BIOMARKER OF POST-COVID-19 LUNG FIBROSIS

Gede Ari Mahendra Mardaningrat[1*], Putu Andrika[2], Isabella Soerjanto Putri[1], I Putu Hendri Aryadi[1]
[1] Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia
[2] Division of Pulmonary and Critical Care, Department of Internal Medicine, Udayana University/ Prof. dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali, Indonesia

ABSTRACT

Introduction: The World Health Organization (WHO) labeled COVID-19 as a pandemic. On January 7, 2024, an estimated 774,075,242 confirmed cases of COVID-19 had occurred, resulting in 7,012,986 deaths. Pulmonary fibrosis is commonly observed as a consequence of COVID-19 infection, with a reported prevalence of up to 83.3% in individuals who have recovered from the disease. Pulmonary fibrosis that develops after a COVID-19 infection arises from the immune system's reaction to the virus, resulting in inflammation and lung damage.

Objective: This systematic review and meta-analysis were conducted to determine the laboratory biomarker findings in patients with post-COVID-19 lung fibrosis.

Methods: Systematic review and meta-analysis adhering to the PRISMA and MOOSE guidelines. We conducted a literature search on PubMed, EMBASE, and Web of Science from January 1, 2020, to January 31, 2024.

Results: Nine eligible studies, including 1,406 patients, were identified. The research results showed that several biomarkers had statistically significant values such as lymphocytes (MD: -0.35; 95% CI: -0.49; -0.21), CRP (MD: 40.73; 95% CI: 27.78; 53.69), D-dimer (MD: 0.76; 95% CI: 0.18; 1.34), lactate (MD: 38.43; 95% CI: 19.73; 57.13), and interleukin-6 (MD: 16.97; 95% CI: 2.57; 31.37). Meanwhile, for biomarkers such as white blood cells (MD: 0.14; 95% CI: -0.54; 0.81) and neutrophils (MD: 3.71; 95% CI: -3.80; 11.23), the values were not statistically significant for the occurrence of lung fibrosis.

Conclusion: The diagnosis of pulmonary fibrosis is generally established using biopsy or CT scans. However, in some hospitals with limitations on healthcare resources and equipment such as CT scans, these biomarkers can be used in diagnosing pulmonary fibrosis, especially in patients after experiencing COVID-19 infection.

Keywords: Biomarker, COVID-19, Lung Fibrosis, Sars-Cov2

Correspondence :
Gede Ari Mahendra Mardaningrat
Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia
Division of Pulmonary and Critical Care, Department of Internal Medicine, Udayana University/Prof. dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali, Indonesia
email: ina.j.chest@gmail.com

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Introduction

Four years ago on 11 March 2020, the World Health Organization (WHO) labeled COVID-19 as a pandemic. On January 7, 2024, an estimated 774,075,242 confirmed cases of COVID-19 had occurred, resulting in 7,012,986 deaths.[1] COVID-19 is an illness affecting the respiratory system, showing various symptoms from no symptoms at all to severe respiratory issues leading to organ damage.[2] COVID-19 is a result of the coronavirus, a type of RNA virus with a diameter varying from 60 nm to 140 nm. Its surface features spike-like projections, giving it a crown-like appearance when viewed through an electron microscope.[3] Within cells, SARS-CoV-2 reproduces leading to tissue harm. The outcome of COVID-19 varies based on factors such as age, existing health conditions, overall health, duration between symptom onset and treatment, and how the individual responds to therapy.[2] COVID-19 presents numerous long-lasting effects, including respiratory issues, notably pulmonary fibrosis, which affects the lungs.[4] Pulmonary fibrosis is commonly observed as a consequence of COVID-19 infection, with a reported prevalence of up to 83.3% in individuals who have recovered from the disease.[5] A recent meta-analysis study stated that approximately 44.9% of COVID-19 survivors suffered from pulmonary fibrosis with various associated factors.[6] Another research conducted by the Faculty of Medicine, Airlangga University at RSUD Dr. Soetomo Surabaya in the ICU and HCU stated that pulmonary fibrosis was found in 94.7% of patients.[7]

