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Exploring Prognostically Significant Factors in COVID-19-Associated Pulmonary Fibrosis after Adaptive Lung Ventilation

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Abstract

Background: Research data on hospitalized coronavirus 2019 (COVID-19) survivors indicate the persistence of symptoms, radiological abnormalities, and physiological disorders months after the initial infection. Given the scale of the ongoing pandemic, a substantial number of patients with severe residual pulmonary fibrosis (PF) and oxygen dependence are anticipated. Currently, the search for risk factors associated with the development of fibrotic radiological abnormalities after moderate to severe COVID-19 is underway. Furthermore, the extent to which computed tomography (CT) data correlate with postdischarge symptoms and physical functions remains unclear. This study aimed to characterize patients experiencing persistent pulmonary consequences after hospital discharge. We examined clinical, radiological, and laboratory predictors of pulmonary fibrosis after COVID-19 infection.

Methods: We retrospectively evaluated fibrosis-like lung changes and their prognostic factors in COVID-19 survivors. Our study included 77 patients with laboratory-confirmed COVID-19 who received inpatient treatment at City Clinical Hospital No. 1 in Almaty between November and December 2020. We assessed patients during the acute phase of the disease and again 6 to 8 months after discharge using high-resolution computed tomography (CT). Patients were classified into 2 cohorts based on semi-quantitative analysis of subsequently added tomograms—those with radiological fibrosis-like abnormalities (main group) and those who had recovered (control group).

Results: Parenchymal cords, irregular interfaces, reticulation, and traction bronchiectasis were common CT findings among all COVID-19 patients. Our study focused on patients who developed pulmonary fibrosis within 1 month after the onset of the disease. After 6 to 8 months, fibrosis-like lung changes persisted in 49.35% of patients (leading group), while 50.65% showed disease resolution (control group). Age, body mass index, high interleukin-6 (IL-6) levels, low IO levels, and the need for mechanical ventilation were identified as prognostic indicators for the persistence of pulmonary fibrosis.

Conclusion: Our study revealed that pulmonary function can return to normal in over half of COVID-19 patients 8 months after infection onset. Despite advancements in COVID-19 treatment, there remains a significant knowledge gap in managing long-term effects, especially pulmonary fibrosis. Continued clinical trials and research on post COVID-19 fibrosis are essential to prevent early mortality due to the long-term impacts on these patients.

Keywords: COVID-19, Interleukin-6, Lung Function, Pulmonary Fibrosis, Ventilator

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Introduction

The outbreak of the 2019 coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome

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↑What is "already known" in this topic:
It is already known that pulmonary fibrosis is a recognized complication in some patients recovering from COVID-19. However, the extent to which severe pneumonia increases the risk of pulmonary fibrosis and its associated prognostic factors has not been comprehensively understood until this study.

→What this article adds:
In summary, this article contributes valuable insights into the understanding of post COVID-19 pulmonary fibrosis, filling gaps in existing knowledge regarding its prevalence, risk factors, course, therapeutic possibilities, and the necessity of vigilant monitoring.

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coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide since its initial emergence in China in December 2019 (1-4). COVID-19 infection can trigger an inflammatory reaction, encompassing a cytokine storm and various regulatory pathways to counteract tissue damage (5). The virus can attach to angiotensin-converting enzyme 2 (ACE2) receptors in the upper respiratory tract (6). This interaction elevates angiotensin 2 levels, activating interleukin-6 (IL-6), tumor necrosis factor-α, increased presence of neutrophils and macrophages, and direct harm to the endothelium (7). Angiotensin 2 also plays a role in regulating the collagen 1 gene through mitogen-activated protein kinase, which controls the extracellular signal of Janus kinase 1 and transforming growth factor-β (TFR-β). These are the primary factors involved in fibrosis (8). Consequently, the uncontrolled production of metalloproteinases damages the epithelium and endothelium (9). IL-6 is a proinflammatory and profibrotic cytokine that activates neutrophils, leading to their accumulation at the injury site and the release of proteases and free oxygen radicals. This process contributes to interstitial pulmonary edema and a severe inflammatory response (10, 11). IL-6 is also considered a predictor of the progression of severe COVID-19, supporting the hypothesis that IL-6 receptor antagonists can effectively control the cytokine storm induced by SARS-CoV-2 (12, 13).

