COVID-19 PULMONARY FIBROSIS: FROM ACUTE INFECTION TO CHRONIC COMPLICATIONS

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ABSTRACT

Background: SARS-CoV-2 is a virus that appeared in 2019 and led to the illness known as COVID-19. In the post-COVID-19 infection stage, a lot of patients suffer from fibrosis sequelae and alterations in pulmonary function. This systematic review and meta-analysis aimed to establish the frequency of pulmonary fibrosis after COVID-19 infection, identify risk factors, and recognize biomarkers linked to pulmonary fibrosis development post-COVID-19 infection.
Methods: Following PRISMA and MOOSE guidelines, studies published between January 1, 2020, and June 31, 2024, were analyzed.
Results: Fifteen studies (2,240 patients) revealed a 42.7% prevalence of post-COVID-19 pulmonary fibrosis. Patients with fibrosis were older (mean age 60 years vs. 49.5 years). Heart disease was a significant comorbidity. Symptoms included shortness of breath, chest pain, and muscle pain ($p<0.05$). Severe COVID-19 (ICU admission, mechanical ventilation, steroid/immunoglobulin therapy) increased fibrosis risk ($p<0.05$). Radiological findings included consolidation, ground-glass opacity, parenchymal bands, and interlobular thickening. Elevated IL-6, TNF-α, LDH, CRP, and D-dimer levels correlated with fibrosis ($p<0.05$).
Conclusion: Post-COVID-19 pulmonary fibrosis affected 42.7% of patients, strongly linked to severe COVID-19 and associated treatments. Common lung abnormalities included consolidation and parenchymal bands. Biomarkers IL-6, TNF-α, LDH, CRP, and D-dimer were significant contributors to fibrosis development.

Keywords: Acute infection, Chronic complications, COVID-19, Pulmonary fibrosis, SARS-CoV-2

ABSTRAK

Metabolit Latar belakang: SARS-CoV-2 adalah virus yang muncul pada tahun 2019 dan menyebabkan penyakit yang dikenal sebagai COVID-19. Pada tahap pasca infeksi COVID-19, banyak pasien yang mengalami gejala sisa fibrosis dan perubahan fungsi paru. Tinjauan sistematis dan meta-analisis ini bertujuan untuk menentukan frekuensi fibrosis paru setelah infeksi COVID-19, mengidentifikasi faktor risiko, dan mengenali biomarker yang terkait dengan perkembangan fibrosis paru pasca infeksi COVID-19.
Metode: Mengikuti pedoman PRISMA dan MOOSE, penelitian yang diterbitkan antara 1 Januari 2020 dan 31 Juni 2024 dianalisis.
Hasil: Lima belas studi (2.240 pasien) mengungkapkan prevalensi 42,7% fibrosis paru pasca-COVID-19. Pasien dengan fibrosis lebih tua (usia rata-rata 60 tahun vs 49,5 tahun). Penyakit jantung adalah komorbiditas yang signifikan. Gejalanya termasuk sesak napas, nyeri dada, dan nyeri otot ($p<0,05$). COVID-19 yang parah (masuk ICU, ventilasi mekanis, terapi steroid/imunoglobulin) meningkatkan risiko fibrosis ($p<0,05$). Temuan radiologis termasuk konsolidasi, opasitas kaca tanah, pita parenkim, dan penebalan interlobular. Peningkatan kadar IL-6, TNF-α, LDH, CRP, dan D-dimer berkorelasi dengan fibrosis ($p<0,05$).
Kesimpulan: Fibrosis paru pasca-COVID-19 memengaruhi 42,7% pasien, sangat terkait dengan COVID-19 yang parah dan perawatan terkait. Kelainan paru yang umum ditemukan termasuk konsolidasi dan pita parenkim. Biomarker IL-6, TNF-α, LDH, CRP, dan D-dimer merupakan kontributor yang signifikan terhadap fibrosis.