Pulmonary fibrosis that develops after a COVID-19 infection arises from the immune system's reaction to the virus, resulting in inflammation and lung damage. The body's response to COVID-19 triggers inflammatory reactions like cytokine storms and other forms of inflammation to repair injured tissues. The virus can attach to angiotensin-converting enzyme (ACE2) receptors in the upper respiratory tract, resulting in elevated levels of angiotensin 2. This process activates interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), increases the presence of neutrophils and macrophages, and causes damage to the endothelial cells. Angiotensin 2 plays a role in controlling collagen gene expression via pathways like mitogen-activated protein kinase/extracellular signal-regulated kinase and transforming growth factor-β (TGF-β), which are key factors in fibrosis. Consequently, excessive production of metalloproteinases due to this regulation leads to damage to both epithelial and endothelial cells. On computed tomography (CT) scans, pulmonary fibrosis appears as ground-glass opacities, thickening of the lung's interstitial tissue, irregular lung surfaces, and bands spread across the lung parenchyma.[6] Prolonged inflammation and immune system imbalances can prompt the formation of scar tissue, impairing the lungs' capacity to function effectively. This can manifest in symptoms like breathlessness, coughing, and fatigue.[2]

Several studies on biomarkers in patients with post-COVID-19 pulmonary fibrosis have been published in China and other countries.[8-16] Other studies have reported the characterization of pulmonary fibrosis and laboratory findings in post-COVID-19 patients. However, the literature still lacks a systematic review of laboratory biomarkers. This systematic review and meta-analysis were conducted to determine laboratory biomarker findings in post-COVID-19 pulmonary fibrosis patients.

Material and Methods

Search Strategy and Selection Criteria

We conducted a systematic review and meta-analysis adhering to the PRISMA and MOOSE guidelines.[17,18] We conducted a literature search on PubMed, EMBASE, and Web of Science from January 1, 2020, to January 31, 2024 using specific search terms such as "biomarker," "lung fibrosis," "COVID-19," "coronavirus disease," and "SARS-CoV-2." We focused on cohort studies pertaining to biomarkers associated with post-COVID-19 pulmonary fibrosis. Only publications in English were considered for inclusion. Three researchers (AM, HA,

and IS) independently screened the literature and evaluated each study for eligibility. Any disagreements were resolved by consulting a senior investigator (PA).

Data Extraction and Quality Assessment

Researcher (HA) extracted biomarker-related data from the chosen studies to be included in the meta-analysis. This data encompassed details such as author names, publication year, study location, study design, sample size, and the inferred association of lung fibrosis biomarkers in post-COVID-19 patients. Microsoft Excel was utilized to document the findings from each study. The quality of the studies was assessed independently by three researchers using the Newcastle-Ottawa Scale (NOS), specifically designed for evaluating cohort studies.

Statistical Analysis

A meta-analysis was conducted to gauge the strength of association between relevant biomarkers and the development of lung fibrosis in post-COVID-19 individuals. We employed a random-effects model to estimate the effect of these biomarkers on the occurrence of lung fibrosis in post-COVID-19 patients, along with their corresponding 95% confidence intervals (CI). The I2 statistic was utilized to evaluate heterogeneity across studies, with values of 25%, 50%, and 75% indicating low, moderate, and high levels of heterogeneity, respectively. Graphical representations were generated for post-COVID-19 lung fibrosis biomarkers analyzed through meta-analysis using STATA version 17.0.

