Prognosis of idiopathic pulmonary fibrosis without anti-fibrotic therapy: a systematic review

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Without anti-fibrotic therapy, patients with IPF have a mortality rate of 31% at ⩾5 years, and a mean overall survival of 4 years over 10 years of follow-up http://bit.ly/2SDiZSb

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ABSTRACT In addition to facilitating healthcare delivery planning, reliable information about prognosis is essential for treatment decisions in patients with idiopathic pulmonary fibrosis (IPF). This review aimed to evaluate the prognosis of patients with IPF without anti-fibrotic therapy. We included all cohort studies and the placebo arms of randomised controlled trials (RCTs) in IPF and follow-up of ⩾12 months. Two reviewers independently evaluated studies for inclusion, assessed risk of bias and extracted data. A total of 154 cohort studies and 16 RCTs were included. The pooled proportions of mortality were 0.12 (95% CI 0.09–0.14) at 1–2 years, 0.38 (95% CI 0.34–0.42) between 2–5 years, and 0.69 (95% CI 0.59–0.78) at ⩾5 years. The pooled mean overall survival was 4 years (95% CI 3.7–4.6) for studies with a follow-up duration of 10 years. At <2 years, forced vital capacity and diffusing capacity of the lung for carbon monoxide declined by a mean of 6.76% predicted (95% CI −8.92−4.61) and 3% predicted (95% CI −5.14 −1.52), respectively. Although heterogeneity was high, subgroup analyses revealed lower pooled proportions of mortality at 1 year in the RCT participants (0.07 (95% CI 0.05–0.09)) *versus* cohort study participants (0.14 (95% CI 0.12–0.17)). This review provides comprehensive information on the prognosis of IPF, which can inform treatment discussions with patients and comparisons for future studies with new therapies.

Introduction

Idiopathic pulmonary fibrosis (IPF) is one of the most common interstitial lung diseases encountered in medical practice [1–6]. A recent systematic review of population-based studies in IPF estimated an incidence of up to nine cases per 100 000 population per year [7]. The British Lung Foundation estimated the prevalence of IPF at 50 per 100 000 people in the UK [8]. In the USA, healthcare utilisation by patients with IPF was approximately twice as high as that by matched controls [9].

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Over time, criteria for diagnosing IPF have changed considerably, from a predominantly histopathological assessment to a multidisciplinary team approach based on clinical, radiologic and histopathologic correlation. Over the last couple of decades, the consensus statement for the diagnosis of IPF has been published and updated [10–12]. Although IPF has previously been reported to have a median survival of 3 years from time of diagnosis [13], this information has been derived mostly from studies performed prior to the publication of the recent consensus statements. It is uncertain whether the prognosis for IPF may have changed over time with changes in the diagnostic criteria.

With the availability of effective therapies for IPF [14, 15], a clear understanding of prognosis is crucial for proper evaluation of the potential impacts of these and other new approaches in the IPF management paradigm. Importantly, patients with IPF wish to have more information about their prognosis [16]. Knowledge of prognosis is essential for thoughtful discussions with patients regarding expectations, in order to ensure the timely offer of supportive care and avoidance of costly, unnecessary therapies with potentially significant adverse effects.

This systematic review and meta-analysis aimed to evaluate the prognosis for survival and respiratory-related outcomes in patients with IPF and without anti-fibrotic therapy.

Methods

This systematic review and meta-analysis were undertaken in collaboration with the Cochrane Airways and Prognosis Methods Groups. The review protocol was published prospectively on the Cochrane Library [17].

Inclusion and exclusion criteria

Eligible studies included cohort studies and randomised controlled trials (RCTs) with a placebo or best supportive therapy arm that enrolled participants with IPF aged ⩾18 years who were either untreated or not treated with effective therapies (nintedanib or pirfenidone) and who were followed for ⩾12 months. The active therapy arms of RCTs were excluded.

Search methods

We searched for relevant studies in the following databases (up to 3 May 2017): MEDLINE, Embase, CINAHL, PubMed and CENTRAL (part of the Cochrane Library *via* the Cochrane Register of Studies Online). For the full search strategies refer to supplementary material S1. The search was supplemented by reviewing reference lists of included studies and related review papers, clinical trial registries and annual conference abstracts from major respiratory societies. Authors of the consensus statements on IPF [10, 11] were contacted for unpublished studies. There was no restriction on language of publication.

Outcomes

Primary outcomes were the proportion of mortality and mean survival duration. Secondary outcomes included progression-free survival, respiratory-specific mortality, change in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}), proportions of patients with a significant decline in FVC or D_{LCO}, dyspnoea, health-related quality of life (HRQoL), and 6-min walk distance (6MWD).

Study selection, data extraction and risk of bias assessment

Two authors (Y.H. Khor and Y. Ng or H. Barnes) independently identified eligible citations on the basis of sequential review of the title, abstract and full text. The agreement of the decisions between the two review authors was calculated using simple κ statistics. Data extraction and risk of bias assessment (supplementary material S2) were performed independently by two authors (Y.H. Khor and H. Barnes) using standardised forms. For RCTs, only data from the placebo or best supportive therapy arm were extracted. For each study, the two sets of data extracted by two review authors were cross-checked. Disagreements were resolved by consensus or a third review author if required. Study authors were contacted for clarification or to provide details of missing data where possible.

