M E T A - A N A L Y S I S

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Assessing the impact of nintedanib and pirfenidone on lung function in idiopathic pulmonary fibrosis: a comprehensive meta-analysis

Procena uticaja nintedaniba i pirfenidona na funkciju pluća kod idiopatske plućne fibroze: sveobuhvatna meta-analiza

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Abstract

Background/Aim. The incidence of idiopathic pulmonary fibrosis (IPF) has been increasing each year. Although pirfenidone and nintedanib were approved in 2014, they received only conditional recommendations, and no medication has yet been strongly endorsed for IPF treatment. The aim of the study was to compare the safety and efficacy of pirfenidone and nintedanib. **Methods.** All randomized and non-randomized clinical trials were identified by searching databases for published studies, including Medline, Embase, Scopus, Google Scholar, and ClinicalTrials.gov. A meta-analysis was conducted to evaluate the impact of pirfenidone and nintedanib on clinical outcomes and safety. Patients treated with pirfenidone were compared with those treated with nintedanib. **Results.** This study included twelve papers. Both pirfenidone and nintedanib were found to significantly reduce the decline in mean forced vital capacity (FVC) and mean diffusion capacity of the lungs for carbon monoxide (DLco) at 6 and 12 months. No significant difference was observed between pirfenidone and nintedanib in terms of improvement in FVC or DLco. Similarly, both antifibrotic agents had similar safety profiles. However, patients receiving nintedanib experienced significantly fewer instances of diarrhea ($p < 0.00001$) compared to those receiving pirfenidone, whereas patients receiving pirfenidone experienced significantly fewer instances of skin rash ($p < 0.00001$) compared with those receiving nintedanib. **Conclusion.** Potential differences between pirfenidone and nintedanib can be inferred from the effectiveness ranking derived from this meta-analysis. Further direct comparative studies are necessary to explore this issue, which will help us better understand the potential of combinatorial, sequential, or adjunctive treatment regimens in which both antifibrotic agents might play a crucial role for a specific group of IPF patients.

Keywords:
drug-related side effects and adverse reactions; drug therapy; idiopathic pulmonary fibrosis; nintedanib; pirfenidone; respiratory function test.

Apstrakt

Uvod/Cilj. Učestalost idiopatske plućne fibroze (IPF) je u porastu iz godine u godinu. Iako su pirfenidon i nintedanib odobreni 2014. godine, dobili su samo uslovne preporuke, a nijedan od ta dva leka još uvek nema snažnu preporuku za lečenje IPF. Cilj rada bio je da se uporede bezbednost i efikasnost pirfenidona i nintedaniba. **Metode.** Sve randomizovane i nerandomizovane kliničke studije identifikovane su pretraživanjem baza podataka objavljenih studija, uključujući Medline, Embase, Scopus, Google Scholar i ClinicalTrials.gov. Sprovedena je meta-analiza kako bi se procenio uticaj pirfenidona i nintedaniba na kliničke ishode i bezbednost. Poređeni su bolesnici lečeni pirfenidonom i bolesnici lečeni nintedanibom. **Rezultati.** Studijom je obuhvaćeno 12 radova. Utvrđeno je da su i pirfenidon i nintedanib značajno smanjivali pad srednje vrednosti forsiranog vitalnog kapaciteta (*forced vital capacity* – FVC) pluća i srednje vrednosti difuzionog kapaciteta pluća za ugljen-monoksid (*diffusion capacity of the lungs for carbon monoxide* – DLco) nakon 6 i 12 meseci. Nije uočena statistički značajna razlika između pirfenidona i nintedaniba u pogledu poboljšanja FVC ili DLco. Takođe, oba agensa protiv fibroze pluća imala su slične bezbednosne profile. Međutim, kod bolesnika lečenih nintedanibom zabeleženo je značajno manje epizoda dijareje ($p < 0,00001$) u poređenju sa bolesnicima lečenim pirfenidonom, dok su bolesnici lečeni pirfenidonom imali značajno manje epizoda kožnog osipa ($p < 0,00001$) u poređenju sa

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bolesnicima lečenim nintedanibom. **Zaključak.** O mogućim razlikama između pirfenidona i nintedaniba može se zaključiti na osnovu rangiranja njihove efikasnosti dobijenog ovom meta-analizom. Neophodne su dodatne direktne uporedne studije kako bi se ovo pitanje detaljnije istražilo, što će omogućiti bolje razumevanje potencijala kombinovanih, sekvencijalnih ili dodatnih režima lečenja, u kojima oba agensa protiv fibroze mogu igrati ključnu ulogu za određenu grupu obolelih od IPF.

Ključne reči:
lekovi, neželjeni efekti i neželjene reakcije; lečenje lekovima; pluća, fibroza, idiopatska; nintedanib; pirfenidon; respiratorna funkcija, test.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic lung disease characterized by scar tissue formation in the lungs [1]. It leads to an irreversible decline in lung function. This disease mainly affects older persons, with a higher incidence in males. Progressive lung tissue scarring is responsible for IPF development [2]. Due to discrepancies in reporting and diagnostic criteria, the original rate of prevalence and incidence for IPF is not well-established. However, recent estimates revealed that approximately 3 million people worldwide have been affected by IPF [3, 4]. However, these estimates did not reflect the exact scenario of IPF because there were so many undiagnosed or misdiagnosed cases present worldwide. Some studies also observed a significant delay (median delay of 2.1 years) in IPF diagnosis, resulting in patients often experiencing worsening sign and symptoms and irreversible lung damage [5–7].

Currently, there is no permanent solution regarding the cure for IPF. The available treatment only focuses on symptom management and slowing down disease progression [5]. There are multiple treatments available for IPF. Treatments include medications such as nintedanib and pirfenidone, which inhibit the progression of lung fibrosis and are approved for IPF treatment [8]. Lung transplantation may be the final treatment option for severe IPF patients when other therapies fail. Pulmonary rehabilitation programs can help improve symptoms, enhance endurance during exercise, and upgrade the individual's overall quality of life (QoL) with IPF [9, 10]. Supplemental oxygen therapy was prescribed to alleviate symptoms and improve breathing when the patient's oxygen level was low. Palliative care seems to focus on relieving symptoms and improving the QoL for individuals with IPF [11].

Nintedanib and pirfenidone are medications used in the treatment of IPF. While the exact mechanism of action of nintedanib and pirfenidone is not fully understood, nintedanib primarily acts as a tyrosine kinase inhibitor (TKI). It was noted that in a canine lung infection model, pirfenidone showed antifibrotic activity and reduced fibrosis while improving lung function in a bleomycin-induced hamster lung injury model [12]. The antifibrotic activity might depend on growth factors and cytokines modulation, such as growth factor transformation. Pirfenidone has been approved due to phase 3 studies in mild-to-moderate IPF patients [13], but the safety and efficacy of pirfenidone in advanced IPF patients are still unclear. However, many experiments found that pirfenidone was well accepted and improved the lung function decline in advanced IPF patients [14, 15].

Nintedanib, an intracellular TKI targeting vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptors, exhibited antifibrotic and anti-inflammatory effects in a preclinical study. In recent randomized controlled trials (RCTs) involving patients with mild-to-moderate IPF, it was found that nintedanib reduced the rate of decline in forced vital capacity (FVC), and disease progression and adverse events were well tolerated.

