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Prevalence and Risk Factors of Post-COVID-19 Pulmonary Fibrosis: A Meta-analysis

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Abstract: *COVID-19 is a global epidemic caused by severe acute respiratory syndrome coronavirus 2 infection. However, the understanding of long-term respiratory diseases in COVID-19 survivors remains limited.To identify the incidence and risk factors of post-COVID-19 pulmonary fibrosis, a comprehensive search of relevant studies published before the 2nd of April 2023 in PubMed, Embase, Web of Science, and Cochrane Library was conducted, and 18 papers were eligible for this study. The existing literature evidence showed that about 36.4% of COVID-19 survivors may have developed pulmonary fibrosis, and people with advanced age, male, hypertension, diabetes, glucocorticoid therapy, mechanical ventilation, prolonged hospitalization, and severe COVID-19 are at higher risk of developing this sequela.*

Keywords: *COVID-19, SARS-CoV-2, Pulmonary Fibrosis, Risk Factors, Meta-analysis*

COVID-19 is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with atypical pneumonia as the main clinical manifestation[1]. The virus spread rapidly after the first case of infection was confirmed in Wuhan, China, causing a worldwide pandemic and a significant health crisis for human beings[2–4] . With a further understanding of SARS-CoV-2, studies have found that many COVID-19 survivors continue to have post-infection complications in various organs and systems after nucleic acid conversion[5]. Previous studies on the long-term consequences of coronavirus pandemics have shown that pulmonary fibrosis is one of its serious and common sequelae[6]. Given the scale of the current COVID-19 pandemic, even if only a small number of COVID-19 survivors develop pulmonary fibrosis, there are also concerns about the resulting health burden and strain on the global public health system. Since the exact prevalence and risk factors of post-COVID-19 pulmonary fibrosis (PCPF) in COVID-19 survivors have not been fully established before, this study aimed to investigate the prevalence and potential risk factors of the disease.

1. Methods

1.1 Search Strategy

Two researchers conducted comprehensive electronic in PubMed, The Cochrane Library, Web of Science, and Embase to identify relevant articles from inception to 2 April 2023. Articles were identified with the following search terms: “COVID-19” OR “SARS-CoV-2” OR “Coronavirus disease 2019” OR “2019-nCoV Infection” AND “lung fibrosis” OR “pulmonary fibrosis” OR “Alveolitis, Fibrosing” OR “fibrotic lung disease”. The search was limited to humans and the English language.

1.2 Inclusion and Exclusion Criteria for Articles

The inclusion criteria were as follows: (1) the study population included recovered COVID-19 patients; (2) observational studies (prospective studies, cross-sectional surveys, and retrospective studies); (3) a definite diagnosis of pulmonary fibrosis; (4) detailed provision of study methods and patient characteristics were provided.

1.3 Data extraction

Literature screening, data extraction, and verification were performed independently by two investigators through the same data extraction method. Any disagreement regarding study selection was

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resolved by discussion with a third author. The extraction template contains the author's name, publication year, geographical location, study design, sample size, baseline data of included patients, clinical characteristics and so on.

1.4 Literature quality and bias risk assessment

The literature included was independently evaluated by two investigators using the Newcastle-Ottawa quality assessment scale (NOS) for study quality and risk of bias. The NOS scale consists of three parts (study object selection, comparability between groups, exposure or result evaluation), and 8 items were evaluated with a full score of 9. A score of ≥ 7 was classified as high-quality literature, 5-6 as moderate-quality literature, ≤ 4 as low-quality literature, and low-quality literature was given for exclusion.

1.5 Statistical Methods

Meta-analysis of proportions was used to pool the incidence of PCPF, and the heterogeneity of the studies included in this meta-analysis was assessed by the Q statistic test and the I^2 statistic test, where $P > 0.1$ and $I^2 \geq 50\%$ indicated evidence of heterogeneity. The random-effects model was selected when I^2 was significant (≥50%); otherwise, the fixed-effects model was selected. A sensitivity analysis was conducted to assess the stability and reliability of the included studies. Egger's test and Begg's test were used to evaluate publication bias, and the trim-and-fill method was used to evaluate the impact of publication bias on the results of the study.The collected study data were synthesized and analyzed using the STATA software, version 17.0 (Stata Corp LLC, College Station, TX 77845, USA).

2. Results

2.1 Study selection

The systematic search initially revealed a total of 5397 articles. Before further screening, 1880 duplicate articles were removed. The titles and abstracts of 3517 articles were screened, of which 3397 were excluded due to irrelevancy. After applying the inclusion criteria of the current study, only 18 articles were included in the meta-analysis. The detailed PRISMA flow chart is shown in Figure 1.

