Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is associated with a fatal prognosis and manifests in patients over 60 years old who may have comorbidities. The prevalence and impact of comorbidities on the clinical course of IPF is unclear.

This systematic literature review examined the prevalence of comorbidities and mortality associated with comorbidities in IPF patients. Relevant observational studies published in English from January 1990 to January 2015 identified *via* MEDLINE and EMBASE were included; bibliographies of articles were also searched.

Among the 126 studies included, prevalence of pulmonary hypertension (PH) was 3–86%, 6–91% for obstructive sleep apnoea, 3–48% for lung cancer and 6–67% for chronic obstructive pulmonary disease (COPD). Nonrespiratory comorbidities included ischaemic heart disease (IHD) (3–68%) and gastro-oesophageal reflux (GER) (0–94%). Mortality was highest among patients with IPF and lung cancer. Most studies assessed relatively small samples of patients with IPF.

PH, COPD, lung cancer, GER and IHD are significant comorbidities; differences in IPF severity, case definitions and patient characteristics limited the comparability of findings. The identification and prompt treatment of comorbidities may have a clinically significant impact on overall outcome that is meaningful for patients with IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe, progressive and debilitating disease with a median survival time of 2–3 years after diagnosis [1]. In this older population with a median age of 66 years at diagnosis [2], multimorbidity is common [3]. Comorbidities frequently associated with IPF include gastro-oesophageal reflux (GER) [4], pulmonary hypertension (PH) [5], chronic obstructive pulmonary disease (COPD)/emphysema [6] and obstructive sleep apnoea (OSA) [7].

Treatment options in IPF are limited, and the impact of comorbidities and their treatment may influence the clinical course of the disease [8]. Identification and treatment of comorbidities may be associated with improved outcomes (*e.g.* improved quality of life and potentially survival). Antacid treatment and GER therapy in patients with IPF has been associated with a decreased rate of IPF progression and longer survival time in observational and retrospective studies [9, 10]. The coexistence of COPD/emphysema can impact lung volumes and disease course as well as response to treatment, and has been suggested as a distinct syndrome of combined pulmonary fibrosis and emphysema (CPFE) [11, 12]. These patients are also at risk of developing PH [11], which is associated with increased mortality [1]. Additionally, microaspiration with increased amounts of pepsin in the bronchoalveolar lavage fluid of patients with acute deteriorations, termed acute IPF exacerbations, might impact the clinical course of the disease. There are varying points of view regarding the aetiology and definition of this rapid decline (*e.g.* an "acute exacerbation" *versus* an aspiration-associated manifestation). However, acute IPF exacerbation, while certainly associated with high morbidity and mortality, was not the focus of this review. In keeping with current perceptions of acute exacerbation of IPF [13], we believe that acute exacerbation is within the spectrum of the natural course of IPF rather than a comorbidity.

It is critical for clinicians to understand the extent of comorbidities in the IPF patient population. Updated, comprehensive knowledge about which comorbidities are most prevalent in IPF patients and how comorbidities modify the disease course is important for providing best care and ultimately improving clinical outcomes in this patient population.

The objective of this systematic literature review was to estimate the prevalence of comorbidities in patients with IPF. A secondary goal was to summarise data on mortality associated with comorbidities in patients with IPF. Comorbidities of interest included both respiratory (COPD, PH, OSA, lung cancer and pulmonary embolism (PE)) as well as nonrespiratory (*e.g.* GER, cardiovascular and metabolic) comorbidities.

Methods

Data sources and searches

The literature search was performed to identify publications reporting on comorbidities among patients with IPF from observational data, published in English since 1990. The methods used to perform this review involved both electronic and manual components, and followed established "best practice" guidelines for systematic review research [14, 15]. Searches were conducted in the MEDLINE (*via* PubMed) and EMBASE databases (through the OvidSP platform) to identify relevant studies on the target population published from January 1, 1990 through January 21, 2015. The specific search terms and strategy used in this review are detailed in the online supplementary material. The electronic searches were further supplemented by a manual review of the reference lists of all accepted studies.

Study selection

Study selection was accomplished through two levels of study screening with pre-specified inclusion and exclusion criteria. During screening of each abstract, reviewers identified the relevant data for each topic of interest. The abstracts of all papers identified were reviewed by two researchers and random samples were cross-checked by the principal investigator. At level I screening, any study meeting an exclusion criterion was rejected. Exclusion criteria included the following: wrong study type (interventional studies or studies based on data extracted from interventional studies, expert opinions, systematic reviews, meta-analyses and studies reporting quality of life outcomes or outcomes after lung transplantation were excluded from this review); studies published in a language other than English; no IPF patients. As the definition of IPF changed over time, we indicate in the online supplementary tables whether the American Thoracic Society (ATS)/European Respiratory Society (ERS) or ATS/ERS/Japanese Respiratory Society (JRS)/Latin-American Thoracic Society (ALAT) definition of IPF published in 2000 or 2011, respectively, was used in the study [1, 16]. Level II screening included a review of the full-text articles of those selected from level I. To pass level II screening and be included in this review, studies must have been observational (noninterventional) in nature and reported at least one of the outcomes of interest (IPF comorbidities). The criteria for definitions of IPF and comorbidities were based on the reported data in the respective studies.

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Data extraction and quality assessment

Data elements of interest from each accepted study were extracted to a data extraction form developed specifically for this review. Extracted information included study-level (*e.g.* year of publication, geographic region, study design and population) and patient-level characteristics (*e.g.* sample size, mean age/gender distribution and prevalence/incidence estimates). One investigator extracted the data from each study, and a second investigator independently reviewed the extracted data for completeness and accuracy against the original study.

As the primary objective of this research was to identify the prevalence of comorbidities in patients reported to have IPF, only observational studies were selected for this review. The University of Oxford's Centre for Evidence Based Medicine (CEBM) Levels of Evidence were used to assess study quality [17]. Under the criteria designed for symptom prevalence studies, prospective cohort studies with a follow-up of >80% are assigned a score of "1b", retrospective cohort studies are assigned a score of "2b" and case series are assigned a score of "4" [17].

Data synthesis and analysis

Due to the heterogeneity of the data extracted, a meta-analysis was not performed and a qualitative synthesis of the evidence is presented here. Study and patient characteristics are presented using descriptive statistics such as means, medians, standard deviations and ranges. Prevalence and mortality data are presented using ranges when applicable.

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Results

Study attrition

A total of 1016 abstracts were identified for screening. Upon review, 606 were rejected for meeting study exclusion criteria (no observational study design, no IPF patients or no outcomes of interest). Of the 410 full-text articles reviewed at level II screening, 146 met inclusion criteria for the initial search. The reference lists of included studies were manually reviewed for identification of relevant papers not identified from the initial search. From the manual review, 48 additional full-text articles were retrieved and 23 met inclusion criteria for the initial search. Of the 169 total number of papers meeting inclusion criteria for the initial search (146 from the MEDLINE/EMBASE search and 23 from manual reference checking), 126 papers reported on outcomes of interest to this review (figure 1).

