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Diabetes mellitus increases the risk of post-COVID-19 pulmonary fibrosis: a meta-analysis of observational studies

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Abstract

Background Pulmonary fibrosis (PF) is a serious respiratory complication observed in coronavirus disease 2019 (COVID-19) patients, and people with diabetes mellitus (DM) are at an increased risk of developing severe COVID-19. However, whether DM is a risk factor for post-COVID-19 pulmonary fibrosis (PCPF) remains unknown.

Methods We conducted a meta-analysis of observational studies to evaluate the association between DM and the development of PCPF. We searched PubMed, EMBASE, and the Cochrane Library for relevant studies published before February 1, 2023, without language or publication type restrictions. We calculated odds ratio (OR) with 95% confidence interval (CI) to compare the prevalence of DM among COVID-19 patients with PCPF with that among non-PCPF controls.

Results This meta-analysis included a total of 5,088 COVID-19 patients. We found a significant association between DM and the development of PCPF (OR = 2.18, 95% CI: 1.15–4.13, $P < 0.001$), with high heterogeneity among the studies ($I^2 = 82.2\%$). Subgroup analysis showed that the association between DM and PCPF was consistent across different geographic regions, study designs, sample sizes, mean ages, DM types, assessment times after COVID-19 onset, and NOS quality ratings.

Conclusions This meta-analysis offers evidence supporting a correlation between DM and the development of PCPF among COVID-19 patients. Despite the considerable heterogeneity in this studies, this research retains significant implications for the clinical management of COVID-19 patients. DM is a potential risk factor for PCPF. It is imperative for clinicians to remain vigilant regarding the development of PCPF in COVID-19 patients who complicated with DM.

Keywords COVID-19, post-COVID-19 pulmonary fibrosis, Diabetes mellitus, Meta-analysis, Prevalence

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Background

Since coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic, millions of individuals have been infected [1]. While the majority of individuals recover from SARS-CoV-2 infection, a proportion of patients may develop post-COVID-19 pulmonary fibrosis (PCPF), which is a potentially life-threatening complication characterized by fibrotic changes in the lungs [2, 3]. The acute manifestations of SARS-CoV-2 infection continue to have a considerable impact on the lives of many individuals worldwide [4, 5]. However, despite the potential severity of PCPF, little is currently understood regarding the risk factors associated with its development.

Diabetes mellitus (DM) is a chronic metabolic disorder that has a substantial impact on the health of millions of people worldwide. Studies have indicated that individuals with metabolic abnormalities, such as hyperglycemia, hyperlipidemia, and hypertension, have a higher risk of developing severe COVID-19 than those with a normal metabolism [6, 7]. Microvascular complications of diabetes in the respiratory tract may impair alveolar gas exchange and lung compliance, leading to reduced lung function and impaired absorption of lung inflammation [8]. Caruso et al. also confirmed that diabetes and hyperglycemia can cause pulmonary remodeling and respiratory restriction [9].

Despite the known associations between DM and COVID-19 severity, the relationship between DM and PCPF is not well established. One study reported a higher prevalence of diabetes among COVID-19 patients with pulmonary fibrosis than among those without fibrosis [10]. Additionally, COVID-19 patients with hyperglycemia are more likely to develop severe and fatal illness [7, 11, 12]. As identifying risk factors for PCPF is crucial for early intervention, it is important to investigate the relationship between DM and PCPF. This meta-analysis aimed to determine whether DM was a risk factor for PCPF.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. This study was previously registered on the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO/) with a registration number of CRD42023398645.

Search strategy

PubMed, EMBASE, and the Cochrane Library were searched to identify relevant studies that were published before February 1, 2023, without any language, publication year, or publication type restrictions. The search strategy applied a form of medical subject headings (MeSH) terms combined with free text words in terms with the keywords "COVID-19" and "pulmonary fibrosis". The keyword "diabetes" was not restricted to avoid missing studies with relevant data. The details of the search strategy are presented in Supplementary Material [14]. We also manually screened the reference lists of eligible studies and relevant reviews to identify additional studies.

Study selection

Studies were included in this meta-analysis if they met the following criteria: (1) observational studies including cohort, cross-sectional, and case–control studies; (2) patients with a confirmed diagnosis of COVID-19 who subsequently developed pulmonary fibrosis manifestations; and (3) studies with a clear definition of pulmonary fibrosis that contained sufficient data to calculate the prevalence of diabetes among COVID-19 patients with and without pulmonary fibrosis. Duplicate studies, animal studies, reviews, notes, case reports, editorials, studies in which all the cases were of patients with pulmonary fibrosis, and studies without diabetes data were excluded. Records were independently screened by two authors according to the eligibility criteria, and disagreements were resolved by discussion.

Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa scale (NOS), which judges the selection of observational study groups according to three domains: selection, comparability and exposure [15]. The NOS adopts the semiquantification principle of the star system for the evaluation of literature quality. The NOS scale has been suitably modified for cross-sectional studies by discarding items that are not aligned with the design of such studies [16]. The adapted NOS scale allows for the award of a maximum of nine stars for high-quality case–control and cohort studies, whereas a maximum of six stars can be awarded for high-quality cross-sectional studies. The quality of studies is categorized as "high quality" when case–control and cohort studies have eight or more stars and cross-sectional studies have five or more stars. Conversely, studies are considered to have moderate quality when case–control and cohort studies have six or seven stars and cross-sectional studies have three or four stars [17].

Data extraction

The following data were extracted from eligible articles by two authors independently into a standard spreadsheet: name of the first author, year of publication, country, study design, study setting, study period, total number of participants, mean age, number of participants with and

without DM in the PCPF and non-PCPF groups, diagnostic methods for COVID-19, PF and DM, assessment time of PCPF, and type of DM. Study authors were contacted as needed to obtain detailed data. Any disagreements over the retrieved information were resolved by consensus by referring back to the original articles.

Statistical analysis

Data synthesis and analysis in this study were performed using Stata software (version 16.0). To compare the prevalence of DM among COVID-19 patients with PF with that among non-PF controls, we used odds ratios (ORs) with 95% confidence intervals (CIs). A random effects model was implemented due to the clinical and methodological heterogeneity among the studies included in the analysis. Heterogeneity among the included studies was examined by the I [2] statistic, which describes true variation across studies as a percentage. High heterogeneity was defined as an I [2] value exceeding 50% [18]. We conducted a sensitivity analysis by removing each study from the pooled analysis to examine the influence of each included study. Additionally, we performed exploratory investigations of heterogeneity by subgrouping studies according to geographic region (Asia or Europe), study design (cohort or cross-sectional study), sample size (< 200 or ≥ 200), mean age (< 60 years or ≥ 65 years), type of DM (type 2 DM or mixed), assessment time after COVID-19 onset (< 3 months or ≥ 3 months), and NOS quality rating (high or moderate). Publication bias was assessed by visual inspection of funnel plot symmetry combined with Egger's and Begg's tests, with a *P* value of less than 0.05 indicating statistical significance [19].

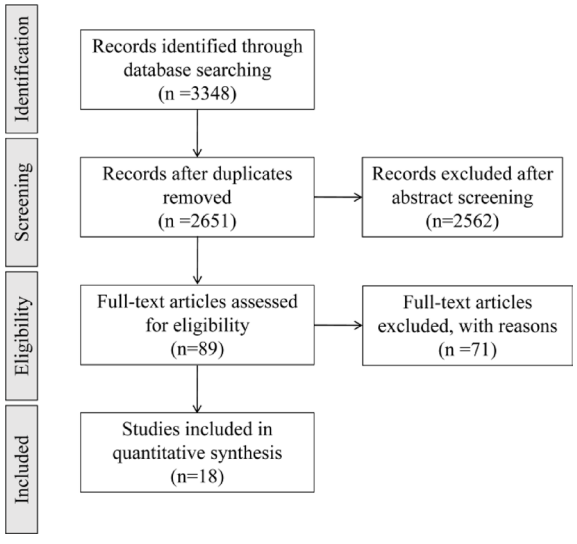

Fig. 1 Flow diagram of the selection process of the studies included in this meta-analysis

Results

Search results

A comprehensive search of electronic databases identified 3348 articles, of which 3259 were excluded based on title and abstract screening due to duplication and irrelevance. Of the remaining 89 articles, 71 were excluded for various reasons, including 16 case reports or case series, four commentaries, editorials, or letters, 14 reviews, and two studies that lacked a control group without fibrosis. Additionally, 28 studies did not report relevant outcomes for diabetes, while six studies did not provide sufficient data on the prevalence of diabetes among patients with PCPF. Finally, one conference abstract was excluded because it reported the same outcomes as another published paper. Ultimately, 18 articles met the inclusion criteria and were included in the meta-analysis. A flowchart illustrating the study selection process is presented in Fig. 1.

