Original Article

Mortality-related risk factors of idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Background: Idiopathic pulmonary fibrosis (IPF) has high mortality and poor prognosis, which brings enormous burdens to families and society. We conducted this meta-analysis to analyze and summarize the risk factors associated with mortality in IPF, hoping to provide reference for clinical prevention and treatment of IPF.

Methods: We conducted a comprehensive search of PubMed, Cochrane Library, Embase, and Web of Science from inception to August 10, 2023, to include cohort studies on mortality in patients with IPF. Two researchers independently screened the studies and extracted data. The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported to identify risk factors for mortality in IPF. In addition, we also carried out sensitivity analysis, Begg's and Egger's tests to evaluate the heterogeneity and publication bias.

Results: Eighteen studies comprising 8,408 patients were included. The meta-analysis suggested that age (HR =1.03; 95% CI: 1.01, 1.04; P<0.001), forced vital capacity (FVC) (HR =0.97; 95% CI: 0.96, 0.99; P=0.005), FVC to predicted value ratio (FVC% pred) (HR =0.98; 95% CI: 0.97, 0.99; P<0.001), diffusing capacity of the lungs for carbon monoxide to predicted value ratio (DL_{CO}% pred) (HR =0.98; 95% CI: 0.97, 0.99; P<0.001), gender-age-physiology (GAP) index (HR =1.70; 95% CI: 1.20, 2.40; P=0.003), and lung cancer (HR =2.75, 95% CI: 1.23, 6.15; P=0.01) were mortality-related risk factors in patients with IPF. Whereas, gender, smoking, body mass index (BMI), diffusing capacity of the lungs for carbon monoxide (DL_{CO}), C-reactive protein (CRP), 6-minute walking distance (6MWD), pulmonary hypertension, gastroesophageal reflux, and cardiovascular disease were not statistically associated with death.

Conclusions: Age, FVC, FVC% pred, DL_{CO}% pred, GAP index, and lung cancer have been identified as potential risk factors for mortality in patients with IPF. Due to the limited number and quality of included studies, the conclusions need to be verified by further studies.

Keywords: Idiopathic pulmonary fibrosis (IPF); mortality; risk factor; meta-analysis

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Introduction

Idiopathic pulmonary fibrosis (IPF) is an obscure etiology chronic, progressive, fibrotic interstitial lung disease predominantly affecting middle-aged and elderly males. Its primary manifestations consist of dyspnea and a gradual decline in pulmonary function. The global prevalence of IPF ranges from 0.09 to 1.30 per 10,000 individuals, exhibiting an escalating trend over time. This ailment manifests rapidly, exhibiting high mortality rates, poor prognoses, and 5-year survival rates ranging only from 20% to 40%. The median survival period following diagnosis is merely 3 to 5 years. Consequently, this condition imposes huge burdens on both patients and society (1-3). As a result, early identification and assessment of mortality-associated risk factors in IPF patients, assume pivotal significance in guiding doctors to implement effective clinical interventions in time, diminishing mortality rates and enhancing long-term prognoses.

Recent years have witnessed a surfeit of studies aimed at investigating mortality-related risk factors in IPF patients, however, the findings from these studies remained incoincident. For instance, Suzuki *et al.* (4) asserted a higher mortality risk in male IPF patients relative to females, whereas Mochizuka *et al.* (5) observed no significant variance in mortality risk between genders in IPF patients. Furthermore, Ghang *et al.* (6) identified forced vital capacity to predicted value ratio (FVC% pred) and diffusing capacity of the lungs for carbon monoxide to predicted value ratio (DL_{CO}% pred) as mortality-related risk factors in IPF; nevertheless, Lee *et al.* (7) posited the absence of a correlation between FVC% pred and DL_{CO}% pred and mortality risk in IPF patients. Given the circumstances, this study included the Cohort study of IPF mortality, and conducted a meta-analysis to summarize mortality-related risk factors, hoping to provide references for the prevention and treatment of IPF. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1908/rc).

Highlight box

Key findings

- Six mortality-related risk factors of idiopathic pulmonary fibrosis (IPF) including age, forced vital capacity (FVC), FVC to predicted value ratio, diffusing capacity of the lungs for carbon monoxide to predicted value ratio, gender-age-physiology index, and lung cancer were identified.

What is known and what is new?

- Recent years have witnessed a surfeit of studies aimed at investigating mortality-related risk factors in IPF patients, however, the findings from these studies remained incoincident.
- This study endeavored to comprehensively explore the association between risk factors and mortality in patients with IPF.

What is the implication, and what should change now?

- We summarized the risk factors associated with mortality in patients with IPF, however, there was heterogeneity among studies and more evidence is needed to support the conclusions.

Methods

The protocol of this study has been registered in PROSPERO (CRD42023458513).