Study characteristics

Nearly two-thirds of the studies (n=85, 67%) were analyses of retrospective cohort studies; 25 (20%) were prospective cohort studies, 10 (8%) were case-control studies, five (4%) were cross-sectional and one (1%) was a case series (table 1). The number of IPF patients included in the studies ranged from 8 to 9286. The mean age of the IPF patients ranged from 53.4 to 80.5 years. Most studies (n=97; 77%) reported patient

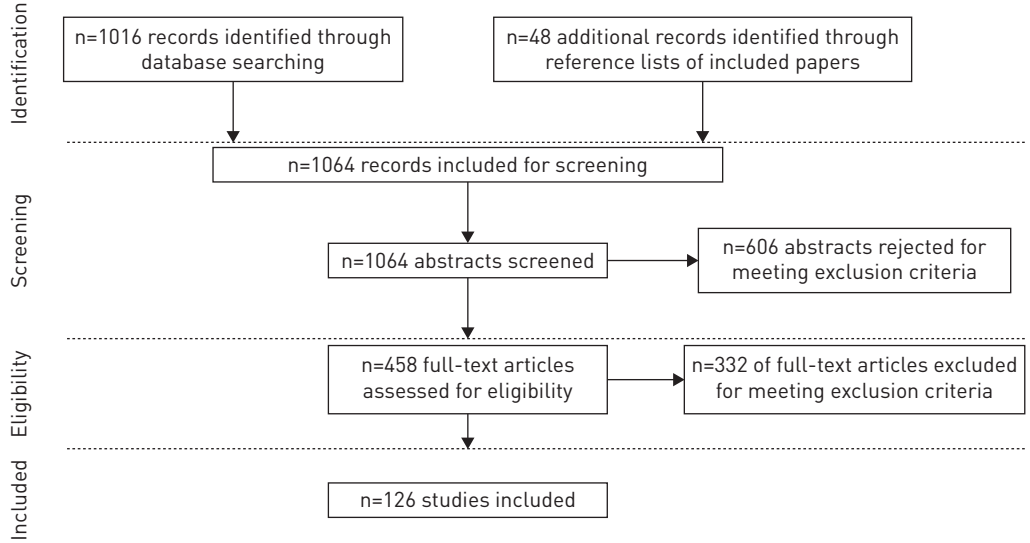

FIGURE 1 Flow diagram of study attrition.

TABLE 1 Study characteristics

Characteristic	
Continent	
North America	50 (40)
Asia	36 (29)
Europe	36 (29)
South America	2 (2)
Africa	1 (1)
Oceania	1 (1)
Total	126 (100)+
Study type	
Retrospective cohort study	85 (67)
Prospective cohort study	25 (20)
Case–control study	10 (8)
Cross-sectional study	5 (4)
Case series	1 (1)
Mean (median, range) number of IPF patients	270 (70, 8–9286)
Mean# age of IPF patients years	65.3
Comorbidities¶	
Respiratory	
Pulmonary hypertension	43 (34)
Chronic obstructive pulmonary disease/emphysema	23 (18)
Lung cancer	15 (12)
Obstructive sleep apnoea	7 (6)
Pulmonary embolism	3 (2)
Nonrespiratory	
Cardiovascular	34 (27)
Metabolic	30 (24)
Gastro-oesophageal reflux disease	23 (18)

Data are presented as n (%), unless otherwise stated. IPF: idiopathic pulmonary fibrosis. #: value is mean of the mean age reported in the studies (n=92 studies); ¶: papers could have reported more than one comorbidity; +: may not total 100% due to rounding.

samples composed of >50% men, although patient gender was not reported in all studies. 72% (n=91) of the papers in this review focused on respiratory comorbidities; 33% (n=41) included data on more than one comorbidity category. Geographically, 40% (n=50) were reports of studies conducted in North America, 29% (n=36) were from Asia, 29% (n=36) were from Europe, two studies were from South America (Brazil), one was from Oceania (Australia) and one was from Africa (Egypt).

Respiratory comorbidities

COPD

The prevalence of COPD (including emphysema) was reported in 23 studies (online supplementary table S1), of which eight were from Europe [18–25], eight were from North America [6, 26–32], six were from Asia [33–38] and one was from South America (Brazil) [39]. The reported prevalence of COPD ranged from 6% to 67% (figure 2) (prevalence ranges by country: 12% [21] to 51% [18] in Europe, 8% [26] to 67% [31] in North America and 34% [36] to 65% [34] in Asia). The highest reported proportion of patients with emphysema (67%) was among IPF patients with isolated diffusing capacity of the lung for carbon monoxide (*D*LCO) decrease, therefore probably overestimating the prevalence of emphysema in IPF [31]. The presence of emphysema on computed tomography was associated with reduced survival time in a study from Japan. In that study, 129 IPF patients with emphysema from a respiratory clinic had a median survival of 7.5 years, which was significantly (p=0.0472) lower compared with the 233 IPF patients in the study who did not have emphysema (8.5 years) [36]. A study from Mexico also found that IPF patients with emphysema had significantly (p=0.01) lower survival (25 months) compared with the median survival of IPF patients in the study who did not have emphysema (34 months) [6]. However, after adjusting for the presence of PH, emphysema was no longer significantly associated with mortality. An analysis of the University of California San Francisco and Mayo Clinic Rochester interstitial lung disease databases did not find a significant difference in mortality comparing patients with CPFE and IPF with those with non-CPFE IPF (hazard ratio (HR) 1.14, 95% CI 0.61–2.13; p=0.69) [32].

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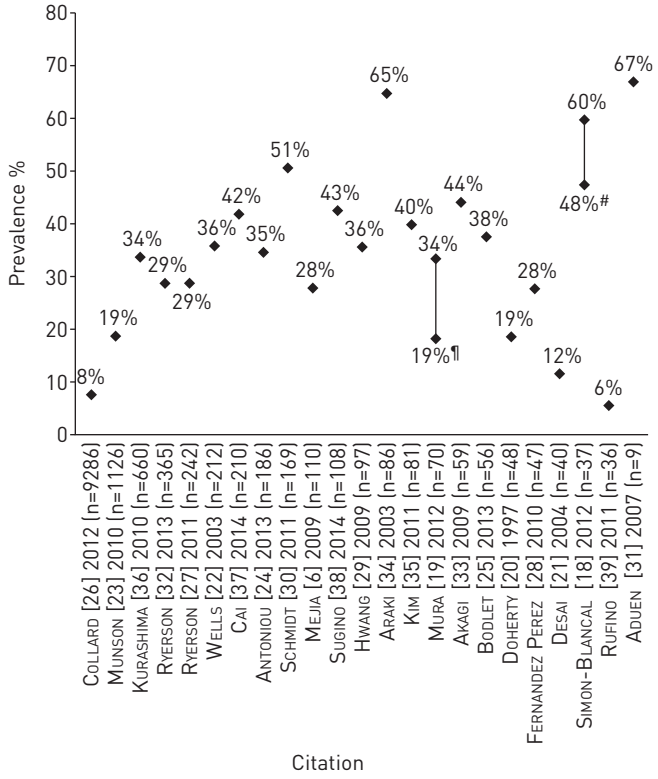

FIGURE 2 Prevalence of chronic obstructive pulmonary disease (COPD)/emphysema among idiopathic pulmonary fibrosis (IPF) patients. See online supplementary table S1 for the definition of COPD/emphysema used in the individual studies and for description of the study sample. #: subjects were hospitalised IPF patients who experienced an acute exacerbation; the prevalence of emphysema ranged from 48% among patients who survived the acute exacerbation to 60% among survivors. ¶: study included newly collected data from IPF patients as well as a retrospective review of existing data from IPF patients; prevalence of emphysema among subjects in the prospective cohort was 34% and among subjects in the retrospective cohort was 19%.

