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Original Research

Impact of antifibrotic therapy on disease progression, all-cause mortality, and risk of acute exacerbation in non-IPF fibrosing interstitial lung diseases: evidence from a meta-analysis of randomized controlled trials and prospective controlled studies

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Abstract

Background: Nintedanib and pirfenidone are preferred pharmacological therapies for patients with idiopathic pulmonary fibrosis (IPF). However, evidence favoring antifibrotic therapy in patients with non-IPF fibrosing interstitial lung diseases (ILD) is limited.

Objective: To investigate the effects of antifibrotic therapy on disease progression, all-cause mortality, and acute exacerbation (AE) risk in patients with non-IPF fibrosing ILDs.

Design: Meta-analysis.

Data sources and methods: Electronic databases were searched for articles published before 28 February 2023. Studies that evaluated the efficacy of antifibrotic agents in patients with fibrosing ILDs were selected. The primary outcome was the disease progression risk, and the secondary outcomes included all-cause mortality and AE risk. The GRADE criteria were used for the certainty of evidence assessment.

Results: Nine studies with 1990 participants were included. Antifibrotic therapy reduced the rate of patients with disease progression (five trials with 1741 subjects; relative risk (RR), 0.56; 95% CI, 0.42–0.75; $p < 0.0001$; $I^2 = 0$; high-certainty evidence). Antifibrotic therapy did not significantly decrease all-cause mortality (nine trials with 1990 subjects; RR, 0.76; 95% CI, 0.55–1.03; $p = 0.08$; $I^2 = 0$; low-certainty evidence). However, in patients with progressive fibrosing ILDs (PF-ILD), antifibrotic therapy decreased all-cause mortality (four trials with 1100 subjects; RR, 0.69; 95% CI, 0.48–0.98; $p = 0.04$; $I^2 = 0$; low-certainty evidence).

Conclusion: Our study supports the use of antifibrotic agents in patients with PF-ILDs, which could slow disease progression and decrease all-cause mortality.

Trial registration: This study protocol was registered with PROSPERO (registration number: CRD42023411272).

Keywords: antifibrotic therapy, disease progression, fibrosing interstitial lung disease, meta-analysis, mortality

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Background

Interstitial lung diseases (ILDs) are a series of disorders, most, but not all, of which are characterized by interstitial inflammation or fibrosis.[1] It is estimated that over 200 separate conditions can lead to ILDs; however, disease progression, respiratory

failure, and eventual death are inevitable in many patients with ILDs, especially in those manifesting as fibrosing ILDs.

Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of fibrosing ILD, with a median untreated survival of only 3–5 years after diagnosis.[2] In recent years, nintedanib and pirfenidone have been shown to delay lung function decline and reduce mortality and acute exacerbations (AE) risk in patients with IPF.[3–5] As for other fibrosing ILDs, while appropriate management is efficacious in improving or stabilizing clinical symptoms, some patients still suffer from progressive fibrosis.[6] Considering the pathophysiological similarities between these diseases, researchers have speculated that non-IPF-fibrosing ILDs would have similar treatment responses to antifibrotic agents. However, the results of these clinical trials were not satisfactory. The SENSCIS and INBUILD trials showed that nintedanib could delay the decline in forced vital capacity (FVC) with no other clinical benefits observed in patients with systemic sclerosis-associated ILD (SSc-ILD) or progressive fibrosing ILDs (PF-ILD).[7,8] Meanwhile, two pirfenidone trials were prematurely terminated because of poor recruitment, and the conclusions may thereby be underpowered.[9,10] Although a meta-analysis suggested that the efficacy of antifibrotic therapy on changes in FVC between IPF and non-IPF PF-ILDs was similar,[11] two other recently published pooled analyses underlined that the current evidence favoring antifibrotic therapy in non-IPF PF-ILDs is weak.[12,13]

Therefore, we conducted this meta-analysis to further evaluate the efficacy of antifibrotic drugs in non-IPF-fibrosing ILDs. In contrast to previous studies, we mainly focused on the following outcomes: (1) progression of ILDs, (2) AE risk, and (3) all-cause mortality.

Methods

We performed and reported the meta-analysis and systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] The PRISMA checklist is provided in Supplemental Appendix E1. The PROSPERO registration number for this meta-analysis is CRD42023411272.