Statistical analysis

Meta-analysis was performed using Stata (v15.1; StataCorp, College Station, TX, USA). The pooled proportions of overall and respiratory-specific mortality were calculated under the random-effects model using the Freeman–Tukey transformation [18]. To perform meta-analyses of median survival and changes in secondary outcomes, the estimates of mean and standard error were first calculated according to published methods [19, 20] and then pooled using the Dersimonian–Laird random-effects model [21]. The magnitude of heterogeneity was measured through the I^2 statistic, as described in the Cochrane Handbook [20]. The thresholds for I^2 values were as follows: low (25–49%), moderate (50–74%) and high (⩾75%).

Pre-specified subgroup analyses were performed based on the types of study design (cohort studies *versus* RCT, retrospective cohort studies *versus* prospective cohort studies) and diagnostic criteria for IPF: group

1: 2000 international consensus statement [10]; group 2: 2011 evidence-based guidelines [11]; group 3: other definitions (including physicians' diagnosis). Post-hoc sensitivity analyses was performed using studies with at least 50 participants who were diagnosed using either the 2000 or 2011 international consensus statements, to explore heterogeneity observed in the primary analyses.

Results

Search results

The literature search flow diagram is shown in figure 1. A total of 12 557 citations was considered, with 1531 being retrieved for full-text assessment. We excluded 1226 studies (supplementary material S3). Of the 305 included in this review, 170 were primary studies and 135 were additional reports of primary studies (supplementary martial S4). Inter-observer agreement for selection of studies was good, with κ=0.77 (95% CI 0.76–0.78).

Study characteristics

Of the 170 included studies, 154 were cohort studies [22–175] and 16 were RCTs [14, 15, 176–189]. Table 1 summarises the characteristics of included studies. Full details of included studies can be found in supplementary material S5. Data from studies with targeted selection of patients with acute exacerbation (n=7) [45, 50, 63, 108, 109, 135, 153] and lung transplants (n=2) [99, 131] were not included in pooled analyses for this review, given the established differences in the prognosis for these groups.

Among the cohort studies, 98 were of retrospective design and the other 55 were prospective, while one study included both prospective and retrospective cohorts of participants [110]. The median (range) number of participants was 67 (7–13 615). Follow-up periods ranged from 1 to 10 years. Most studies were single-centre based (n=118), with the remaining using data from multiple centres (n=23) or national registry (n=11) and two being unclear. The diagnosis of IPF was based on the 2000 [10] and 2011 [11] consensus statements in 46 and 36 studies, respectively. Other nonstandardised diagnostic criteria were used for 72 studies. Different therapies used for management of IPF were documented, with the absence of details in 64 studies (supplementary material S6).

For the RCTs, the median (range) number of participants in the placebo arm was 94 (28–423). The study duration ranged from 52 to 96 weeks, with participants being diagnosed based on either the 2000 (n=11) [10]

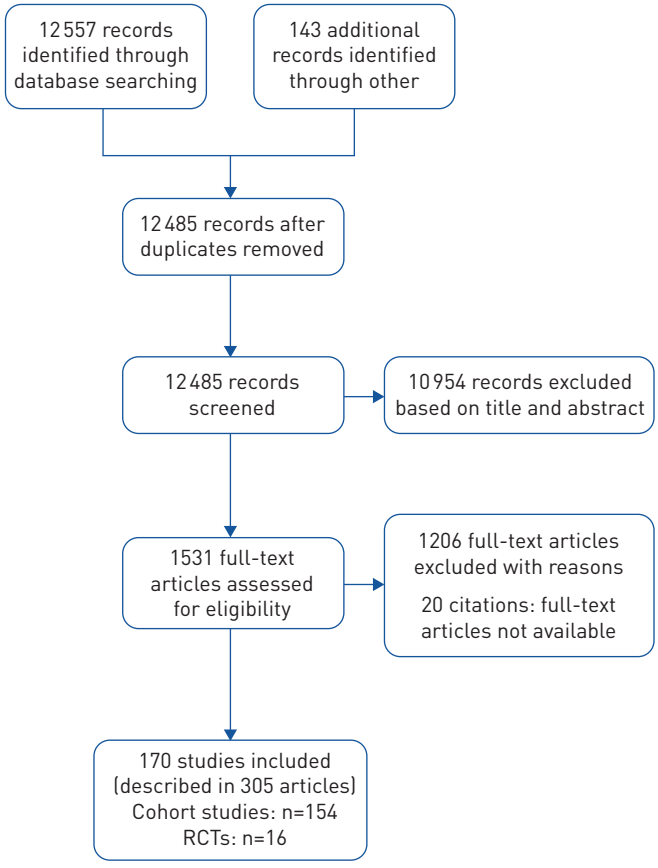

FIGURE 1 Study flow diagram. RCTs: randomised controlled trials.