Current advancements in understanding the molecular processes in fibrogenesis have opened innovative avenues for targeted therapeutic interventions [1, 16]. One such promising approach is the use of antifibrotic drugs for the treatment of IPF. These drugs act through specific mechanisms involved in preventing or reducing the accumulation of scar tissue in the lungs. Clinical trials have shown that antifibrotic drugs, such as pirfenidone and nintedanib, can reduce the decline in lung function and improve overall QoL in patients with IPF. However, it is important to note that these drugs are not curative and may have side effects. Based on previous qualitative and quantitative reviews, nintedanib and pirfenidone were evaluated for their antifibrotic effects in patients with and without IPF [17, 18]. To gain a deeper understanding of the potential effects of the two antifibrotic agents in patients with IPF, a systematic literature review and meta-analysis was conducted to determine which agent inhibits IPF progression more effectively.

Methods

Literature search

This systematic literature review and meta-analysis was performed using electronic databases such as Medline, Embase, Scopus, Google Scholar, and ClinicalTrials.gov from inception to August 31, 2025. In addition, two independent reviewers conducted an abstract review of all records. For more relevant studies, we used Medical Subject Headings (MeSH) terms "pirfenidone" and "nintedanib" alone and in combination with other terms in the following way: ("pirfenidone" [Supplementary Concept] OR "antifibrotic medication, nintedanib" [MeSH]) AND ("idiopathic pulmonary fibrosis" [MeSH]). The complete search strategy has been provided in the supplementary file (Supplementary Table 1). In addition, a manual bibliographic search was performed for reference lists of published review

articles to collect additional information, and conference abstracts were searched for relevant information.

We have included RCTs and observational studies that reported the pulmonary functions of pirfenidone and nintedanib for IPF patients.

Study selection

Studies were eligible for inclusion if they met the following criteria: the patients in the selected studies were older than 18 years and had IPF; observational studies and RCTs comparing nintedanib and pirfenidone; studies that reported at least one clinical outcome. Full articles were retrieved when titles and/or abstracts met this objective. A manual cross-reference search of relevant articles was conducted. Only English language studies were included. Disagreement about study inclusion between the two reviewers was resolved through discussion with the third reviewer until 100% agreement was reached on the final interpretation of the data.

Studies were excluded if they were published in a language other than English, were animal or *in vitro* studies, were conducted in athletes, children, pregnant or lactating women, or did not have the necessary data, or analyzed the effects of combination therapy involving nintedanib or pirfenidone with other drugs or components. Notably, we did not include papers reporting the mentioned outcomes in formats that could not be converted to mean values and standard deviations (SD).

Quality assessment

The quality of each study included in the analysis was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) [19] and the Modified Jadad score (MJS) scale [20]. This validated NOS tool consisted of the following three categories: selection, comparability, and outcome assessment. Each category was scored as good, fair, or poor. The MJS scale mainly assesses the randomization, blinding, withdrawals, inclusion-exclusion criteria, adverse events, and statistical analysis. A score of 0 to 3 is considered low-quality, and a score of 4 to 8 is considered high-quality study. Two independent reviewers performed the quality assessment, and disagreements on scores were resolved through discussion.

Data extraction and outcome measure

Two independent reviewers performed data extraction and analysis. Study methodological homogeneity was assessed. In extracting the assessed outcomes, study heterogeneity would not be justified. A customized data-extraction form, as described in the Cochrane Handbook for Systematic Reviews of Interventions, was used to record the duration of the trial, sample size, dropouts, and effect of interventions. The included effectivity in the analysis was as follows: the effect of antifibrotic therapy on diffusing capacity of the lungs for carbon monoxide (DLco) at 6 and 12 months; the effect of antifibrotic therapy on FVC for 6 and 12 months; the effect of antifibrotic therapy on forced expiratory volume in 1 sec (FEV1), 6-min walk test (6-MWT), and total lung capacity; the effect of antifibrotic therapy on all-cause mortality (ACM); the effect of antifibrotic therapy on adverse events, including all adverse events, skin-related adverse events, and diarrhea events.

Sensitivity analysis

The robustness of the pooled estimates was evaluated through sensitivity analyses. We repeated the meta-analyses by excluding studies with a high risk of bias and sequentially removing one study at a time (a process known as "leave-one-out" analysis). These methods examined whether methodological decisions or any single study had an excessive impact on the overall results.

Statistical analysis

Quantitative data were analyzed using the Cochrane Review Manager (RevMan) version 5.2 software and RStudio version 4.3. Summary estimates, including 95% confidence intervals (CIs), were calculated. For continuous outcome data, means and SDs were used to calculate a weighted standardized mean difference (SMD). For studies with different statistical data, the data were converted to mean and SD to calculate and remove missing outcome bias. For dichotomous outcomes, odds ratios (ORs) were calculated. Statistical heterogeneity was assessed using the I^2 test. Random-effect models were used unless significant evidence of statistical heterogeneity or clinical diversity was found. For results showing significant heterogeneity ($I^2 > 50\%$), a p-value < 0.05 was considered statistically significant. For publication bias analysis, we conducted Egger's regression (ER) test and funnel plot. Subgroup and sensitivity analyses were conducted in order to eliminate the heterogeneity from the analysis.

Results

Search results

The detailed database search procedure and study selection are shown in Figure 1 [21–32]. The flow chart of study selection shows the literature search and selection for RCT [28] and non-RCT [21–27, 29–32] studies on the effects of nintedanib and pirfenidone on IPF patients.

Two reviews searched the Medline, Embase, Scopus, Google Scholar, and ClinicalTrials.gov databases independently from inception until April 2025. A total of 1,285 articles were extracted for screening. Articles were excluded due to duplicates, different outcomes and interventions, and lack of data availability. Finally, 12 studies [21–32] were included for extraction and meta-analysis (11 were observational studies [21–27, 29–32], one was an RCT study [28]). A total of 1,631 subjects were administered nintedanib, and 2,218 subjects were in the pirfenidone group [21–32].