Two researchers were independently responsible for literature retrieval, data extraction, risk of bias evaluation, and certainty of evidence assessment of outcomes. A third researcher was consulted if a disputation could not be resolved through discussion.

Literature search and study selection

We performed a literature search without language restrictions using the following electronic databases: PubMed, Embase, Cochrane Library, and Web of Science. Articles published before 28 February 2023 were retrieved. The whole search strategy is presented in Supplemental Appendix E2. We also reviewed the references of previous publications related to our topic to avoid missing eligible studies.

Randomized controlled trials (RCT) and prospective controlled studies evaluating the efficacy of antifibrotic agents (nintedanib or pirfenidone) in patients with fibrosing ILDs were selected. Fibrosing ILDs included autoimmune-related, exposure-related, unclassifiable ILD.[1,15] Other ILDs characterized by chronic progressive fibrosis were also considered. The following studies were excluded: (1) those recruited patients aged $<$18 years; (2) those without complete data related to outcomes; and (3) published in the form of letters, comments, or conference abstracts.

Data extraction and risk of bias assessment

The extracted data included author name, publication year, region, study design, population characteristics of included study, sample size, intervention for treatment and control groups, and duration of follow-up.

We assessed the risk of bias for the RCTs using a tool recommended by the Cochrane Collaboration.[16] Each trial was considered to have a low, high, or unclear risk of bias according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel to the study protocol, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. A trial was regarded as high-risk if it had high risk of bias in any of the domains mentioned above. Trials with a low risk in all domains were regarded as having a low risk of bias. The other trials were categorized as having an unclear risk. The

Newcastle-Ottawa Scale (NOS) was used for quality evaluation of prospective controlled studies.[17,18] Details are presented in Supplemental Table E1. The scale consists of three parts, including the assessment of selection bias, information bias, and confounding bias. Additionally, publication bias was evaluated using Egger's test.

Outcomes and certainty of evidence evaluation

The primary outcome of this meta-analysis was the rate of disease progression. Secondary outcomes included all-cause mortality and risk of AE. The certainty of evidence was assessed using the GRADE criteria and classified as high, moderate, low, and very low according to risk of bias, inconsistency of results, indirectness of evidence, imprecision, and reporting bias.[19]

Data synthesis and statistical analysis

The Mantel-Haenszel method was used to pool the individual data. The random-effects model was selected considering the clinical heterogeneity across studies. The relative risk (RR) with a 95% confidence interval (95% CI) was selected as the effect measure. Forest plots were used to show individual and pooled results. *I*-squared (I^2) statistics were used to assess the heterogeneity. A leave-one-out sensitivity analysis was performed to check the robustness of the results. Subgroup analyses were conducted according to the drug (nintedanib vs. pirfenidone) and the type of fibrosing ILDs (non-progressive fibrosing ILDs versus PF-ILDs). PF-ILDs were defined based on worsening respiratory symptoms and physiological or radiological evidence of disease progression. We conducted all statistical analyses using Review Manager 5.3 (Nordic Cochrane Centre) and Stata 15.0 (StataCorp, College Station, Texas).

Results

Study selection and characteristics of eligible studies

6018 records in all were obtained. We screened the titles and abstracts of the articles and obtained 42 potentially eligible studies. We then reviewed the full text and included nine studies for quantitative synthesis. The study selection process is illustrated in Figure 1.

Seven RCTs and two prospective controlled studies were included, and the details are presented in Table 1. Two studies were from the United States,[20,21] two from China,[22,23] one from Germany,[9] and the other four were global multicenter studies.[7,8,10,24] These studies were published between 2002 and 2023. The participants were patients with fibrosing ILDs, and the sample sizes ranged from 21 to 663. The follow-up duration ranged from 24 to 52 weeks. The population characteristics of each study, including age, gender, lung function at baseline, and background therapy, are summarized in Table 2.

As there are currently no recognized criteria, the definitions of the progression of fibrosing ILDs differ. In four trials, disease progression was identified by the investigators based on the worsening of symptoms and lung function, as well as the extent of fibrosis on HRCT.[7,9,10,24] In the SENSCIS trial,[8] disease progression was defined as an absolute decline in FVC $\geqslant$ 10%. An absolute decline in FVC $\geqslant$ 10% has been consistently reported to be a strong death predictor in patients with fibrosing ILDs,[25–27] and it has been considered as evidence of progression in several clinical trials.[7]

Risk of bias assessment

Supplemental Figure E1 shows the results of the quality evaluation. Six trials[7–10,21,24] were considered to have a low risk of bias. One trial[20] was terminated prematurely because of futility and was therefore considered to have a high risk of bias. According to the NOS, two prospective controlled studies[22,23] were considered to be of high quality. Please see the details in Supplemental Table E2.