Pulmonary hypertension

A total of 43 studies included data on the prevalence of PH in patients with IPF using various definitions based on right heart catheterisation or echocardiography (online supplementary table S2). In general, the prevalence of PH was similar in studies from Europe [18, 25, 40–45, 47–49], North America [5, 6, 26, 28, 46, 50–67], Asia and Africa [37, 68–75], although the majority of evidence was reported from North America (n=23, 53%). Across studies, the prevalence of PH among IPF patients ranged from 3% to 86%; most estimates tended to be between 30% and 50% (figure 3) [25, 43, 44, 47, 50, 52–66, 68, 71–73]. Seven studies reported mortality or survival time of patients with IPF plus PH. From three European studies [44, 45, 76], median survival time from IPF diagnosis among patients with PH ranged from approximately 2–3 to 4 years [44, 45, 76]. Presence of PH was found to be associated with an increased risk for death (HR for death, PH *versus* no PH 4.03, 95% CI 1.17–27.9; p=0.03 (study population was CPFE patients) [76]; HR 3.6, 95% CI not reported; p=0.0001 [44]). However, an analysis of data from 121 IPF patients from a hospital in Denmark did not find a significant association between PH and mortality, although a numerical trend remained after adjustment for age, gender and forced vital capacity (FVC) (HR 2.2, 95% CI 0.94–5.2; p=0.068) [48]; similarly, a review of IPF patients evaluated for lung transplantation at a US university hospital did not find a significant association between mean pulmonary artery pressure (mPAP) and mortality [67]. Among a review based on existing data of 25 IPF patients from the USA with PH, 1-year mortality was 29% [57]. A second study from the USA found that patients with severe PH (*i.e.* systolic pulmonary arterial pressure (sPAP) >50 mmHg in transthoracic echocardiography) had significantly (p=0.009) worse survival (median survival 0.7 years) compared with patients without PH (median survival 4.8 years) or patients with mild or moderate PH (median survival 4.1 years) [5]. From a study of clinical records for consecutive IPF patients at the National Institute of Respiratory Diseases, Mexico, presence of severe PH (sPAP⩾75 mmHg as measured by transthoracic echocardiography) was significantly associated with mortality in the multivariable model (HR 2.25, 95% CI 1.12–4.54; p=0.022) [6]. Mortality among 24 IPF patients from Japan with mPAP on right heart catheterisation of >17 mmHg was 83% at 5 years with a median survival time of 29 months [69]. Among six patients with mPAP

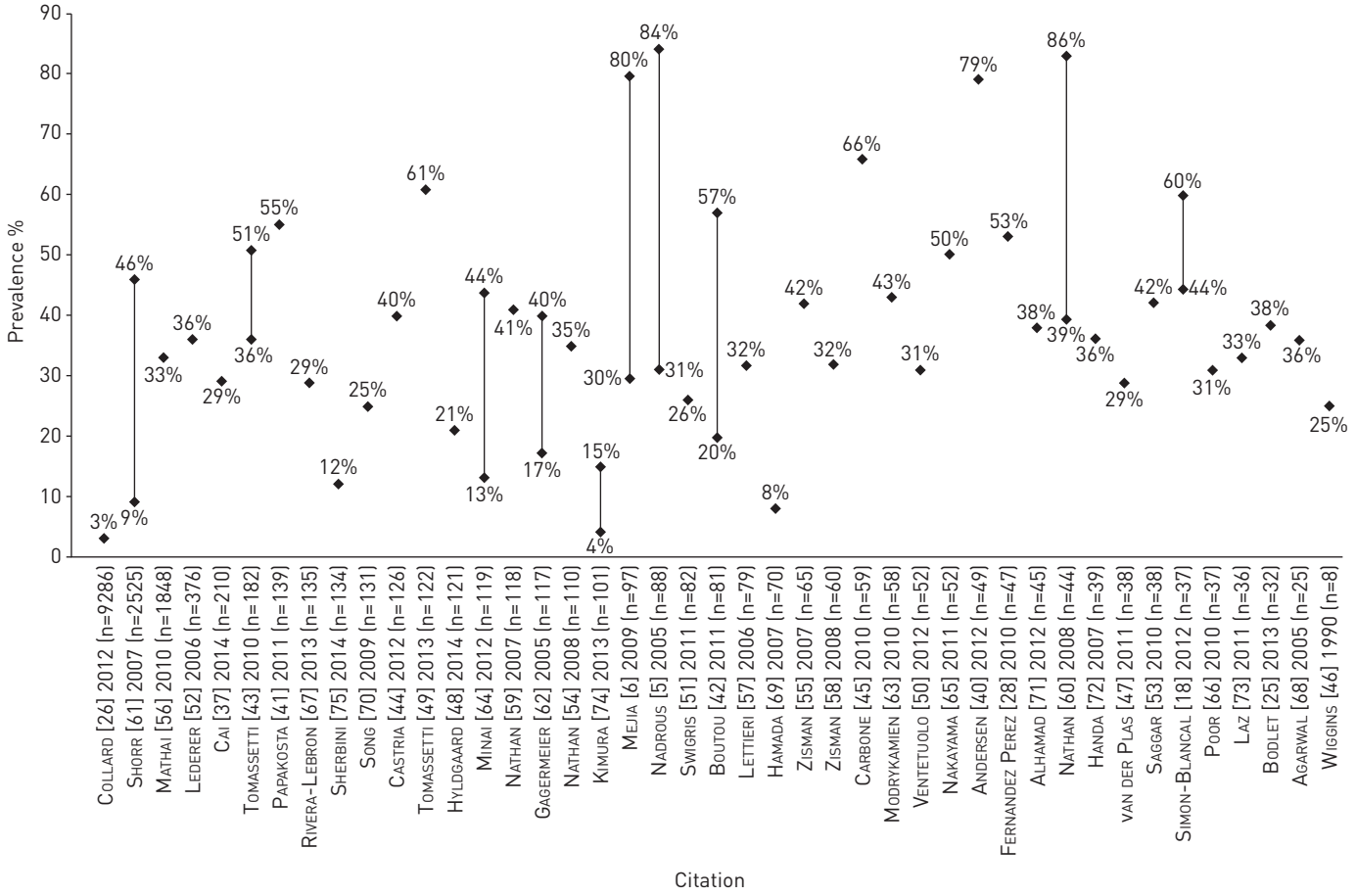

FIGURE 3 Prevalence of pulmonary hypertension (PH) among idiopathic pulmonary fibrosis patients. See online supplementary table S2 for the definition of PH used in the individual studies.

>25 mmHg from the same cohort, 5-year mortality was 100%. Data from 210 IPF patients identified from a hospital database in China found that the mean survival time in patients with and without sPAP ⩾37 mmHg was 24 *versus* 57 months, respectively (p=0.008); in the multivariable analysis, PH was associated with a significantly increased mortality risk (risk ratio 3.393, 95% CI 1.444–7.973; p=0.005) [37]. mPAP was also independently, significantly, associated with 5-year mortality (risk ratio 1.064, 95% CI 1.015–1.116; p=0.010) in an analysis of 101 IPF patients from a hospital in Japan [74]. A receiver operating curve analysis found that a value of 20 mmHg was the optimal (area under the curve 0.679, sensitivity 55.0%, specificity 75.4%) cut-off. A Kaplan–Meier curve revealed significantly worse survival among patients whose mPAP was >20 mmHg than among those whose mPAP was ⩽20 mmHg (log-rank test p=0.001). The median survival estimates were 20.8 and 37.5 months, respectively [74].

