Comorbidities in the idiopathic pulmonary fibrosis and progressive pulmonary fibrosis trial population: a systematic review and meta-analysis

Tyson M. Walters [1], Marcus C.H. Leong [2], Sydney B. Montesi[3], Christopher J. Ryerson[4,5] and Yet H. Khor [2,6,7,8]

[1]Department of Medicine, Austin Health, Heidelberg, Australia. [2]Faculty of Medicine, University of Melbourne, Melbourne, Australia. [3]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA, USA. [4]Department of Medicine, University of British Columbia, Vancouver, BC, Canada. [5]Centre for Heart Lung Innovation, St. Paul's Hospital, Vancouver, BC, Canada. [6]Respiratory Research@Alfred, School of Translational Medicine, Monash University, Melbourne, Australia. [7]Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Australia. [8]Institute for Breathing and Sleep, Heidelberg, Australia.

Corresponding author: Yet H. Khor (yet.khor@monash.edu)

Shareable abstract (@ERSpublications)
Reporting of comorbidities in pharmaceutical randomised controlled trials of IPF and PPF varied widely. The prevalence of different comorbidities in the trial cohorts were generally lower than those reported in the real-world cohorts. https://bit.ly/4jzYqBS

Cite this article as: Walters TM, Leong MCH, Montesi SB, *et al*. Comorbidities in the idiopathic pulmonary fibrosis and progressive pulmonary fibrosis trial population: a systematic review and meta-analysis. *Eur Respir Rev* 2025; 34: 240238 [DOI: 10.1183/16000617.0238-2024].

Received: 24 Oct 2024
Accepted: 19 Jan 2025

Abstract

Background Comorbidities can affect drug tolerability and health outcomes in patients with fibrotic interstitial lung disease. This systematic review and meta-analysis evaluated the types and prevalence of comorbidities amongst participants in pharmaceutical randomised controlled trials (RCTs) of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF).

Methods Ovid Medline, Embase and CENTRAL databases were searched to identify phase II and III pharmaceutical RCTs of IPF or PPF. Reporting of comorbidities was evaluated, with meta-analyses being performed for the prevalence of different conditions.

Results 34 articles were included, with 23 unique trials for IPF and one for PPF. A mean of 14 (range 1–44) comorbidities per study was reported in the IPF RCTs, with 11 being reported in the PPF RCT. Common comorbidities in the IPF RCT cohorts were systemic hypertension (pooled prevalence 45%, 95% CI 39–50%), hyperlipidaemia (38%, 95% CI 27–49%), gastro-oesophageal reflux disease (45%, 95% CI 36–54%), ischaemic heart disease (18%, 95% CI 13–42%) and diabetes mellitus (16%, 95% CI 13–20%). The PPF trial cohort had similar types and prevalence of comorbidities to those reported in the IPF trial cohorts.

Conclusions Reporting of comorbidities varied across previous IPF RCTs, with limited data available for PPF. Prevalence of comorbidities reported in the IPF and PPF trial cohorts appear to be lower than those reported in prospective patient registries. There is a need for careful consideration of trial eligibility criteria with detailed reporting of comorbidities in future pharmaceutical RCTs to better understand the applicability of trial findings to real-world patients.

Introduction

Interstitial lung disease (ILD) is a large heterogeneous group of inflammatory and fibrosing conditions affecting the lungs. Idiopathic pulmonary fibrosis (IPF), one of the most common subtypes, is the prototypical chronic progressive ILD with a mean survival of 4 years if untreated [1, 2]. Progressive pulmonary fibrosis (PPF) describes a subgroup of non-IPF ILDs that exhibit a similar disease course and prognosis to IPF [3, 4]. Both IPF and PPF are chronic debilitating conditions with high morbidity and substantial healthcare costs, leading to premature mortality [4–7]. While antifibrotic medications, such as nintedanib and pirfenidone, slow disease progression in patients with IPF and PPF, they are not curative [8–12].

Multimorbidity affects approximately 37% of the global population and over 50% of those above 60 years old [13]. This poses significant impact on individual and healthcare burden, with worsened functional status, increased mortality and high healthcare cost [14–16]. IPF has a predilection for older individuals [17], while patients with PPF from real-world studies had a mean or median age ranging from the late 50s to early 60s [18–20]. Comorbidities can affect different aspects of IPF and PPF, including symptom burden, disease progression, treatment and prognosis [21, 22]. These comorbidities increase the complexity of disease management; however, the extent to which comorbidities are present in the clinical trial populations of IPF or PPF is unclear. This knowledge is crucial to better inform the relevance of randomised controlled trial (RCT) findings for clinical decision-making and patient discussion, as well as to guide future research and clinical trial design. This systematic review and meta-analysis aimed to evaluate the types and prevalence of comorbidities amongst participants in pharmaceutical RCTs of IPF and PPF.

Methods

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [23]. The protocol was prospectively registered on the PROSPERO register of systematic reviews (CRD42023471100).