We found no significant publication bias based on the results of the funnel plots and Egger's test ($p = 0.598$). Please see the details of Supplemental Figures E2 and E3.

Meta-analysis

Disease progression: Five trials with 1741 participants reported results, including measurements of progression of ILDs.[7–10,24] Compared with placebo, antifibrotic agents reduced the rate of patients with disease progression (RR, 0.56;

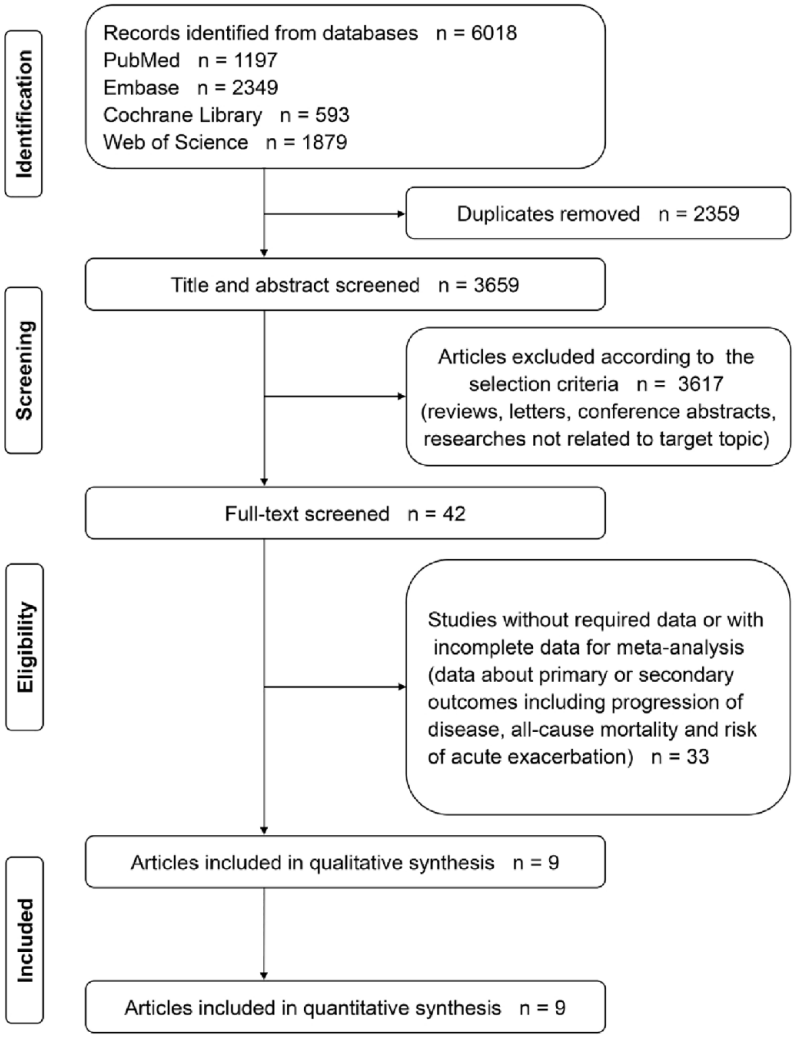

Figure 1. The flowchart of study selection.

95% CI, 0.42–0.75; $p < 0.0001$; $I^2 = 0$; see Figure 2). Additionally, the sensitivity analysis suggested the results were robust and unlikely to be influenced by any single trial (see Supplemental Figure E4). The results were consistent in patients with PF-ILDs [RR, 0.48; 95% CI, 0.34–0.68; $p < 0.0001$; $I^2 = 0$; see Figure 3(a)]. However, antifibrotic agents failed to significantly delay the disease progression in patients with non-progressive fibrosing ILDs [RR, 0.80; 95% CI, 0.48–1.33; $p = 0.39$; $I^2 = 0$; see Figure 3(a)]. Pirfenidone reduced the rate of patients with disease progression [RR, 0.55; 95% CI, 0.36–0.82; $p = 0.004$; $I^2 = 0$; see Figure 3(b)] while Nintedanib failed to significantly delay the disease progression [RR, 0.58; 95% CI, 0.29–1.18; $p = 0.13$; $I^2 = 67$; see Figure 3(b)].