Study characteristics

Table 1 provides an overview of the characteristics of the studies included in this meta-analysis, which were published between 2020 and 2022. Among the 18 selected studies, four were conducted in Europe [20–23]13 in Asia [10, 24–35]and one in the USA [36]. Two of the studies were cross-sectional studies, while the remaining 16 were cohort studies, and all were conducted in hospital settings. Sample sizes ranged from 32 to 2,545 participants, with a total of 877 individuals with PCPF and 4,211 controls. Participant ages ranged from 45 to 66 years on average. Most studies utilized real-time reverse transcription-polymerase chain reaction (RT−PCR) to confirm COVID-19 diagnosis, followed by lung computed tomography (CT) scans to detect pulmonary fibrosis during the follow-up period. The duration of follow-up varied, with pulmonary fibrosis detected as early as 14 days after hospitalization and as late as 1 year after discharge. Most studies aimed to identify the characteristics of pulmonary fibrosis after COVID-19 infection and included diabetes as a comorbidity of interest. Specifically, two studies exclusively recruited individuals with type 2 DM, while none exclusively recruited individuals with type 1 DM, and 16 did not differentiate between types of diabetes.

NR, not reported; PF, pulmonary fibrosis; DM, diabetes mellitus; RT-PCR, real-time reverse transcription-polymerase chain reaction; HRCT, high-resolution computed tomography; WHO, World Health Organization.

The details of the quality assessment are presented in Table 2. The cohort studies were evaluated based on nine criteria and received a rating of six to nine stars. The cross-sectional studies were evaluated based on six criteria and were awarded a maximum of four stars. In general, 11 studies were classified as high quality and 7 as

Table 1 Basic characteristic and design of the included studies

Author (Year)	County	Study design	Study setting	Study period	Group	Participants (Male:Female)	Mean age, y
Hu et al. (2020)	China	Cohort study	Hospital-based	2020.1.21–2020.3.20	Fibrosis	19:27	58.0
					Non-fibrosis	15:15	38.9
Marvisi et al. (2020)	Italy	Cohort study	Hospital-based	NR	Fibrosis	15:8	75.0
					Non-fibrosis	32:34	61.0
Yu et al. (2020)	China	Cohort study	Hospital-based	2020.1.5–2020.2.16	Fibrosis	12:2	54.0
					Non-fibrosis	10:8	37.0
Aul et al. (2021)	UK	Cohort study	Hospital-based	2020.3–2020.7	Fibrosis	28:8	61.5
					Non-fibrosis	191:160	63.0
Colarusso et al. (2021)	Italy	Cohort study	Hospital-based	NR	Fibrosis	17:10	50.0
					Non-fibrosis	16:9	50.0
Han et al. (2021)	China	Cohort study	Hospital-based	2019.11.25–2020.2.20	Fibrosis	30:10	60.0
					Non-fibrosis	50:24	51.0
Huang et al. (2021)	China	Cohort study	Hospital-based	2019.12.19–2020.3.5	Fibrosis	31:11	63.0
					Non-fibrosis	19:20	50.8
Li et al. (2021)	China	Cohort study	Hospital-based	2020.1.11–2020.4.26	Fibrosis	90:83	50.7
					Non-fibrosis	51:65	33.1
Liu et al. (2021)	China	Cohort study	Hospital-based	2020.2.10–2020.3.23	Fibrosis	7:5	63.0
					Non-fibrosis	15:14	45.0
McGroder et al. (2021)	USA	Cohort study	Hospital-based	2020.3.1–2020.5.15	Fibrosis	25:7	53.4
					Non-fibrosis	20:24	54.4
Nabahati et al. (2021)	Iran	Cross-sectional study	Hospital-based	2020.3	Fibrosis	34:56	54.7
					Non-fibrosis	23:60	52.5
Patil et al. (2021)	India	Cohort study	Hospital-based	2020.5–2020.11	Fibrosis	70:12	NR
					Non-fibrosis	NR	NR
Kumar et al. (2022)	India	Cross-sectional study	Hospital-based	NR	Fibrosis	24:12	NR
					Non-fibrosis	NR	NR
Bai et al. (2022)	China	Cohort study	Hospital-based	2020.1.10–2020.2.10	Fibrosis	3:20	59.7
					Non-fibrosis	14:3	54.1
Lee et al. (2022)	Korea	Cohort study	Hospital-based	2021.4.12–2021.10.22	Fibrosis	29:14	60.7
Li et al. (2022)	China	Cohort study	Hospital-based	2020.3.26–2021.3.26	Fibrosis	22:38	64.0
					Non-fibrosis	85:82	40.0
Vijayakumar et al. (2022)	England	Cohort study	Hospital-based	2020.3–2020.6	Fibrosis	8:1	59.0
					Non-fibrosis	45:26	< 60.0
Chai et al. (2022)	China	Cohort study	Hospital-based	2020.1.1–2020.3.18	Diabetes	241:198	≥ 65.0
					Denied diabetes	964:1142	< 65.0