Search strategy

Two researchers independently conducted literature searches. PubMed, Cochrane Library, Embase, and Web of Science were searched from their inception to August 10, 2023. Medical Subject Headings (MeSH) terms and keywords used in the search were ("Idiopathic Pulmonary Fibrosis" OR "IPF") AND ("mortality" OR "mors*" OR "mortality*" OR "died" OR "die" OR "dying" OR "death" OR "fatal*" OR "decease*") AND ("Risk Factors" OR "risk factor*" OR "influencing factor*" OR "influence factor*" OR "affecting factor*" OR "relevant factor*" OR "correlative factor*" OR "associated factor*" OR "Predicting factor*" OR "related factor*"). Furthermore, the reference lists of the included studies were meticulously reviewed for relevant articles. The detailed search strategies can be found in Appendix 1.

Eligibility criteria

Inclusion criteria: (I) type of study: cohort studies; (II) participants: patients diagnosed with IPF; (III) outcomes: risk factors that may be associated with mortality in patients with IPF; and (IV) study data: analysis of hazard ratios (HRs) from multivariable analysis for each risk factor and corresponding 95% confidence intervals (CIs). Exclusion criteria: (I) duplicate publications; (II) reviews, conference papers, and other types of studies; and (III) literature for which full-text access was not available.

Data extraction and quality assessment

Literature screening and data extraction were carried

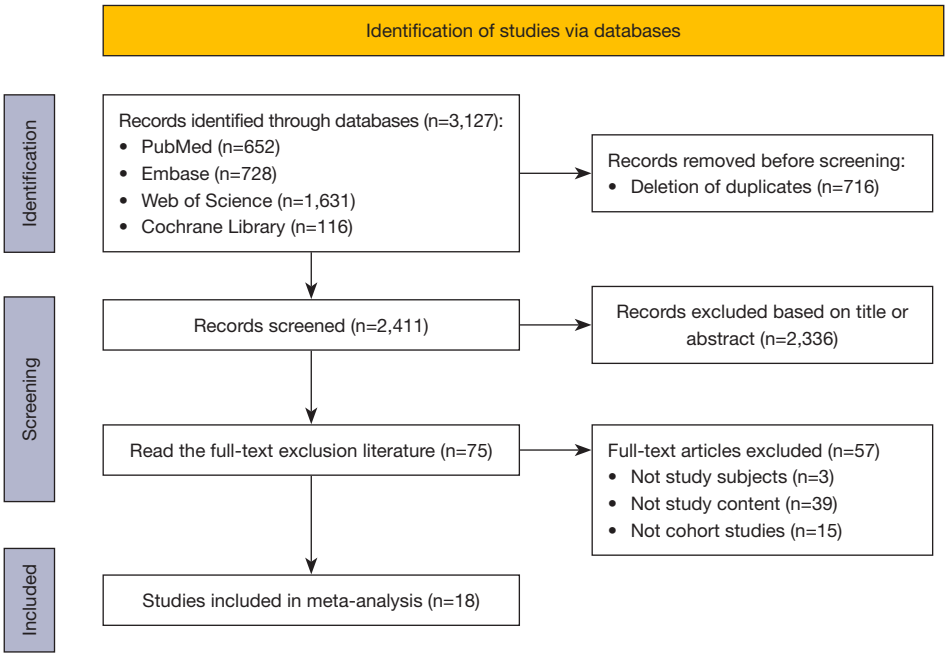

Figure 1 Literature screening process.

out independently by two researchers and cross-checked. In the event of any disparities, consensus was reached in consultation with the third researcher. Following the exclusion of duplicate literature, an initial screening was carried out based on titles and abstracts, after which the full texts were read to make the final determination. The extracted information encompassed the first author, publication year, country of origin, sample size, age, gender, follow-up time, outcome indicators, etc.

The quality of the included literature was evaluated using the Newcastle-Ottawa Scale (NOS). The assessment included three sections, comprising a total of eight items, each of which corresponded to a specific score. Studies scoring 5 to 9 were classified as high-quality research, while studies scoring 0 to 4 were regarded as low-quality research (8).

Statistical analysis

Data were analyzed using STATA (version 17.0), with the HRs as the effect indicator and corresponding 95% CIs provided. I^2 statistic was used for the heterogeneity analysis. Meta-analysis was performed using a fixed-effects model if $P>0.1$ and $I^2<50\%$ and a random-effects model if $P\leq0.1$ and $I^2\geq50\%$. Sensitivity analysis was performed by transforming the different effect models and excluding articles at a time. The subgroup analysis was conducted according to geographical region. Publication bias of the results was examined using Begg's and Egger's tests.

Results

Literature screening process and results

A total of 3,127 articles were retrieved. After deleting 716 duplicate references, 2,336 were excluded by reading titles and abstracts, and 18 were finally included by reading the full texts (4-7,9-22). The flowchart of the literature selection process is shown in *Figure 1*.

