

Clinical characteristics and outcomes of post-COVID-19 pulmonary fibrosis

A case-control study

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Abstract

The development of pulmonary fibrosis is a rare complication of the novel coronavirus disease 2019 (COVID-19). Limited information is available in the literature about that, and the present study aimed to address this gap.

This case-control study included 64 patients with post-COVID-19 pulmonary fibrosis who were hospitalized for COVID-19.

The percentage of patients aged ≥ 65 years (44%) who demised was higher than those who survived (25%). Male patients (62%) had higher mortality than female patients (37%). The most frequently reported clinical symptoms were shortness of breath (98%), cough (91%), and fever (70%). Most COVID-19 patients with pulmonary fibrosis (81%) were admitted to an intensive care unit (ICU), and 63% required mechanical ventilation. Bilateral lung infiltrates (94%), “ground glass” opacity (91%), “honeycomb” lung (25%), and pulmonary consolidation (9%) were commonly identified in COVID-19 patients with pulmonary fibrosis who survived. The findings for computed tomography and dyspnea scale were significantly higher in severe cases admitted to the ICU who required mechanical ventilation. A higher computerized tomography score also correlated significantly with a longer duration of stay in hospital and a higher degree of dyspnea. Half of the COVID-19 patients with pulmonary fibrosis (50%) who survived required oxygen therapy, and those with “honeycomb” lung required long-term oxygen therapy to a far greater extent than others. Cox regression revealed that smoking and asthma were significantly associated with ICU admission and the risk of mortality.

Post-COVID-19 pulmonary fibrosis is a severe complication that leads to permanent lung damage or death.

Abbreviations: ARDS = acute respiratory distress syndrome, BMI = body mass index, CIs = confidence intervals, COVID-19 = coronavirus disease 2019, CT = computerized tomography, HRs = hazard ratios, ICU = intensive care unit, ILD = interstitial lung disease, SD = standard deviation.

Keywords: acute respiratory syndrome coronavirus 2, coronavirus disease 2019, lung fibrosis, pulmonary fibrosis

1. Introduction

Pulmonary fibrosis is an interstitial lung disease (ILD) that is characterized by progressive scarring of the lung tissue, impacting lung function, and leading to impaired gas exchange and

difficulty breathing.^[1] Currently, the incidence of pulmonary fibrosis is increasing significantly.^[2] The development of pulmonary fibrosis is associated with many risk factors, such as aging, smoking, genetic predisposition, and exposure to occupational dust and asbestos.^[3] The risk of mortality is increased in patients with pulmonary fibrosis owing to a lack of effective therapies to halt disease progression.^[4] Pulmonary fibrosis has been linked to viral pneumonia, such as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, it is thought to be uncommon.^[5,6] COVID-19 may cause atypical pneumonia that progresses to acute lung injury and acute respiratory distress syndrome (ARDS). The symptoms associated with COVID-19 range from mild upper respiratory tract involvement to severe ARDS requiring long-term oxygen therapy due to pulmonary fibrosis.^[7] The risk of mortality in COVID-19 patients with pulmonary fibrosis increases as pulmonary fibrosis is a progressive disease that leads to respiratory failure and is associated with a poor prognosis; lung transplantation is the only treatment demonstrated to improve outcomes.^[8] To the best of our knowledge, very few published papers have reported on the clinical characteristics of patients with post-COVID-19 pulmonary fibrosis^[9–11]; thus, there is a need to increase the available evidence in this regard, particularly in Saudi Arabia whose population has different culture, genetic, and ethnic factors. In addition, the clinical characteristics of patients with post-COVID-19 pulmonary fibrosis in Jazan Province, Saudi Arabia,

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

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have not yet been evaluated. Thus, the current study aimed to address this gap with assessment of clinical characteristics and outcomes of post-COVID-19 pulmonary fibrosis among hospitalized Saudi patients in Jazan, Saudi Arabia.

