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REVIEW

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Higher body mass index was associated with a lower mortality of idiopathic pulmonary fibrosis: a meta-analysis

Dengyun Pan[1†], Qi Wang[1†], Bingdi Yan[1] and Xiaomin Su[1*]

Abstract

Purpose In the past few years, there has been a notable rise in the incidence and prevalence of idiopathic pulmonary fibrosis (IPF) on a global scale. A considerable body of research has highlighted the 'obesity paradox,' suggesting that a higher body mass index (BMI) can confer a protective effect against numerous chronic diseases. However, the relationship between BMI and the risk of mortality in IPF patients remains underexplored in the existing literature. We aim to shed light on this relationship and potentially offer novel insights into prevention strategies for IPF.

Methods We conducted a systematic search of the PubMed, Embase, and Web of Science databases to collect all published studies examining the correlation between Body Mass Index (BMI) and the mortality risk in patients with IPF, up until February 14, 2023. For the synthesis of the findings, we employed random-effects models. The statistical significance of the association between BMI and the mortality risk in IPF patients was evaluated using the hazard ratio (HR), with the 95% Confidence Interval (CI) serving as the metric for effect size.

Results A total of 14 data sets involving 2080 patients with IPF were included in the meta-analysis. The combined results of the random-effects models were suggestive of a significant association between lower BMI and a higher risk of death (HR = 0.94, 95% CI = 0.91–0.97, $P < 0.001$). For baseline BMI, the risk of death from IPF decreased by 6% for each unit increase. The results of the subgroup analysis suggest that geographic location (Asian subgroup: HR = 0.95, 95%CI = 0.93–0.98, $P = 0.001$; Western subgroup: HR = 0.91, 95%CI = 0.84–0.98, $P = 0.014$), study type (RCS subgroup: HR = 0.95, 95%CI = 0.92–0.98, $P = 0.004$; PCS subgroup: HR = 0.89, 95%CI = 0.84–0.94, $P < 0.001$), and sample size (< 100 groups: HR = 0.93, 95%CI = 0.87–1.01, $P = 0.079$; >100 groups: HR = 0.94, 95%CI = 0.91–0.97, $P < 0.001$) were not significant influences on heterogeneity. Of the included literature, those with confounding factors corrected and high NOS scores reduced heterogeneity (HR = 0.93, 95%CI = 0.90–0.96, $P < 0.001$). Sensitivity analyses showed that the combined results were stable and not significantly altered by individual studies (HR = 0.93 to 0.95, 95% CI = 0.90–0.96 to 0.92–0.98). Egger's test suggested no significant publication bias in the included studies ($P = 0.159$).

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Conclusions Higher BMI (BMI ≥ 25 kg/m2) is negatively correlated to some extent with the risk of death in IPF patients, and BMI may become a clinical indicator for determining the prognosis of IPF patients.

Keywords BMI, IPF, Mortality, Meta-analysis

Introduction

IPF is a chronic, progressive, fibrous interstitial pneumonia of unknown etiology. The currently recognized mechanism of IPF is that it is a chronic inflammatory and abnormal repair process. In persistent microinjury of the alveolar epithelium from multiple causes, abnormal activation of fibroblasts and excessive accumulation of extracellular matrix lead to an abnormal repair process of lung scar formation as the inflammatory response progresses [1–3]. In the United States, the median age of newly diagnosed patients is 62 years, 54% of whom are men [4]. The global incidence and prevalence of IPF is between 0.09 and 1.3 per 10,000 people with a rising trend year by year. Compared to other countries studied, the United States, Korea, and Canada have the highest incidence rates, with a median survival of less than 4 years and a worse prognosis than many common cancers [5, 6]. Although corresponding epidemiological data are lacking in China, clinical practice has revealed a significant trend of increasing IPF cases in recent years. The etiology of IPF remains unclear. Several studies have identified potential risk factors, including genetic alterations, viral infections, lifestyle habits, environmental influences, and occupational hazards. However, current evidence suggests that IPF is the result of a complex interaction between genetic and environmental factors. In addition, the occurrence of several diseases can increase the incidence of IPF, such as gastroesophageal reflux (GERD) [7, 8], diabetes (DM) [9], and obstructive sleep apnea (OSA) [10]. Two introduced antifibrotic drugs, pirfenidone and nintedanib, may significantly delay the decline in lung function and reduce the incidence and severity of associated complications [6]. However, they are not a cure for IPF. Therefore, the continuous exploration of new specific biomarkers and therapeutic targets will become a major trend in the future.

Obesity is a growing global health problem that affects multiple organ systems and is a potentially modifiable factor in many diseases. Studies have shown that overweight or obesity also increases the risk of a number of diseases, such as: hypertension, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, chronic kidney disease, coronary heart disease, cerebral vascular lesions, gallbladder stones, arthropathies, polycystic ovary syndrome, sleep apnea syndrome, and a number of tumors [11]. Current research suggests that the mechanisms of action of obesity in IPF may be related to factors such as chronic inflammation, oxidative stress, and insulin resistance, all of which may be associated with obesity-induced ectopic fat deposition. Obesity-induced low-grade aseptic inflammation and over-infiltration of immune cells in adipose tissue is accompanied by a decreased ability of adipose tissue to store lipids, leading to ectopic fat deposition, which accelerates the onset and progression of pulmonary fibrosis [12, 13]. However, multiple studies have reported that adipose tissue plays a protective role, which is called the "obesity paradox" [14]. A French study showed that nearly one-third of IPF patients were malnourished, and the worse the nutritional status of the patients, the worse their prognosis [15]. Due to the ease of measurement and relatively high acceptance, BMI has been adopted by most research institutes as an indicator of obesity and health status. It has been found that higher BMI increases the risk of IPF, but the degree of pulmonary fibrosis and the risk of death are low relative to patients with lower BMI, and more refined subgroups have been found to be associated with a higher risk of death with lower BMI [14, 16]. In addition, in antifibrotic therapy, higher BMI patients also have relatively better treatment outcomes [17]. However, the existence of an "obesity paradox" in IPF patients is controversial, with some studies finding no correlation between BMI and mortality [18].

