for patients with the delta variant compared to the alpha variant (498 [5.7%] with the delta variant vs. 1448 [4.2%] with the alpha variant, adjusted HR 1.45 [1.80–1.95])[33]. Kumar et al., in a study including 636 delta and 737 alpha variant patients, reported that the median length of hospitalization for SARS-CoV-2 delta variant was longer compared to those with the alpha variant (unvaccinated, 5.2 days in delta variant vs. 4.4 days in alpha variant; vaccinated, 3.0 days in delta vs. 2.9 days in alpha, $P < 0.001$)[44]. Ong et al., in their retrospective study including 829 patients with SARS-CoV-2 infection in Singapore, reported that delta variant was associated with a higher composite outcome including oxygen requirement, ICU admission or death compared to wild-type SARS-CoV-2 (adjusted odds ratio, 4.90; 95% CI : 1.43–30.78)[45].

Comparison of clinical and radiologic data on pulmonary fibrosis-like changes in severe COVID-19 pneumonia among SARS-CoV-2 dominant variants periods are still lacking. To clarify this, we compared clinical characteristics and pulmonary fibrosis-like changes across two SARS-CoV-2 variant dominant periods (delta vs. pre-delta) in South Korea. Our findings suggest that pulmonary fibrosis-like changes may differ among SARS-CoV-2 variant dominant periods and that distinct strategies for the care of patients who survived from severe COVID-19 pneumonia and suffered post-pulmonary sequelae are needed to take account of the variants. While there is no clear reason to explain why pulmonary fibrosis-like changes are more prominent in the delta

variant, one possibility is that the delta variant has more transmissibility to the lower respiratory tract, such as the alveolar level, with higher viral loads, making more severe COVID-19 pneumonia and ARDS[27282945]. These features might also induce more alveolar injury and post-acute pulmonary fibrotic-like change than other variants.

Some limitations in our study exist. First, clinical data for patients in the pre-delta period were collected retrospectively, while those in the delta periods were collected prospectively. Therefore, selection bias may not be avoided in clinical data of pre-delta period. Second, the number of patients included in the delta period was smaller han the number f patients included in the pre-delta period, but even with the smaller number of patients, significant differences were found. Third, because we separated time periods by epidemic predominance rather than genetically identifying variant types, some patients may not be infected with delta variant during the delta period and vice versa. Fourth, there were no data of chest CT scan of all patients before COVID-19 pneumonia, so what fibrotic changes existed before in these patients and which could be developed because of COVID-19 and MV are not known. However, at the time of enrollment, patients with pre-existing interstitial lung disease were excluded from this study. Fifth the interval from enrollment to chest CT scan was relatively short compared to previous reports[18,23,25,46,47]. Therefore, we also used a more stringent definition of pulmonary fibrosis in this study to reduce differences. It remains to be elucidated whether pulmonary fibrosis-like changes in our study will sustain over the long-term period. In addition, the time from index date to CT scan was longer in the delta period than in the pre-delta period. Therefore, we cannot exclude the possibility that this may have led to more fibrosis-like changes in the lungs of patients in the delta period. However, after propensity score matching, the time from index date to CT scan was not statistically different between the two groups, and patients in the delta period still have more pulmonary fibrosis-like changes than those in the pre-delta period. Sixth, radiological qualitative assessment of pulmonary fibrosis-like changes by radiologists was performed in our study. Further studies using quantitative scales to more accurately capture pulmonary fibrosis-like changes are needed.

In conclusion, our results suggest that patients with severe COVID-19 in the delta period have more severe pulmonary fibrosis-like changes than those in the pre-delta period, even after adjustment for relevant clinical variables. Further studies are required to clarify the differences of pulmonary fibrosis-like changes across variants.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Authors' contributions

JWY and JWS substantially contributed to study conception and design. WYK, CRC, YJC, JL, YJ, JK, JSJ, TYP, ARB, JHP, GC, JHH and JWS substantially contributed to data acquisition and analysis JWY and JWS substantially contributed to data interpretation and manuscript writing. JWY, WYK, CRC, YJC, JL, YJ, JK, JSJ, TYP, ARB, JHP, GC, JHH and JWS substantially contributed to critical revision and final approval of the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and approved by the local institutional review board (IRB) of each hospital approved the study protocol (IRB of Asan Medical Center,

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Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to J.W.S.

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