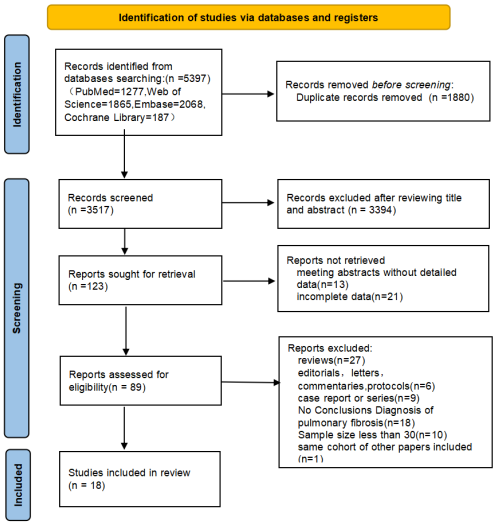

Figure 1: Study selection PRISMA flow chart.

2.2 Study characteristics

All the included studies were observational, including 15 cohort studies [7–21] and 3 cross-sectional studies, [22–24] of which 9 were conducted in China, 3 in the United Kingdom, 2 in Italy, and 1 in New Zealand, Spain, South Korea, and Brazil. Among the included studies, only one had an NOS score of 6, while the rest scored above 7, indicating a generally high methodological quality of the included research. More details regarding the characteristics of the included studies are shown in Table 1.

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Table 1: Baseline characteristics of the included studies.

Author	year	Country	Study Design	Sample Size	Gender		Age	Assessment time	NOS
					Male N(%)	Female N(%)			
Aul R et al[7]	2021	UK	Cohort	387	219(57%)	165(43%)	NA	2 months	7
Bocchino M et al[8]	2022	UK	Cohort	84	56(67%)	28(33%)	61±11	12 months	8
Caruso D et al[9]	2021	Italy	Cohort	118	56(47%)	62(53%)	65±12	6 months	8
Han X et al[10]	2021	China	Cohort	114	80(70%)	34(30%)	54+12	6 months	8
Lee I et al[11]	2022	Korea	Cohort	98	65(66%)	33(34%)	NA	3 months	7
Li D et al[12]	2022	China	Cohort	155	81(52%)	74(48%)	43 (34–55)	2 years	7
Li F et al[22]	2022	China	Cross-sectional	227	107(47%)	120(53%)	64 (47- 67)	within 1 year	8
Li X et al[13]	2021	China	Cohort	289	141(47%)	148(53%)	NA	4 months	8
Liao T et al[14]	2021	China	Cohort	303	59(20%)	244(80%)	38 (33–48)	1 year	7
Liu M et al[15]	2021	China	Cohort	41	12(29%）	29(81%)	50+14	7 months	8
Marvisi M et al[23]	2020	Italy	Cross-sectional	90	23(26%)	67(74%)	NA	2 months	7
Ribeiro C et al[16]	2023	Brazil	Cohort	175	88(50%)	87(50%)	NA	Almost 18 months	7
Robey R et al[17]	2021	UK	Cohort	221	135(61%)	86(39%)	58	4 months	7
Tarraso J et al[18]	2022	Spain	Cohort	284	157(55%)	127(45%)	60.5±11.9	1 year	8
Van G et al[19]	2021	Netherlands	Cohort	48	33(69%)	16(31%)	63 (55–68)	3 months	6
Yang Z et al[24]	2020	China	Cross-sectional	166	69(42%)	97(58%)	57+15	2 months	7
Zhao Y et al[20]	2021	China	Cohort	94	54(57%)	40(43%)	NA	1 year	7
Zhou F et al[21]	2021	China	Cohort	120	49(41%)	71(59%)	51.6 ± 10.8	1 year	7

Note: Values are shown as mean ± SD or median [Q1–Q3]; NA: not available; NOS: Newcastle-Ottawa quality assessment scale.

2.3 Prevalence of PCPF

After conducting a comprehensive analysis of the 18 included studies, it was found that out of the 2442 patients included, a total of 782 cases were diagnosed with PCPF, resulting in a pooled prevalence of 36.4%(95%CI:25.3%-47.5%, I^2=98.2%, P<0.01). The random-effects model was employed for the final analysis. The forest plot is shown in Figure 2.