Currently, many research studies have focused on the diagnosis and treatment modalities of IPF, while other risk factors influencing disease pathogenesis and disease prognosis have received less attention. The available studies suggest that BMI and the risk of death from IPF are uncertain [19–22].

Therefore, this study systematically reviewed the relevant literature and defined the relationship between BMI and the mortality of IPF, aiming to provide basis for evaluating the prognosis of IPF patients.

Materials and methods

This meta-analysis was planned and conducted according to the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA) list [23]. In addition, since the included studies were observational in design, we also followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [24].

Literature search strategy

In this article, a literature search was conducted through PubMed, Embase, and Web of Science databases according to a pre-defined search strategy. The search terms included: "idiopathic pulmonary fibrosis", "body mass index", and "BMI". Subject terms were searched in

combination with free terms, adapting the search formula to the characteristics of the database (see Supplementary Tables 1–3 for specific search steps of the database). The search was conducted up to February 14, 2023, with no language restrictions. In addition, this study screened references of relevant reviews and included literature in the hope of obtaining more studies that could be used for meta-analysis.

Inclusion and exclusion criteria

The following were eligible for inclusion in this study: (1) the study population was patients diagnosed with IPF; (2) the exposure factor was BMI at baseline; (3) the study reported a hazard ratio (HR) (95% CI) for change in risk of death with a 1 kg/m^2 increase in BMI; and (4) the study type was a prospective or retrospective cohort study.

Meanwhile, we excluded the following: (1) non-thesis studies such as reviews, conference abstracts, and commentaries; (2) studies with acute exacerbation of IPF; (3) for duplicate publications or the same data used in multiple articles, only the one with the most complete study information was included, and the rest were excluded. Two of the authors independently searched all references, and any discrepancies were resolved by all authors on a voting basis.

Data extraction

Two investigators (Xiaomin Su and Dengyun Pan) independently completed the literature screening according to the inclusion and exclusion criteria described above. After identifying the literature to be included in the analysis, they carried out the data extraction exercise independently according to a pre-designed form. For each study, the following information was collected: name of the first author, publication year, region where the study was conducted, study type, basic characteristics of the study population (sample size, sex, age), follow-up time, drugs used to treat IPF, study outcome and correction factors. After both of them finished the above data extraction work, they exchanged audit extraction forms and discussed and resolved any inconsistencies.

Quality assessment

Quality assessment of eligible studies was performed by two researchers (Xiaomin Su and Bingdi Yan) using the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for use in non-randomized observational studies [25]. The evaluation included three aspects of study subject selection, comparability, and exposure. Scores ranged from 0 to 9 points. Depending on the score, they can be classified as low (0–3 points), medium (4–6 points) and high-quality studies (7–9 points).

Statistical analysis

HR and 95% CI were used as effect sizes to assess whether the association between BMI and the risk of death in patients with IPF was statistically significant. Heterogeneity was tested using Cochran' s Q test and I^2 test. For the Q statistic, $P<0.05$, or $I^2>50\%$, indicated significant heterogeneity between studies, and a random-effects model was used for meta-analysis; if $P\geq0.05$ and $I^2\leq50\%$, heterogeneity was not significant and a fixed-effects model was used [26].

Subgroup analysis was performed based on geographic location, study type, sample size, whether to correct for confounders, and methodological quality grouping. The effect of individual included studies on the results of the meta-analysis was evaluated for significance using the one-by-one exclusion test. Egger's test was used to assess whether there was significant publication bias in the included studies [27]. If significant publication bias existed, the stability of the combined results was assessed using the cut-and-patch method [28].

The above statistical analysis was done using Stata 12.0 software.

Results

Literature search

A total of 1270 publications (163 in PubMed, 904 in Embase, and 203 in Wen of Science) were searched in electronic databases for this meta-analysis. Two hundred ninety-two duplicates were excluded, and 957 papers that clearly did not meet the inclusion criteria were excluded after browsing the titles and abstracts. Finally, 21 publications were excluded after full-text reading of 8, and the remaining 13 were included in the meta-analysis. The details of literature search are shown in Fig. 1.

Study characteristics and quality assessment

The characteristics of the participating studies and patients are shown in Table 1. As of February 14, 2023, a total of 13 papers were included in this meta-analysis. Ten of them were retrospective cohort studies [9, 19, 29–36] and three were prospective cohort studies [20, 37, 38]. Study publication years range from 2007 to 2022. Nine of these studies were conducted in Asia [9, 29–35, 38], including Saudi Arabia ($n=1$), China ($n=1$), Japan ($n=6$) and Korea ($n=1$); Five were conducted in Europe [20, 30, 36, 37], which includes France ($n=1$), Italy ($n=2$) and the UK ($n=1$); One was conducted in the United States ($n=1$), located in North America. The baseline mean/median BMI values in these studies ranged between 21 and 30 kg/m^2. Twelve studies assessed the BMI as a continuous variable [9, 19, 20, 29, 31–33, 35–38], and one as both a continuous variable and a cut-off value [34]. The 14 data sets included in this study involve a combined total of 2,080 individuals (1657 males and 423 females).