Kata Kunci: Acute infection, Chronic complications, COVID-19, Pulmonary fibrosis, SARS-CoV-2

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Introduction

SARS-CoV-2 is a virus that was first identified in 2019 and is responsible for the illness known as COVID-19. In March 2020, the World Health Organization (WHO) announced that COVID-19 was officially classified as a pandemic. The illness is very easily spread, mostly through coughing, talking in close proximity, or sneezing and exhibit mild symptoms like loss of taste or smell, fever, fatigue, and dry cough, or are asymptomatic.[1]

WHO data shows that around 14% of COVID-19 cases are categorized as severe and require oxygen therapy, while around 6% are deemed critical and necessitate treatment in an ICU and mechanical ventilation.[2] While most COVID-19 cases are expected to fully recover, recent studies suggest that 70-80% of patients may experience post-infection complications.[3] The respiratory morbidity that has the greatest long-term impact on a patient's respiratory health is pulmonary fibrosis.[4]

Research conducted by Amin et al in 2022 discovered that 44.9% of individuals who recovered from COVID-19 had pulmonary fibrosis, which was strongly linked to the onset of post-COVID-19 pulmonary fibrosis.[5] Another study stated that the occurrence of pulmonary fibrosis was 62% and 33% following SARS-CoV and MERS-CoV, respectively.[6,7]

Pulmonary fibrosis can occur as an impact of severe pulmonary damage or excessive healing. Many COVID-19 patients experience sequelae of fibrosis and changes in pulmonary function during the post-infection stage This indicates that patients with post-COVID-19 pulmonary fibrosis typically have restrictive pulmonary disease. Therefore, pulmonary fibrosis is considered one of the complications of severe COVID-19 infection.[8]

The respiratory tract is entered by the SARS coronavirus 2 (SARS-CoV-2) through the ACE-2 receptor on the lung epithelium. This virus has the ability to penetrate the lower respiratory tract and invade type II alveolar cells within the lungs, resulting in widespread alveolar injury.4 An increase in MMP2, MMP8, and cathepsin proteins, along with a decrease in E-cadherin protein, can also result in pulmonary fibrosis. Proteins like laminin, collagen VI, annexin A2, and fibronectin, found in the extracellular matrix of the lung basement membrane, were also downregulated.[9] The main stimulant for fibrosis, TGF-β, is directly increased by the nucleocapsid protein of SARS-CoV-1. This is due to the fact that the nucleocapsid protein in SARS-CoV-2 is 90% similar to SARS-CoV-1. Moreover, angiotensin II controls the activity of TGF-β, which increases in the lungs as ACE-2 is suppressed by viruses, enabling the development of pulmonary fibrosis.[10]

Currently, there are very few systematic reviews and meta-analyses in the literature that address pulmonary fibrosis after COVID-19 infection. Therefore, this meta-analysis seeks to elucidate the occurrence of pulmonary fibrosis after contracting COVID-19, identify possible factors contributing to disease advancement, and examine biomarkers linked to the development of pulmonary fibrosis.

Material and Methods

Search Strategy and Selection Criteria

The systematic review and meta-analysis followed the PRISMA and MOOSE guidelines.[11,12] We conducted a search in PubMed, Cochrane Library, EMBASE, and Web of Science for articles published from January 1, 2020, to May 31, 2024, using terms such as "lung fibrosis", "pulmonary fibrosis", "COVID-19", "coronavirus disease" and "sars-cov-2". This meta-analysis only included studies that met specific criteria: 1) recovered COVID-19 cases, 2) prospective studies and retrospective observations (cross-sectional and cohort), 3) studies with clearly defined fibrosis groups (fibrotic and non-fibrotic) for comparison and 4) english language. Three researchers (AM, HA, and IS) independently reviewed the located literature and evaluated each study for eligibility. All studies that were alike were excluded when selecting studies for the

research. Disputes were settled through discussions with experienced researchers (PA).

Data Extraction and Quality Assessment

The data was extracted from chosen studies by the researcher (HA) for inclusion in the meta-analysis. This data consists of information related to the author's name, publication year, research location, study type, sample size, coexisting conditions, symptoms, and factors affecting the severity of pulmonary fibrosis. The results of every study were logged using Microsoft Excel. Three researchers independently assessed the research quality using the Risk of Bias in Non-randomized Studies - of Exposure (ROBINS-E) tool.

Statistical Analysis

The data extracted was utilized for qualitative synthesis. Stata software version 24.0 was utilized for quantitative synthesis analysis of the data. Summary tables were produced displaying key variables in the form of frequencies, means, percentages, odds ratios, and p values. The statistical significance level was established at 0.05. A significance level was considered met with a p-value below 0.05.

RESULTS

A total of 671 articles were found in online databases. After conducting an initial search based on abstract and title, 15 articles were selected for a full-text evaluation. An in-depth assessment of those studies and eligibility criteria were applied. In the final results, a total of 15 articles were found to meet the criteria for inclusion and exclusion in the meta-analysis. The process of choosing articles is illustrated in (Figure 1.)

