

Effectiveness of antifibrotics on health-related quality of life in patients with interstitial lung disease: a systematic review and meta-analysis

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Abstract

Background: Interstitial lung disease (ILD) leads to progressive lung function decline and significant respiratory symptoms. Although antifibrotic agents preserve lung function and reduce mortality in ILD, their impact on health-related quality of life (HRQoL) remains unclear.

Objectives: We aimed to evaluate whether antifibrotic agents improve HRQoL and their effectiveness in treating HRQoL-related symptoms in patients with ILD.

Design: Systematic review and meta-analysis.

Data sources and methods: A literature search was conducted using MEDLINE, EMBASE, and the Cochrane Library from inception to August 25, 2025. The search included terms related to ILD, antifibrotic agents, and measures of HRQoL. HRQoL outcomes were assessed using the St. George's Respiratory Questionnaire (SGRQ), including total and domain scores. Data were pooled using a random-effects model, with outcomes reported as mean differences (MD) or relative risks (RR) and heterogeneity evaluated using the I^2 statistic.

Results: A total of 13 randomized controlled trials were included. Antifibrotic agents showed significant improvement in SGRQ scores, particularly in the symptom (MD: -2.59 , 95% confidence interval [CI]: -4.56 to -0.61 ; $I^2=32\%$) and activity (MD: -2.88 , 95% CI: -4.82 to -0.94 ; $I^2=34\%$) domains. Antifibrotics reduced the rate of cough (RR: 0.77 , 95% CI: 0.64 – 0.94 ; $I^2=0\%$) and dyspnea (RR: 0.71 , 95% CI: 0.56 to 0.89 ; $I^2=0\%$). However, fatigue was frequently observed in patients treated with antifibrotics (RR: 1.48 , 95% CI: 1.20 – 1.83 ; $I^2=0\%$) compared with the non-antifibrotic group. Most trials were judged to have low-to-moderate risk of bias, and the certainty of evidence was rated very low for total SGRQ scores but low to moderate for domain-specific outcomes and symptoms.

Conclusion: Antifibrotic agents may improve HRQoL and reduce dyspnea and cough in patients with ILD, but the certainty of evidence is low, and they may increase fatigue, requiring careful monitoring.

Trial registration: The study protocol was registered in PROSPERO (CRD42023450917).

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Plain language summary

Do antifibrotic drugs help people with lung disease feel better in daily life?

Interstitial lung disease (ILD) is a group of diseases that cause scarring in the lungs. This scarring makes it harder to breathe and can lead to symptoms like coughing, shortness of breath, and feeling very tired. These symptoms can affect a person's daily life and overall well-being. Doctors often use antifibrotic medications (such as pirfenidone and nintedanib) to slow down the lung damage in ILD. These drugs can help prevent the lungs from

getting worse over time. But it hasn't been clear whether these treatments actually help patients feel better in their daily lives. To find out, we looked at the results of 13 clinical trials that included nearly 4,500 people with ILD. We focused on how these medications affected symptoms like breathlessness and coughing, as well as how patients felt overall. We also looked at treatment-related problems, especially tiredness (fatigue), which is common in people with lung disease. We found that people who took antifibrotic medications had some improvement in their breathing and physical activity. They also coughed less and felt less short of breath compared to people who didn't take these drugs. However, many people who took antifibrotics reported feeling more tired than those who didn't. In summary, antifibrotic medications may help people with ILD feel better in some ways, especially by improving breathing and reducing coughing. But they can also make people feel more tired. These benefits and side effects should be discussed between patients and their doctors to make the best treatment decisions. However, because the studies done so far are not very large and sometimes give mixed results, we cannot be completely sure yet. More research will help us understand better.

Keywords: antifibrotic agents, health-related quality of life, idiopathic pulmonary fibrosis, interstitial lung disease, patient-reported outcome measures

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Introduction

Interstitial lung disease (ILD) encompasses a diverse group of lung diseases that affect the interstitium. ILD is characterized by inflammation and fibrosis in the lung parenchyma, leading to a progressive decline in lung function with respiratory and systemic symptoms.¹ ILD has various subtypes, including idiopathic pulmonary fibrosis (IPF), the most common subtype in the idiopathic interstitial pneumonia, connective tissue disease-associated ILD, hypersensitivity pneumonitis (HP), drug-induced ILD, and ILD due to environmental exposure.² The common symptom experienced by patients with ILD is respiratory distress, which can significantly limit daily activities and lead to fatigue and discomfort. This is often concomitant with symptoms of depression and anxiety, thereby markedly affecting patients' overall quality of life (QoL).^{3,4} A meta-analysis of health-related QoL (HRQoL) in patients with IPF demonstrated the substantial negative impact of the disease on HRQoL.⁵ Consequently, evaluating HRQoL using patient-reported outcome measures (PROMs) is crucial for effective management of patients with ILD.

The antifibrotic pirfenidone and nintedanib have been shown to effectively maintain lung function, reduce mortality, and lower the risk of acute exacerbation in patients with IPF.^{6,7} Antifibrotics have also demonstrated comparable efficacy in fibrotic ILD, particularly in cases marked by progressive pulmonary fibrosis or a usual interstitial pneumonia pattern.^{8,9} However, the use of antifibrotics in patients with ILD can cause several adverse effects, such as appetite loss, diarrhea, and photosensitivity, potentially deteriorating their HRQoL.^{10,11} Several studies have investigated the use of antifibrotic treatment in patients with IPF or ILD. However, due to inconsistent results, the effectiveness of antifibrotics on HRQoL remains unclear. Although numerous systematic reviews have examined antifibrotics,^{12–17} most have primarily focused on mortality or physiological outcomes such as lung function, with limited assessment of HRQoL or patient-reported outcomes. Moreover, none have comprehensively evaluated the certainty of evidence across PROM domains. Thus, this study aimed to systematically review and meta-analyze the effectiveness of antifibrotic agents on HRQoL in patients with ILD, focusing on PROM-measured

outcomes and key quality-of-life symptoms such as dyspnea, cough, and fatigue.

Methods

Literature search

A comprehensive literature search was conducted using the electronic databases of MEDLINE via PubMed, EMBASE, and Cochrane Library. The final search was performed on August 25, 2025. The search strategy included the following MeSH terms, Emtree terms, and synonyms related to “interstitial lung disease,” “interstitial pulmonary disease,” “idiopathic pulmonary fibrosis,” “antifibrotic agent,” and specific antifibrotic agents such as “pirfenidone” and “nintedanib.” Searches were limited to peer-reviewed articles published in English. The complete search strategies for each database, including Boolean operators and filters, are shown in Supplemental Tables 1–3, in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA-S) guideline.¹⁸ In addition, the reference lists of the selected articles and relevant reviews were manually searched to identify eligible studies. This meta-analysis followed the guidelines outlined in the PRISMA 2020 and the PRISMA-S extension.^{18,19} The study protocol was registered in PROSPERO (CRD42023450917). This study analyzed existing literature, not human subjects, and was thus exempt from the Institutional Review Board.