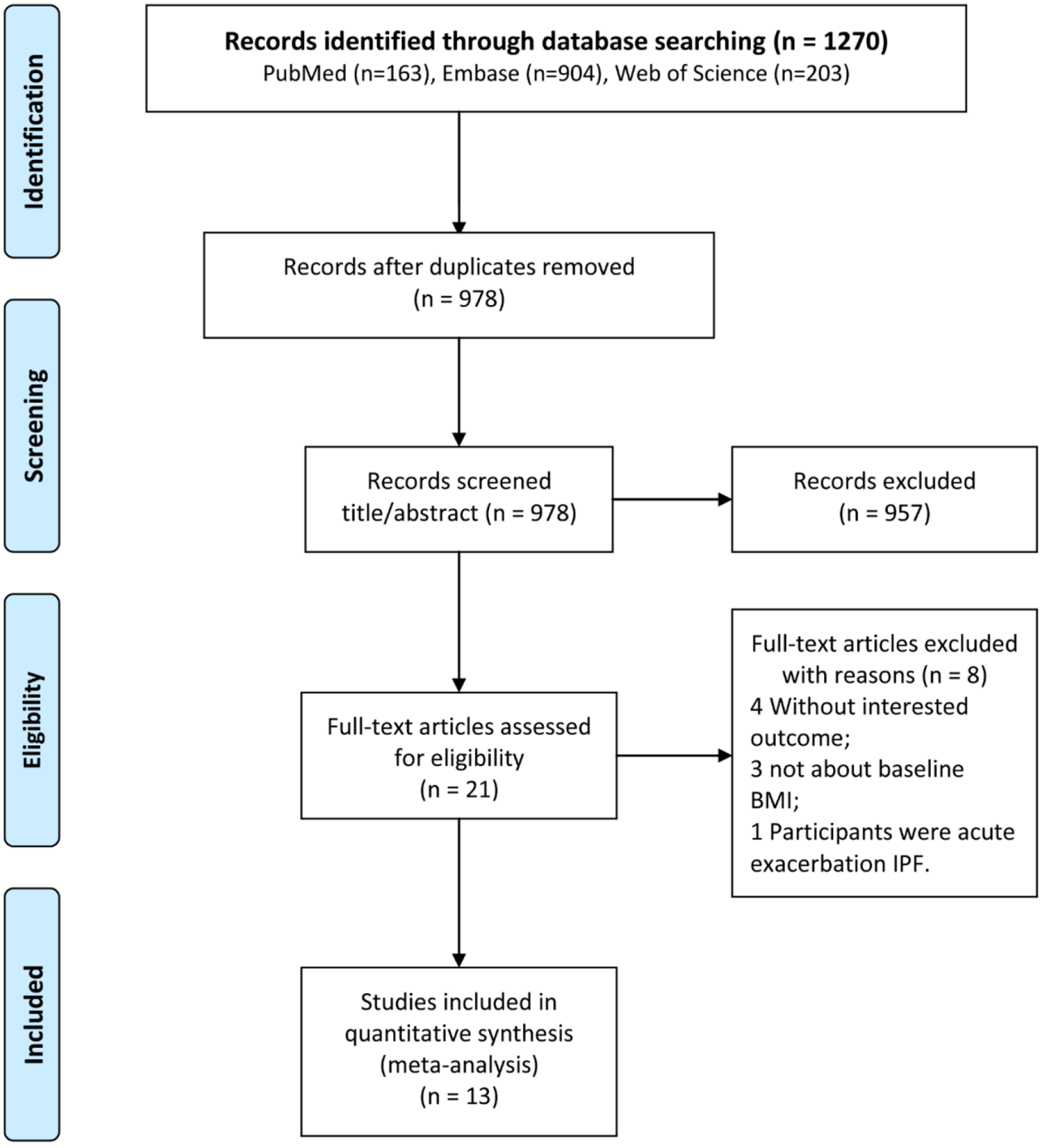

Fig. 1 Literature search results and flowchart of the literature screening process

The sample size ranged from 44 to 445 cases. Baseline BMI of study subjects was obtained from medical records, and survival status was confirmed by medical records or telephone callbacks. Information on age, treatment protocol study outcomes, and correction factors are shown in Table 1.

The NOS scores of the included studies ranged from 4 to 8 points. Thus, nine of the included studies were of high-quality [9, 19, 20, 29, 31, 33–36] and the others were of moderate methodological quality [30, 32, 37, 38]. The main types of bias in the included studies were recall bias and confounding bias.

Table 1 Characteristics of 13 included studies in this meta-analysis

Study	Location	Design	Follow-up, years	Therapeutic	*N*, M/F	Age, years	HR (95%CI)	Adjusted factors
Alakhras, M 2007 [20]	USA	RCS	up to 4	Prednisone, colchicine, or none	197, 137/60	71.4 ± 8.9	0.86 (0.79, 0.94)	Gender, oxygen saturation with exercise, Age, smoking, FVC, DLco, treatment, oxygen saturation at rest
Alhamad, EH 2020 [9]	Saudi Arabia	RCS	up to 12	Nintedanib, Pirfenidone	212, 150/62	66.4 ± 11.7	0.95 (0.90, 1.00)	Acute exacerbation, SpO2, antifibrotic therapy, 6MWT distance, TLC, FVC
Jouneau, S 2022 [21]	France	PCS	≥ 1	Nintedanib, Pirfenidone, or none	153, 119/34	72.4 ± 8.1	0.89 (0.82, 0.96)	GAP score, food intake
Kono, M 2019 [33]	Japan	RCS	Mean 1.8	Pirfenidone	96, 77/19	71.5 ± 7.5	0.61 (0.11, 3.17)	None
Li, B 2019 [30]	China	RCS	up to 6	NR	148, 133/15	Median 65	0.97 (0.89, 1.04)	FVC, albumin, globumin, prealbumin
Mura, M 2012 [38]	Italy	PCS	3	NR	70, 57/13	67 ± 8	0.89 (0.80, 0.98)	None
Nakatsuka, Y 2018 [31]	Japan	RCS	2	Pirfenidone, Corticosteroid, PPI/H2 blocker, Diuretics	124, 105/19	68.6	0.99 (0.90, 1.12)	None
	UK	RCS	2		86, 69/17	65.5	1.01 (0.97, 1.06)	None
Nishimoto, K 2018 [34]	Japan	RCS	Median 3	Prednisolone, immunosuppressive agents, antifibrotic agents	84, 74/10	71 (64–75)	1.01 (0.88, 1.15)	Gender, Age, FVC, Pneumothorax
Nishiyama, O 2017 [39]	Japan	PCS	Mean 2.3	No treatment	44, 35/9	72.3 ± 7.2	0.88 (0.76, 1.02)	None
Suzuki, Y 2018 [32]	Japan	RCS	Median 4.4	NR	131, 117/14	69 (64–75)	1.01 (0.89, 1.14)	Gender, Age, ESM_{CSA}, ESM_{MA}, FVC
Suzuki, Y 2021 [35]	Japan	RCS	Median 2.8	Pirfenidone, Nintedanib	208, 176/32	72 (66–76)	0.92 (0.85, 1.00)	Gender, Age, ESM_{CSA}, FVC, DLco
Yoo, JW 2022 [36]	Korea	RCS	Median 3.1	Steroid, IM	445, 335/110	66.4 ± 7.7	0.94 (0.89, 1.00)	Age, FVC, DLco, 6MWT distance, 6MWT lowest SpO2, disease progression, acute exacerbation
Zinellu, A 2021 [37]	Italy	RCS	4	Nintedanib, Pirfenidone, or none	82, 73/9	72 ± 7	0.86 (0.77, 0.96)	Gender, Age, Smoking, Disease stage, Antifibrotic drugs, AISI