Inclusion/exclusion criteria

Eligible studies included phase II or III pharmaceutical RCTs of IPF and PPF in adults aged ⩾18 years. The diagnosis of IPF or PPF was based on the specified eligibility criteria defined for each clinical trial. Non-English publications were excluded.

Search strategy

Relevant studies were searched using three databases from inception until October 2023, including Ovid Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL). Full search terms are available in table S1.

Study selection, data extraction and risk of bias assessment

Study selection was performed independently by two authors (T.W. and M.L.). Sequential review of titles and abstracts followed by full-text articles was undertaken to identify eligible studies for inclusion. Disagreement regarding study inclusion was resolved by consensus or by a third author (Y.H.K.) if required. Data were extracted by two authors (T.W. and M.L.) using a standardised data extraction form with data verification performed independently by a second author (T.W. or M.L.). Risk of bias assessment was performed independently by two authors (T.W. and M.L.) using the Risk of Bias Tool 2, which includes five domains, namely the randomisation process, deviation from intended intervention, missing outcome data, measurement of the outcome and selection of the reported result [24].

Statistical analysis

Data for IPF and PPF were analysed separately. Reporting of comorbidities was summarised by organ systems or disease types using descriptive statistics, including mean±SD for continuous data and count and percentages for categorical data. For prevalence of comorbidities that were reported in more than five RCTs, meta-analyses of a random-effects model were performed using Stata (v18 StataCorp, College Station, Texas, USA). Heterogeneity of data was assessed using I^2 statistics and rated as low (0–40%), moderate (30–50%) and high (>50–90%) [25]. The prevalences of the remaining reported comorbidities were synthesised narratively. Subgroup analyses by the phases of clinical trials (phase II *versus* phase III) and sponsor type (investigator-led trials with or without support from a pharmaceutical company *versus* industry-driven trials that were initiated by a pharmaceutical company) were performed for RCTs of IPF. Pre-specified subgroup analyses by ILD subtypes for RCTs of PPF could not be performed, as there was only one included trial.

Results

Characteristics of included studies

Of the 9620 unique articles identified from the search, 417 underwent full-text assessment (figure 1). 34 articles met eligibility for inclusion with 23 unique RCTs for IPF and one for PPF, with 10 being secondary articles for *post hoc* analyses. Key characteristics of the included studies are summarised in table 1, with details presented in tables S2 and S3. All included RCTs began after 2000, with the latest one being completed in 2020 [29]. Among the IPF RCTs, most were phase III (n=17, 74%) and conducted as multicentre international studies (n=15, 65%), with the contemporary IPF guidelines being used for diagnosis (n=21, 91%). Most included RCTs were industry-driven (n=15, 65%). The only included PPF