Inclusion and exclusion criteria

The inclusion criteria for the studies were as follows: (1) randomized controlled trials (RCTs); (2) patients diagnosed with ILD aged 18 years or older; (3) use of pirfenidone or nintedanib as intervention and placebo as control; (4) outcomes including HRQoL measures; (5) studies written in English. The exclusion criteria were as follows: (1) animal studies or in vitro studies; (2) conference abstracts or posters without full texts. In cases where a study reported subgroup analyses, we ensured that participants were not double counted by including only one nonoverlapping dataset per outcome in the main analysis, prioritizing the dataset with the larger sample size.

Study selection, data extraction, and quality assessment

Two independent reviewers (J.L. and S.P.) screened the titles and abstracts of studies to

check for eligibility. Full-text articles of relevant studies were retrieved and assessed for inclusion. Discrepancies were resolved through discussion or consultation with a third reviewer (H-Y.Y.). Each study was evaluated based on predefined eligibility criteria. Data were extracted using a standardized form that included general study characteristics, participant demographics, intervention details, HRQoL measurement tools and outcomes, and occurrence of patient-reported symptoms following medication administration. The primary outcome was the mean difference (MD) in HRQoL scores between the intervention and control groups at follow-up. HRQoL was evaluated using various PROMs, including the St. George's Respiratory Questionnaire (SGRQ), King's Brief Interstitial Lung Disease (K-BILD) questionnaire, University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ), Baseline Dyspnea Index-Transition Dyspnea Index (BDI-TDI), and Fletcher-Hugh-Jones (F-H-J) score. Results reported as medians were converted to means and standard deviations for inclusion in the analysis. When the median and range were available, the method proposed by Hozo *et al.*,²⁰ was applied, whereas when the median and interquartile range were reported, the approaches described by Wan *et al.*,²¹ and Luo *et al.*²² were used. We also analyzed patient-reported symptoms related to antifibrotics, such as cough, fatigue, and dyspnea, that could affect HRQoL. In cases where a single publication reported results independently for different participant populations, each population was analyzed as a separate study. When multiple time points were reported, we used the latest on-treatment assessment common to both arms. In cases where a single study reported multiple PROMs, we prioritized the PROM with more available data across all included studies for the standardized MD (SMD) analysis.

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2 tool for RCTs.²³ This tool evaluates five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was judged as having a low, high risk, or some concerns. Two independent reviewers conducted the assessments and resolved any disagreements

through discussion and consensus. The certainty of the evidence for the RCTs was also assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was rated as high, moderate, low, or very low based on these criteria. Two reviewers (J.L. and S.P.) independently performed the assessments, and disagreements were resolved by consensus.

Data synthesis and statistical analysis

A narrative synthesis of the included studies was conducted to summarize the key findings of the effectiveness of antifibrotics on HRQoL. For the meta-analysis, HRQoL outcomes were pooled using a random-effects model to account for heterogeneity among studies. Changes in HRQoL scores were reported as MD for the same assessment tools and SMD for different assessment tools. For pooled SMDs across different PROMs, we harmonized scale directions so that negative effects reflect improvement in HRQoL. Binary outcomes, such as symptoms, were expressed as relative risks (RR). Statistical heterogeneity was evaluated using the I^2 statistic, with values of $\geq 75\%$ indicating substantial heterogeneity. Subgroup analyses (medication type [pirfenidone vs nintedanib], and ILD type [IPF vs non-IPF]) were conducted to assess heterogeneity. Publication bias was assessed using funnel plots or Egger's test for overall dyspnea scales, as ≥ 10 studies were included. Data synthesis and analysis were performed using R Statistical Software (version 4.3.2; The R Foundation for Statistical Computing, Vienna, Austria) and RevMan software (version 5.4; The Cochrane Collaboration, Oxford, UK), with a p value of < 0.05 considered statistically significant.

Results

Study selection

A total of 5252 records were identified. After removing duplicates, 4657 records remained. The remaining records were screened based on the titles and abstracts, resulting in the exclusion of 4606 studies that did not meet the inclusion criteria. The full texts of the remaining 48 studies were assessed for eligibility, and 35 studies were excluded for reasons including lack of intervention

($n=6$), nonreporting of appropriate outcome ($n=9$), duplicate study populations ($n=5$), cohort subgroup analyses ($n=11$), and non-RCTs ($n=4$). The final meta-analysis included 13 studies. A PRISMA flow diagram detailing the study selection process is presented in Figure 1.

Study characteristics

All 13 studies were published between 2011 and 2025 and conducted across various regions (Table 1). The total sample size across all studies was 4491, with individual study sizes ranging from 22 to 1061. The mean age of participants ranged from 53.4 to 68.8 years, with the males comprising 60.2% of the total population. Among the studies, when classified by ILD subtypes, seven were IPF studies, and six were non-IPF studies. By medication type, eight studies evaluated pirfenidone and five assessed nintedanib. HRQoL outcomes were reported using various instruments, including the SGRQ ($n=8$), UCSD-SOBQ ($n=4$), K-BILD ($n=1$), BDI-TDI ($n=1$), A Tool to Assess QoL-IPF ($n=1$), EuroQoL-visual analog scale ($n=1$), and F, H-J dyspnea score ($n=1$). Symptoms of cough were reported in six studies, dyspnea in five studies, and fatigue in seven studies.

In the overall patient population, antifibrotics marginally reduced SGRQ total score compared with controls, but the reduction was not statistically significant (MD: -1.61 , 95% confidence interval [CI]: -3.35 to 0.13 , $p=0.07$; $I^2=51\%$; Figure 2(a)), and did not reach the minimum clinically important difference (MCID) of 4 points. Subgroup analysis revealed a statistically significant reduction of SGRQ total scores in the pirfenidone group (MD: -2.66 , 95% CI: -4.98 to -0.34 ; $I^2=0\%$), though this also remained below the MCID threshold, but not with the nintedanib group (Figure 2(b)). In addition, no differences were observed based on ILD type (Figure 2(c)).