RESULTS

An initial search across online databases yielded 848 articles. Following screening based on abstracts and titles, 12 articles were retained for full-text evaluation. After a comprehensive assessment of these studies and the application of eligibility criteria, 9 articles were found to meet the criteria for inclusion and exclusion in the meta-analysis. The selection process is depicted in Figure 1

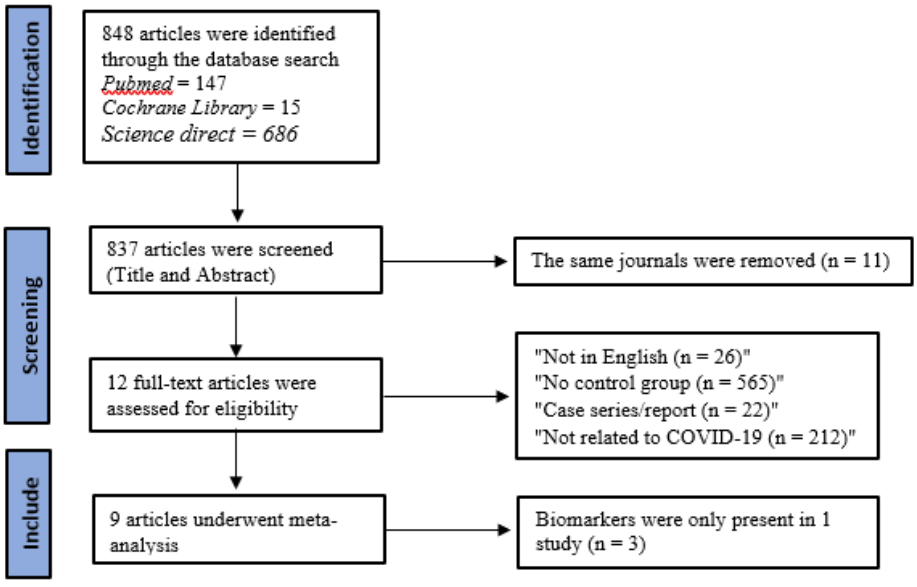

Figure 1. PRISMA flow diagram of study selection

Table 1. Study Characteristic

Author	Year	Country	Study Type	Number of Samples	
				Pulmonary Fibrosis	Non-Pulmonary Fibrosis
Fanglin Li,etc [8]	2022	China	*Retrospective*	60	167
Jia-Ni Zou, etc [9]	2021	China	*Retrospective*	239	45
Maurizio Marvisi, etc [10]	2020	Italy	*Retrospective*	23	67
Mengqi Liu, etc [11]	2021	China	*Retrospective*	12	29
Doina-Clementina Cojocaru, etc [12]	2023	Romania	*Retrospective*	49	68
Xiaohe Li, etc [13]	2021	China	*Retrospective*	40	74
Minhua Yu, etc [14]	2020	China	*Retrospective*	14	18
Raminder Aul, etc [15]	2021	Inggris	*Retrospective*	36	367
Inhan Lee, etc [16]	2022	Korea	*Retrospective*	43	55

Table 2. Assessment of Cohort Study Quality

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Overall assessment
Fanglin Li,etc [8]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Jia-Ni Zou, etc [9]	✔	✔	✔	✔	✔	✔	✔	-	Good
Maurizio Marvisi, etc [10]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Mengqi Liu, etc [11]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Doina-Clementina Cojocaru, etc [12]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Xiaohe Li, etc [13]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Minhua Yu, etc [14]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Raminder Aul, etc [15]	✔	✔	✔	✔	✔	✔	✔	✔	Good
Inhan Lee, etc [16]	✔	✔	✔	✔	✔	✔	✔	✔	Good

Pulmonary Fibrosis Biomarkers

White Blood Cell Count

Nine studies examined the comparison of white blood cell counts between patients with lung fibrosis and those without fibrosis. The mean white blood cell count recorded was notably higher in patients with lung fibrosis compared to those without fibrosis (Mean Difference: 0.14; 95% Confidence Interval: -0.54; 0.81). However, there was considerable variability in the data distribution among the study findings (I-square: 81%). This marker did not show significance for the occurrence of post-COVID-19 lung fibrosis (p-value: 0.69), as illustrated in Figure 2.