USA, United States of America; TLC, Total lung capacity; FVC, Forced vital capacity; DLco, Diffusing capacity of the lung for carbon monoxide; GAP, Gender-age-physiology; RCS, Retrospective cohort study; PCS, Prospective cohort study; 6MWT, 6-min walk test; PPI, Proton pump inhibitor; UK, The United Kingdom of Great Britain and Northern Ireland; ESM_{CSA}, Cross-sectional area of elector spine muscles; ESM_{MA}, Muscle attenuation of elector spine muscles; IM, Azathioprine, Mycophenolate mofetil, Cyclosporine; AISI, Aggregate systemic inflammation index; NR, Not reported; M,Male; F, Female

Meta regression

Since the study by Nakatsuka et al. [30]. had data from two cohorts of the study, there were 14 data sets. A forest plot of the association analysis between BMI and the risk of death from IPF is shown in Fig. 2. The results of the heterogeneity test of the included studies suggested a statistically significant heterogeneity (I^2=46.3%, P=0.029). And the random effects model was applied, the summary HR for 14 data sets showed that the association between BMI and the risk of death in IPF patients is significant (HR=0.94, 95%CI=0.91–0.97, P<0.001). For baseline BMI, the risk of death from IPF decreased by 6% for each unit increase.

Subgroup analysis

The results of the subgroup analysis are shown in Table 2, based on geographic location, study type, sample size, whether or not to correct for confounding factors, and methodological quality grouping.

The combined results of Asian subgroup (HR=0.95, 95%CI=0.93–0.98, P=0.001) and Western subgroup (HR=0.91, 95%CI=0.84–0.98, P=0.014) were statistically significant (Fig. 3A). Similarly, according to the study type grouping (Fig. 3B), the combined results of the two subgroups were significantly (RCS subgroup: HR=0.95, 95%CI=0.92–0.98, P=0.004; PCS subgroup: HR=0.89, 95%CI=0.84–0.94, P<0.001). However, subgroup analysis of sample size (Fig. 3C), for <100 groups, combined results were not meaningful (HR=0.93, 95%CI=0.87–1.01, P=0.079). In addition, geographic location, study type, and sample size were not influential factors on heterogeneity in any significant way. The grouping scheme of whether to correct for confounding factors and methodological quality grouping was consistent, and the within-group heterogeneity of subgroups was not at a significant level (Fig. 3D **and E**), which indicates that these two factors are sources of heterogeneity. Studies with high multifactor correction or methodological quality had statistically significant combined results (HR=0.93, 95%CI=0.90–0.96, P<0.001). Furthermore, considering the significant role of Forced Vital Capacity (FVC) in IPF patients, we conducted a subgroup analysis correcting for FVC. The results indicate that the pooled outcomes are statistically significant, regardless of whether FVC adjustments were applied or not (Fig. 3F).

