

Pulmonary fibrosis followed by severe pneumonia in patients with COVID-19 infection requiring mechanical ventilation: a prospective multicentre study

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ABSTRACT

Backgrounds The management of lung complications, especially fibrosis, after COVID-19 pneumonia, is an important issue in the COVID-19 post-pandemic era. We aimed to investigate risk factors for pulmonary fibrosis development in patients with severe COVID-19 pneumonia. **Methods** Clinical and radiological data were prospectively collected from 64 patients who required mechanical ventilation due to COVID-19 pneumonia and were enrolled from eight hospitals in South Korea. Fibrotic changes on chest CT were evaluated by visual assessment, and extent of fibrosis (mixed disease score) was measured using automatic quantification system.

Results 64 patients were enrolled, and their mean age was 58.2 years (64.1% were males). On chest CT (median interval: 60 days [IQR; 41–78 days] from enrolment), 35 (54.7%) patients showed ≥3 fibrotic lesions. The most frequent fibrotic change was traction bronchiectasis (47 patients, 73.4%). Median extent of fibrosis measured by automatic quantification was 10.6% (IQR, 3.8–40.7%). In a multivariable Cox proportional hazard model, which included nine variables with a p value of <0.10 in an unadjusted analysis as well as age, sex and Body Mass Index, male sex (HR, 3.01; 95% CI, 1.27 to 7.11) and higher initial Sequential Organ Failure Assessment (SOFA) score (HR, 1.18; 95% CI, 1.02 to 1.37) were independently associated with pulmonary fibrosis (≥3 fibrotic lesions).

Conclusion Our data suggests that male gender and higher SOFA score at intensive care unit admission were associated with pulmonary fibrosis in patients with severe COVID-19 pneumonia requiring mechanical ventilation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ After infection of COVID-19, several pathophysiological changes have been suggested including pulmonary fibrosis. However, it is still inconclusive whether risk factors present to predict fibrosis or the characteristics of these changes to prolong or not. Moreover, the results for patients who survived from intensive care have been still sparse.

WHAT THIS STUDY ADDS

⇒ Risk factors including male and higher Sequential Organ Failure Assessment (SOFA) score had an association with higher likelihood of pulmonary fibrosis, suggesting the possibility of predicting future occurrence of pathophysiological lung changes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggested feasible predictors of pulmonary fibrosis, male and higher SOFA score, in patients with severe COVID-19 pneumonia requiring mechanical ventilation.

INTRODUCTION

COVID-19 has resulted in a global pandemic since the first case of infection with SARS-CoV-2 was reported in Wuhan, China, in December 2019.¹ As of 9 June 2023, 767 million confirmed cases and 6.9 million deaths have been reported globally, according to the WHO epidemiological data.² Clinical features of COVID-19 ranged from asymptomatic patients to those with severe complication of pneumonia requiring mechanical ventilation,

which had been reported to be approximately one-fifth of hospitalised patients with COVID-19 infection.^{3–4} Pneumonia due to COVID-19 showed various radiological findings, including ground glass opacity (GGO) pattern and whole lung bilateral infiltration in cases of acute respiratory distress syndrome.^{5,6} Patients who required mechanical ventilation showed more extensive pulmonary radiological features, suggesting pulmonary sequelae in terms of pulmonary fibrosis, which cause residual respiratory symptoms, such as dyspnoea and cough for months.^{6,7} Pulmonary fibrosis has the potential of causing permanent damage to the lungs, even after treatment.^{8,9} To our knowledge, the mechanisms of pulmonary fibrosis are associated with activation of the pulmonary fibrosis pathway, which are related to microenvironmental