Patients afflicted with COVID-19 exhibit a range of symptoms, notably respiratory issues that can escalate into severe pneumonia and ARDS. Initial studies have documented cases where patients continue to grapple with persistent symptoms despite recovering and testing negative for the polymerase chain reaction (PCR) test. These symptoms span from mild to severe respiratory distress requiring extended oxygen therapy, often attributable to lingering complications such as pulmonary fibrosis (PF) (14). In the aftermath of the global COVID-19 pandemic, a subset of patients experiences persistent symptoms and complications affecting multiple organs. These symptoms endure for weeks or even months after the acute phase of the disease (15). The enduring clinical manifestations, frequently referred to as the long-term course of COVID-19, are a source of mounting concern for health care systems (16).

Any infection—whether bacterial or viral—can potentially damage the epithelium of the respiratory tract, thereby influencing the response to injury. Substantial evidence establishes a clear link between respiratory viral infections and the development of PF (17).

PF is considered a significant challenge associated with the respiratory consequences of COVID-19, as it involves architectural changes in lung tissue and a general disruption of lung function, resulting in a diminished quality of life. Our understanding of the pulmonary effects of COVID-19 remains limited. Therefore, insights in this area can aid in identifying at-risk populations requiring vigilant monitoring (18).

In a study conducted by Zou JN et al, a notably higher incidence of PF was proposed among patients with severe or critical pneumonia attributed to COVID-19 compared with those with moderate COVID-19 (5). Today, 4% to 25% of hospitalized patients with COVID-19 were treated in the intensive care unit (ICU), with the mortality rate reportedly ranging from 25% to 63.25%. Patients with severe pneumonia tend to worsen quickly, often leading to acute respiratory distress syndrome (ARDS) or multiple organ failure and death (19). Fatal cases can manifest as ARDS with significant alveolar damage, causing loss and hyperplasia of type II pneumocyte cells, formation of hyaline membrane, exudation of fibrin, thickening of the alveoli, and damage to the basement membrane (20). CT plays a vital role in both diagnosing and monitoring patients with COVID-19 (21). It provides valuable insights into the extent of lung damage, ranging from mild to severe, in cases of COVID-19 pneumonia. Previous research has also highlighted the occurrence of fibrotic complications after infection, which poses significant clinical challenges for patients (22). Identifying population groups at the highest risk of post COVID complications is crucial for enabling timely interventions and support measures to reduce morbidity and enhance patient outcomes. In this study, we conducted a retrospective assessment of fibrosis-like changes in lung CT scans and investigated their associated prognostic factors in patients who had survived COVID-19 infection. In this study, we also aimed to monitor ongoing changes in the radiograph images of discharged patients who had previously contracted COVID-19. We sought to determine whether persistent PF developed in this survivor population within the 6 to 8 months after infection. Furthermore, we aimed to identify early warning indicators related to lung conditions, with the ultimate goal of developing early intervention strategies to mitigate PF occurrence.

Methods

In this retrospective cross-cohort study, we carefully selected 77 patients treated for moderate to severe COVID-19 pneumonia at City Clinical Hospital No. 1 in Almaty who were discharged in December 2020.

To gauge the clinical severity of COVID-19 pneumonia, we adhered to the definition criteria of the World Health Organization. Upon admission, we evaluated the severity of each patient's condition using chest CT scans. Our study encompassed patients who subsequently underwent a follow-up chest CT scan within 8 months of their initial hospitalization.

Based on our analysis of the follow-up CT scans, we categorized the patients into 2 distinct groups—the primary group, displaying fibrosis-like lung changes (FIL); and the control group, showing no such alterations (BFIL).

Inclusion Criteria

Patients who tested positive for SARS-CoV-2 RNA by PCR from samples collected from both the nasopharynx and oropharynx at the time of their hospitalization were included in the study.

