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New Insights on Post-COVID-19 Pulmonary Fibrosis: Risk Factors and Clinical Correlations

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Abstract

Background: The coronavirus disease 2019 (COVID-19) effect on the lungs ranges from an asymptomatic infection to a critical illness with acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, or multiorgan failure. Pulmonary fibrosis, as a short-term or long-term complication of SARS-CoV-2 infection, is a progressive and fatal sequel to COVID-19. The present study assessed the risk factors and clinical findings associated with post-COVID-19 pulmonary fibrosis.

Methods and Results: This case-control study was conducted among Omani citizens and residents of Sohar State, Oman, from 01 Jan 2020 to 31 Dec 2022. The study involved 106 patients with post-COVID-19 pulmonary fibrosis (the main group) and 102 subjects who recovered from COVID-19 without pulmonary fibrosis (the control group). Advanced age, length of hospital stay, and the need for mechanical ventilation were significantly associated with post-COVID-19 pulmonary fibrosis. Moreover, the current study reported a significant elevation in total white blood cell count, serum lactate dehydrogenase, serum creatinine, and D-dimer levels among patients with post-COVID-19 pulmonary fibrosis.

Conclusion: The current study demonstrated a potential association between post-COVID-19 pulmonary fibrosis and severity-associated markers of COVID-19.**(International Journal of Biomedicine. 2024;14(4):664-672.)**

Keywords: SARS-CoV-2 • COVID-19 • risk factors • pulmonary fibrosis

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Abbreviations

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **COVID-19**, coronavirus disease 2019; **CTPA**, computed tomography pulmonary angiography; **CRP,** C-reactive protein; **HRCT**, high-resolution computed tomography; **ICU**, intensive care unit; **IMV**, invasive mechanical ventilation; **LHS**, length of hospital stay; **LDH**, lactate dehydrogenase; **NIV**, non-invasive ventilation; **PCPF**, post-COVID-19 pulmonary fibrosis; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **WBC**, white blood cell.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a single-stranded RNA virus known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The virus mainly targets the respiratory system. Unlike other coronaviruses, this virus is associated with the development of pneumonia rather than the common cold.[1] The effects on the lung ranged from asymptomatic infection to a critical illness with acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, or multiorgan failure.[2] In addition, patients with SARS-CoV-2 infection can present with extrapulmonary complications such as myocardial infarction, pancreatitis, and acute renal failure.[2] Predictors of a poor outcome in patients with COVID-19 included advanced age, male gender, African-American, Asian, and Hispanic ethnicities, and the presence of comorbidities.[2] Age was associated with the highest morbidity and mortality among all predictors.[3] Other risk factors like body mass index, immunosuppression, and socioeconomic status also modified the risk of poor outcomes.[3] The comorbidities more likely associated with an adverse outcome were hypertension, diabetes, chronic lung and kidney disease.[4] It was also suggested that certain medications like nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), were associated with severe infection.[4] Certain laboratory indices have also been considered predictors for poor outcomes in COVID-19 patients. These indices included increased leucocyte and neutrophil count, decreased lymphocyte and eosinophil count, decreased platelet count, increased enzymes like LHD, ALT, and AST, increased D-dimer and fibrinogen, change in prothrombin time and activated partial thromboplastin time, increased inflammatory markers like C-reactive protein, as well as increased proinflammatory cytokines (IL-6, IL-8, IL-10, IL-2R, and TNF-α).[5] COVID-19 vaccines, on the other side, greatly reduced the severity of the disease. For example, CoronaVac had a protective effect against developing severe interstitial pneumonia in patients with COVID-19 infection.[5]

In addition to the short-term complications, some COVID-19 patients developed long-term complications.[6] The reason and mechanisms by which those patients had these complications are not fully understood. The long-term pulmonary complications included lung fibrosis, ventilator and oxygen dependence, and abnormal respiratory function tests. Extrapulmonary complications involved arterial, venous, and cardiac thromboses, stroke, dermatological, and neuropsychiatric complications.[6]