In the analysis according to SGRQ domains, patients treated with antifibrotics exhibited lower SGRQ scores in both symptom (MD: -2.59 , 95% CI: -4.56 to -0.61 ; $I^2=32\%$) and activity domain (MD: -2.88 , 95% CI: -4.82 to -0.94 ; $I^2=34\%$) compared with untreated patients (Supplemental Figures 1 and 2). There were no differences between antifibrotic type and ILD types in the symptom domain (Supplemental

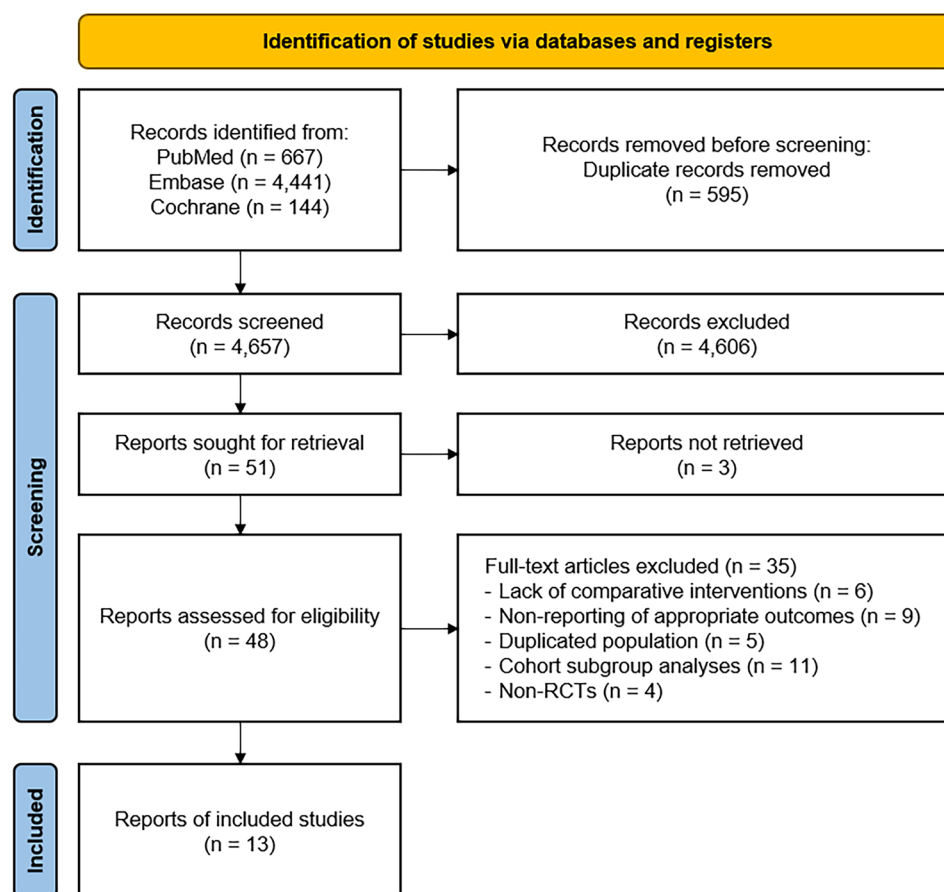


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the study selection process.

Figure 1). On the other hand, a significant improvement was observed in the activity domain for the nintedanib (MD: -3.20 , 95% CI: -5.90 to -0.50 ; $P=50\%$), not for the pirfenidone group (Supplemental Figure 2). In addition, a significant reduction in SGRQ was found in the IPF group (MD: -3.20 , 95% CI: -5.90 to -0.50 ; $P=50\%$), but not in the non-IPF group. However, no differences in the SGRQ impact domain were found between the antifibrotics and no antifibrotics groups (Supplemental Figure 3). Certainty was very low for total SGRQ scores due to risk of bias, heterogeneity, and imprecision, while domain-specific scores ranged from low to moderate (Supplemental Table 4).

Analysis of dyspnea scales using SMD demonstrated significant improvement in patients treated with antifibrotics (SMD: -0.16 , 95% CI: -0.29 to -0.04 ; $P=60\%$; Figure 3(a)), with low certainty (Supplementary Table 4). Subgroup

analysis revealed significant improvements only in the pirfenidone group (SMD: -0.28 , 95% CI: -0.50 to -0.07 ; $P=50\%$) and IPF group (SMD: -0.23 , 95% CI: -0.39 to -0.07 ; $P=59\%$) with no significant changes in the nintedanib or non-IPF group (Figures 3(b) and (c)). Visual inspection of the funnel plot did not reveal obvious asymmetry (Supplemental Figure 4). Consistently, Egger's linear regression test showed no evidence of small-study effects ($t=-1.62$, $df=11$, $p=0.13$), suggesting that publication bias was unlikely.

Impact of antifibrotics on patient-reported symptoms

The incidence of cough was significantly lower in patients treated with antifibrotics compared with those without antifibrotics (RR: 0.77 , 95% CI: 0.64 – 0.94 ; $P=0\%$; Figure 4(a)), with moderate certainty (Supplemental Table 4). Subgroup

Table 1. Characteristics of the included studies.

Author, year and references	Study	Enrollment period	Design	ILD type	Intervention	Follow-up time (weeks)	Population		
							Number		Age
							Antifibrotics	Placebo	Antifibrotics
Richeldi et al., 2011 ²⁴	TOMORROW	2007–2010	RCT	IPF	Nin 150 mg twice	52	85	85	65.4 ± 7.8
Noble et al., 2011 ²⁵	CAPACITY	2006–2008	RCT	IPF	PFD 2403 mg/d	72	345	347	66.3 ± 8
Nathan et al., 2019 ²⁶	CAPACITY advanced	2006–2008, 2011–2013	RCT	IPF	PFD 2403 mg/d	52	90	80	70 (46–80)
Azuma et al., 2011 ²⁷	NA	2005–NA	RCT	IPF	PFD 1200/1800 mg/d	52	430	104	65.0 ± 6.7
Richeldi et al., 2014, ⁶ Taniguchi et al., 2016, ²⁸ Azuma et al., 2017, ²⁹ Kolb et al., 2017, ³⁰ Xu et al., 2019, ³¹ Ryerson et al., 2019, ³² Richeldi et al., 2020 ³³	INPULSIS	2011–2013	RCT	IPF	Nin 150 mg twice	52	638	423	66.6 ± 8.1
Flaherty et al., 2019, ⁸ Inoue et al., 2023 ³⁴	INBUILD	2017–2019	RCT	PF-ILD	Nin 150 mg twice	52	332	331	65.2 ± 9.7
Distler et al., 2019, ³⁵ Azuma et al., 2021, ³⁶ Highland et al., 2021, ³⁷ Kuwana et al., 2021, ³⁸ Volkman et al., 2022 ³⁹	SENSCIS	2015–2018	RCT	SSc-ILD	Nin 150 mg twice	52	288	288	54.6 ± 11.8
Huang et al., 2015 ⁴⁰	NA	2012–2013	RCT	IPF	PFD 1800 mg/d	48	38	38	59.0 ± 5.94
Lancaster et al., 2020 ⁴¹	NA	2013–2014	RCT	IPF	Nin 150 mg twice	24	56	57	68.8 ± 7.6
Maher et al., 2020 ⁴²	NA	2017–2018	RCT	PF-ILD	PFD 2403 mg/d	24	127	126	70 (61–76)
Acharya et al., 2020 ⁴³	NA	2017–2018	RCT	SSc-ILD	PFD 600–2400 mg/d	24	17	17	42 (26–55)
Mateos-Toledo et al., 2020 ⁴⁴	NA	2015–2017	RCT	cHP	PFD 900 mg twice	48	13	9	55 ± 7
Behr et al., 2021 ⁹	RELIEF	2016–2018	RCT	PF-ILD	PFD 267 mg, 534 mg, 801 mg tid	48	64	63	63.2 ± 10.6