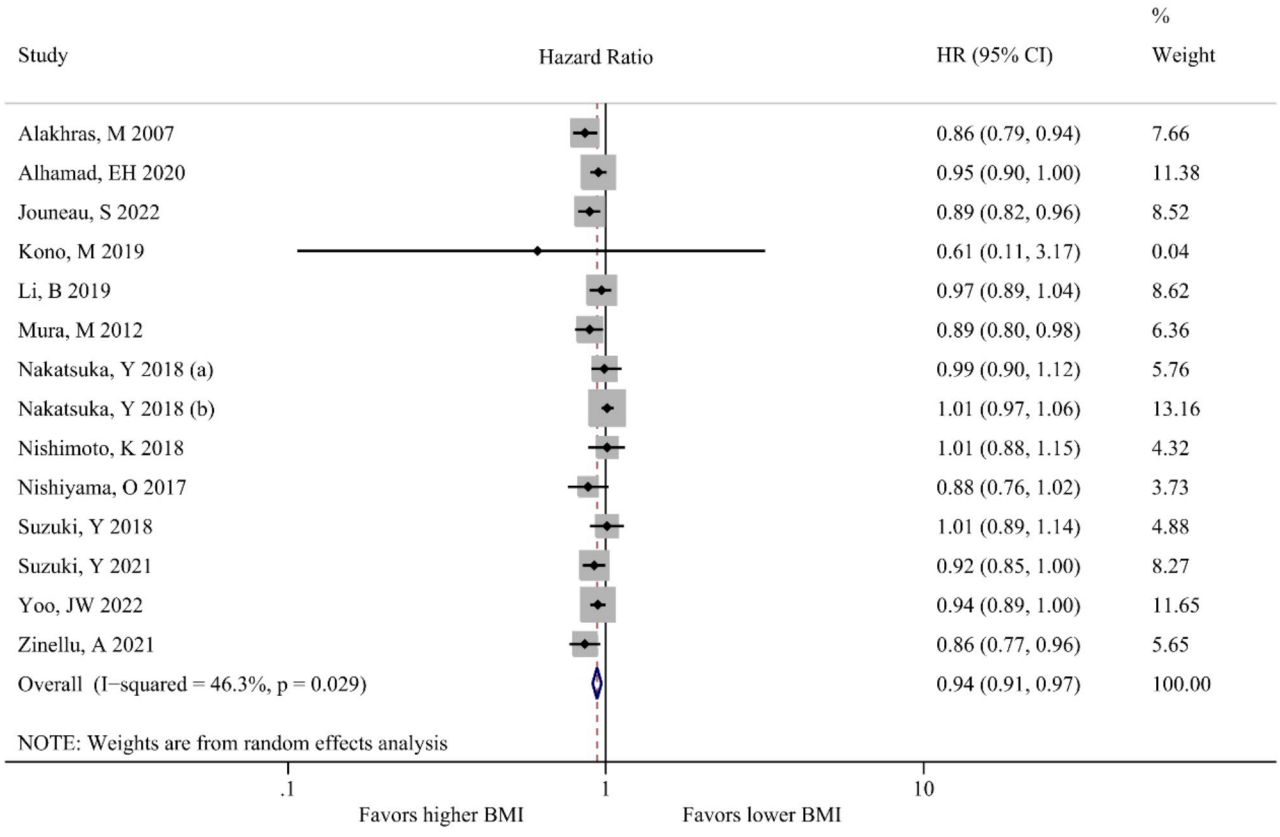

Fig. 2 Forest plot of BMI and risk of death in patients with IPF

Table 2 Subgroup analyses of the relationship between BMI and mortality

Outcomes	No. of study	HR (95%CI)	*P* value	Heterogeneity test	
				I^2 (%)	P_H
Overall	14	0.94 (0.91, 0.97)	< 0.001	46.3	0.029
Area					
Asian	9	0.95 (0.93, 0.98)	0.001	0.0	0.811
Western	5	0.91 (0.84, 0.98)	0.014	79.5	0.001
Design					
RCS	11	0.95 (0.92, 0.98)	0.004	45.8	0.048
PCS	3	0.89 (0.84, 0.94)	< 0.001	0.0	0.990
Sample Size					
> 100	8	0.94 (0.91, 0.97)	< 0.001	21.6	0.258
< 100	6	0.93 (0.87, 1.01)	0.079	61.2	0.024
Adjusted					
Yes	9	0.93 (0.90, 0.96)	< 0.001	29.4	0.184
No	5	0.96 (0.89, 1.02)	0.196	47.5	0.107
Quality					
High	9	0.93 (0.90, 0.96)	< 0.001	29.4	0.184
Moderate	5	0.96 (0.89, 1.02)	0.196	47.5	0.107
Controlling FVC in model					
Yes	7	0.94 (0.91, 0.97)	< 0.001	18.7	0.287
No	7	0.93 (0.87, 0.99)	0.018	63.5	0.012

RCS, Retrospective cohort study; PCS, Prospective cohort study

Sensitivity analysis and publication Bias test

Sensitivity analysis showed that excluding the literature one by one, the value of the change in the combined results was HR (95% CI): 0.93 (0.90, 0.96) to 0.95 (0.92, 0.98), and excluding any one of the studies, the combined results of the remaining studies had a $P<0.05$. Therefore, the combined results were stable and did not change significantly by individual studies (Fig. 4).

Egger's test was used to assess whether there was significant publication bias between studies, and the results showed $P=0.159$ (Fig. 5), suggesting that there was no significant publication bias in the included studies.

Discussion

IPF is the most common type of (Idiopathic interstitial pneumonias, IIPs) and has a high degree of individual variability in prognosis. IPF is common in patients over 60 years of age, especially in men who smoke. According to epidemiologic data, the prevalence of IPF is increasing year by year, and the prognosis of IPF worsens with age. Currently, the diagnosis of IPF is mainly based on HRCT imaging and histopathological examination. IPF is incurable, and the main clinical methods are to slow down the progression of the disease, improve the quality of life and prolong the survival period through antifibrotic drug treatment and rehabilitation training. Therefore, the search for markers for the diagnosis and treatment of IPF and for predicting prognosis is crucial.

Studies have found that the 6-minute walk test (6MWT) and its alterations were found to be highly correlated with the prognosis of IPF. 1-year mortality was 2.65 times higher in patients with a 6MWT < 250 m than in patients with a 6MWT ≥ 350 m, and 1-year mortality in patients with a 6-month alteration of > 50 m was 4 times higher in patients with a 6-month alteration ≤ 25 m [39]. Lung function can also play a role in the prognosis of IPF, with the rate of decline in forced vital capacity of percentage prediction (FVC%pred) being more indicative of disease progression and a better predictor of patient prognosis [40]. In addition, Ley et al [41] proposed a four-component gender, age, FVC%pred and Diffusing capacity of the lung for carbon monoxide of percentage prediction (DL_{CO}%pred) gender- age-lung function model and a composite physiological index reflecting the degree of pulmonary fibrosis proposed by Wells et al [42] are also good predictors of IPF prognosis. Currently, the biomarkers identified are Krebs von den lungen 6 (KL-6), Matrix metalloproteinase 7 (MMP-7), chemokines and their ligands, Surfactant associated protein A (SP-A), SP-D and other markers [43]. However, biomarkers are still relatively unspecific and do not predict disease progression and regression.

Higher BMI has been shown to be a risk factor in IPF and may increase the incidence of IPF [44]. Alakhras et al [19] first reported that there was a negative correlation between BMI and mortality, with relatively lower mortality in patients with higher BMI. This was validated by the results of several subsequent studies. However, some studies have also suggested that higher BMI increases their mortality, especially in IPF patients with lung transplantation. Therefore, this view is still highly controversial.

