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Pulmonary Fibrosis in Critically Ill Patients With COVID-19: A Multi-Center Retrospective Cohort Study in Korea

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ABSTRACT

Background: Pulmonary fibrosis can persist long after recovery from coronavirus disease 2019 (COVID-19) infection, thereby reducing quality of life and lung function. We aimed to evaluate the frequency and risk factors for pulmonary fibrosis in patients with severe COVID-19 pneumonia requiring mechanical ventilation (MV), a high-risk group for developing pulmonary fibrosis.

Methods: Clinical data and chest computed tomography (CT) scans of patients with severe COVID-19 pneumonia requiring MV were retrospectively collected from nine hospitals in South Korea. Fibrotic-like changes on chest CT were visually assessed.

Results: We included 125 patients with a mean age of 68.5 years, 60.8% men and 7.2% having underlying lung disease. Based on follow-up chest CT (the median interval, 38.0 days; interquartile range, 24.0–68.0 days), 94 (75.2%) patients exhibited fibrotic-like changes, with traction bronchiectasis and/or bronchiolectasis being the most common change (60.8%). Among all patients, 17.6% died during hospitalization and 71.2% experienced complications, including intubation-related airway injury (12.8%), ventilator-associated pneumonia (44.8%), lung injury (11.2%), and hemodynamic disturbance (33.4%). In-hospital mortality (16.1% vs. 18.1%) and complications (67.7% vs. 72.3%) were similar between

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Disclosure

The authors have no potential conflicts of interest to disclose.

Data Sharing Statement

Data sharing statement is provided in
Supplementary Data 1.

Author Contributions

Conceptualization: Chae G, Joh JS, Kim J, Park TY, Baek AR, Kim WY, Jegal Y, Chung CR, Lee J, Park JH, Song JW; Data curation: Song JW; Formal analysis: Cho D, Chae G, Song JW; Funding acquisition: Song JW; Investigation: Cho D, Chae G, Song JW; Methodology: Cho D, Chae G, Song JW; Project administration: Song JW; Resources: Joh JS, Kim J, Park TY, Baek

patients with and without fibrotic-like changes. In multivariable logistic regression analysis, a higher daily steroid dose (odds ratio, 0.961; 95% confidence interval, 0.849–0.993; $P = 0.018$) was associated with a reduced risk of pulmonary fibrosis, along with a higher heart rate on intensive care unit admission.

Conclusion: Our study demonstrated that in patients with severe COVID-19 pneumonia requiring MV, chest CT revealed fibrotic-like changes in approximately three-quarters of patients. In addition, our results suggest that higher daily doses of steroids may be associated with a reduced risk of pulmonary fibrosis. Further research is needed to determine the appropriate steroid dose that may reduce the progression of pulmonary fibrosis and improve clinical outcomes.

Trial Registration: Clinical Research Information Service Identifier: KCT0006312

Keywords: Coronavirus Disease 2019; Pulmonary Fibrosis; Computed Tomography; Complication; Risk Factor; Mechanical Ventilation; Corticosteroid

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has imposed a substantial global burden, resulting in > 700 million confirmed cases and > 6 million deaths by August 2023.¹ As the disease persists over a long period, the concept of “long COVID” emerged, referring to its long-term effects that extend beyond the period of active infection,² including persistent symptoms such as fatigue, dyspnea, impaired pulmonary function, abnormal chest computed tomography (CT) findings such as pulmonary fibrosis.³ A meta-analysis on pulmonary sequelae of COVID-19 revealed that > 50% of recovered patients exhibit residual abnormalities on chest CT scans after 3 months.⁴ Furthermore, the recent emergence of the highly transmissible SARS-CoV-2 omicron variant has posed new challenges in the battle against the pandemic.⁵ Despite its reduced pathogenicity, the omicron variant shows significant resistance to the neutralizing activities of vaccines, convalescent serum, and most antibody therapies. Consequently, critically ill COVID-19 patients continue to be encountered.

Complications such as pulmonary fibrosis are common in severe COVID-19 patients. Understanding the patterns and identifying risk factors for pulmonary fibrosis in this high-risk group are paramount in managing the long-term sequelae of COVID-19. In a meta-analysis, Lee et al.⁶ reported that studies with > 50% of patients experiencing severe COVID-19 revealed a significantly higher prevalence of pulmonary fibrosis than that of studies with fewer severe cases (36% vs. 18%; $P = 0.014$).