Obstructive sleep apnoea

Seven papers reported data on the prevalence of OSA in patients with IPF, of which three were from Europe [77, 79, 80] and four were from the USA [7, 26, 28, 81] (online supplementary table S3). The prevalence of OSA ranged from 5.9% in an analysis of 9286 patients with IPF identified from two US claims databases [26] to 91% among 31 patients from an outpatient interstitial lung disease unit in Greece who underwent a polysomnogram (figure 4) [79]. OSA appeared to be more common among patients with a higher body mass index (BMI) in the studies included in this review. In one US study that reported a prevalence of 61% among patients with IPF, OSA was observed only in moderately to severely obese IPF patients (*i.e.* BMI 35.3–44.3 $kg \cdot m^{-2}$) [81]. In a US study that found an 88% prevalence, mean BMI was significantly (p=0.05) greater in patients with OSA (mean BMI 33±6.7 $kg \cdot m^{-2}$) *versus* those without (26 ±2 $kg \cdot m^{-2}$); however, BMI was only weakly correlated with OSA (r=0.30, p=0.05) [7]. An analysis of 21 IPF patients found that BMI was higher in patients with an apnoea–hypopnoea index (AHI) ⩾5 (29.72 ±0.81) *versus* <5 (27.50±1.71; p=0.053) and BMI was positively correlated with AHI (r=0.59, p=0.001) [80]. One study examined the association between OSA and mortality [79]. A significant association was

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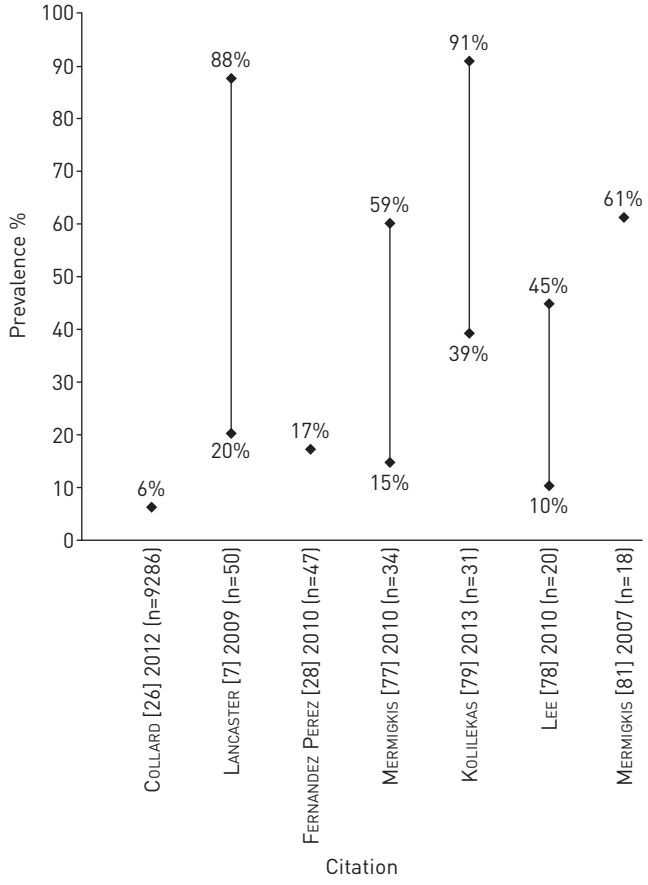

FIGURE 4 Prevalence of obstructive sleep apnoea (OSA) among idiopathic pulmonary fibrosis patients. See online supplementary table S3 for the definition of OSA used in the individual studies.

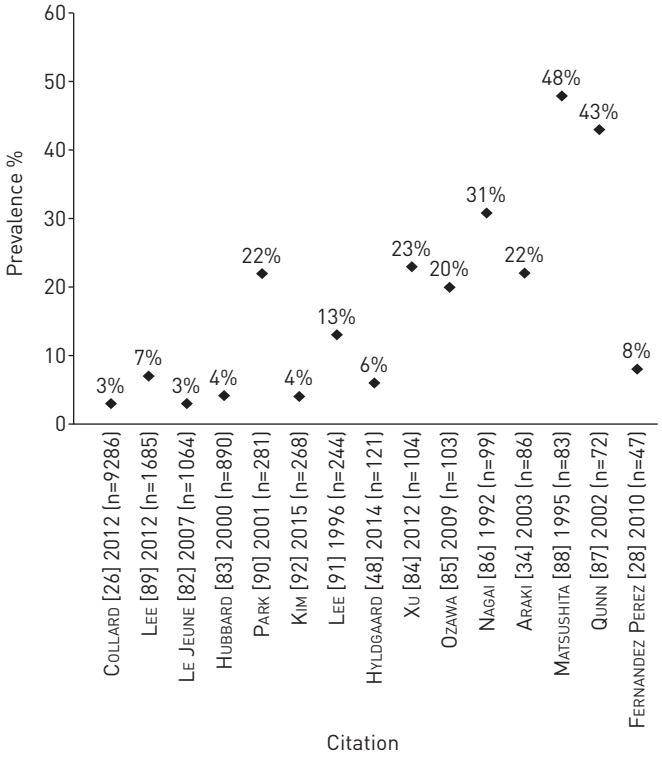

FIGURE 5 Prevalence of lung cancer among idiopathic pulmonary fibrosis patients. See online supplementary table S4 for the definition of lung cancer used in the individual studies.

found between nocturnal hypoxaemia and mortality with a hypothesis that intermittent oxygen desaturation, which occurs during sleep as a result of OSA, contributes to PH and associated mortality.

Lung cancer

The prevalence of lung cancer among IPF patients was reported in 15 studies [26, 28, 34, 48, 82–92] (online supplementary table S4 and figure 5) and was typically lower than the prevalence of other respiratory comorbidities of interest. Analyses of insurance claims and electronic medical records databases from the USA and the UK estimated the prevalence of lung cancer to be 3–4% [26, 82, 83]. Two hospital databases of IPF patients, one from Denmark and one from Korea, reported similarly low prevalences of 6% and 4%, respectively [48, 92]. The estimated prevalence of lung cancer was higher in other studies of medical records and autopsy data of IPF patients in Asia, ranging from 20% to 23% [34, 84, 85, 90]. Estimating the mortality in IPF patients with lung cancer is confounded by differing follow-up times across studies, varying severity of cancer and IPF, differences in cancer treatments, and other patient characteristics. The papers that reported mortality and survival among IPF patients with lung cancer were limited by small sample sizes. One study from the USA included 24 patients with both histologically proven usual interstitial pneumonia (UIP) and primary lung carcinoma identified through a computerised search of the Rochester Mayo Clinic database from 1990 to 1998. With a mean follow-up of 2.2 years from diagnosis of IPF and 1.2 years from diagnosis of carcinoma, the reported mortality was 67% [93]. The mean survival was 2.3 years after the diagnosis of IPF and 1.6 years after the diagnosis of carcinoma [93]. Among 21 patients with IPF and nonsmall cell lung cancer treated with systemic chemotherapy, the median overall survival and the 1-year survival rate from start of chemotherapy were 11.4 months and 28.6%, respectively [94]. In patients who received surgical treatment for lung cancer, post-operative mortality (*e.g.* 30-day, 90-day, in-hospital) tended to be low (0 deaths [95, 96], 4% [96, 97], 5% [98], 7% [97], 8% [98, 99], 12% [93, 98]), although a small database review from China reported a post-operative mortality rate of 33.3% (two of six patients) [84]. Median survival from IPF diagnosis was between 7 (95% CI 2.51–11.49) and 26.9 months (95% CI 14.67–39.05) [84, 89]. Two studies reported no significant difference in median survival between IPF-alone and IPF patients with lung cancer [84, 85]. However, survival tended to be longer for the IPF-alone patients and those studies may have been limited by small sample sizes. A larger study found that IPF patients without lung cancer (n=1571) had a significantly longer survival time compared with IPF patients with cancer (n=114) (the survival time is presented in graphical format in the paper and the specific time for patients without lung cancer is not reported) [89]. The adjusted HR for death for lung cancer *versus* no lung cancer was reported as 2.4 (95% CI 1.4–4.3; p=0.002) [89]. In a retrospective Japanese single-centre study, histopathologically confirmed IPF was identified as a significant negative prognostic factor for post-operative mortality and long-term survival in 387 primary lung cancer patients treated by surgical resection [98].