2. Methodology

2.1. Study design and setting

Jazan Region, located in southwestern Saudi Arabia, is characterized by a relatively homogenous population with similar ethnic and socioeconomic characteristics.^[12–14] This case-control study included 64 patients who were hospitalized for COVID-19 between June 1, 2020 and October 31, 2020, at King Fahad Central Hospital, Jazan Province, Saudi Arabia. The 64 patients who were hospitalized during the mentioned period, developed pulmonary fibrosis post-COVID-19. We distributed them as 32 survived patients (as cases) matched with 32 deceased patients (as controls), with a ratio 1:1 as we interested to assess clinical characteristics of post-COVID-19 pulmonary fibrosis between the survived and deceased patients rather than assessing the mortality rate. Survived patients were followed-up for 6 months. Because of the development of pulmonary fibrosis post-COVID-19 is rare, we included only 64 patients during a specific period, and this could be a limitation of sample size.

Following the guidelines of the Saudi Center for Disease Prevention and Control,^[15] a diagnosis of COVID-19 was confirmed by the identification of viral RNA in nasopharyngeal swab samples using real-time reverse transcription polymerase chain reaction (LightCycler 480 Instrument II, Roche). The Jazan Health Ethics Committee (reference number H-10-Z-073) granted ethical approval (no. 2047) for the study to be conducted. The research complied with the Declaration of Helsinki. Consent was waived as the data were anonymous and collected retrospectively (secondary data).

2.2. Data collection

The data were collected retrospectively from medical records and included information about the patients' age, sex, smoking history, comorbidities, clinical symptoms, laboratory test results, radiological findings, need for intensive care unit (ICU) admission, need for mechanical ventilation support, hospitalization duration, development of complications, and outcomes (recovery or death). Major comorbidities and chronic diseases included diabetes, hypertension, cardiovascular disease, kidney disease, obesity, tuberculosis, chronic obstructive pulmonary disease, and asthma. The most prevalent clinical symptoms of COVID-19 were fever, cough, sputum, hemoptysis, dyspnea, chest pain, diarrhea, and loss of smell. Laboratory tests were performed to assess the complete blood count, c-reactive protein, erythrocytes sedimentation rate, d-dimer, ferritin levels. The radiological investigations included chest X-ray and a computerized tomography (CT) scan. The dates of COVID-19 diagnosis, hospital admission, and death were also recorded. Disease severity was categorized according to the World Health Organization guidelines.^[16] Severe cases were defined as those with oxygen saturation of $\leq 90\%$, a respiratory rate of ≥ 30 breaths per minute, and signs of severe respiratory distress. The survival time during hospitalization (i.e., the hospitalization duration) was defined as the period between hospital admission and recovery or death. The disease duration (in days) was defined

as the period between the manifestation of clinical symptoms of COVID-19 and recovery or death. The criteria for recovery were based on the guidelines of the Ministry of Health, Saudi Arabia. Recovery was considered to have occurred when at least 3 days had passed after the resolution of fever and respiratory symptoms along with 2 negative polymerase chain reaction results obtained ≥ 24 hours apart; alternatively, at least 10 days had to have passed since symptom onset.^[17]

2.3. Inclusion and exclusion criteria

This study included patients who developed pulmonary fibrosis after testing positive for COVID-19. A diagnosis of lung fibrosis was made based on persistent respiratory symptoms following the initial recovery phase of acute infection (defined as 4 weeks after the onset of infection) with ILD using high-resolution CT and no previous history of ILD.^[18] Pregnant women and patients with a previous history of ILD were excluded from the study.

2.4. Chest CT scan

With the patients in the supine position, CT of the chest was performed without intravenous contrast using a 64-channel multidetector CT scanner (Siemens Medical Solutions, Forchheim, Germany) (i.e., an Aquilion scanner with 4×1 mm collimation [120 kV]). The transverse images were reconstructed to 0.55 to 0.75 mm. A CT scan was carried out at discharge and at the first, third, and sixth months after discharge for survived patients. The CT score was calculated to evaluate the degree of lung involvement in patients at discharge and follow-up.^[19] The score was determined by dividing the lung into 5 lung lobes; each affected lobe was scored on a scale of 0 to 5, with 0, 1, 2, 3, 4, and 5 indicating no involvement, $<5\%$ involvement, 5% to 25% involvement, 26% to 49% involvement, 50% to 75% involvement, and $>75\%$ involvement, respectively. The total CT score was the sum of the lobar scores, and it ranged from 0 to 25. The CT images were reviewed by a radiologist who was blinded to the current study.