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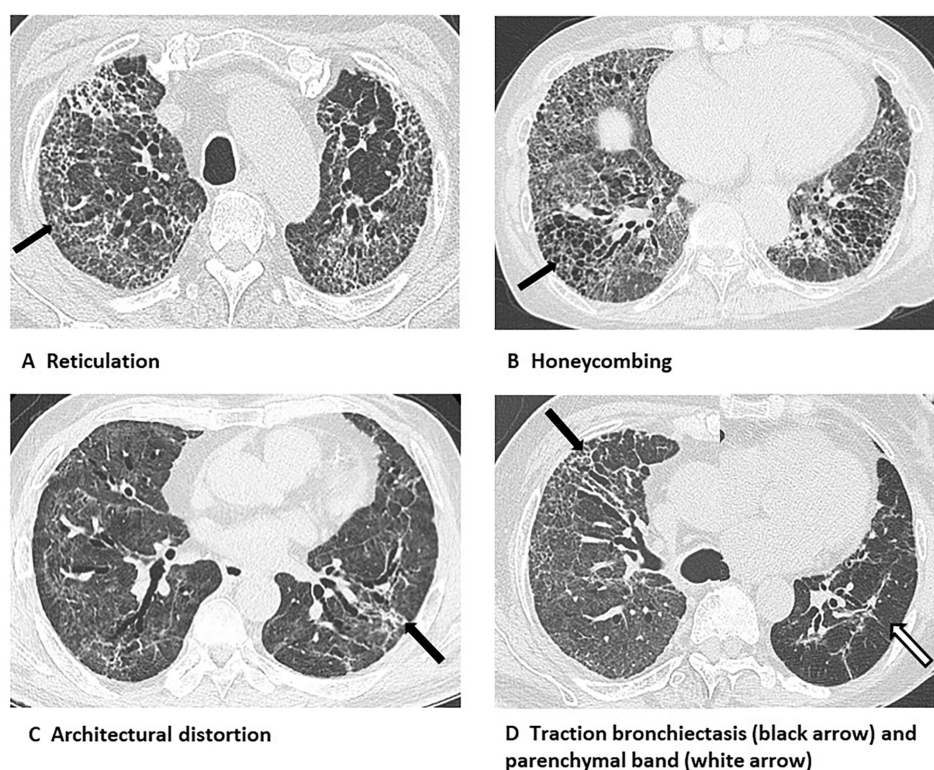


Figure 1 Representative radiological findings of pulmonary fibrosis in study participants. (A) CT showing predominantly subpleural reticulation (arrow). (B) Honeycombing is indicated by the arrow in the right lower lobe. (C) Architectural distortion is indicated by the arrow in the left lower lobe. (D) Traction bronchiectasis and parenchymal band in the right lower lobe (black arrow) and left lower lobe (white arrow).

insults and viral infections, resulting in direct alveolar and cytokine-related lung damages.^{10 11} Damages caused by positive pressure ventilation may also affect pulmonary fibrosis in patients who underwent mechanical ventilation.¹²

Since the COVID-19 pandemic, previous studies have reported that older age was significantly related to pulmonary fibrosis after COVID-19 infection.^{13 14} Disease severity, such as higher initial oxygen demand^{7 15} and some biomarkers, including inflammatory cytokines (interleukin-6 (IL-6), lactate dehydrogenase, interferon gamma and serum Krebs von den Lungen (KL-6)), have been suggested as possible predictors for pulmonary fibrosis.^{6 16 17} However, data on pulmonary fibrosis among critically ill patients requiring intensive care unit (ICU) admission with mechanical ventilation are still limited. Therefore, in this study, we aimed to evaluate the prevalence and risk factors of pulmonary fibrosis development in critically ill patients with COVID-19 pneumonia requiring mechanical ventilation.

MATERIAL AND METHODS

Study population

This multicentre prospective study was conducted in eight centres (the Asan Medical Centre, National Medical Centre, Ulsan University Hospital, Chung-Ang University Hospital, Samsung Medical Centre, Seoul National

University Bundang Hospital, Seoul National University Hospital and Seoul Metropolitan Government-Seoul National) involved in COVID-19 infection care in the Republic of Korea. We initially enrolled 110 consecutive patients who were admitted and managed for COVID-19 pneumonia between July and December 2021. Inclusion criteria were as follows: (1) age ≥ 19 years; (2) SARS-CoV-2 infection confirmed by nasopharyngeal swab reverse transcriptase-polymerase chain reaction; (3) definite evidence of pneumonia on initial chest radiography (chest X-ray or CT); (4) patients requiring mechanical ventilation; and (5) severe or critical COVID-19 infection, according to the WHO clinical classification for COVID-19 pneumonia.¹⁸ All those who agreed to use the ventilator were registered, and those who refused to consent were excluded. In addition, patients were excluded if they had a previous diagnosis of interstitial lung disease.

According to the study protocol, survivors were followed up in each hospital's outpatient department 1 month after discharge where chest CT scans and pulmonary function test were performed. For patients who died before discharge or were transferred to other hospitals, the last scans performed during the hospitalisation were retrieved. Of the patients enrolled, 64 patients with available follow-up CT images were finally included.