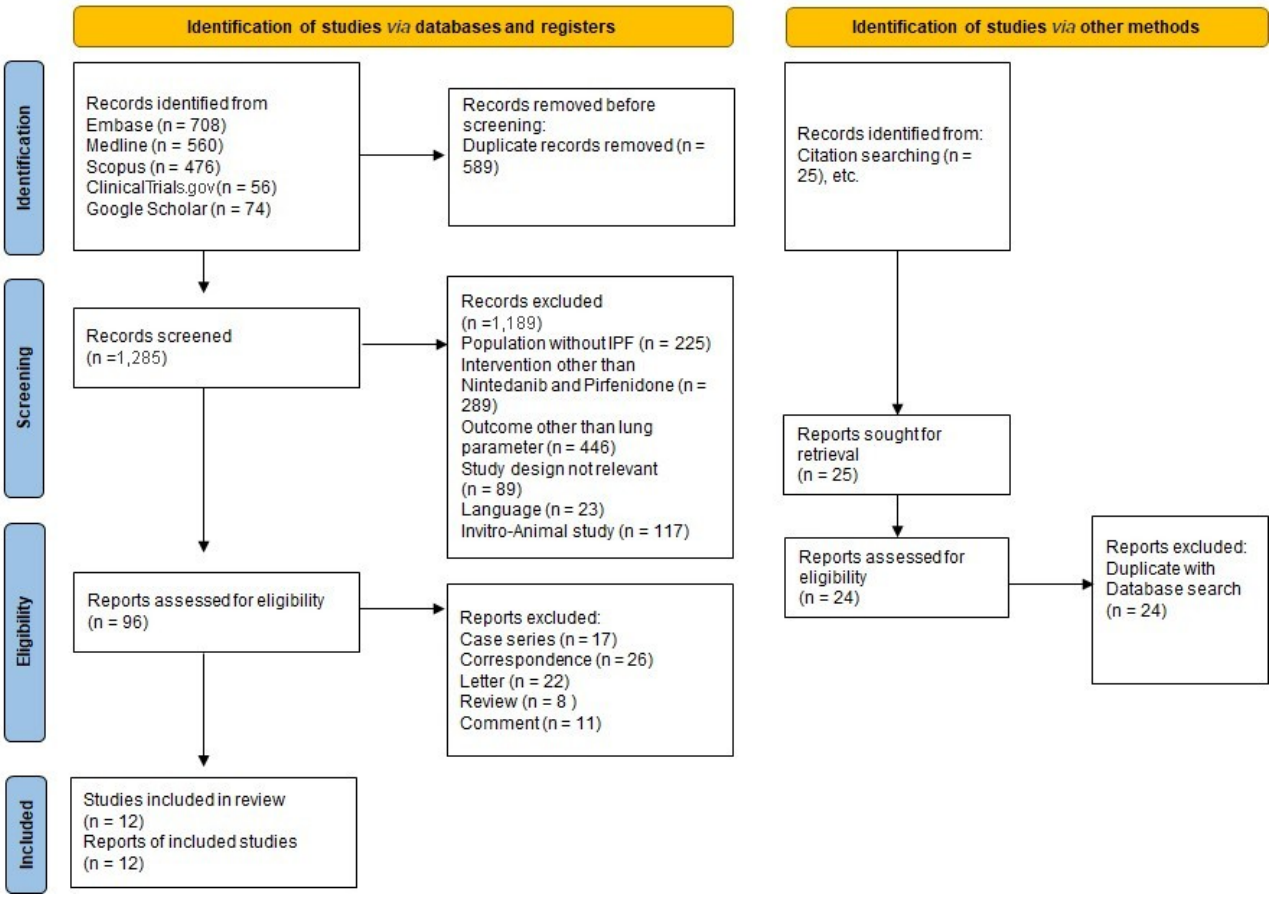

Fig. 1 – PRISMA flow diagram depicting the selection of studies for systematic review and meta-analysis.
PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Study characteristics

The characteristics of the included studies are presented in Table 1 [21–32]. The included participants were aged between 18 and 65 years. Study duration also varied from months to years. Of 12 studies, nine [21, 24–29, 31, 32] reported the DLco, and nine [21, 24–29, 31, 32] reported FVC, four [21, 24, 25, 28] reported FEV1 data, and all studies reported adverse events.

Diffusing capacity of the lungs for carbon monoxide at six and twelve months

The effects of nintedanib and pirfenidone for DLco were documented in one RCT [28], three retrospective observational studies [21, 26, 27], one retrospective cohort study [24], and one prospective cohort study [25]. At 6 and 12 months, pooled data from all investigations were assessed. A total of 645 subjects reported nintedanib and pirfenidone effects. According to the pooled analysis of six studies, nintedanib non-significantly ($p = 0.56$) improved the DLco at 12 and 6 months ($p = 0.10$). A significant ($I^2 = 80\%$) heterogeneity was observed in the 12-and 6-month DLco analysis. The details of the forest plot analysis are described in Figure 2 [21, 24–26, 28, 29] and Table 2. Forest plot of the effect of nintedanib and pirfenidone on DLco in total participants for a 6-month duration was $z = 1.67$, $p = 0.10$, and for 12 months, duration was $z = 0.59$, $p = 0.56$.

Forced vital capacity at six and twelve months

The 12-month FVC with pirfenidone and nintedanib treatment was reported in six trials involving 567 patients [21, 24–26, 28, 29]. A meta-analysis of these six investigations observed there was no significant difference between 12 months of FVC with pirfenidone and nintedanib treatment ($p = 0.40$). In a similar vein, four [21, 24–26] of the six trials, comprising 474 people, reported 6-month FVC following pirfenidone and nintedanib therapy; those receiving nintedanib and pirfenidone therapy demonstrated similar FVC improvement, and no significant ($p = 0.10$) difference was observed. A substantial ($I^2 = 94\%$) heterogeneity was observed in the 12-month FVC analysis. The details of the forest plot analysis are described in Figure 3 [21, 24–26, 28, 29] and Table 2. Forest plot of the effect of nintedanib and pirfenidone on FVC in total participants for a 6-month duration shows $z = 1.63$, $p = 0.10$, and for a 12-month duration, $z = 0.84$, $p = 0.40$.

Table 1

Characteristics of included studies (n = 12)

Author	Design	Intervention and sample size (number)		Study duration (months)	Outcome measure	AE report	Author conclusion
Bargagli et al. 2019 [21]	Re, O	P (52)	N (30)	12	FEV1, FVC, TLC, DLco	yes	A major number of IPF patients showed a good tolerability profile with P. AEs were manageable, but skin reactions and gastrointestinal disorder AEs were observed frequently.
Burgos et al. 2019 [22]	Re, O	P (43)	N (21)	11	FEV1	yes	FVC was improved for those treated with P; however, more AEs were observed with P. On the other hand, the spirometric profile was stabilized with N and better tolerated than P.
Belhassen et al. 2021 [23]	Re, C	P (804)	N (509)	12	ACM, acute respiratory-related hospital admissions, treatment discontinuation	yes	As compared to P, N was associated with a risk of acute respiratory-related hospitalizations, a greater risk of ACM, and a lower risk of treatment discontinuation.
Cameli et al. 2020 [24]	Re, C	P (139)	N (124)	60	FEV1, FVC, TLC, DLco, FEV1/FVC	yes	After 1 year of treatment with N, due to its antiangiogenic properties, it showed a slight decrease in DLco compared with P.
Cerri et al. 2019 [25]	Pr, C	P (78)	N (28)	24	FEV1, FVC, DLco	yes	It was revealed that P and N were equally effective in lowering the DLco and FVC decline vs. non-treated patients after 24 months of treatment.
Feng et al. 2020 [26]	Re, O	P (36)	N (31)	31	FVC, DLco	yes	P decreases the disease progression and improves lung function with very few side effects.
Fournier et al. 2022 [27]	Re, O	P (115)	N (61)	20	FVC, DLco	yes	The occurrence of AEs was higher in the N group compared to the P group.
Kerget et al. 2023 [28]	Ra, Pr	P (15)	N (15)	3	FEV1, FVC, DLco, 6-MWT	yes	It was revealed that P and N were effective in improving radiological scores and PFT parameters. However, it was observed that N had more potential to increase the saturation values and exercise capacity, but it resulted in more AEs than P.
Khan et al. 2023 [29]	Re, C	P (45)	N (36)	12	FVC, DLco	yes	Hospital admission and gastrointestinal disorders were increased in P.
Marijic et al. 2021 [30]	Re, C	P (840)	N (713)	12	ACM, respiratory-related hospitalization	yes	Patient-related outcomes, hospitalization, costs, and mortality rate did not differ between currently available antifibrotic drugs, N and P.
Moor et al. 2020 [31]	Pr, C	P (39)	N (51)	6	FVC, DLco	yes	The incidence of ADR in the N group is higher compared to the P-treated group.
Ntolios et al. 2021 [32]	Pr, C	P (12)	N (12)	12	ΔFVC, ΔDLco, 6-MWT	yes	Patients can continue with the N therapy, those who discontinued P due to ADRs.

AE – adverse events; Re – retrospective study; O – observational study; P – perfenidone; N – nintedanib; FEV1 – forced expiratory volume in 1 sec; FVC – forced vital capacity; TLC – total lung capacity; DLco – diffusing capacity of the lungs for carbon monoxide; IPF – idiopathic pulmonary fibrosis; C – cohort study; ACM – all-cause mortality; Pr – prospective study; Ra – randomized; ACM – all-cause mortality; 6-MWT – 6-minute walk test; PFT – pulmonary function test; ADR – adverse drug reaction.