Author (Year)	Diagnostic methods of COVID-19	Diagnostic methods of PF	Assessment time	Diagnostic methods of DM	Type of DM
Hu et al (2020)	RT-PCR; based on the WHO interim guideline	AI-based CT imaging system; defined as consolidation index greater than 0	At the time of discharge around 14 days of hospitalization	Medical history	Mixed
Marvisi et al. (2020)	medical history, clinical symptoms and a positive SARS-COV2 naso-pharyngeal swab on RT-PCR	Chest CT; defined according to the Fleischner Society glossary of terms for thoracic imaging: reticulation, architectural distortion, traction bronchiectasis, and honeycombing	60 days after admission	Medical history	Mixed
Yu et al (2020)	Pharyngeal swab nucleic acid testing	Chest CT; defined as a combination of findings including parenchymal bands, irregular interfaces, coarse reticular pattern, and traction bronchiectasis	9 days after discharge	Medical history	Mixed
Aul et al (2021)	A positive SARS-COV2 naso-pharyngeal swab on RT-PCR, or a clinico-radiological diagnosis of COVID-19	CT scans; showed established fibrosis ± ground glass abnormalities (PCVCT3)	6 weeks after discharge	Medical history	Mixed

Table 1 (continued)

Author (Year)	Diagnostic methods of COVID-19	Diagnostic methods of PF	Assessment time	Diagnostic methods of DM	Type of DM
Colarusso et al. (2021)	A positive SARS-COV2 oral-pharyngeal swab on RT-PCR	According to functional and clinical parameters such as spirometry, FEV1, FVC, and the presence of ground-glass opacities and reticular/fibrotic areas at the chest CT scan	1–3 months after the first negative oral-pharyngeal swab	NR	Mixed
Han et al (2021)	A positive SARS-COV2 pharyngeal swab on RT-PCR	CT; defined as the presence of traction bronchiectasis,parenchymal bands, and/or honeycombing	175 ± 20 days after symptom onset	Medical history	Mixed
Huang et al (2021)	RT-PCR	CT scans; defined as the presence of parenchymal bands, irregular interfaces, reticular opacities, and traction bronchiectasis with or without honeycombing	58 days after discharge	Medical history	Mixed
Li et al (2021)	qRT-PCR; based on the WHO interim guideline	Chest CT; defined as a combination of findings including parenchymal bands, irregular interfaces, reticulation and traction bronchiectasis	90–150 days after COVID-19 onset	Medical history	Mixed
Liu et al (2021)	Based on the New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial 7)	Chest CT; defined as a combination of findings including parenchymal bands, reticular pattern, and traction bronchiectasis	7 months after discharge	Medical history	Mixed
McGroder et al. (2021)	A positive SARS-COV2 nasopharyngeal swab on RT-PCR	Non-contrast HRCT scan; fibrotic-like patterns included those with reticulations, traction bronchiectasis or honeycombing	4 months after hospitalisation	Medical history	Mixed
Nabahati et al. (2021)	A positive SARS-COV2 nasopharyngeal swab on RT-PCR	CT imaging; including traction bronchiectasis, honeycombing, parenchymal bands, and interlobar septal thickening	3 and 6 months after discharge	Medical history	Mixed
Patil et al (2021)	NR	HRCT	6 weeks after discharge	NR	Mixed
Kumar et al. (2022)	NR	HRCT	NR	Medical history	Mixed
Bai et al (2022)	Based on the New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial 7)	Lung CT features; examination report can be summarized as follows: ground glass opacity, fiber streak shadow, tractive bronchiectasis, reticulation, and bronchovascular bundle distortion	6 months after discharge	Medical history	T2DM
Lee et al (2022)	A positive SARS-COV2 nasopharyngeal swab on RT-PCR	Defined when any of the following radiologic features were present: parenchymal bands; traction bronchiectasis with or without volume loss; reticulation; and honeycombing	3 months after discharge	Medical history	Mixed
Li et al (2022)	Medical records	Based on the CT scoring system for fibrosis	one year after discharge	Medical history	Mixed
Vijayakumar et al. (2022)	A positive SARS-COV2 nasopharyngeal swab on RT-PCR and/or serum antibody to SARS-COV2	CT scans; defined as volume loss and/or traction bronchiectasis	3 months after discharge	Medical history	T2DM
Chai et al (2022)	RT-PCR detection of SARS-CoV-2 in respiratory tract samples and clinically confirmation	Lung scans	One year after discharge	Medical history	Mixed

NR, not reported; PF, pulmonary fibrosis; DM, diabetes mellitus; RT-PCR, real-time reverse transcription-polymerase chain reaction; HRCT, high-resolution computed tomography; WHO, World Health Organization

moderate quality. The evaluation criteria for the cohort studies included the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of the exposure, outcome of interest absent at the start of the study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, length and adequacy of follow-up, and completeness of follow-up. The criteria for the cross-sectional studies were the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, comparability of cohorts on the basis of the design or analysis, and assessment of outcome.