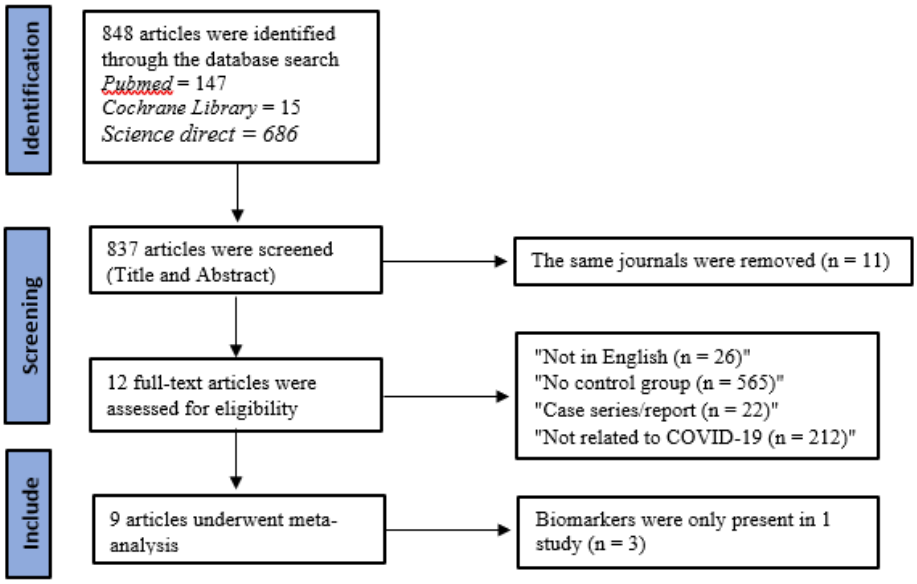

Figure 1. PRISMA flow diagram of study selection

Table 1. Study Characteristics

Authors	Year of Publication	Study Design	Country	Number of Samples		Assessment Time
				Fibrosis	No Fibrosis	
McGroder, et al.[13]	2021	Cohort	USA	32 (42%)	44 (58%)	4 months after entering the hospital
Cojocaru, et al.[14]	2023	Cohort	Romania	49 (42%)	68 (58%)	2 years after entering the hospital
Aul, et al.[15]	2021	Cohort	United Kingdom	36 (9.3%)	351 (90.7%)	6 weeks after discharge from hospital
Fanglin Li, et al.[16]	2022	Cohort	USA	60 (26.4%)	167 (73.6%)	15 days after discharge from hospital
Lee, et al.[17]	2022	Cohort	South	43	55	3 months after discharge from hospital

			Korea	(44%)	(56%)	
Zou, et al.[18]	2021	Cohort	China	239 (84.2%)	45 (25.8%)	30, 60 and 90 days after discharge from hospital
Marvisi, et al.[19]	2020	Cohort	Italy	23 (25.5%)	67 (74.5%)	8 weeks after discharge from hospital
Nabahati, et al.[20]	2021	Cross-sectional	Iran	90 (52%)	83 (48%)	after discharge from hospital
Liu, et al.[21]	2021	Cohort	China	12 (29.2%)	29 (70.8%)	7 months after discharge from hospital
Yu, et al.[22]	2020	Cohort	China	14 (43.75%)	18 (56.25%)	2 months after discharge from hospital
Ali, et al.[23]	2021	Cross-sectional	Egypt	25 (35.8%)	45 (64.2%)	4–6 weeks and 9–12 weeks after recovery
Li, et al.[24]	2021	Cohort	China	173 (60%)	116 (40%)	90-150 days after being declared infected with COVID-19
Han, et al.[25]	2021	Cohort	China	40 (35%)	74 (65%)	6 months after being declared infected with COVID-19
Yang, et al.[26]	2020	Cohort	China	76 (46%)	90 (54%)	51-63 days after being declared infected with COVID-19
Hu, et al.[27]	2020	Cohort	China	46 (60%)	30 (40%)	After recovery