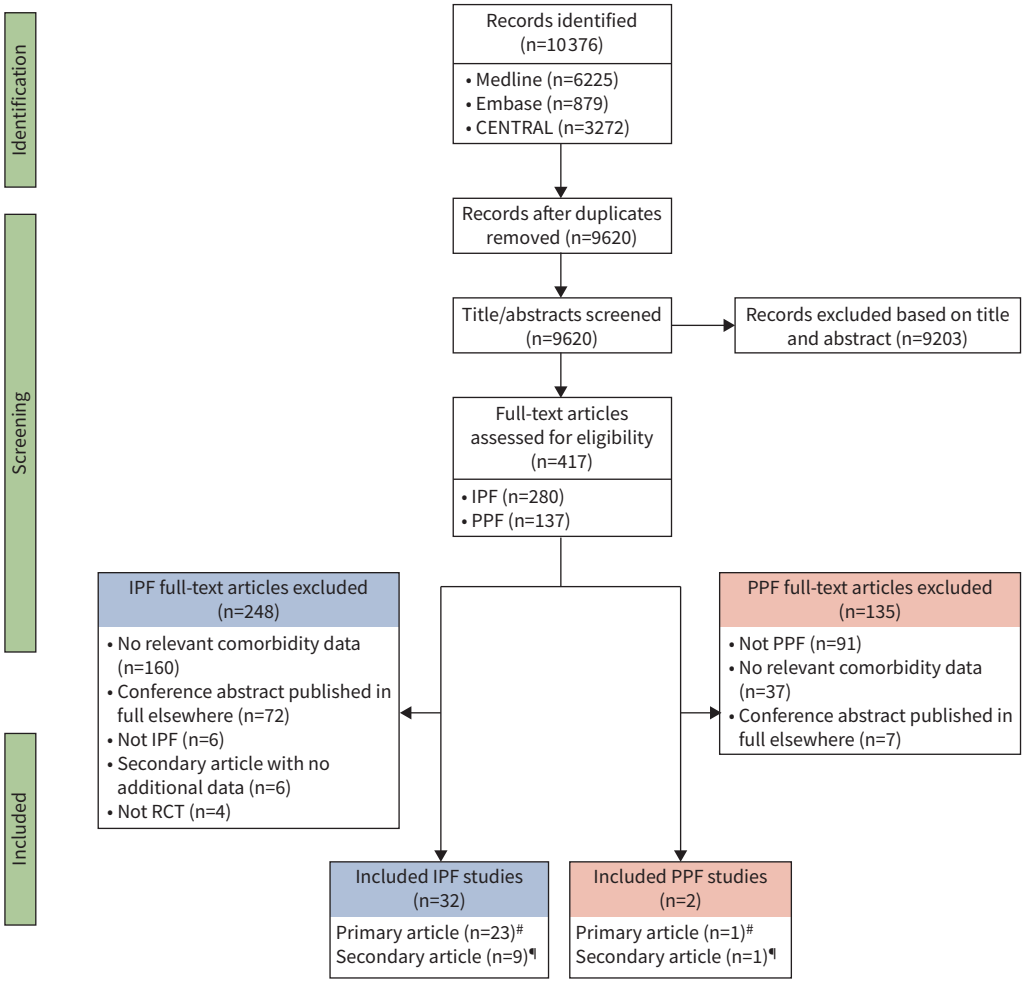

FIGURE 1 Study flow diagram. #: Primary articles refer to original publications of the randomised controlled trials. ¶: Secondary articles refer to additional publications of *post hoc* analyses of previously published randomised controlled trials. CENTRAL: Cochrane Central Register of Controlled Trials; IPF: idiopathic pulmonary fibrosis; PPF: progressive pulmonary fibrosis; RCT: randomised controlled trial.

RCT was an international multicentre industry-driven phase III trial of nintedanib [28], with data on comorbidities reported in the rheumatoid arthritis associated-ILD (RA-ILD) cohort [30].

Participants of IPF RCTs were of male predominance and had mean age ranging from 63 to 72 years, with mild-to-moderate forced vital capacity (FVC) impairment and moderate-to-severe reduction in diffusing capacity for carbon monoxide (D_{LCO}) (table S4). The RA-ILD cohort of the included PPF RCT had 54% of males, with mean age of 67 years, FVC of 71% pred and D_{LCO} of 48% pred.

Risk of bias assessment

The majority of included RCTs in IPF had low risk of bias (n=17, 72%) (figures S1 and S2). There were some concerns in one or more domains in six RCTs [29, 31–35]. The blinding of participants domain was the most commonly judged as high risk (n=6), followed by the randomisation process domain (n=2 [29, 34]) and the blinding of outcome assessors domain (n=1 [35]). The only included RCT for PPF had some concerns about participant blinding (figures S1 and S2).

Comorbidity reporting

A mean±SD of 14±12 comorbidities per study was reported, ranging from 1 to 44 comorbidities in the IPF trials (figure 2a) and with 11 comorbidities reported in the RA-ILD cohort of the included PPF trial (table S5).

TABLE 1 Included study characteristics for idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF)

Characteristic	IPF		PPF	
	Number of studies	Total number of participants	Number of studies	Total number of participants
RCT phase				
Phase II	6	1289	0	0
Phase III	17	6459	1	89[§]
Year commenced				
2000–2009	10	3881	0	0
2010–2020	13	3867	1	89
Study location by continent				
North America	19	7139	1	89
Europe	16	6360	1	89
Asia	9	3553	1	89
UK	9	5801	1	89
Oceania/Australia	8	4056	0	0
Other[#]	6	2326	0	0
Study design				
Single centre	1	45	0	0
Multicentre (national)	7	1856	0	0
Multicentre (international)	15	5847	1	89
Diagnostic criteria for IPF				
ATS/ERS IPF guidelines 2000 [26]	6	2646	0	0
ATS/ERS/JRS/ALAT IPF guidelines 2011 [27]	15	4466	0	0
Other[¶]	2	636	1	89
Sponsor type[+]				
Industry-driven	15	5847	1	89
Investigator-led	8	1901	0	0

[#]: Other continents: Africa n=3, South America n=3. [¶]: Other: IPF diagnostic criteria not described n=2, PPF criteria defined by investigators no guideline referenced. [+]: Industry-driven trials refer to randomised controlled trials (RCTs) that were initiated by a pharmaceutical company; investigator-led trials refer to RCTs that were initiated by healthcare professionals with or without support from a pharmaceutical company. [§]: Comorbidity data only available for the rheumatoid arthritis associated interstitial lung disease cohort of the INBUILD trial (n=89 out of 663) [28]. ATS: American Thoracic Society; ALAT: Latin American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society.

For IPF, a range of comorbidities for different organ systems were reported at varying frequencies among the included RCTs. Non-ILD respiratory disorders and cardiac disorders were most frequently reported, with commonly reported conditions including COPD and pulmonary hypertension for the former and ischaemic heart disease for the latter (figure 2b and table 2). Cardiovascular risk factors, including systemic hypertension and hyperlipidaemia, and gastrointestinal disorders were also frequently reported. A similar range of comorbidities was reported in the RA-ILD cohort of the included PPF RCT (table S5).