Associations between PCPF and DM

The findings of the meta-analysis regarding the prevalence of DM among individuals with PCPF are illustrated in Fig. 2. The overall combined OR of DM for PCPF patients compared to controls was 2.18 (95% CI: 1.15–4.13; $P = 0.017$). A noteworthy level of heterogeneity was observed among the included studies ($I^2 = 82.2\%$; $P < 0.001$). Consequently, a sensitivity analysis was carried out by excluding each study individually, and the results demonstrated that none of the studies had a significant impact on the conclusions.

Table 2 Modified Newcastle–Ottawa Scale (NOS) for assessment of the risk of bias of the included studies

	Selection				Comparability	Outcome			Total
Author (Year)	**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***	
Hu et al. (2020)	*	*	*	*	**	*	*		8
Marvisi et al. (2020)	*	*	*	*	**	*	*	*	9
Yu et al. (2020)		*	*	*	**	*	*		7
Aul et al. (2021)		*		*	**	*	*	*	7
Colarusso et al.(2021)		*		*	**	*	*		6
Han et al. (2021)	*	*	*	*	**	*	*	*	9
Huang et al. (2021)	*	*	*	*	**	*	*	*	9
Li et al. (2021)		*	*	*	**	*	*	*	8
Liu et al. (2021)		*	*	*	**	*	*	*	8
McGroder et al. (2021)		*	*	*	**	*	*	*	8
Nabahati et al. (2021)			*	N/A	**	*	N/A	N/A	4
Patil et al. (2021)				*	**	*	*	*	6
Kumar et al. (2022)		*		N/A	**	*	N/A	N/A	4
Bai et al. (2022)		*	*	*	**	*	*	*	8
Lee et al. (2022)			*	*	**	*	*	*	7
Li et al. (2022)		*	*	*	**	*	*	*	8
Vijayakumar et al. (2022)	*	*	*	*	**	*	*	*	9
Chai et al. (2022)	*	*	*	*	**	*	*	*	9