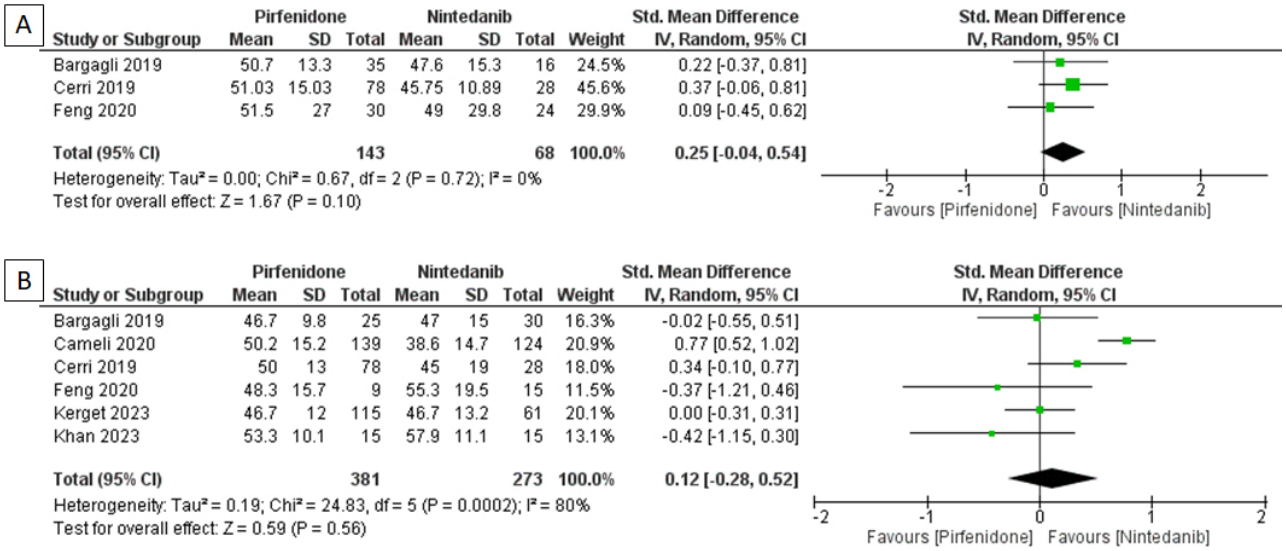

Fig. 2 – Forest plot comparing pirfenidone and nintedanib for DLco: (A) at 6 months; (B) at 12 months.
DLco – diffusion capacity of the lungs for carbon monoxide; SD – standard deviation; Std – standard; CI – confidence interval.

Table 2

Clinical outcomes of the nintedanib group compared to the pirfenidone group

Variables	Study (numbers)	SMD [95% CI]	Value for test (MD = 0)	I^2 (%)	*p*-value for Q test
6-month DLco	3	0.25 [-0.04, 0.54]	0.10	0	0.72
12-month DLco	6	0.12 [-0.28, 0.52]	0.56	80	0.0002
6-month FVC	4	0.16 [-0.03, 0.34]	0.10	0	0.55
12-month FVC	6	0.33 [-0.43, 1.09]	0.40	94	0.00001

SMD – standard mean difference (MD); CI – confidence interval; DLco – diffusing capacity of the lungs for carbon monoxide; FVC – forced vital capacity.

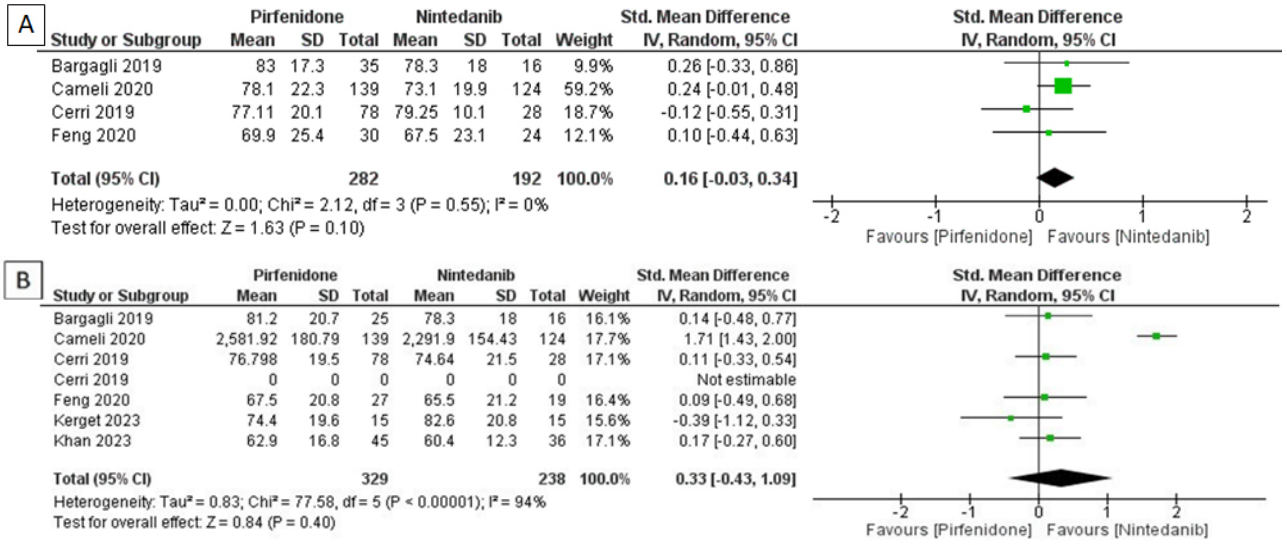

Fig. 3 – Forest plot comparing pirfenidone and nintedanib for forced vital capacity: (A) at 6 months; (B) at 12 months.
SD – standard deviation; Std – standard; CI – confidence interval.

All-cause mortality

A total of three studies [24, 25, 29] reported ACM outcomes. The pooled analysis revealed no significant ($p = 0.38$) difference in mortality between nintedanib and pirfenidone treatment after 12 months (Figure 4 [24, 25, 28, 29] and Table 3). Forest plot of the effect of nintedanib and pirfenidone shows for ACM, $z = 0.88$, $p = 0.38$, and for nausea, $z = 0.05$, $p = 0.96$.

Safety and adverse events

Diarrhea [21, 22, 24, 25, 29], nausea [24, 25, 28, 29], and skin related adverse events [25, 28, 29] were recorded in five, four, and three studies, respectively, involving IPF patients. A pooled analysis revealed that, in comparison to individuals treated with pirfenidone, IPF patients treated with nintedanib experienced considerably (p = 0.006) fewer diarrhea events. On the other hand, skin rash events were considerably (p = 0.002) lower in patients receiving pirfenidone. The OR values are presented in Table 3. The forest plot of the detailed analysis is shown in Figure 5 [21, 22, 24, 25, 28, 29]. Forest plot of the effect of nintedanib and pirfenidone on skin rash shows z = 3.14, p = 0.002, and on diarrhea, z = 2.77, p = 0.006.