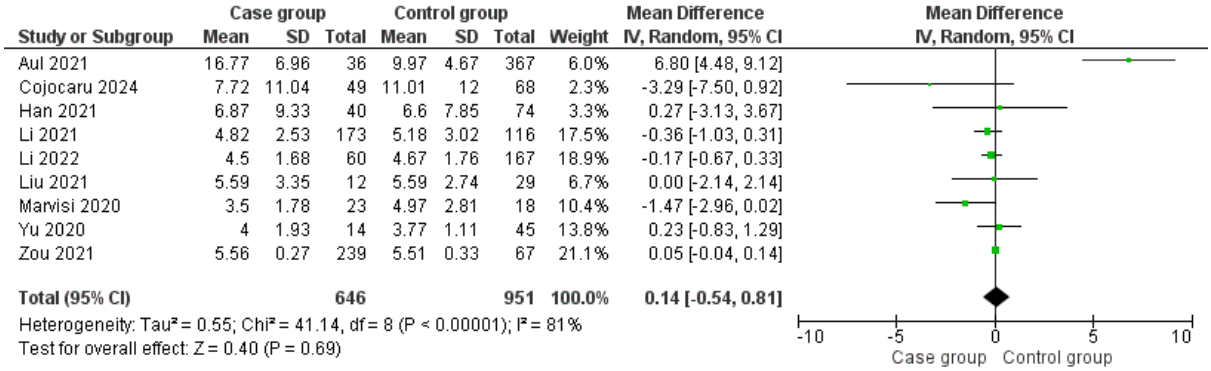

Figure 2. The impact of white blood cells on the development of post-COVID-19 lung fibrosis. A mean difference > 0 suggests that patients with lung fibrosis have higher white blood cell counts compared to those without fibrosis.

Neutrophils

Two studies examined the comparison of neutrophil levels between patients with lung fibrosis and those without fibrosis. The mean neutrophil levels measured were notably higher in patients with lung fibrosis compared to those without fibrosis (Mean Difference: 3.71; 95% Confidence Interval: -3.80; 11.23). However, there was significant variability in the data distribution among the study findings (I-square: 92%). This marker did not demonstrate significance for the occurrence of post-COVID-19 lung fibrosis (p-value: 0.33), as depicted in Figure 3.

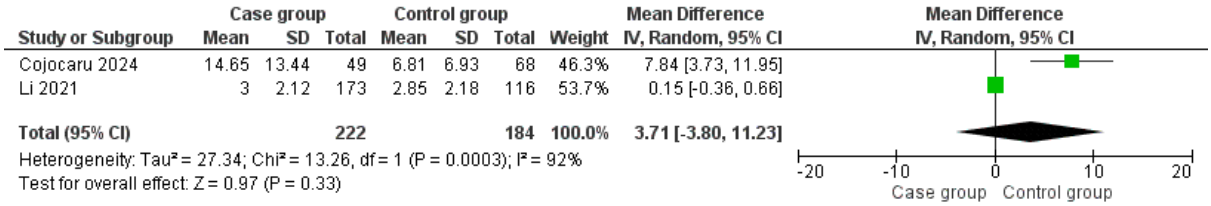

Figure 3. The impact of neutrophils on the development of post-COVID-19 lung fibrosis. A mean difference > 0 suggests that patients with lung fibrosis exhibit higher levels of neutrophils compared to those without fibrosis.

Lymphocytes

Eight studies examined the comparison of lymphocyte levels between patients with lung fibrosis and those without fibrosis. The mean lymphocyte level measured was significantly lower in patients with lung fibrosis compared to those without fibrosis (Mean Difference: -0.35; 95% Confidence Interval: -0.49; -0.21). There was substantial variability in the distribution of data among the study findings (I-square: 79%). This marker proved to be significant for the occurrence of post-COVID-19 lung fibrosis (p-value: <0.00001), as illustrated in Figure 4.