Pulmonary embolism

Two US studies and one from Italy reported the prevalence of PE among patients with IPF, which ranged from 3% [26] among 9286 patients IPF patients identified by medical claims and among 122 IPF patients from a hospital database in Italy [49] to 6% of 38 patients with IPF who were admitted to an intensive care unit [100] (online supplementary table S5). One US retrospective study of a large administrative claims database reported that the incidence of PE among patients with IPF was 10.7/1000 person-years compared with 4.8/1000 person-years among patients without IPF (risk ratio 2.24, 95% CI 1.69–2.98) [26]. Mortality related to PE among patients with IPF was only reported in one study performed in Saudi Arabia, in which 15 of 61 patients with IPF/UIP died during the follow-up period (24.6%) [71]. Of those 15 deceased patients, the cause of death for one was PE [71].

Nonrespiratory comorbidities

Gastro-oesophageal reflux disease

The prevalence of abnormal GER was reported in 23 studies [4, 10, 26, 27, 48, 75, 79, 80, 101–115] (online supplementary table S6) and ranged from 0 among 20 IPF patients in Ireland who were participating in a study exploring the degree and mechanisms of sleep-disordered breathing, and for whom no history of GER was noted [80], to 94.1% in an analysis of consecutive, newly diagnosed IPF patients recruited from a single US centre [112] (figure 6). However, the 94% prevalence was based on a 24-h ambulatory physiological definition of abnormal acid GER: a most sensitive method of ascertaining abnormal acid GER that included abnormal acid exposure in the distal and/or proximal oesophagus. The incidence of GER in IPF patients was reported in only one abstract from the USA, in which GER was found in 11.5% of 26 nonhospitalised patients and 71.4% of hospitalised IPF patients; the definition of GER was not reported in the abstract [116]. Although no studies published mortality rates for patients with IPF and GER, one retrospective US study reported that the median survival time for IPF patients with GER was 1499 days from the date of IPF diagnosis [10]. Median survival was observed to be higher

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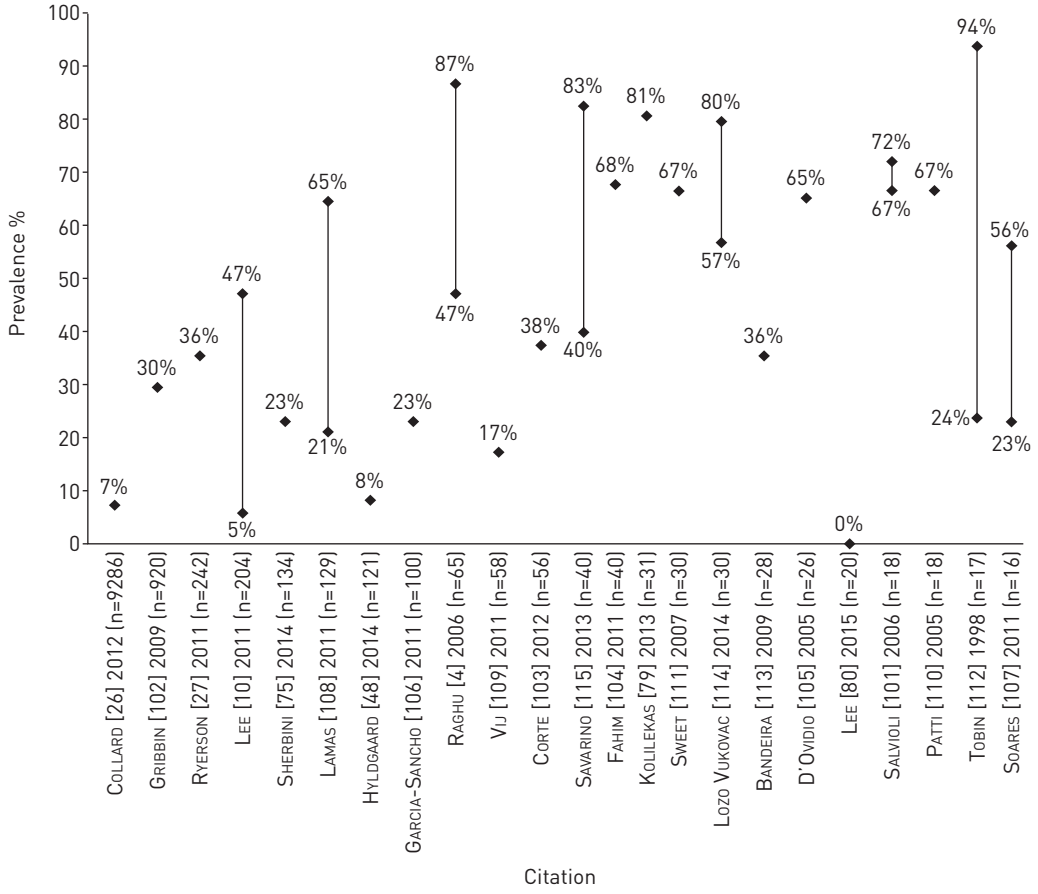

FIGURE 6 Prevalence of gastro-oesophageal reflux disease among idiopathic pulmonary fibrosis patients. See online supplementary table S6 for the definitions of gastrointestinal comorbidities used in the individual studies.

for those taking GER medications (1967 days) and those who received a Nissen fundoplication procedure for the indication of GER (2252 days) [10]. After adjustment for baseline demographic and clinical characteristics, GER medication use was still associated with longer survival (HR 0.47, 95% CI 0.24–0.93; p=0.03), but no association between a history of Nissen fundoplication and survival was observed after adjustment (HR 0.74, 95% CI 0.21–2.59; p=0.64) [10].