Furthermore, COVID-19 disease severity has been suggested to be significantly associated with an increased risk of developing pulmonary fibrosis.^{7,8} Although previous studies have investigated the prevalence and associated risk factors of pulmonary fibrosis in COVID-19 patients across various degrees of severity, detailed data for patients requiring mechanical ventilation (MV), a high-risk group for developing pulmonary fibrosis, remain limited. In particular, by identifying the frequency and risk factors for pulmonary fibrosis in this group, it is crucial to enable clinicians treating severe cases to develop effective strategies to prevent and manage pulmonary fibrosis, thereby reducing its occurrence and alleviating the burden of long-term sequelae associated with COVID-19. Therefore, we aimed to evaluate the frequency and risk factors for pulmonary fibrosis in patients with severe COVID-19 requiring MV.

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METHODS

Study design and participants

This multicenter, retrospective observational cohort study included patients who required MV for COVID-19 pneumonia between February 2020 and October 2021, enrolled from nine South Korea hospitals. The inclusion criteria were as follows: 1) age ≥ 18 years; 2) confirmation of SARS-CoV-2 infection using real-time polymerase chain reaction assays conducted on nasopharyngeal swabs; 3) classification as severe or critical condition according to the COVID-19 World Health Organization (WHO) clinical classification; 4) admission to the intensive care unit (ICU) with a requirement for MV; and 5) patients with follow-up chest CT conducted 1 month post-discharge in an outpatient setting, or the last CT scans conducted during hospitalization in cases of patient's death or transfer to another medical facility. Patients previously diagnosed with interstitial lung disease were excluded from this study. A total of 353 patients with COVID-19 pneumonia who required MV were admitted to the ICU. Among them, 228 patients who did not undergo follow-up CT during hospitalization or post-discharge were excluded from the study. Ultimately, 125 patients were included in the analysis and categorized into pulmonary fibrosis and no pulmonary fibrosis groups, based on the fibrotic-like changes detected on chest CT scans (Fig. 1).

Data collection

Patients' demographic and clinical data at ICU admission were retrospectively collected. Treatment-related data, including antiviral drugs and steroid administration, MV settings, extracorporeal membrane oxygenation use, and continuous renal replacement therapy application, were collected to evaluate the effects of medical interventions on pulmonary fibrosis. Additionally, data on mortality and ventilator-associated complications, including intubation-related airway injury (IRAI), ventilator-associated pneumonia (VAP), ventilator-induced lung injury (VILI), and hemodynamic disturbance, were collected. IRAI was defined as an injury to the airway, including the nasal cavity, oral cavity, oropharynx, and larynx, following intubation.⁹ VAP was defined as the occurrence of pneumonia > 48 hours after MV initiation.¹⁰ VILI was defined as lung damage, including atelectrauma, barotrauma, volutrauma, and biotrauma, that manifests after MV initiation.¹¹ Hemodynamic disturbances were defined as instances of reduced blood pressure caused by positive pressure ventilation after MV initiation.

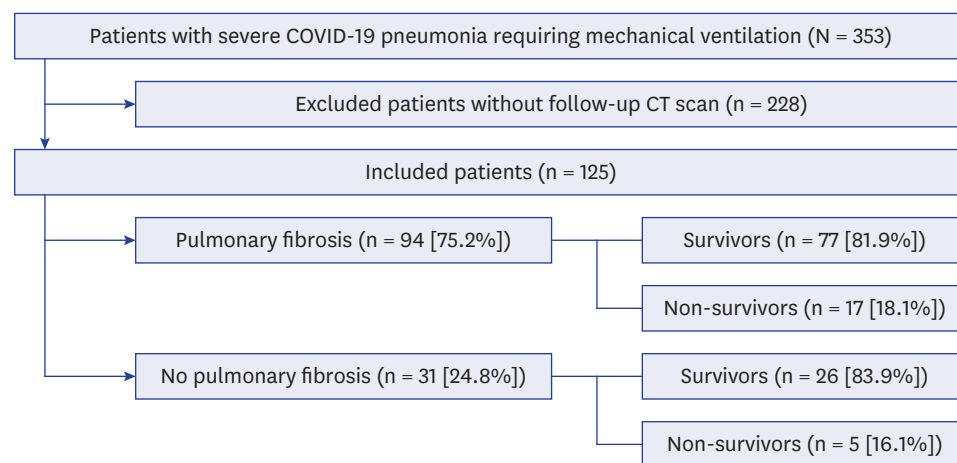


Fig. 1. Flowchart of selection of the study participants.
COVID-19 = coronavirus disease 2019, CT = computed tomography.