Table 2. Study Quality Assessment

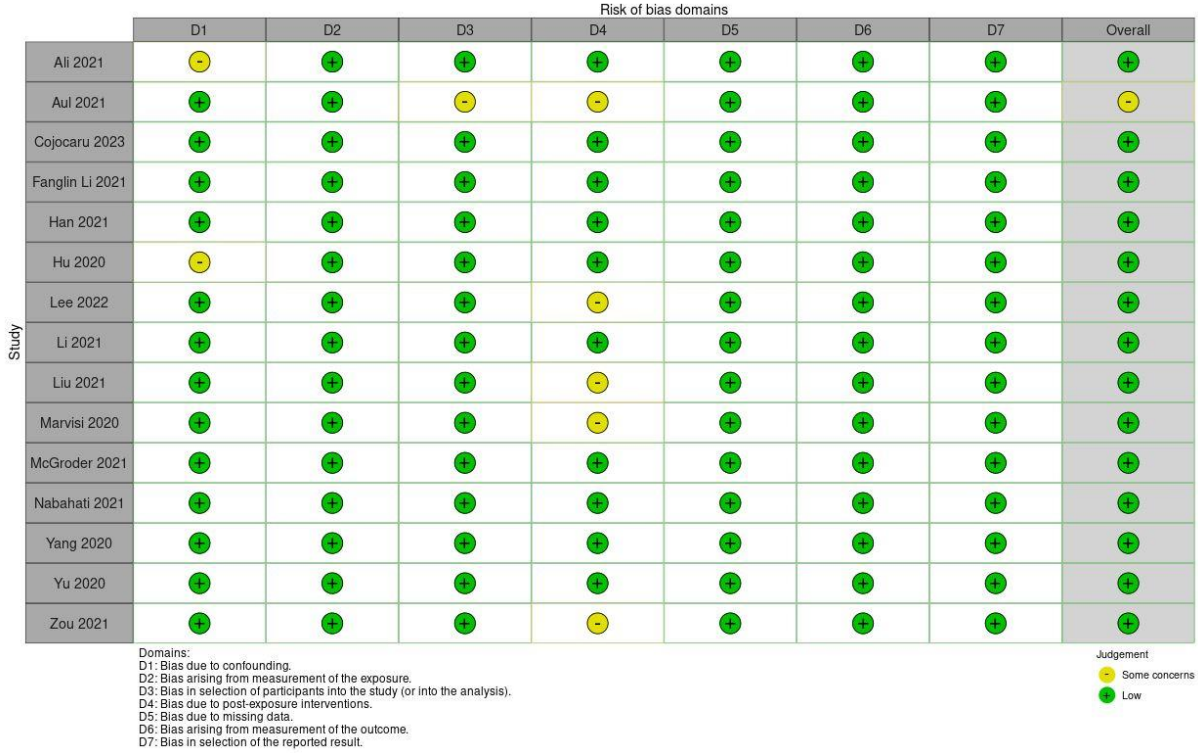

Table 3 . Characteristics of fibrotic and non-fibrotic patients

Characteristics	Total	Fibrosis	No Fibrosis
Overall	2240	958	1282
Age (average)	-	60	49.5
Male	876	410	466
Female	885	409	476

Table 4 . Comorbidities in fibrosis and non-fibrosis patients

Comorbidity	Total	Fibrosis	No Fibrosis	p-value	Odds ratio (95% CI)
Smoking	418	110	308	0.07	1.79 (0.94-3.41)
Diabetes	276	112	164	0.47	1.36 (0.59-3.14)
Hypertension	422	182	240	0.11	2.01 (0.84-4.80)
Asthma	82	31	51	0.33	1.38 (0.72-2.63)
COPD	49	33	16	0.09	2.12 (0.88-5.08)
Heart disease	225	92	133	0.03	2.14 (1.09-4.19)
Kidney disease	34	14	20	0.44	1.57 (0.50-4.96)

Table 5 . Factors associated with severity in fibrosis and non-fibrosis patients

Severity Factors	Total	Fibrosis	No Fibrosis	p-value	Odds ratio (95% CI)

Severe cases (CT score ≥ 18)	200/690	83/166	117/524	0.77	1.31 (0.21-8.06)
Enter the ICU	118/533	47/93	71/440	<0.00001	6.42 (2.97-13.87)
Invasive mechanical ventilation	86/1240	44/397	42/843	<0.00001	12.03 (6.49-22.30)
Non-invasive mechanical ventilation	68/569	29/289	39/280	0.73	1.99 (0.04-104.79)
Steroid therapy	348/967	219/418	129/549	<0.00001	5.56 (3.95-7.83)
Antiviral therapy	341/446	154/173	187/273	0.14	2.35 (0.75-7.43)
Antibiotic therapy	235/378	114/159	121/219	0.24	1.86 (0.65-5.6)
Immunoglobulin therapy	125/434	70/148	55/286	<0.00001	3.78 (2.34-6.11)