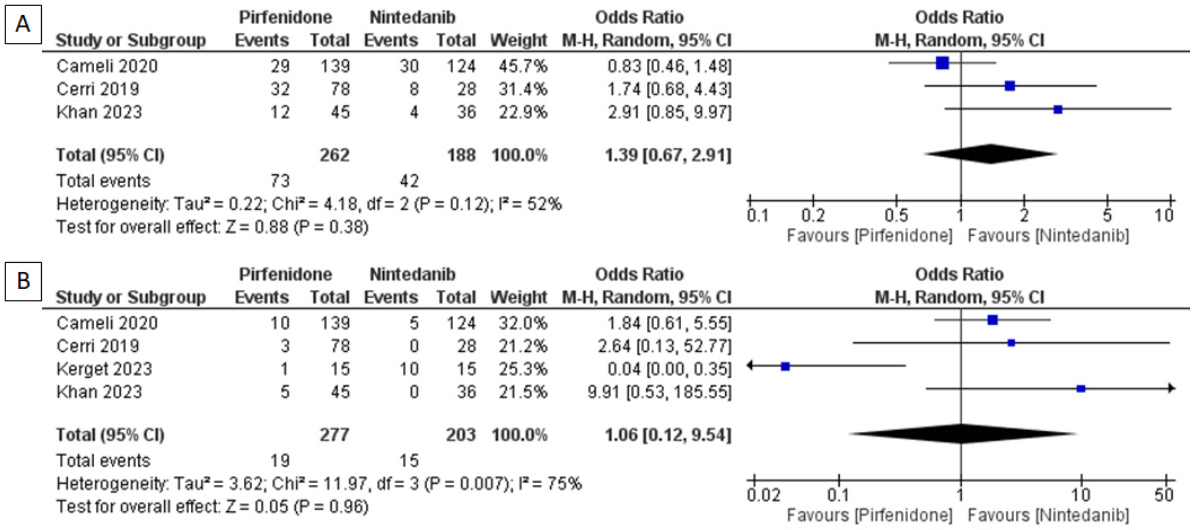

Fig. 4 – Forest plot comparing pirfenidone and nintedanib for: (A) all-cause mortality; (B) nausea. CI – confidence interval.

Table 3

All-cause mortality and safety outcomes of the nintedanib group compared to the pirfenidone group

Variables	No. of study	OR [95% CI]	p-value for test (MD = 0)	I^2 (%)	p-value for Q test
All-cause mortality	3	1.39 [0.67, 2.91]	0.38	52	0.12
Nausea	4	1.06 [0.12, 9.54]	0.96	75	0.007
Skin rash	3	7.22 [2.10, 24.80]	0.002	0	0.77
Diarrhea	5	0.08 [0.01, 0.48]	0.006	78	0.001

No. – number; OR – odds ratio; CI – confidence interval; MD – mean difference.

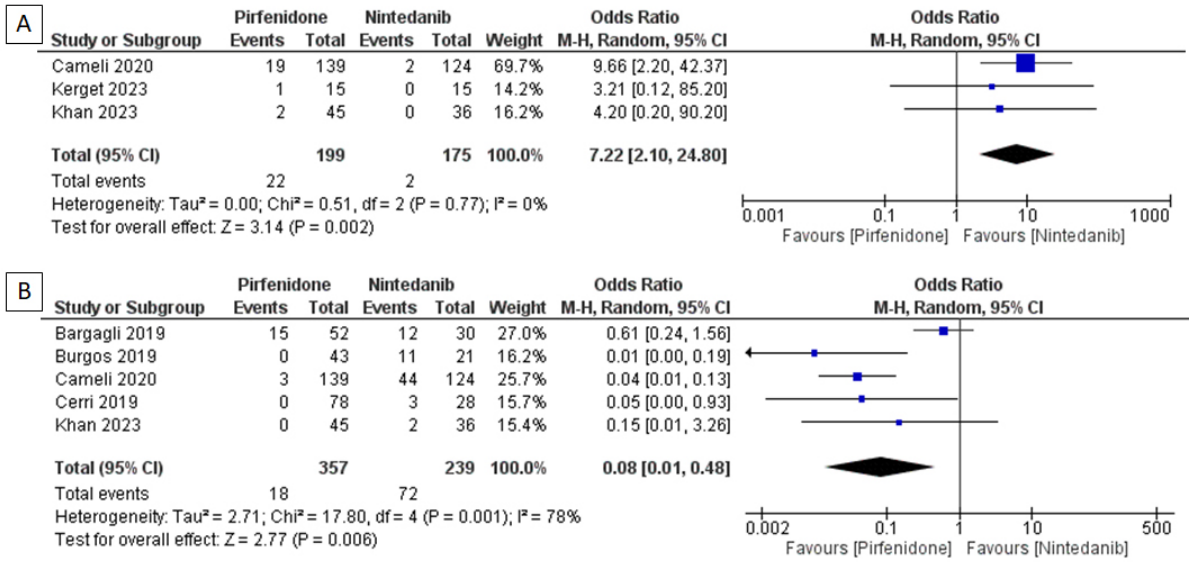

Fig. 5 – Forest plot comparing pirfenidone and nintedanib for: (A) skin rash; (B) diarrhea. CI – confidence interval.

Risk of bias

The quality of each observational study included in the analysis was assessed using the NOS tool [19], and one randomized prospective study was assessed using the MJS scale. Two independent reviewers performed the quality assessment, and disagreements on scores were resolved through discussion. Most studies (n = 9) [21, 23–27, 29, 30, 32] were rated as being of good or fair quality. Only two studies were assessed as poor quality [22, 31]. The quality of one study [28] was assessed using the MJS scale and was rated as good. Detailed quality assessments are presented in Figure 6 [21–27, 29–32] and Supplementary Table 2.

Publication bias

Funnel plots and the ER test were applied to evaluate publication bias for each pulmonary function. The ER test indicated no significant publication bias for DLco at 12 months, DLco at 6 months, FVC at 6 months, nor for ACM, nausea, diarrhea, and skin rash. However, significant publication bias was observed for FVC at 12 months (ER test p = 0.0045). This implies that the underrepresentation of smaller studies with neutral or negative results may inflate the pooled effect size. The results of sensitivity analyses showed that the overall treatment effect was generally robust, even though this finding should be interpreted cautiously. To better understand the actual impact on FVC at 12 months, future research with bigger sample sizes and prospective registration is required. Detailed results are shown in Figure 7 and Supplementary Table 3.

Subgroup analysis

Subgroup analyses based on study design were performed for DLco at 12 months, FVC at 12 months, and nausea to explore potential sources of heterogeneity. Other outcomes included only observational studies and were therefore not subgrouped.

For 12-month DLco, analysis of observational studies showed a small, non-significant improvement in the nintedanib group compared with the pirfenidone group (SMD = 0.14, 95% CI: -0.34 to 0.62; I^2 = 79%). This represented a slight reduction in heterogeneity compared with the overall analysis (SMD = 0.12, 95% CI: -0.28 to 0.52; I^2 = 80%) (Figure 8A [21, 24–26, 29]).

Study ID	Selection	Comparability	Outcome	Quality
Bargagli_2019	4	1	3	GOOD
Burgos_2019	3	1	0	POOR
Belhassen_2021	4	1	2	FAIR
Cameli_2020	4	1	3	GOOD
Cerri_2019	3	1	2	FAIR
Feng_2020	4	1	3	GOOD
Fournier_2022	4	1	3	GOOD
Khan_2023	4	1	1	FAIR
Marijic_2021	4	1	1	FAIR
Moor_2020	3	1	0	POOR
Ntolios_2021	4	1	3	GOOD

Fig. 6 – Risk of bias graph of included trials: risk of bias summary review authors' judgments about each risk of bias item presented as percentages across all included studies. Risk of bias table to assess the quality of the included studies: low risk of bias (green colored), unclear risk of bias (yellow colored), and high risk of bias (red colored).