Assessment of pulmonary fibrosis

We collected outpatient chest CT scans acquired 1 month post-discharge or the last scan obtained during hospitalization for patients who died or were transferred to another hospital. Two thoracic radiologists (Jinwoo Lee and Soyeoun Lim) with 9 years of experience independently reviewed the scans to assess pulmonary fibrosis, blinded to clinical information except for the presence of COVID-19. Disagreements between the two readers were resolved by consensus. Fibrotic-like changes, including reticulation, architectural distortion and/or parenchymal band, traction bronchiectasis and/or bronchiolectasis, and honeycombing, were considered indicative of pulmonary fibrosis on CT imaging (**Supplementary Fig. 1**). Reticulation refers to several linear opacities resembling a mesh or net resulting from thickening of the interlobular or intralobular septa.¹² Architectural distortion is the abnormal displacement of bronchi, vessels, fissures, or septa caused by diffuse or localized lung disease.¹² Parenchymal band is characterized by a linear opacity, usually 1–3 mm thick and approximately 5 cm long, extending to the visceral pleura.¹² Traction bronchiectasis and/or bronchiolectasis is the dilatation of bronchi and bronchioles within areas of pulmonary fibrosis or distorted lung parenchymal architecture.¹² Honeycombing describes clustered cystic air spaces, typically subpleural, peripheral, and basal in distribution.¹²

Statistical analysis

Data were presented as mean $\pm$ standard deviation or median $\pm$ interquartile range (IQR) for continuous variables and number (%) for categorical variables. The Student's *t*-test or Mann–Whitney *U* test was used to compare continuous variables, and the χ^2 or Fisher's exact test was used to compare categorical variables. Univariable logistic regression analyses were conducted to identify which potential variables were associated with fibrotic-like changes. All variables that were statistically significant were entered into a multivariable logistic regression model using a non-stepwise (enter) method to assess the differential contribution of individual variables. Statistical analyses were performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA) and R (version 4.2.0; The R Foundation for Statistical Computing, Vienna, Austria). *P* values of less than 0.05 were considered statistically significant.

Ethics statement

The Institutional Review Board (IRB) of each participating hospital, including Asan Medical Center (IRB No. 2021-1353) approved the study and waived the need of informed consent. This study was registered with the Korea Clinical Research Informative Service (No. KCT0006312), and was performed in accordance with the principles of the Declaration of Helsinki. All methods were performed in accordance with applicable guidelines and regulatory requirements.

RESULTS

Baseline characteristics and pulmonary fibrosis

Among the 125 enrolled patients, the mean age was 68.5 years, 60% of them were male, and 7.2% had pre-existing lung disease. One or more fibrotic-like changes were identified in 75.2% (94/125) of all patients. No differences were observed in baseline characteristics, including body mass index and smoking history, between patients with fibrotic-like changes and those without them (**Table 1**). However, for baseline characteristics at ICU admission, the pulmonary fibrosis group exhibited lower Sequential Organ Failure Assessment (SOFA)

Table 1. Comparison of baseline characteristics between the pulmonary fibrosis and no pulmonary fibrosis groups