N/A, Not Applicable

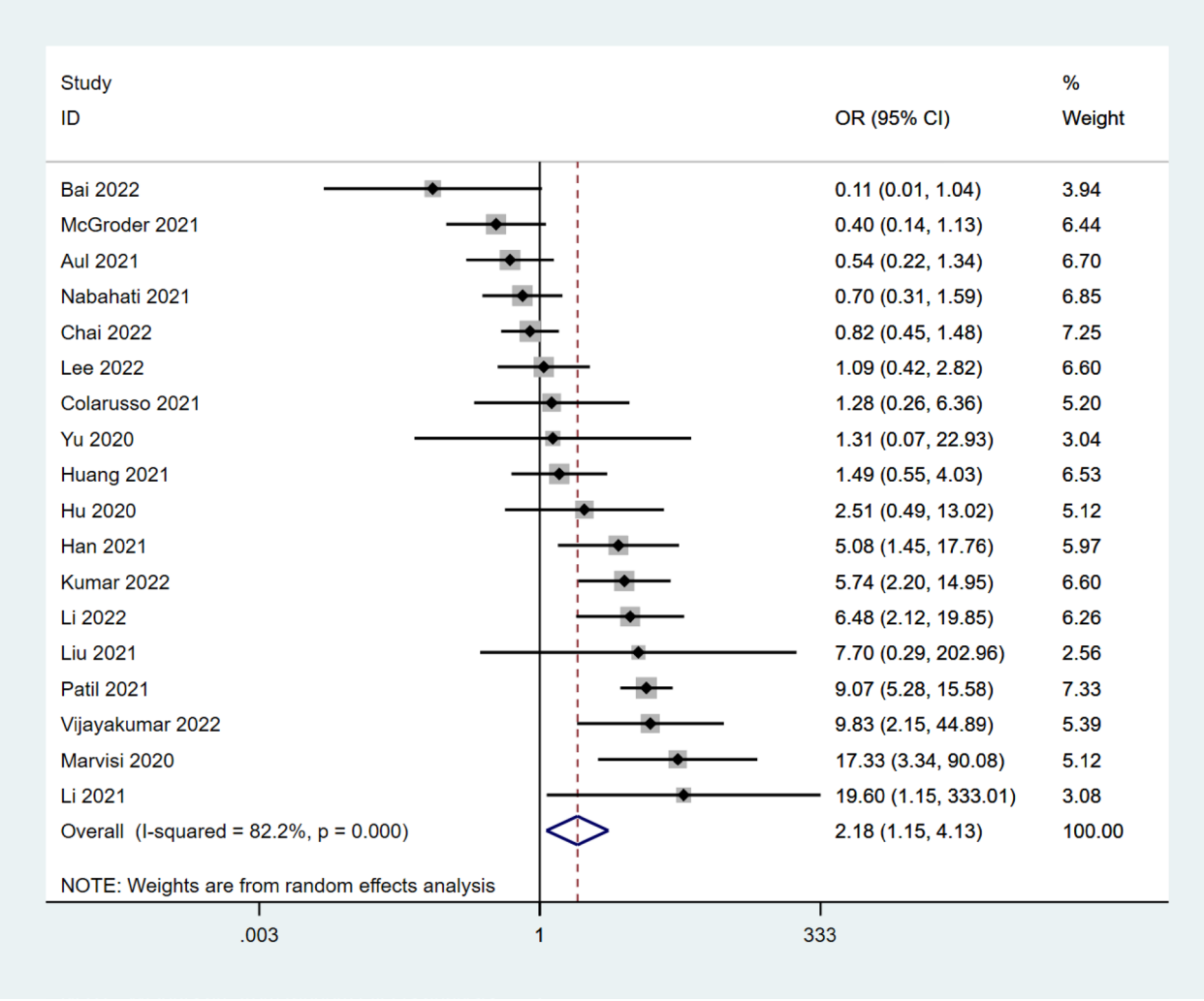

Fig. 2 Forest plot showing the ORs and 95% CIs of DM for people with PCPF (cases) compared to people without PCPF (controls)

Subgroup analysis and meta-regression

Table 3 presents the results of the subgroup analysis and meta-regression performed to investigate potential sources of heterogeneity among the studies that reported the prevalence of DM among individuals with PCPF. The analysis revealed a significantly higher prevalence of DM among PCPF subjects than among controls in studies conducted in Asia (OR: 2.31, 95% CI: 1.11–4.78), cohort studies (OR: 2.22, 95% CI: 1.09–4.50), studies that included all types of DM (OR: 2.26, 95% CI: 1.17–4.34), and studies with high NOS quality scores (OR: 2.55, 95% CI: 1.09–5.97).

However, no significant association was found between the prevalence of DM or PCPF in subgroups based on sample size, mean age, or assessment time after COVID-19 onset.

Publication bias

The funnel plot for the studies evaluating the OR of DM prevalence among people with and without PCPF was symmetric, indicating no publication bias. Moreover, the results of Egger's and Begg's regression tests showed no evidence of publication bias in the overall analysis (*P* value for Egger's test: 0.954; *P* value for Begg's test: 0.325), as shown in Fig. 3. These findings suggested that the results of this meta-analysis were robust and reliable.

Discussion

Principal findings

This meta-analysis included 18 studies with a total of 5,088 participants, and it revealed that individuals with DM were 2.18 times more likely to have PCPF than controls. The positive association between DM and PCPF was observed consistently across various subgroups, as indicated by OR values greater than 1. The prevalence of DM among PCPF patients was higher in Asia, in cohort

Table 3 Subgroup analyses for the prevalence of DM in people with PCPF

Subgroup	No. of studies	OR (95% CI)	*P* value	I^2 (%)	*P* for interaction
Geographic region				< 0.001	0.771
Asia	13	2.31 (1.11 to 4.78)	0.024	81.6	
Europe	4	3.07 (0.54 to 17.54)	0.206	84.3	
Study design					0.903
Cohort study	16	2.22 (1.09 to 4.50)	0.028	82.2	
Cross-sectional study	2	1.97 (0.25 to 15.56)	0.519	90.6	
Sample size					0.622
N < 200	13	1.94 (0.96 to 3.90)	0.063	71.2	
N ≥ 200	5	2.91 (0.72 to 11.72)	0.133	92.2	
Mean age					0.797
< 60 years	13	1.81 (0.92 to 3.57)	0.087	66.5	
≥ 60 years	2	2.85 (0.10 to 85.33)	0.546	92.4	
Assessment time after COVID-19 onset					0.605
< 3 months	7	2.51 (0.83 to 7.61)	0.103	83.7	
≥ 3 months	10	1.71 (0.77 to 3.77)	0.187	76.4	
Type of DM					0.705
T2DM	2	1.12 (0.01 to 103.88)	0.961	91.0	
Mixed	16	2.26 (1.17 to 4.34)	0.015	82.4	
NOS quality					0.578
High	11	2.55 (1.09 to 5.97)	0.030	77.3	
Moderate	7	2.18 (1.15 to 4.13)	0.304	87.7	

CI, confidence interval; DM, diabetes mellitus; PCPF, post-COVID-19 pulmonary fibrosis; NOS, Newcastle–Ottawa Scale; OR, odds ratio; T2DM, type 2 diabetes mellitus

Furthermore, univariable meta-regression analysis was performed to explore possible sources of heterogeneity between studies. The results showed that publication year ($P = 0.591$), sample size ($P = 0.556$), mean age ($P = 0.715$), and NOS quality score ($P = 0.923$) did not significantly contribute to the observed heterogeneity

studies, in studies that investigated all types of DM, and in high-quality NOS studies. However, there was no significant association between the prevalence of DM or PCPF in subgroups stratified by different sample sizes, mean ages, or assessment times after COVID-19 onset. Our study indicates that DM is a potential risk factor for PCPF and underscores the importance of monitoring DM in patients with PCPF. It is imperative for clinicians to remain vigilant regarding the development of PCPF in COVID-19 patients who complicated with DM.