Exclusion Criteria

This study did not include COVID-19 patients who did not have a thin-section chest CT scan. In this study, 77 COVID-19 patients were included, of whom 40 (51.95%) were men and 37 (48.05%) women. The mean age of the

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participants was 55.36 ± 14.37 years.

Imaging Procedure

Each patient was positioned in a prone posture and instructed to take a deep breath with breath-holding from the thoracic entrance to the diaphragm. A 16-row CT scan without enhancement was conducted using a SIEMENS SOMATOM Emotion 16 scanner (Siemens Healthcare; Med Image Systems). The following scanning parameters were employed: tube voltage of 100 kV for patients with a body mass index (BMI) <30 and 120 kV for patients with a BMI >30; tube current ranging from 50 to 100 wt; step size of 0.8 to 1.5; slice thickness between 1 and 3 mm; and a matrix of 512. No additional image reconstructions were necessary.

PF Assessment

The resolution of PF was evaluated by examining the patient's CT scan for the disappearance of initial fibrosis indicators. CT image features—such as traction bronchiectasis, honeycomb patterns, parenchymal cords, and thickening of the intervertebral septum—were considered indicative of fibrosis-like changes. Furthermore, parenchymal cords and thickening of the interlobular septa were categorized as mild to moderate fibrosis, while traction bronchiectasis and honeycomb patterns were classified as severe fibrosis.

Statistical Analysis

Categorical variables were described as absolute (n) and relative values (%), whereas continuous variables were expressed as median and range. To compare demographic and clinical data between the PHIL and BFIL groups, if necessary, the chi-square criterion and the Fisher exact criterion (n <5) for categorical variables and the Mann-Whitney criterion for continuous variables were used.

To determine prognostic factors of radiological consequences (FIL, BFIL) during the follow-up, 1-dimensional logistic regression analysis was used to create an adjusted model for predicting the persistence of PF, accounting for gender, age, oxygenation index (PaO2/FiO2 IO), oxygen dependence, and FiO2 max upon admission. The Mann-Whitney U test for continuous variables was used to compare radiological parameters at CT 1 in patients with BFIL. In contrast, the Wilcoxon sign rank criterion was used to compare radiological parameters between CT 0 and CT 1. All data were analyzed using IBM SPSS software Version 25.0 (IBM Corp). $P < 0.05$ was considered statistically significant.

Results

Among 77 patients in the study, the median (interquartile range [IQR]) age was 55.36 ± 14.37 years—40 (51.95%) men. The main characteristics of the participants are listed in Table 1. Inpatient clinical data were retrospectively collected from case histories using the DAMUMED medical information system. Data entry was done by clinicians involved in treating patients with COVID-19. Pseudonymization of patients was performed. We collected data on the demographic characteristics of patients and regular medication intake, symptoms during the diagnosis of COVID-19, and complications during hospital stay (retrospectively documented), as well as on the type and number of concomitant diseases, including hypertension, type 2 diabetes, chronic obstructive pulmonary disease, obesity, chronic liver disease, autoimmune diseases, coronary heart disease, atrial fibrillation, endocrine diseases, chronic kidney disease), stroke, TIA, or active malignant neoplasm (Table 1).

It is worth highlighting that the symptoms of respiratory system disorders endured for an extended period. In some instances, even after 6 months, patients with remaining fibrotic lung changes did not see these symptoms dissipate. Refer to Figure 1 for details. Interestingly, only a

Table 1. Demographic characteristics and concomitant diseases of the study population with COVID-19