Pulmonary fibrosis is a subgroup of interstitial lung diseases (ILD) that affect the lung parenchyma with varying degrees of inflammation and fibrosis.[7] Pulmonary fibrosis can be secondary to a systemic or connective tissue disease, infection, or drugs or without apparent cause (idiopathic). Idiopathic pulmonary fibrosis is the most common and severe form of chronic and progressive fibrosis.[7] Several viruses are proposed to contribute to the pathogenesis of pulmonary fibrosis, such as human herpes viruses 7 and 8, Epstein-Barr virus, and cytomegalovirus.[8] Accordingly, it is understandable that pulmonary fibrosis can arise as a complication of SARS-CoV-2 infection.[8] Post-COVID-19 pulmonary fibrosis (PCPF) is defined as persistent fibrosis with functional impairment during the follow-up.[9] In other words, patients with post-COVID-19 pulmonary fibrosis usually have symptoms that are persistent with a progressive decline in quality of life and persistent or deteriorating lung function tests and radiological findings.[10]

Pulmonary fibrosis was reported as a short-term [11-13] and a long-term complication of COVID-19.[14,15] The pathophysiology of post-COVID-19 pulmonary fibrosis is not fully understood. Scientific theories suggest the virus can trigger the fibrosis cascade via direct and indirect mechanisms.[8] The direct mechanism involves the virus binding to the angiotensin-converting enzyme 2 (ACE2) receptors that activate the fibrotic cascade.[16,17] The indirect mechanism results from the activation of the innate epithelial cells following injury to alveolar epithelial cells.[18,19]

Our review of the prevalence of post-COVID-19 pulmonary fibrosis found heterogeneous results. For example, a study by Aul et al.[20] reported a prevalence of post-COVID-19 pulmonary fibrosis in 9.5% of the patients, which was associated with persistent breathlessness at 6 weeks and inpatient ventilation [adjusted OR 5.02(1.76-14.27) and 4.45(1.27-15.58)], respectively. Another study reported that more than 30% of patients who recovered from COVID-19 developed pulmonary fibrosis.[21]A meta-analysis by Hama Amin et al.[22] found that about 44.9% of COVID-19 survivors appear to have developed pulmonary fibrosis. A study by Zou et al.[23] revealed that pulmonary fibrosis, evaluated by artificial intelligence-assisted high-resolution computed tomography (HRCT), was present in 84.2% of COVID-19 patients at discharge CT.

The factors that increase the risk of acquiring post-COVID-19 pulmonary fibrosis can be categorized as patient-related and disease-related factors. Patient-related factors associated with a higher risk of pulmonary fibrosis included advanced age, smoking, male gender, alcohol abuse, and the existence of a comorbidity.[24] Disease-related risk factors, on the other hand, involved the long stay in the intensive care unit (ICU), the prolonged mechanical ventilation duration, the use of a high-flow nasal cannula, the existence of acute respiratory distress syndrome (ARDS), and the degree of systemic inflammation.[24] A study by Arnold et al.[25] reported unstable vital signs or cough at presentation and persistent dyspnoea. In addition, some laboratory findings, such as inflammatory and coagulation biomarkers and radiological abnormalities, were also found to increase the likelihood of encountering pulmonary fibrosis following COVID-19 infection. A narrative review by Tanni et al.[9] showed that high C-reactive protein and lactate dehydrogenase levels increased the risk of pulmonary fibrosis in COVID-19 patients. Elevated total white blood cell count, neutrophil and lymphocyte count, increased total bilirubin, elevated procalcitonin, decreased serum albumin, and increased IL-6, elevated D-dimer and brain natriuretic peptide (BNP) were reported as risk factors for post-COVID-19 pulmonary fibrosis.[25] A study by Xue et al.[26] found that Krebs Von den Lungen-6 (KL-6), as a sensitive

marker, could be an important predictor to evaluate the secondary pulmonary fibrosis degree for COVID-19. Some studies investigated matrix metalloproteinase-7, hepatocyte growth factor, and lipocalin-2 as fibrosis biomarkers.[8,27]

Among the radiological abnormalities associated with a high risk of pulmonary fibrosis were interstitial thickening, bronchiectasis, and parenchymal bands on HRCT.[28] Moreover, the radiological abnormalities like the presence of consolidation, irregular surface, parenchymal bands, pleural effusion, and poor aerated lung volume,[25] in addition to high chest severity score (CSS) on the initial chest CT scan,[29] were all correlated with an increased risk of post-COVID-19 lung fibrosis.