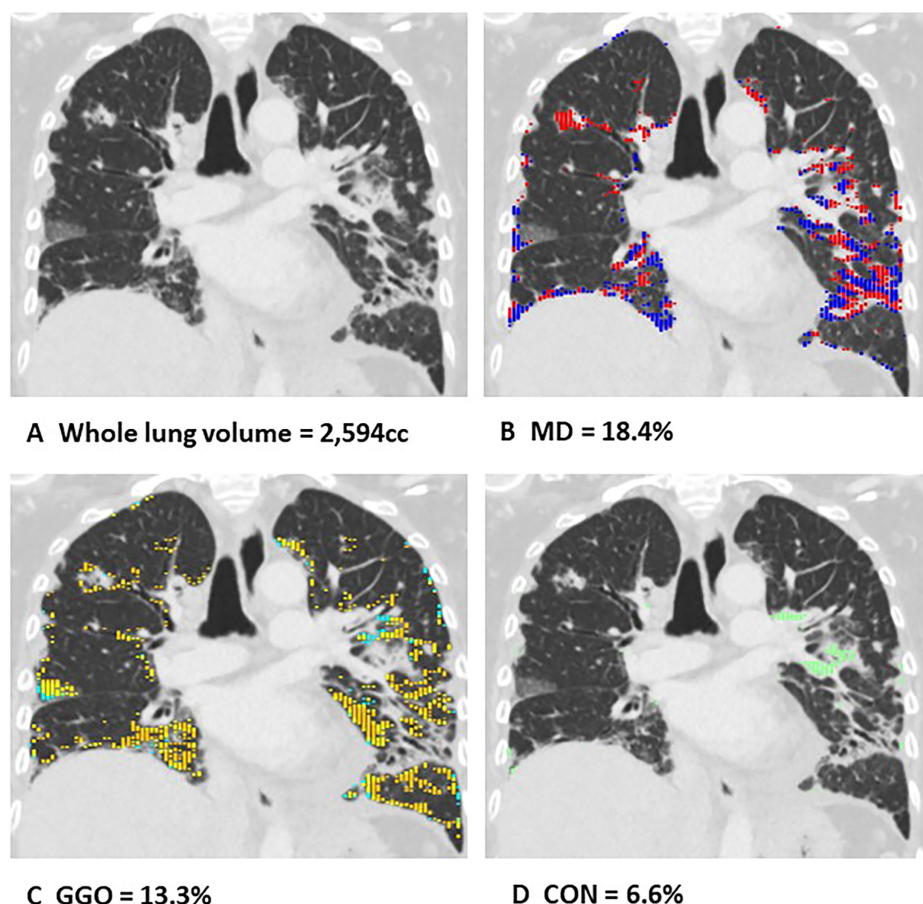


Figure 2 Automated quantification system evaluated by computer-based analysis of high-resolution CT imaging. GGO, ground glass opacities; MD, mixed disease; CON, consolidation.

The study protocol was approved by the Institutional Review Board of the eight individual centres, including the Asan Medical Centre (IRB No. 2021-0769). The present study was registered with the Clinical Research Informative Service (No. KCT0006312). Written informed consent was provided to individual patients or their caregivers who were unable to state their own will due to medical status.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Clinical data

All information was prospectively collected from each centre and recorded into a central electronic Case Report Form (iCReaT, <https://icreat.nih.go.kr/icreat/>). No identifiable data were collected. Data on demographic characteristics (age, sex, Body Mass Index (BMI), smoking history and underlying comorbidities) and clinical status at ICU admission (vital signs, laboratory results, Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores and ventilator parameters) were collected.

During hospitalisation, the length of hospital and ICU stay and duration of ventilator use were recorded. Data on treatment (use of continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), nitric oxide gas inhalation, and prone positioning and medication use, including antiviral agents and steroids) were also collected. Forced vital capacity (FVC) and diffusing capacity (DLco) by spirometry or plethysmography were measured, according to the European Respiratory Society/American Thoracic Society recommendations.^{19 20}

Radiologic assessment

Fibrosis-like changes on chest CT were evaluated by visual assessment of two radiologists (B.D.N and J.H.H) who specialise in chest radiology with 7 and 26 years of experience in chest radiology, respectively. Findings compatible with fibrosis-like changes were as follows: (1) reticulation, (2) architectural distortion±parenchymal band, (3) traction bronchiectasis/bronchiolectasis or (4) honeycombing²¹ (figure 1). Definition of pulmonary fibrosis was valid if there are ≥3 components of fibrosis-like changes. To minimise inter-reader variability, a consensus meeting was held for sample cases before conducting further analyses.