Characteristics		Patients, n (%)		
		Overall Population	Leading Group	Control Group
		77 (100)	38 (49.35)	39 (50.65)
Age, median (IQR), years		59 (45-70)	67 (54-70)	54 (48-57)
Gender				
Male		40 (51.95)	28 (73.69)	12 (30.77)
Female		37 (48.05)	9 (23.68)	28 (71.79)
Chronic medication usage		39 (50.65)	18 (47.37)	21 (53.85)
Smoking status	Non-smoker	36 (46.75)	15 (39.47)	21 (53.85)
	Former smoker	26 (33.77)	7 (18.42)	19 (48.72)
	Current smoker	15 (19.48)	4 (10.53)	11 (28.21)
Concurrent diseases				
Arterial hypertension		27 (35.06)	10 (26.32)	17 (33.33)
COPD		13 (16.88)	5 (13.16)	8 (20.51)
Diabetes		10 (12.99)	4 (10.53)	6 (11.76)
Obesity (BMI >30)		37 (48.05)	25 (65.79)	12 (30.77)
Chronic liver disease		1 (1.3)	0	1 (2.56)
Autoimmune disease		1 (1.3)	0	1(2.56)
Chronic kidney disease		2 (2.6)	1 (2.63)	1 (2.56)
Atrial fibrillation		2 (2.6)	1 (2.63)	1(2.56)
Coronary heart disease		19 (24.68)	9 (23.68)	10 (26.32)
Stroke or TIA		2 (2.6)	2 (5.26)	2 (5.13)
Myocardial infarction		2 (2.6)	1 (2.63)	1 (2.56)
Malignant neoplasm		2 (2.6)	1 (2.63)	1 (2.56)

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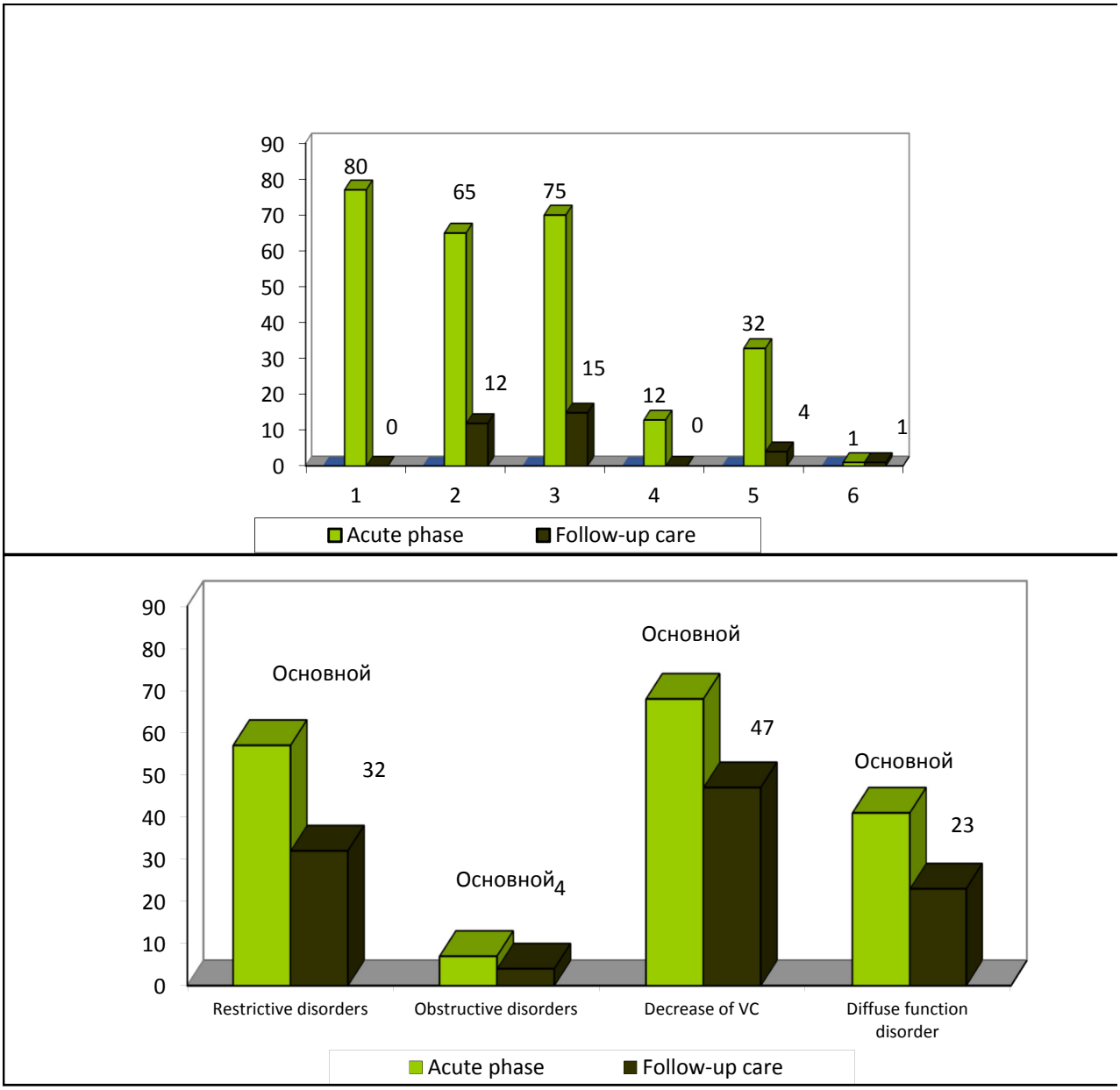