In a retrospective study, low lymphocyte count, high erythrocyte sedimentation rate, decreased prothrombin time and activated partial thromboplastin time, increased platelet count, and decreased hemoglobin were also associated with increased risk of pulmonary fibrosis among COVID-19 patients.[30] The same study also reported increased liver function test parameters (ALT, AST and total bilirubin) as well as elevated kidney function parameters like blood urea nitrogen and creatinine as risk factors for pulmonary fibrosis. [30] A longitudinal prospective study conducted in 2021 showed that pneumonia and a persistent viral infection were predictive factors for developing post-COVID-19 pulmonary fibrosis.[31]

The exact cause of pulmonary fibrosis can be identified using a combination of clinical, laboratory, radiological, and histological findings.[29] Pulmonary fibrosis is a progressive and fatal disease that even requires immediate lung transplantation. [8]

The aim of this study was to assess the risk factors and clinical findings associated with post-COVID-19 pulmonary fibrosis.

Materials and Methods

Study Population

This retrospective case-control study was conducted among Omani citizens and residents of Suhar State, Sultanate of Oman, who tested positive for SARS-CoV-2 infection from Jan 2020 to March 2023. Participants were recruited from COVID-19-confirmed patients admitted to Suhar Hospital during the specified time. The study included 106 patients (the main group [MG]) with post-COVID-19 pulmonary fibrosis. All patients were diagnosed by expert physicians using clinical, histological, and radiological findings. The study also recruited 102 subjects who recovered from COVID-19 without pulmonary fibrosis (the control group [CG]). Patients under 13 years old, patients with underlying comorbidities (diabetes, hypertension, cardiac, hepatic, and renal diseases), and patients with a previous diagnosis of pulmonary fibrosis or having missed or insufficient data were excluded from the study. Patients with a history of smoking were not included in the study to avoid potential confounding effects on the outcomes

Sample Size Calculation

The sample size was calculated taking into account the recommendations of A. Althubaiti[32] and the equation presented in a study by Rodríguez Del Águila et al.[33] was applied. We calculated the required sample size based on data published by Aul et al.,[20] who described a proportion of fibrotic abnormalities on CTPA in 9.5% of patients six weeks post-hospital discharge after COVID-19, assuming a maximum error of 5% and 95% confidence.

Data Collection

Essential data was gathered upon reviewing the patient's medical records, which encompassed demographic data (age and gender) and medical data related to pulmonary fibrosis and COVID-19 (clinical, laboratory, and radiological findings, vaccination, medications, hospitalization period, ICU stay period, and need for mechanical ventilation).

Statistical Analysis

Statistical analysis was performed using the statistical software package SPSS version 18.0 (Chicago: SPSS Inc.). Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean (M) ± standard deviation (SD) for continuous variables. A probability value of $P<0.05$ was considered statistically significant.

Results

The mean age was 51.69±16.23 years in MG and 51.77±16.61 years in CG (Tables 1 and 2).

Table 1.

Mean age for cases and control subjects.

	Cases (MG)	Controls (CG)
Count, N	106	102
Sum, Σx	5480	5281
Mean age, years,	51.698113207547	51.774509803922
Variance, s2	263.48894878706	276.1961754999
SD	16.232342677108	16.61915086579
Margin of error	1.5766244955213	1.6455411396121

Table 2.

Unpaired t-test for comparison between mean age of cases and control subjects.

t	0.0335	Two-tailed *P*-value
df	206	0.973
Standard error of difference	2.278	

The men comprised 65% and 62% in MG and CG, respectively. (Table 3). Omani citizens represented 90% and 81% of MG and CG, respectively (Table 4). The average length of hospital stay (LHS) and the need for admission to the ICU and mechanical ventilation were measured among PCPF patients and control subjects. The mean LHS was 7.13±7.32 days in MG and 3.80±5.77 days in CG (Table 5). The ICU admission rate was 11.3% and 5.9% MG and CG, respectively (Table 6). The rate of invasive mechanical ventilation (IMV) and non-invasive ventilation (NIV) among cases and control subjects is shown in Table 7. In MG, 72.6% of patients received oxygen, 17.9% had non-invasive mechanical ventilation, and no one had invasive mechanical ventilation. Regarding CG, 82.3% received oxygen, 2.9% had non-invasive mechanical

ventilation, and 2.9% had invasive mechanical ventilation. Table 8 presents the platelet count, total WBC count, and the serum levels of ferritin, serum D-dimer, CRP, lactate dehydrogenase, albumin, ALT, urea, and creatinine in both study groups. Our results found a significant difference between MG and CG in the LHS (P<0.001), total WBC count (P=0.017), serum LDH (P=0.049), serum creatinine (P=0.012), and D-dimer level (P=0.018). All the above parameters were significantly higher in the MG than in CG. In the MG patients with post-COVID-19 pulmonary fibrosis, we revealed positive correlations between patient age and serum levels of creatinine, urea, and ALT.