Table 1 Baseline characteristics of the study population (at ICU admission)

Variables	Total	Fibrosis	No-fibrosis	P value*
Number of patients	64	35	29	
Age, years	58.2±13.7	60.5±11.4	55.4±15.9	0.144
Males	41 (64.1)	21 (60.0)	20 (69.0)	0.457
BMI, kg/m ²	26.3±5.4	25.4±3.9	27.3±6.6	0.160
Smoking history				
Never-smoker	43 (67.2)	27 (77.1)	16 (55.2)	0.273
Ex-smoker	7 (10.9)	2 (5.7)	5 (17.2)	
Current smoker	7 (10.9)	3 (8.6)	4 (13.8)	
Missing	7 (10.9)	3 (8.6)	4 (13.8)	
Alcohol drinking, yes	26 (40.6)	12 (34.3)	14 (48.3)	0.256
Diabetes mellitus, yes	21 (32.8)	15 (42.9)	6 (20.7)	0.060
Hypertension, yes	25 (39.1)	15 (42.9)	10 (34.5)	0.493
Cardiovascular disease, yes	8 (12.5)	5 (14.3)	3 (10.3)	0.635
Cerebrovascular disease, yes	3 (4.7)	3 (8.6)	0	–
Liver disease, yes	4 (6.3)	2 (5.7)	2 (6.9)	0.845
Kidney disease, yes	1 (1.6)	1 (2.9)	0	–
Malignancy, yes	4 (6.3)	2 (5.7)	2 (6.9)	0.845
Lung diseases, yes	3 (9.4)	1 (2.9)	2 (6.9)	0.585
Asthma	2 (3.2)	1 (2.9)	1 (3.5)	0.892
TB destroyed lung	1 (1.6)	0 (–)	1 (3.5)	–
Charlson Comorbidity Index ≥2	8 (12.5)	6 (17.1)	2 (6.9)	0.217

Data are expressed as number (%) or mean±SD unless otherwise indicated.

*P values were obtained by χ^2 test for categorical variable and by Mann-Whitney U test for continuous variable.

BMI, body mass index; ICU, intensive care unit; TB, tuberculosis.

The extent of pulmonary fibrosis was measured by computer-based analysis of high-resolution CT images using an automated quantification system for a more objective evaluation of the extent of fibrosis in patients with interstitial lung disease. GGO, mixed disease (MD), which the summation of field of reticulation and honey-combing, consolidation (CON) or total lung density (TLD: summation of the field of GGO, MD and CON) were scored (figure 2).

Statistical analyses

In this study, primary outcome was identifying the prevalence and risk factors of pulmonary fibrosis on chest CT at 1 month after hospital discharge. Descriptive statistics are presented as numbers (percentages) for categorical variables and mean±SD for continuous variables. We compared two groups (fibrosis and no-fibrosis groups) using the χ^2 or Fisher's exact test for categorical variables. The Mann-Whitney U test was used for the comparison of median and IQR for continuous variables between the two groups. The association between possible risk factors and pulmonary fibrosis was estimated using Cox proportional hazards analysis with crude and multivariable adjusted models. After including variables with p values of

<0.10 in the univariate model, as well as age, sex and BMI, adjusted HR (aHR) and 95% CIs were calculated in the multivariable analysis by enter methods after excluding selected variables showing collinearity in the model. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical package (V.9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

In this study, 64 patients were included, with a mean age of 58.2 years, and 64.1% of the patients were males. Median follow-up duration from the index date (enrolment) to the date of the CT was 60 days (IQR, 41–78 days). Mean SOFA and APACHE scores were 4.7 (SD, 2.9) and 13.6 (SD, 9.3), respectively. In terms of treatment after the ICU admission, about 90% of the patients were administered antiviral agents (remdesivir), and all the patients were administered steroid. 34 (53.1%) patients were placed in the prone position, 11 (17.2%) underwent ECMO support, followed by 6 (9.4%) who underwent CRRT.

Fibrosis-like changes were identified on chest CT: ≥1 in 49 patients (76.6%), ≥2 in 48 (75.0%) and ≥3 in 35

Table 2 Clinical and laboratory findings of the study population (at ICU admission)