Comorbidity prevalence

IPF

Gastrointestinal disorders had the highest pooled prevalence of 53% (95% CI 43–63%), with gastro-oesophageal reflux disease (GORD) being the most prevalent disease at 45% (95% CI 36–54%) (table 2). There were high prevalences for cardiovascular risk factors, with pooled estimates of 45% (95% CI 39–50%) for systemic hypertension and 38% (95% CI 27–49%) for hyperlipidaemia. Non-ILD respiratory disorders were also prevalent with pooled estimates of 25% (95% CI 11–42%), with COPD (9%, 95% CI 3–16%) being the most common condition, followed by pulmonary hypertension (4%, 95% CI 2–6%). Endocrine disorders had a pooled prevalence of 27% (95% CI 17–38%), with diabetes mellitus having a pooled prevalence of 16% (95% CI 13–20%). The pooled prevalence for cardiac disorders was 23% (95% CI 15–33%), with ischaemic heart disease having pooled prevalence of 18% (95% CI 13–42%). Other common comorbidities included musculoskeletal disorders (pooled prevalence 28%, 95% CI 15–44%), vascular disorders (pooled prevalence 23%, 95% CI 3–54%) and psychiatric disorders inclusive of depression (pooled prevalence 22%, 95% CI 13–33%). The I^2 statistic for all pooled estimates of prevalence ranged between 75% and 99%, indicating high heterogeneity.

Subgroup analyses comparing phase II and phase III RCTs of IPF demonstrated similar prevalence for most comorbidities (table S6). Immunological disorders and neurological disorders were more prevalent in phase II trials, while higher prevalence of diabetes mellitus was seen in phase III trials. Subgroup analyses

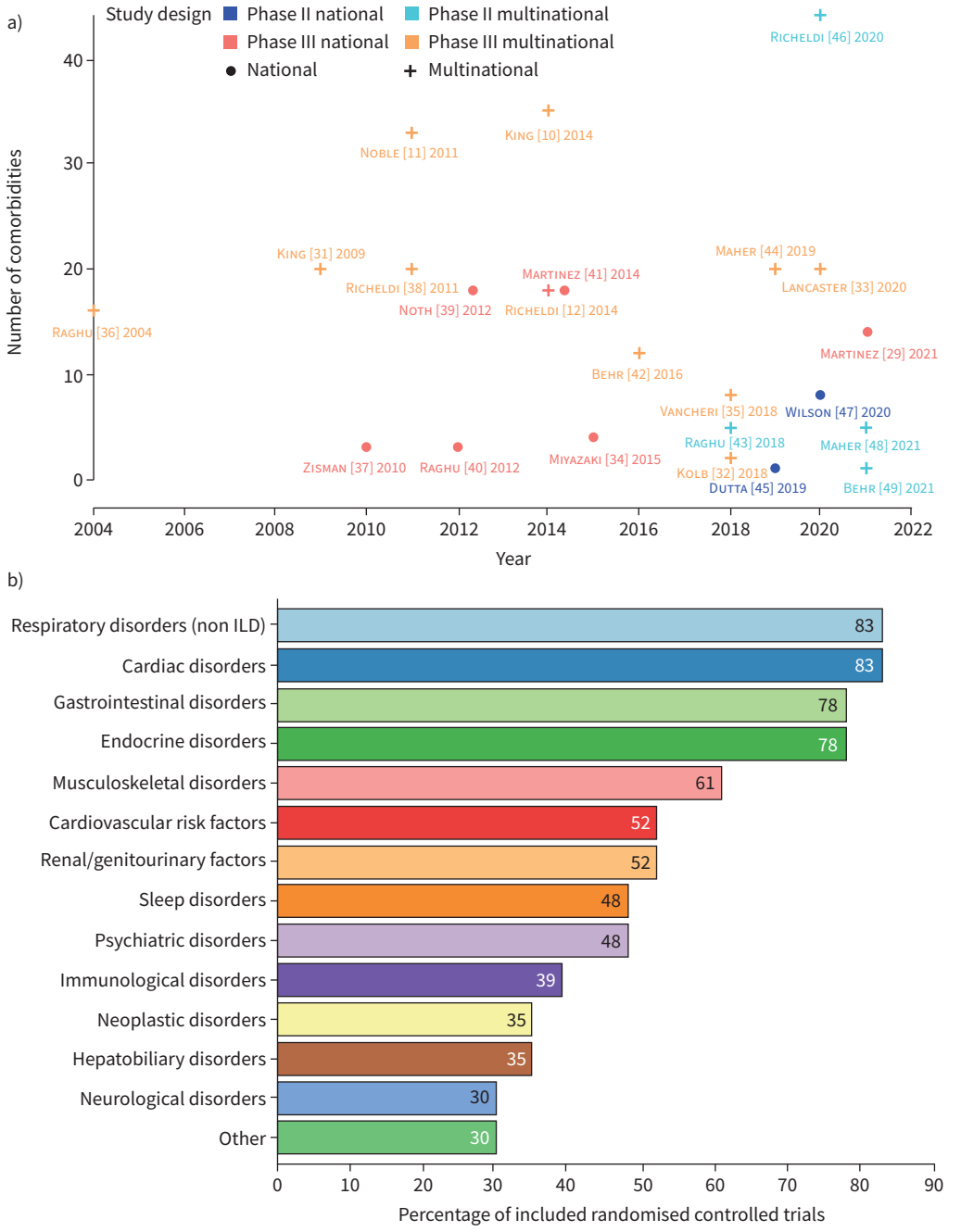

FIGURE 2 Reporting of comorbidities in randomised controlled trials of idiopathic pulmonary fibrosis (IPF). Studies are cited as first author, reference, year. a) Number of comorbidities reported for individual included randomised controlled trials of IPF. b) Percentages of included randomised controlled trials of IPF reporting comorbidity classified by organ system. ILD: interstitial lung disease.

