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Review Article

Efficacy and safety of nintedanib combined with pirfenidone versus monotherapy in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Abstract: This systematic review and meta-analysis, registered in PROSPERO (CRD420261306598) and conducted following PRISMA guidelines, evaluates the efficacy and safety of nintedanib combined with pirfenidone versus monotherapy in idiopathic pulmonary fibrosis (IPF). PubMed, Embase, Cochrane Library, Web of Science, and Chinese databases (CNKI, Wanfang, VIP) were searched from inception to January 15, 2026. Eleven studies comprising 629 unique patients were included. For efficacy, the combination therapy group showed a trend toward reduced monthly forced vital capacity (FVC) decline (mean difference [MD]=8.50 mL, 95% CI: -1.18 to 18.18, P=0.085), which became significant after excluding a small-sample study (MD=11.76 mL, 95% CI: 4.71 to 18.81, P<0.05). The 6-minute walk distance (6MWD) significantly improved with combination therapy (MD=21.81 m, 95% CI: 4.84 to 38.77, P=0.012). For safety, no significant differences were found between groups in gastrointestinal adverse reactions (risk ratio [RR]=0.67, 95% CI: 0.26 to 1.70), treatment discontinuation (RR=1.23, 95% CI: 0.41 to 3.73), or serious adverse events (SAEs) (RR=0.93, 95% CI: 0.24 to 3.65). Subgroup and sensitivity analyses confirmed result robustness. In conclusion, nintedanib combined with pirfenidone may offer additional benefits in preserving lung function and improving exercise capacity in IPF patients without compromising safety, supporting its consideration as a therapeutic strategy.

Keywords: Idiopathic pulmonary fibrosis, nintedanib, pirfenidone, combination therapy, meta-analysis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, life-threatening lung disease of unknown etiology, characterized by progressive interstitial pulmonary fibrosis as its core feature. Its pathologic process is irreversible, presenting with progressive dyspnea and persistent decline in lung function, which seriously endangers patients' health [1]. As the most common type of idiopathic interstitial pneumonia, IPF has an extremely poor prognosis: without effective treatment, the median survival time of patients is only 2-3 years, and the 5-year survival rate is merely 20%-40%, with survival outcomes even worse than many common malignant tumors [2, 3]. Globally, IPF-related mortality is on the rise, with significant differences in sex, age, and region; mortality rates are particularly prominent among males and the elderly population [4].

Nintedanib and pirfenidone, both antifibrotic drugs currently approved worldwide, have addressed the limitation of limited efficacy in traditional treatments. The pathologic core of IPF lies in excessive fibroblast proliferation and extracellular matrix deposition caused by abnormal repair after alveolar epithelial cell injury, involving synergistic activation of multiple pathways such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF). These two drugs block the fibrotic process through complementary mechanisms [5, 6]: nintedanib directly inhibits fibroblast activation by targeting multiple kinases including

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platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR); pirfenidone, on the other hand, inhibits TGF-β-mediated signaling pathways and possesses both anti-inflammatory and antioxidant activities [7]. Large-scale studies [8] have confirmed that antifibrotic therapy can significantly improve patients' survival: nintedanib and pirfenidone reduce the risk of death in IPF patients by 15%-31%, and this benefit remains consistent across patients of different ages and comorbidity statuses. Long-term treatment data further verify their clinical value: for IPF patients receiving antifibrotic drug treatment for ≥1 year, the 2-year survival rate can reach 89.0%, and the 5-year survival rate increases to 52.4% - much higher than the survival level of populations not receiving standardized treatment, bringing significant survival benefits to IPF patients [9].

Although the survival-improving effect of antifibrotic drugs has been confirmed, many unresolved issues remain in clinical practice: no consensus has been reached on differences in efficacy and safety between different drugs, treatment tolerance, or selection of treatment strategy [10, 11]. The geographical imbalance in global IPF mortality suggests that the accessibility and standardization of treatment in some regions still needs to be enhanced. Current studies have found that when molecules regulating TGF-β signaling are used in combination with nintedanib and pirfenidone, the antifibrotic effect can be enhanced by synergistically inhibiting Smad and translocation - suggesting that combination therapy may improve efficacy through multi-target synergy [12]. However, the meta-analysis by Finnerty et al. (2021) [13] focused on antifibrotic treatment effects in IPF and non-IPF patients, without investigating the combination of pirfenidone and nintedanib; additionally, that study centered on the universality of monotherapy in IPF and non-IPF populations, with no discussion of combination therapy effects. Although the meta-analysis by Lee (2023) [14] focused on the nintedanib-pirfenidone combination regimen, it included only 4 studies, had a single evaluation dimension (focusing solely on safety and tolerance), and did not incorporate core efficacy indicators - thus failing to clarify the clinical benefit value of combination therapy.

Based on this, this study aimed to conduct a systematic review and meta-analysis, comprehensively integrating existing clinical evidence to explore the efficacy and safety of nintedanib combined with pirfenidone versus monotherapy for the treatment of IPF. It will clarify differences between the two groups in core efficacy and safety indicators, and verify the consistency of survival benefits of antifibrotic combination therapy across different populations - providing reliable evidence for optimizing clinical IPF treatment strategy.

Materials and methods

Literature search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was structured based on the predefined Population, Intervention, Comparison, and Outcome (PICO) framework. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD420261306598). Computerized searches were conducted to collect comprehensive single-arm clinical study literature on nintedanib combined with pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF). The search was restricted to English databases, including PubMed, Embase, Cochrane Library, and Web of Science Core Collection. The search strategy was constructed using a combination of MeSH terms and free words, with the specific English search formula as follows: ("idiopathic pulmonary fibrosis"[Mesh] OR "IPF"[Title/Abstract]) AND ("nintedanib"[Title/Abstract] AND "pirfenidone"[Title/Abstract]) AND ("combination therapy"[Title/Abstract] OR "concomitant treatment"[Title/Abstract]) AND ("single-arm study"[Title/Abstract] OR "before-after study"[Title/Abstract] OR "pre-post study"[Title/Abstract]). The search time frame for both English and Chinese databases was from the inception of each database to January 15, 2026. Supplementary search strategies included: ① manual retrieval of the reference lists of included studies; ② screening of literature such as abstracts from international conferences in related fields; ③ contacting corresponding authors by email to obtain original data or supplementary information for studies with incomplete data. Detailed search histories with all steps and results are provided in the Supplementary Materials.

Inclusion and exclusion criteria

Inclusion criteria: Inclusion criteria were defined using the PICO framework: a. Study type: Randomized controlled trials (RCTs) and publicly published single-arm self-controlled before-after clinical studies, which must fully report paired follow-up data on efficacy and safety before and after treatment with a clear and traceable study design. b. Study population: Adult patients with a definite diagnosis of IPF in accordance with current international guidelines. c. Intervention measures: The experimental group received combined treatment with nintedanib and pirfenidone; the control group received nintedanib monotherapy, pirfenidone monotherapy, or placebo. d. Outcome indicators: Primary efficacy indicators included annual rate of forced vital capacity (FVC) decline (mL/year or % predicted/year), progression-free survival, and all-cause mortality; secondary indicators included diffusing capacity for carbon monoxide (DLCO), 6-minute walk distance (6MWD), quality of life scores, and incidence of various adverse events.

Exclusion criteria: a. Studies with incomplete outcome indicator data, or those where effect sizes and confidence intervals required for pooled analysis cannot be calculated from raw data; b. Duplicate publications: only the version with the most complete data and longest follow-up duration was retained; c. Study types including animal experiments, in vitro cell experiments, reviews, case reports, or expert commentaries without original clinical data; d. Study populations with comorbidities such as other interstitial lung diseases, malignant tumors, or severe organic lesions of the heart, liver, and kidneys, which may interfere with the evaluation of efficacy and safety; e. Non-standard interventions, such as combination with other antifibrotic drugs, unclear dosage, or treatment duration <3 months.

Data extraction

A pre-designed standardized data extraction form was used for data extraction, with the specific process as follows: Shengbo Xu and Wen Lu independently performed double-blind data extraction. Prior to extraction, unified training was conducted by Rui Liu to clarify the definition and standards of each extraction item, with the participation of all four researchers to ensure the consistency of extraction results. Extracted content included: ① basic study information (first author, publication year, study region, sample size); ② baseline characteristics of the study population (mean age, gender ratio, baseline FVC% predicted, type and proportion of comorbidities); ③ details of intervention measures (initial doses of nintedanib and pirfenidone, basis for dosage adjustment, treatment follow-up duration); ④ outcome indicator data (number of cases with gastrointestinal adverse reactions, total sample size, mean difference (MD) and 95% confidence interval (CI) of annual FVC% predicted decline rate); ⑤ methodological information (standards for efficacy and safety evaluation, follow-up protocol, attrition rate, and handling methods of lost-to-follow-up cases).

Dispute resolution: After data extraction, Shengbo Xu and Wen Lu cross-verified the results. Disputes were resolved through discussion and consultation; if no consensus was reached, Lan Li and Rui Liu participated in the evaluation to finalize the included data.

Patient counting rules for descriptive analysis

Specific counting rules were established to quantify the study population accurately based on different study designs. For controlled studies, patients in the combination and monotherapy groups were counted separately as unique individuals. For self-controlled single-arm studies, the same patients were included in both groups for descriptive analysis but counted only once in the total unique patient population to avoid duplication. All comparative meta-analyses were based solely on controlled study data, and thus unaffected by these descriptive counting rules.

Risk of bias assessment

An internationally recognized stratified assessment strategy was adopted for literature quality evaluation to ensure the objectivity and comparability of results. For included RCTs, the Cochrane Risk of Bias Assessment Tool [15] was used, covering 7 core domains: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases. Each domain was classified into three levels:

"low risk", "high risk", and "unclear". For non-randomized studies (including retrospective cohorts, prospective observational studies, and single-arm studies), the Newcastle-Ottawa Scale (NOS) [16] was used. This scale has a total score of 9 points, divided into 3 domains: selection of study population (4 points, including representativeness of the exposed group, selection of the non-exposed group, determination of exposure, and selection of non-confounding factors), comparability between groups (2 points, including adjustment for important confounders and additional confounders), and outcome measurement (3 points, including determination of outcomes, completeness of follow-up, and duration of follow-up). For the 'additional confounding factor correction' dimension in the NOS scale (2 points), the scoring criteria were defined as follows: 1 point for correcting 1-2 key additional confounders (e.g., smoking history, concurrent lung infection, nutritional status, comorbidities such as hypertension/diabetes), and 2 points for correcting ≥3 additional confounders; 0 point if no additional confounders were corrected.