Variables	Total	Fibrosis	No-fibrosis	P value
Number of patients	64	35	29	
Vital sign				
Systolic BP, mm Hg	129.8±27.3	129.6±5.1	130.1±24.7	0.944
Diastolic BP, mm Hg	74.2±17.2	73.7±18.4	74.9±15.8	0.785
Heart rate	89.6±23.5	85.6±25.3	94.6±20.3	0.129
Respiratory rate	26.0±6.0	25.4±6.5	26.6±5.3	0.443
Oxygen saturation, %	91.4±6.4	90.8±7.5	92.1±5.0	0.407
P/F ratio	102.4±50.7	103.9±54.8	100.0±44.8	0.778
Severity Assessment Score†				
SOFA score	4.7±2.9	5.1±3.0	4.3±2.8	0.203
APACHE score	13.6±9.3	15.1±10.9	11.7±6.1	0.139
Laboratory findings				
WBC 10 ³	9900±4460	10 740±4250	9000±4600	0.129
Lymphocyte, %	9.0±5.6	8.4±4.7	10.0±6.6	0.284
Neutrophil, %	85.8±7.2	87.1±6.4	84.1±7.9	0.114
ANC/μL	8470±4240	9010±4040	7800±4470	0.272
Haemoglobin, g/L	132.7±19.6	132.4±20.4	133.1±18.5	0.849
Platelet, 10 ³	238.4±106.9	250.4±121.5	223.9±85.7	0.318
AST, U/L	75.7±66.3	65.2±46.7	88.5±83.4	0.205
ALT, U/L	58.9±70.9	45.6±38.6	75.1±95.0	0.172
Total protein, g/dL	6.0±0.7	6.0±0.7	6.0±0.7	0.909
Albumin, g/dL	3.1±0.6	3.0±0.5	3.1±0.8	0.465
PT, sec	13.1±1.8	13.3±2.0	12.8±1.3	0.261
BUN, mg/dL	21.8±10.9	22.7±10.0	20.7±12.1	0.466
Creatinine, mg/dL	0.8±0.4	0.8±0.7	0.8±0.7	0.857
Sodium, mmol/L	136.9±5.4	136.7±6.2	137.1±4.4	0.738
Potassium, mmol/L	4.1±0.6	4.1±0.7	4.2±0.6	0.919
LDH, U/L	602.0±242.9	646.1±283.3	554.2±183.9	0.177
CRP, mg/L	11.2±10.2	12.1±10.6	10.1±9.7	0.461
Procalcitonin, ng/mL	1.3±5.5	1.0±3.4	1.7±7.3	0.660
Troponin, I ng/mL	0.4±1.9	0.6±2.7	0.1±0.3	0.294
D-dimer, μg/mL	2.2±3.5	2.1±3.0	2.4±4.0	0.842
Fibrinogen, mg/dL	535.9±202.6	544.1±221.5	524.1±176.1	0.719

Data are expressed as mean±SD and p values were tested by Mann-Whitney U test.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; APACHE, acute physiology and chronic health evaluation; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CRP, C reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; P/F ratio, PaO₂/FiO₂ (ratio of arterial oxygen partial pressure to fractional inspired oxygen); PT, prothrombin time; SOFA, sequential organ failure assessment; WBC, white blood cell.

(54.7%). When a fibrosis group was defined as patients with ≥3 fibrosis-like changes on chest CT, there was no significant difference in demographic characteristics and comorbidities between the fibrosis and no-fibrosis groups (table 1). Most laboratory and clinical findings at ICU admission and treatment were also not different between the two groups (tables 2 and 3). However, CRRT was performed more frequently in the no-fibrosis group

compared with that performed in the fibrosis group (17.2% vs 2.9%, p=0.05).

Radiological findings and lung function

The most frequent findings of fibrotic change were traction bronchiectasis (n=47, 73.4 %), followed by architectural distortion with or without parenchymal band

Table 3 Treatment of the study population (during ICU care)

Variables	Total	Fibrosis	No-fibrosis	P value
Number of patients	64	35	29	
Use of remdesivir	57 (89.1)	32 (91.4)	25 (86.2)	0.505
Duration, days	5.0 (5.0–10.0)	5.0 (5.0–10.0)	5.0 (5.0–10.0)	0.959
Use of steroid	64 (100.0)	35 (100.0)	29 (100.0)	1.000
Duration, days	6.0 (3.0–9.5)	6.0 (3.0–9.0)	6.0 (4.0–10.0)	0.347
Equivalent dose (dexamethasone)/day	6.0 (6.0–10.6)	6.0 (6.0–11.7)	6.0 (6.0–6.0)	0.635
Total equivalent dose	42.0 (22.0–60.0)	42.0 (20.0–60.0)	42.0 (24.0–60.0)	0.787
Use of antibiotics	63 (98.4)	34 (97.1)	29 (100.0)	0.547
Use of neuromuscular blocker	47 (73.4)	26 (74.3)	21 (72.4)	0.433
Duration, days	4.0 (3.0–7.0)	4.0 (3.0–7.0)	4.0 (3.0–6.0)	0.747
Use of monoclonal antibody	20 (31.3)	8 (22.9)	12 (41.4)	0.114
Tocilizumab	17 (85.0)	7 (87.5)	10 (83.3)	
Regdanvimab	2 (10.0)	1 (12.5)	1 (8.3)	
Basiliximab	1 (5.0)	0 (–)	1 (8.3)	
NO inhalation	9 (14.1)	5 (14.3)	4 (13.8)	0.955
Duration, days	5.0 (3.0–8.0)	5.0 (4.0–10.0)	4.5 (2.5–7.0)	0.623
Prone position	34 (53.1)	20 (57.1)	14 (48.3)	0.479
Duration, days	3.0 (2.0–4.0)	3.0 (2.0–3.5)	3.5 (3.0–6.0)	0.104
CRRT	6 (9.4)	1 (2.9)	5 (17.2)	0.054
Duration, days	11.5 (3.0–12.0)	12.0 (12.0–12.0)	11.0 (3.0–12.0)	0.768
ECMO	11 (17.2)	5 (14.3)	6 (20.7)	0.502
Duration, days	27.5 (9.0–62.0)	62.0 (8.0–64.0)	19.0 (17.0–36.0)	0.685

Data are expressed as number of patients (%) or median (IQR) unless otherwise indicated.