Data are presented as mean ± standard deviation, median [interquartile range], or number (%) except for [*] mmol/min/kPa.

ATAQ-IPF, A Tool to Assess Quality of Life in idiopathic pulmonary fibrosis; BDI-TDI, Baseline Dyspnea Index-Transition Dyspnea Index; cHP, chronic hypersensitivity pneumonitis; DLco, diffusing capacity for carbon monoxide; EQ-VAS, EuroQol-visual analog scale; F, H-J, Fletcher, Hugh-Jones; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease; NA, not available; Nin, nintedanib; PFD, pirfenidone; PF-ILD, progressive fibrosing interstitial lung disease; PROMs, patient-reported outcome measures; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UCSD-SOBQ, University of California, San Diego Shortness of Breath Questionnaire. Impact of antifibrotics on HRQoL; TID, ter in die.

analysis demonstrated a significant reduction in cough in the nintedanib group (RR: 0.77, 95% CI: 0.61–0.97; $I^2 = 16\%$), and the non-IPF group (RR: 0.70, 95% CI: 0.52–0.93; $I^2 = 0\%$; Figures 4(b) and (c)). Since the pirfenidone group included one study, a meta-analysis was not performed.

Dyspnea was less frequent in the group treated with antifibrotics than in those not treated with antifibrotics (RR: 0.71, 95% CI: 0.56 to 0.89; $I^2 = 0\%$; Figure 5), with moderate certainty (Supplementary Table 4). Subgroup analysis showed that a significant reduction in dyspnea was observed in the nintedanib group (RR: 0.71,

Placebo	Male		PROMs	Baseline FVC		Baseline DLco	
	Antifibrotics	Placebo		Antifibrotics	Placebo	Antifibrotics	Placebo
64.8 ± 8.6	65 [76.5]	63 [74.1]	SGRQ	79.1 ± 18.5	81.7 ± 17.6	3.7 ± 1.0*	3.8 ± 1.1*
66.6 ± 7.7	241 [69.9]	252 [72.6]	UCSD-SOBQ	74.7 ± 13.9	74.5 ± 14.9	47.0 ± 9.7	46.8 ± 9.7
69 [40–80]	74 [82.2]	59 [73.8]	UCSD-SOBQ	59.2 [53.8–67.9]	64.2 [56.4–75.8]	32.5 [30.8–34.5]	32.1 [30.9–33.8]
64.7 ± 7.3	132 [81.0]	81 [77.9]	F, H-J classification dyspnea	77.0 ± 17.5	79.1 ± 17.4	52.5 ± 17.6	55.2 ± 18.2
67.0 ± 7.9	507 [79.5]	334 [79.0]	SGRQ	79.7 ± 17.6	79.3 ± 18.2	47.4 ± 13.5	47.0 ± 13.4
66.3 ± 9.8	179 [53.9]	177 [53.5]	K-BILD	68.1 ± 16.0	69.3 ± 15.2	44.4 ± 11.9	47.9 ± 15.0
53.4 ± 12.6	67 [23.3]	76 [26.4]	SGRQ	72.4 ± 16.8	72.7 ± 16.6	52.9 ± 15.1	53.2 ± 15.1
61.6 ± 6.3	33 [86.8]	38 [100.0]	SGRQ	75.6 ± 14.7	79.0 ± 18.3	47.4 ± 12.7	47.7 ± 13.8
66.2 ± 9.4	45 [80.4]	37 [64.9]	SGRQ, UCSD-SOBQ	78 ± 17.4	78.1 ± 19.4	53.6 ± 13.6	52.5 ± 14.7
69 [63–74]	70 [55]	69 [55]	SGRQ, UCSD-SOBQ	71.0 [59.0–87.3]	71.5 [58.0–88.0]	44.6 [36.9–53.5]	48 [38.4–59.0]
40 [20–63]	0 [0.0]	3 [17.6]	BDI-TDI	65 [51–75]	62.7 [52–78]	45 [35–65]	50 [34–89]
57 ± 9	2 [15.4]	4 [44.4]	SGRQ, ATAQ-IPF, EQ-VAS	59 ± 15	62 ± 20	47 ± 23	59 ± 14
63.5 ± 9.1	43 [67.2]	32 [50.8]	SGRQ	62.6 ± 14.5	62.2 ± 13.5	38.1 ± 14.1	37.7 ± 14.2

95% CI: 0.55–0.93; $I^2=0\%$) and the IPF group (RR: 0.66, 95% CI: 0.50 to 0.87; $I^2=0\%$; Figures 5(b) and (c)). For the non-IPF group, meta-analysis was not performed due to the inclusion of only one study.

Fatigue was significantly higher in the group treated with antifibrotics compared with the group not treated with antifibrotics (RR: 1.48, 95% CI: 1.20–1.83; $I^2=0\%$; Supplemental Figure 5), with moderate certainty (Supplemental

Table 4). When stratified by the antifibrotic type, a significant increase in fatigue was observed in the pirfenidone group (RR: 1.47, 95% CI: 1.15–1.87; $I^2=0\%$), while nintedanib group showed a borderline significance (RR: 1.51, 95% CI: 0.99–2.30, $p=0.05$; $I^2=0\%$; Supplemental Figure 5). Similarly, significant results were found in patients with IPF (RR: 1.47, 95% CI: 1.15–1.88; $I^2=0\%$), with a trend toward significance in those with non-IPF ILD (RR: 1.50, 95% CI: 0.98–2.28, $p=0.06$; $I^2=0\%$; Supplemental Figure 5).