Quality assessment was independently completed by Shengbo Xu and Wen Lu, who received unified training by Rui Liu to calibrate standards prior to assessment. Disputes during the assessment process were resolved through mutual discussion or consultation with a third senior researcher. Final quality grading criteria: For RCTs, "high quality" was defined as ≥6 domains rated as "low risk", and "low quality" as ≥3 domains rated as "high risk"; for the NOS scale, "high quality" was 8-9 points, "moderate quality" was 6-7 points, and "low quality" was ≤5 points. Kappa consistency test was used to verify the inter-assessor consistency, with a Kappa value ≥0.75 indicating good consistency.

Statistical methods

All statistical analyses were performed using R 4.3.1 software (R Foundation for Statistical Computing, Vienna, Austria) and its supporting packages (meta, metaprop, dplyr). The significance level was set at $\alpha=0.05$, and all *P*-values were two-tailed.

For dichotomous data, the metaprop function was used for pooled analysis. Incidence rates were converted to continuous variables through logit transformation, and the pooled effect size was the pooled incidence rate with 95% CI to reflect the true risk of gastrointestinal adverse reactions after combination therapy. For continuous data, the mean difference (MD) between pre- and post-treatment values was calculated, and the metacont function was used for pooled analysis. The pooled MD and 95% CI were computed using the inverse variance method; a negative MD indicated a slowed rate of lung function decline after treatment, representing clinical benefit.

Subgroup analysis was conducted for Asian and European populations using the same statistical methods as the overall analysis. Pooled effect sizes, 95% CIs, and heterogeneity parameters were calculated for each subgroup, and interaction tests between subgroups were performed to explore the regulatory role of regional factors on the efficacy of combination therapy and the statistical significance of differences.

Heterogeneity testing and handling: The Q test was used for qualitative heterogeneity assessment; a *P*-value <0.1 in the Q test indicated significant heterogeneity between studies. The I^2 statistic was used for quantitative heterogeneity assessment, with the grading criteria: low heterogeneity ($I^2 \leq 50\%$), moderate heterogeneity ($50\% < I^2 < 75\%$), and high heterogeneity ($I^2 \geq 75\%$). For results with high heterogeneity, subgroup analysis was used to explore the sources of heterogeneity, and the effect on pooled results was discussed in the Discussion section.

The one-by-one study exclusion method was used to verify the stability and reliability of the pooled results. One included study was excluded sequentially, and pooled analysis was re-performed using the same statistical methods. Changes in effect size, 95% CI, and heterogeneity indicators before and after exclusion were compared. If the 95% CI of the pooled effect size showed no directional change after excluding any study, the overall result was considered stable; if the result changed significantly after excluding a specific study, that study was identified as a highly influential study, and its influencing factors were analyzed in detail in the Discussion.

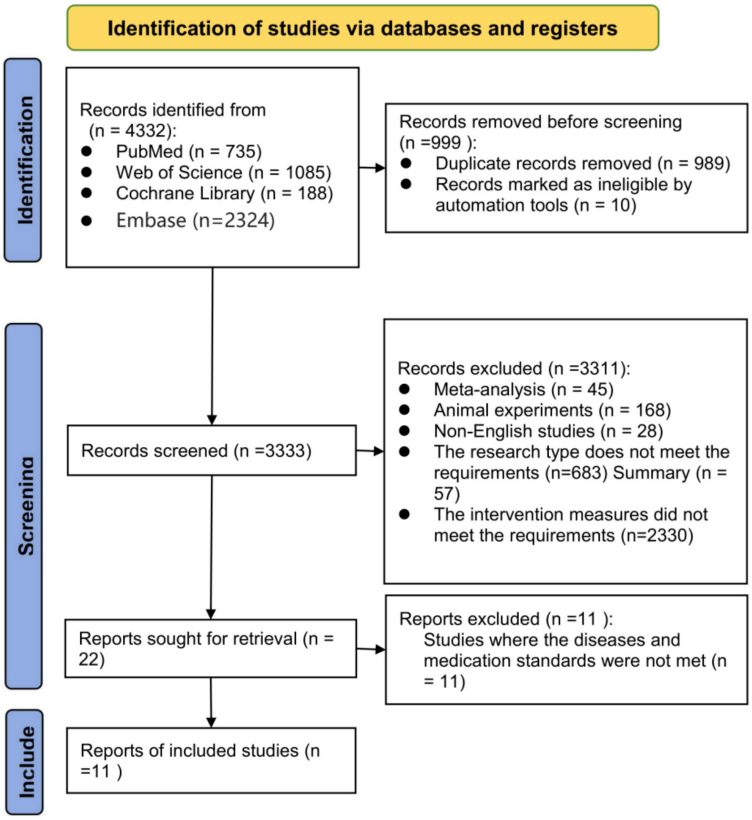

Figure 1. Literature screening flowchart.

Results

Literature inclusion process

This study conducted literature screening in strict accordance with the PRISMA guidelines. An initial search of English databases yielded 4332 relevant papers, and 3333 articles remained after deduplication using EndNote X9 software. After reading the titles and abstracts, 3311 articles were excluded, including animal experiments, *in vitro* studies, reviews, case reports, and studies with inconsistent intervention measures. The remaining 22 articles were further evaluated by full-text reading, and 11 studies with incomplete data or non-standard interventions were ultimately excluded. A total of 11 eligible studies were included [17-27], consisting of 3 randomized controlled trials (RCTs) [17-19], 4 retrospective cohort studies [20, 23-25], and 4 single-arm studies [21, 22, 26, 27] (**Figure 1**).

Basic characteristics of included studies

A total of 11 eligible studies were included, covering multiple countries and regions in Asia (Japan, South Korea, India), Europe (United Kingdom, France, Spain, etc.), and the Americas (United States, Canada). The publication years ranged from 2015 to 2025, showing overall multicenter and cross-regional research characteristics. The 11 included studies comprised 629 unique patients, contributing 417 patient-exposures to the combination therapy group (185 from controlled studies and 232 from single-arm studies) and 444 patient-exposures to the monotherapy group (212 from controlled studies and 232 from single-arm studies) for the descriptive analysis of baseline characteristics.

Regarding study design: 3 were RCTs, of which 2 were multinational and multicenter studies [18, 19], and 1 was a single-country dose-escalation RCT [17]; 8 were non-randomized studies, including 4 retrospective cohort studies [21, 22, 26, 27], 2 prospective observational studies [24, 25], 1 single-arm open-label Phase IV study [27], and 1 pharmacokinetic special study [20]. In terms of sample size: the sample size of the combination group varied significantly, ranging from 3 cases [19] to 89 cases [27], among which 4 studies had a combination group sample size ≥45 cases, with sufficient statistical power; the sample size of the monotherapy control group ranged from 4 cases to 64 cases. Some studies balanced baseline differences between groups through propensity score matching [23] or three-group parallel design [24, 25].

Baseline characteristics of the study population showed that the included patients were predominantly male, with a mean age ranging from 64.1 years to 70.1 years, reflecting the epidemiological feature of high incidence in middle-aged and elderly males. All interventions were combination therapy with nintedanib and pirfenidone, with regional differences in dosage regimens: in Asian studies, the dosage of pirfenidone was mostly 400-1800 mg/d, and nintedanib was mostly 100-150 mg twice

daily (bid); in European and American studies, pirfenidone was mostly titrated to 801 mg three times daily (tid), and nintedanib was mostly 150 mg bid. Some studies adopted a low-dose combination regimen [24, 25] to improve tolerance.

Regarding outcome indicators: core efficacy indicators were mainly lung function-related data, including forced vital capacity (FVC) decline rate/change and 6-minute walk distance (6MWD). Core safety indicators focused on the incidence of gastrointestinal adverse reactions, treatment discontinuation rate, and incidence of serious adverse events (SAEs). Secondary safety indicators included elevated liver enzymes, weight loss, and rash/photosensitivity reactions, as shown in **Table 1**.

Results of literature quality assessment

A total of 11 studies were included, among which 3 were RCTs [17-19] and 8 were non-randomized studies [20-27]. Through stratified quality assessment, the overall quality distribution was reasonable, with no extremely low-quality studies, and the core outcome data were highly reliable.

Among the 3 RCTs: 2 were rated as high-quality [17, 18], and 1 was rated as low-quality [19]. High-quality RCTs all had complete random sequence generation and allocation concealment mechanisms, adopted double-blind design to reduce performance bias, standardized outcome measurement with good data integrity (follow-up completion rate ≥90%), and no risk of selective reporting, providing high-level core evidence for the meta-analysis. Ikeda et al. (2022) [19] was classified as high risk for other biases, mainly due to an extremely small sample size (only 7 patients in total) leading to severe sampling bias, unadjusted baseline disease severity and other confounding factors, and the absence of blinding design that superimposed performance and detection bias. The low-quality RCT had a sample size of only 7 cases, leading to significant sampling bias; the lack of blinding increased the risk of participant and outcome assessor bias; meanwhile, confounders such as baseline disease severity were not adjusted. This study needed to be excluded through sensitivity analysis to reduce interference with the pooled results.

The 8 non-randomized studies were evaluated using the NOS scale, with total scores ranging from 7 to 9 points: 7 were high-quality studies, and 1 was a moderate-quality study (Huh et al. 2021, 7 points).

The study by Huh et al. balanced key confounders such as age, gender, and baseline lung function through propensity score matching, achieving full marks in the comparability between groups; meanwhile, the exposed and non-exposed groups were from the same source, outcomes were measured using objective detection standards, and follow-up was complete, resulting in a low overall risk of bias. Most studies performed well in the selection and comparability domains, and all achieved full marks in the outcome measurement domain. The main source of bias was the incomplete exclusion of additional confounders such as diet and metabolic status. The moderate-quality study (Huh et al. 2021) had a single-center design, leading to insufficient representativeness of the non-exposed group, but no bias related to outcome measurement or follow-up.

A common advantage of the included studies was the high reliability of outcome measurement: all outcome indicators adopted objective detection methods or internationally unified criteria, ensuring the credibility of the pooled data in the meta-analysis. The main biases were insufficient confounder adjustment in non-randomized studies, selection bias in some single-center studies, and performance bias in small-sample RCTs. However, the effect of these biases on the results could be partially controlled through statistical methods such as sensitivity analysis and subgroup analysis, providing robust support for the conclusions (**Tables 2**, **3**).