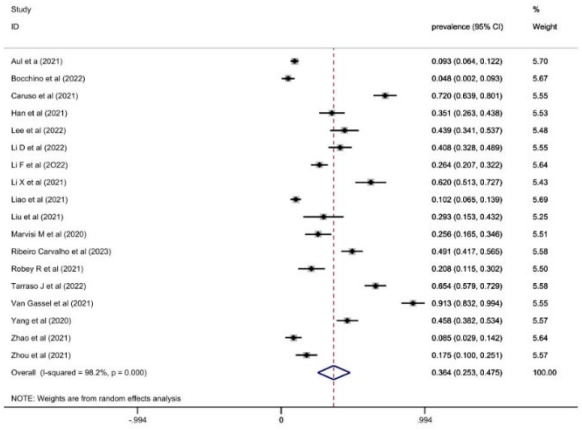

Figure 2: Forest plot (random-effects model) for the pooled prevalence of post-COVID-19 pulmonary fibrosis.

2.4 Risk factors of pulmonary fibrosis after COVID-19

In the included 18 studies, various risk factors for PCPF were reported, including age, gender, BMI, some comorbidities and so on. For factors that were mentioned in ≥ 3 studies were combined and analyzed showing that the risk factors for PCPF included advanced age(SMD:0.854,95%CI:0.560-1.147), male(OR:1.280,95%CI:1.014-1.616), hypertension(OR:3.633,95%CI:1.709-7.722), diabetes (OR:4.529,95%CI:1.314-15.612), hormone therapy(OR:5.537,95%CI:4.038-8.151), mechanical ventilation (OR:6.241,95%CI:2.582-15.088), prolonged hospitalization(SMD:0.569,95%CI:0.403-0.735), and severe COVID-19(OR:4.242,95%CI:2.581-6.972) (As is shown in Table 2.).

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Table 2: Risk factors related variables for the prevalence of post COVID-19 pulmonary fibrosis.

Risk factors		Sample size	Heterogeneity Test		Effect model	Effect	
			I^2(%)	P		OR*/SMD† (95%CI)	P
Age		1587	82.8	<0.001	Random	0.854(0.560,1.147)†	<0.001
Gender(male/female)		1586	40.6	0.097	Fixed	1.280(1.014,1.616)*	0.038
BMI		949	91.7	<0.001	Random	0.045(-0.498,0.589)†	0.870
Smoking history		916	70.4	0.009	Random	1.791(0.780,4.112)*	0.169
Commodities	Cardiac diseases	1042	49.6	0.094	Fixed	2.105(0.997,4.445)*	0.051
	Hypertension	1246	75.3	<0.001	Random	3.633(1.709,7.722)*	<0.001
	Chronic pulmonary disease	1019	64.7	0.015	Random	2.666(0.920,7.722)*	0.071
	Diabetes mellitus	1246	81.4	<0.001	Random	4.529(1.314,15.612)*	0.017
Treatment	Glucocorticoid	935	0.01	0.544	Fixed	5.737(4.038,8.151)*	<0.001
	Antiviral agents	378	63.3	0.066	Random	2.353(0.749,7.394)*	0.143
	Antibacterial agents	378	81.2	0.005	Random	1.856(0.655,5.258)*	0.245
	Mechanical ventilation	1110	55.8	0.035	Random	6.241(2.582,15.088)*	<0.001
days of hospitalized		603	41.1	0.165	Fixed	0.569(0.403,0.735)†	<0.001
severe COVID-19		2025	68.9	<0.001	Random	4.242(2.581,6.972)*	<0.001

Note: OR: Odds ratio; SMD†: Standardized mean difference.*

2.5 Sensitivity Analysis

Sensitivity analysis was performed by sequentially eliminating individual studies, indicating that none of the primary studies significantly impacted the results. Thus, it can be concluded that the meta-analysis result of this study was stable (Details of the sensitivity analysis are presented in the Figure 3.).