by sponsor type showed that pulmonary hypertension, sleep disorders and hyperlipidaemia were more prevalent in investigator-led trials, while industry-driven trials had higher prevalence of endocrine, musculoskeletal, renal, psychiatric, hepatobiliary, neurological, haematological and vascular disorders (table S6). High heterogeneity remained for both subgroup analyses.

PPF

In the RA-ILD cohort of the included PPF RCT, the most prevalent comorbidity was systemic hypertension (54%), followed by GORD (25%) (table S5). Other common comorbidities affecting the

TABLE 2 Prevalence of comorbidities by organ systems for randomised controlled trials of idiopathic pulmonary fibrosis

Modalities	Total number of studies	Total number of participants	Prevalence, % (95% CI)	I^2 heterogeneity (%)
Respiratory disorders (non-ILD)	19	5826	25 (11–42)	99
COPD	16	5228	9 (3–16)	98
Pulmonary hypertension	7	2295	4 (2–6)	77
Cardiac disorders	19	5461	23 (15–33)	99
IHD	16	5461	18 (13–24)	96
Arrhythmia	7	2529	4 (2–7)	89
Gastrointestinal disorders	18	5910	53 (43–63)	98
GORD	16	5467	45 (36–54)	98
Hiatus hernia	6	2897	10 (6–14)	91
Endocrine disorders	18	5820	27 (17–38)	99
Diabetes mellitus	15	5346	16 (13–20)	90
Systemic hypertension	12	3997	45 (39–50)	89
Musculoskeletal disorders	14	4251	28 (15–44)	99
Renal/genitourinary disorders	12	3676	15 (8–23)	97
Sleep disorders	11	3754	17 (14–20)	75
OSA	11	3754	16 (11–21)	93
Psychiatric disorders	11	3325	22 (13–33)	98
Hyperlipidaemia	9	3678	38 (27–49)	97
Immunological disorders	9	2860	16 (7–27)	98
Neoplastic disorders	8	2765	10 (4–20)	98
Hepatobiliary disorders	8	1779	4 (2–6)	85
Neurological disorders	7	1828	20 (9–35)	98
Haematological disorders	6	1315	6 (3–10)	84
Vascular disorders	6	1488	23 (3–54)	99

GORD: gastro-oesophageal reflux disease; IHD: ischaemic heart disease; ILD: interstitial lung disease; OSA: obstructive sleep apnoea.

participant cohort were dyslipidaemia (12%), hyperlipidaemia (18%), sleep disorders (13.5%), diabetes mellitus (13.5%) and asthma (10%). The prevalence of COPD was not reported.

Discussion

This systematic review and meta-analysis is the first to comprehensively evaluate the reported comorbidities present in participants of RCTs for IPF and PPF. While comorbidities were reported in the recent IPF trials, there was substantial inter-study variability in the numbers and types of conditions evaluated. Common comorbidities in participants of IPF RCTs were non-ILD respiratory disorders, gastrointestinal disorders, endocrine disorders, cardiac disorders and cardiovascular risk factors. Subgroup analyses by trial phase and sponsor type of IPF RCTs demonstrated largely similar comorbidity prevalence. For PPF, comorbidities were only reported in the RA-ILD cohort of the INBUILD trial. Further data on comorbidity from the PPF cohort is needed, given this condition affects patients of different demographics with and without an associated systemic disease depending on the ILD subtypes.

Comorbidities were common in both IPF and PPF trial cohorts. However, the prevalence of different comorbidities in the trial cohorts are often at the lower end of the reported prevalence in registry cohorts [50–55]. These differences can be attributed to the trial eligibility criteria, which often exclude individuals with organ dysfunction or significant comorbidities [56]. While comorbidities are associated with reduced survival and worse health-related quality of life in patients with fibrotic ILD [5, 57], uncertainties remain regarding the effects and significance of individual diseases. Not all comorbidities individually or in combination will have similar clinical relevance to influence health outcomes or interact with the therapy under investigation in patients with IPF and PPF. Thus, it is essential to consider potential risks and benefits in deciding the inclusion of different comorbidities as eligibility criteria for each RCT rather than using criteria from previous protocols.