Comparisons with previous studies

A previous meta-analysis investigated the prevalence of PCPF and potential risk factors, revealing an overall PCPF prevalence of 44.9% across all included studies and a higher average age among fibrotic patients (59 years) compared to those without fibrotic changes (48.5 years) [37]. However, the study identified only COPD as significantly associated with an increased risk of PCPF, with an OR of 0.51 (95% CI: 0.37–0.70) for diabetes. In addition, only nine articles reported diabetes as a comorbidity in the study, which included 1,521 participants. This limited finding prompted the current study to conduct a more comprehensive systematic review and meta-analysis to further assess the relationship between DM and PCPF.

Potential mechanisms

Despite extensive research on PCPF, the precise mechanisms underlying its development remain inadequately understood. Pulmonary fibrosis is characterized by aberrant healing of the injured lung parenchyma [38]. In patients with COVID-19, potential sources of lung injury include cytokine storms resulting from dysregulated inflammatory responses, bacterial coinfections, and thromboembolic events leading to microvascular damage and endothelial dysfunction [39]. Additionally, the involvement of the renin-angiotensin system is suggested by the high affinity of the SARS-CoV-2 spike protein for the angiotensin-converting enzyme 2 (ACE2) receptor [40]. In COVID-19 patients with concurrent DM, hyperglycemia impairs the chemotaxis and phagocytic function of neutrophils, macrophages, and monocytes, thereby compromising innate cell-mediated immunity [41–45]. This condition is further characterized by an increased proportion of proinflammatory Th17 CD4 + T cells and cytokines, alongside a reduction in peripheral CD4 + and CD8 + T cell populations. Consequently, DM may lead to an impaired antiviral interferon response and delayed activation of Th1/Th17 cells, exacerbating the inflammatory response in COVID-19 patients which may contribute to the occurence of pulmonary fibrosis [46].

Strengths and limitations

The current meta-analysis exhibits numerous strengths that warrant emphasis. Initially, a comprehensive search strategy was developed that included major online databases without language or date constraints. This approach helped retrieve a large number of relevant articles from all over the world and minimized the potential impact of publication bias. Additionally, several statistical approaches, such as subgroup analysis,