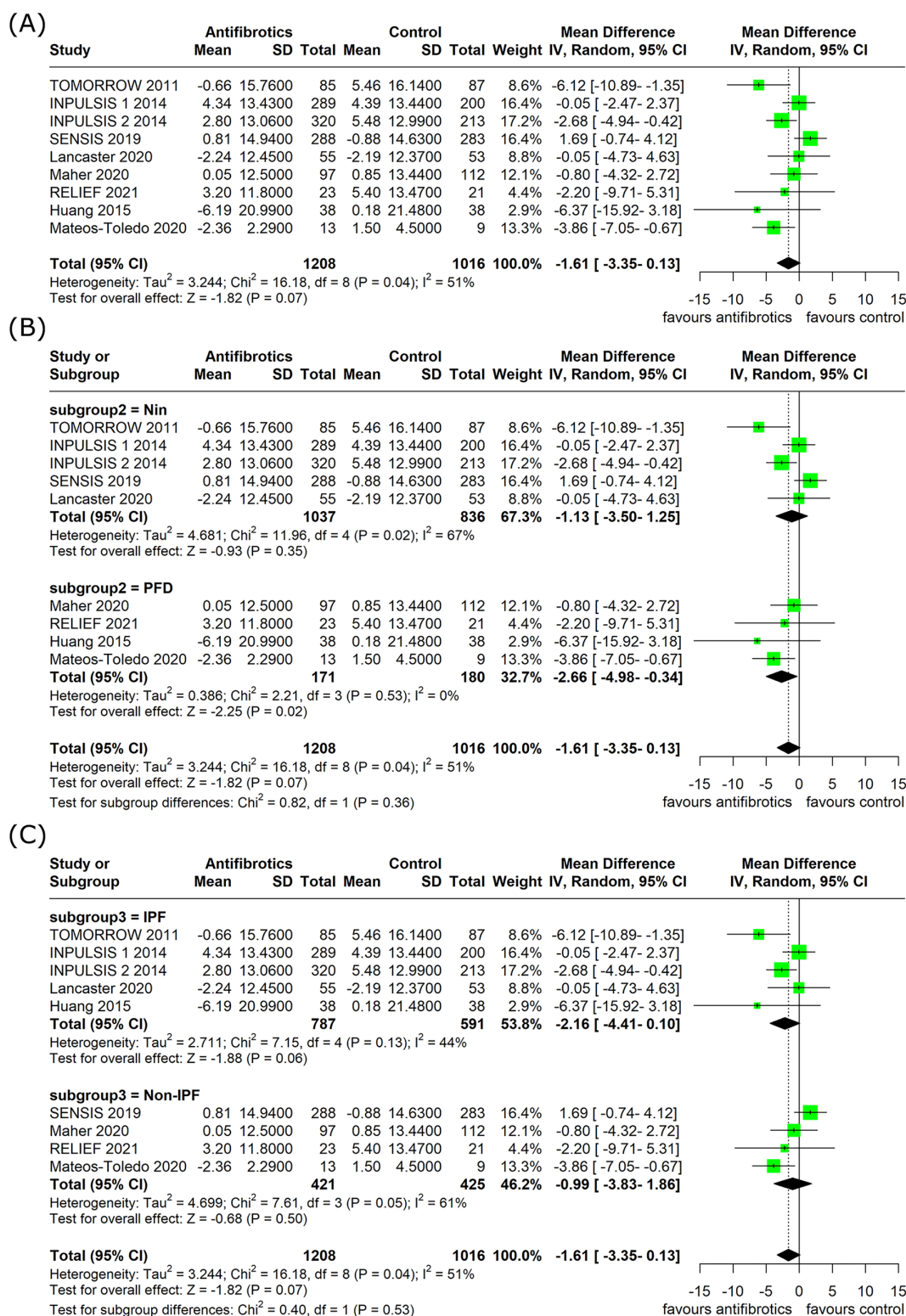


Figure 2. Forest plot presenting the pooled mean difference in total SGRQ scores between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF. CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IV, inverse variance; Nin, nintedanib; PFD, pirfenidone; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