2.5. Management plan

The patients with COVID-19 were managed according to the COVID-19 protocol approved by the Saudi Ministry of Health.^[20] The patients with post-COVID pulmonary fibrosis were discharged and prescribed oral prednisolone (1 mg/kg for 2 weeks) with gradual tapering, inhaled corticosteroids, anti-coagulants, and vitamins.

2.6. Data analysis

Data entry and analysis were performed using the Statistical Package for the Social Sciences software. Categorical variables are presented as percentages, while continuous variables are presented as the mean \pm standard deviation (SD) for normally distributed variables and as the mean \pm standard error of the mean for non-normally distributed variables. The chi-square test was used to detect any significant associations between categorical variables. Correlation between 2 continuous variables was assessed using Pearson correlation coefficient. The independent samples *t* test and Mann–Whitney *U* test were used to compare the differences in mean values of normal and non-normal variables, respectively, between groups (adjusted for sex,

age, and body mass index [BMI]). The paired sample *t* test used to determine the mean difference between 2 measurements at 2 different times (pre- and post). Cox regression analyses were used to determine hazard ratios (HRs) for the outcomes with 95% confidence intervals (CIs) and adjusted age, sex, BMI. Significance was set at $P < .05$.

3. Results

3.1. Demographic characteristics and comorbidities

Table 1 shows the demographic characteristics and comorbidities of COVID-19 patients with pulmonary fibrosis stratified according to sex and survival status. The percentage of patients aged ≥ 65 years (44%) who demised was higher than that of those who survived (25%). However, a significant association was not identified between age and mortality risk in COVID-19 patients with pulmonary fibrosis ($P = .204$) (Table 1). The mean age of the overall study population was 59 ± 13.7 years (a range of 23–89 years). The mean age of the surviving patients was 56 years ($SD = 11.2$) and that of deceased patients, 62 years ($SD = 15.5$). The

Table 1
Demographic characteristics and comorbidities of COVID-19 patients with pulmonary fibrosis.

Variables	Overall (N=64)	Survived (N=32)	Deceased (N=32)	P
Age				
23–45	7 (10.9%)	5 (15.6%)	2 (6.2%)	.204
46–64	35 (54.7%)	19 (59.4%)	16 (50.0%)	
65–89	22 (34.4%)	8 (25.0%)	14 (43.8%)	
Sex				
Male	46 (71.9%)	26 (81.2%)	20 (62.5%)	.095
Female	18 (28.1%)	6 (18.8%)	12 (37.5%)	
Smoking				
Non-smoker	40 (66.7%)	28 (87.5%)	12 (37.5%)	<.001*
X-smoker	8 (13.3%)	0	8 (25.0%)	
Smoker	12 (20.0)	4 (12.5%)	12 (37.5%)	
Diabetes				
No	22 (34.4%)	12 (37.5%)	10 (31.2%)	.599
Yes	42 (65.6%)	20 (62.5%)	22 (68.8%)	
Hypertension				
No	22 (34.4%)	12 (37.5%)	10 (31.2%)	.599
Yes	42 (65.6%)	20 (62.5%)	22 (68.8%)	
Obesity				
No	37 (57.8%)	19 (59.4%)	18 (56.2%)	.802
Yes	27 (42.2%)	13 (40.6%)	14 (43.8%)	
Heart disease				
No	58 (90.6%)	28 (87.5%)	30 (93.8%)	.391
Yes	6 (9.4%)	4 (12.5%)	2 (6.2%)	
Kidney disease				
No	62 (96.9%)	32 (100.0%)	30 (93.8%)	.151
Yes	2 (3.1%)	0	2 (6.2%)	
Asthma				
No	54 (84.4%)	32 (100.0%)	22 (68.8%)	.001*
Yes	10 (15.6%)	0	10 (31.2%)	
Tuberculosis				
No	63 (98.4%)	31 (96.9%)	32 (100.0%)	.313
Yes	1 (1.6%)	1 (3.1%)	0	
COPD†				
No	63 (98.4%)	31 (96.9%)	32 (100.0%)	.313
Yes	1 (1.6%)	1 (3.1%)	0	

* Significant results (P value $< .05$).