*P values were obtained by χ^2 test for categorical variable and by Mann-Whitney U test for continuous variable.

CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NO, nitric oxide.

(n=44, 68.8%) and reticulation (n=40, 62.5%) (table 4). The median extent of fibrosis (MD) was 10.6% (IQR, 3.8–40.7%), as measured by automatic quantification (table 5). The median extent of fibrosis was numerically higher in the fibrosis group (12.4% vs 4.4%, p=0.15) than that in the no-fibrosis group without statistical

significance; however, the extent of GGO was significantly higher in the fibrosis group (20.1% vs 14.0%, p=0.003) (table 5).

Pulmonary function test was performed in 27 (42.2%) of the 64 patients. The median follow-up duration from the index date to the date of the pulmonary function test was 147 days (IQR, 128–231 days). Both FVC and DLco were numerically lower in the fibrosis group than those in the no-fibrosis group without statistical significance (table 5).

Table 4 Visual assessment for chest CT in the study population

Variables	
Number of patients	64
Fibrosis-like change	
Reticulation	40 (62.5)
Architectural distortion±parenchymal band	44 (68.8)
Traction bronchiectasis/bronchiectasis	47 (73.4)
Honeycombing	11 (17.2)
Number of fibrosis-like change component ≥ 1	49 (76.6)
Number of fibrosis-like change component ≥ 2	48 (75.0)
Number of fibrosis-like change component ≥ 3	35 (54.7)
Data are expressed as number (%).	

Risk factors for post-COVID-19 pulmonary fibrosis

12 variables (hypertension and cardiovascular disease, SOFA score, respiratory rate, serum level of white blood cells, blood urea nitrogen (BUN) and creatinine, and use of neuromuscular blockers and ECMO) that were associated with pulmonary fibrotic changes in the univariate Cox analysis with a p value of <0.10 (online supplemental table 1) were selected as candidate variables in the multi-variable analysis, along with age, sex and BMI.

In the multivariable Cox analysis, males (aHR, 3.14; 95% CI, 1.08 to 9.14) and higher SOFA score (aHR, 1.18; 95% CI, 1.02 to 1.37) were independently associated with

Table 5 Automatic quantification for chest CT images and lung function in the study population

Variables	Total	No-fibrosis	Fibrosis	
Number of patients	64	29	35	
Automatic quantification				p value
GGO, %	18.9 (13.2–24.9)	14.0 (11.1–20.1)	20.1 (16.2–26.9)	0.003
Mixed disease, %	10.6 (3.8–40.7)	4.4 (1.4–47.6)	12.4 (6.6–36.2)	0.149
Consolidation, %	0.1 (0.00.5)	0.1 (0.0–0.9)	0.1 (0.1–0.3)	0.977
TLD, %	40.5 (20.864.4)	28.5 (15.6–66.5)	42.5 (25.7–60.2)	0.373
Variables	Total	No-fibrosis	Fibrosis	
Number of patients	27	11	16	
Pulmonary function test				p value
FVC % predicted	74.0 (60.0–82.0)	79.0 (71.0–90.0)	70.5 (60.0–76.5)	0.108
DLco % predicted	62.0 (46.0–71.0)	69.0 (61.0–83.0)	55.0 (41.0–67.0)	0.069

Data are expressed as median(IQR) and p values were tested by Mann-Whitney U test.
DLco, diffusing capacity; FVC, forced vital capacity; GGO, ground glass opacity; TLD, total lung density.

lung fibrosis (table 6 and figure 3). Additionally, higher levels of serum BUN ≥ 19 had higher risk of pulmonary fibrosis (aHR, 2.69; 95% CI, 1.20 to 7.25, $p=0.05$), with marginal significance in the final model.

DISCUSSION

This multicentre study found risk factors, including various clinical characteristics for pulmonary fibrosis in patients with COVID-19 pneumonia requiring mechanical ventilation. About half of the patients (54.7%) had significant fibrosis, and male sex and higher SOFA scores at ICU admission were found to be risk factors for fibrotic changes. To our knowledge, this is the first study

to explore pulmonary fibrosis in patients with severe COVID-19 pneumonia requiring mechanical ventilation.