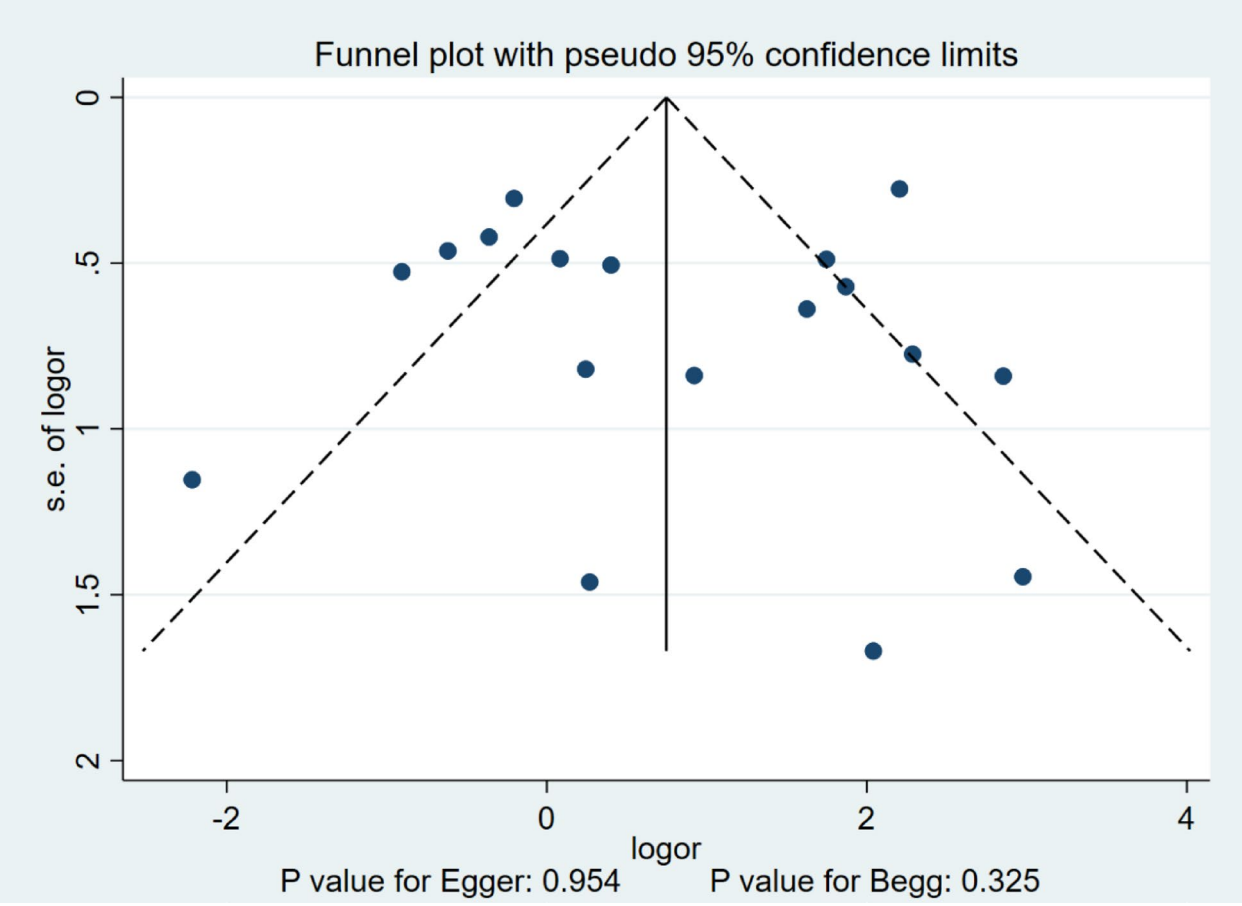

Fig. 3 Funnel plot for the meta-analysis of the association between DM and PCPF

sensitivity analysis, and meta-regression, were utilized to thoroughly investigate potential sources of heterogeneity based on study-level baseline characteristics. Despite significant heterogeneity being observed among the studies included in our analysis, our findings remained consistent throughout. Finally, publication bias was assessed using both Egger's and Begg's tests, which indicated no significant evidence of publication bias.

This meta-analysis is subject to several limitations that should be considered when interpreting the results. Firstly, the predominance of hospital-based studies included may restrict the applicability of the findings to the wider population. Secondly, most included studies use medical history as the diagnostic basis for DM. The lack of explicit descriptions of diagnostic methods for diabetes may have led to heterogeneity in the results. Thirdly, 16 out of 18 studies failed to differentiate between types of DM, a limitation that could contribute to increased heterogeneity in our analysis. Lastly, potential confounding factors, such as body mass index (BMI), smoking status, and socioeconomic status may have contributed to the high level of heterogeneity observed in the analysis. Unfortunately, relevant stratified analyses could not be performed due to the limited information of the included studies. Furthermore, the omission of information regarding the specific type of diabetes among participants was noted, although the treatment methods and drugs used are different for different types of diabetes. Additionally, the duration of follow-up in the studies analyzed was limited, ranging from 14 days of hospitalization to 1 year post-discharge, thereby hindering a comprehensive evaluation of the enduring impact of diabetes on the progression and severity of PCPF.

Conclusions

In summary, this meta-analysis offers compelling evidence of a substantial link between DM and the incidence of PCPF among COVID-19 patients, with DM patients displaying a 2.18-fold higher likelihood of developing PCPF than non-DM individuals. The implications of our findings underscore the importance for health care practitioners to remain vigilant of the heightened risk of PCPF among DM patients with COVID-19 and to proactively explore early screening measures and preventative interventions. Nevertheless, additional investigations are

warranted to validate our results and ascertain potential confounding factors that may influence this association.

Abbreviations

ACE2	Angiotensin-converting enzyme-2
CI	Confidence interval
DM	Diabetes mellitus
HRCT	High-resolution computed tomography
MeSH	Medical subject headings
NOS	Newcastle–Ottawa scale
OR	Odds ratio
PCPF	Post-COVID-19 pulmonary fibrosis
PF	Pulmonary fibrosis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RT–PCR	Real-time reverse transcription-polymerase chain reaction
SARS	Severe acute respiratory syndrome

Supplementary Information

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Supplementary Material 1

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Author contributions
F.T. contributed to data curation, formal analysis, investigation, methodology, original draft writing, and funding acquisition. C.L. and J.H. were responsible for software development, and visualization. S.L. and W.P. focused on data curation, methodology, and validation. H.P., C.H., and C.W. were involved in methodology and validation. Z.Z. provided expertise in methodology, supervision, and validation. Y.X. was responsible for conceptualization, funding acquisition, project administration, and writing, including review and editing.

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Availability of data and materials
Data is provided within the manuscript or supplementary information files.

Declarations

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The authors declare no competing interests.

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