TABLE 1 Characteristics of studies identified

Characteristics	Details
Study type	154 cohort studies (64% retrospective design)[#] 16 RCTs
Publication year	Before 1990: n=6 1990–1999: n=17 2000–2009: n=38 Since 2010: n=109
Location	Europe: n=60 Asia: n=47 American continent: n=45 Australia: n=5
IPF diagnostic criteria	2011 ATS/ERS/JRS/ALAT guideline: n=41 2000 ATS/ERS international consensus statement: n=57 Other: n=72
Design	Cohort study[#] Prospective design (n=55): 73% single-centre, 20% multicentre, 5% registry/database, 2% unclear Retrospective design (n=98): 79% single-centre, 12% multicentre, 8% registry/database, 1% unclear RCT (n=16): all multicentre trials
Participant number	Cohort study[#] Prospective design (n=55): median (range) 44 (7–588) Retrospective design (n=98): median (range) 81 (11–13 615) RCT (n=16): median (range) 94 (28–423)[¶]
Duration	Cohort study[#,+] Prospective design (n=55): 40% between 1 year and <2 years; 33% between 2–5 years; 13% ⩾5 years Retrospective design (n=98): 43% between 1 year and <2 years; 12% between 2–5 years; 10% ⩾5 years RCT (n=16): all with a study duration of 1 year and <2 years

IPF: idiopathic pulmonary fibrosis; ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; ALAT: Latin American Thoracic Association; RCT: randomised controlled trial. [#]: not including Mura *et al.* [110]: a single-centre study with both prospective (n=70) and retrospective (n=68) cohorts, with a study duration ⩾3 years; [¶]: number of participants in the placebo arm only; [+]: all studies had a study duration ⩾1 year. Some studies provided mean or median follow-up duration which could not be incorporated into the table.

or 2011 (n=5) [11] consensus statements. Prohibited concomitant treatments for each RCT varied (supplementary material S7).

Risk of bias assessment

Assessments were performed based on the information available from study articles and clarification provided by study authors. Overall, the risk of bias in the 170 included studies was moderate. A summary of the risk of bias assessment is presented in supplementary material S8. Most cohort studies (97%) used a clinical source for selecting the study population. While the diagnosis of IPF for study participants was established at baseline for almost all studies (99.5%), only 35% of cohort studies enrolled study participants prospectively. The reasons for loss to follow-up were inadequately described in 79% of cohort studies. For RCTs, all study participants were selected from a clinical source. The percentage of dropouts (along with reasons for dropouts) were described in 81% and 88% of RCTs, respectively. The methods of blinding and use of intention-to-treat principle for data analysis were inadequately described in 19% of RCTs.

Overall survival outcomes

Proportion of mortality

Data on proportions of mortality at various timeframes were available from 100 cohort studies and 16 RCTs. The pooled proportions of mortality were 0.12 (95% CI 0.09–0.14) at 1 year to <2 years (figure 2),

0.38 (95% CI 0.34–0.42) between 2 and 5 years (figure 3), and 0.69 (95% CI 0.59–0.78) for ⩾5 years (figure 4). Tests of heterogeneity were high for all analyses of pooled proportions of mortality.

Duration of survival

Data on the duration of survival were available from 72 cohort studies. Due to variable in follow-up duration, pooled analyse for durations of overall and transplant-free survival were not able to be performed using available data from 18 studies [34, 44, 53–55, 57, 76, 78, 79, 87, 88, 102, 104, 105, 107, 110, 121, 155] and three studies [33, 72, 73], respectively. For studies with a follow-up duration of 2 years, the pooled mean overall survival was 0.9 years (95% CI 0.4–1.4; high heterogeneity I^2=94%). The pooled mean overall survival was 4 years (95% CI 3.7–4.6; low heterogeneity I^2=0%) for studies with a follow-up duration of 10 years.