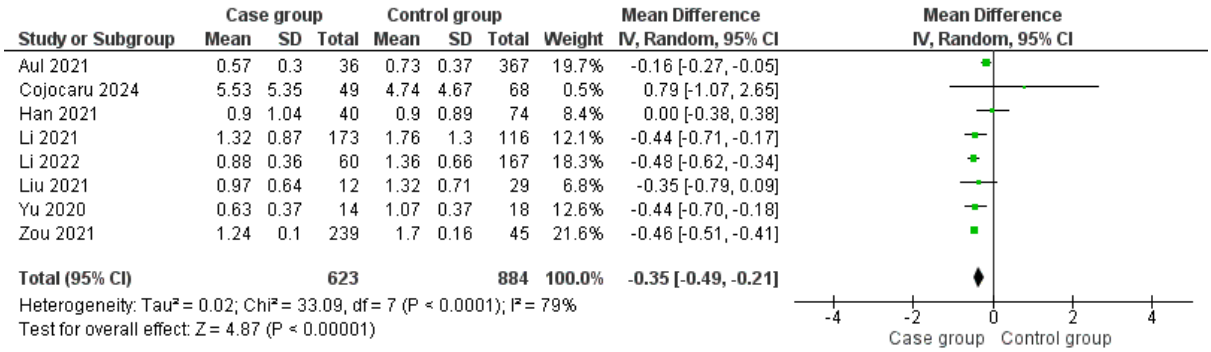

Figure 4. The impact of lymphocytes on the development of post-COVID-19 lung fibrosis. A mean difference < 0 suggests that patients with lung fibrosis have lower levels of lymphocytes compared to those without fibrosis.

C-Reactive Protein (CRP)

Ten studies investigated the comparison of C-reactive protein (CRP) levels between patients with lung fibrosis and those without fibrosis. The mean CRP level measured was notably higher in patients with lung fibrosis compared to those without fibrosis (Mean Difference: 40.73; 95% Confidence Interval: 27.78; 53.69). Significant variability was observed in the data distribution among the study findings (I-square: 78%). This marker was found to be significant for the occurrence of post-COVID-19 lung fibrosis (p-value: <0.00001), as depicted in Figure 5.

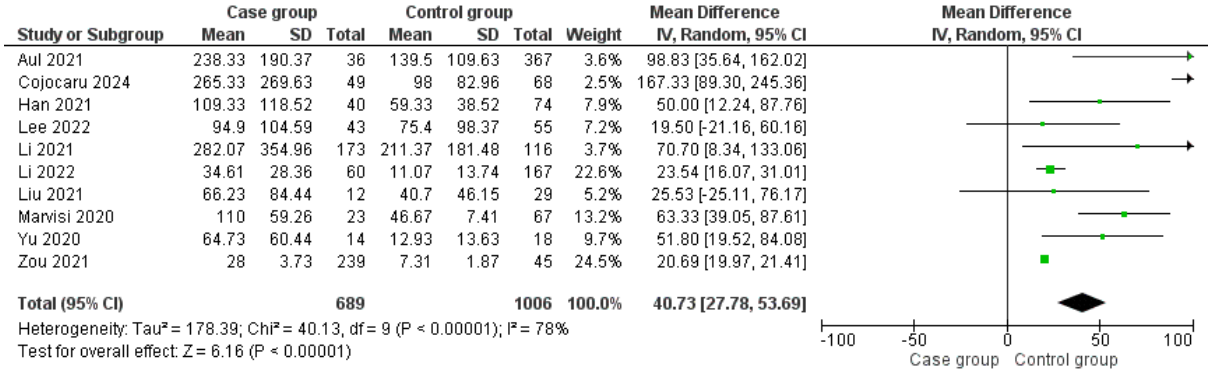

Figure 5. The influence of C-reactive protein (CRP) on the development of post-COVID-19 lung fibrosis. A mean difference > 0 suggests that patients with lung fibrosis exhibit higher CRP levels compared to those without fibrosis.