Forced vital capacity (FVC) decline rate

Five studies [18, 19, 23-25] involving 410 patients (164 in the combination group and 246 in the monotherapy group) were included, with the outcome indicator being monthly FVC decline (mL/month). Analysis using a random-effects model showed that the monthly FVC decline in the combination therapy group was reduced by an average of 8.50 mL compared to the monotherapy group (MD=8.498, 95% CI: -1.1815-18.1781, z=1.72, P=0.085). The difference was not significant, but there was a trend

Table 1. Characteristics of included studies

Number	Study	Country	Study Design	Sample Size of the Combined Group	Sample Size of the Control Group	Male	Age (Mean ± SD)	Intervention Measures	Core Efficacy Endpoints	Core Safety Endpoints	Secondary Safety Endpoints
1	Ogura, T, et al. (2015) [17]	Japan	Randomized, double-blind, phase II, dose escalation trial	21	Nintedanib monotherapy + placebo group: 29 (including placebo)	70.00%	65.2 ± 8.2 years old	Combined group: Nintedanib (50/100/150 mg bid) + Pirfenidone (200/400/600 mg tid); Control group: Nintedanib monotherapy (50/100/150 mg bid) or placebo	FVC stability (no significant decline); Nintedanib exposure (lower by 32%-41% in the combination group compared to the monotherapy group)	Incidence of gastrointestinal adverse reactions (combined group 69.2%, control group 54.5%); treatment interruption rate (combined group 15.4%, control group 18.2%)	Liver enzyme elevation (0% in the combined group, 18.2% in the control group); rash/photosensitivity reaction (≤5.3%); nausea/vomiting (30.8%/38.5% in the combined group, 9.1%/0% in the control group)
2	Vancheri, C, et al. (2018) [18]	Several countries (Italy, Germany, Canada, etc.)	Open-label, randomized controlled trial (INJOURNEY Trial)	53	Nintedanib monotherapy group: 52	82.70%	68.9 ± 6.6 years old	Combined group: Nintedanib 150 mg bid + Pirfenidone (titrated to 801 mg tid); Control group: Nintedanib 150 mg bid	FVC change (combination group -13.3 mL, control group -40.9 mL); 6MWD stable	Incidence of gastrointestinal adverse reactions (combined group 69.8%, control group 52.9%); incidence of severe adverse reactions (combined group 3.8%, control group 9.8%)	Diarrhea (37.7% in the combined group, 31.4% in the control group); nausea/vomiting (41.5%/28.3% in the combined group, 11.8%/11.8% in the control group); liver enzyme elevation (5.7% in the combined group, 0% in the control group)
3	Ikeda, S, et al.(2022) [19]	Japan	Randomized, open-label, phase II trial	3	Nintedanib monotherapy group: 4	100%	70.1 ± 6.8 years old	Combined group: Nintedanib 150 mg bid + Pirfenidone (600-1800 mg/d); Control group: Nintedanib 150 mg bid	6-month ≥5% FVC decline rate (combination group 66.7%, control group 50.0%); FVC decline inhibition (both groups showed a slower reduction compared to baseline)	Treatment interruption rate (combined group 66.7%, control group 0%); dose adjustment rate (combined group 66.7%, control group 75.0%)	Diarrhea (33.0% in the combined group, 100% in the control group); liver enzyme elevation (both grade 1, 33.0% in the combined group, 25.0%-75.0% in the control group); acute exacerbation (33.0% in the combined group, 0% in the control group); weight loss (33.0% in the combined group, 50.0% in the control group)
4	Richeldi, L, et al. (2019) [20]	Britain	Open-label, two-arm pharmacokinetic trial	37 (Group 1: 20; Group 2: 17)	No single drug control group (both arms were combined treatment sequences)	70.30%	70.0 ± 7.7 years old	Group 1: Nintedanib 150 mg single dose → Pirfenidone 801 mg tid → Nintedanib 150 mg single dose; Group 2: Pirfenidone 801 mg tid → Nintedanib 150 mg bid	No significant difference in efficacy (pharmacokinetic focus); Nintedanib/AUC has no interaction effect	Incidence of any adverse reactions (group 1 70.0%, group 2 88.2%); incidence of drug-related adverse reactions (group 1 60.0%, group 2 41.2%)	Diarrhea (group 1 30.0%, group 2 23.5%); nausea/vomiting (group 1 25.0%/15.0%, group 2 17.6%/11.8%); treatment interruption rate (group 1 15.0%, group 2 0%)

5	Hisata, S, et al. (2020) [21]	Japan	Multicenter, retrospective, observational study	46	No single drug control group	82.60%	68.0 ± 8.5 years old	Combined group: Nintedanib + Pirfenidone (32 cases with Nintedanib escalated to current anti-fibrotic therapy; 13 cases with Pirfenidone escalated to current; 1 case with both initiated simultaneously)	No individual efficacy endpoint, focusing on safety and tolerability	Any adverse drug reaction (ADR) incidence (71.7%); treatment permanent interruption rate (30.4%); incidence of severe ADR (4.3%)	Loss of appetite (39.1%); diarrhea (34.8%); severe ADR type (hepatotoxicity 1 case, pneumothorax 1 case); higher discontinuation rate for patients in Japanese Respiratory Society (JRS) grade II/III (90.9% vs 61.1%)
6	Huh, J.Y., et al. (2021) [22]	South Korea	Retrospective observational study	22	No single drug control group	Not reported	Not reported	Combined group: 95.5% were on stable doses of Pirfenidone (average 1773.9 mg/d, median use 31 months) combined with Nintedanib	Significantly reduced FVC decline rate (pre-combination -0.41% predicted value/month, post-combination -0.12% predicted value/month, P=0.045)	Incidence of major adverse reactions (diarrhea 63.6%); treatment interruption rate (15.6%, 3 cases due to anorexia/dyspepsia)	Gastrointestinal discomfort/abdominal pain (13.6%); anorexia (9.1%)
7	Huh, J-Y, et al. (2023) [23]	South Korea	Multicenter retrospective cohort study (propensity score matching)	45	Pirfenidone monotherapy group: 64	82.20%	68.8 ± 6.2 years old	Combined group: Nintedanib (229.5 mg/d) + Pirfenidone (1800 mg/d); Control group: Pirfenidone monotherapy	FVC decline rate (combination group -10.6 mL/month, control group -44.8 mL/6 months); Disease progression rate (DP5: combination group 21.4%, control group 26.8%)	Incidence of adverse reactions (combined group 71.1%, control group 82.8%); treatment interruption rate (combined group 26.7%)	Diarrhea (43.8% in the combined group, 14.1% in the control group); anorexia (31.2% in the combined group, 53.1% in the control group); incidence of serious adverse reactions (9.4% in the combined group, 3.1% in the control group); pruritus (6.2% in the combined group, 31.2% in the control group)
8	Patil, S, et al. (2023) [24]	India	Single-center, prospective observational study	28	Pirfenidone monotherapy group: 28; Nintedanib monotherapy group: 28	Not reported	Not reported	Combined group: Nintedanib 100 mg tid + Pirfenidone 400 mg tid; Control group 1: Pirfenidone 1800-2400 mg/d; Control group 2: Nintedanib 100 mg tid	FVC stability (combination group optimal, P<0.0089); 6MWD improvement (combination group P<0.0017); Radiological progression rate (combination group lowest, P<0.0019)	Incidence of gastrointestinal adverse reactions (significantly higher in the single-agent control group, slightly higher in the combined group); acute exacerbation rate (lowest in the combined group, P<0.0004)	Nausea/vomiting/weight loss (significantly in the single-agent control group, slightly in the combined group); recovery time of heart rate/oxygen saturation (optimal in the combined group, P<0.0038)

9	Patil, S.V., et al. (2024) [25]	India	Single-center, prospective observational study	35	Pirfenidone monotherapy group: 35; Nintedanib monotherapy group: 35	Not reported	Not reported	Combined group: Nintedanib 100 mg tid + Pirfenidone 400 mg tid; Control group 1: Pirfenidone 1800-2400 mg/d; Control group 2: Nintedanib 100 mg tid	FVC stability (P<0.00003); 6-minute walking distance improvement (P<0.0004, P<0.0053); Radiological progression rate reduction (P<0.00009, etc.); Acute exacerbation risk reduction (P<0.00005)	Incidence of gastrointestinal adverse reactions (significantly higher in the single-agent control group, slightly higher in the combined group)	Nausea/vomiting/weight loss (significantly in the single-agent control group, slightly in the combined group)
10	Meersseman, C, et al. (2025) [26]	Many countries (France, Spain, etc.)	Multicenter retrospective cohort study (Combi-PF)	38	No single drug control group	89.50% 80.00%	64.1 ± 11.0 years old	Combined group: Nintedanib 150 mg bid + Pirfenidone 801 mg tid	FVC decline rate (combination group -11.1 mL/month, baseline -26.7 mL/month); Overall survival rate (5-year 21.7%)	Incidence of any adverse reactions (84.2%); incidence of severe adverse reactions (28.9%); treatment interruption rate (26.3%); dose adjustment rate (28.9%)	Weight loss (52.6%); diarrhea (36.8%); abdominal pain/anorexia (both 28.9%); liver enzyme elevation (5.3%); nausea/vomiting (13.2%)
11	Flaherty, K.R, et al. (2018) [27]	Many countries (Canada, Denmark, France, Germany, Italy, Netherlands, Spain, United States)	International, single-arm, open-label, phase IV study (NCT02598193)	89	No single drug control group	70.00%	68.2 ± 6.8 years old	Combined group: Pirfenidone (1602-2403 mg/d, stable dose ≥1602 mg/d for ≥28 days) + Nintedanib (200-300 mg/d)	Exploratory efficacy: FVC% pred change (decreased by 0.4 ± 0.5% from baseline to 24 weeks); DLCO% pred change (decreased by 1.9 ± 0.8%)	Proportion of patients completing 24-week treatment (78%); incidence of treatment-related adverse reactions (83%); treatment interruption rate (15%, due to treatment-related adverse events)	Gastrointestinal adverse reactions (75%, diarrhea 49%, nausea 46%, vomiting 24%); incidence of serious treatment-related adverse reactions (2%); liver enzyme elevation (7%); photosensitivity reaction/rash (8%); fatigue (12%)

Note: The patient counts presented in this table reflect exposures to each treatment arm. For single-arm studies [20-22, 26, 27], the same patients contributed data to both the combination and monotherapy groups as they served as their own controls. The total number of unique patients across all 11 studies is 629. All comparative meta-analyses were performed solely on the controlled studies. IPF = Idiopathic Pulmonary Fibrosis; FVC = Forced Vital Capacity; 6MWD = 6-Minute Walk Distance; bid = twice daily; tid = three times daily; ADR = Adverse Drug Reaction; JRS = Japanese Respiratory Society.