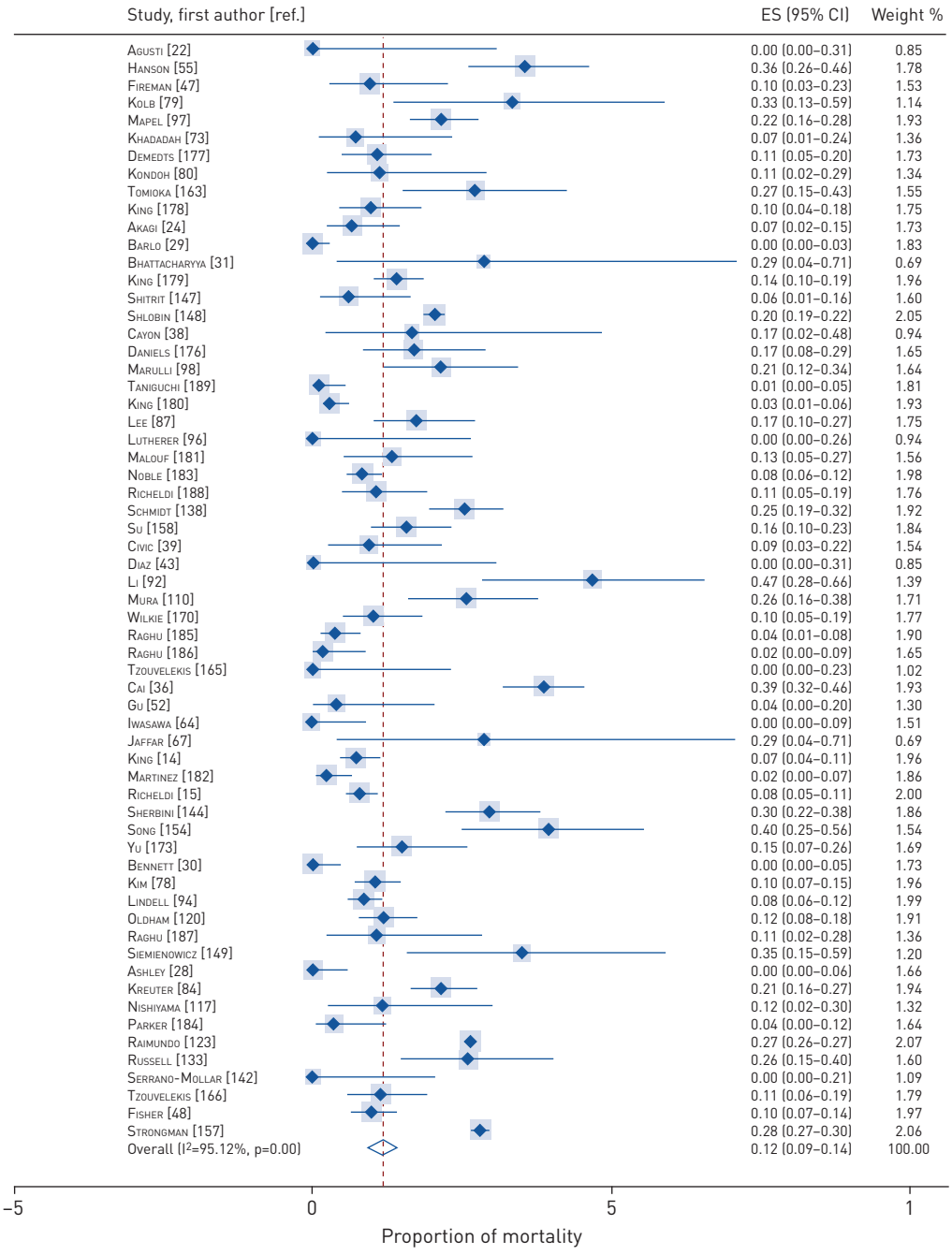

FIGURE 2 Pooled proportions of mortality at 1 year to <2 years. ES: effect size.

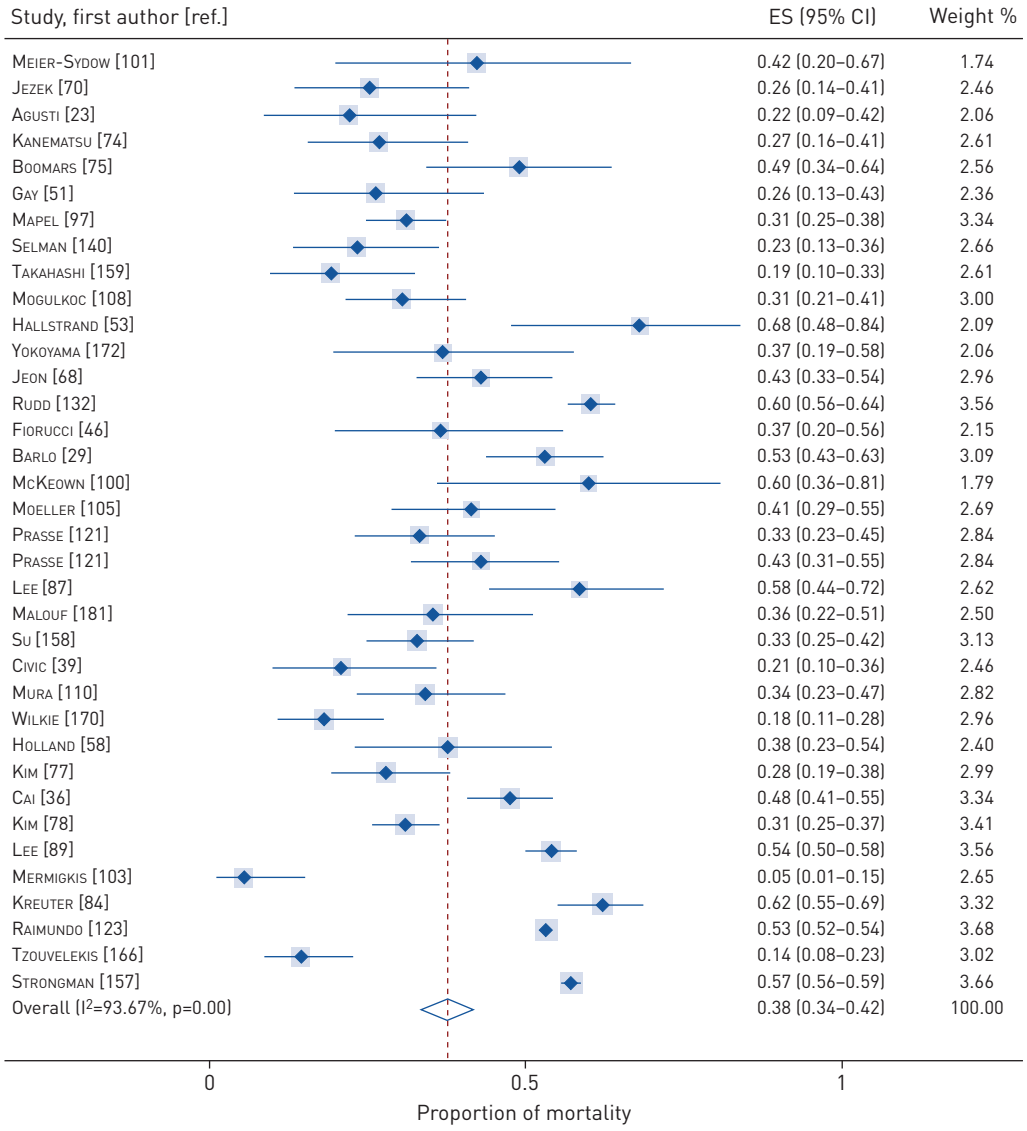

FIGURE 3 Pooled proportions of mortality between 2–5 years. ES: effect size.