Among the different comorbidities, the pooled estimate and 95% CI for the prevalence of COPD and pulmonary hypertension in the IPF trial cohort is substantially lower than the reported prevalence in most observational studies of clinical registries and healthcare claim databases [58, 59]. This discrepancy is likely due to the common exclusion of patients with significant obstructive lung disease or low D_{LCO} in IPF RCTs [56]. Combined pulmonary fibrosis and emphysema affects between 8% and 67% of patients with IPF [58]. *Post hoc* analyses of the INPULSIS trial showed no differences in the effect of nintedanib

on reducing FVC decline when stratified by the presence of emphysema on imaging or forced expiratory volume in 1 s (FEV_1)/FVC ratio, although patients with FEV_1/FVC ratio <0.7 were excluded from this trial [60]. Different criteria have been used to define the presence of significant obstructive lung disease for trial exclusion in IPF, with FEV_1/FVC ratio <0.7 being commonly used [56]. However, given that FEV_1/FVC ratio decreases with age, the use of fixed FEV_1/FVC ratio <0.7 cut-off to define airway obstruction can lead to overdiagnosis in adults aged over 40 years [61], which portends an issue in patients with IPF given its predilection for individuals aged over 60 years.

Many common comorbidities identified in the IPF trial cohort are similar to those affecting the general population, including GORD, ischaemic heart disease, systemic hypertension, hyperlipidaemia, diabetes mellitus and obstructive sleep apnoea [62]. Use of medications that slow disease progression, such as nintedanib and pirfenidone, will result in an increasing number of patients living with IPF for longer periods of time, with these patients then having potential to develop other comorbidities that may impact health outcomes and management. Thus, management of comorbidities form an important pillar in clinical care of IPF and will likely become even more important over time [63]. The presence of comorbidities as well as medication burden inform prognosis in patients with IPF [21, 64]. Increased concomitant medication burden, a surrogate for multimorbidity, is found to be associated with intolerance of antifibrotic medications and worse transplant-free survival [64]. With increasing prevalence of multimorbidity in the general population, RCT eligibility criteria that exclude patients with multiple comorbidities will impact trial accrual and generalisability of drug efficacy and safety post-approval.

The importance of comorbidities on health outcomes in patients with fibrotic ILD is increasingly recognised. The TORVAN index, which incorporates the addition of selected comorbidities to the Gender–Age–Physiology (GAP) index, has superior performance in predicting survival in patients with IPF [21]. Several comorbidities included in the TORVAN index were prevalent in the IPF trial cohort, including diabetes mellitus, systemic hypertension, GORD and depression (based on the reporting of psychiatric disorders). It is noteworthy that the IPF trial cohort had low prevalence of pulmonary hypertension, which is likely related to the predilection of recruiting patients with early disease stages in clinical trials [56]. The prevalence of lung cancer was not reported in IPF trials, which is expected to be low given these patients are often excluded from clinical trial participation [56]. While cardiac disease was common in the IPF trial cohort, the prevalence of arrhythmia was low with a lack of data for valvular heart disease. Further evaluation is needed to understand how comorbidities may influence survival and other clinical trial outcomes in patients with IPF.

This systematic review is limited by the substantial number of RCTs, 76 for IPF and nine for PPF, that did not report comorbidity data. Of note, most recent IPF RCTs were included in our analyses. Given that PPF is an emerging entity since 2019, there were a limited number of completed RCTs for PPFs, with comorbidity data only available for the RA-ILD cohort of the INBUILD trial. High heterogeneity was observed in the meta-analyses of IPF RCTs, which persisted with subgroup analyses by trial phase and sponsor type. There may be other factors that influenced the observed inter-study heterogeneity, such as trial eligibility criteria and study location with geographical and racial variation in comorbidities.

Conclusion

This systematic review and meta-analysis provides important insights into comorbidities affecting patients who have participated in IPF and PPF RCTs. Reporting of comorbidities varies substantially across different RCTs of IPF, with limited data available for PPF RCTs. Prevalence of reported comorbidities in the trial cohorts are generally lower, compared to those reported in clinical cohorts. Given that phase II and III RCTs are critical to establish treatment efficacy and safety, comorbidities collected at baseline trial eligibility assessment should be reported in the publications of future RCTs to better understand the representativeness of clinical trial cohorts. Furthermore, there is a need for careful consideration of comorbidities as trial eligibility criteria in future RCTs of IPF and PPF to support the application and translation of trial results to real-world patients with increasing multimorbidity.

Points for clinical practice and future research

- Non-ILD respiratory disorders, cardiovascular comorbidities and gastro-oesophageal reflux disease are common in both IPF and PPF RCT cohorts.
- Comorbidities in RCT populations for IPF and PPF appear lower than those reported in clinical registries.
- Reporting of comorbidities should be undertaken in future RCTs to better understand applicability of trial findings.

Provenance: Submitted article, peer reviewed.