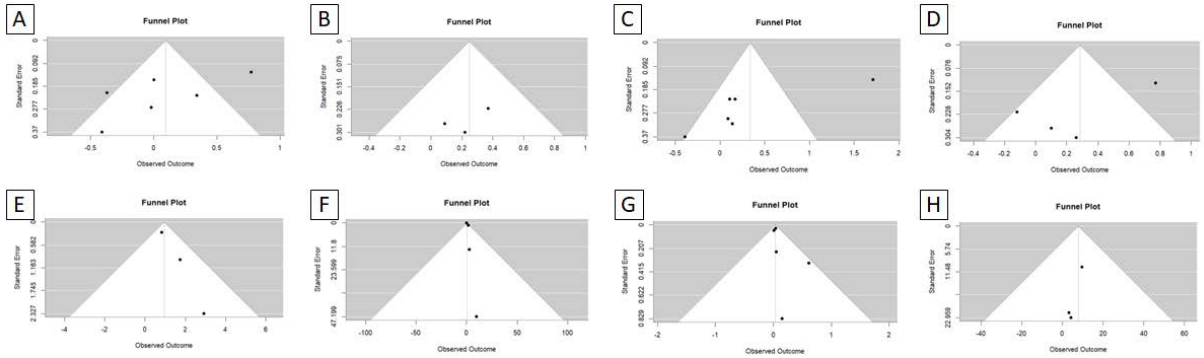

Fig. 7 – Funnel plots assessing publication bias for each endpoint: (A) DLco at 6 months; (B) DLco at 12 months; (C) FVC at 6 months; (D) FVC at 12 months; (E) all-cause mortality; (F) nausea; (G) skin rash; (H) diarrhea. DLco – diffusing capacity of the lungs for carbon monoxide; FVC – forced vital capacity.

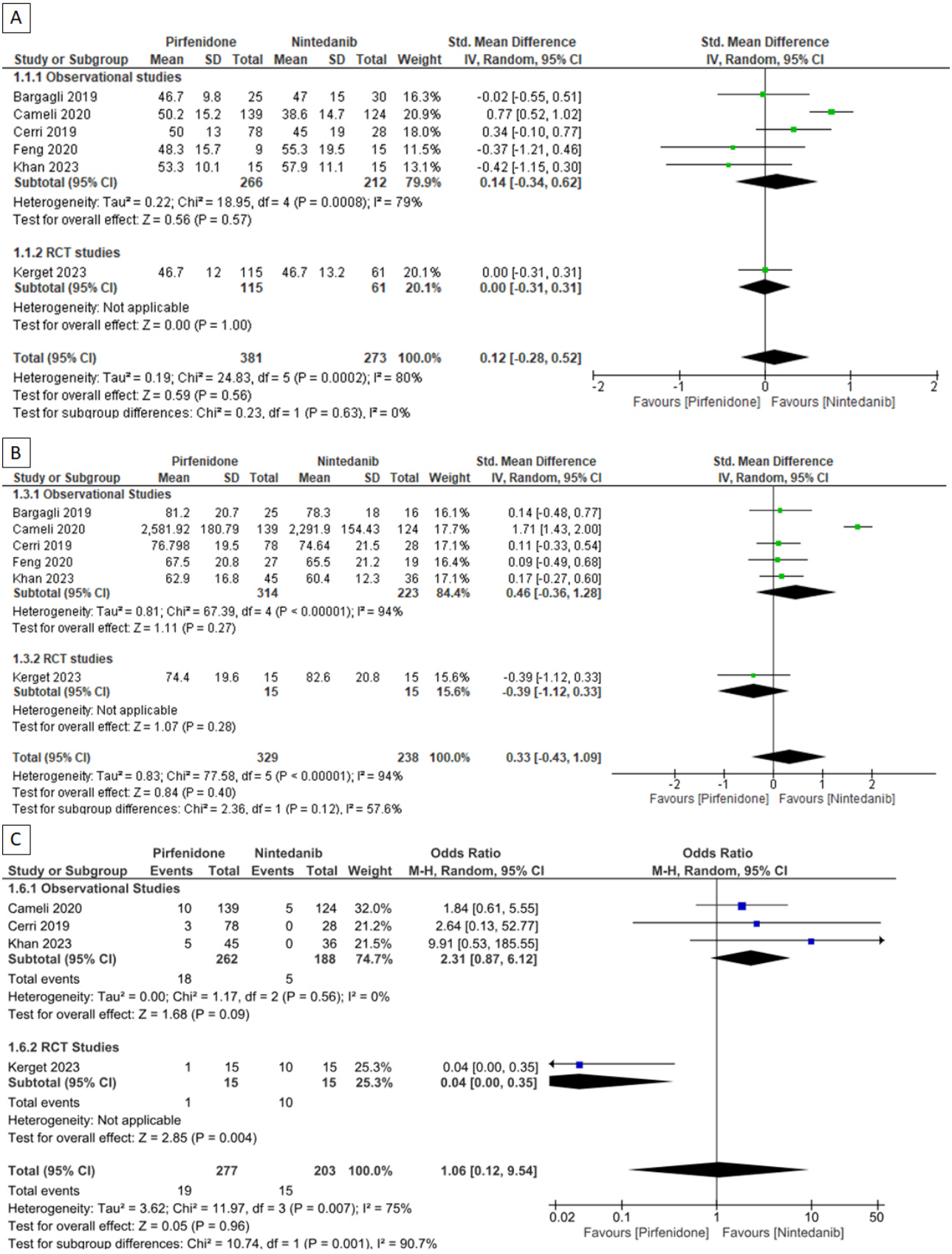

Fig. 8 – Forest plot of subgroup analysis comparing pirfenidone and nintedanib for: (A) DLco at 12 months; (B) FVC at 12 months; (C) nausea.
SD – standard deviation; Std – standard; CI – confidence interval; RCT – randomized controlled trials.

For 12-month FVC, the observational studies subgroup showed no change in heterogeneity compared with the overall analysis (SMD = 0.46, 95% CI: -0.36 to 1.28; I^2 = 94%). The overall effect size was SMD = 0.33 (95% CI: -0.43 to 1.09; I^2 = 94%) (Figure 8B [21, 24–26, 29]).

For nausea, subgroup analysis revealed differences in heterogeneity between study designs. In observational studies, the pooled effect was OR = 2.31 (95% CI: 0.87 to 6.12; I^2 = 0%), whereas in RCTs, the pooled effect was OR = 1.06 (95% CI: 0.12 to 9.54; I^2 = 90.7%) (Figure 8C [24, 25, 29]).

The forest plot analysis of nintedanib and pirfenidone showed the following effects: DLco at 12 months, z = 0.59, p = 0.56; FVC at 12 months, z = 0.84, p = 0.40; nausea, z = 0.05, p = 0.96.

Sensitivity analysis

Sensitivity analysis by sequential exclusion of each study revealed that heterogeneity was primarily driven by Bargagli et al. [21] and Cameli et al. [24] for the individual outcome. For DLco at 12 months and FVC at 12 months, heterogeneity becomes 8% and 0%, respectively, after removing Cameli et al [24]. Similarly, for the diarrhea outcome, removing the Bargagli et al. [21] study reduced the heterogeneity to 0%. Excluding these studies reduced heterogeneity to almost 0%, while the pooled effect estimates for DLco at 12 months and FVC at 12 months remained consistent in direction and magnitude. However, the overall effect size of diarrhea [21, 22, 24, 25, 29] outcome found to be significantly (p < 0.00001) improved with pirfenidone treatment (OR = 0.04, 95% CI (0.01, 0.10) (Figure 9 [21, 22, 24–26, 28, 29]).

The forest plot analysis of nintedanib and pirfenidone showed the following effects: DLco at 12 months, z = 0.10, p = 0.92; FVC at 12 months, z = 0.69, p = 0.49; diarrhea, z = 6.55, p < 0.00001.