Study characteristics

Among 18 included studies, six studies (4,5,11,12,18,19) were conducted in Japan, five studies (6,7,14,17,22) in South Korea, two studies (15,21) in China-Taiwan, three studies (9,10,20) in Italy, one studies (16) in Germany, one study (13) in Denmark. A total of 8,408 subjects were enrolled, among the included studies, the minimum sample size was 40 and the maximum one was 5,665. The basic characteristics of the included studies were shown in *Table 1*. Two studies (4,18) scored 8 points on the NOS scale, while 16 studies (5-7,9-17,19-22) scored 9 points, indicating high-quality research. The quality assessment of the included studies was

Table 1 Basic characteristics of included studies

Inclusion of studies	Country/area	Number of patients [M/F]	Age (years)	Follow-up time (months)	Risk factors	Quality evaluation
Biondini *et al.*, 2021 (9)	Italy	88 [71/17]	70.0	68	GERD, respiratory failure, FVC, TLC	High
Caminati *et al.*, 2009 (10)	Italy	44 [23/21]	61.9	60	Age, gender, 6MWD, VC, FVC, DL_{CO}, SaO_2	High
Furukawa *et al.*, 2017 (11)	Japan	182 [155/27]	65.6	67	FVC% pred, SGRQ	High
Ghang *et al.*, 2019 (6)	South Korea	512 [412/100]	NR	86	Age, malignancy, FVC% pred, DL_{CO}% pred, 6MWD, CRP, WBC, SaO_2	High
Hachisu *et al.*, 2019 (12)	Japan	84 [59/25]	78	60	CRP, LDH, T-chol	High
Hyldgaard *et al.*, 2020 (13)	Denmark	260 [205/55]	72.6	60	Gender, age, smoking, FVC, DL_{CO}	High
Kim *et al.*, 2022 (14)	South Korea	215 [175/40]	71.8	60	Age, FVC% pred, DL_{CO}% pred, weight loss	High
Lai *et al.*, 2019 (15)	China-Taiwan	114 [99/15]	77.8	132	Pulmonary hypertension, heart disease, lung cancer, GERD, pulmonary fibrosis score, SpO_2	High
Lee *et al.*, 2023 (7)	South Korea	134 [124/10]	67.3	44	Albumin, heart disease, FVC% pred, DL_{CO}% pred, 6MWD, weight loss	High
Loeh *et al.*, 2019 (16)	German	70 [48/22]	66.4	108	Gender	High
Mochizuka *et al.*, 2023 (5)	Japan	301 [247/54]	72	164	Age, gender, FVC% pred, GAP index	High
Moon *et al.*, 2019 (17)	South Korea	180 [143/37]	69.1	72	BMI, smoking, GAP index	High
Nakano *et al.*, 2020 (18)	Japan	119 [98/21]	67.0	6	BMI, FVC% pred	High
Oda *et al.*, 2018 (19)	Japan	5,665 [4,122/1,543]	73.5	36	Age, gender, bacterial pneumonia, pulmonary hypertension, lung cancer	High
Sonaglioni *et al.*, 2023 (20)	Italy	103 [82/21]	70.7	36	CCI, CRP, NT-proBNP, 6MWD, LVEF	High
Suzuki *et al.*, 2021 (4)	Japan	208 [176/32]	NR	NR	Age, gender, BMI, FVC% pred, DL_{CO}% pred	High
Tseng *et al.*, 2022 (21)	China-Taiwan	40 [31/9]	75.6	29	Chest tightness, pestle finger, acute exacerbation, FVC% pred, FEV_1% pred	High
Yoon *et al.*, 2021 (22)	South Korea	89 [84/5]	68.1	144	FVC, DL_{CO}, 6MWD	High

Data types: number of patients: number; age: mean or median; follow-up time: number. M, male; F, female; GERD, gastro-oesophageal reflux disease; FVC, forced vital capacity; TLC, total lung capacity; 6MWD, 6-minute walk distance; VC, vital capacity; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; SaO_2, oxygen saturation; FVC% pred, forced vital capacity to predicted value ratio; SGRQ, Saint George Respiratory Questionnaire; DL_{CO}% pred, diffusing capacity of the lungs for carbon monoxide to predicted value ratio; CRP, C-reactive protein; WBC, white blood cell; LDH, low-density lipoprotein; T-chol, total cholesterol; SpO_2, peripheral oxygen saturation; GAP, gender-age-physiology; BMI, body mass index; CCI, Charlson comorbidity index; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; FEV_1% pred, forced expiratory volume at 1 second to predicted value ratio; NR, not reported.

shown in Appendix 2.

Meta-analysis results

The results of meta-analysis were shown in *Table 2*.