† Chronic obstructive pulmonary disease.

proportion of male COVID-19 patients with pulmonary fibrosis (72%) was higher than that of the female patients (28%). In addition, a higher number of male patients (62%), compared with female patients (37%), died of COVID-19 (Table 1). Smoking was significantly associated with an increased risk of mortality in COVID-19 patients with pulmonary fibrosis ($P < .001$) (Table 1). The most common comorbidities identified were hypertension (66%), diabetes mellitus (66%), obesity (42%), asthma (15%), heart disease (10%), kidney disease (3%), tuberculosis (2%), and chronic obstructive pulmonary disease (2%). Mortality in COVID-19 patients with pulmonary fibrosis and asthma was more than double that in COVID-19 patients with other comorbidities (odds ratio=2.5, $P = .001$) (Table 1).

3.2. Clinical characteristics and duration of stay in hospital

The most frequently reported clinical symptoms in COVID-19 patients with pulmonary fibrosis on admission were shortness of breath (98%), cough (91%), fever (70%), sputum (19%), and chest pain (16%); a small percentage of patients reported having diarrhea (6%) and a loss of smell (3%) (Table 2). Most COVID-19 patients with pulmonary fibrosis (81%) were admitted to ICU, and 19% were admitted to an isolation room in the general medical ward (Table 2). Sixty-three per cent and 22% of admitted COVID-19 patients with pulmonary fibrosis required mechanical ventilation and high-flow nasal cannula, respectively. All deceased patients (100%) were admitted to ICU and intubated (Table 2). The median duration between hospital admission and recovery was 20 days, while the median duration from hospital admission to death was 18 days. Fifty-six per cent of COVID-19 patients with pulmonary fibrosis did not have associated complications. In those who did, significant complications included respiratory failure (94%), sepsis (56%), and acute kidney injury (44%), which led to death ($P < .001$).

3.3. Clinical laboratory findings

The clinical laboratory findings of COVID-19 patients with pulmonary fibrosis on admission are depicted in Table 3. Hemoglobin concentration was significantly lower in patients

Table 2
Clinical symptoms and signs of COVID-19 patients with pulmonary fibrosis.

Symptoms and signs	Overall (N=64)	Survived (N=32)	Deceased (N=32)	P
Difficulty breathing	63 (98.4%)	31 (96.9%)	32 (100%)	.313
Cough	58 (90.6%)	30 (93.8%)	28 (87.5%)	.391
Sputum	12 (18.8%)	12 (37.5%)	0	<.001*
Hemoptysis	1 (1.6%)	1 (3.1%)	0	.313
Fever	45 (70.3%)	21 (65.6%)	24 (75.0%)	.412
Chest pain	10 (15.6%)	6 (18.8%)	4 (12.5%)	.491
Diarrhea	4 (6.2%)	2 (6.2%)	2 (6.2%)	.999
Loss of smell	2 (3.1%)	2 (6.2%)	0	.151
Low SpO2 (<95%)	42 (65.6%)	18 (56.2%)	24 (75.0%)	.114
PaO2/FiO2 (<100)	32 (50.0%)	13 (40.6%)	19 (59.4%)	.251
Isolation ward admission	12 (18.8%)	12 (37.5%)	0	<.001*
ICU admission†	52 (81.2%)	20 (62.5%)	32 (100%)	<.001*
Mechanical ventilation	40 (62.5%)	8 (25.0%)	32 (100%)	<.001*
High flow nasal cannula	14 (21.9%)	14 (43.8%)	0	<.001*

* Significant results (P value $< .05$).

† Intensive care unit.

Table 3
Clinical laboratory findings adjusted for age, sex, and BMI.

Lab Test	Overall (N=64)	Survived (N=32)	Deceased (N=32)	P
Hemoglobin, mmol/L	12.6±1.8	12.4±1.8	8.9±2.9	<.001*
White blood cell (×10 ⁹ /L)	8.2±4.2	8.1±4.0	22.3±11.5	<.001*
Neutrophils (%)	6.6±4.1	6.3±4.1	85.6±9.1	<.001*
Lymphocytes (%)	1.6±2.1	1.9±2.8	9.7±10.1	<.001*
C-reactive protein, mg/L	7.6±5.1	8.2±6.4	4.9±5.1	.149
ESR [†] , mm/h	75.2±31.3	76.1±30.4	64.7±63.9	.552
D-dimer, mcg/mL	3.1±7.5	2.7±6.5	7.6±6.4	.008*
Serum ferritin, pmol/L	753±696	738±658	1674±1860	.027*

* Significant results (*P* value <.05).