Table 3.

Gender distribution among cases and control subjects.

		Males	Females	Row totals	
Cases (MG)	Observed	69(65%)	37(35%)	106	Chi-Square Statistic: 0.1244 df: 1 P-value = 0.724
	Expected	67.7788	38.2212		
	Chi-Square Contribution	0.022	0.039		
Controls (CG)	Observed	64(62%)	38(38%)	102	
	Expected	65.2212	36.7788		
	Chi-Square Contribution	0.0229	0.0405		
Column totals	133	75	208	208	

Table 4.

Nationality distribution among cases and control subjects.

		Omanis	Non-Omanis	Row totals	
Cases (MG)	Observed	90(84%)	16(16%)	106	Chi-Square Statistic: 0.4636 df: 1 P-value = 0.495
	Expected	88.1635	17.8365		
	Chi-Square Contribution	0.0383	0.1891		
Controls (CG)	Observed	83(81%)	19(19%)	102	
	Expected	84.8365	17.1635		
	Chi-Square Contribution	0.0398	0.1965		
Column totals	173	35	208	208	

Table 5.

Length of hospital stay (LHS) among cases and control subjects.

Parameter	MG	CG	*P*-value
LOS, days	7.13 ± 7.32	3.80 ± 5.77	<0.001

Table 6.

ICU admission among cases and control subjects

		ICU admission		Row totals	
		ICU	No ICU		
Cases (MG)	Observed Expected Chi-Square contribution	12(11.3%) 9.1731 0.8712	94(88.7%) 96.8269 0.0825	106	Chi-Square Statistic: 1.9448 df: 1 P-value = 0.1631
Controls (CG)	Observed Expected Chi-Square contribution	6(5.9%) 8.8269 0.9054	96(94.1%) 93.1731 0.0858	102	
Column totals		18	190	208	

Table 8.

Clinical and laboratory findings among cases and controls.

Parameter	Cases (MG)	Controls (CG)	*P*-value
Platelet count, K/µL	277.65±111.36	264.14±118.34	0.38
WBC count, K/µL	9.8188	8.1234	0.017
Lymphocytes count K/µL	2.9778	2.9773	0.072
CRP, mg/L	108.43±83.50	124.61 ± 95.72	0.231
Ferritin, ng/mL	408.56±845.11	440.26±742.30	0.84
LDH, U/L	206.71±302.15	134.41 ± 223.45	0.049
Albumin, g/L	35.29 ± 4.85	34.59 ± 4.88	0.388
Creatinine, µmol/L	95.66 ± 76.84	77.50 ± 28.41	0.012
Urea, mmol/L	3.42 ± 6.03	5.26 ± 26.90	0.497
ALT, U/L	59.01 ± 91.08	46.62 ± 56.05	0.21
D-dimer, mg/L	6.09 ± 12.358	2.4016 ± 8.9652	0.018

Table 7.

Mechanical ventilation among cases and control subjects.

		None	Oxygen	NIV	IMV	Row totals	
Cases (MG)	Observed Expected Chi Square contribution	10(9.4%) 11.2115 0.1309	77(72.6%) 82.0481 0.3106	19(17.9%) 11.2115 5.4105	0 (0%) 1.5288 1.5288	106	Chi Square Statistic: 15.0512 df: 3 P-value = 0.0018
Controls (CG)	Observed Expected Chi Square contribution	12(11.7%) 10.7885 0.1361	84 (82.3%) 78.9519 0.3228	3 (2.9%) 10.7885 5.6227	3 (2.9%) 1.4712 1.5888	102	
Column totals		22	161	22	3	208	

Table 9.

Correlation of age, gender, and LHS with sociodemographic, clinical, and laboratory findings.

Parameter	Age	Gender	LHS	Platelet	CRP	Ferritin	Creatinine	Urea	ALT
Age	1	0.018 0.855	-0.006 0.956	0.045 0.648	0.147 0.138	-0.011 0.912	0.348** <0.001	0.407** <0.001	0.248* 0.011
Gender	0.018 0.855	1	-0.001 0.990	0.064 0.514	-0.047 0.635	-0.033 0.740	-0.100 0.308	-0.145 0.138	0.152 0.122
LHS	-.006 .956	0.001 0.990	1	0.007 0.947	0.097 0.337	0.114 0.253	-0.063 0.528	-0.135 0.175	0.041 0.688