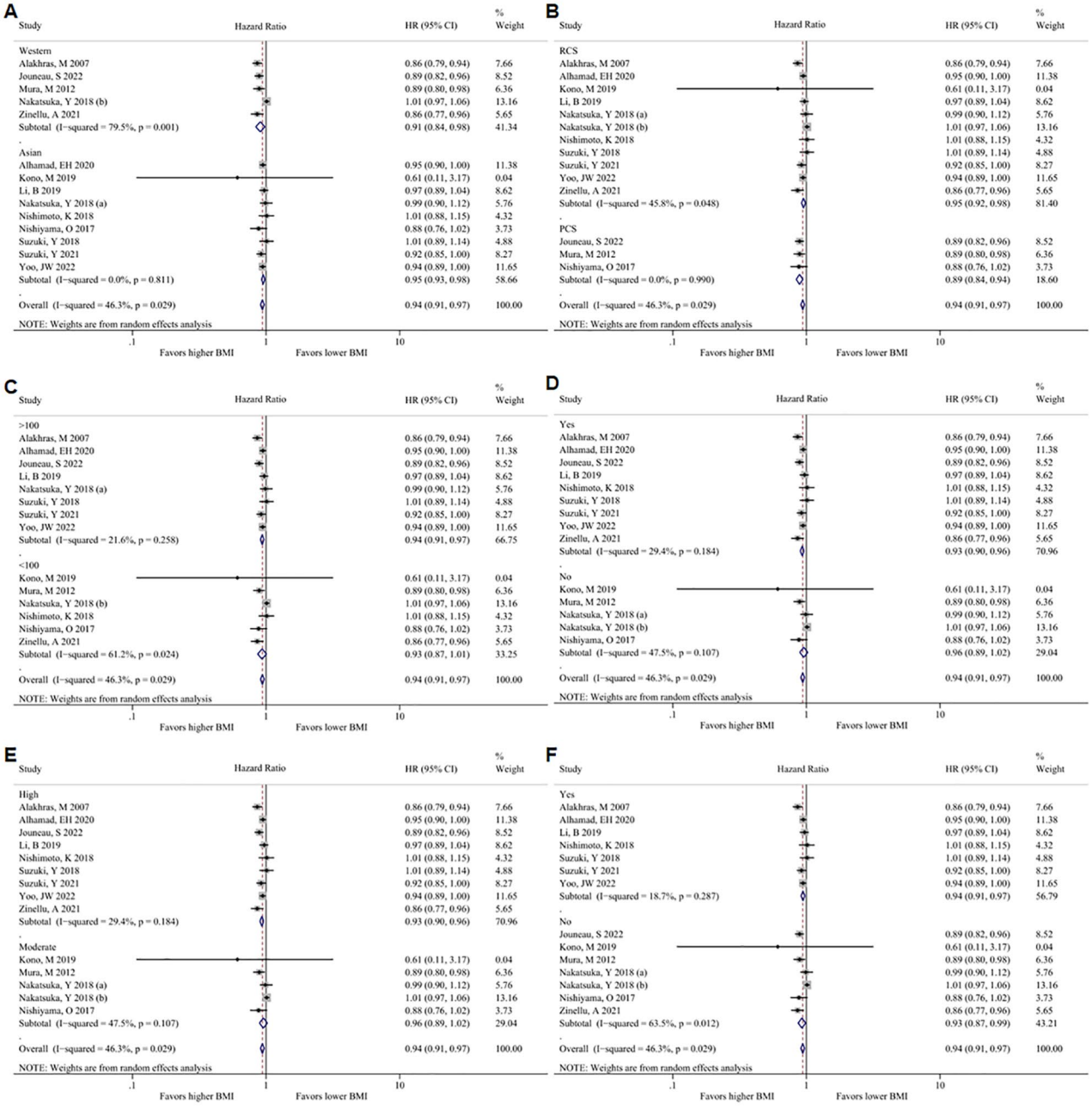

Fig. 3 Subgroup analysis: geographic location (**A**), types of studies (**B**), sample size (**C**), correcting for confounders and methodological quality(**D**), quality of studies (**E**), correcting for FVC**(F).** RCS, Retrospective cohort study; PCS, Prospective cohort study

In this study, the exposure levels of BMI were consistent, and meta-analysis indicated that there was a significant linear association between baseline BMI and the risk of death in patients with IPF. The results of the heterogeneity test for the included studies showed that there was statistically significant heterogeneity. Nevertheless, subgroup analyses found that heterogeneity could be avoided by studies that were corrected for confounders or used high methodological quality. The results by the one-by-one exclusion method suggested that the combined results were not dramatically changed by individual studies, and the results were stable. Moreover, the studies we included had no significant publication bias test and were highly credible.

Over the past few decades, BMI has been shown to be a risk factor for a number of diseases, including cardiovascular disease, diabetes, subarachnoid haemorrhage, cerebral haemorrhage, and some cancers [45]. This has led to active lifestyle interventions aimed at reducing this risk for individuals and populations. However, in recent years,