All-cause mortality: Data on all-cause mortality were provided in nine studies (1900 participants).[7–10,20–24] In the overall population, antifibrotic therapy did not show benefits on survival (RR, 0.76; 95% CI, 0.55–1.03; $p = 0.08$; $I^2 = 0$; see Figure 4). We performed subgroup analyses according to the drug, and the results were consistent [RR, 0.72; 95% CI, 0.45–1.17; $p = 0.18$; $I^2 = 0$; and RR, 0.78; 95% CI, 0.52–1.18; $p = 0.25$; $I^2 = 0$; see Figure 5(b)]. Antifibrotic therapy had no impact in patients with non-progressive fibrosing ILDs [RR, 1.03; 95% CI, 0.54–1.95; $p = 0.93$; $I^2 = 0$; see Figure 5(a)]. However, in patients with PF-ILDs, antifibrotic therapy decreased all-cause mortality [RR, 0.69; 95% CI, 0.48–0.98; $p = 0.04$; $I^2 = 0$; see Figure 5(a)].

Table 1. Characteristics of included studies.

Study	Publication year	Region	Study design	Population	Sample size	Intervention, TG/CG	Treatment duration
INBUILD[7]	2019	Multicenter, 15 countries	Randomized, double-blind, placebo-controlled	Patients with non-IPF PF-ILD	663	Nintedanib (300 mg, daily)/ placebo	52-week
SENSCIS[8]	2019	Multicenter, 32 countries	Randomized, double-blind, placebo-controlled	Patients with SSc-ILD	576	Nintedanib (300 mg, daily)/ placebo	52-week
RELIEF[9]	2021	Multicenter, Germany	Randomized, double-blind, placebo-controlled	Patients with non-IPF PF-ILD	127	Pirfenidone (2403 mg daily)/ placebo	48-week
TRAIL1[10]	2023	Multicenter, 4 countries	Randomized, double-blind, placebo-controlled	Patients with RA-ILD	123	Pirfenidone (2403 mg daily)/ placebo	52-week
Maher *et al.*[24]	2020	Multicenter, 14 countries	Randomized, double-blind, placebo-controlled	Patients with unclassifiable PF-ILD	253	Pirfenidone (2403 mg daily)/ placebo	24-week
Wang *et al.*[22]	2022	Single-center, China	Prospective, open-label, controlled	Patients with CTD-ILD	111	Pirfenidone (1800 mg daily)/ no intervention	24-week
Li *et al.*[23]	2016	Single-center, China	Prospective, open-label, controlled	Patients with rapidly progressive ADM-ILD	57	Pirfenidone (1800 mg daily)/ placebo	12-month
O'Brien *et al.*[20]	2011	Single-center, United States	Randomized, double-blind, placebo-controlled	Patients with HPS-1 pulmonary fibrosis	35	Pirfenidone (2403 mg daily)/ placebo	12-month
Gahl *et al.*[21]	2002	Single-center, United States	Randomized, double-blind, placebo-controlled	Patients with HPS-1 pulmonary fibrosis	21	Pirfenidone (2400 mg daily)/ placebo	TG: 18.8 ± 14.8 months; CG: 23.2 ± 14.0 months

ADM-ILD, amyopathic dermatomyositis-associated interstitial lung disease; CG, control group; CTD-ILD, connective tissue disease-associated interstitial lung disease; HPS, Hermansky-Pudlak syndrome; IPF, idiopathic pulmonary fibrosis; PF-ILD, progressive fibrosing interstitial lung disease; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease; TG, treatment group.

Risk of AE: A double-blind, placebo-controlled trial conducted in 15 countries recruited 663 patients with non-IPF PF-ILDs.[7] The incidence of acute exacerbation or death at 52 weeks was 7.8% (26/332) in the treatment group (TG; nintedanib) and 9.7% (32/331) in the control group. The differences between the groups were not statistically significant (HR, 0.80; 95% CI, 0.48–1.34). Another multicenter, double-blind trial recruited 123 patients with RA-ILD from four countries.[10] The incidence of respiratory exacerbations at 52 weeks was 1.6% (1/63) in the TG (pirfenidone) and 3.3% (2/60) in the control group. The difference between the groups was not statistically significant ($p = 0.62$).