Table 2. Risk of bias assessment table for randomized controlled trials

Number	Study	Study Type	Generation of Random Sequences	Allocation Concealment	Participant/ Researcher Blinding	Outcome Assessor Blinding	Completeness of Outcome Data	Selective Reporting	Other Bias	Overall Quality Grade
1	Ogura et al. (2015) [17]	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High
2	Vancheri et al. (2018) [18]	RCT	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High
3	Ikeda et al. (2022) [19]	RCT	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	Low

Table 3. Non-randomized study quality assessment form

Number	Study	Study Type	Dimension of Choice (4 points)				Dimension of Comparability (2 points)		Dimension of Outcome (3 points)			Total Score (9 points)	Overall Quality Grade
			1. Representativeness of the exposed group	2. Selection of the non-exposed group	3. Determination of exposure	4. Selection without confounding factors	1. Important confounding factor correction	2. Additional confounding factor correction	1. Outcome determination	2. Completeness of follow-up	3. Duration of follow-up		
4	Richeldi et al. (2019) [20]	Open-label study	1	1	1	0	1	1	1	1	1	8	High
5	Hisata et al. (2021) [21]	Retrospective cohort	1	1	1	0	1	1	1	1	1	8	High
6	Huh et al. (2021) [22]	Retrospective cohort	1	0	1	0	1	1	1	1	1	7	Medium
7	Huh et al. (2023) [23]	Retrospective cohort	1	1	1	1	1	1	1	1	1	9	High
8	Flaherty et al. (2018) [24]	Single-arm prospective study	1	1	1	0	1	1	1	1	1	8	High
9	Patil et al. (2023) [25]	Prospective observation	1	1	1	0	1	1	1	1	1	8	High
10	Patil et al. (2024) [26]	Prospective observation	1	1	1	0	1	1	1	1	1	8	High
11	Meersseman et al. (2025) [27]	Retrospective cohort	1	1	1	0	1	1	1	1	1	8	High

Note: Scoring criteria for "additional confounding factor correction": 2 points for correcting ≥3 factors (smoking history, concurrent lung infection, nutritional status, comorbidities, etc.), 1 point for correcting 1-2 factors, 0 point for no correction. NOS = Newcastle-Ottawa Scale.

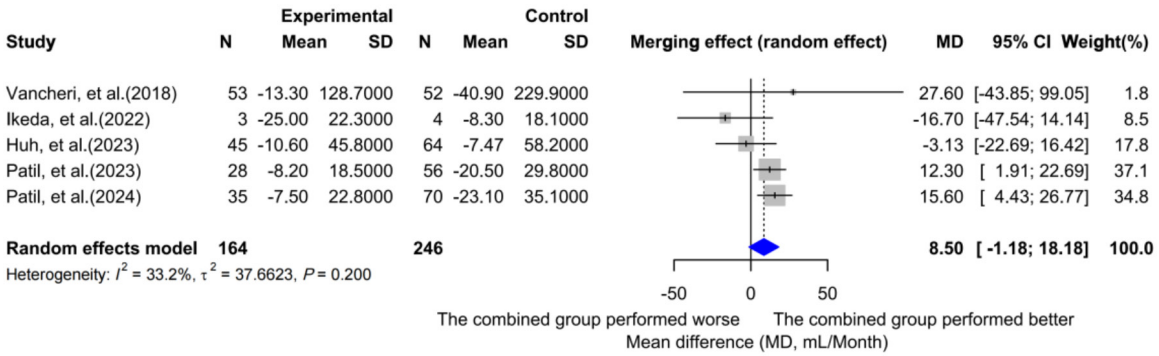

Figure 2. Forest plot of pooled analysis of monthly FVC (Forced Vital Capacity) decline (mL/month) between the combination therapy group and monotherapy group in controlled studies.

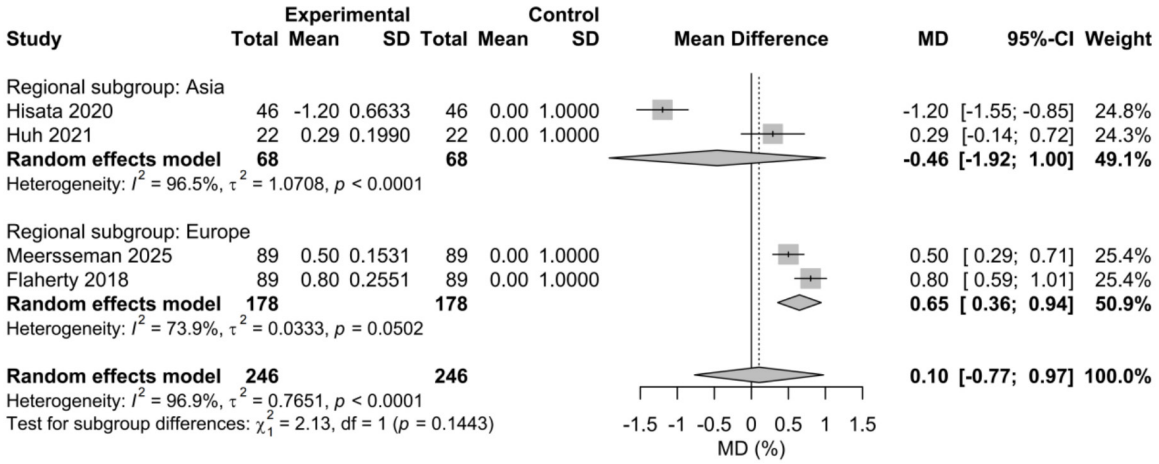

Figure 3. Forest plot of subgroup analysis of annual FVC%pred (Forced Vital Capacity percentage predicted) decline rate before and after combination therapy in single-arm studies.

of clinical benefit, as shown in **Figure 2**. Heterogeneity analysis indicated low heterogeneity between studies (Q test P=0.200, I^2=33.2%), and the heterogeneity was mainly derived from random error.

Four single-arm studies involving 246 patients were included, with the outcome indicator being the annual decline rate of forced vital capacity percentage predicted (FVC%pred). There was no significant change in the annual FVC%pred decline rate after combination therapy compared to before treatment (MD=0.10, 95% CI: -0.77-0.97, P=0.816), and there was extremely high heterogeneity between studies (I^2=96.9%, P<0.001). Subgroup analysis of Asian and European populations showed that the MD of the Asian subgroup was -0.46 (95% CI: -1.92-1.00, I^2=96.5%), and the MD of the European subgroup was 0.65 (95% CI: 0.36-0.94, I^2=73.9%). The subgroup interaction test yielded χ^2=2.130, P=0.144, indicating no significant difference in efficacy between Asian and European populations, but the benefit was more definite in European populations, as shown in **Figure 3**. Subgroup analysis was stratified by baseline FVC% predicted (≥80% vs <80%): In the mild IPF subgroup (FVC≥80%), the pooled MD=13.79 (95% CI: 8.88-18.70, P<0.001, I^2=0.0%); in the moderate-to-severe IPF subgroup (FVC<80%), the pooled MD= 10.09 (95% CI: -39.73-59.90, P=0.691, I^2= 92.5%). The test for interaction yielded P= 0.885, suggesting that patients across different disease severities may benefit from combination therapy, as shown in **Figure 4**.

6-minute walk distance (6MWD)

Four controlled studies [18, 23-25] involving 308 patients (161 in the combination group and 247 in the monotherapy group) were

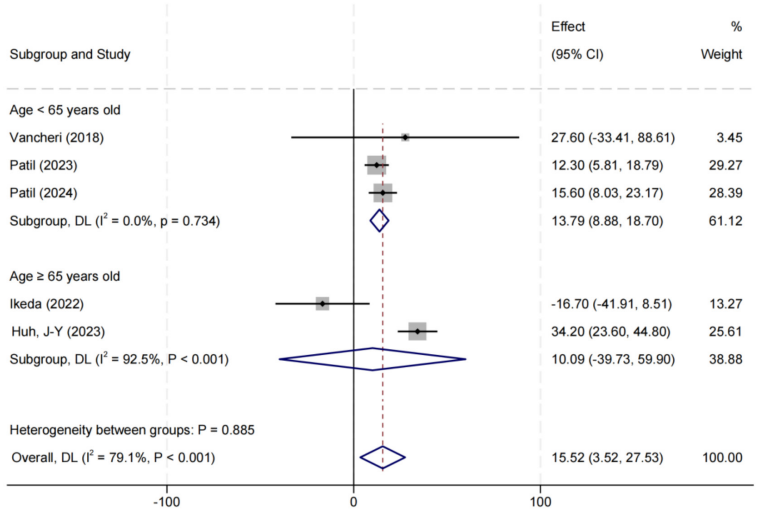

Figure 4. Subgroup analysis of monthly FVC (forced vital capacity) decline rate stratified by baseline FVC%pred. Note: Subgroup 1 (Baseline FVC≥80%): MD (Mean Difference)=13.79, 95% CI (Confidence Interval): 8.88-18.70, P<0.001, heterogeneity I^2 (Heterogeneity index)=0.0%; Subgroup 2 (Baseline FVC<80%): MD=10.09, 95% CI: -39.73-59.90, P=0.691, I^2=92.5%; Test for interaction: χ^2 (Chi-square)=0.57, df (degrees of freedom)=1, P=0.885.

included, with the outcome indicator being the change in 6MWD within 6 months (meters/6 months). Under the fixed-effects model, the 6MWD in the combination therapy group was improved by an average of 21.09 meters compared to the monotherapy group (95% CI: 14.01-28.17, z=5.84, P<0.001); under the random-effects model, the improvement was 21.81 meters (95% CI: 4.84-38.77, z=2.52, P=0.012), showing significant clinical value. There was high heterogeneity between studies (Q test P<0.001, I^2=82.5%), and the core source of heterogeneity was regional differences: the improvement amplitude in Indian studies was significantly higher than that in South Korean and multinational studies, as shown in **Figure 5**. Subgroup analysis was stratified by age (<65 years vs ≥65 years): In the non-elderly subgroup (<65 years), the pooled MD=26.59 (95% CI: 12.99-40.20, P<0.001, I^2=84.2%); in the elderly subgroup (≥65 years), the pooled MD=10.21 (95% CI: 3.99-16.42, P=0.001, I^2=0.0%). The test for interaction yielded P=0.032, indicating a more pronounced improvement in exercise capacity in non-elderly patients, while elderly patients still achieved stable benefits, as shown in **Figure 6**.