Respiratory-related outcomes

Changes in FVC were measured in 15 studies. At <2 years, pooled changes in FVC were −6.76% predicted (95% CI −8.92–−4.61; n=9 studies, 1000 participants; high heterogeneity I^2=89%) (figure 5) [40, 42, 64, 179, 182–185, 188] and −0.18 L (95% CI −0.22–−0.13; n=9 studies, 629 participants; high heterogeneity I^2=63%) (figure E2) [40, 73, 176, 180, 182, 184, 185, 187, 188]. In a study of 13 participants, Agusti *et al.* [23] reported a mean± SD decline of 0.46±0.09 L in 13 participants after 3 years of follow-up. Changes in D_{LCO} were measured in seven studies. At 1 year to <2 years, pooled changes in D_{LCO} were −3.33% predicted (95% CI −5.14–−1.52; n=5 studies, 277 participants; high heterogeneity I^2=76%) (figure 6) [40, 176, 182, 184, 185] and −0.81 mL·mmHg^{-1}·min^{-1} (95% CI −1.17–−0.46; n=4 studies, 428 participants; low heterogeneity I^2=30%) (figure E3) [40, 180, 182, 186].

Seven studies reported changes in 6MWD as an outcome measure. At 1 year to <2 years, the pooled mean change in 6MWD was −37 m (95% CI −88–15; n=4 studies, 444 participants; high heterogeneity I^2=96%) (figure E4). Data pooling was not possible for three studies due to insufficient data [90, 182, 183]. Le Rouzic *et al.* [90] reported median changes of 6MWD of −35 m to 15 m in three subgroups of patients with IPF (total n=34) at 12 months. A study from the Idiopathic Pulmonary Fibrosis Clinical Research Network [182] reported a mean decline of 47.5 m in 6MWD in a 12-month study of 131 participants. In a study of 275 participants, Noble *et al.* [183] found a mean decline of 76.8 m in 6MWD at 72 weeks.