Figure 1. Symptoms in patients during and after recovery from COVID-19 and after 6 months in the quantitative ratio

very small proportion of patients with resolved fibrotic changes on radiographs still experienced signs of respiratory distress 6 months after the onset of the disease. Importantly, none of them required oxygen support at this point. Currently, most patients in this group are receiving low-flow oxygen therapy.

A total of 77 patients had PF, 39 of whom had a regression. In contrast, 38 patients still had PF during the last examination. Lung anomalies found in patients with fibrosis were reticulations (34/77), cellular structure (10), traction bronchiectasis (12), parenchymal cords (58), irregular interfaces (36), thickening of the interlobular septa (31), pulmonary distortion (5), opacity by the type of frosted glass (76), grid structure (9), consolidation (35) and the "stone paving" feature (57). The dynamics of these signs are reflected in Table 2. Upon admission to the hospital, the PHIL group had a worse gas exchange with a lower PiO2/FiO2 ratio than the non-PHIL group (50% [19] vs 43.59% [17]; $P = 0.04$). In addition, compared with non-FILS, high-intensity medical care (ICU) was more often required during hospitalization of FILS (18.42% [7] vs 7.69% [3]; $P = 0.002$); higher FiO2 max (100% [38] vs 86.84% [33]; $P < 0.0001$), and a prolonged hospital stay of >20 days (58.97% [23] vs 34.21% [13] days; $P < 0.0001$).

A total of 10 patients (12.99%) were admitted to the ICU with a median (IQR) stay of 10.5 (5-20) days. During the hospital stay, 71 patients (92.21%) needed additional oxygen, 44 patients (57.14%) received oxygen through nasal cannulas or Venturi masks, 19 patients received high-flow oxygen therapy through nasal cannulas (24.68%), 4 patients (5.19%) required noninvasive ven-

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Table 2. Features of computer tomography in 77 patients at different stages of COVID-19 and after discharge from the hospital

Signs of PF on Thoracic Organs CT	Disease Onset	In 4 Months	In 6-8 Months
Opacity by type of frosted glass	76	53	36
Sponginess	10	7	4
Parenchymal cords	58		38
A reticulation process	34	30	11
Traction bronchiectasis	12	8	3
Thickening of interlobular partitions	31	29	17
Non-standard interface	36	33	32
The "stone paving" attribute	57	48	35
Consolidation	35	27	22

Table 3. The need of the studied population for oxygen support in case of respiratory insufficiency in the acute disease case

Type of Oxygen Support	General Population	Group With LIF	Group Without LIF
Without O_2	6	3	3
With O_2	71	38	33
Suppl.O_2	44	26	18
High-flow oxygen	19	11	8
NIV	4	2	2
ALV	4	3	1

tilation, and 4 patients (5.19%) were subjected to artificial lung ventilation. The distribution by cohort is shown in Table 3 and Figure 2.

Our study found that, throughout an 8-month follow-up period, some patients' chest CT scans showed a decrease in fibrotic abnormalities, whereas others did not. We concluded that independent predictors of PF development after a COVID-19 infection include male gender, a high BMI, elevated IL-6 levels, increased oxygen requirements, a low lymphocyte count, and the presence of "frosted glass" opacities on the initial CT scans. It is important to note that PF is a severe complication of respiratory infections.