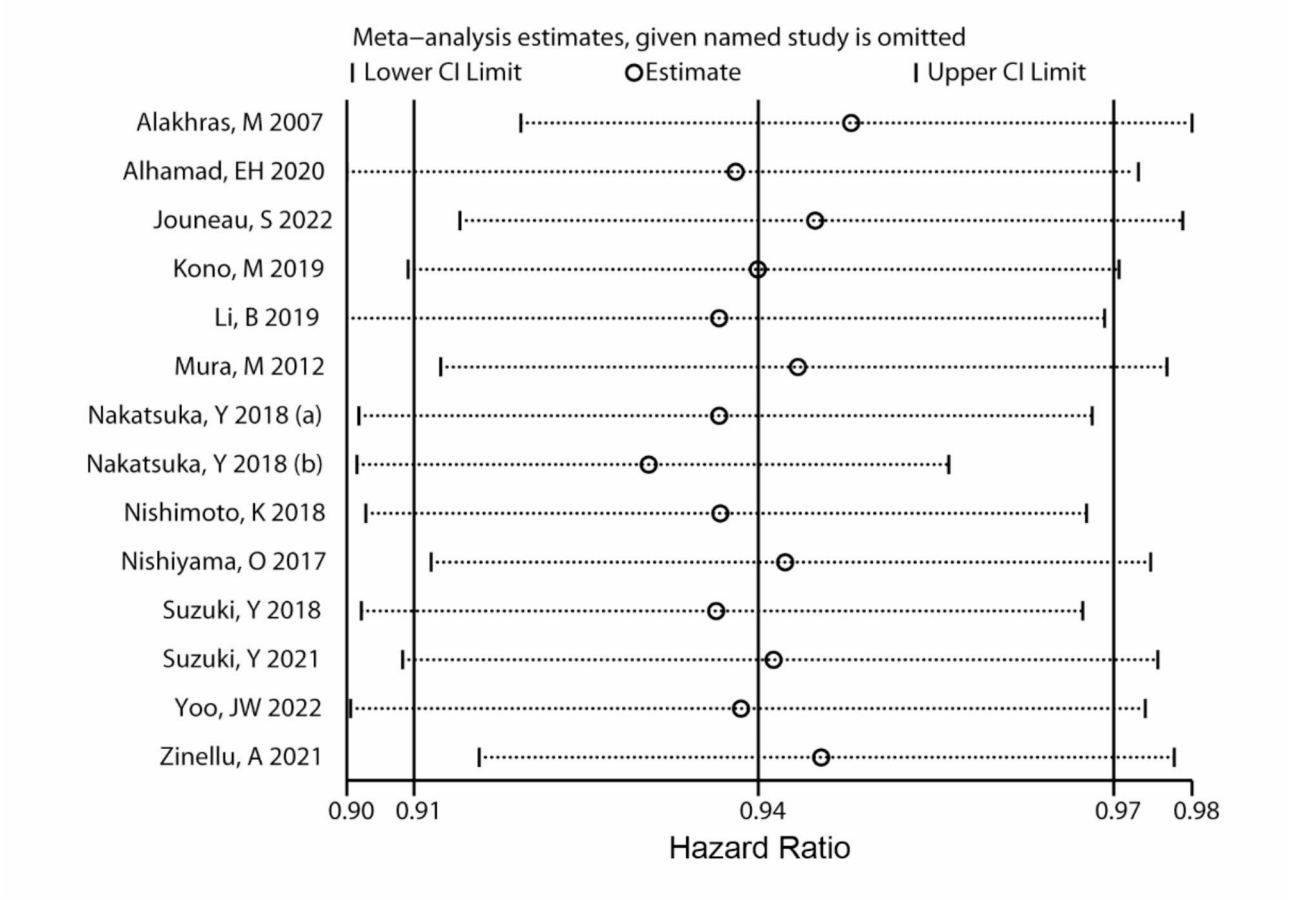

Fig. 4 sensitivity analysis

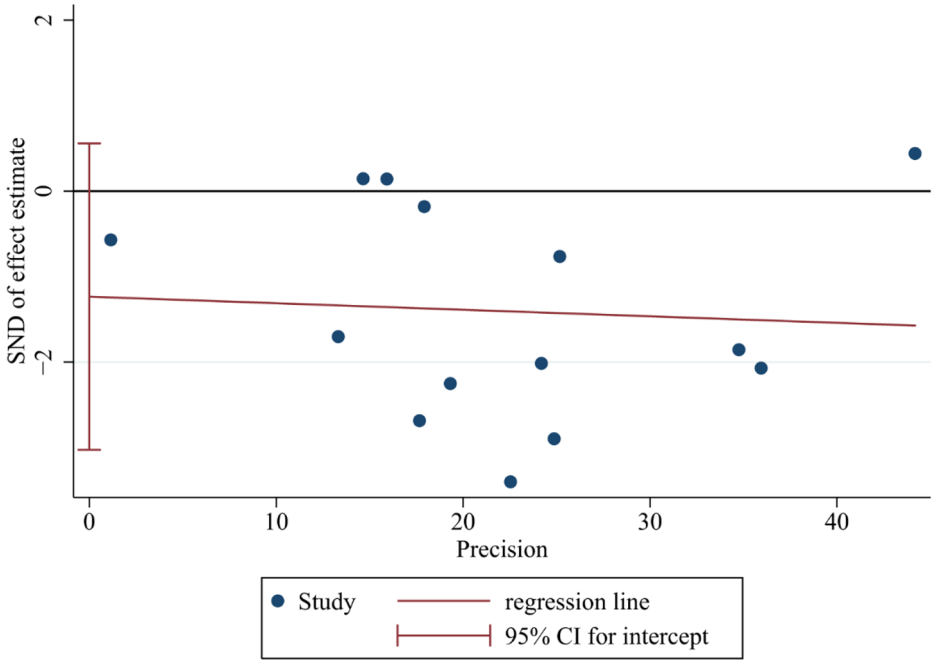

Fig. 5 Egger's test for detecting publication bias in included studies

the newly proposed idea of the "obesity paradox" has caused great controversy. This refers to the fact that individuals with relatively higher values of BMI have a better prognosis than those with lower values of BMI, which has been validated in COPD, cardiovascular disease, certain cancers and other diseases [46].

Alakhras et al. [19]. were the first to report a significant relationship between BMI and survival in 197 patients with IPF. Three groups (<25, 25–30, and >30 kg/m^2) were categorized according to BMI, and median survival was 3.6, 3.8, and 5.8 years, respectively. Proportional risk regression showed a significant, independent negative association between baseline BMI and mortality. Yoo et al. [35]. similarly reported that lower baseline BMI was independently associated with higher three-year mortality among 445 patients with IPF after adjusting for several confounders including the Charlson Comorbidity Index, disease progression, and acute exacerbations. Suzuki et al. [34]. conducted a cohort study of 208 patients with IPF in two groups receiving antifibrotic therapy with pirfenidone or nintedanib. A significant, negative and independent association with five-year mortality was observed when BMI was considered as a continuous variable and a threshold value of 24.1 kg/m^2 was used. Similarly, Jouneau et al. [20]. found that patients with a baseline BMI<25 kg/m^2, or an annual weight loss of >0–5% or ≥5% may have a poorer prognosis at 1 year than patients with a BMI≥25 kg/m^2 or no weight loss. This negative correlation was also found in a study by Mura et al [37] (HR=0.89, 95% CI=0.80–0.98, p=0.0155), but was not corrected for other confounders.