Age

Seven studies reported association between age and mortality in patients with IPF (4-6,10,13,14,19). There was significant heterogeneity among the included studies (P=0.02, I^2=59.3%), and the random-effects model was used for meta-analysis. The results suggested that older age was associated with a higher risk of mortality in IPF patients (HR =1.03; 95% CI: 1.01, 1.04; P<0.001).

Gender

Six studies reported association between gender and mortality in patients with IPF (4,5,10,13,16,19). There

Table 2 Meta-analysis results of risk factors for mortality in IPF patients

Risk factors	Number of studies included	Heterogeneity test		Effect model	Meta-analysis results	
		I^2 (%)	P value		HR (95% CI)	P value
Age	7 (4-6,10,13,14,19)	59.3	0.02	Random-effects model	1.03 (1.01, 1.04)	<0.001
Gender	6 (4,5,10,13,16,19)	63.8	0.02	Random-effects model	1.21 (0.85, 1.71)	0.29
Smoking	2 (13,17)	0.0	0.99	Fixed-effects model	0.99 (0.98, 1.01)	0.39
BMI	3 (4,17,18)	83.0	0.003	Random-effects model	0.95 (0.86, 1.05)	0.33
FVC	3 (10,13,22)	54.7	0.11	Random-effects model	0.97 (0.96, 0.99)	0.005
FVC% pred	7 (4-7,11,14,21)	61.0	0.02	Random-effects model	0.98 (0.97, 0.99)	<0.001
DL_{CO}	3 (10,13,22)	82.7	0.003	Random-effects model	0.96 (0.93, 1.00)	0.03
DL_{CO}% pred	4 (4,6,7,14)	0.0	0.96	Fixed-effects model	0.98 (0.97, 0.99)	<0.001
6MWD	5 (6,7,10,20,22)	74.8	0.003	Random-effects model	1.00 (0.99, 1.00)	0.003
SaO_2	2 (6,10)	68.4	0.08	Random-effects model	1.04 (0.87, 1.25)	0.64
GAP index	2 (5,17)	72.6	0.06	Random-effects model	1.70 (1.20, 2.40)	0.003
CRP	3 (6,12,20)	84.5	0.002	Random-effects model	1.02 (0.90, 1.15)	0.77
Lung cancer	2 (15,19)	69.6	0.07	Random-effects model	2.75 (1.23, 6.15)	0.01
Pulmonary hypertension	2 (15,19)	43.0	0.19	Fixed-effects model	1.06 (0.75, 1.51)	0.73
GERD	2 (9,15)	89.6	0.002	Random-effects model	0.49 (0.03, 8.81)	0.63
Heart disease	2 (7,15)	0.0	0.85	Fixed-effects model	1.28 (0.69, 2.37)	0.43

IPF, idiopathic pulmonary fibrosis; HR, hazard ratio; CI, confidence interval; BMI, body mass index; FVC, forced vital capacity; FVC% pred, forced vital capacity to predicted value ratio; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; DL_{CO}% pred, diffusing capacity of the lungs for carbon monoxide to predicted value ratio; 6MWD, 6-minute walk distance; SaO_2, oxygen saturation; GAP, gender-age-physiology; CRP, C-reactive protein; GERD, gastro-oesophageal reflux disease.

was significant heterogeneity among the included studies (P=0.02, I^2=63.8%), and the random-effects model was used for meta-analysis. The results suggested that gender was not statistically associated with mortality in IPF patients (HR =1.21; 95% CI: 0.85, 1.71; P=0.29).

Smoking

Two studies reported association between smoking and mortality in patients with IPF (13,17). There was no heterogeneity among the included studies (P=0.99, I^2=0.0%), and the fixed-effects model was used for meta-analysis. The results suggested that smoking was not statistically associated with mortality in IPF patients (HR =0.99; 95% CI: 0.98, 1.01; P=0.39).

Body mass index (BMI)

Three studies reported association between BMI and mortality in patients with IPF (4,17,18). There was significant heterogeneity among the included studies (P=0.003, I^2=83.0%), and the random-effects model was used for meta-analysis. The results suggested that BMI was not statistically associated with mortality in IPF patients (HR =0.95; 95% CI: 0.86, 1.05; P=0.33).

Forced vital capacity (FVC)

Four studies reported association between FVC and mortality in patients with IPF (9,10,13,22). As one study (9) did not use unified methods to analyze the indicators, it assessed the risk of death in patients with FVC <2.60 at the start of treatment, and FVC <2.56 after antifibrotic therapy, so we performed a meta-analysis of the remaining three studies (10,13,22). There was significant heterogeneity among the included studies (P=0.11, I^2=54.7%), and the random-effects model was used for meta-analysis. The results suggested that lower FVC was associated with a higher risk of mortality in IPF patients (HR =0.97; 95% CI: 0.96, 0.99; P=0.005).