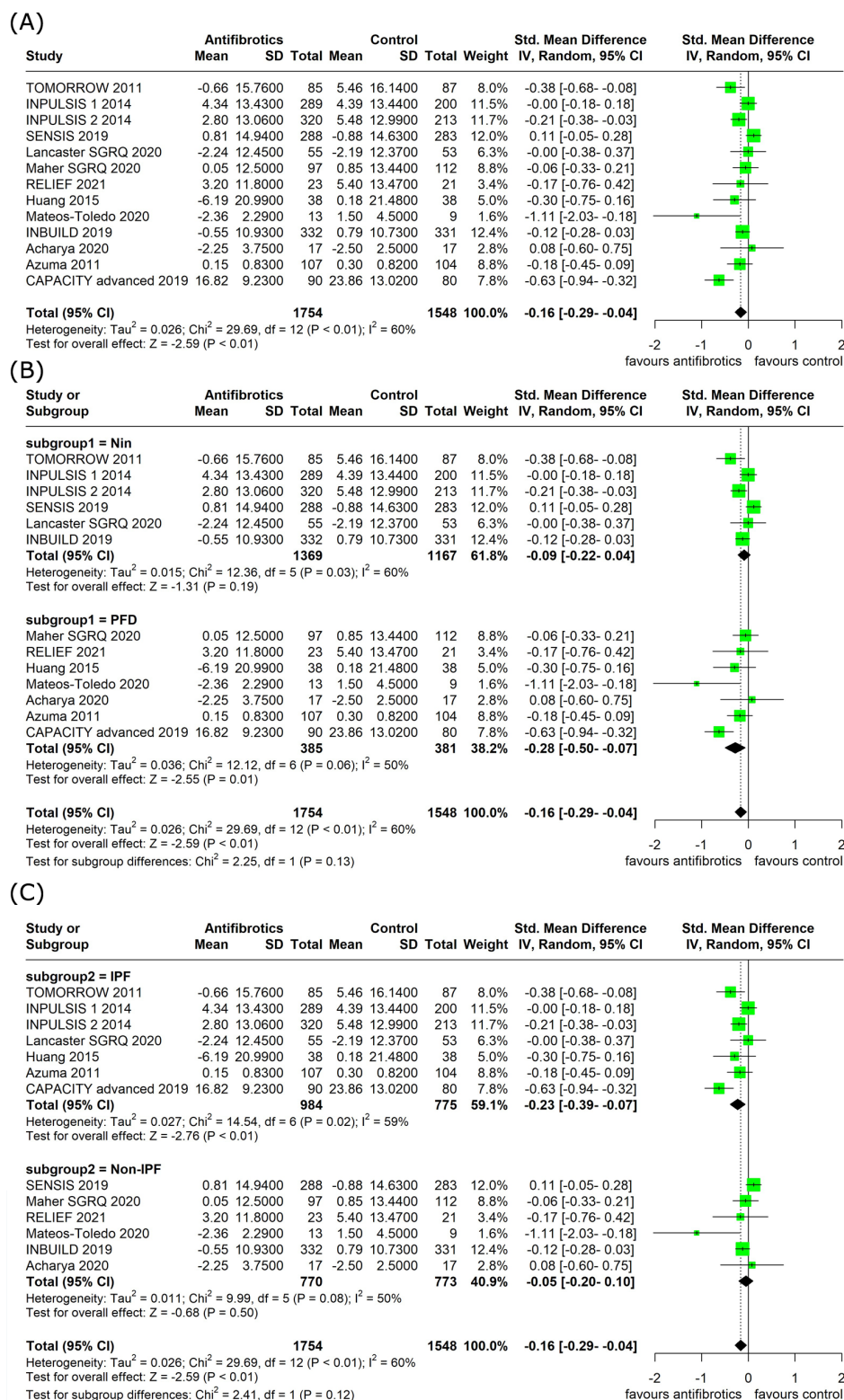


Figure 3. Forest plot presenting the pooled standardized mean difference in dyspnea scales between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD. CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IV, inverse variance; Nin, nintedanib; PFD, pirfenidone; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; Std., standard; UCSD-SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

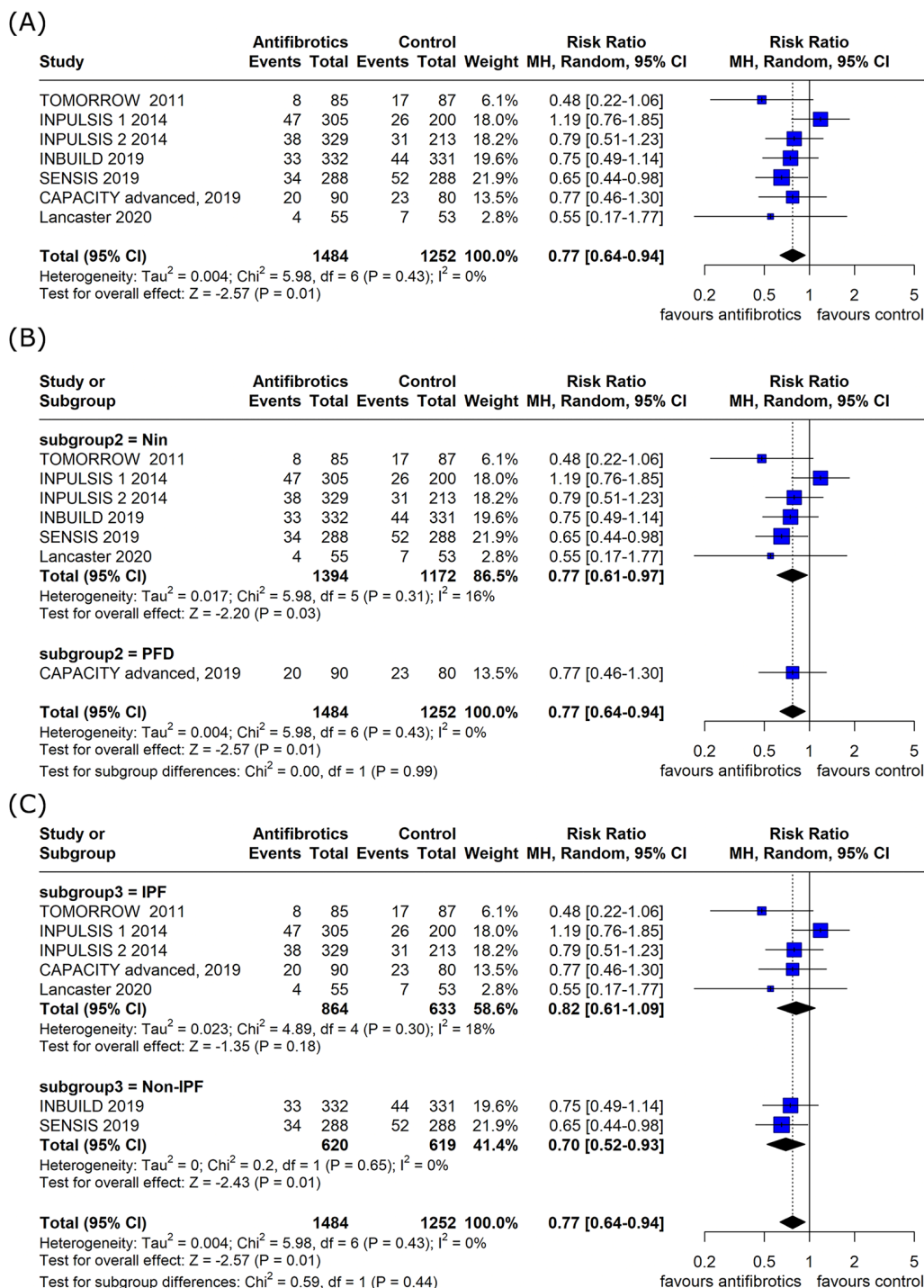


Figure 4. Forest plot presenting the pooled relative risk for cough symptoms between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD. CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MH, Mantel-Haenszel; Nin, nintedanib; PFD, pirfenidone.