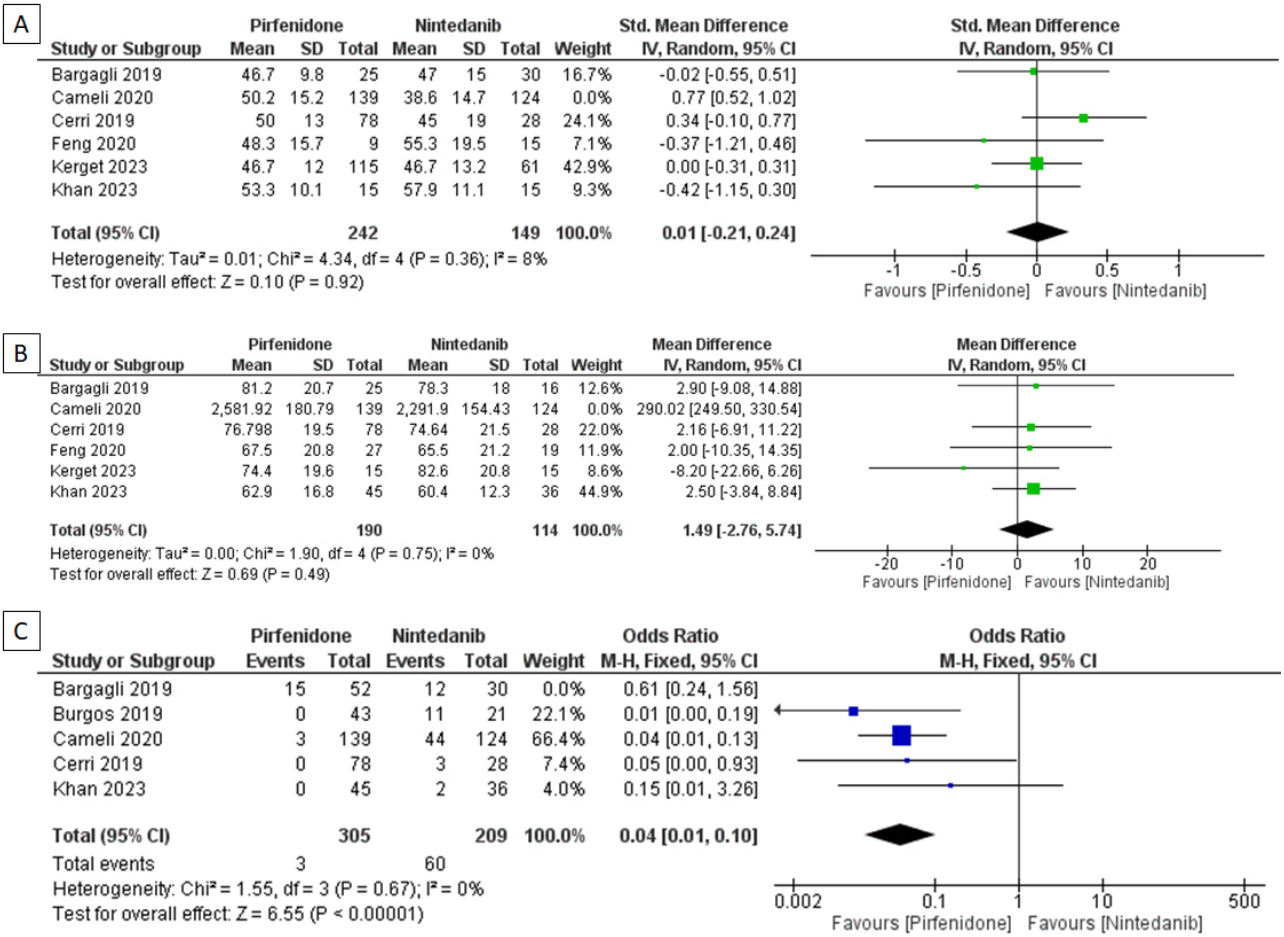

Fig. 9 – Forest plot of subgroup analysis comparing pirfenidone and nintedanib for: (A) DLco at 12 months; (B) FVC at 12 months; (C) diarrhea. FVC – forced vital capacity. For other abbreviations, see Figures 2 and 3.

Discussion

This systematic review and meta-analysis showed an overall reduction in DLco and FVC attributable to nintedanib and pirfenidone.

Although the overall safety profiles of the two antifibrotic agents were similar, they exhibited differences in specific adverse events. Nintedanib was associated with significantly fewer instances of diarrhea, whereas pirfenidone showed significantly fewer cases of skin rash (both p < 0.00001).

The DLco measures how effectively oxygen moves from the lungs into the bloodstream. In IPF, the lungs become scarred and stiff over time, leading to breathing difficulties and reduced lung function [33, 34]. DLco testing is often performed as part of the diagnostic workup for IPF and other respiratory conditions. Due to fibrotic changes in the lungs, DLco is frequently reduced in IPF, impairing gas exchange. The extent of lung tissue scarring and IPF progression can be evaluated through the severity of reduction in DLco [35, 36]. However, it is also important to note that the reduction of DLco in IPF is not always specific to a similar condition; it can be affected by other mechanisms as well, such as pulmonary hypertension, emphysema, or heart failure [37, 38]. Hence, DLco findings are typically interpreted in terms of different clinical and diagnostic findings. Studies that reported the association between DLco and IPF observed that this was a useful tool in monitoring and diagnosing IPF. Moreover, studies have found that DLco correlates with progression and disease severity in IPF, and changes in DLco over time can help predict outcomes and provide guidance for treatment decisions [24, 39, 40]. In general, DLco does not provide a diagnostic picture of IPF, but helps in the evaluation and management of patients with IPF. As a result, clinicians can assess the severity of the disease, monitor its progression, and make informed treatment choices based on this information [41, 42].

DLco improvement in patients with IPF may be explained by several underlying mechanisms. Inhibition of fibrosis: nintedanib and pirfenidone inhibit multiple tyrosine kinases, including FGF receptors, VEGF receptors and PDGF receptors. The receptors are involved in signaling pathways that promote proliferation, fibrosis, differentiation, and migration of fibroblasts, as well as angiogenesis. By inhibiting these pathways, nintedanib and pirfenidone may reduce lung fibrosis progression, lung function prevention, and potentially DLco improvement [43]. Anti-inflammatory effects: nintedanib and pirfenidone exhibit anti-inflammatory properties. Inflammation plays a crucial role in IPF pathogenesis, contributing to fibroblast activation, extracellular matrix deposition, and tissue remodeling. Nintedanib and pirfenidone may ameliorate lung damage and improve DLco by suppressing inflammation [41, 44]. The reduction of excessive extracellular matrix deposition: In IPF, excessive extracellular matrix components, such as collagen, accumulate in the lungs, leading to the formation of scar tissue [45, 46]. The inhibition of PDGF receptors by nintedanib and pirfenidone can result in a decrease in the proliferation and activation of fibroblasts, which are responsible for producing collagen and other extracellular matrix proteins. As a result of reducing the deposition of scar tissue, nintedanib and pirfenidone may improve lung function, including DLco [47]. Preservation of alveolar structure: The alveoli are minute air sacs responsible for gas exchange within the lungs. IPF distorts the alveolar structure due to fibrotic changes, impairing gas exchange and reducing DLco. Due to the antifibrotic properties of both drugs, further deterioration of lung function may be prevented, as well as an improvement in DLco, as a result of their antifibrotic effects [21].

As a whole, nintedanib and pirfenidone exhibit multi-targeted mechanisms of action. This includes inhibition of fibrosis, inflammation, and excessive extracellular matrix deposition, which contribute to its ability to improve DLco in patients with IPF. However, further research is required to fully understand the mechanisms of action of this compound and how it affects DLco in IPF [47]. As a result, in our research, DLco measurement is crucial for assessing antifibrotic agents for IPF. According to the pooled analysis, nintedanib and pirfenidone both revealed the potential to improve the DLco after 6 and 12 months of treatment.