Certainty of evidence classification for outcomes

The GRADE evidence levels are presented in Table 3. For the RR of disease progression, the certainty of the evidence was regarded as high. For subgroup analyses of the RR of disease progression, the certainty of the evidence ranged from low to moderate. For the RR of all-cause mortality, the certainty of the evidence was low,

Table 2. Baseline information of subjects in each study.

Study	Age	Gender, male (%)	Lung function	Background therapy
INBUILD[7]	⩾18 years	TG: 53.9% CG: 53.5%	FVC ⩾ 45%, and DLCO 30–80%	Use of azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or glucocorticoids was allowed after 6 months of trial treatment
SENSCIS[8]	⩾18 years	TG: 23.3% CG: 26.3%	FVC ⩾ 40%, and DLCO 30–89%	Prednisone (10 mg/day) or mycophenolate or methotrexate for more than6 months
RELIEF[9]	18–80 years	TG: 67% CG: 51%	FVC 40–90%, and DLCO 10–90%	NA
TRAIL1[10]	18–85 years	TG: 60.3% CG: 65.0%	FVC ⩾ 40, and DLCO ⩾ 30%	Any management of RA-related pulmonary manifestations (e.g. cytotoxic, immunosuppressive) was not allowed
Maher *et al.*[24]	18–85 years	TG: 55% CG: 55%	FVC ⩾ 45, and DLCO ⩾ 30%	NA
Wang *et al.*[22]	⩾18 years	16.2%	FVC ⩽ 80%, or DLCO ⩽ 80%	Glucocorticoid and/or immunosuppressant at baseline
Li *et al.*[23]	TG: 46.3 ± 11.3 years CG: 51.8 ± 7.8 years	TG: 33.3% CG: 44.4%	NA	Glucocorticoid and/or immunosuppressant at baseline
O'Brien *et al.*[20]	TG: 41.5 ± 12.1 years CG: 34.0 ± 9.2 years	TG: 34.8% CG: 50.0%	FVC 51–85%	NA
Gahl *et al.*[21]	19–55 years	TG: 45.5% CG: 40.0%	FVC 40–75%	Use of high-dose steroids at baseline was not allowed

CG, control group; DLCO, diffusion lung capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; NA, not available; SD, standard deviation; TG, treatment group.

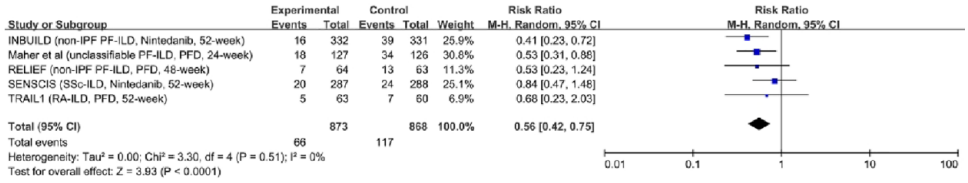

Figure 2. The relative risk of antifibrotic therapy on disease progression in patients with fibrosing interstitial lung diseases.

owing to the risk of bias. For subgroup analyses of the RR of all-cause mortality, the certainty of the evidence ranged from low to moderate.

Discussion

Main findings

After a systematic review of the current literature and meta-analyses of available data, we found that (1) antifibrotic therapy could slow the progression of fibrosing ILDs, (2) antifibrotic treatment might decrease the all-cause mortality in patients with PF-ILDs, and (3) no evidence currently supports that antifibrotic agents could decrease AE risk in patients with fibrosing ILDs.

Comparison with previous meta-analyses

We noticed two recently published meta-analyses (one for nintedanib and one for pirfenidone) that were related to this topic.[12] These two studies