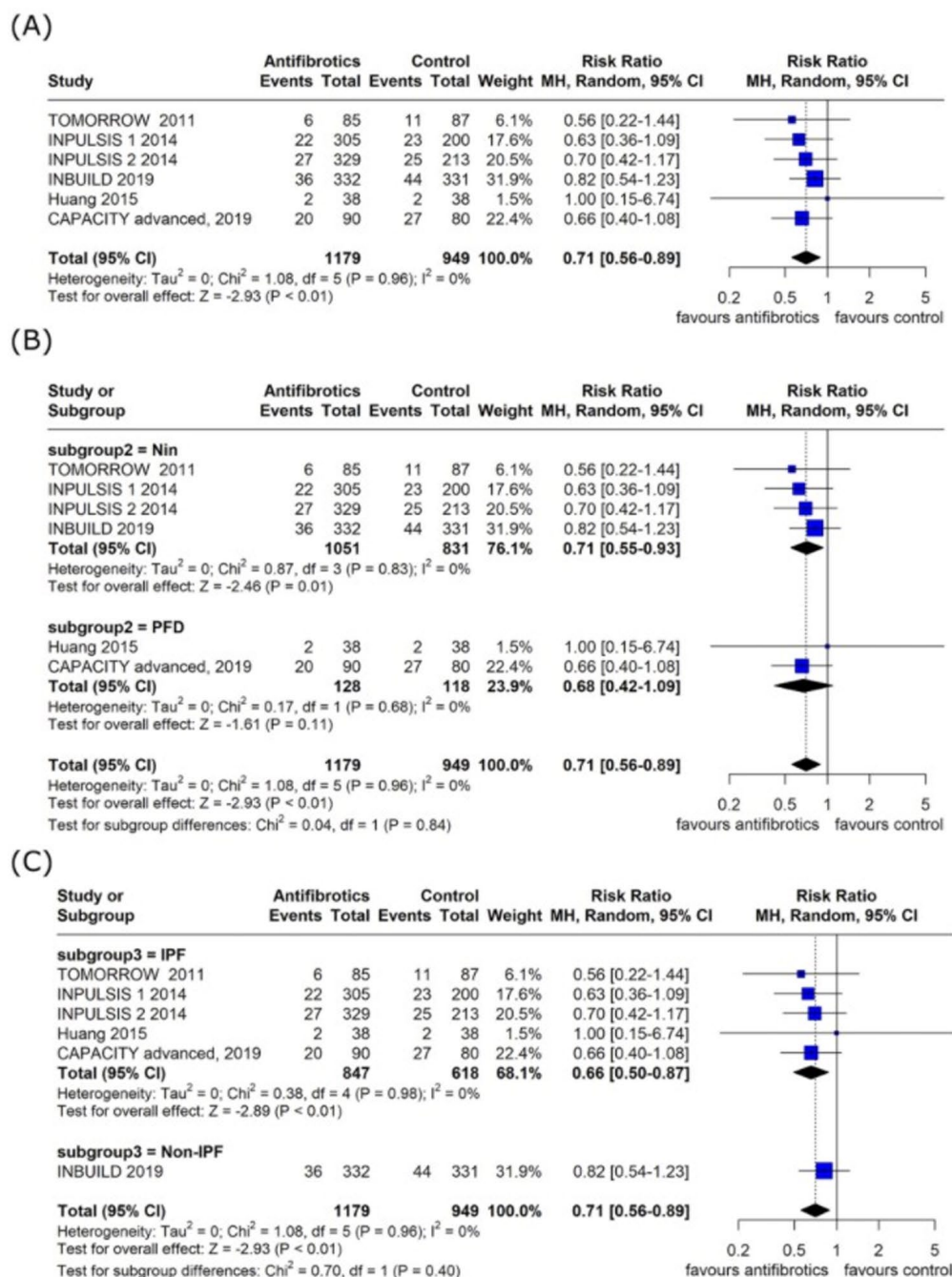


Figure 5. Forest plot presenting the pooled relative risk for dyspnea symptoms between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD.

CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MH, Mantel-Haenszel; Nin, nintedanib; PFD, pirfenidone.

Quality of included studies

Among the 13 studies, 5 were assessed to be at low risk of bias across all domains (Supplemental Figure 6). Four RCTs were classified with some

concerns in certain domains, mainly related to missing outcome data, outcome measurement, or bias in the selection of the reported results. The remaining five RCTs were judged to be at high risk

of bias, reflecting problems identified across multiple domains, including deviations from intended interventions, issues in the randomization process, selective reporting, or early termination.

Discussion

To the best of our knowledge, this was the first comprehensive meta-analysis to evaluate the effectiveness of antifibrotic agents on HRQoL in patients with ILD. Our findings suggested improvements in HRQoL scores in patients with antifibrotics, especially in activity limitations, reducing dyspnea, and cough, compared with placebo. Notably, an increase in fatigue due to antifibrotics was also observed. Overall, our results highlighted the potential of antifibrotic treatments to improve HRQoL in patients with ILD, while emphasizing the need for careful monitoring of fatigue during treatment. These findings are broadly consistent with earlier systematic reviews that primarily examined mortality and lung function outcomes^{7,16,17} and extend the literature by incorporating PROMs, which were not comprehensively evaluated in prior reviews.

Our study indicated that antifibrotic treatments were associated with lower SGRQ scores, particularly in symptomatic and activity domains in patients with ILD. Patients who were not treated with antifibrotics experienced a decline in the HRQoL, supported by a pooled analysis by Khor et al.,⁴⁵ which reported a mean increase in SGRQ scores by 3.65 (95% CI: -1.46 to 8.76; $P = 96\%$) over 1–2 years in patients with IPF ($n = 389$). Although antifibrotic agents may not directly improve lung function, they can slow the decline in lung function,⁴⁶ which has been associated with more favorable patient-reported outcomes. Since dyspnea is a frequent and significant symptom of ILD,⁴⁷ maintaining lung function and reducing disease activity may help to preserve daily functioning and mitigate symptom burden, thereby supporting HRQoL. The anti-inflammatory effectiveness of antifibrotics may also further reduce the inflammation associated with fibrosis, contributing to symptom relief.⁴⁸ However, it should be noted that the observed improvements in SGRQ total and domain scores did not consistently exceed the MCID of approximately 4 points,⁴⁹ and the certainty of evidence for total scores was very low due to risk of bias, heterogeneity, and imprecision, whereas domain-specific scores and symptom measures ranged

from low-to-moderate certainty. Combining the slowing of lung function decline, inflammation reduction, and relief of respiratory symptoms, such as dyspnea, antifibrotic therapy may enhance the overall HRQoL in patients with ILD, while the modest magnitude of effect and limited certainty of evidence warrant cautious interpretation. Taken together with recent real-world evidence of antifibrotic effectiveness in clinical practice,¹⁷ our results provide updated insight into the modest impact of antifibrotics on HRQoL.