D-Dimer

Eight studies examined the comparison of D-Dimer levels between patients with lung fibrosis and those without fibrosis. The mean D-Dimer level measured was notably higher in patients with lung fibrosis compared to those without fibrosis (Mean Difference: 0.76; 95% Confidence Interval: 0.18; 1.34). Significant variability was observed in the data distribution among the study findings (I-square: 95%). This marker was found to be significant for the occurrence of post-COVID-19 lung fibrosis (p-value: 0.01), as illustrated in Figure 6.

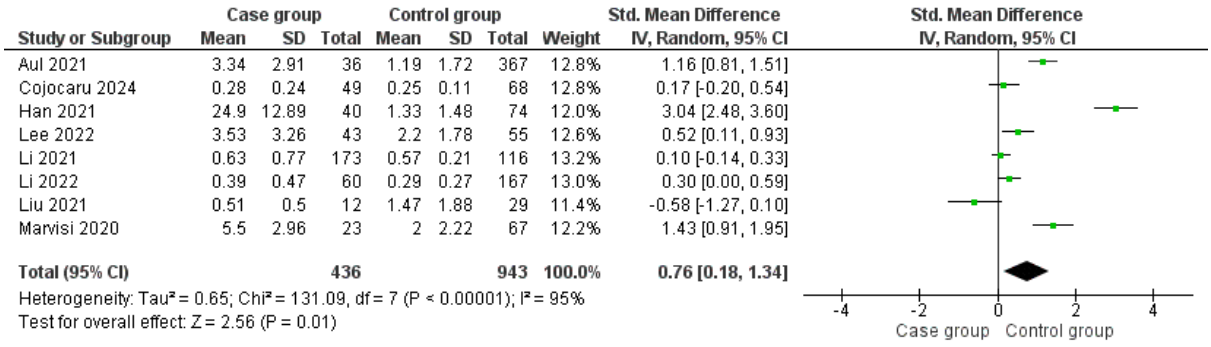

Figure 6. The impact of D-Dimer on the development of post-COVID-19 pulmonary fibrosis. A mean difference > 0 suggests that patients with pulmonary fibrosis exhibit higher

levels of D-Dimer compared to those without fibrosis.

Lactate

Six studies examined the comparison of lactate levels between patients with pulmonary fibrosis and those without fibrosis. The mean lactate level measured was notably higher in patients with pulmonary fibrosis compared to those without fibrosis (Mean Difference: 38.43; 95% Confidence Interval: 19.73; 57.13). There was no observed heterogeneity in the data distribution among the study findings (I-square: 0%). This marker was found to be significant for the occurrence of post-COVID-19 pulmonary fibrosis (p-value: <0.0001), as depicted in Figure 7.

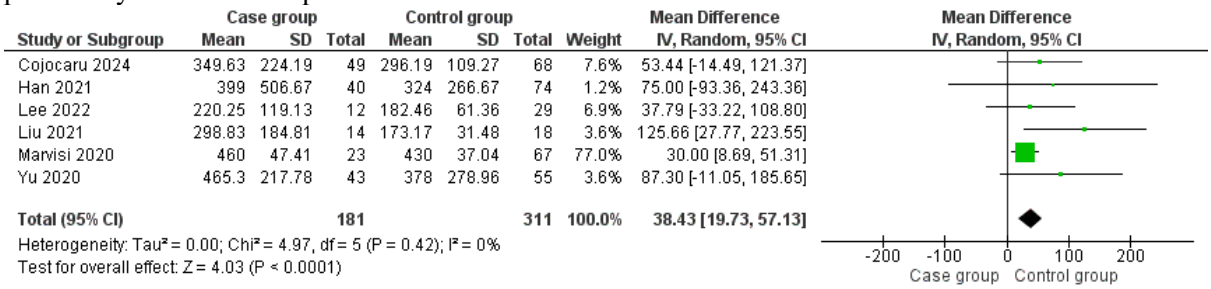

Figure 7. The impact of lactate on the development of post-COVID-19 pulmonary fibrosis. A mean difference > 0 suggests that patients with pulmonary fibrosis exhibit higher levels of lactate compared to those without fibrosis.