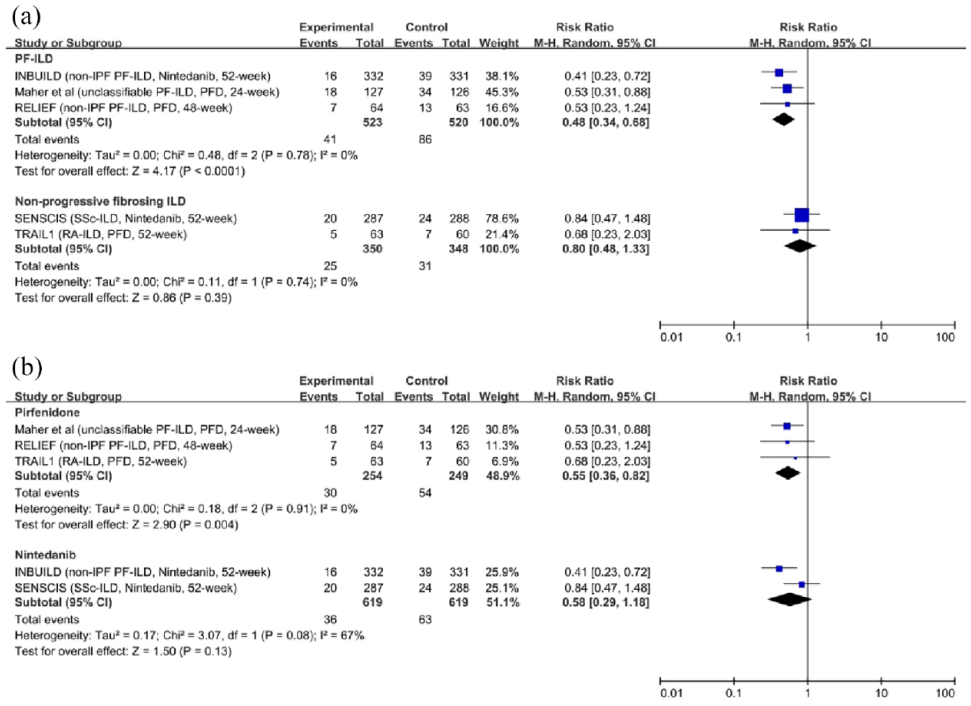

Figure 3. Subgroup analyses for the relative risk of disease progression. (a) The relative risk of antifibrotic therapy on disease progression in patients with progressive fibrosing interstitial lung diseases and non-progressive fibrosing interstitial lung diseases. (b) The relative risk of pirfenidone and nintedanib on disease progression in patients with fibrosing interstitial lung diseases.

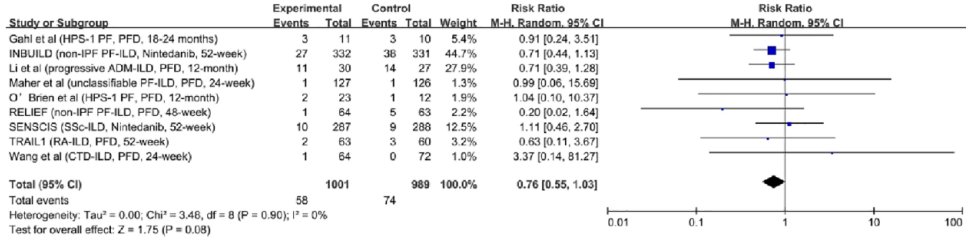

Figure 4. The relative risk of all-cause mortality in patients with fibrosing interstitial lung diseases who received antifibrotic therapy.

mainly focused on lung-function-related outcomes, similar to the initial trials. However, the certainty of evidence for most outcomes ranged from very low to low owing to the limited number of included studies (two in each). Considering the similar antifibrotic effects of nintedanib and pirfenidone, we pooled data from studies related to both drugs to investigate the impact of antifibrotic therapy on fibrosing ILDs. The present meta-analysis included five trials with a low risk of bias and indicated that antifibrotic agents delayed the disease progression (high-certainty evidence). We found no significant heterogeneity across the trials, and the results of the sensitivity analysis were consistent with those of the primary quantitative synthesis. Further sub-analyses indicated that the effect of antifibrotic therapy on disease progression differed between the groups. However, the certainty of the evidence for these sub-analyses was downgraded due to imprecision, and the conclusion may be statistically insignificant.