Variables	All patients	PF group	No PF group	P value
No. of patients	125	94	31	
Age, yr	68.5 ± 12.3	68.7 ± 11.0	67.8 ± 15.7	0.775
BMI, kg/m ²	25.0 ± 4.2	25.0 ± 3.6	24.9 ± 5.8	0.941
Sex, male	76 (60.8)	56 (59.6)	20 (64.5)	0.625
Smoking history				0.152
Never-smoker	80 (75.5)	60 (76.9)	20 (71.4)	
Ex-smoker	19 (17.9)	15 (19.2)	4 (14.3)	
Current smoker	7 (6.6)	3 (3.8)	4 (14.3)	
Comorbidity				
No. of comorbidities ≥ 1	97 (77.6)	74 (78.7)	23 (74.2)	0.600
Diabetes mellitus	53 (42.4)	39 (41.5)	14 (45.2)	0.720
Hypertension	83 (66.4)	61 (64.9)	22 (71.0)	0.535
Cardiovascular disease	16 (12.8)	11 (11.7)	5 (16.1)	0.542
Cerebrovascular disease	18 (14.4)	13 (13.8)	5 (16.1)	0.711
Liver disease	4 (3.2)	2 (2.1)	2 (6.5)	0.257
Kidney disease	10 (8.0)	6 (6.4)	4 (12.9)	0.263
Malignancy	13 (10.4)	9 (7.4)	4 (12.7)	0.735
Lung disease	9 (7.2)	6 (6.4)	3 (9.7)	0.689
COPD	3 (33.3)	2 (33.3)	1 (33.3)	1.000
Asthma	4 (44.4)	3 (50.0)	1 (33.3)	1.000
Bronchiectasis	1 (11.1)	1 (16.7)	0 (0.0)	1.000
Lung cancer	1 (11.1)	0 (0.0)	1 (33.3)	0.333
TB destroyed lung	2 (22.2)	1 (16.7)	1 (33.3)	1.000
CCI	1.2 ± 1.2	1.1 ± 1.5	1.5 ± 1.4	0.148

Data are presented as mean ± standard deviation or number (%), unless otherwise stated.

PF = pulmonary fibrosis, BMI = body mass index, COPD = chronic obstructive pulmonary disease, TB destroyed lung = tuberculosis destroyed lung, CCI = Charlson Comorbidity Index.

score, heart rate, and aspartate transaminase (AST) levels than the no pulmonary fibrosis group (**Supplementary Table 1**).

Among all patients, 54 (43.2%) exhibited two or more fibrotic-like changes and 7 (5.6%) exhibited three or more such changes (**Table 2**). Traction bronchiectasis and/or bronchiolectasis were the most frequently observed findings (60.8%), followed by architectural distortion and/or parenchymal bands (44.8%), reticulation (18.4%), and honeycombing (0.8%). The median interval between ICU admission and CT evaluation was 38.0 days (IQR, 24.0–68.0 days). Non-survivors had a shorter interval between ICU admission and CT evaluation compare to survivors (30.5 days, IQR, 24.5–81.5 vs. 44.0 days, IQR, 21.0–47.0; $P = 0.038$).

Treatment

In total, 94.4% (118/125) of patients received systemic steroids and 74.7% (93/125) received antiviral therapy, mostly remdesivir (**Supplementary Table 2**). The mean daily dose of

Table 2. Radiographic findings detected on chest computed tomography scan

Radiographic findings	No. of patients
All patients	125
Fibrosis (any component)	94 (75.2)
Reticulation	23 (18.4)
Architectural distortion and/or parenchymal band	56 (44.8)
Traction bronchiectasis/bronchiolectasis	76 (60.8)
Honeycombing	1 (0.8)
Fibrosis (≥ 2 components)	54 (43.2)
Fibrosis (≥ 3 components)	7 (5.6)

Data are presented as number (%), unless otherwise stated.

dexamethasone (or equivalent drugs) was 11.1 ± 15.6 mg (median 6.0 mg; IQR, 6–10.6), and the mean total amount administered during treatment was 72.6 ± 138.2 mg (median 54.0 mg; IQR, 18–66). These values were not significantly different between the fibrosis and no fibrosis groups. The median MV duration for all patients was 17.5 days (IQR, 8.0–43.0). Additionally, no differences were observed in terms of initial ventilator settings or utilization of adjuvant therapies, including neuromuscular blocking agent use and prone position.

Mortality and ventilator-associated complications

Overall, 22 (17.6%) patients died during hospitalization, and 89 (71.2%) experienced one or more ventilator-associated complications. No differences in in-hospital mortality and occurrence of complications were observed between the two groups (Table 3). However, when pulmonary fibrosis was defined as two or more fibrotic-like changes, in-hospital mortality was higher in the no pulmonary fibrosis group than in the pulmonary fibrosis group (23.9% [17/71] vs. 9.3% [5/54]). This trend was also observed when the pulmonary fibrosis group was defined as having three or more fibrotic-like changes (18.6% [2/118] vs. 0% [0/7]).