Cardiovascular and metabolic conditions

The majority of studies also reported cardiovascular comorbidities (*i.e.* arrhythmia and atrial fibrillation [26, 28, 48, 75, 96, 117, 118] (online supplementary table S7 and figure 7), cardiac failure or congestive heart failure [5, 26, 28, 43, 49, 96, 100, 119, 120] (online supplementary table S8 and figure 8), ischaemic heart disease (IHD) [5, 26, 28, 41, 43, 48, 49, 52, 80, 108, 118, 119, 121–132] (online supplementary table S9 and figure 9), cerebrovascular disease and stroke [26, 48, 117, 118] (online supplementary table S10), and systemic arterial hypertension [5, 23, 28, 39, 41, 48, 52, 75, 119, 125–127, 129–131, 133–135] (online supplementary table S11 and figure 10)), as well as metabolic comorbidities (*i.e.* diabetes [23, 39, 41, 48, 75, 80, 92, 102, 106, 108, 119, 125, 127, 129–131, 134, 136] (online supplementary table S12 and figure 11), hypercholesterolaemia/hyperlipidaemia [102, 125–127, 129, 131, 134, 135] (online supplementary table S13 and figure 12) and weight disorders [10, 23, 26, 125, 131, 134, 137] (online supplementary table S14)) among patients with IPF. IHD was the most frequently reported cardiovascular comorbidity (reported in 24 papers). Prevalence estimates, which ranged from 3.2% [26] for myocardial infarction (MI) among patients identified from medical claims in the US to 68% for nonsignificant or significant coronary artery disease (CAD) among those with IPF who were screened for lung transplant eligibility, varied widely due to the differing patient populations assessed and case definitions of IHD used in these studies. In terms of specific IHD diagnoses, CAD ranged from ~4% among IPF patients listed for lung transplantation with the United Network for Organ Sharing to the aforementioned 65.8% of IPF screened for lung transplant eligibility. From a claims database, International Classification of Diseases, Ninth Revision (ICD-9) codes for MI were found for 3.2% of IPF patients [26], 7% of consecutive patients with

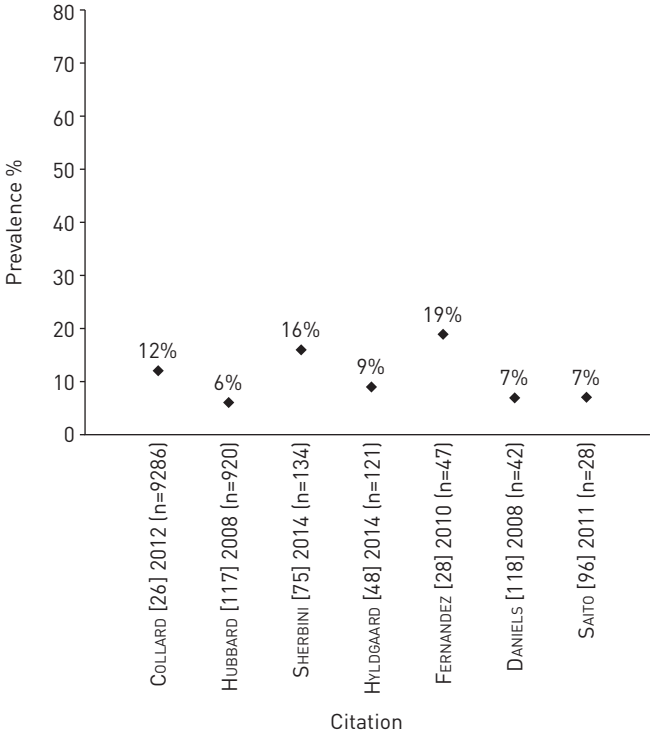

FIGURE 7 Prevalence of arrhythmia or atrial fibrillation among idiopathic pulmonary fibrosis patients. See online supplementary table S7 for the definition of arrhythmia or atrial fibrillation used in the individual studies.

IPF who underwent a *post mortem* evaluation [118] and 12% of IPF patients identified in a database of an Italian hospital's pneumology unit [49]. From an abstract, it was reported that, among 38 consecutive IPF patients from a healthcare provider, eight (21%) had ST-elevation MI [127]. Among studies assessing metabolic comorbidities, diabetes was reported most frequently (n=18). The prevalence of diabetes among patients with IPF generally ranged from 10% in the UK [102] to 32.7% in Japan [134], although the highest prevalence (39%) was reported in a subsample of 31 US patients who delayed medical care for

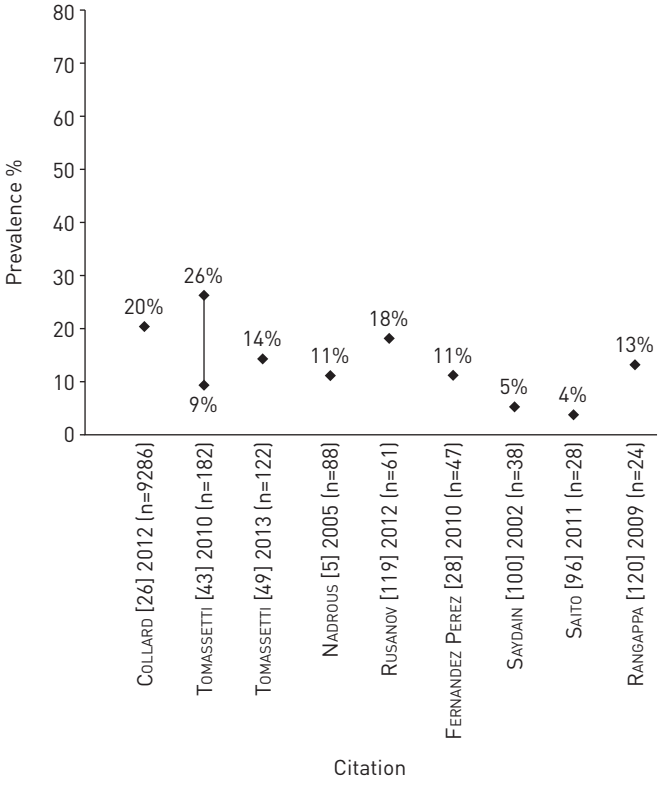

FIGURE 8 Prevalence of cardiac failure among idiopathic pulmonary fibrosis patients. See online supplementary table S8 for the definition of cardiac failure used in the individual studies.

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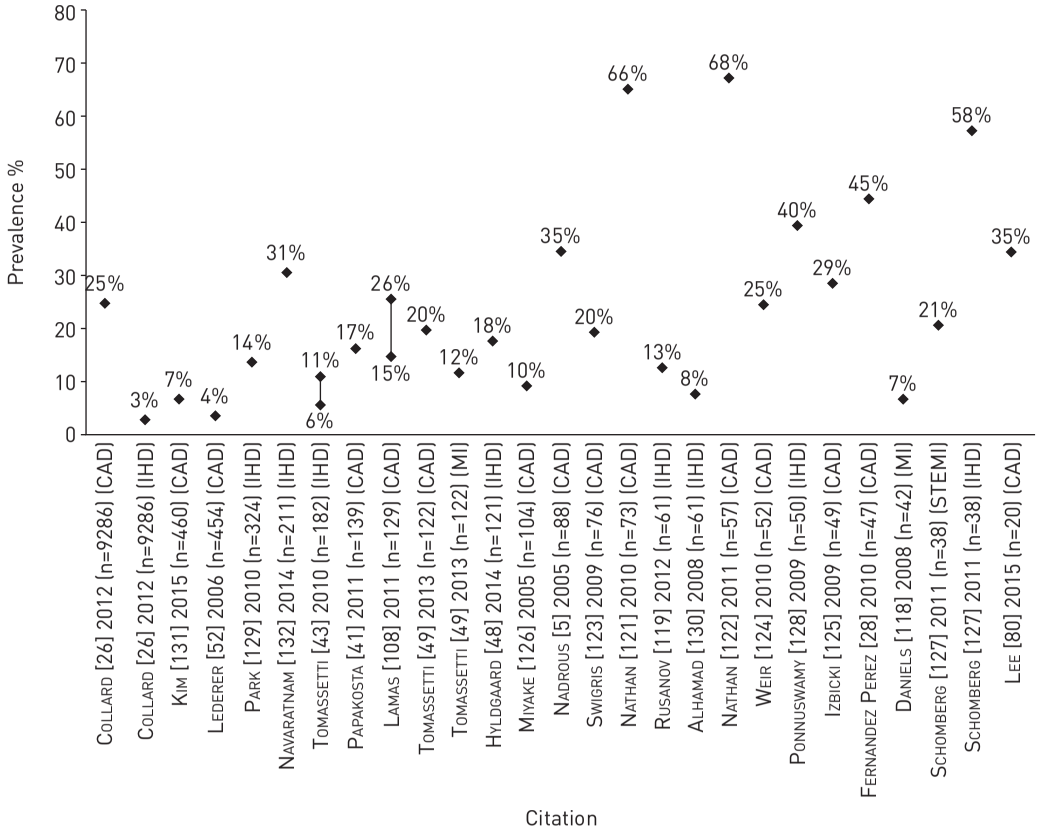