Although mortality is a vital outcome for the efficacy evaluation of antifibrotic agents in patients

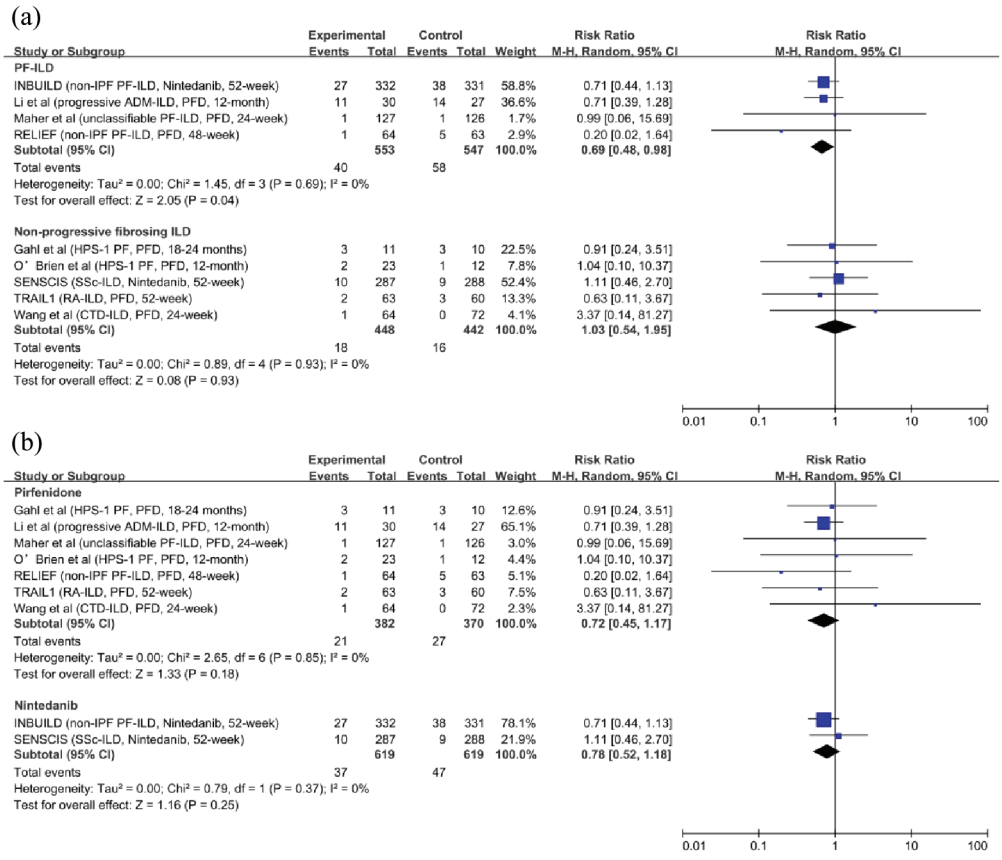

Figure 5. Subgroup analyses for the relative risk of all-cause mortality. (a) The relative risk of antifibrotic therapy on all-cause mortality in patients with progressive fibrosing interstitial lung diseases and non-progressive fibrosing interstitial lung diseases. (b) The relative risk of pirfenidone and nintedanib on all-cause mortality in patients with fibrosing interstitial lung diseases.

with fibrosing ILDs, there are only a few records of death in initial trials owing to insufficient sample size and follow-up. A meta-analysis by Petnak *et al.* showed that antifibrotic therapy decreases AE risk and mortality in patients with IPF.[5] The present study indicated that patients with fibrosing ILDs did not benefit from antifibrotic treatment on survival, which is coincidence with those of a previous pooled analysis.[11] However, our meta-analysis included more studies, and the subgroup analysis suggested that mortality decreased significantly in patients with PF-ILDs treated with antifibrotic agents. Although one prospective controlled study was also pooled for quantitative analysis, in which the risk of bias was high due to the lack of blinding, the outcome (i.e. mortality) was less likely to be influenced. In addition, only two studies were included in the analysis of AE risk, and the conclusions may lack statistical power.

Implications for clinical practice

According to the recent ATS/ERS/JRS/LATS clinical practice guidelines, nintedanib and pirfenidone are the preferred pharmacological therapies for patients with IPF.[27] With regard to PF-ILDs, the guideline committee merely made a 'conditional recommendation' for the use of nintedanib and suggested the need for more research. Our meta-analysis suggests that patients with PF-ILDs could benefit from antifibrotic treatment in terms of total survival and maintenance of their condition. Therefore, the timely identification of patients whose fibrosing ILDs are progressing is of great importance, and antifibrotic agents could be a potential therapeutic strategy for these patients. A previous study found that patients with IPF treated with nintedanib had a higher risk of respiratory-related hospitalization and all-cause mortality.[29] However, another observational study identified no differences in

Table 3. Certainty of evidence for each outcome.