[†] Erythrocyte sedimentation rate.

who later died compared with those who recovered. Compared with survivors, leukocytosis and neutrophilia concentrations were higher in patients who later demised (Table 3). In addition, levels of D-dimer and ferritin were higher in patients who later died compared with those who recovered (Table 3).

3.4. Radiological findings and dyspnea degree in recovered patients

The CT scans and chest X-rays revealed bilateral lung infiltrates in most of the COVID-19 patients with pulmonary fibrosis who recovered (94%). “Ground glass” opacity (91%), “honeycomb” lung (25%), and pulmonary consolidation (9%) were observed on the CT scans of these patients.

The overall mean CT scores of the patients at discharge and at the 6-month follow-ups were 12.9 and 2.4, respectively. At the 6-month follow-up (Table 4), the CT score was significantly higher in patients with “ground glass” opacity, “honeycomb” lung, and pulmonary consolidation (*P*=.036, *P*<.001, and *P*<.001, respectively) (Table 4). The CT scores at discharge and at the 6-month follow-up were significantly higher for severe cases admitted to the ICU and those requiring mechanical ventilation, compared with patients in the medical ward (*P*<.001 and *P*=.010, respectively) (Table 4). Associations between the CT scores at discharge and other variables, such as length of hospital stay, dyspnea scale, and the laboratory findings, were also evaluated. Higher CT scores were demonstrated to significantly correlate with a lengthy stay in hospital (*P*=.029, *r*=0.393) and a greater degree of dyspnea (*P*=.001, *r*=0.578); however, an association was not found between the CT scores and the laboratory findings.

The overall mean dyspnea scales for recovered patients at discharge and at the 6-month follow-up were 2.8 and 1.1, respectively. The mean dyspnea scale at 6 months was significantly higher in patients with bilateral lung infiltrates and “honeycomb” lung (*P*=.002 and *P*=.048, respectively) (Table 5). The dyspnea scales at discharge were also significantly higher in severe cases admitted to the ICU, compared with those admitted to the medical ward (*P*=.025) (Table 5). Typically, patients with a high degree of dyspnea at discharge required long-term oxygen therapy (*P*=.024) (Table 5). Half of the COVID-19 patients with pulmonary fibrosis (50%) who recovered required oxygen therapy, and those with “honeycomb” lung required long-term oxygen therapy to a considerably greater extent than others (*P*<.01).

Table 4
CT scores in survived COVID-19 patients with pulmonary fibrosis during follow up.

Variable	CT score (mean±SD)			
	At discharge	1st month	3rd month	6th month
Bilateral lung infiltrations				
No	11.1±2.5	6.5±1.8	2.8±1.2	1.6±0.8
Yes	13.8±1.1	8.2±0.8	3.5±0.8	2.6±0.5
<i>P</i> [†]	.272	.367	.684	.414
Ground-glass opacity				
No	12.7±1.0	7.7±0.8	3.0±0.7	2.0±0.4
Yes	18.7±2.9	9.3±1.8	7.0±2.1	5.3±2.7
<i>P</i> [†]	.081	.522	.068	.036*
Honeycomb				
No	12.4±1.3	6.7±0.8	2.0±0.6	1.3±0.4
Yes	15.9±0.7	11.4±0.8	7.3±0.8	5.6±0.7
<i>P</i> [†]	.132	.003*	<.001*	<.001*
Consolidation				
No	12.9±1.1	7.5±0.8	2.8±0.6	1.8±0.4
Yes	16.3±1.2	11.3±0.7	9.3±.07	7.3±0.7
<i>P</i> [†]	.329	.123	.001*	<.001*
ICU admission				
No	9.0±1.6	4.6±0.6	1.5±0.6	0.7±0.5
Yes	15.8±0.9	9.9±0.8	4.6±0.9	3.3±0.6
<i>P</i> [†]	<.001*	<.001*	.018*	.01*
Mechanical ventilation				
No	11.8±1.1	6.8±0.7	2.5±0.6	1.6±0.4
Yes	17.6±1.3	11.7±1.5	6.4±1.5	4.6±1.0
<i>P</i> [†]	.009*	.003*	.009*	.003*
High flow nasal canula				
No	12.8±1.5	7.5±1.1	3.2±0.9	2.4±0.7
Yes	13.8±1.2	8.4±0.9	3.3±0.9	2.3±0.6
<i>P</i> [†]	.644	.542	.890	.917
Long term oxygen therapy				
No	12.1±1.5	6.1±0.8	2.0±0.8	1.6±0.5
Yes	14.6±1.3	9.6±1.1	4.7±0.9	3.1±0.7
<i>P</i> [†]	.210	.014*	.037*	.054

* Significant results (*P* value <.05).