Among survivors of severe COVID-19, our findings indicated that 25% of those who did not require ventilation and 75% of those who did require ventilation exhibited

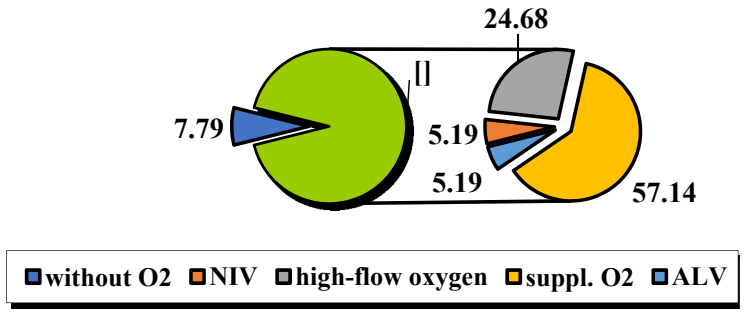

Figure 2. The need for the oxygen support in case of respiratory insufficiency in the acute disease phase

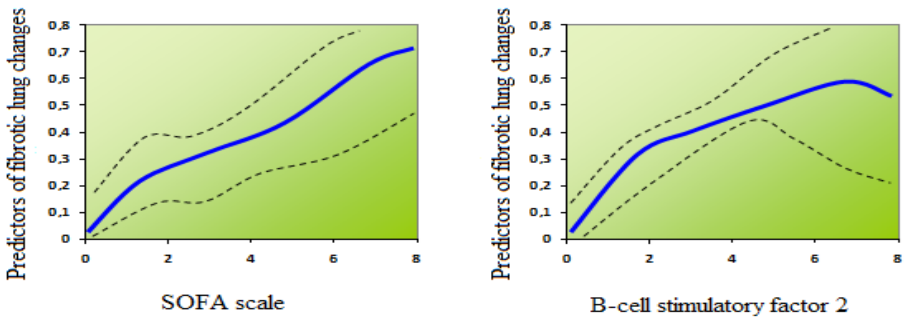

Figure 3. The need for the oxygen support in case of respiratory insufficiency in the acute disease phase

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Table 4. The Result of a multifactorial logistic regression analysis conducted to predict fibrotic changes in the lungs

Variables	OR	CI (95%)	*P* Value
Gender	2.003	(1.514-3.297)	0.033
Age	1.836	(0.321-2.289)	0.114
BMI	2.614	(1.674-4.022)	0.132
B-cell stimulatory factor 2	1.215	(0.267-3.215)	0.202
ALV	1.937	(1.039-3.106)	0.153
SOFA scale	2.363	(1.119-4.461)	0.053
ARDS	0.789	(0.124-1.672)	0.061

OR, odds ratio; CI, confidence interval; BMI, body mass index; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment

radiological fibrotic anomalies 8 months after hospitalization.

Our study identified a consistent relationship between the presence of fibrosis-like patterns during hospitalization. Analyzing such factors as the Sequential Organ Failure Assessment (SOFA) score, IL-6 levels in the blood serum, the duration of ventilation, and age-adjusted BMI allowed us to establish a linear correlation with the likelihood of developing predicted PF. In fully adjusted logistic regression models, each 1-unit increase in the SOFA score, a 0.5 pg/mL rise in IL-6 levels, and 1 day on a ventilator were associated with an increased likelihood of forming fibrotic structures on chest CT scans. Similarly, for each 1-unit increase in the BMI beyond the standard limit, the possibility of developing fibrotic lung changes increased by 1.35 times (Figure 3 and Table 4).