Outcome	Number of patients	RR	95% CI	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence
Relative risk of disease progression	1741	0.56	0.42–0.75	No	No	No	No	No	High
Relative risk of disease progression in patients with PF-ILDs	1043	0.48	0.34–0.68	No	No	No	Yes	No	Moderate
Relative risk of disease progression in patients with non-progressive ILDs	698	0.80	0.48–1.33	No	No	No	Yes	No	Moderate
Relative risk of pirfenidone on disease progression in patients with fibrosing ILDs.	503	0.55	0.36–0.82	No	No	No	Yes	No	Moderate
Relative risk of nintedanib on disease progression in patients with fibrosing ILDs	1238	0.58	0.29–1.18	No	Yes	No	Yes	No	Low
Relative risk of all-cause mortality	1990	0.76	0.55–1.03	Yes	No	No	No	No	Low
Relative risk of all-cause mortality in patients with PF-ILDs	1100	0.69	0.48–0.98	Yes	No	No	No	No	Low
Relative risk of all-cause mortality in patients with non-progressive fibrosing ILDs	890	1.03	0.54–1.95	Yes	No	No	No	No	Low
Relative risk of pirfenidone on all-cause mortality in patients with fibrosing ILDs.	752	0.72	0.45–1.17	Yes	No	No	No	No	Low
Relative risk of nintedanib on all-cause mortality in patients with fibrosing ILDs	1238	0.78	0.52–1.18	No	No	No	Yes	No	Moderate

AE, acute exacerbation; CI, confidence interval; ILD, interstitial lung diseases; PF-ILD, progressive fibrosing interstitial lung disease; RR, relative risk.

patient-related outcomes between the two drugs.[30] Currently, it is difficult to determine which agent is superior, and further studies are required.

Additionally, current evidence favoring antifibrotic treatment in patients with non-progressive fibrosing ILDs is limited. Although the SENSCIS trial and another multicenter real-world study showed that nintedanib could slow the decline in lung function in patients with SSc-ILD,[8,31] significant adverse gastrointestinal events should also be considered. Thus, clinicians should fully weigh the advantages and disadvantages while managing these patients, which is critical to prognosis.

Strength and limitations

This is the latest and most comprehensive meta-analysis designed to evaluate the effects of antifibrotic agents on disease progression, mortality, and the risk of AE. We performed the analyses in strict compliance with the PRISMA guidelines and identified potential participants who would show a better treatment response to antifibrotic agents. Moreover, the GRADE score was used to assess the certainty of evidence for the outcomes to make clinical decisions.

An obvious limitation of our meta-analysis is that the findings were based on a pooled analysis of aggregate data reported in previous studies rather than individual data. The definitions of disease progression differed among the studies, which could have led to bias. Selection bias may also exist, considering that the diagnosis of PF-ILD varied among the trials. Although different criteria were employed, the included studies recruited eligible participants based on worsening respiratory symptoms and physiological or radiological evidence of disease progression. This is roughly consistent with the consensus recommendations,[28] and could help identify patients whose disease has progressed similarly. Therefore, the results of our study may be applicable to patients with ILDs who manifest with progressive fibrosis.

Furthermore, because the included studies were limited, stratified analyses according to different baseline characteristics were not conducted. Several subgroup analyses of the INBUILD and SENSCIS trials have indicated that the protective effects of nintedanib on lung function are not subject to race, background treatment, and cause of ILDs.[32–34] Nevertheless, whether the association between antifibrotic therapy and reduced mortality is modified by specific factors needs to be clarified in future studies.

Conclusion

Antifibrotic treatments can reduce the rate of disease progression. However, it should be noted that the definition of disease progression was established mainly based on the worsening of symptoms, lung function, and extent of fibrosis on HRCT. We also found that antifibrotic treatment might decrease all-cause mortality in patients with PF-ILDs, although the certainty of the evidence is low. Our study supports the routine use of antifibrotic agents in these patients, as no preferred therapeutic strategies are currently available.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

De-yu Li: Investigation; Methodology; Writing – original draft.

Xin Liu: Data curation; Formal analysis; Investigation; Methodology.

Jing-yi Huang: Investigation; Methodology; Resources.

Wen-lu Hang: Writing – review & editing.

Gu-ran Yu: Conceptualization.

Yong Xu: Conceptualization.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data relevant to the study are included in the article or uploaded as supplementary imformation.

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Supplemental material

Supplemental material for this article is available online.

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