[†] *P* value of independent sample *t* test.

3.5. Predictors of ICU admission and mortality risk using Cox regression analysis

The multivariate Cox proportional hazards regression model revealed statistically significant findings (*P*<.001); it is provided in Table 6. It revealed that the mortality risk increased with smoking (HR 2.8 [95% CI 1.6–4.9]; *P*<.001) and that the risk was significantly more than twofold higher in smoker patients than in non-smokers (Table 6). The mortality risk in COVID-19 patients with pulmonary fibrosis and asthma was more than threefold higher than that in the others (HR 3.1 [95% CI 1.0–9.4]; *P*=.001) (Table 6). Obesity (HR 1.1 [95% CI 1.0–1.2]; *P*=.012) was also significant risk factors associated with mortality in COVID-19 patients with pulmonary fibrosis (Table 6). The mortality risk was notably higher in patients who developed sepsis (HR 2.3 [95% CI 1.2–4.7]; *P*=.017) and acute kidney injury (HR 4.7 [95% CI 2.2–9.9]; *P*=.001); these patients had a 2.3- and 4.5-fold higher mortality risk respectively than those without any complications (Table 6). Smoking (HR 1.5 [95% CI 1.0–2.1]; *P*=.026), asthma (HR 2.7 [95% CI 1.1–6.7]; *P*=.033), and acute kidney injury (HR 3.2 [95% CI 1.6–6.8]; *P*=.012) were also significant risk factors associated with ICU admission in COVID-19 patients with pulmonary fibrosis (Table 6).

Table 5
Dyspnea scores in survived COVID-19 patients with pulmonary fibrosis during follow up.

Variable	Dypnea score (mean ± SD)			
	At discharge	1st month	3rd month	6th month
Bilateral lung infiltrations				
No	2.8 ± 0.1	1.9 ± 0.1	1.5 ± 0.1	1.0 ± 0.1
Yes	2.8 ± 0.1	2.2 ± 0.2	1.5 ± 0.2	1.3 ± 0.2
<i>P</i> [†]	.946	.086	.850	.002*
Ground-glass opacity				
No	2.8 ± 0.1	2.0 ± 0.1	1.3 ± 0.3	1.0 ± 0.1
Yes	3.0 ± 0.1	2.0 ± 0.1	1.6 ± 0.1	1.1 ± 0.1
<i>P</i> [†]	.419	.998	.476	.554
Honeycomb				
No	2.8 ± 0.1	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.1
Yes	3.0 ± .01	2.1 ± 0.1	1.9 ± .01	1.3 ± 0.2
<i>P</i> [†]	.142	.122	.022*	.048*
Consolidation				
No	2.8 ± 0.1	2.0 ± 0.3	1.5 ± 0.1	1.1 ± 0.1
Yes	3.0 ± .01	2.0 ± 0.1	2.0 ± .01	1.1 ± 0.1
<i>P</i> [†]	.419	.928	.094	.398
ICU admission				
No	2.6 ± 0.1	1.9 ± 0.1	1.3 ± 0.2	1.1 ± 0.1
Yes	2.9 ± 0.2	2.1 ± 0.1	1.6 ± 0.1	1.1 ± 0.1
<i>P</i> [†]	.025*	.147	.150	.599
Mechanical ventilation				
No	2.8 ± 0.1	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.1
Yes	3.0 ± 0.1	2.1 ± 0.1	1.9 ± 0.1	1.1 ± 0.1
<i>P</i> [†]	.142	.122	.229	.738
High flow nasal canula				
No	2.8 ± 0.1	2.0 ± 0.1	1.5 ± 0.1	1.1 ± 0.1
Yes	2.9 ± 0.1	2.0 ± 0.1	1.5 ± 0.2	1.1 ± 0.1
<i>P</i> [†]	.283	.917	.754	.971
Long term oxygen therapy				
No	2.7 ± 0.1	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.1
Yes	2.9 ± 0.1	2.1 ± 0.1	1.7 ± 0.1	1.2 ± 0.1
<i>P</i> [†]	.024*	.168	.061	.370

* Significant results (*P* value < .05).
[†] *P* value of independent sample *t* test.