FVC% pred

Seven studies reported association between FVC% pred

and mortality in patients with IPF (4-7,11,14,21). There was significant heterogeneity among the included studies (P=0.02, I^2=61.0%), and the random-effects model was used for meta-analysis. The results suggested that the decrease of FVC% pred increased the risk of mortality in IPF patients (HR =0.98; 95% CI: 0.97, 0.99; P<0.001).

Diffusing capacity of the lungs for carbon monoxide (DL_{CO})

Three studies reported association between DL_{CO} and mortality in patients with IPF (10,13,22). There was significant heterogeneity among the included studies (P=0.003, I^2=82.7%), and the random-effects model was used for meta-analysis. The results suggested that DL_{CO} was not statistically associated with mortality in IPF patients (HR =0.96; 95% CI: 0.93, 1.00; P=0.03).

DL_{CO}% pred

Four studies reported association between DL_{CO}% pred and mortality in patients with IPF (4,6,7,14). There was no heterogeneity among the included studies (P=0.96, I^2=0.0%), and the fixed-effects model was used for meta-analysis. The results suggested that the decrease in DL_{CO}% pred was a risk factor for mortality in patients with IPF (HR =0.98; 95% CI: 0.97, 0.99; P<0.001).

6-minute walk distance (6MWD)

Five studies reported association between 6MWD and mortality in patients with IPF (6,7,10,20,22). There was significant heterogeneity among the included studies (P=0.003, I^2=74.8%), and the random-effects model was used for meta-analysis. The results suggested that 6MWD was not statistically associated with mortality in IPF patients (HR =1.00; 95% CI: 0.99, 1.00; P=0.003).

Oxygen saturation (SaO_2)

Two studies reported association between SaO_2 and mortality in patients with IPF (6,10). There was significant heterogeneity among the included studies (P=0.08, I^2=68.4%), and the random-effects model was used for meta-analysis. The results suggested that SaO_2 was not associated with an increased risk of mortality in IPF patients (HR =1.04; 95% CI: 0.87, 1.25; P=0.64).

Gender-age-physiology (GAP) index

Two studies reported association between GAP index and mortality in patients with IPF (5,17). There was significant heterogeneity among the included studies (P=0.06, I^2=72.6%), and the random-effects model was used for meta-analysis. The results suggested that higher score of the GAP index was associated with an increased risk of mortality in IPF patients (HR =1.70; 95% CI: 1.20, 2.40; P=0.003).

C-reactive protein (CRP)

Three studies reported association between CRP and mortality in patients with IPF (6,12,20). There was significant heterogeneity among the included studies (P=0.002, I^2=84.5%), and the random-effects model was used for meta-analysis. The results suggested that CRP was not statistically associated with mortality in IPF patients (HR =1.02; 95% CI: 0.90, 1.15; P=0.77).

Lung cancer

Two studies reported association between lung cancer and mortality in patients with IPF (15,19). There was significant heterogeneity among the included studies (P=0.07, I^2=69.6%), and the random-effects model was used for meta-analysis. The results suggested that IPF patients with lung cancer had a 2.75-fold increased risk of mortality compared with those with IPF alone (HR =2.75; 95% CI: 1.23, 6.15; P=0.01).

Pulmonary hypertension

Two studies reported association between pulmonary hypertension and mortality in patients with IPF (15,19). There was no heterogeneity among the included studies (P=0.19, I^2=43.0%), and the fixed-effects model was used for meta-analysis. The results suggested that pulmonary hypertension was not statistically associated with mortality in IPF patients (HR =1.06; 95% CI: 0.75, 1.51; P=0.73).

Gastro-oesophageal reflux disease (GERD)

Two studies reported association between GERD and mortality in patients with IPF (9,15). There was significant heterogeneity among the included studies (P=0.002, I^2=89.6%), and the random-effects model was used for meta-analysis. The results suggested that GERD was not statistically associated with mortality in IPF patients (HR =0.49; 95% CI: 0.03, 8.81; P=0.63).

Heart disease

Two studies reported association between heart disease and mortality in patients with IPF (7,15). There was no heterogeneity among the included studies (P=0.85, I^2=0.0%), and the fixed-effects model was used for meta-analysis. The results suggested that heart disease was not

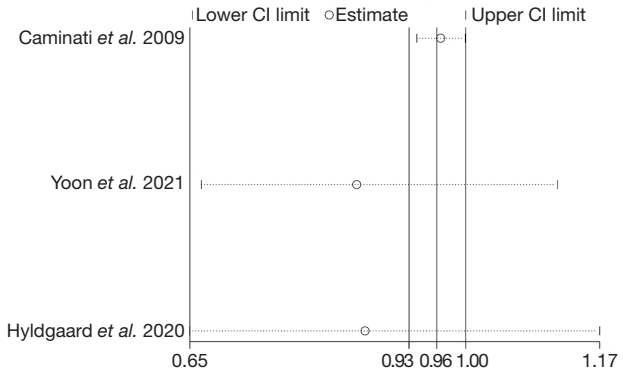

Figure 2 Sensitivity analysis of DL_{CO}. X-axis represented the HRs and 95% CIs of DL_{CO} associated with mortality in patients with IPF. Y-axis represented the names of the individual studies. Every effect size was located between 0.65 and 1.17 while none of 95% CIs crossed the invalid line "0", signifying that the result was stable. CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.