In this study, 54.7% of the patients had significant pulmonary fibrosis (≥ 3 fibrosis-like changes on chest CT), which was similar to previous studies.^{7 22 23} The prevalence of pulmonary fibrotic changes in patients with COVID-19 following ICU admission has been reported to range between 30% and 70%.^{22 24–26} A study by Huang *et al* reported that 41 (50.6%) of 81 survivors of severe COVID-19 pneumonia had fibrosis on CT after hospital discharge.²² In another study by Han *et al*, which assessed pulmonary sequelae and the risk factor for lung fibrotic-like changes in survivors of severe COVID-19 pneumonia,

Table 6 Cox analysis of risk factors for pulmonary fibrosis in the study population

Variables	Crude HR (95% CI)	P value	Adjusted HR (95% CI) *	P value
Age, year	1.04 (1.01 to 1.07)	0.024	1.01 (0.96 to 1.06)	0.758
Male	1.41 (0.71 to 2.79)	0.324	3.14 (1.08 to 9.14)	0.036
BMI, kg/m ²	0.97 (0.90 to 1.05)	0.487	1.02 (0.91 to 1.14)	0.727
Hypertension, yes	2.05 (1.00 to 4.18)	0.049	1.70 (0.66 to 4.36)	0.271
Cardiovascular disease, yes	2.72 (1.01 to 7.34)	0.048	2.45 (0.77 to 7.77)	0.129
Respiratory rate, /min [†]	0.93 (0.87 to 0.98)	0.013		
SOFA score, 1-point increase	1.15 (1.04 to 1.27)	0.008	1.18 (1.02 to 1.37)	0.028
WBC $\geq 12\,000$, /mm ³	2.09 (1.00 to 4.38)	0.051	0.91 (0.35 to 2.36)	0.843
BUN ≥ 19 , mg/dL	2.57 (1.26 to 5.24)	0.008	2.69 (0.99 to 7.33)	0.053
Creatinine >1.4 , mg/dL [†]	2.76 (0.95 to 8.05)	0.098		
Use of neuromuscular blocker, yes	0.29 (0.12 to 0.68)	0.005	0.39 (0.12 to 1.30)	0.124
ECMO, yes	0.41 (0.16 to 1.08)	0.069	0.42 (0.11 to 1.62)	0.206

*All variables were included in the multivariable model.

†Respiratory rate and serum creatinine level which were parameters included in SOFA score were excluded in the final model due to their collinearity with SOFA score (variance inflation factor 0.96 for respiratory rate and 0.67 for serum creatinine level, respectively).

BMI, body mass index; BUN, blood urea nitrogen; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; WBC, white blood cell.

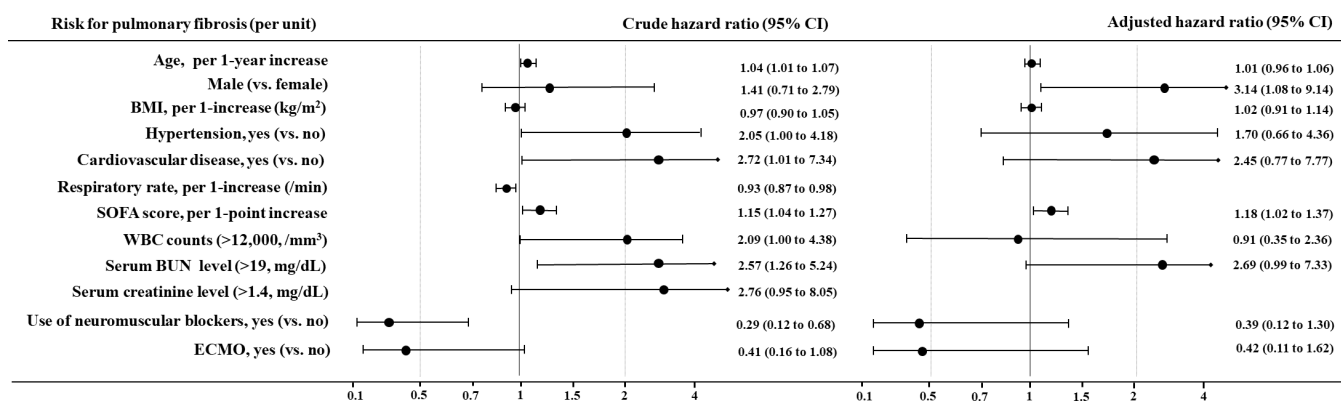


Figure 3 Forest plot of HRs for risk factors for pulmonary fibrosis. BMI, Body Mass Index; WBC, white blood cell; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation.