Factors associated with pulmonary fibrosis

Univariable logistic regression analysis identified that a higher heart rate (odds ratio [OR], 0.966; 95% confidence interval [CI], 0.944–0.989; $P = 0.004$), higher SOFA score (OR, 0.868; 95% CI, 0.754–0.999; $P = 0.049$), and higher daily steroid dose (OR, 0.964; 95% CI, 0.933–0.996; $P = 0.028$) were associated with a reduced risk of pulmonary fibrosis (Table 4). No significant associations were observed with age, male sex, smoking history, lactate dehydrogenase (LDH), C-reactive protein (CRP), or D-dimer, despite these factors being previously reported as potential risk factors for pulmonary fibrosis in severe COVID-19 patients.^{6,7,13-16} Multivariable logistic regression analysis also confirmed that a higher daily steroid dose (OR, 0.961; 95% CI, 0.849–0.993; $P = 0.018$) were independently associated with a reduced risk of pulmonary fibrosis, along with a higher heart rate (OR, 0.963; 95% CI, 0.937–0.990; $P = 0.008$) (Table 4).

DISCUSSION

In our study, pulmonary fibrotic-like changes were observed in about three-quarters of patients with severe COVID-19 pneumonia requiring MV. A higher daily steroid dose was associated with a decreased risk of pulmonary fibrosis, along with a higher heart rate on ICU admission. The reported incidence of pulmonary fibrosis in patients with COVID-19 varies from 25.5% to 84.1%,^{7,8,13-17} which could be attributed to the variations in disease severity

Table 3. Comparison of mortality and complications between pulmonary fibrosis and no pulmonary fibrosis groups

Variables	All patients	PF group	No PF group	P value
No. of patients	125	94	31	
Complication	89 (71.2)	68 (72.3)	21 (67.7)	0.624
IRAI	16 (12.8)	13 (13.8)	3 (9.7)	0.759
VAP	56 (44.8)	45 (49.7)	11 (35.5)	0.229
VILI	14 (11.2)	10 (10.6)	4 (12.9)	0.747
Hemodynamic disturbance	43 (34.4)	32 (34.0)	11 (35.5)	0.884
Mortality	22 (17.6)	17 (18.1)	5 (16.1)	0.804

Data are presented as number (%), unless otherwise stated.

PF = pulmonary fibrosis, IRAI = intubation-related airway injury, VAP = ventilator associated pneumonia, VILI = ventilator induced lung injury.

Table 4. Logistic regression analysis for identifying risk factors associated with pulmonary fibrosis

Variables	Univariate analysis		Multivariate analysis ^b	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, yr	1.006 (0.973–1.039)	0.730	-	-
Sex, male	1.234 (0.531–2.867)	0.625	-	-
BMI, kg/m ²	1.005 (0.912–1.107)	0.926	-	-
Current or past smoker	1.333 (0.503–3.533)	0.563	-	-
Lung disease	1.571 (0.369–6.697)	0.541	-	-
CCI	0.797 (0.584–1.086)	0.150	-	-
Systolic BP, mmHg	1.010 (0.994–1.027)	0.214	-	-
Diastolic BP, mmHg	1.010 (0.986–1.036)	0.416	-	-
Heart rate, /min	0.966 (0.944–0.989)	0.004	0.963 (0.937–0.990)	0.008
Respiratory rate, /min	0.986 (0.927–1.049)	0.654	-	-
P/F ratio	1.000 (0.991–1.008)	0.934	-	-
SOFA score	0.868 (0.754–0.999)	0.049	1.013 (0.849–1.209)	0.886
APACHE score	0.996 (0.944–1.050)	0.877	-	-
Leukocyte, × 10 ³ /L	0.982 (0.924–1.043)	0.546	-	-
Neutrophil, %	1.010 (0.975–1.047)	0.584	-	-
Hemoglobin, g/dL	0.961 (0.777–1.188)	0.714	-	-
Platelet, × 10 ³ /uL	0.999 (0.996–1.003)	0.741	-	-
AST, IU/L	0.991 (0.980–1.002)	0.120	-	-
ALT, IU/L	0.993 (0.982–1.005)	0.245	-	-
Total bilirubin, mg/dL	0.371 (0.123–1.117)	0.078	-	-
Total protein, g/dL	0.929 (0.526–1.641)	0.799	-	-
Albumin, g/dL	1.164 (0.469–2.888)	0.744	-	-
BUN, mg/dL	0.987 (0.965–1.009)	0.238	-	-
Creatinine, mg/dL	0.893 (0.592–1.346)	0.589	-	-
LDH, U/l	0.999 (0.997–1.000)	0.086	-	-
CRP, mg/L	0.998 (0.948–1.051)	0.953	-	-
Procalcitonin, ng/mL	1.015 (0.796–1.294)	0.905	-	-
Troponin I, ng/mL	0.995 (0.988–1.002)	0.177	-	-
D-dimer, mcg/mL	1.016 (0.967–1.067)	0.533	-	-
Minute ventilation, L/min	1.043 (0.881–1.233)	0.627	-	-
Peak pressure, cm H ₂ O	0.989 (0.889–1.101)	0.846	-	-
Use of antiviral agents	0.642 (0.263–1.565)	0.329	-	-
Use of steroid	0.815 (0.150–4.426)	0.812	-	-
Steroid duration days	0.989 (0.940–1.041)	0.678	-	-
Steroid dose per day, mg ^a	0.964 (0.933–0.996)	0.028	0.961 (0.849–0.993)	0.018
Steroid total dose, mg ^a	1.000 (0.997–1.003)	0.974	-	-
Use of NMBA	0.886 (0.290–2.704)	0.832	-	-
NO inhalation	2.045 (0.237–17.686)	0.516	-	-
Prone duration, days	1.064 (0.627–1.806)	0.819	-	-
CRRT duration, days	1.013 (0.968–1.059)	0.580	-	-
ECMO duration, days	1.073 (0.949–1.215)	0.262	-	-