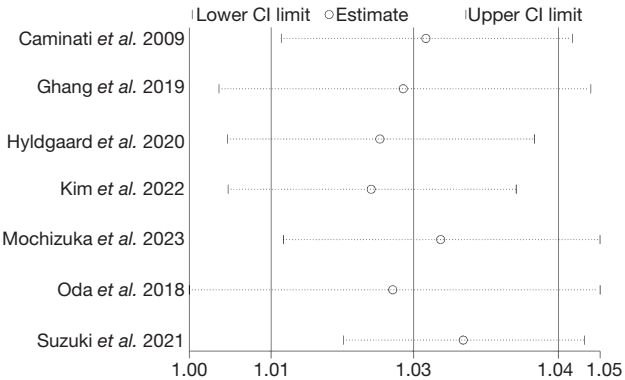

Figure 3 Sensitivity analysis of age. X-axis represented the HRs and 95% CIs of age associated with mortality in patients with IPF. Y-axis represented the names of the individual studies. Every effect size was located between 1.00 and 1.05 while none of 95% CIs crossed the invalid line "0", signifying that the result was stable. CI, confidence interval; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.

statistically associated with mortality in IPF patients (HR =1.28; 95% CI: 0.69, 2.37; P=0.43).

Other risk factors

The Saint George Respiratory Questionnaire (SGRQ), smoking, forced expiratory volume at 1 second to predicted value ratio (FEV_1% pred), bacterial pneumonia,

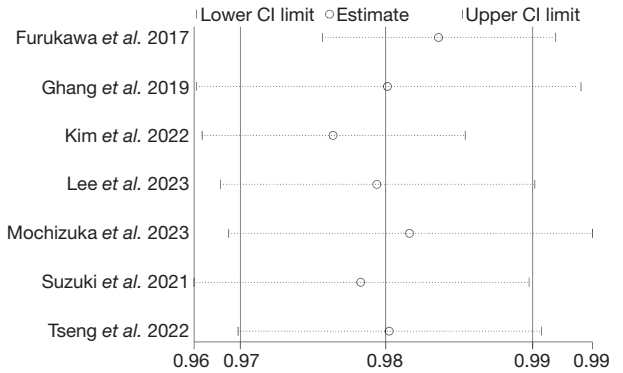

Figure 4 Sensitivity analysis of FVC% pred. X-axis represented the HRs and 95% CIs of FVC% pred associated with mortality in patients with IPF. Y-axis represents the names of the individual studies. Every effect size was located between 0.96 and 0.99 while none of 95% CIs crossed the invalid line "0", signifying that the result was stable. CI, confidence interval; FVC% pred, forced vital capacity to predicted value ratio; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.

acute exacerbations, Charlson comorbidity index (CCI), malignant tumors, respiratory failure, peripheral oxygen saturation (SpO_2), N-terminal pro-brain natriuretic peptide (NT-proBNP), chest tightness, clubbing, and pulmonary fibrosis score were referenced solely in individual studies, without undergoing meta-analysis.

Sensitivity analysis, subgroup analyses, and publication bias

HRs and 95% CIs were calculated using both fixed-effects and random-effects models respectively. The results indicated that, except for DL_{CO}, minimal changes were observed in the meta-analysis results of other risk factors, suggesting relatively robust outcomes. We performed sensitivity analysis for DL_{CO} by excluding articles at a time, and the results were robust (*Figure 2*). Among the risk factors related to mortality in IPF patients, the heterogeneity of age and FVC% pred was high, sensitivity analysis by excluding one study at a time suggested that the results were stable (*Figures 3,4*).