Incidence of gastrointestinal adverse reactions

Six controlled studies [17, 18, 23-25] involving 509 patients (205 in the combination group and 304 in the monotherapy group) were included, with the effect size expressed as relative risk (RR). Analysis using a random-effects model showed that there was no significant difference in the incidence of gastrointestinal adverse reactions between the combination therapy group and the monotherapy group (RR=0.6687, 95% CI: 0.2635-1.6967, z=-0.85, P=0.3970). There was extremely high heterogeneity between studies (I^2=91.1%, P<0.001), as shown in **Figure 7**. Notably, the forest plot revealed opposite directions of effect size between Ogura et al. [17] (RR=0.67, 95% CI: 0.26-1.70) and Huh et al. [23] (RR=3.03, 95% CI: 0.65-14.12), which contributed substantially to the high observed heterogeneity (I^2=91.1%). Four single-arm studies [21, 22, 26, 27] involving 246 patients were included. The pooled incidence of gastrointestinal adverse reactions after combination therapy was 49% (95% CI: 28%-71%), with extremely high heterogeneity between studies (I^2=93.6%, P<0.001). The heterogeneity was mainly derived from ethnic metabolic differences, different dosage adjustment strategies, and inconsistent definitions of adverse reactions, as shown in **Figure 8**.

Treatment discontinuation rate

Three studies [17-19] on the treatment discontinuation rate of IPF patients were included, covering 162 patients (77 in the combination group and 85 in the monotherapy group). The regional distribution of the included studies was: 2 from Japan [17, 21] and 1 multinational multicenter study [21]. All studies reported the number of treatment discontinuations due to any reason (including adverse reactions, insufficient efficacy, and patient willingness) and the total sample size. Pooled effect size analysis showed that there was no significant difference in the treatment discontinuation rate between the combination group and the monotherapy group (RR=1.23, 95% CI: 0.41-3.73), indicating that the treatment discontinuation risk in the combination group could not be confirmed to be significantly higher or lower than that in the

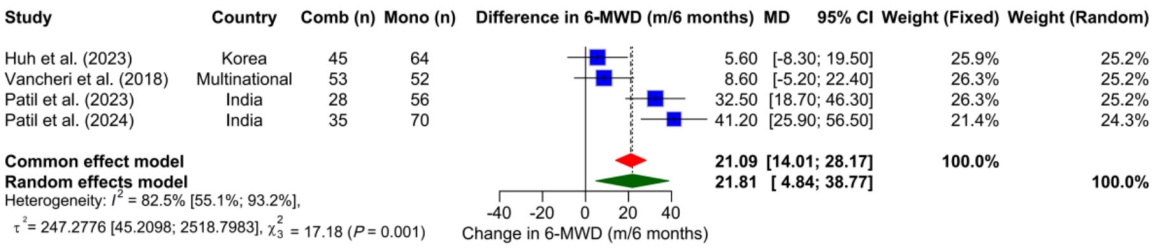

Figure 5. Forest plot of pooled analysis of 6-month 6MWD (6-Minute Walk Distance) change (meters/6 months) between the combination therapy group and monotherapy group in controlled studies.

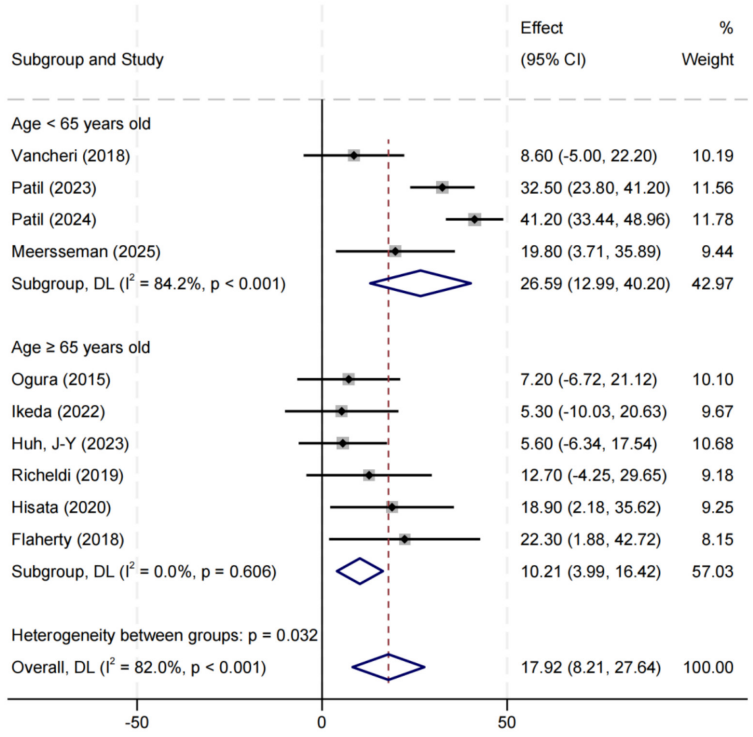

Figure 6. Subgroup analysis of 6-month 6MWD (6-Minute Walk Distance) change stratified by age. Note: Subgroup 1 (Age <65 years): MD (Mean Difference)=26.59, 95% CI (Confidence Interval): 12.99-40.20, P<0.001, heterogeneity I^2 (Heterogeneity index)=84.2%; Subgroup 2 (Age ≥65 years): MD=10.21, 95% CI: 3.99-16.42, P=0.001, I^2=0.0%; Test for interaction: χ^2 (Chi-square)=4.61, df (degrees of freedom)=1, P=0.032.

monotherapy group. Ikeda (2022) [19] was the only study showing a significantly increased discontinuation risk in the combination group (RR=9.00, 95% CI: 1.12-72.25), but this study had an extremely small sample size (only 3 cases in the combination group and 4 cases in the monotherapy group), and the results were susceptible to sampling error. Both Ogura et al. [17] and Vancheri et al. [18] showed a lower discontinuation risk in the combination group (RR=0.85, 95% CI: 0.32-2.27; RR=0.75, 95% CI: 0.42-1.34). There was moderate and near-statistically significant heterogeneity between studies: P= 0.079 for the Q statistic (indicating heterogeneity), I^2= 60.6%, τ^2=0.618, suggesting that approximately 60.6% of the variation in effect size was derived from true differences between studies, and 39.4% was random error, as shown in **Figure 9**.

Incidence of serious adverse events (SAEs)

Three controlled studies [17-19] involving 264 patients (119 in the combination group and 145 in the monotherapy group) were included. Analysis using a random-effects model showed that there was no significant difference in the incidence of SAEs between the combination therapy group and the monotherapy group (RR=0.9282, 95% CI: 0.2358-3.6542, z=-0.11, P=0.915> 0.05). The effect sizes of individual studies were divergent in direction but not significant, with low to moderate heterogeneity between studies (I^2=44.9%, P=0.163>0.05), and the heterogeneity was not significant, as shown in **Figure 10**.

Sensitivity analysis

The one-by-one study exclusion method was adopted to conduct sensitivity analysis on all core outcome indicators, so as to verify the stability and reliability of the pooled results. The results showed that the 95% confidence inter-

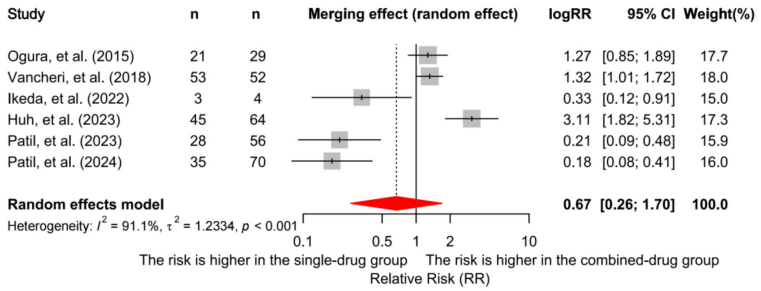

Figure 7. Forest plot of pooled analysis of the incidence of gastrointestinal adverse reactions between the combination therapy group and monotherapy group in controlled studies.

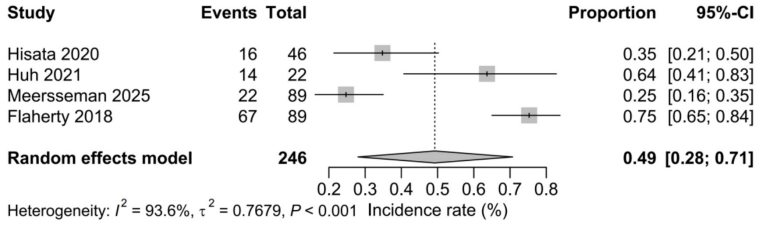

Figure 8. Forest plot of pooled analysis of the incidence of gastrointestinal adverse reactions after combination therapy in single-arm studies.

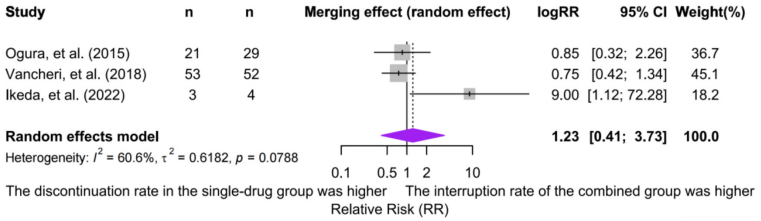

Figure 9. Forest plot of pooled analysis of treatment discontinuation rate between the combination therapy group and monotherapy group in controlled studies.

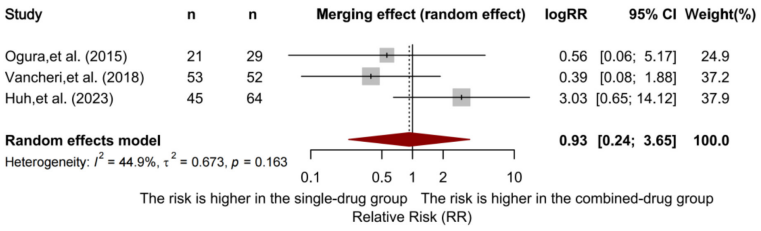

Figure 10. Forest plot of pooled analysis of the incidence of serious adverse events between the combination therapy group and monotherapy group in controlled studies.

val (CI) of the pooled effect size of each indicator had no directional change after excluding a single study in sequence, and the core conclusion remained consistent, indicating that the meta-analysis results of this study had good robustness. The detailed results of each indicator were as follows.