OR = hazard ratios, CI = confidence interval, BMI = body mass index, CCI = Charlson Comorbidity Index, BP = blood pressure, P/F = PaO₂/FiO₂, SOFA = Sequential Organ Failure Assessment, APACHE = Acute Physiology and Chronic Health Evaluation, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, CRP = C-reactive protein, NMBA = neuromuscular blocking agent, NO = nitric oxide, CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation.

^aDose based on dexamethasone or equivalent drugs.

^bVariables with statistical significance in univariate analysis were entered into the multivariate logistic regression model using the enter method.

among study participants, definitions of pulmonary fibrosis, and heterogeneity of the study periods. Although most patients in our study received antiviral and steroid treatment, the high prevalence of pulmonary fibrosis emphasizes the need for post-recovery monitoring with follow-up CT in patients recovering from severe COVID-19 pneumonia. Further research is needed to explore MV strategies to reduce the incidence of pulmonary fibrosis in patients with COVID-19 pneumonia requiring MV.

Previous studies have suggested patient-related factors such as older age, male sex, smoking, obesity, and underlying disease^{7,8,13-16} and laboratory findings including interleukin-6, interferon-gamma, and Krebs Von den Lungen-6 levels,¹⁸⁻²⁰ as risk factors for pulmonary fibrosis. Laboratory findings associated with the pathophysiology of COVID-19, such as excessive proinflammatory cytokines or suppressed immune response, including elevated CRP, D-dimer, LDH, and procalcitonin levels, as well as lymphopenia and leukocytosis, have been linked to disease severity.^{21,22} As previous meta-analyses have indicated that increased COVID-19 severity is linked to a higher risk of pulmonary fibrosis, our study also attempted to confirm the association of these various factors and laboratory findings with pulmonary fibrosis.^{23,24} However, the findings of our study revealed that these variables did not demonstrate a statistically significant association with pulmonary fibrosis. Instead, univariable logistic regression analysis indicated that higher SOFA scores and higher heart rates were associated with a reduced risk of pulmonary fibrosis. Patients in the fibrosis group exhibited lower SOFA scores, heart rates, and AST concentrations at the time of ICU admission compared to those in the no pulmonary fibrosis group. The statistical analysis indicated that the no pulmonary fibrosis group exhibited higher mortality rates, particularly when more stringent criteria for defining pulmonary fibrosis were applied. Furthermore, deceased patients demonstrated shorter intervals between ICU admission and CT assessment compared to survivors. This observation suggests the presence of survivor bias, where patients with higher disease severity died prematurely before fibrosis could develop or be detected. This finding underscores the intricate, multifactorial nature of pulmonary fibrosis development in patients with COVID-19²⁵ and suggests that survivor bias should be carefully considered when interpreting associations between disease severity markers and fibrosis outcomes.