FIGURE 9 Prevalence of ischaemic heart (IHD) disease among idiopathic pulmonary fibrosis patients. See online supplementary table S9 for the definition of IHD used in the individual studies. CAD: coronary artery disease; MI: myocardial infarction; STEM: ST-elevation myocardial infarction.

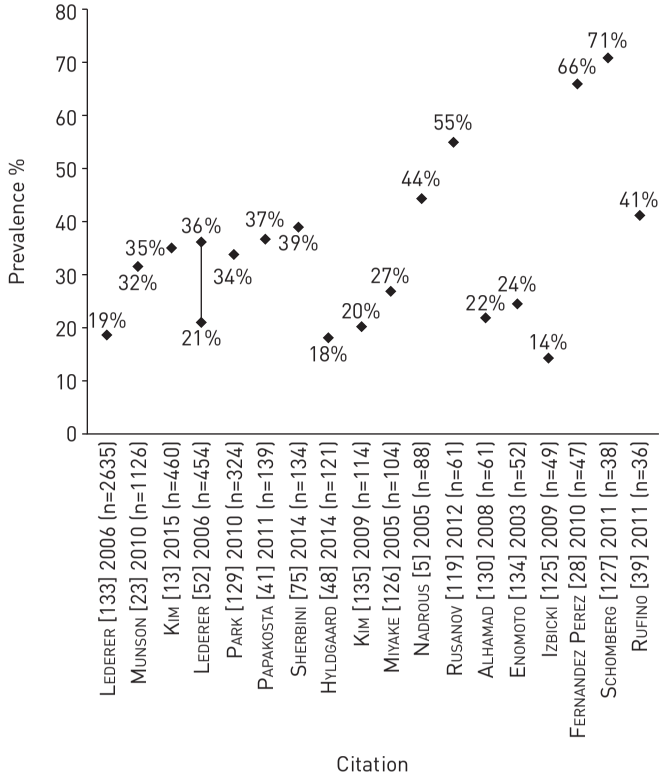

FIGURE 10 Prevalence of arterial hypertension among idiopathic pulmonary fibrosis patients. See online supplementary table S11 for the definition of arterial hypertension used in the individual studies.

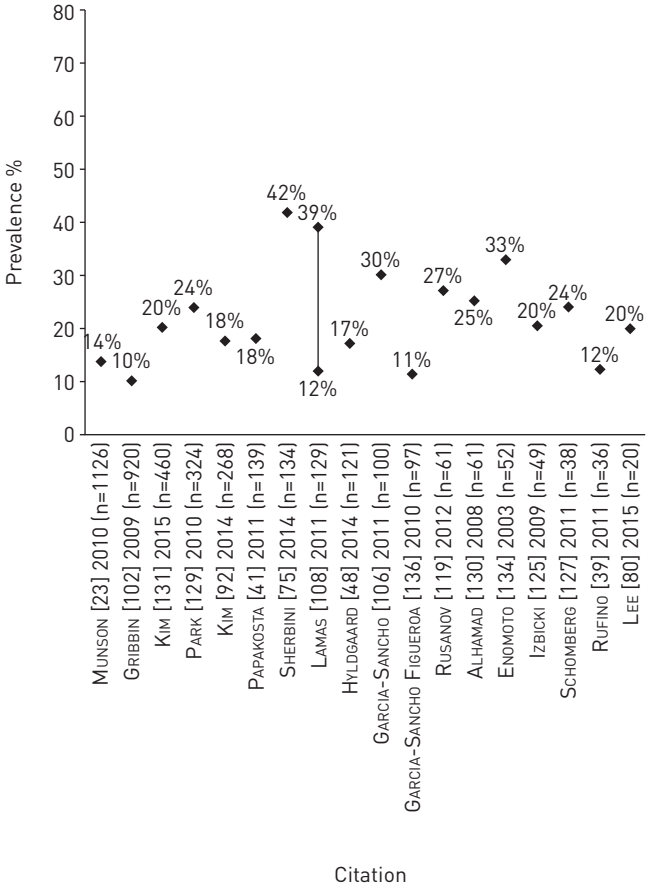

FIGURE 11 Prevalence of diabetes among idiopathic pulmonary fibrosis (IPF) patients. See online supplementary table S12 for the definition of diabetes used in the individual studies. #: prevalence of diabetes among IPF patients reported stratified by time from symptom onset to care at tertiary care centre and ranged from 12% to 39%.

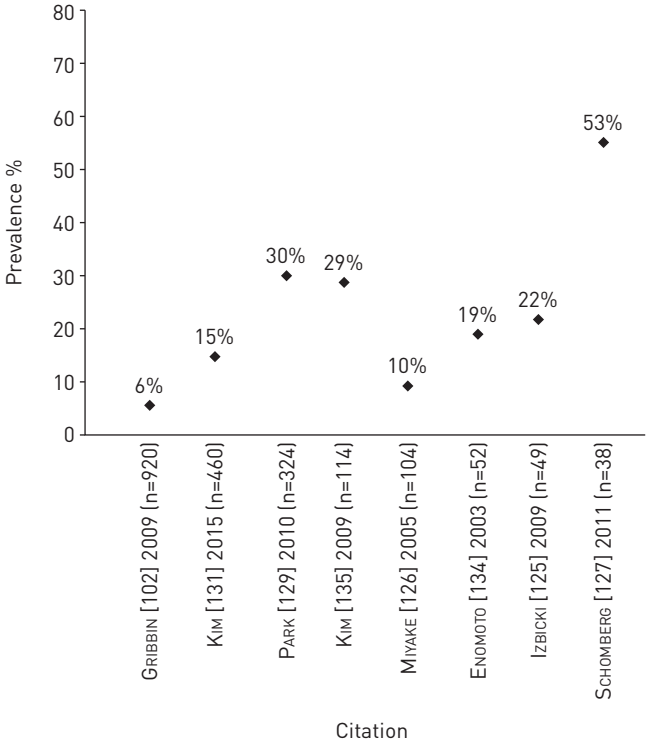

FIGURE 12 Prevalence of hypercholesterolaemia/hyperlipidaemia among idiopathic pulmonary fibrosis patients. See online supplementary table S13 for the definition of hypercholesterolaemia/hyperlipidaemia used in the individual studies.