4. Discussion

The development of pulmonary fibrosis is a rare complication of COVID-19. The objective of the current study was to address the

gap in knowledge regarding the clinical characteristics and outcomes of patients who developed pulmonary fibrosis after infection with COVID-19 and hospitalized at King Fahad Central Hospital, Jazan Province, Saudi Arabia.

Advanced age was identified as a significant risk factor for the development of pulmonary fibrosis post-COVID-19.^[21] Similarly, a finding of pulmonary fibrosis correlated with age in cases of severe acute respiratory syndrome. In the current study, recovered COVID-19 patients with pulmonary fibrosis had a mean age of 56 years, and the deceased patients had a mean age of 62 years. In previous studies,^[22,23] it was established that elderly patients with viral pneumonia, including Middle East Respiratory Syndrome and COVID-19, were more likely to develop pulmonary fibrosis. In addition, old age has been confirmed to be associated with poor outcomes in COVID-19 patients.^[24] With advanced age, cell-mediated immunity and the humoral immune response decrease, and this can result in poor control of viral replication and extensive inflammatory responses, potentially leading to poor outcomes.^[25,26]

In the current study, a greater proportion of male COVID-19 patients had pulmonary fibrosis (72%) compared with female patients (28%). In addition, a higher number of male patients (62%), relative to the number of female patients (37%), died of COVID-19. Hossain et al^[24] reported that survival was significantly higher in female patients than in male patients (*P* ≤ .001). This may be explained by the effect of androgen, which promotes the transcription of transmembrane serine protease 2, a protein-coding gene that impairs the antibody response to acute respiratory syndrome coronavirus 2, thereby enhancing fusion of the virus and host cells.^[27]

Smoking has been linked to the pathogenesis of various lung diseases, including chronic obstructive pulmonary disease and pulmonary fibrosis.^[28] Smoking history was also identified in the current study as a risk factor for pulmonary fibrosis in post-COVID-19 patients. The present study showed that smokers were more likely to develop severe pulmonary fibrosis post-COVID-19 than non-smokers, and it was a predictor of mortality since smoking leads to oxidative stress and increased mucosal inflammation and inflammatory cytokines results in severe symptoms.^[28]

Elsewhere, associated comorbidities, such as hypertension, diabetes, and coronary artery disease, have been associated with

Table 6
Predictors of mortality and intensive care admission in COVID-19 patients with pulmonary fibrosis.

Predictors	ICU admission			Mortality		
	HR	95% CI	<i>P</i> -value	HR	95% CI	<i>P</i> -value
Age	1.0	0.9–1.2	.742	1.0	0.9–1.4	.107
Sex	1.1	0.5–1.9	.877	1.1	0.2–3.2	.844
Smoking	1.5	1.0–2.1	.026*	2.8	1.6–4.9	<.001*
Comorbidities						
Hypertension	1.4	0.6–2.9	.433	2.7	0.9–5.7	.089
Diabetes	1.8	0.3–2.8	.071	1.1	0.4–2.5	.954
Cardiovascular disease	1.3	0.4–4.3	.590	1.0	0.3–1.7	.112
Kidney disease	1.5	0.3–8.4	.657	2.5	0.6–3.1	.392
Obesity	1.2	0.6–2.4	.517	1.1	1.0–1.2	.012*
Asthma	2.7	1.1–6.7	.033*	3.1	1.0–9.4	.001*
Associated complications						
Sepsis	2.2	0.4–2.9	.089	2.3	1.2–4.7	.017*
Acute kidney injury	3.2	1.6–6.8	.001*	4.7	2.2–9.9	.001*

* Comorbidities adjusted for one another + age, BMI, and sex; Lab investigations were adjusted for age, BMI, and sex; significant results (*P* value < .05).