Interleukin-6 (IL-6)

Five studies investigated the comparison of interleukin-6 (IL-6) levels between patients with pulmonary fibrosis and those without fibrosis. The mean IL-6 levels measured were notably higher in patients with pulmonary fibrosis compared to those without fibrosis (Mean Difference: 16.97; 95% Confidence Interval: 2.57; 31.37). Significant variability was observed in the data distribution among the study findings (I-square: 98%). This marker was found to be significant for the occurrence of post-COVID-19 pulmonary fibrosis (p-value: 0.02), as depicted in Figure 8.

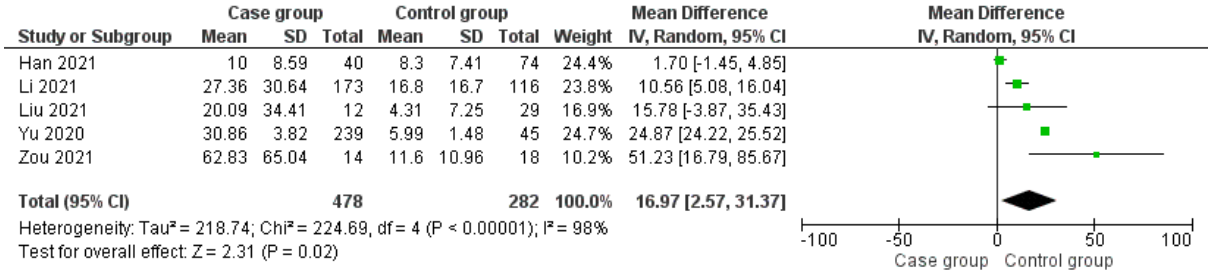

Figure 8. The impact of interleukin-6 on the development of post-COVID-19 pulmonary fibrosis. A mean difference > 0 suggests that patients with pulmonary fibrosis exhibit higher levels of interleukin-6 compared to those without fibrosis.

DISCUSSION

Infection with SARS-CoV-2 triggers diverse human immune defense responses, including immune responses (e.g., WBC, lymphocytes, and neutrophils), inflammatory processes (e.g., c-reactive protein and procalcitonin), and activation of blood clotting factors (e.g., platelet count and procalcitonin). When the virus attacks tissues, inflammation significantly increases, as indicated by elevated inflammatory marker levels.[19] This meta-analysis study showed increased leukocytes, neutrophils, CRP, D-Dimer, lactate, ESR, and IL-6 levels in COVID-19 patients with pulmonary fibrosis compared to those without fibrosis. The severity of pneumonia is recognized as a risk factor for post-COVID-19 pulmonary fibrosis. Past research indicates that COVID-19 patients with pulmonary fibrosis tend to exhibit increased levels of serum inflammatory markers such as leukocytes, neutrophils, D-

Dimer, CRP, and procalcitonin compared to COVID-19 patients without fibrosis.[20] Another study by Alkhayat demonstrated that CRP levels, an indicator for post-COVID-19 pulmonary fibrosis, correlate with the level of inflammation and are not influenced by factors such as gender, age, and physical condition.[21] Excessive inflammatory responses due to severe lung inflammation and necrosis result in the overproduction of inflammatory cytokines associated with increased CRP levels in severe COVID-19 patients. Cytokines have a "double-edged sword" effect; they play a protective role in controlling infections, while in a hyperactive state, they cause excessive lung inflammation, lung damage, and resulting pulmonary fibrosis [22]