We also performed subgroup analyses for age, gender, and 6MWD based on geographic region (Europe and Asia). The results showed that older age was a risk factor for mortality in patients with IPF in Asia (HR =1.02; 95% CI: 1.01, 1.04; P=0.002); while the European results showed no association (HR =1.03; 95% CI: 0.97, 1.09; P=0.35), considering that there were only two European studies,

Table 3 Transformation effect model analysis and publication bias results

Risk factors	Effect model and HR (95% CI)		P value (Begg's test)	P value (Egger's test)
	Fixed-effects model	Random-effects model		
Age	1.03 (1.02, 1.04)	1.03 (1.01, 1.04)	0.37	0.53
Gender	0.94 (0.81, 1.10)	1.21 (0.85, 1.71)	0.13	0.007
Smoking	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	–	–
BMI	0.98 (0.95, 1.02)	0.95 (0.86, 1.05)	0.30	0.02
FVC	0.97 (0.96, 0.98)	0.97 (0.96, 0.99)	>0.99	0.56
FVC% pred	0.98 (0.97, 0.98)	0.98 (0.97, 0.99)	>0.99	0.90
DL_{CO}	0.96 (0.95, 0.98)	0.96 (0.93, 1.00)	>0.99	0.62
DL_{CO}% pred	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.73	0.38
6MWD	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	0.22	0.42
SaO_2	0.98 (0.96, 1.00)	1.04 (0.87, 1.25)	–	–
GAP index	1.62 (1.37, 1.92)	1.70 (1.20, 2.40)	–	–
CRP	1.01 (0.97, 1.04)	1.02 (0.90, 1.15)	>0.99	0.87
Lung cancer	2.18 (1.64, 2.90)	2.75 (1.23, 6.15)	–	–
Pulmonary hypertension	1.06 (0.75, 1.51)	1.11 (0.68, 1.82)	–	–
GERD	0.64 (0.26, 1.60)	0.49 (0.03, 8.81)	–	–
Heart disease	1.28 (0.69, 2.37)	1.28 (0.69, 2.37)	–	–

HR, hazard ratio; CI, confidence interval; BMI, body mass index; FVC, forced vital capacity; FVC% pred, forced vital capacity to predicted value ratio; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; DL_{CO}% pred, diffusing capacity of the lungs for carbon monoxideto predicted value ratio; 6MWD, 6-minute walk distance; SaO_2, oxygen saturation; GAP, gender-age-physiology; CRP, C-reactive protein; GERD, gastro-oesophageal reflux disease.

the results need to be further analyzed in future studies. Subgroup analysis of gender and 6MWD did not change the overall results.

Additionally, Begg's and Egger's tests were conducted on risk factors included in more than two studies. Among them, gender and BMI had potential publication bias, and Egger's test showed the P values were 0.007 and 0.02 (*Table 3*).

Discussion

This study included only cohort studies that conducted multivariable analysis to enhance the reliability of the results. In total, 18 articles comprising 8,408 IPF patients from six different countries were included. The methodological quality of the included studies was notably high, with NOS scores ranging from 8 to 9. The findings revealed that age, FVC, FVC% pred, DL_{CO}% pred, GAP index, and lung cancer were established as mortality risk factors among IPF patients. Nevertheless, the effects of gender, smoking, DL_{CO}, SaO_2, CRP, 6MWD, BMI, pulmonary hypertension, GERD, and heart disease on mortality still need further studies to explore.

In this study, we found an association between age and risk of mortality in patients with IPF, which was in consistent with previous studies (23,24). According to du Bois *et al.* (25), patients over the age of 70 years had almost twice the risk of death as those below 60 years. Leuschner *et al.* (26) observed an 11.2% higher mortality rate in patients aged 75 and older compared to those below. This could be attributed to age-related comorbidities such as cognitive impairment, malnutrition, and frailty, which accelerate disease progression, and elevate the risk of mortality (27).

Regarding lung function, FVC is a common endpoint of lung function, multiple studies have identified lower FVC as an independent predictor of mortality in patients with IPF (28,29), our meta-analysis showed similar results. FVC is negatively correlated with interstitial involvement in patients with IPF, and its reduction indicates more severe lung injury and poorer prognosis, studies have reported that FVC in IPF patients can decrease by more than

200 mL/year (30,31). DL_{CO} is also a widely accepted predictor of poor prognosis in patients with IPF (32), our included studies also suggest unanimous conclusion. However, our results showed no statistical association between them. Given the high heterogeneity due to differences in population, region, and sample size, we tend to be conservative about the association between DL_{CO} and IPF mortality, and look forward to high-quality clinical trials providing more data to help draw more firm evidence. Additionally, our findings show that reductions in FVC% pred and DL_{CO}% pred were also associated with IPF patient mortality, as corroborated by multiple previous studies (33,34). Snyder *et al.* (35) found that for per 10% decrease in FVC% pred predicted at enrollment, the risk of death or lung transplant increased by 28%, similarly, for per 10% decrease in DL_{CO}% pred at enrollment, the risk of death or lung transplant increased by 25%. The decreases in FVC% pred and DL_{CO}% pred indicate limited lung ventilation and impaired gas diffusion, which is characteristic of advanced IPF. As the disease progresses, lung function further deteriorates, ultimately leading to respiratory failure and death, critically impacting prognosis (36,37).