40 (35.1%) of 114 patients showed fibrosis-like changes.²⁴ Additionally, in a prospective study by Caruso *et al*, they found that 72% (85 of 118) of patients with COVID-19 pneumonia had fibrosis-like changes on CT.²⁶ However, the definition and terminology of fibrosis, such as fibrosis-like changes, fibrotic-like changes or fibrosis,^{25–27} has been inconsistent in previous studies. Additionally, fibrosis-like changes at baseline CT improved on follow-up CT,^{6, 28} suggesting that some of the initial fibrosis may be transient. Authors in previous studies argued that the ground-glass attenuation on CT is likely to reflect inflammatory disease and this lesion was not true fibrosis after COVID-19 infection. However, initial CT score including the extent of ground glass and the total extent of disease at 6 months was the CT features correlating most strongly with the extent of fibrotic-like abnormalities at 6 months.²⁷ Histological and clinical significance of the radiological fibrosis-like change in early CT finding is also not clearly denied. Therefore, to overcome this limitation, we used strict criteria to define fibrosis in this study.

The SOFA score on the day of admission to the ICU was a predictive factor for pulmonary fibrosis in our study. In a previous study that prospectively enrolled survivors of COVID-19 pneumonia requiring oxygen supplement, the SOFA score at admission was linearly associated with the risk of fibrosis-like changes.²⁹ However, in this study, the risk of patients (about 40% of survivors) requiring mechanical ventilation was not explored. As a component of the SOFA score, lower PaO₂/FiO₂ ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) was suggested as a predictive factor of lung fibrosis in patients with COVID-19 infection patient in previous studies.^{7, 15, 30} The other components of the SOFA score, including acute kidney injury and liver disease, which were reported to be associated with patients with severe COVID-19 pneumonia requiring ICU care in previous studies have been reported as predictive factors for pulmonary fibrosis.^{31, 32} Additionally, previous studies reported hypertension and cardiovascular disease as risk factors associated with pulmonary fibrosis development; however, no significant association was found after

further adjustment for clinical and laboratory parameters.^{33, 34} In our study, cardiovascular disease was not a predictive factor for pulmonary fibrosis in the final multivariate analysis.

Our findings suggested that male sex was associated with pulmonary fibrosis after COVID-19 pneumonia, which was not consistently found in previous studies. Some studies reported that males were more likely to present with COVID-19 pulmonary fibrosis,^{34, 35} although others did not show any significant result.^{8, 30, 33} However, a meta-analysis reported that males had higher mortality after COVID-19 than females.³⁶ Given the sex difference in the risk of idiopathic pulmonary fibrosis, in this study, the higher risk of pulmonary fibrosis after COVID-19 infection found in males seems possible, but further studies are needed to confirm the association.

Higher level of serum BUN has been suggested as an indicator for poor prognosis of pneumonia³⁷ and was independently associated with mortality of critically ill patients, regardless of creatinine level.^{38, 39} In COVID-19 pneumonia, one retrospective cohort study reported that initial BUN and D-dimer levels were associated with mortality in COVID-19 patients with high predictive value (c-index, 0.94).⁴⁰ However, since studies have rarely explored the association of BUN and development of pulmonary fibrosis, future longitudinal studies should be performed to find the association with pulmonary fibrosis in COVID-19 infection.

An antiviral therapy, an anti-inflammatory therapy (corticosteroids) and supportive care are the main cornerstone of COVID-19 pneumonia treatment. In addition to that basic treatment, for severe COVID-19 patients requiring mechanical ventilation care, treatment including ECMO may be necessary, and research on this is ongoing.^{41, 42} In our study, approximately 17.2% received this treatment, but there was no statistically significant difference in fibrosis. Additionally, antifibrotics not yet approved for routine treatment of COVID-19 were not included in this study.⁴³

This study has some limitations. First, the number of patients included in this study was relatively small, which may have limited the ability to generate statistically

significant results. Nevertheless, in our study, the multivariate analysis allowed us to identify significant risk factors associated with the development of pulmonary fibrosis after COVID-19 pneumonia. Second, this study did not collect baseline CT images; thus, it did not completely exclude patients with pre-existing fibrosis. However, we excluded patients with a history of pre-existing pulmonary fibrosis by taking a detailed medical history. Third, the follow-up CTs were performed within a relatively short period of time, and the prevalence of pulmonary fibrosis at long-term follow-up may differ. Therefore, we used a stricter definition of pulmonary fibrosis in this study to reduce differences. Nevertheless, the strength of our study is that it was a multicentre prospective study, it focused on patients with severe COVID-19 requiring mechanical ventilation and analysed fibrotic changes by both visual assessment and automated quantification of CTs.

In conclusion, our findings suggest that in patients with severe COVID-19 pneumonia requiring mechanical ventilation, 54.7% have significant pulmonary fibrosis, and male sex and higher SOFA scores indicate an increased risk of pulmonary fibrosis.

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