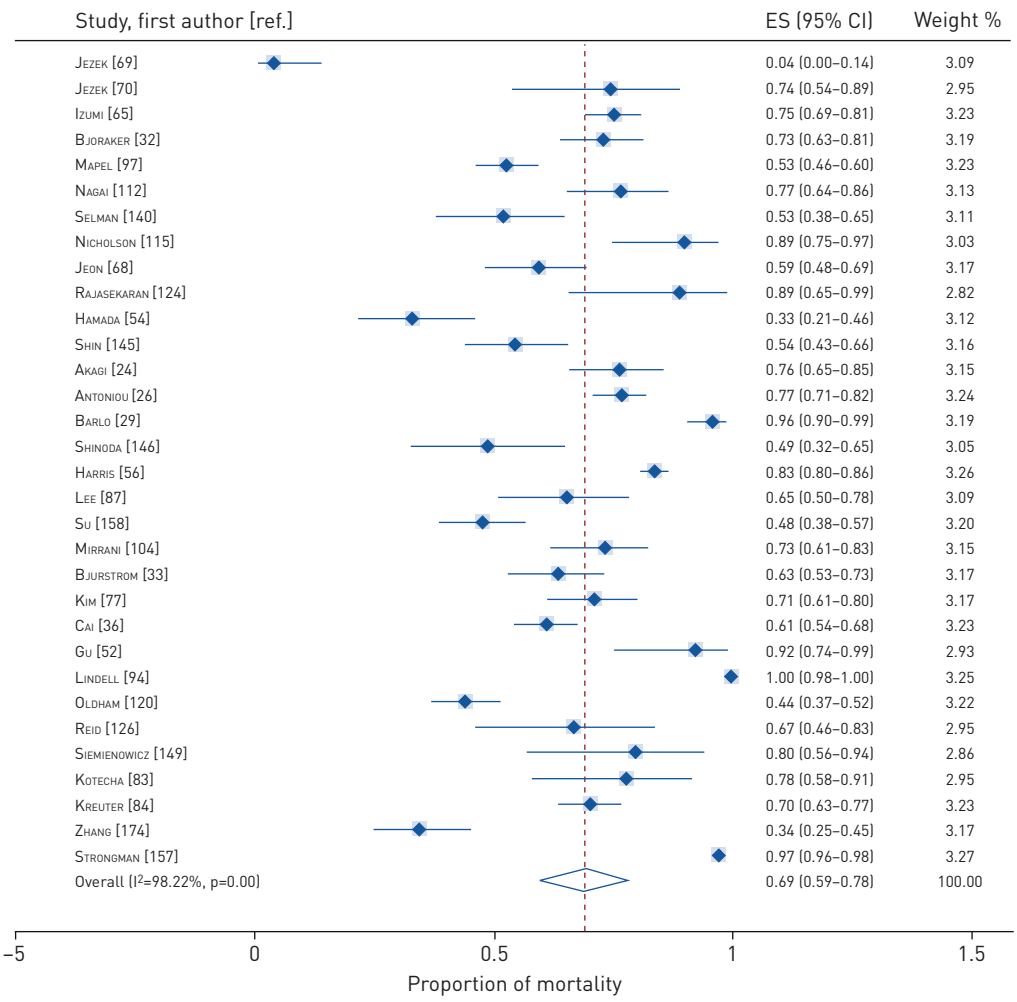

FIGURE 4 Pooled proportions of mortality at ⩾5 years. ES: effect size.

Due to insufficient data and use of different questionnaires, it was not possible to perform pooled analysis of change in dyspnoea. Using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ), King *et al.* [179] reported worsening dyspnoea with a mean± SD increment of 20.2±30.4 in 275 participants over a median follow-up duration of 77 weeks. the Idiopathic Pulmonary Fibrosis Clinical Research Network study reported [182] deterioration in dyspnoea with a mean increment of 5.8 in the UCSD SOBQ at 60 weeks in 131 patients. At 72 weeks, Noble *et al.* [183] and Parker *et al.* [184] reported worsening dyspnoea with a mean increment of 14.5 and 14.4 in the UCSD SOBQ in 347 and 57 patients, respectively.

A pooled analysis of St Georges Respiratory Questionnaire (SGRQ) total scores in three studies (389 participants) showed a decline in HRQoL at 1 year to <2 years, with a mean increase of 3.65 (95% CI −1.46–8.76; high heterogeneity I^2=96%) [179, 187, 188]. Two studies provided insufficient data for inclusion in the meta-analysis, although the reported mean changes in the SGRQ total score were similar [15, 184]. Richeldi *et al.* [15] reported a mean increase of 4.39 to 5.48 for SGRQ total scores in 414 patients at 1 year. The mean increase of SGRQ total score at 60 weeks was 4.06 in a study of 57 patients by Parker *et al.* [184]. Two studies were pooled for analysis of mean changes in different SGRQ domain scores at 1 year: symptoms domain: 4.14 (95% CI 2.10–6.18); activity domain: 6.67 (95% CI 5.28–8.05); and impacts domain: 4.88 (95% CI 3.49–6.27) [15, 188].

Results on progression-free survival, respiratory-specific mortality, proportions of patients with a significant decline in lung function, dyspnoea measured using the Transition Dyspnoea Index and HRQoL measured using the EuroQol-5 Dinemsion are available in supplementary material S10.

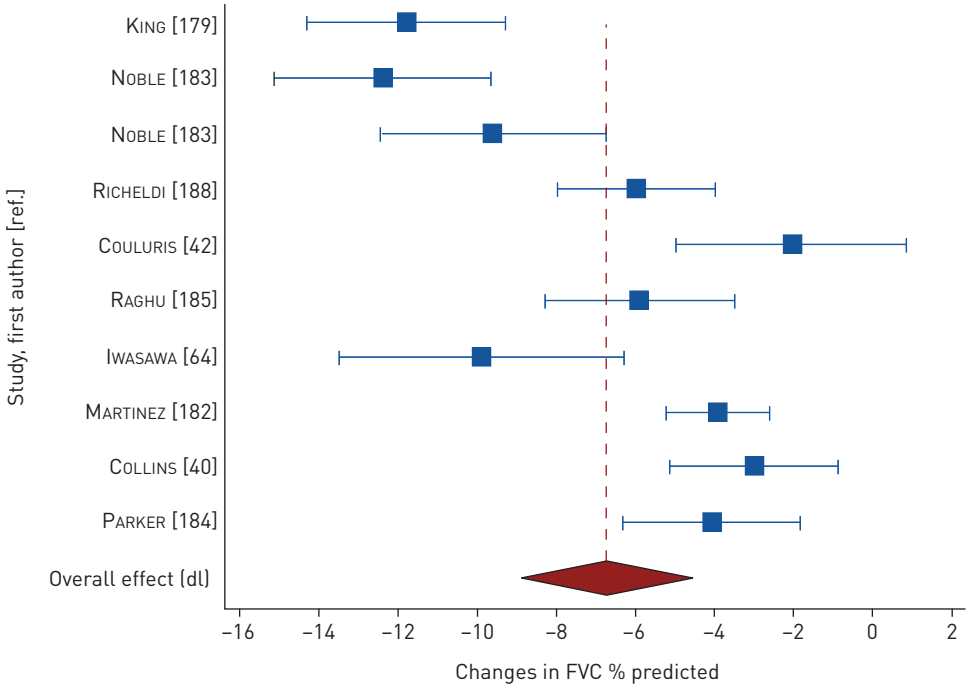

FIGURE 5 Pooled mean changes in forced vital capacity (FVC) at 1 year to <2 years.