Our analysis suggested that antifibrotic agents may have a greater impact on HRQoL, especially on the dyspnea scale in patients with IPF than in those with non-IPF ILD. The INPULSIS trials on patients with IPF treated with nintedanib showed mixed results regarding changes in the SGRQ score. INPULSIS-2 indicated a notable improvement over placebo (difference: -2.69 points; 95% CI: -4.95 to -0.43; $p = 0.02$). However, pooled data from INPULSIS-1 and 2 ($n = 1,066$) suggested only a marginally significant improvement with nintedanib (difference: -1.43 points; 95% CI: -3.09 to 0.23; $p = 0.09$).⁶ The 52-week RCT ($n = 432$) demonstrated a significant reduction in SGRQ scores with nintedanib compared with placebo (adjusted mean absolute change from baseline: -0.66 vs 5.46 points; $p = 0.007$).²⁴ However, other studies, such as a 24-week phase IIIb RCT ($n = 113$) and a Chinese Phase RCT ($n = 86$), did not find significant differences in SGRQ scores with antifibrotic treatment in patients with IPF.^{40,41} Conversely, any evidence of antifibrotic therapy improving SGRQ scores is limited and inconsistent for patients with non-IPF ILDs.^{9,35,42} Only one small study on chronic HP ($n = 22$) found that pirfenidone improved SGRQ scores compared with the control group.³⁴ These findings suggest that the efficacy of antifibrotic therapy for improving HRQoL is more prominent in fibrotic ILDs such as IPF and chronic HP, because in these conditions it can target fibrotic pathways.^{50,51} In contrast, non-fibrotic ILDs exhibit a combination of inflammation and fibrosis⁵² and demonstrate more varied responses to antifibrotic treatments, leading to less consistent improvements in HRQoL.

Our meta-analysis found that antifibrotic therapy notably reduced cough in patients with ILD. These findings were consistent with another

meta-analysis of six studies, where nintedanib treatment decreased the rate of cough compared with placebo (odds ratio (OR): 0.73; 95% CI: 0.56–0.96; $I^2 = 23\%$).¹¹ In an observational Italian IPF study ($n = 52$), cough incidence dropped from 50% to 21.2% within 12 months after nintedanib treatment.⁵³ Similarly, a 12-week international study ($n = 34$) reported a 34% improvement in 24-hour cough symptoms (95% CI: –48% to –15%) in patients with IPF treated with pirfenidone.⁵⁴ In patients with IPF, frequent coughing is attributed to heightened cough sensitivity, architectural distortion, and MUC5B-associated mucus production.⁵⁵ Animal studies have shown that pirfenidone can reduce capsaicin-induced cough sensitivity and lower cough-related mediators, including prostaglandin E2, substance P, and leukotriene B4.⁵⁶ Nintedanib has the potential to lower pro-inflammatory cytokines such as interleukin-6 in response to tumor necrosis factor- α , which could contribute to a reduction in cough by the effectiveness on cough-related mediators.⁵⁷ Recent real-world data are consistent. In a registry study ($n = 237$), pirfenidone showed no overall benefit in PROM; however, in Gender–Age–Physiology stage 2/3, there was a trend of less dyspnea at 12 months on the UCSD-SOBQ and improved cough at 18 months on the Leicester Cough Questionnaire.⁵⁸ These results underscore the importance of antifibrotic therapy in improving the HRQoL in patients with ILD, particularly in managing cough symptoms.

Our study, along with various other RCTs,^{24,25,35,41,42} showed a significant increase in fatigue among patients receiving antifibrotic therapy compared with those receiving placebo. The precise mechanism for an increase in symptoms of fatigue is unclear but it might be linked to gastrointestinal side effects, such as anorexia and weight loss, which are often associated with antifibrotics.⁵⁹ These side effects could lead to reduced energy levels and physical weakness, thereby further exacerbating fatigue. Another factor could be the psychological toll of managing side effects and the long-term nature of antifibrotic therapy. While antifibrotics themselves may not directly cause fatigue, the polypharmacy common in chronic disease management is known to contribute to iatrogenic fatigue,⁶⁰ potentially affecting these patients. In addition to fatigue, it should be recognized that common treatment-related adverse events such as diarrhea, nausea, and weight loss are frequently observed in clinical

practice and can substantially reduce HRQoL by limiting daily functioning and treatment adherence.⁶¹ Although our review focused on PROMs reported in RCTs, these adverse events remain an important determinant of the overall treatment experience and must be considered when interpreting patient-reported outcomes. These findings emphasize the need for identifying effective strategies to reduce fatigue in patients on antifibrotic treatment, which could greatly improve their overall treatment experience and enhance the HRQoL of patients with ILD.

Our study has several limitations. First, the heterogeneity among the included studies, particularly regarding the HRQoL assessment tools and patient populations, may have impacted the overall findings. However, the observed heterogeneity was moderate, with I^2 values below 50% in most analyses, indicating that the variability across studies was within an acceptable range. Despite some subgroup results not reaching statistical significance, the overall trends remained consistent across groups, supporting the reliability of the findings. Second, the relatively short follow-up duration in the included studies, which typically ranged from weeks to months, might not have been sufficient to fully capture the long-term effectiveness of antifibrotic therapies. Long-term investigation will provide a more comprehensive understanding of treatment sustainability. Third, for non-IPF ILD, the number of individual studies was insufficient for a separate analysis. The inconsistent results in patients without IPF warrant further research for a more detailed analysis. Fourth, our findings should be interpreted as associations rather than direct causation. Patients who initiate antifibrotic therapy may have more advanced disease, and their greater symptom burden and fatigue could reflect underlying disease severity rather than treatment effects. Finally, our review included only English-language studies due to resource constraints for translation, which may have introduced language bias. Moreover, we searched only three major databases and did not include gray literature or trial registries, which may increase the risk of publication bias and limit generalizability. Despite these limitations, the strength of our study lies in its detailed analysis of the effectiveness of antifibrotic therapy on the HRQoL in patients with ILD, underscoring the potential benefits of antifibrotic agents in ILD management.

Conclusion

Our meta-analysis suggests that antifibrotics may have a beneficial impact on HRQoL-related symptoms—particularly dyspnea and cough—with low-to-moderate certainty of evidence. By contrast, the effect on overall HRQoL totals remains uncertain (very low certainty), and fatigue appears to increase, requiring careful monitoring. The effectiveness was more pronounced in patients with fibrotic ILDs. These findings indicate potential benefits of antifibrotic therapy for improving patients' well-being, while underscoring the need for further high-quality studies to clarify its impact on HRQoL.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Jihye Lee: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Shinhee Park: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Hee-Young Yoon: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data generated and/or analyzed during the study are available from the corresponding author upon reasonable request.

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Supplemental material

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Artificial intelligence use disclosure

Generative AI (ChatGPT, OpenAI) was used only for language polishing.

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