Discussion

Post-acute complications of COVID-19 affect most survivors. There is growing evidence suggesting that COVID-19 can have subacute and long-lasting impacts. Post-COVID-19 pulmonary fibrosis has the most significant long-term impact on patients' respiratory health. Pulmonary fibrosis is a subgroup of interstitial lung diseases (ILD) that affect the lung parenchyma with varying degrees of inflammation and fibrosis The disease can be primary (idiopathic) or secondary to an infection, drug, or systemic disease.[7] Post-COVID-19 pulmonary fibrosis has the most significant long-term impact on patients' respiratory health.[8,9] Only some studies have looked explicitly into lung fibrosis as the primary result of COVID-19. A meta-analysis by Hama Amin et al.,[22] based on 24 articles, showed the prevalence of post-COVID-19 pulmonary fibrosis from 9.3% to 84.15%.

In our study, the mean age for PCPF patients was 51.69±16.23 years. Literature findings in this aspect were quite similar. For example, a meta-analysis by Hama Amin et al.[22] found that the prevalence of post-COVID-19 pulmonary fibrosis was 44.9%, and the mean age was 59 years in fibrotic patients and 48.5 years in non-fibrotic patients. Another study by Farghaly et al.[34] found that the percentage of PCPF patients aged ≥65 years (44%) who demised was higher than those who survived (25%). Similarly, a prospective study by Nabahati et al.[35] found that the mean age of PCPF patients was 53.62±13.67 years. It was confirmed that advanced age, in the presence of viral infection like COVID-19, was associated with an increased tendency to develop pulmonary fibrosis.[34] Moreover, advanced age was established as a significant risk factor for the development of post-COVID-19 pulmonary fibrosis.[24] This is quite understandable as both the cellular and humoral defense mechanisms are greatly diminished with advanced age.[34] In the current study, the mean age of PCPF patients was not statistically different from that of control subjects. This finding, in particular, was similar to the study by Aul et al.,[20] who reported no difference between fibrotic and non-fibrotic patients.

In our study, men comprised 65% and 62% of MG and CG, respectively. Literature has suggested that male gender is a risk factor for developing pulmonary fibrosis after COVID-19.[24] Similarly, some studies supported this finding, concluding that the prevalence of post-COVID-19 pulmonary fibrosis was higher in males than females. (20,36) However, the majority of studies, including the current study, have discredited this assumption.[27,35,37-41]

The current study demonstrated a potential association between post-COVID-19 pulmonary fibrosis and several indicators of COVID-19 severity. These indicators involved processes like inflammation, organ dysfunction, and coagulopathy. It is well known that pulmonary fibrosis can develop immediately after discharge or a few weeks later.[22] However, the exact definition, prevalence, pathophysiology, and treatment of pulmonary fibrosis secondary to COVID-19 are not fully understood, making it a new entity.[42] Nonetheless, the development of pulmonary fibrosis among COVID-19 survivors is associated with the severity of the infection.[8]

To better comprehend the progression and pertinent risk elements of pulmonary fibrosis in individuals with COVID-19, we explored the association between pulmonary fibrosis and some clinical and laboratory findings. Accordingly, we have assessed the LHS as an early indicator of COVID-19 severity. Both stay time in the ICU and LHS were considered indicators of the disease severity and, hence, the likelihood of developing pulmonary fibrosis.[24,40] In our study, the average LHS was 7.13±7.32 days for PCPF patients and 3.80±5.77 days for control subjects (P<0.001).

The current study reported a significant elevation in some inflammatory biomarkers, including WBC count and D-dimer, among PCPF patients. The mean WBC was 9.8188 K/μL and 8.1234 K/μL for the fibrotic and non-fibrotic subjects, respectively (P=0.017). This finding was consistent with the retrospective study by Li et al.[29] Additionally, the current study reported a significant elevation in the D-dimer level among patients with pulmonary fibrosis: 6.09±12.358 mg/L versus 2.4016±8.9652 mg/L for non-fibrotic subjects. In this context, our study was consistent with a study by Huang et al.,[41] who found elevated WBC count and D-dimer levels in patients with post-COVID-19 pulmonary fibrosis. Other studies also found elevated D-dimer levels in patients with pulmonary fibrosis.[29] A high D-dimer level was among the

most important factors in developing pulmonary fibrosis after COVID-19 infection in a study by Bridi et al.[42] Thachil et al.[43] concluded that COVID-19 can lead to multiple activation events, including inflammation, primary and secondary hemostasis, and fibrinolysis, all of which may contribute to cumulative D-dimer development.