Table 6. Description of lung abnormalities

Description of Lung Abnormalities	Fibrosis	No Fibrosis	p-value	Odds ratio (95% CI)
Consolidation	167/218	148/276	0.02	2.67 (1.20-5.95)
Reticulation	36/334	14/203	0.1	6.61 (0.68-64.36)
Honeycombing	18/322	0/174	0.03	7.16 (1.28-40.01)
Parenchymal bands	121/294	18/129	0.006	135.77 (4.10-4,497.53)
Interlobular thickening	82/367	41/238	<0.00001	5.74 (3.22-10.25)
Ground glass opacity	232/480	251/388	0.56	0.64 (0.14-2.93)
Crazy paving	18/102	15/112	0.62	1.21 (0.57-2.57)

Table 7. Biomarkers of pulmonary fibrosis

Biomarkers	Fibrosis	No Fibrosis	p-value	Odds ratio (95% CI)
IL-1	122	120	0.07	0.05 (0.00-0.10)
IL-6	600	402	0.002	8.49 (3.23-13.75)
Il-8	122	120	0.37	1.11 (-1.30-3.51)
Il-10	122	120	0.28	2.27.77 (2.08-4.29)
TNF-α	122	120	<0.00001	3.19 (2.08-4.29)
LDH	364	397	0.0002	47.04 (21.92-72.16)
CRP	636	626	0.0005	16.76 (7.29-26.24)
D-dimer	622	608	<0.0001	199.79 (102.48-297.10)

DISCUSSION

Since the onset of the COVID-19 pandemic, over 293 million individuals across the globe have contracted the virus, with 256 million of them having recovered.[28] However, around 10–20% of people experience various medium and long-term complications, one of which is complications in the respiratory system.[29] It is important to gather data on pulmonary complications that could still exist or appear after recovering from COVID-19 for at least 4 weeks. The respiratory complications of COVID-19 are not well understood at this time; as a result, knowledge about this can assist in determining which groups are at risk and need continued monitoring. The occurrence of pulmonary fibrosis is seen as a significant issue in connection with lung complications from COVID-19, causing changes in the structure of lung tissues and overall decrease in lung function leading to lower quality of life.[30]

During the COVID-19 pandemic, several COVID-19 cases have progressed to a critical stage, requiring intensive care in the ICU. Invasive ventilation is often necessary for patients with acute respiratory failure.[31] Patients in critical condition in the ICU can be given antiviral drugs such as remdesivir, corticosteroids such as dexamethasone to reduce inflammation, and anticoagulants to prevent thrombosis.[32] Apart from that, strict monitoring of vital functions and organs must be carried out, as well as treatment efforts if the patient experiences sepsis and septic shock.[33]

In the latest meta-analysis, the total incidence rate of post-COVID-19 infection pulmonary fibrosis across all studies was 42.7%. In this research, the mean age of patients with fibrosis was significantly greater (60 years) compared to those without fibrosis (49.5 years). Out of all the comorbidities examined in this meta-analysis, only heart disease showed a correlation with the likelihood of developing pulmonary fibrosis. Yet, research by Minhua Yu, et al and Xiaohe Li, et al show that individuals with high blood pressure are at higher risk for developing post-COVID-19 pulmonary fibrosis.[22,24]

Research conducted by Zou et al revealed that monitoring post-COVID-19 pulmonary fibrosis patients for 30, 60, and 90 days confirmed that pulmonary fibrosis may improve in some patients with time. Nevertheless, in most other patients it will persist.18 Another study was conducted by Nabahati et al, where follow-up was examined

on post-COVID-19 pulmonary fibrosis patients for 6 months. Results of this study indicated that 33.9% of patients saw no improvement in pulmonary fibrosis on their CT scan results in the following 3 months.20 Furthermore, Han et al found in their research that the majority of patients with fibrosis continued to experience pulmonary fibrosis even one year after recovering from COVID-19.[25]

Previous research has discussed how serious COVID-19 is and its role as a risk factor for the onset of pulmonary fibrosis. Listed severity factors comprise invasive and non-invasive mechanical ventilation, CT score exceeding 18, and admission to the ICU.[13-27] This meta-analysis also found similar results. Zou et al's research found that the severity of COVID-19 correlated with the severity of pulmonary fibrosis.[18] The current meta-analysis shows that post-COVID-19 pulmonary fibrosis is more common in patients who had 6.42 times ICU admission, invasive mechanical ventilation 12.03 times, received steroid treatment 5.56 times, and received immunoglobulin therapy 3.78 times.