FVC is an important measure of lung function and is the maximum amount of air that a person can forcefully exhale after taking a deep breath. FVC is often used as a diagnostic and monitoring tool in the context of IPF. In IPF, lung tissue becomes stiff, thickened, and scarred over time, which impairs its ability to expand and contract efficiently. This fibrotic process leads to a decrease in lung volume, including vital capacity. Therefore, FVC tends to decrease as IPF progresses, reflecting the decline in lung function. Clinically, monitoring FVC is essential in managing IPF because it is a marker for disease progression. A decline in FVC over time indicates worsening lung function and progression of the disease. Conversely, stabilization or improvement in FVC may suggest a positive response to treatment or a slower disease progression [35]. Moreover, FVC is often used with other pulmonary function tests, FEV1, and imaging studies (such as high-resolution computed tomography) to diagnose and monitor IPF, assess disease severity, and evaluate treatment response [48]. In summary, there is a strong association between FVC and IPF. Monitoring FVC over disease time is essential for assessing disease progression, determining treatment efficacy, and guiding clinical management decisions for patients with IPF.

The mechanism of action of nintedanib and pirfenidone involves targeting multiple tyrosine kinases, enzymes involved in various cellular processes such as cell growth, proliferation, and angiogenesis (formation of new blood vessels) [49]. In IPF, abnormal activation of certain growth factors and signaling pathways leads to excessive collagen deposition and other proteins in the lung tissue, causing fibrosis and impairing lung function, including reduced FVC. Nintedanib and pirfenidone work by inhibiting the activity of several key receptors and signaling pathways involved in fibrosis, particularly those mediated by growth factors such as FGF, PDGF, and VEGF [46, 47, 50]. By blocking these signaling pathways, nintedanib and pirfenidone help suppress fibroblast proliferation, reduce the production of extracellular matrix proteins like collagen, and inhibit the formation of new blood vessels within the fibrotic tissue. These effects collectively contribute to slowing down fibrosis progression and preserving lung function in patients with IPF, including improved FVC [48].

It is important to note that while pirfenidone and nintedanib can help reduce the decline in lung function and improve FVC in some patients with IPF, they may not

completely halt the progression of the disease, and individual responses to treatment can vary. Additionally, the exact mechanisms underlying their effects on FVC improvement may involve complex interactions within lung tissue and other systemic factors beyond their direct antifibrotic actions [48].

One limitation of this meta-analysis is that it included mostly non-RCTs, which limits the strength of causal inference. Most of the included studies were observational, introducing a risk bias. In addition, without any head-to-head trials to better estimate relative effects between interventions, no strong conclusions can be made on comparative effectiveness based on the findings of this meta-analysis. There was a high degree of heterogeneity among the studies, presumably due to differences in characteristics of patients at baseline, disease severity, concomitant therapies, and follow-up time. Any confounding bias could affect our pooled estimates of effect, resulting in either overestimation or underestimation of the treatment effect. The residual heterogeneity that we were unable to explain in the subgroup and sensitivity analyses should also be considered in the interpretability of this systematic review. Therefore, high-quality RCTs, especially head-to-head trials, are required to address the limitations of non-RCTs, strengthen causal inference, and better inform evidence-based clinical decision-making.

Bias may have existed because the search was limited to English-language publications only. In addition, studies were excluded from the meta-analysis if the publication presented results of the mentioned outcomes in forms that could not be converted into means and SDs, which may have influenced the results.

Conclusion

In this evaluation, quantitative evidence suggests that both nintedanib and pirfenidone are effective in slowing the progression of idiopathic pulmonary fibrosis in terms of improvement in diffusion capacity of the lungs for carbon monoxide and forced vital capacity at 6 and 12 months of treatment with similar safety profiles. Therefore, pirfenidone and nintedanib can be considered for managing idiopathic pulmonary fibrosis progression. Consequently, further observational and randomized controlled studies are required to evaluate the robust evidence regarding nintedanib and pirfenidone effects on lung function.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Table 1

Database search strategy for nintedanib and pirfenidone in idiopathic pulmonary fibrosis

Search Strategy (last search date 31 August 2025)

Embase (Ovid):

1. idiopathic pulmonary fibrosis.tw.
2. cryptogenic fibrosing alveolitis.tw.
3. usual interstitial pneumonitis.tw.
4. usual interstitial pneumonia.tw.
5. fibrosing alveolitis.tw.
6. IPF.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. pirfenidone.tw.
9. nintedanib.tw.
10. 8 or 9
11. 7 and 10
12. limit 11 to (human)

PubMed:

((((((((idiopathic pulmonary fibrosis[MeSH Terms]) OR (idiopathic pulmonary fibrosis[Text Word])) OR (cryptogenic fibrosing alveolitis[Text Word])) OR (usual interstitial pneumonitis[Text Word])) OR (usual interstitial pneumonia[Text Word])) OR (fibrosing alveolitis[Text Word])) OR (IPF[Text Word])) AND (((pirfenidone [MeSH Terms]) OR (pirfenidone[Text Word])) OR ((nintedanib[MeSH Terms]) OR (nintedanib [Text Word])))) AND Filters: Humans.

Scopus:

((TITLE-ABS-KEY ("PIRFENIDONE") OR TITLE-ABS-KEY ("NINTEDANIB")) AND ((TITLE-ABS-KEY (" IDIOPATHIC PULMONARY FIBROSIS") OR TITLE-ABS-KEY ("CRYPTOGENIC FIBROSING ALVEOLITIS") OR TITLE-ABS-KEY ("USUAL INTERSTITIAL PNEUMONITIS") OR TITLE-ABS-KEY ("USUAL INTERSTITIAL PNEUMONIA") OR TITLE-ABS-KEY ("FIBROSING ALVEOLITIS") OR TITLE-ABS-KEY ("IPF")))

ClinicalTrials.gov

idiopathic pulmonary fibrosis AND nintedanib AND pirfenidone

Google Scholar

idiopathic pulmonary fibrosis AND nintedanib AND pirfenidone

Supplementary Table 2

Study quality assessment trough Modified Jadad scale

Jadad tool	Kerget 2023	
	yes/no	points
Was the study described as randomized?	yes	1
Was the method of randomization appropriate?	yes	1
Was the study described as blinding?	no	0
Was the blinding method appropriate?	no	0
Was there a description of withdrawal and dropouts?	no	0
Was there a clear description of the inclusion/exclusion criteria?	yes	1
Was the method used to assess the adverse effect described?	yes	1
Was the method of statistical analysis described?	yes	1
Total score		5

Supplementary Table 3

Findings of Egger's regression test

Outcomes	Z-value	b (95% CI)	*p*-value	Interpretation
DLco at 6 months	-0.6020	0.9419 (-1.3329, 3.2166)	0.5472	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
DLco at 12 months	-1.6993	0.9129 (-0.0686, 1.8945)	0.0893	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
FVC at 6 months	-1.3631	1.0755 (-0.0974, 2.2485)	0.1729	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
FVC at 12 months	-2.8408	2.3573 (0.9397, 3.7748)	0.0045	Z < 1.96 indicates $p > 0.05$ Presence of publication bias
All-cause mortality	1.2481	0.5441 (-0.2177, 1.3059)	0.2120	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
Nausea	0.9630	0.0385 (-0.5407, 0.6177)	0.3355	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
Skin rash	-0.3155	14.6802 (-30.7697, 60.1301)	0.7524	Z < 1.96 indicates $p > 0.05$ No presence of publication bias
Diarrhea	0.9805	0.0099 (-0.0613, 0.0812)	0.3269	Z < 1.96 indicates $p > 0.05$ No presence of publication bias

CI – confidence interval; DLco – diffusing capacity of the lungs for carbon monoxide; FVC – forced vital capacity.