Discussion

The emergence of the COVID-19 pandemic has brought forth numerous challenges for health care systems worldwide. Beyond the immediate health crisis, the long-term effects of the disease have become an area of increasing concern (23, 24). Among these long-term effects, PF has garnered significant attention because of its severity and potential impact on survivors' quality of life (25-27). The results of this study underscore the significance of investigating the long-term effects of COVID-19, recognizing that a considerable number of patients experience health issues persistently, even months after their initial infection. This emphasizes the need for a deeper understanding of the post COVID-19 complications. Furthermore, these findings contribute to the identification of risk factors linked to the onset of PF after moderate to severe COVID-19. This aspect of the research is of paramount importance, given that PF can profoundly impact a patient's lung function and overall well-being. Notably, nearly half of the patients studied (49.35%) continued to exhibit fibrosis-like lung changes months after their initial COVID-19 infection. This finding emphasizes the potential long-lasting impact of the disease on the respiratory system. The underlying cause of PF after COVID-19 is still unclear; nonetheless, some theories refer to abnormal immune mechanisms and the resulting cytokine storm. More research is needed to determine why some patients develop PF and others do not.

Although we tried to assess the condition of PF during 2 follow-up periods (6 and 8 months), further studies should evaluate patients over a more extended follow-up period to determine whether the fibrotic abnormalities are temporary or permanent. Also, future studies should be conducted with a large sample size. Our study consistently observed a relationship between the presence of fibrosis-like patterns during a patient's hospitalization. We conducted an in-depth analysis, considering various factors, including the SOFA score, IL-6 levels in the blood serum, the duration of mechanical ventilation, and an age-adjusted BMI. This comprehensive examination allowed us to establish a linear correlation with the likelihood of developing predicted PF. The underlying cause of PF after COVID-19 is still unclear; however, some theories refer to abnormal immune mechanisms and the resulting cytokine storm. More research is needed to determine why some patients develop PF and others do not.

Although we tried to assess the condition of PF during two follow-up periods (6 and 8 months), further studies should evaluate patients over a more extended follow-up period to determine whether the fibrotic abnormalities are temporary or permanent. Also, it is planned to conduct studies with a large sample size in the future. Our study consistently observed a relationship between the presence of fibrosis-like patterns during a patient's hospitalization.

In summary, our research highlighted the significance of several critical factors—including SOFA score, IL-6 levels, duration of ventilation, and BMI—in predicting the development of PF in COVID-19 survivors. These findings highlight the importance of considering these factors when assessing the risk of fibrotic lung changes in post COVID-19 patients.

Lung fibrosis is a notable consequence in roughly half of COVID-19 survivors. Notably, patients who had endured severe pneumonia due to their COVID-19 infection faced a heightened risk of developing PF. Furthermore, our study revealed a clear connection between the risk of post COVID-19 PF and the severity level observed during the initial chest CT scan.

One of the key conclusions from the finding is that therapy interventions might help reduce post COVID-19 PF. The mention of antifibrotic and glucocorticosteroid medicines inspires hope in both patients and medical professionals. Further research into the efficacy of these treatments is warranted, as it may open doors to interventions that can slow down or even reverse the progression of fibrosis. It is crucial to assess not only the effectiveness of these medications but also their safety and long-term consequences.

Conclusion

PF is one of the most severe and frequently reported complications from COVID-19. We must work to determine the precise prevalence of this complication among

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COVID-19 survivors and its relationship to the consequences of the viral infection in the days to come. It is still too early to predict how post COVID fibrosis will develop naturally given the ongoing pandemic. Several research centers have already initiated follow-up studies of cohorts comprising COVID survivors. Based on our findings, post COVID-19 PF manifested in half of the survivors studied. Notably, patients who suffered severe pneumonia due to COVID-19 had a heightened risk of developing PF. The presence of consolidation during the initial chest CT scan was associated with an elevated likelihood of subsequent lung fibrosis after recovering from COVID-19. It is worth highlighting that while some patients exhibited a decrease in fibrotic abnormalities on chest CT scans after a 6-month follow-up, others did not. Identifying and managing these prognostic factors and evaluating the clinical utility of antifibrotic and glucocorticosteroid medications can play a pivotal role in averting the development or mitigating the progression of PF, a grave consequence of COVID-19. Patients who have experienced moderate to severe COVID-19-related clinical and radiological pneumonia need structured respiratory monitoring.

Conflict of Interests

The authors declare that they have no competing interests.

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