Consider the GAP index, our result suggested that it was an independent risk factors for mortality in IPF patients, aligning with the findings reported by Lee *et al.* (38). Introduced by Ley *et al.* (39) in 2012, the GAP index encompassed four variables: gender, age, FVC% pred, and DL_{CO}% pred. These metrics are widely employed globally to analyze the mortality prognosis of IPF patients (40-42). Oldham *et al.* (43) determined that each progression of one stage in the GAP index system corresponded to approximately double the risk of death in IPF patients. Furthermore, other studies have established median survival periods of 64, 45, and 17 months for stage 1, stage 2, and stage 3 of the GAP index, respectively (44). Precisely evaluating the GAP index can enhance the predictive accuracy concerning IPF mortality rates, facilitating the implementation of effective measures to improve the prognosis of IPF patients.

This study found a significant association between the risk of mortality in patients with IPF and lung cancer, and it has been consistently demonstrated in previous research (45,46). Tomassetti *et al.* (47) discovered that IPF patients with coexisting lung cancer had a considerably shorter median survival time compared to those without, specifically 38.7 and 63.9 months, respectively. Another study revealed that approximately 10.20% of IPF-related deaths were attributed to lung cancer (48). This can be attributed to two primary factors. Firstly, the incidence of lung cancer is notably higher among individuals with IPF, with lung cancer being the most prevalent complication accompanying IPF. Research indicates that IPF patients are five times more likely to develop lung cancer than the general population, with a 10-year incidence rate of 54.7% (49,50). Secondly, there are common biological pathways between lung cancer and IPF, resulting in their frequent co-occurrence in clinical settings, this overlap exacerbates the prognosis, leading to a worse outcome for IPF patients who have also been diagnosed with lung cancer compared to those with IPF alone (51).

6MWD was a widely utilized measure to assess the overall functioning of the pulmonary, cardiovascular, peripheral circulatory, and muscular systems in individuals with chronic respiratory ailments (52,53). In a study by du Bois *et al.* (25), it was observed that a baseline 6MWD of less than 250 m was linked to a twofold increase in the risk of death, while a decline of more than 50 m in 6MWD after 24 weeks correlated with an almost threefold increase in the risk of death. However, our study found no significant association between the 6MWD and the mortality risk in patients diagnosed with IPF, although opposite results were observed in almost all included studies. Further investigation is necessary to ascertain the potential relevance of 6MWD as a prognostic factor for mortality in IPF.

In addition, pulmonary hypertension and hypoxemia are common manifestations of advanced IPF and are also considered to be important factors for poor prognosis. Lai *et al.* (15) reported that SpO_2 <90% increases the risk of death by more than 5 times in patients with IPF. However, in our meta-analysis of pulmonary hypertension and SaO_2, we found no statistically association between them and IPF mortality. Definitive relationship between pulmonary hypertension, hypoxemia, and mortality needs to be confirmed by further studies. Our results showed no association between the gender of patients with IPF and the risk of death. Presently, there is insufficient evidence to support notable differences in mortality risk mechanisms between males and females. Consequently, this study suggested that gender is unlikely to be a contributing risk factor for mortality in IPF patients. Due to the limited number of studies and available data on variables such as BMI, CRP, GERD, and heart disease, the potential impact of these factors on outcomes remains uncertain, necessitating further investigation into their relationship with mortality in IPF patients.

Several limitations exist in this study. Firstly, over two-thirds of the included studies were conducted in Asia, which raises the possibility of result bias. Second, the included

studies did not perform subgroup analyses for age, FVC% pred, BMI, and 6MWD, limiting the exploration of potential differences in the mortality risk between different age groups and different levels of FVC%, BMI, and 6MWD. Thirdly, the available literature on some risk factors was limited, potentially influencing the study outcomes. Fourth, in terms of treatment, as is known that the use of drugs, especially anti-fibrotic drugs, are believed to have certain impact on the prognosis of IPF. However, due to limited reporting, we were unable to perform subgroup analyses based on pre- and post-therapy, which may have contributed to results bias. In addition, the studies we included in the meta-analysis covered a period of time, during which great changes had taken place in the treatment for IPF, and the use of different drugs also may increase bias of results. Moreover, certain risk factors may be associated with mortality, due to the scarcity of studies, we were unable to conduct a meta-analysis to evaluate their impact on mortality in patients with IPF.

Conclusions

In conclusion, this study applies the meta-analysis method to analyze and summarize the risk factors associated with mortality in patients with IPF. The identified potential risk factors include age, FVC, FVC% pred, DL_{CO}% pred, GAP index, and lung cancer. However, it is important to note that the conclusions drawn from this analysis are subject to certain limitations stemming from restrictions in both the number and quality of the included studies. Therefore, further research is necessary to validate these findings. Moving forward, it is recommended to place greater emphasis on these identified risk factors during the diagnostic and treatment process for IPF. This enhanced focus will enable clinicians to make more informed clinical decisions and effectively reduce the mortality risk for patients with IPF.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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