Conflict of interest: T.M. Walters and M.C.H. Leong have nothing to disclose. S.B. Montesi reports grants from NIH/NHLBI, Merck, Boehringer Ingelheim and Pliant Therapeutics; royalties or licenses from Wolters Kluwer; consulting fees from Roche, DevPro Biopharma, Mediar Therapeutics and Accendatech USA; payment or honoraria for lectures, presentations or educational events from Cowen; support for attending meetings from DevPro Biopharma; participation on a data safety monitoring board or advisory board with Pliant Therapeutics and APIE Therapeutics; and a leadership role with Massachusetts Thoracic Society. C.J. Ryerson reports grants from Boehringer Ingelheim, Hoffmann-La Roche and VIDA Diagnostics; payment or honoraria for lectures, presentations, manuscript writing or educational events from Boehringer Ingelheim, Hoffmann-La Roche, Veracyte, Plaint Therapeutics, AstraZeneca, Cipla Ltd and Trevi Therapeutics; and a leadership role with the American Thoracic Society Documents Development and Implementation Committee. Y.H. Khor reports grants from NHMRC, MRFF, Air Liquide Healthcare (in-kind trial support), Austin Medical Research Foundation, Lung Foundation Australia/Thoracic Society of Australia and New Zealand and RACP; and leadership roles with the Thoracic Society of Australia and New Zealand (Board Director, Chair for Clinical Care and Resources Sub-Committee, OLIV Special Interest Group Convenor), American Thoracic Society (Clinical Problems Assembly Program Committee; guideline methodologist) and European Respiratory Society (Associate Editor for the *European Respiratory Journal*).

References

1 Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet* 2017; 389: 1941.
2 Khor YH, Ng Y, Barnes H, *et al.* Prognosis of idiopathic pulmonary fibrosis without anti-fibrotic therapy: a systematic review. *Eur Respir Rev* 2020; 29: 190158.
3 Raghu G, Ho L, Remy-Jardin M, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care* 2022; 205: E18–E47.
4 Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. *Respir Res* 2019; 20: 57.
5 Kreuter M, Ehlers-Tenenbaum S, Palmowski K, *et al.* Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. *PLoS One* 2016; 11: e0151425.
6 Cox IA, de Graaff B, Ahmed H, *et al.* The economic burden of idiopathic pulmonary fibrosis in Australia: a cost of illness study. *Eur J Health Econ* 2023; 24: 1121–1139.
7 Collard HR, Ward AJ, Lanes S, *et al.* Burden of illness in idiopathic pulmonary fibrosis. *J Med Econ* 2012; 15: 829–835.
8 Ghazipura M, Mammen MJ, Herman DD, *et al.* Nintedanib in progressive pulmonary fibrosis: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2022; 19: 1040–1049.
9 Ghazipura M, Mammen MJ, Bissell BD, *et al.* Pirfenidone in progressive pulmonary fibrosis: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2022; 19: 1030–1039.
10 King TE, Jr., Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
11 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.
12 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
13 Chowdhury SR, Chandra Das D, Sunna TC, *et al.* Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine* 2023; 57: 101860.
14 Ryan A, Wallace E, O'Hara P, *et al.* Multimorbidity and functional decline in community-dwelling adults: a systematic review. *Health Qual Life Out* 2015; 13: 168.
15 GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–1544.
16 Soley-Bori M, Ashworth M, Bisquera A, *et al.* Impact of multimorbidity on healthcare costs and utilisation: a systematic review of the UK literature. *Br J Gen Pract* 2021; 71: e39–e46.
17 Nalysnyk L, Cid-Ruzafa J, Rotella P, *et al.* Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev* 2012; 21: 355–361.
18 Nasser M, Larrieu S, Si-Mohamed S, *et al.* Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). *Eur Respir J* 2021; 57: 2002718.
19 Khor YH, Farooqi M, Hambly N, *et al.* Patient characteristics and survival for progressive pulmonary fibrosis using different definitions. *Am J Respir Crit Care Med* 2023; 207: 102–105.
20 Pugashetti JV, Adegunsoye A, Wu Z, *et al.* Validation of proposed criteria for progressive pulmonary fibrosis. *Am J Respir Crit Care Med* 2023; 207: 69–76.