Subgroup analyses

Analysis by study design

The RCT subgroup had a significantly lower mortality rate than the cohort study subgroup (0.07% *versus* 0.14%, p<0.0001) (figure E5). However, there was substantial heterogeneity between the studies within each subgroup. Subgroup analyses for pooled estimates of the proportion of mortality at other timeframes and survival duration were not performed owing to the lack of RCTs for these outcome measures. There

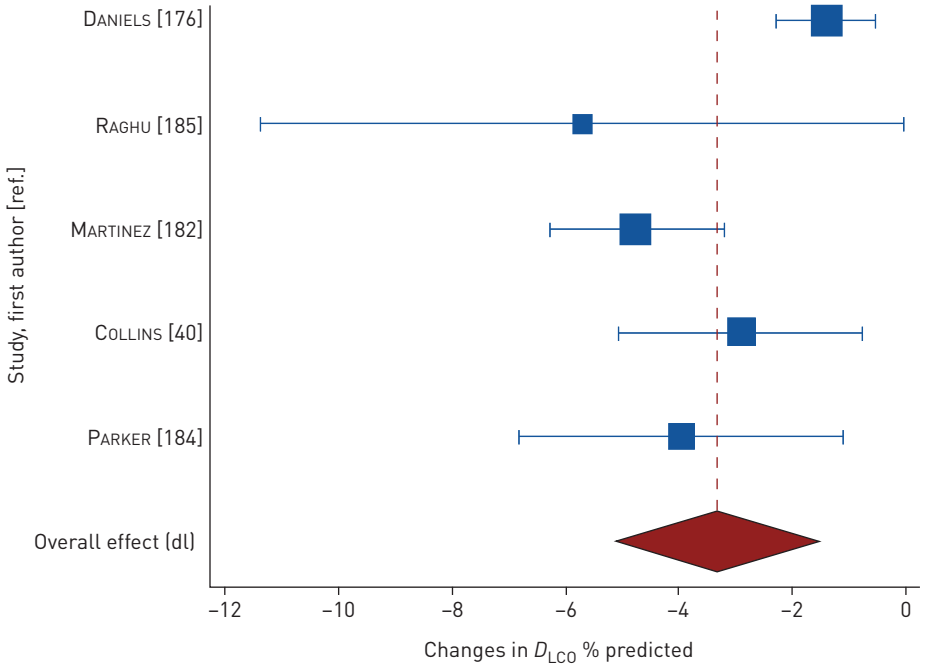

FIGURE 6 Pooled mean changes in diffusing capacity of the lung for carbon monoxide (D_{LCO}) at 1 year to <2 years.

was no statistically significant difference in the proportion of mortality at different timeframes between retrospective and prospective cohort studies (table 2).

Analysis by diagnostic criteria

At <2 years, the pooled proportions of mortality were 0.07 (95% CI 0.05–0.09), 0.10 (95% CI 0.06–0.15) and 0.18 (95% CI 0.15–0.22) for studies which diagnosed IPF based on the 2011 and 2000 consensus statements and other criteria, respectively. The test of overall interaction among these subgroups was statistically significant ($p<0.0001$). There was no significant difference in the proportion of mortality at other timeframes according to the diagnostic criteria (table 3).

Sensitivity analysis

Sensitivity analyses using studies with at least 50 participants diagnosed based on the consensus statement criteria revealed pooled proportions of mortality of 0.10 (95% CI 0.07–0.13) at 1 year to <2 years, 0.36 (95% CI 0.27–0.44) between 2 and 5 years, and 0.58 (95% CI 0.43–0.71) for ⩾5 years (figure E6). Tests of heterogeneity remained high in sensitivity analyses (range 92–95%). Sensitivity analyses for survival duration were not performed owing to the lack of studies meeting the specified criteria.

Discussion

This is the first systematic review with a meta-analysis of studies examining the prognosis of IPF. Collectively, overall survival rates for this population were 88% at 1 year to <2 years and 31% at ⩾5 years. The pooled estimate of mean survival, derived from a meta-analysis of two studies with follow-up durations of 10 years was 4 years. Respiratory-related causes and IPF accounted for 50% and 30% of deaths at 1 year to <2 years, respectively. At <2 years, FVC and D_{LCO} had fallen by an average of 7% predicted and 3% predicted, respectively. Dyspnoea worsened significantly over a period of <2 years, reaching the minimal important differences (MID) of 5 points using the UCSD SOBQ [190]. For HRQoL measured using the SGRQ, the mean activity domain score of 6.67 exceeded the MID of 5 at <2 years [191]. Although mean changes in total and other domain scores for SGRQ did not reach the MID, their CIs exceeded the MID. The mean decline in 6MWD was significant at 37 m, given a MID of 30 m [192].

This review confirmed the previously described poor prognosis of patients with IPF who have not received effective therapies. A recent editorial which incorporated a review of 24 study cohorts published between 2000 and 2017, each containing at least 50 consecutively enrolled participants with IPF, found an overall median survival of 3.2 years [193]. A meta-analysis of five clinical trials of pirfenidone *versus* placebo revealed 1-year overall mortality rate of 6.5% for the placebo group [194]. These results are similar to the

TABLE 2 Subgroup analyses for pooled analyses of the proportion of mortality according to study design