Forced vital capacity (FVC) decline rate: After sequentially excluding each single study involved in the pooled analysis of monthly FVC decline rate, the pooled mean difference (MD) fluctuated in the range of 3.42-12.25 mL/month. After excluding the extremely small-sample study by Ikeda (2022) with high heterogeneity risk, the heterogeneity of the pooled results decreased to I^2=0%, and the combined effect size reached statistical significance (MD=11.76, 95% CI: 4.71-18.81, P<0.05), and the overall conclusion of FVC decline rate improvement in the combination therapy group remained unchanged, as shown in **Figure 11**.

Small-sample studies were defined as those with a total sample size <10 participants. After excluding the small-sample study by Ikeda et al. (2022), the pooled effect size of monthly FVC decline rate was MD=14.21 (95% CI: -5.26-33.68, P>0.05). The core conclusion that combination therapy mitigates FVC decline remained unchanged, as shown in **Figure 12**.

To enhance the comprehensiveness of sensitivity analysis, we supplemented an analysis excluding the potentially high-heterogeneity study by Patil et al. (2024). Results showed a pooled MD=16.04 (95% CI: -2.53-34.61, P>0.05), which did not reverse the beneficial trend of combination therapy, as shown in **Figure 13**.

6-minute walk distance (6MWD): For the 6-month 6MWD change value, the pooled

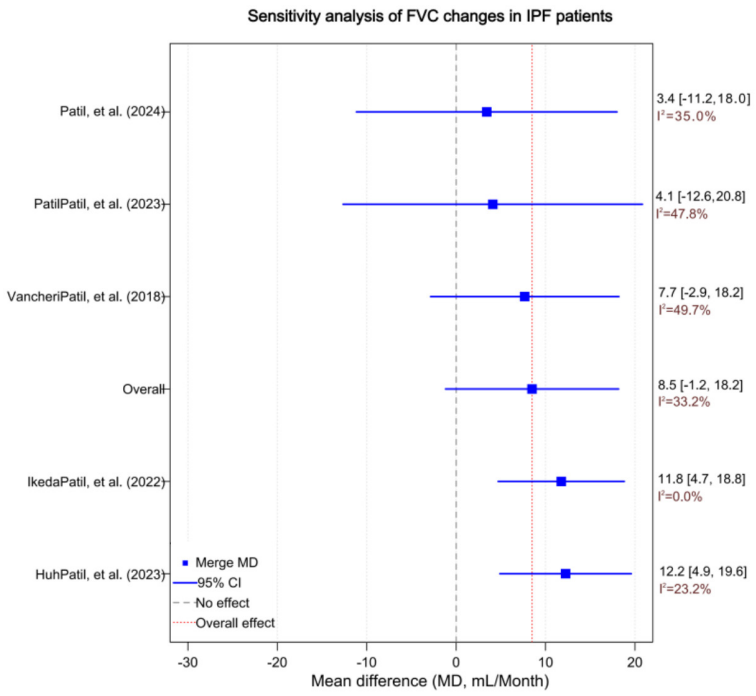

Figure 11. Forest plot of sensitivity analysis for monthly FVC (Forced Vital Capacity) decline in controlled studies.

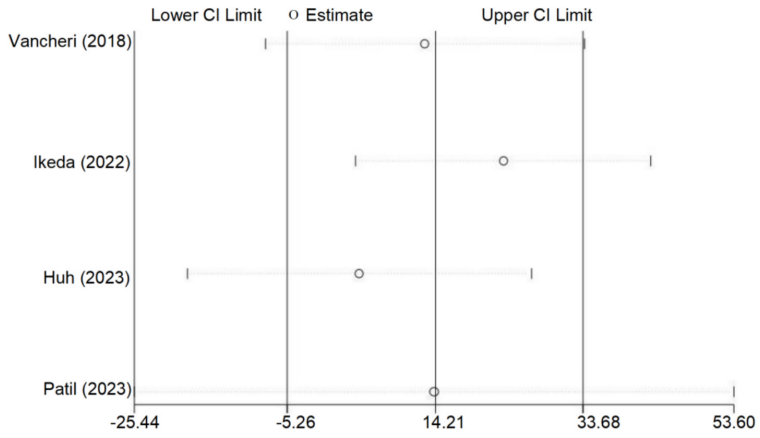

Figure 12. Sensitivity analysis of monthly FVC (Forced Vital Capacity) decline rate following exclusion of a small-sample study. Note: Small-sample studies were defined by a total sample size <10 participants. Post-exclusion, the pooled mean difference (MD)=14.21 (95% confidence interval [CI]: -5.26-33.68, P>0.05), confirming the robust trend of combination therapy in reducing FVC decline.

MD fluctuated between 15.58-27.25 meters/6 months after sequentially excluding each single controlled study. The 95% CI of the pooled effect size was always in the positive value range (P<0.05). Thus the conclusion that the combination therapy group could significantly improve the exercise capacity of patients was not affected by a single study, as shown in **Figure 14**.

Incidence of gastrointestinal adverse reactions: Leave-one-out sensitivity analysis showed that no single study drove the overall conclusion: after excluding any study, the pooled RR remained non-significant (range 0.49-0.87, all 95% CIs crossing 1). The opposite effect directions of Huh et al. [23] (RR=3.03) and Ogura et al. [17] (RR=0.67) contributed to the high heterogeneity (I^2=91.1%), but excluding either did not change the non-significant finding. The lowest heterogeneity (I^2=88.7%) was observed after excluding Patil et al. [25], as shown in **Figure 15**.

Treatment discontinuation rate: For the treatment discontinuation rate, the pooled RR fluctuated between 0.77-2.30 after sequentially excluding each single study. Although the effect size had a certain range of variation, the 95% CI of the pooled results all contained 1, and there was no significant difference in the treatment discontinuation rate between the two groups. After excluding the small-sample study Ikeda (2022), the heterogeneity of the pooled results disappeared (I^2=0%), and the conclusion was more stable, as shown in **Figure 16**.

Incidence of serious adverse events (SAEs): After sequentially excluding each single study involved in the SAE incidence analysis, the pooled RR fluctuated in the range of 0.44-1.59, and the 95% CI all contained 1, with no significant difference between the two groups. After excluding the study by Huh et al. [23], the pooled RR decreased to 0.44 and the heterogeneity was reduced to I^2=0%, but the overall conclusion that the SAE

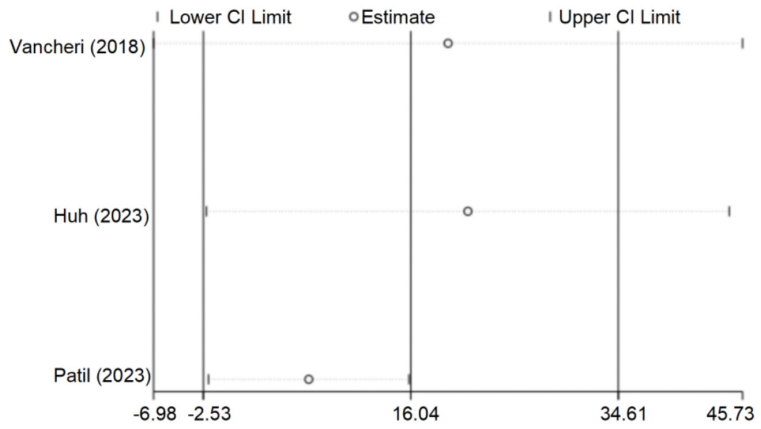

Figure 13. Sensitivity analysis of monthly FVC (Forced Vital Capacity) decline rate following exclusion of a high-heterogeneity study. Note: After excluding Patil *et al.* (2024), the pooled mean difference (MD)=16.04 (95% confidence interval [CI]: -2.53-34.61, P>0.05), indicating that high-heterogeneity studies do not alter the beneficial trend of combination therapy for FVC preservation.

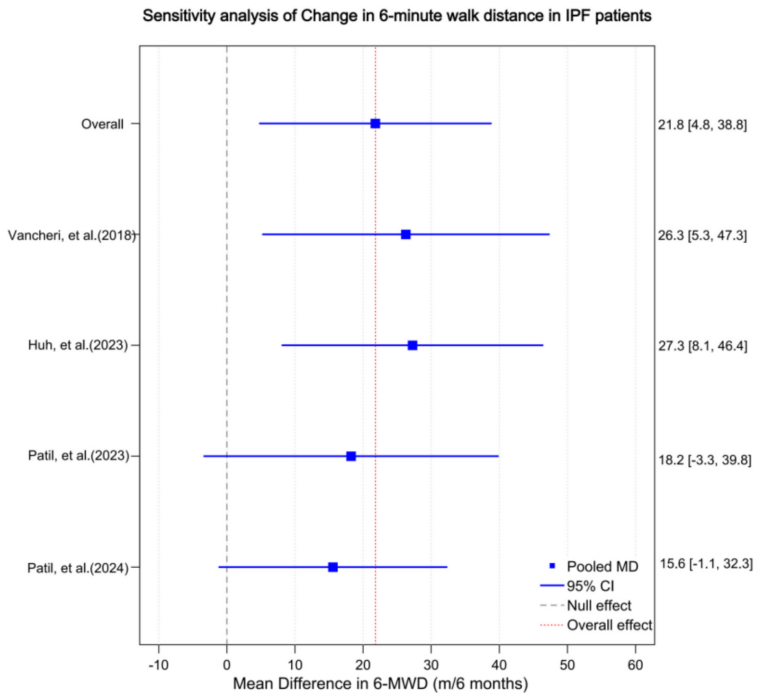

Figure 14. Forest plot of sensitivity analysis for 6-month 6MWD (6-Minute Walk Distance) change in controlled studies.

risk of the combination therapy group was comparable to that of the monotherapy group remained unchanged, as shown in **Figure 17**.

Publication bias assessment

Publication bias was evaluated using a contour-enhanced funnel plot for gastrointestinal adverse events, the outcome with the largest number of included studies (n=6), as shown in **Figure 18**. The funnel plot showed generally symmetrical distribution of studies around the pooled effect, with no overt evidence of asymmetry. Egger's test also did not detect significant asymmetry (P=0.243). As recommended by the Cochrane Handbook, such tests have low reliability when fewer than 10 studies are included. The scattered points beyond the expected confidence interval may reflect high heterogeneity (I^2=91.1%) rather than publication bias. Publication bias was not formally assessed for other outcomes that included fewer than six studies.