an increase in disease severity in COVID-19 patients.^[29] In the current study, diabetes and hypertension accounted for 65% of COVID-19 patients with pulmonary fibrosis, and the laboratory findings showed that lymphopenia, leukocytosis, and neutrophilia were observed 24 hours prior to patient deaths. These findings correlate with the increase in disease severity reported in a previous study.^[30] In other research, an elevation in serum lactate dehydrogenase levels was used as a marker of disease severity and the development of pulmonary fibrosis after acute lung injury, suggestive of the destruction of pulmonary tissue, and a correlation with increased mortality risk.^[22]

Bronchial asthma was identified in 15% of the participants in the current study, and it was shown to be a significant risk factor for mortality in COVID-19 patients with pulmonary fibrosis. The risk of mortality was twice as great in COVID-19 patients with pulmonary fibrosis and asthma than in other patients. Pulmonary fibrosis primarily develops around the alveoli; however, fibrosis in the lungs, along with asthma, causes thickening of the airway walls that may increase disease severity and worsen outcomes.^[31]

Severe COVID-19 cases may require ICU admission, and this, in combination with mechanical ventilation, is a risk factor for the development of pulmonary fibrosis, especially with a lengthy ICU stay. A significant relationship has been observed between mechanical ventilation and development of pulmonary fibrosis.^[32] In the current study, 81% of the hospitalized COVID-19 patients were admitted to the ICU, and 62% required intubation and mechanical ventilation. In general, the need for mechanical ventilation is closely linked to ventilator-induced lung injury.^[33] It has been shown that the prolonged use of mechanical ventilation leads to the release of proinflammatory cytokines with severe lung injury, which increases the risk of mortality and the development of pulmonary fibrosis.^[33]

Clinically, in the present study, despite a general improvement in the degree of dyspnea among COVID-19 patients with pulmonary fibrosis, dyspnea was seen to persist in some patients until 6 months post discharge. This supports the finding of a previous study conducted in Italy that reported the persistence of dyspnea in 43% of patients for months after discharge from hospital.^[34]

A chest CT was used in the current study to diagnose post-COVID-19 pulmonary fibrosis and during follow-ups. In this regard, “ground glass” opacity, “honeycomb” lung, and pulmonary consolidation were the most common CT findings. Francone et al^[35] reported that “ground glass” opacity was predominant in the early phase (≤ 7 days) of the onset of COVID-19 symptoms, while pulmonary consolidation and fibrosis characterized late-phase disease (> 7 days). In the current study, the overall mean CT scores of the recovered patients improved over a 6-month period (i.e., scores of 12.9 and 2.4 at discharge and 6 months). The CT score correlated highly with disease severity, and it was useful for predicting the outcomes of COVID-19 patients and mortality risk.^[35] It was observed that the CT scores at discharge and at the 6-month follow-up were significantly higher in severe cases admitted to the ICU and who required mechanical ventilation, compared with patients in the medical ward ($P \leq .001$ and $P = .010$, respectively). These results are consistent with the findings of a previous study.^[35] Further analysis established an association between the CT score, duration of hospitalization, and the degree of dyspnea. It is well-known that radiographical abnormalities strongly correlate with the long-term impairment of lung function.^[36] Zuo et al^[37] also demonstrated a correlation between the degree of pulmonary fibrosis and the duration of COVID-19

disease. Clinical data have shown that fibrous organization was more common in patients in the late stages, rather than in the early stages, of pneumonia.^[38]

For the management in the present study of post-COVID-19 pulmonary fibrosis, prednisolone was prescribed as the first-line treatment, with gradual tapering of the dose, and it was associated with an improvement in the symptoms of the recovered patients. Corticosteroids have an anti-inflammatory action and are effective in the fibroproliferative phase of ARDS.^[39–41] They remain part of the management of the usual interstitial pneumonia. Early treatment with corticosteroids is well-tolerated in patients with post-COVID-19 pulmonary fibrosis and is associated with a rapid and significant improvement in well-being.^[42] A few case reports documented that antifibrotic agents, for example, pirfenidone and nintedanib, were effective in treating post-COVID-19 pulmonary fibrosis.^[43–45] At present, there is no approved treatment for the management of post-COVID-19 pulmonary fibrosis. Thus, more clinical trials are warranted to identify the most suitable treatment approach to this disease.

5. Conclusion

Post-COVID-19 pulmonary fibrosis is a severe complication that leads to permanent lung damage or death. Early detection may help to prevent or at least delay its development.

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