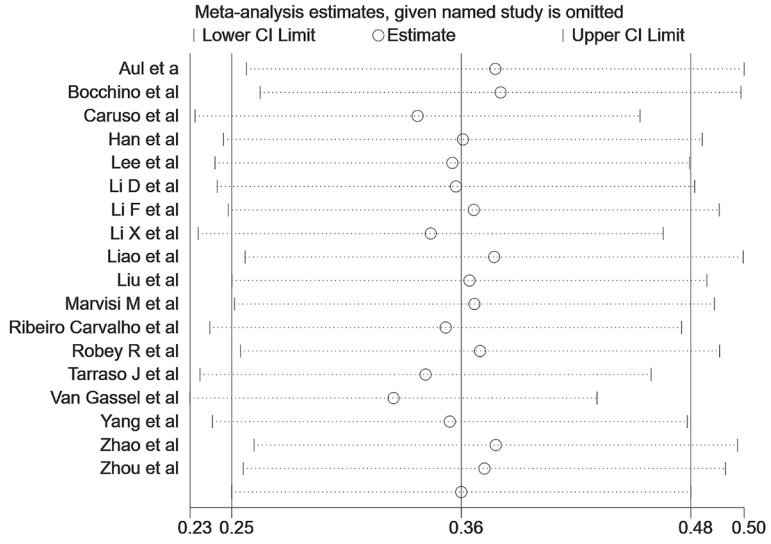

Figure 3: Sensitivity analysis of the effect of each primary study on the pooled results.

2.6 Publication Bias

Publication bias was assessed by Begg's test and Egger's test. The results showed that there was no publication bias detected by Begg's test (p=0.058), while significant publication bias was found by Egger's test p<0.001). Therefore, the trim-and-fill-adjusted prevalence of PCPF (p=13.6%, 95% CI: 1.1%-26.5%) was generated, which did not significantly differ from the original prevalence of PCPF (p=36.4%, 95% CI: 25.3-47.5%). The results before and after trimming showed statistical consistency, indicating the stability of the study results and that publication bias did not significantly affect the

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research findings.

3. Discussion

This study aims to investigate the prevalence and related risk factors of PCPF in COVID-19 survivors, and we concluded that the pooled prevalence of PCPF is 36.4%, which is more common compared to 25% for SARS and 33% for MERS. [25,26] Our study shows that advanced age is a notable risk factor for PCPF, which has received substantial support from numerous related studies. [9,10,20] Additionally, gender also plays a role in the incidence of PCPF, with male patients being more susceptible compared to their female counterparts, [7,23,16] which may be attributed to the protective effects of the X chromosome and sex hormones that play important roles in both innate and adaptive immunity. [27] Several studies consider that smoking is a risk factor for PCPF, [7,23] while other studies do not emphasize this association. [11,22] In our meta-analysis, smoking status and BMI were not found to be significant risk factors for the development of PCPF. Additionally, among all the comorbidities studied, hypertension and diabetes were found to be risk factors for PCPF. Other comorbidities such as Cardiac diseases and Chronic pulmonary disease were not identified to be significant risk factors for PCPF.

Patients treated with glucocorticoids and mechanical ventilation are associated with the development of pulmonary fibrosis in COVID-19 survivors, which is worth exploring. Mechanical ventilation is a recognized factor in the development of fibrosis,[28] which exerts mechanical damage on the airways leading to a release of proinflammatory modulators, like cytokines, chemokines, and growth factors, who cause biotrauma and drive fibrosis in injured tissues.[29] And corticosteroids may also increase the risk of PCPF, which has been confirmed by existing studies.[30] Theoretically, corticosteroids can indeed suppress lung inflammation and improve the progression of COVID-19. [31] However, while suppressing lung inflammation, they also inhibit immune responses and pathogen clearance, leading to an increase in plasma viral load with the risk of causing lung damage, thereby increasing the risk of pulmonary fibrosis.[32,33] Further studies are needed to validate this possibility and investigate the specific mechanisms through which corticosteroids may increase the risk of post-COVID-19 fibrosis.

This study has several limitations. Firstly, it shows a certain statistical heterogeneity, so caution should be exercised when interpreting estimates. Secondly, the patient populations included in the studies differed in the time and region of virus infection, and there may be some differences in the SARS-CoV-2 variant types they infected, treatment guidelines, vaccination rates and effectiveness in the early stages of the pandemic compared to later, which may also have a certain impact on the results. Finally, most of the studies included had a follow-up duration within two years, we cannot conclude whether these pulmonary sequelae would persist or improve over longer periods. Studies have shown that over 38.5 % of patients with SARS have PCPF one year after discharge, but only 25 % of patients still have lung CT abnormalities fifteen years later. [26] Therefore, there are still many uncertainties in the current research, and further larger multicenter studies with longer follow-ups are needed.

4. Conclusion

This study showed that about 36.4% of COVID-19 survivors may have developed pulmonary fibrosis, and people with advanced age, male, hypertension, diabetes, hormone therapy, mechanical ventilation, prolonged hospitalization, and severe COVID-19 are at higher risk of developing this sequela. It is necessary to identify individuals at risk of developing PCPF and take timely measures to protect them from progression to PCPF and improve their prognosis. Furthermore, larger multicenter studies with longer follow-ups are needed to provide further diagnostic and therapeutic recommendations.

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