Discussion

Idipathic pulmonary fibrosis (IPF) still faces significant unmet clinical needs. Although nintedanib and pirfenidone monotherapy can significantly reduce patients' mortality risk and prolong survival, some patients in clinical practice show poor response to monotherapy, with persistent decline in lung function and high risk of disease progression [28]. Based on the complementarity of the mechanisms of action of the two drugs, combination therapy is considered a possiblel direction to break through the efficacy ceiling of monotherapy, and relevant clinical studies have been carried out in recent years. However, existmeaningful and whether safety is controllable, nor are there individualized treatment recommendations for different populations. This has led to controversies in the clinical application of this regimen.

The 24-week single-arm study conducted by Flaherty et al. [27] first provided short-to-me-

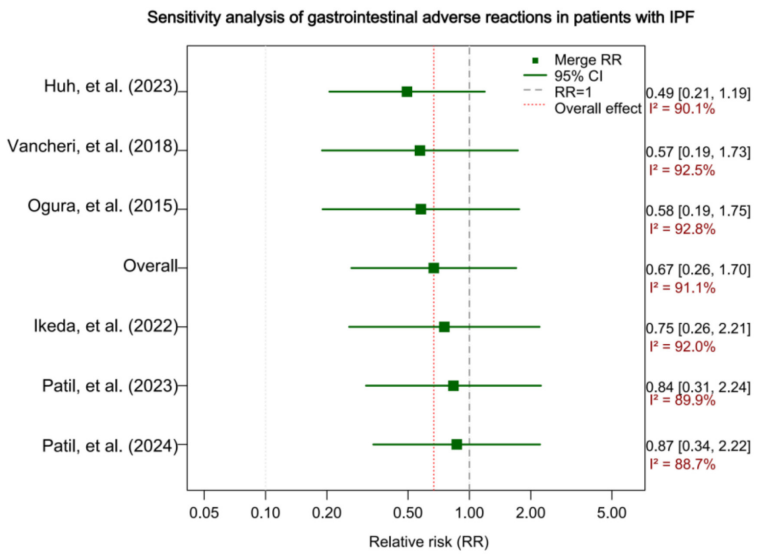

Figure 15. Forest plot of sensitivity analysis for the incidence of gastrointestinal adverse reactions in controlled studies.

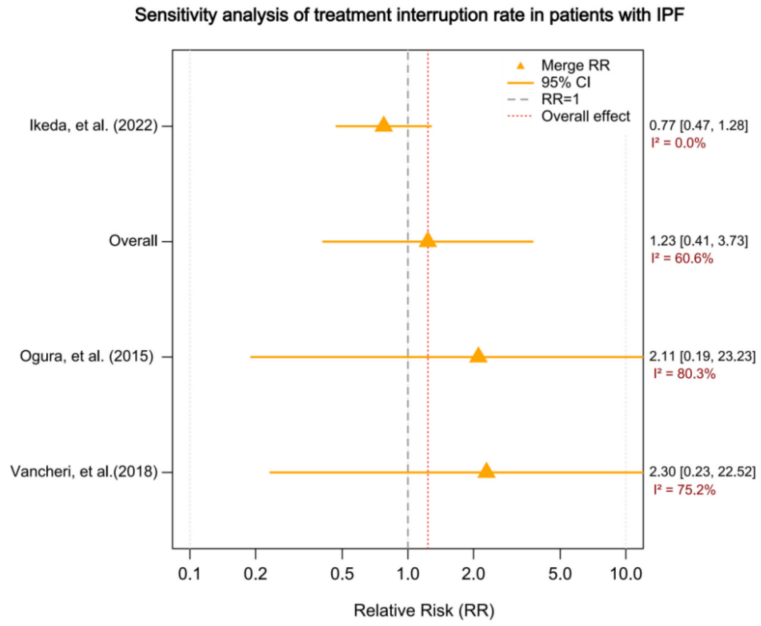

Figure 16. Forest plot of sensitivity analysis for treatment discontinuation rate in controlled studies.

dium-term safety evidence for combination therapy: 78% of IPF patients could complete 24 weeks of nintedanib combined with pirfenidone treatment. Treatment-related adverse reactions were mainly gastrointestinal symptoms, and the incidence of serious adverse events (SAEs) was only 2%. The INJOURNEY trial by Vancheri et al. [18], as the first randomized open-label controlled study, randomly assigned 105 IPF patients who had tolerated nintedanib to the combination therapy group or the nintedanib monotherapy group. Although the incidence of gastrointestinal adverse reactions in the combination therapy group (69.8%) was higher than that in the monotherapy group (52.9%), the overall safety profile was consistent with monotherapy. Exploratory efficacy analysis showed that the absolute decline in forced vital capacity (FVC) in the combination therapy group (-13.3 mL) was significantly smaller than that of the monotherapy group (-40.9 mL), suggesting that combination therapy may more effectively delay the decline in lung function.

By integrating clinical data from 11 studies, this study systematically evaluated the clinical value of nintedanib combined to pirfenidone in the treatment of IPF from both efficacy and safety dimensions, and the core results have important evidence-based medical significance. The efficacy of individual antifibrotic agents has been well-established: a recent updated meta-analysis by Qiu et al. [29] confirmed that both pirfenidone and nintedanib monotherapy significantly improve FVC predicted (WMD 3.12%), FVC volume (WMD 87.44 mL), and 6-minute walk distance (WMD 24.63 m) compared to placebo in patients with pulmonary fibrosis. Building on this foundation, combination therapy has emerged as a potential strategy to further enhance clinical outcomes. However, previous meta-analyses on this topic have been limited in scope: Finnerty et al. [13] investigated antifibrotic agents across fibrotic lung diseases but did not examine the nintedanib-pirfenidone combination specifically; Lee et al. [14] focused solely on safety and tolerability of

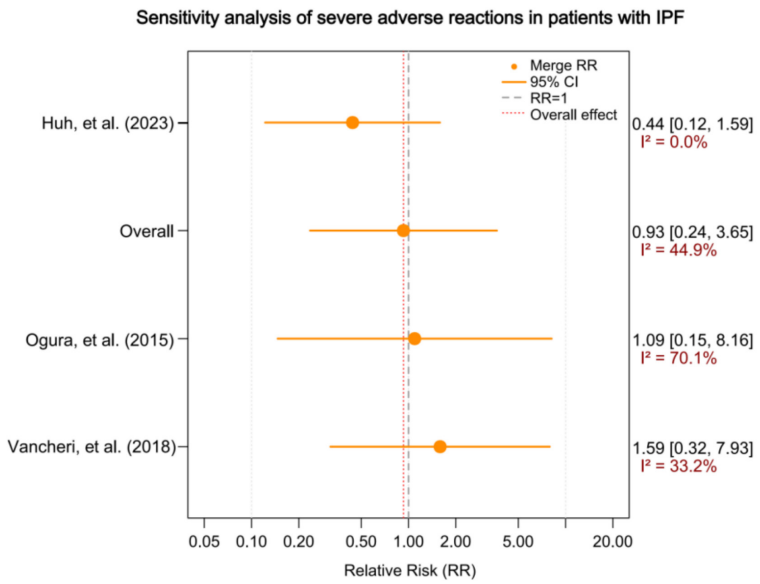

Figure 17. Forest plot of sensitivity analysis for the incidence of serious adverse events in controlled studies.

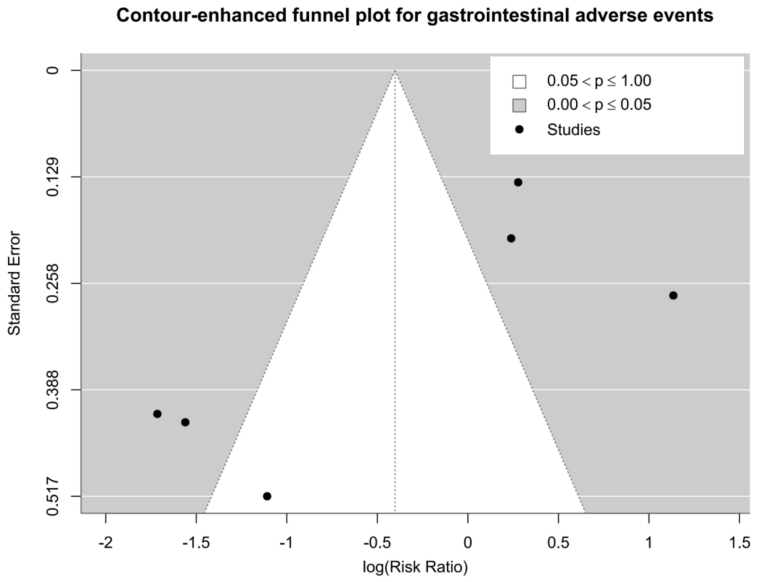

Figure 18. Contour-enhanced funnel plot for the incidence of gastrointestinal adverse reactions. Note: Each point represents a single study. The pseudo 95% confidence limits are shown as dashed lines, forming the expected funnel shape in the absence of heterogeneity and publication bias. Contour regions represent different levels of statistical significance (dark gray: P<0.01; gray: P<0.05; light gray: P<0.10). The plot appears roughly symmetrical, and Egger's test was not significant (P=0.243), suggesting no clear evidence of publication bias. Interpretation is limited by the small number of studies (n=6) and high heterogeneity (I^2=91.1%).

the combination, including only four studies and no efficacy outcomes. In contrast, our meta-analysis integrates both efficacy and safety data from 11 studies, demonstrating not only a comparable safety profile but also significant benefits in exercise capacity (6MWD) and a potential for enhanced FVC preservation, particularly after excluding small-sample studies.