Dexamethasone has become a standard treatment for severe COVID-19 patients who require oxygen therapy and MV due to its significant protective effect against mortality.^{26,27} Both the WHO and the National Institutes of Health recommend a dexamethasone dosage of 6 mg/day for 7-10 days.^{28,29} Other immunomodulators, including interleukin-6 receptor antagonists and Janus kinase-1 inhibitors such as baricitinib, have also demonstrated improved outcomes in moderate-to-severe COVID-19 patients.³⁰⁻³² However, compared to newer agents, systemic corticosteroids remain a strongly recommended treatment for severe or critically ill COVID-19 patients due to their extensive clinical use, short-term safety, affordability, and ease of administration.³³ Concerns have been raised that glucocorticoid use may delay viral clearance in COVID-19 patients,³⁴ but meta-analyses suggest that low-dose corticosteroids have minimal impact on the duration of SARS-CoV-2 viral shedding.³⁵ Steroid therapy remains an important treatment option for clinicians, yet few studies have explored the association between glucocorticoid use and the development of pulmonary fibrosis. The potential of corticosteroids to reduce the risk of pulmonary fibrosis is hypothesized to be result of their ability to inhibit fibroblast proliferation caused by inflammatory cytokines. This inhibition is thought to be achieved by increasing anti-inflammatory protein production and decreasing pro-inflammatory proteins.³⁶

However, the dose of dexamethasone used in the standard treatment of severe COVID-19 is considerably lower than the corticosteroid dose used in the treatment of acute exacerbations of idiopathic pulmonary fibrosis.³⁷ A recent study comparing the effects of 6 mg versus 12 mg of dexamethasone administered daily for 10 days in 982 patients with severe COVID-19 showed that the 12 mg group had better clinical outcomes, with similar rates of serious adverse event rates between the two groups.³⁸ In addition, in our study, the median daily dose of dexamethasone (or equivalent drugs) was 6 mg, and logistic regression analysis suggested

that increased steroid dose may be associated with reduced risk of pulmonary fibrosis. However, given the adverse consequences associated with additional high-dose steroid therapy in patients with unresolved acute respiratory distress syndrome following standard dexamethasone treatment,³⁹ further investigation is necessary to determine whether early increases in dexamethasone dosage during the course of severe COVID-19 could mitigate pulmonary fibrosis progression and improve clinical outcomes.

To our knowledge, this is the first observational study investigating the characteristics and risk factors associated with pulmonary fibrosis in patients with severe COVID-19 requiring MV. However, our study is subject to several limitations due to its retrospective nature. First, there is a possibility of selection bias, as only patients who underwent CT scans were included, potentially favoring those suspected of having fibrosis. Since data from patients without CT scans were not collected per study criteria, additional analyses to address this bias were not feasible. Second, defining fibrosis onset based on CT diagnosis may have caused outcome misclassification, particularly if CT evaluations occurred after fibrosis had already developed. Such misclassification could introduce bias, potentially affecting the accuracy of association estimates in the analysis. Third, CT used to assess pulmonary fibrosis development was performed within a short period of time after ICU admission. Notably, long-term follow-up CT studies including patients with severe COVID-19 pneumonia have demonstrated that lung fibrosis can resolve over time. The lack of long-term follow-up and assessment of pulmonary function in our study limited our understanding of progression or resolution of pulmonary fibrosis in patients with severe COVID-19.^{7,13,40} Despite these limitations, our study's multicenter design and the inclusion of a large number of patients with severe COVID-19 increased the reliability of the results. The adjusted analyses for multiple variables revealed important risk factors associated with pulmonary fibrosis in patients with severe COVID-19, while taking into account the potential influence of confounding variables.

In conclusion, our study demonstrated that fibrotic-like changes were observed on chest CT scans in approximately three-quarters of patients with severe COVID-19 pneumonia requiring MV. Furthermore, our findings suggest that higher daily dose of steroid may play a critical role in mitigating fibrotic progression. Further research is needed to determine the optimal timing, dosage, and duration of corticosteroid therapy, particularly in patients with severe COVID-19, to improve clinical outcomes and prevent long-term pulmonary sequelae.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Data sharing statement

Supplementary Table 1

Comparison of clinical findings at intensive care unit admission between the pulmonary fibrosis and no pulmonary fibrosis groups

Supplementary Table 2

Comparison of treatment between PF and no PF groups

Supplementary Fig. 1

Fibrotic-like changes detected on computed tomography scans. (A) Reticulation (red arrows), (B) architectural distortion (white arrows) and/or parenchymal band (red arrows), (C) traction bronchiectasis (red arrows) and/or bronchiolectasis, (D) honeycombing (red arrows).

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