The current study detected a significant increase in serum LDH levels with a mean value of 206.71±302.15 U/L for patients with pulmonary fibrosis and 134.41±223.45 U/L for non-fibrotic subjects (P=0.049). It was established that high serum LDH signified a poor prognosis in COVID-19 patients, including both acute alveolitis and fibrosis stages.[44] Furthermore, high serum LHD levels were associated with reduced survival in COVID-19 patients Elevated serum lactate dehydrogenase level was used as a severity marker and an indicator of high mortality risk.[45] In addition, in the present study, the mean serum creatinine was significantly higher in patients with post-COVID-19 pulmonary fibrosis than in non-fibrotic subjects (95.66±76.84 μmol/L and 77.50±28.41 μmol/L, respectively, P=0.012). These results may indicate both renal involvement in the development of the disease and concomitant renal pathology, which increase the risk of pulmonary fibrosis in patients with COVID-19. It is worth noting that elevated serum creatinine was one of the risk factors for developing pulmonary fibrosis after COVID-19 in a study by Jha et al.[46] In contrast, serum creatinine was normal in patients diagnosed with pulmonary fibrosis, according to Rai et al.[45] and Ahmad Alhiyari et al.[47]

Age, sex, and medical comorbidities have all been identified in several studies as linked to the severity of COVID-19 and the development of lung fibrosis, which can complicate the course of the disease and lead to other complications.[8] Our research revealed a potential link between post-COVID-19 pulmonary fibrosis and various important markers of inflammation, coagulation, and organ function, which could be important for the progression, outcome, and long-term effects of COVID-19.

N.N. Alrajhi[8] considers ICU among the risk factors for post-COVID-19 pulmonary fibrosis. Furthermore, a longer ICU stay was significantly associated with an outcome of pulmonary fibrosis.[48,49] The current study, however, did not find a significant difference between the patients with post-COVID-19 pulmonary fibrosis and control subjects regarding the need for ICU admission. In this regard, the current study agreed with the study by Townsend et al.,[50] who found no association between ICU admission and COVID-19 respiratory complications, including pulmonary fibrosis. The study attributed this finding to the multifactorial nature of pulmonary fibrosis complicating COVID-19 infection.

The current study found a significant association between pulmonary fibrosis and the need for mechanical ventilation. Our study was consistent with the study by Nabahati et al.,[35] which concluded that mechanical ventilation and prolonged ventilation, in particular, were a risk factor for pulmonary fibrosis. Prolonged mechanical ventilation can induce lung injury in COVID-19 patients.[48] McGroder et al.[51] examined pulmonary fibrosis that developed during the recuperation phase following SARS-CoV-2 infection. Their findings showed that high-resolution CT scans revealed fibrotic irregularities in 72% of patients receiving mechanical ventilation, whereas only 20% of nonmechanically ventilated patients had such abnormalities.

In a study by Li et al.,[29] a negative correlation between serum albumin level and pulmonary fibrosis was found. In our study, creatinine positively correlated with age (r=0.348, P<0.001). In addition, urea positively correlated with age (r=0.407, P<0.001). These clinical correlations were quite expected as the clinical and biological characteristics associated with post-COVID-19 pulmonary fibrosis are usually consistent with those patients' clinical and biological profiles.[8]

Even though smoking, whether active or passive, was recognized as a risk factor for post-COVID-19 pulmonary fibrosis,[8] the current study did not find a significant difference between patients with post-COVID-19 pulmonary fibrosis cases and control subjects, which corresponded to findings obtained by Li et al.[29] In contrast, Yoon and Uh[24] showed that smoking was a potential risk factor for the development of pulmonary fibrosis in COVID-19 patients. Similarly, a study by Ali and Ghonimy[49] found that smoking was significantly associated with the development of post-COVID-19 pulmonary fibrosis.

Our study had some limitations. First, we could not calculate the incidence of the disease as a case-control study. Additionally, it was difficult to generalize our findings as the study was conducted in a small, remote town in Oman. Moreover, participants did not receive an initial examination before contracting the infection, making evaluating changes from the starting point difficult.

Conclusion

The current study demonstrated a significant association between post-COVID-19 pulmonary fibrosis and certain clinical and laboratory parameters of inflammation, coagulopathy, and organ dysfunction. Those parameters can be used as predictors for late pulmonary permanent damage.

Ethical Considerations

The study was approved by the Ethics Committee of the Faculty of Medicine at the National University and the Ministry of Health, North Batinah Province, Oman.

Competing Interests

The authors declare that they have no competing interests.

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