	Studies	Participants	Proportion	95% CI	Heterogeneity
1 year to <2 years					
Overall[#]	62	25770	0.12	0.09–0.14	I^2=95%
RCT	16	2420	0.07	0.05–0.09	I^2=75%
Prospective study	18	769	0.11	0.05–0.18	I^2=81%
Retrospective study	28	22581	0.16	0.13–0.19	I^2=95%
Test for heterogeneity between subgroups 0.36					
2 to <5 years					
Overall	35	20787	0.38	0.34–0.42	I^2=94%
Prospective study	18	1650	0.33	0.25–0.43	I^2=92%
Retrospective study	17	19092	0.43	0.38–0.47	I^2=93%
Test for heterogeneity between subgroups=0.08					
⩾5 years					
Overall	32	6369	0.69	0.59–0.78	I^2=98%
Prospective study	9	1060	0.58	0.38–0.78	I^2=97%
Retrospective study	23	5309	0.73	0.61–0.83	I^2=98%
Test for heterogeneity between subgroups=0.21					

Data are presented as n, unless otherwise stated. RCT: randomised controlled trial. [#]: included data from RCTs.

TABLE 3 Subgroup analyses for pooled analyses of the proportion of mortality

	Studies	Participants	Proportion	95% CI	Heterogeneity
1 year to <2 years					
Overall	62	25770	0.12	0.09–0.14	I^2=95%
2011 ATS/ERS/JRS/ALAT guideline	16	2283	0.07	0.05–0.09	I^2=72%
2000 ATS/ERS consensus statement	25	2382	0.10	0.06–0.15	I^2=92%
Other criteria	21	21105	0.18	0.15–0.22	I^2=92%
Test for difference between subgroups <0.0001					
2 to <5 years					
Overall	35	20787	0.38	0.34–0.42	I^2=94%
2011 ATS/ERS/JRS/ALAT guideline	4	1026	0.25	0.08–0.47	I^2=98%
2000 ATS/ERS consensus statement	13	995	0.42	0.37–0.47	I^2=54%
Other criteria	18	18766	0.38	0.33–0.43	I^2=94%
Test for difference between subgroups=0.17					
⩾5 years					
Overall	32	6369	0.69	0.59–0.78	I^2=98%
2011 ATS/ERS/JRS/ALAT guideline	4	326	0.62	0.38–0.83	I^2=93%
2000 ATS/ERS consensus statement	9	815	0.62	0.47–0.75	I^2=94%
Other criteria	19	5228	0.74	0.62–0.84	I^2=98%
Test for difference between subgroups=0.37					

Data are presented as n, unless otherwise stated. ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; ALAT: Latin American Thoracic Association.

findings from this review. The strength of this review lies in the large study populations from more than 28 countries on four continents, ranging from 6369 to 25799 participants. Given that the majority of studies are longitudinal cohort studies with participants selected from clinical settings, the survival outcomes in this study likely reflect real world data.

At <2 years, the pooled survival rate was significantly higher in the RCT subgroup than in the cohort study subgroup. This difference is likely due to differences in disease severity and patient characteristics of the study populations in RCTs and cohort studies. Patients included in RCTs predominantly had mild-to-moderate disease severity and fewer comorbidities, while cohort studies included real-world populations, including patients with end-stage IPF and multimorbidities. Interventions for IPF also differs between these two study populations. Some of these interventions, such as the combined use of prednisolone, azathioprine and N-acetylcysteine [195], may affect survival outcomes in IPF. Similarly, such variations likely explain differences in the pooled survival rates according to the diagnostic criteria. Approximately one-third of the studies for subgroups using the consensus statement diagnostic criteria were RCTs, while all studies for the subgroup using other diagnostic criteria were cohort studies.

Limitations

There are limitations with this review. There was statistically significant heterogeneity in pooled results, which was not explained by the subgroup analyses. This observed heterogeneity may be attributed to variations of clinical characteristics across study populations for pooled analyses, including duration of diagnosis, disease severity, comorbidities and patient characteristics. The overall quality of included studies was moderate. It is important to note that almost all studies had used clinical sampling rather than population sampling, which may limit the generalisability of the findings to a wider population. The risk of bias was increased by differences in assessment methods and reporting timing of outcome measures, limiting the ability to perform pooled analyses. The included studies, particularly cohort studies, had variable follow-up periods, which may have affected reported outcomes. Due to the limited data reported, subgroup analyses of survival duration based on follow-up periods were not possible. The quality of evidence for mortality and survival outcomes was moderate due to significant heterogeneity with inconsistency between studies. Sensitivity analyses, including only studies of at least 50 participants diagnosed according to well-established criteria, did not show any notable changes in the overall survival outcomes and degrees of heterogeneity. This suggests that there are other, as yet undocumented, sources of heterogeneity contributing to these outcomes. The quality of evidence for all other secondary outcomes was low to moderate due to substantial heterogeneity or fewer studies for pooled analyses, or both. This review did not include any studies which diagnosed IPF based on the latest 2018 consensus statement [12]. However, given the similarities in the diagnostic criteria between the 2011 and 2018 consensus

statements, findings from this review are relevant as references for IPF diagnosed using the 2018 consensus statement.

In conclusion, this review provides a comprehensive evaluation of all relevant studies regarding the prognosis of patients with IPF who either were untreated or had not received effective treatments. Without anti-fibrotic therapy, the overall survival rates for this condition are poor. Although limited by significant heterogeneity in study design and population, findings from this review can inform management discussions with patients and can provide a solid basis for comparisons in future studies with new therapies.

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