This is consistent with the results of our analysis. BMI and risk of death from IPF were significantly associated. We also found that for baseline BMI, the risk of death from IPF decreased by 6% for each unit increase. This is also consistent with the findings of Alakhras et al. [19]. (HR=0.93, 95%CI=0.89–0.97, P=0.002 per 1-U increase in BMI).

Internationally we regard a BMI≥30 kg/m^2 as obese, but the use of this value alone as a criterion to define obesity in many studies is controversial. Body composition variability in patients with the same BMI, such as the co-occurrence of low muscle and high adipose tissue may occur in different subgroups of BMI. The BMI formula does not take into account body composition (muscle mass vs. adipose tissue content) and distribution (visceral fat vs. subcutaneous fat). Other tests such as dual-energy X-ray absorptiometry (DEXA), computed tomography (CT) and MRI are more expressive of obesity typing. But their application is limited by their cost, radiation and the technical expertise required. Therefore, BMI is more widely used and accepted than other tests [47].

As has been suggested in patients with heart failure, higher BMI in patients with IPF may not be primarily associated with increased fat mass, but rather with increased fat-free mass (muscle mass). This may increase oxygen consumption through increased muscle diffusion, mitochondrial respiratory capacity, and skeletal muscle strength, thereby improving exercise tolerance and cardiorespiratory fitness [48–51]. Suzuki et al. [34]. showed that BMI was remarkably associated with cross-sectional area of elector spine muscles (ESM_{CSA}) (r=0.500, P<0.0001). In COPD this is also known as the muscle mass hypothesis, which states that obese patients are better able to adapt to acute exacerbations due to increased reserves from greater muscle mass [52]. In addition, respiratory failure is one of the leading causes of death in patients with IPF. This theory of muscle mass loss could also explain the poor prognosis of patients with IPF disease, as patients with better tolerance to muscle mass depletion have a higher chance of survival. Based on this hypothesis, we can assume that metabolically healthy overweight and obese patients with higher muscle mass have a higher chance of recovery than the non-obese population [49].

Another theory is that of brown adipose tissue and its anti-inflammatory effects on the body. Brown adipose tissue has properties similar to lean body mass, as it decreases the levels of lipopolysaccharides in the body, which stimulate pro-inflammatory cytokines, thus effectively reducing systemic inflammation levels. White adipose tissue functions in the opposite way and can have deleterious effects on the body. A shift from white adipose tissue to brown fat occurs in some obese individuals [52].

In addition, it may also be a possibility that the interaction between BMI and clinical symptoms in patients with IPF is influenced by disease states, such as heart failure, in which a negative correlation between BMI and poor outcomes has been described [53].

However, there are still some shortcomings in our study. The sample sizes of the included studies were relatively small, and we need more high-quality, large-sample studies to validate the extrapolation of the results. The included studies were all observational and had many confounders. Although most studies performed multifactorial corrections, the corrections were also not uniform and may have exaggerated the strength of the association between BMI and risk of death. Due to the lack of sufficient original studies, this meta-analysis was unable to quantitatively group the associations between different BMI classes, levels of BMI change, and the risk of death, and it is hoped that subsequent studies will focus on these two parts of the results.

Conclusions

Higher BMI (BMI≥25 kg/m^2) is negatively correlated to some extent with the risk of death in IPF patients, and BMI may become a clinical indicator for determining the prognosis of IPF patients.

Abbreviations

IPF	Idiopathic pulmonary fibrosis
BMI	Body mass index
HR	Hazard ratio
GERD	Gastroesophageal reflux
DM	Diabetes
OSA	Obstructive sleep apnea
PRISMA	Preferred reporting items for systematic evaluation and meta-analysis
BMI	Body mass index
HR	Hazard ratio
GERD	Gastroesophageal reflux
DM	Diabetes
OSA	Obstructive sleep apnea
PRISMA	Preferred reporting items for systematic evaluation and meta-analysis
MOOSE	Meta-analysis of observational studies in epidemiology
NOS	Newcastle-ottawa quality assessment scale
DEXA	Dual-energy X-ray absorptiometry
CT	Computed tomography
TLC	Total lung capacity
FVC	Forced vital capacity
Dlco	Diffusing capacity of the lung for carbon monoxide
GAP	Gender-age-physiology
RCS	Retrospective cohort study
PCS	Prospective cohort study
6MWT	6-min walk test
PPI	Proton pump inhibitor
USA	United States of America
UK	The United Kingdom of Great Britain and Northern Ireland
ESMCSA	Cross-sectional area of elector spine muscles
ESMMA	Muscle attenuation of elector spine muscles
IM	Azathioprine, Mycophenolate mofetil, Cyclosporine
AISI	Aggregate systemic inflammation index
NR	Not reported
M	Male
F	Female
IIPs	Idiopathic interstitial pneumonias
KL-6	Krebs von den lungen 6
MMP-7	Matrix metalloproteinase 7
SP-A	Surfactant associated protein A
FVC%pred	Forced vital capacity of percentage prediction
DLCO%pred	Diffusing capacity of the lung for carbon monoxide of percentage prediction

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Xiaomin Su designed the project, retrieved and analyzed the data, revised manuscript. Dengyun Pan retrieved and analyzed the data, wrote the manuscript. Qi Wang wrote the manuscript. Bingdi Yan revised the manuscript. All authors contributed and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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