The primary cause of fibrosis attributed to SARS-CoV-2 is the hyperinflammatory state it induces. The "cytokine storm" is characterized by an overproduction of proinflammatory cytokines triggered by the host's exaggerated immune response to SARS-CoV-2. Among the most significant mediators of the cytokine storm in COVID-19 are interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).[23] Another investigation conducted by Chen et al. revealed that COVID-19 patients experiencing severe symptoms demonstrate elevated levels of IL-6 and TNF-α, along with increased levels of alanine aminotransferase, lactate dehydrogenase (LDH), CRP, and D-Dimer, as well as decreased levels of albumin and lymphocyte counts, in comparison to patients with moderate COVID-19 symptoms.[24] In COVID-19 patients, elevated IL-6 levels are observed in individuals treated in intensive care units (ICUs) and among those who do not survive. IL-6 has been found to promote profibrotic pathways in fibroblasts among patients with pulmonary fibrosis, while it triggers apoptosis pathways in normal fibroblasts. Studies in mice with bleomycin-induced pulmonary fibrosis have shown significantly increased levels of circulating IL-6 compared to control mice. In laboratory experiments, the IL-6Rα-mediated pathway has been demonstrated to activate fibroblast proliferation and the production of extracellular matrix proteins. Additionally, COVID-19 leads to the release of various profibrotic cytokines, contributing to the development of pulmonary fibrosis.[25]

In this research, COVID-19 patients diagnosed with pulmonary fibrosis exhibited lower lymphocyte counts compared to COVID-19 patients without pulmonary fibrosis. This finding aligns with prior studies where COVID-19 patients with mild symptoms displayed normal lymphocyte counts, whereas those with severe symptoms demonstrated reduced lymphocyte counts.[26,27] Lymphocyte counts are essential for the body's defense against SARS-CoV-2. When the virus interacts with the immune system, it leads to various clinical symptoms, making lymphocyte count a significant indicator. A decrease in lymphocyte count suggests immune compromise and can worsen the prognosis for COVID-19 patients. SARS-CoV-2 infection particularly impacts T lymphocytes, notably CD4+ and CD8+ T cells, which play crucial roles in the pathological mechanisms of COVID-19.[20]

In the pathophysiological mechanism of COVID-19 pneumonia, various pathways involving immune system activation, inflammation, blood clotting, and the direct impact of the virus on the lungs and other tissues outside the lungs can lead to increased D-Dimer levels. This meta-analysis study showed an increase in D-Dimer in COVID-19 patients with pulmonary fibrosis compared to COVID-19 patients without pulmonary fibrosis. Fibrinogen degradation products (FbDP) are a diverse array of soluble fragments present in the bloodstream due to two simultaneous physiological processes. Firstly, blood clotting transforms soluble fibrinogen into stable, insoluble fibrin through the actions of the enzyme thrombin and factor XIIIa. Secondly, fibrinolysis breaks down fibrin clots via the enzyme plasmin, resulting in the generation of the D-Dimer fragment. In COVID-19 patients, levels of D-Dimer increase notably in severe cases, with the highest elevations observed in critically ill patients and those who do not survive.[28]

In COVID-19 patients diagnosed with pulmonary fibrosis, lactate dehydrogenase (LDH) levels are elevated compared to those without pulmonary fibrosis. This finding is in line with previous studies indicating that high serum LDH concentrations are linked to an increased risk of death from pneumonia in COVID-19 patients. Serious infections such as interstitial pneumonia or acute respiratory distress syndrome (ARDS) can lead to tissue damage due to cytokine production, resulting in the release of LDH into the bloodstream. When assessing inflammation, LDH is closely associated with direct lung damage and shows a marked increase in cases of extensive tissue damage.[29]

CONCLUSION

Overall, the findings of this meta-analysis, which included 9 retrospective cohort studies involving 1,406 patients, indicate that several statistically significant biomarkers can be used to assess the occurrence of pulmonary fibrosis in patients after experiencing COVID-19 infection, such as lymphocytes, CRP, D-Dimer, lactate, and interleukin-6. The diagnosis of pulmonary fibrosis is generally established using biopsy or CT scans. However, in some hospitals with limitations on healthcare resources and equipment such as CT scans, these biomarkers can be used in diagnosing pulmonary fibrosis, especially in patients after experiencing COVID-19 infection. Further research is needed to further explore other biomarkers that can be used as references for assessing pulmonary fibrosis and to address the limitations of this study.

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