In this meta-analysis, the features of consolidation, interlobular thickening, honeycombing and parenchymal bands are radiological features that determine the development of pulmonary fibrosis after COVID-19. This is not much different from research conducted by Rabab Yasin, et al and Die Zhang, et al, where the radiological features of pulmonary abnormalities found most often in fibrosis patients were parenchymal bands, reticulations, and thickening of interlobular septal.[34,35]

Pulmonary fibrosis is a condition in which lung tissue becomes scarred and stiff, which can interfere with lung function. The development of pulmonary fibrosis has been linked to various inflammatory biomarkers and other molecules such as IL-6, TNF-α, LDH, CRP, and D-Dimer. IL-6 and TNF-α are inflammatory cytokines that have a significant impact on the immune system. Elevated levels of IL-6 and TNF-α are frequently seen in acute inflammatory conditions such as severe pneumonia and COVID-19. Studies show that high levels of IL-6 and TNF-α can trigger lung tissue damage through complex inflammatory mechanisms, ultimately contributing to the development of pulmonary fibrosis.[36,37] LDH is an enzyme released during tissue damage and is a marker of cell damage. Elevated LDH is often associated with the severity of lung disease, including COVID-19. Studies show that high LDH is associated with increased inflammation and damage to lung tissue, which can lead to pulmonary fibrosis.[38] CRP is an acute phase protein whose levels increase in response to inflammation. High CRP levels indicate an active inflammatory process in the body. In the context of pulmonary fibrosis, elevated CRP is often associated with disease severity and progressive lung damage, which may accelerate the process of pulmonary fibrosis.[39] D-dimer is a fibrin degradation product that is often used as an indicator of thrombotic activity. In diseases such as COVID-19, elevated D-dimer indicates excessive coagulation and inflammation, which can lead to micro thrombosis and endothelial damage in the lungs. This condition can worsen lung damage and accelerate fibrosis.[40] These biomarkers are not only interrelated but can also be used in combination to predict disease severity and possible progression of pulmonary fibrosis. By monitoring levels of IL-6, TNF-α, LDH, CRP, and D-dimer, clinicians can better understand and manage the risk of pulmonary fibrosis in patients with severe inflammatory conditions.

This meta-analysis has several limitations. The assessment timing in the studies varied widely in terms of both scale and duration, potentially causing bias in the overall prevalence of post-COVID-19 pulmonary fibrosis. Certain studies include a limited number of participants. Not all studies can be compared simultaneously due to the limited availability of complete and detailed data in only a few studies.

LIMITATION

This meta-analysis has several limitations that need to be considered. First, variations in the timing of assessment between the studies analyzed may lead to bias in the prevalence of post-COVID-19 pulmonary fibrosis. Second,

some studies had limited numbers of participants, so the results may not fully reflect the broader population. Third, the lack of complete and detailed data in some studies limits the ability to compare results directly. In addition, the diversity of diagnostic methods and definitions of pulmonary fibrosis between studies may affect the generalizability of the findings. Therefore, further studies with uniform designs and larger populations are needed to support these findings.

CONCLUSION

Most COVID-19 patients experienced pulmonary fibrosis (42.7%). ICU admission, invasive mechanical ventilation, steroid therapy, and immunoglobulin are all factors that are linked to a higher risk of developing post-COVID-19 pulmonary fibrosis. The most frequent pulmonary abnormalities seen in patients with pulmonary fibrosis are consolidation, ground glass opacity, parenchymal bands, and interlobular thickening. Biomarkers IL-6, TNF-α, LDH, CRP, and D-Dimer influence the development of pulmonary fibrosis. Further monitoring and evaluation are necessary to evaluate the development of pulmonary fibrosis.

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CONFLICTS OF INTEREST

All authors have disclosed no conflicts of interest

AUTHORS' CONTRIBUTIONS

Study Design: AM, IS, and HA. Data Collection and analysis: AM and IS. Data analyses and interpretation: AM and HA. Manuscript Writing: AM, IS, HA and PA. All authors contributed to revisions and have read and approved the final manuscript.

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