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⩾4 years [108]. Cardiovascular comorbidities were negatively associated with survival in one study, as the median survival time of patients with CAD and IPF was 572 days from the date of left heart catheterisation compared with 1499 days for those with nonsignificant or no CAD [121]. One study provided evidence that obesity was associated with longer survival. Among 197 patients with IPF who were evaluated at the Mayo Clinic in Rochester, MN, USA from 1994 to 1996, the median survival time ranged from 3.6 years among those with a normal/underweight BMI (<25) to 5.8 years among obese patients with a BMI ⩾30 [137]. In a multivariate model, survival was significantly associated with BMI (HR 0.93 for each 1-unit increase in BMI, 95% CI 0.89–0.97; p=0.002) [137].

Discussion

IPF is a fatal disease and the vast majority of patients are males above 60 years of age [2]. While people in this age group are indeed at risk for several health problems and diseases, the incidence and prevalence of the comorbid conditions in patients with IPF are unknown. The awareness of the specific comorbid conditions that may be present in patients with IPF is important as prompt detection and treatment of comorbid conditions may have a clinically significant and meaningful impact on overall outcomes in patients with IPF. To our knowledge, this systematic review presents the very first summary of literature related to the prevalence of comorbidities and related mortality among patients with IPF. Respiratory comorbidities, including COPD, PH and OSA, were common in many of the study samples, although estimates varied widely depending on the source population. Nonrespiratory comorbidities such as GER, systemic arterial hypertension, IHD and diabetes were also highly prevalent in this population of elderly patients. It is noteworthy that, given the lack of efficacious treatments until recently, systemic steroids had been a major treatment regimen for the treatment of IPF and might have contributed to the high prevalence of diabetes mellitus in this population. Mortality was reported less frequently, but was highest among patients with concomitant COPD (23–77%) and lung cancer (38–81%); PH and IHD were also associated with an increased risk of death. In one clinical trial, right heart catheterisation in well-defined patients with IPF and mild-to-moderate impairment in FVC and *D*LCO demonstrated that 10% of patients had PH [138]. Functional decline associated with PH has been observed among IPF patients [139, 140].

The wide variation of prevalence estimates reported in the literature is likely due to several factors. Analyses using administrative claims and electronic medical record data generally reported lower prevalence estimates due to an underreporting of comorbidities when compared to prospective cohort studies. For instance, a US retrospective claims analysis found that the prevalence of obesity among patients with IPF was 0.6% as identified by ICD-9 diagnosis codes (278.0x) [26]. A 2012 brief published by the National Center for Health Statistics of the Centers for Disease Control and Prevention, however, reported that 35.7% of American adults were obese (defined as BMI ⩾30) in 2009–2010 [141].

Differences in the case definition and diagnostic criteria for IPF and comorbidities of interest likely also contributed to the variation in estimates observed here. The ATS/ERS 2000 consensus guidelines relevant at that time were used to diagnose patients with IPF in over half of studies (70/126; 56%), although other studies identified patients with IPF using results of a lung biopsy or diagnosis codes in claims data. In addition, many studies included in this review were conducted and reported before the recent ATS/ERS/JRS/ALAT guidelines were published in 2011 [1]. The term IHD was frequently used to categorise related conditions such as acute coronary syndromes, angina pectoris and CAD, but definitions of these conditions varied over time and by investigator or were often lacking from study methods. For instance, the term "significant" in CAD was used differently in three separate studies: to define the need for an intervention or major vessel with >50% lesions [121], the quantification of coronary calcification in left heart catheterisation/high-resolution computed tomography results [124] and ⩾50% stenosis of one or more coronary arteries as diagnosed by coronary angiography [125].

Under the University of Oxford's CEBM Levels of Evidence, the majority of studies included in this review qualified for a score of "2b", reserved for retrospective cohort studies and prospective cohort studies with poor follow-up [17]. Studies based on existing data may be affected by information bias: pertinent data may be missing due to loss to follow-up or differences in how outcomes are measured over time. Recall bias may also be present if patients are asked to remember detailed medical history or treatments. As this review did not evaluate specific study outcomes, such as efficacy or safety, the risk of bias within individual studies was not assessed.

The majority of the studies included in this review assessed relatively small samples of patients with IPF, which may limit generalisability to larger populations of patients with IPF. Relevant studies that met the criteria for this review were not frequently found in the literature from Africa (n=1), Australia (n=1) and South America (n=2), which also limits the generalisability of the conclusions of this report. As only studies published in English were included, we may have missed relevant data on comorbidities in IPF patients in non-English literature. Similarly, we limited our review to papers indexed in MEDLINE and

EMBASE, and there is the possibility that we did not include relevant data that were published outside of these databases. Nevertheless, a strength of this study is the systematic methodology employed. Additionally, while other investigators have reported the prevalence of individual selected comorbidities among IPF patients, this review provides the first summary of a multitude of comorbidities in one document.

While this review concentrates on specific comorbidities that patients with IPF have, a clearer understanding of underlying definitions and of the effect that different comorbidities and their treatment have on survival in IPF patients is needed. Both nintedanib and pirfenidone have been shown to slow disease progression in separate phase III clinical trials, and have been recently approved in the USA [142, 143] and the European Union based on a significant reduction in lung function decline assessed by longitudinal measures of FVC over 1 year; both were associated with numerical risk reductions for all-cause mortality in these studies [144]. However, to date, no pharmacological treatment has been shown to improve survival in an adequately designed study. It is currently unknown if the new antifibrotic agents have an impact on the outcomes of patients with IPF complicated with comorbid conditions [145]. Prompt detection of comorbid conditions and appropriate treatment of these comorbidities may contribute to enhanced survival of patients with IPF. Diagnosis and treatment of respiratory and nonrespiratory comorbidities that are prevalent in patients with IPF are appropriate considerations, as undetected and thus untreated comorbid conditions have independent poor outcome. For example, undiagnosed OSA does contribute to fatigue and subsequent development of PH; treatment for PH may be a worthwhile consideration and early diagnosis of lung cancer may all lead to overall improved outcome. In this regard, while a treatment regimen to improve survival in patients with IPF is yet to be determined, the relatively low mortality (~10%) observed in well-defined patients with IPF and mild-to-moderate physiological impairment participating in clinical trials during a 52-week study period, as well as patients maintaining stabilisations without any specific treatment for IPF, raises the possibility of improved survivability in patients with IPF due to "treatment" targeting comorbidities [142, 143]. A recent retrospective study demonstrated improved survival in patients with IPF treated with antacid and surgical treatment for abnormal GER [10]. In a well-defined cohort of patients with IPF participating in three prospective clinical trials, a decreased rate of progression of IPF was documented with antacid treatment [9]. However, as treatment groups were not randomised, "bias by indication" may play a role here and formal randomised placebo controlled trials are urgently needed in this area. It is also apparent that the standard of care in general for patients with IPF has improved and may have accounted for the apparent change in the natural course of IPF [146].

Although this review summarised data on individual comorbidities, the wide range of prevalences of the comorbidities described in here reflects the varying definitions utilised in individual studies. Future studies should use well-established definitions for comorbid conditions to obtain greater insight into the comorbidities affecting patients with IPF. This information is needed to enable clinical trials to be more effectively designed and to address the treatment of comorbid conditions that may improve the overall health outcomes of patients with IPF. Additional research on the independent effects of patient characteristics (*e.g.* age, gender, ethnicity and disease severity) *versus* the effects of comorbidities on morbidity and mortality would aid in understanding the overall impact comorbidities have on the clinical course of IPF. In addition to treatment of individual comorbid conditions, the design of future clinical trials for IPF stratified by specific comorbidities known to be prevalent in patients with IPF may lead to a better understanding of true treatment effects and to better overall outcomes.

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