21 Torrisi SE, Ley B, Kreuter M, *et al.* The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicentre observational study. *Eur Respir J* 2019; 53: 1801587.
22 Caminati A, Lonati C, Cassandro R, *et al.* Comorbidities in idiopathic pulmonary fibrosis: an underestimated issue. *Eur Respir Rev* 2019; 28: 190044.
23 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
24 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
25 Deeks JJ, Higgins JPT, Altman DG, *et al.* Analysing data and undertaking meta-analyses. *In*: Higgins JPT, Thomas J, Chandler J, *et al.*, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, Cochrane, 2023. https://training.cochrane.org/handbook
26 American Thoracic Society and European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2020; 161: 646–664.
27 Ragu G, Collard HR, Egan JJ, *et al*. An Official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
28 Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
29 Martinez FJ, Yow E, Flaherty KR, *et al.* Effect of antimicrobial therapy on respiratory hospitalization or death in adults with idiopathic pulmonary fibrosis: the CleanUP-IPF randomized clinical trial. *JAMA* 2021; 325: 1841–1851.
30 Matteson EL, Aringer M, Burmester GR, *et al.* Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial. *Clin Rheumatol* 2023; 42: 2311–2319.
31 King TE, Jr, Albera C, Bradford WZ, *et al.* Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; 374: 222–228.
32 Kolb M, Raghu G, Wells AU, *et al.* Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2018; 379: 1722–1731.
33 Lancaster L, Goldin J, Trampisch M, *et al.* Effects of nintedanib on quantitative lung fibrosis score in idiopathic pulmonary fibrosis. *Open Respir Med J* 2020; 14: 22–31.
34 Miyazaki Y, Azuma A, Inase N, *et al.* Cyclosporine A combined with low-dose corticosteroid treatment in patients with idiopathic pulmonary fibrosis. *Respir Investig* 2015; 53: 288–295.
35 Vancheri C, Kreuter M, Richeldi L, *et al.* Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. *Am J Respir Crit Care* 2018; 197: 356–363.
36 Raghu G, Brown KK, Bradford L, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; 350: 125–133.
37 Zisman DA, Schwarz M, Anstrom KJ, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.
38 Richeldi L, Costabel U, Selman M, *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365: 1079–1087.
39 Noth I, Anstrom KJ, Calvert SB, *et al.* A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; 186: 88–95.
40 Raghu G, Anstrom KJ, King TE, Jr., *et al.* Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968–1977.
41 Martinez FJ, de Andrade JA, Anstrom KJ, *et al.* Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2093–2101.
42 Behr J, Bendstrup E, Crestani B, *et al.* Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2016; 4: 445–453.
43 Raghu G, van den Blink B, Hamblin MJ, *et al.* Effect of recombinant human pentraxin 2 *vs* placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA* 2018; 319: 2299–2307.
44 Maher TM, Stowasser S, Nishioka Y, *et al.* Biomarkers of extracellular matrix turnover in patients with idiopathic pulmonary fibrosis given nintedanib (INMARK study): a randomised, placebo-controlled study. *Lancet Respir Med* 2019; 7: 771–779.
45 Dutta P, Funston W, Mossop H, *et al.* Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019; 74: 346–353.
46 Richeldi L, Fernandez Perez ER, Costabel U, *et al.* Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2020; 8: 25–31.
47 Wilson AM, Clark AB, Cahn T, *et al.* Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) *vs* placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis: the EME-TIPAC randomized clinical trial. *JAMA* 2020; 324: 2282–2291.

48 Maher TM, Costabel U, Glassberg MK, *et al.* Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2021; 57: 1902442.

49 Behr J, Nathan SD, Wuyts WA, *et al.* Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; 9: 85–95.

50 Lee CT, Hao W, Burg CA, *et al.* The impact of antifibrotic use on long-term clinical outcomes in the Pulmonary Fibrosis Foundation registry. *Respir Res* 2024; 25: 255.

51 Lee JH, Park HJ, Kim S, *et al.* Epidemiology and comorbidities in idiopathic pulmonary fibrosis: a nationwide cohort study. *BMC Pulm Med* 2023; 23: 54.

52 Wong AW, Lee TY, Johannson KA, *et al.* A cluster-based analysis evaluating the impact of comorbidities in fibrotic interstitial lung disease. *Respir Res* 2020; 21: 322.

53 Jovanovic DM, Šterclová M, Mogulkoc N, *et al.* Comorbidity burden and survival in patients with idiopathic pulmonary fibrosis: the EMPIRE registry study. *Respir Res* 2022; 23: 135.

54 Jo HE, Glaspole I, Grainge C, *et al.* Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J* 2017; 49: 1601592.

55 Behr J, Kreuter M, Hoeper MM, *et al.* Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J* 2015; 46: 186–196.

56 Khor YH, Schulte M, Johannson KA, *et al.* Eligibility criteria from pharmaceutical randomised controlled trials of idiopathic pulmonary fibrosis: a registry-based study. *Eur Respir J* 2023; 61: 2202163.

57 Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respir Med* 2014; 108: 647–653.

58 Cottin V, Selman M, Inoue Y, *et al.* Syndrome of combined pulmonary fibrosis and emphysema: an official ATS/ERS/JRS/ALAT research statement. *Am J Respir Crit Care Med* 2022; 206: e7–e41.

59 Ang HL, Schulte M, Chan RK, *et al.* Pulmonary hypertension in interstitial lung disease: a systematic review and meta-analysis. *Chest* 2024; 166: 778–792.

60 Cottin V, Azuma A, Raghu G, *et al.* Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. *Eur Respir J* 2019; 53: 1801655.

61 Miller MR, Levy ML. Chronic obstructive pulmonary disease: missed diagnosis *versus* misdiagnosis. *BMJ* 2015; 351: h3021.

62 Kuan V, Denaxas S, Patalay P, *et al.* Identifying and visualising multimorbidity and comorbidity patterns in patients in the English National Health Service: a population-based study. *Lancet Digit Health* 2023; 5: e16–e27.

63 Khor YH, Cottin V, Holland AE, *et al.* Treatable traits: a comprehensive precision medicine approach in interstitial lung disease. *Eur Respir J* 2023; 62: 2300404.

64 Khor YH, Goh NSL, Wong AW, *et al.* Impact of concomitant medication burden on tolerability of disease-targeted therapy and survival in interstitial lung disease. *Ann Am Thorac Soc* 2022; 19: 962–970.