In terms of efficacy, the monthly FVC decline in the combination therapy group was reduced by 8.50 mL compared to the monotherapy group, and the benefit of combination therapy reached statistical significance after excluding an extremely small-sample single-center study. A recent basic study by Roger et al. [30] confirmed that Interleukin 11 (IL-11) is highly expressed in the lung tissue and serum of IPF patients, which can induce endothelial-mesenchymal transition (EnMT) of pulmonary artery, smooth muscle cell proliferation, and extracellular matrix deposition. Nintedanib and pirfenidone can significantly block the IL-11-mediated vascular remodeling process by inhibiting the extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation pathway, reduce the destruction of lung tissue structure and lung function decline, and delay FVC reduction. Another potential mechanism involves the janus kinase 2 (JAK2) signaling pathway. Yang et al. [31] demonstrated in both bleomycin-induced mouse models and TGF-β1-stimulated alveolar epithelial cells that pirfenidone and nintedanib attenuate pulmonary fibrosis by inhibiting the expression of JAK2 and its phosphorylation. Their study revealed a reciprocal interaction between the TGF-β1 and JAK2 pathways: TGF-β1 promotes JAK2 phosphorylation through a non-classical pathway, while inhibition of JAK2 expression in turn downregulates TGF-β receptor expression and α-smooth mus-

cle actin, a key marker of myofibroblast activation. Our finding of a slowed FVC decline with combination therapy aligns with this synergistic inhibition of fibrotic pathways, suggesting that dual blockade may offer a more robust attenuation of disease progression than monotherapy alone. From a clinical perspective, the 2022 clinical practice guidelines jointly issued by the American Thoracic Society/European Respiratory Society and other institutions defined an absolute FVC decline of ≥5% within one year as rapid disease progression. The benefit amplitude of combination therapy in this study reached the level of delaying disease progression, suggesting that combination therapy is expected to reverse disease progression in some patients [32].

In terms of patients' functional benefits, the 6-minute walk distance in the combination therapy group was increased by an average of 21.81 meters within 6 months, confirming that combination therapy can not only delay the decline in lung function but also effectively improve patients' exercise capacity and activities of daily living. Combination therapy improves lung ventilation function through antifibrotic effects and reduces exercise-related pulmonary hypoxia through anti-inflammatory effects, thereby enhancing patients' cardiopulmonary reserve capacity. In terms of safety, this study confirmed that there were no significant differences in the incidence of gastrointestinal adverse reactions, treatment discontinuation rate, or incidence of SAEs between combination therapy and monotherapy, providing clinical evidence for the safety of combination therapy in clinical practice. A pharmacokinetic study by Richeldi et al. [20] clearly showed that there was no significant drug-drug interaction between nintedanib and pirfenidone, providing a pharmacokinetic basis for the safety of combination therapy.

In-depth analysis of heterogeneity shows that regional differences are the core driving factor: a study on Japanese populations by Ogura et al. [17] found that the maximum plasma concentration (Cmax) of nintedanib was reduced by 41% during combination therapy, which may be related to the low activity of cytochrome P450 1A2 (CYP1A2) in patients, leading to anorexia as the main gastrointestinal adverse reaction, with an incidence of 39.1% in a real-world study of Japanese populations by Hisata et al. [21]. However, a Korean cohort study by Huh et al. [23] showed that the incidence of diarrhea in combination therapy reached 40.0%, which was significantly higher than that in the monotherapy group (14.1%). An Indian study by Patil et al. [24] indicated that the low-dose combination regimen could reduce the incidence of gastrointestinal adverse reactions to lower than that of full-dose monotherapy, which was consistent with the result of better safety in the Indian subgroup in this study. These regional variations may be attributable to underlying genetic differences in drug-metabolizing enzymes. Rajman et al. [33] highlighted the substantial genetic diversity in cytochrome P450 enzymes across different populations, noting significant differences in allele frequencies between African, Asian, and Caucasian populations. Focusing on East Asian populations, Lin et al. [34] demonstrated that these genetic differences translate into clinically meaningful pharmacokinetic variations, with East Asians exhibiting higher plasma concentrations of drugs metabolized by specific CYP enzymes compared to Western populations. These pharmacogenetic differences likely contribute to the distinct safety and efficacy profiles observed between Asian and European populations in our analysis, and support the need for ethnicity-specific dosing strategies. In addition, a long-term multicenter study by Meersseman et al. [26] with a follow-up of 17.4 months found that the main SAE of combination therapy was weight loss (23.7%), and it could be used as a bridging therapy in patients waiting for lung transplantation, further supporting the feasibility of combination therapy in advanced IPF patients, but also suggesting the need to pay attention to nutritional support. The root cause of the differences lies in the different dosage strategies and race-specific pharmacokinetic characteristics: most Indian studies adopted low-dose pirfenidone regimens, while Korean studies used full-dose regimens, indicating that individualization of dosage is the key to balancing the efficacy and safety of combination therapy.

Although this study provides key evidence-based basis for IPF combination therapy, there are still multiple limitations in the research on pirfenidone combined with nintedanib. First, the study design had inherent limitations: the study by Flaherty [27] had a single-arm design, and the included population was patients who

had tolerated pirfenidone monotherapy. Only 3 of the studies [17-19] were RCTs, and the follow-up of the study by Vancheri [18] was only 12 weeks, which did not evaluate long-term efficacy and safety, with efficacy indicators being exploratory analysis. Four were retrospective cohort studies [20, 23-25], and retrospective design inevitably has selection bias and confounding factor interference. Some studies did not adjust for variables such as patients' baseline lung function and comorbidities, which may affect the reliability of the results. Second, there was high heterogeneity between studies, especially the I^2 value of gastrointestinal adverse reaction indicators was as high as 91.1%. Although sensitivity analysis verified the robustness of the core conclusions, the core driving factors of heterogeneity have not been fully clarified. The definition of gastrointestinal adverse reactions was inconsistent among different studies: some studies included mild transient symptoms, while others only included moderate to severe symptoms requiring clinical intervention, making it impossible to directly compare effect sizes. Third, the risk of publication bias cannot be ruled out: the number of studies included in each outcome indicator (3-6 studies) was less than the recommended threshold (≥10 studies) for reliable publication bias assessment (e.g., funnel plot, Egger's test). Due to the small number of included studies, it is difficult to distinguish whether potential asymmetry is caused by publication bias, true heterogeneity, or chance, and positive results may be more likely to be published, which may overestimate the efficacy and safety of combination therapy. Fourth, the statistical power is limited: the sample size included in the incidence of SAEs is only 264 cases, and the number of SAE events in individual studies is small, which may lead to insufficient statistical power. Fifth, there is a lack of long-term follow-up data and patient-reported outcomes. The follow-up duration of the studies included in this study is mostly 3-12 months, and the effect of combination therapy on patients' overall survival has not been evaluated. Moreover, patient-reported outcomes such as dyspnea scores and quality of life scales are not included, making it difficult to fully evaluate the clinical value of combination therapy.

In response to the above limitations, future research should focus on the following directions: conduct large-sample, multicenter, double-blind RCTs, unify the dosage, follow-up duration, and efficacy evaluation standards of combination therapy, and reduce heterogeneity between studies; second, carry out stratified studies based on pharmacokinetic enzyme genotypes and baseline biomarkers, with mitogen-activated protein kinase kinase kinase 19 (MAP3K19) gene expression level as a reference indicator, to screen populations with advantages in combination therapy and achieve precise treatment; expand the dimensions of efficacy evaluation, include patient-reported outcomes and long-term survival data, and comprehensively evaluate the benefit-risk ratio of combination therapy; conduct clinical studies to include populations excluded from RCTs such as the elderly and patients with multiple comorbidities, and improve the external validity of the research results.

Conclusions

Nintedanib combined with pirfenidone in the treatment of IPF has significant potential for clinical benefit in delaying lung function decline and improving exercise capacity, without significantly increasing the risks of gastrointestinal adverse reactions, treatment discontinuation, or SAEs. In clinical practice, individualized treatment regimens should be formulated according to patients' ethnic characteristics, baseline lung function, and gastrointestinal tolerance: European populations may prioritize standard-dose combination therapy to maximize efficacy; Asian populations may adopt a low-dose pirfenidone plus nintedanib regimen, with enhanced dynamic monitoring of gastrointestinal symptoms and timely dose adjustment.

Through a systematic meta-analysis, this study provided high-level evidence-based support for the IPF combination therapy strategy, filling the evidence gap in existing research. In the future, standardized, high-quality clinical RCTs are needed to further verify the long-term efficacy and safety of combination therapy, promoting the evolution of IPF treatment models from standardized regimens to individualized precision strategies, and bringing survival benefits to more IPF patients.

Disclosure of conflict of interest

None.

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Supplementary Materials

Table S1. PubMed search strategy

PubMed
("nintedanib"[Supplementary Concept] OR nintedanib[Title/Abstract] OR "BIBF 1120"[Title/Abstract] OR Vargatef[Title/Abstract] OR Ofev[Title/Abstract]) AND ("pirfenidone"[Supplementary Concept] OR pirfenidone[Title/Abstract] OR "5-methyl-1-phenyl-2-(1H)-pyridone"[Title/Abstract] OR Esbriet[Title/Abstract]) AND ("Idiopathic Pulmonary Fibrosis"[Mesh] OR IPF [Title/Abstract] OR "Usual Interstitial Pneumonia"[Title/Abstract])

Table S2. Embase search strategy

Embase
('nintedanib'/exp OR 'nintedanib': ti,ab,kw OR 'bibf 1120': ti,ab,kw OR 'vargatef': ti,ab,kw OR 'ofev': ti,ab,kw) AND ('pirfenidone'/exp OR 'pirfenidone': ti,ab,kw OR 'esbriet': ti,ab,kw OR '5-methyl-1-phenyl-2-(1h)-pyridone':ti,ab,kw) AND ('idiopathic pulmonary fibrosis'/exp OR 'ipf': ti,ab,kw OR 'fibrosing alveolitis': ti,ab,kw OR 'usual interstitial pneumonia': ti,ab,kw) AND ('randomized controlled trial'/exp OR 'rct': ti,ab,kw)

Table S3. Web of science core collection search strategy

Web of Science
TS=(nintedanib OR "BIBF 1120" OR Vargatef OR Ofev) AND TS=(pirfenidone OR Esbriet OR "5-methyl-1-phenyl-2-(1H)-pyridone") AND TS=("Idiopathic Pulmonary Fibrosis" OR IPF OR "Usual Interstitial Pneumonia")

Table S4. Chinese databases search strategy

Chinese Databases
CNKI: (SU='Nintedanib' OR SU='Vargatef') AND (SU='Pirfenidone' OR SU='Esbriet') AND (SU='Idiopathic Pulmonary Fibrosis' OR SU='IPF') Wanfang Data: Topic: (Nintedanib OR Vargatef) AND Topic: (Pirfenidone OR Esbriet) AND Topic: (Idiopathic Pulmonary Fibrosis OR IPF) VIP: M = (Nintedanib + Vargatef) * M = (Pirfenidone + Esbriet) * M = (Idiopathic Pulmonary Fibrosis + IPF)

Note: CNKI = China National Knowledge Infrastructure; Wanfang Data = Wanfang Database; VIP = Chinese Scientific Journal Database; SU = Subject; M = Subject; Topic = Topic.