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Survival impact and safety comparison of pirfenidone and nintedanib for idiopathic pulmonary fibrosis: A meta-analysis

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Abstract. *Background and aim:* Idiopathic pulmonary fibrosis (IPF) is a severe restrictive lung disease affecting approximately 3 million people worldwide, with two approved antifibrotics, nintedanib and pirfenidone, available for use. This review aims to compare their survival impact and safety profile. *Methods:* Two databases and two trial registers, along with additional sources, were searched for cohorts reporting IPF patients of any age or stage, receiving either pirfenidone or nintedanib. The Inverse-Variance and Mantel-Haenszel method, along with either a fixed- or random-effects model, was used for analysing survival and other dichotomous outcomes, respectively. *Results:* 23 cohorts were included. The pooled analysis showed that compared to pirfenidone, nintedanib group had similar survival (HR=1.12; 95%-CI:0.99-1.27; P=0.07), all-cause mortality (OR=1.11; 95%-CI:0.94-1.31; P=0.22), drug switches (OR=1.82; 95%-CI:0.69-4.78; P=0.22), and treatment discontinuations (OR=0.92; 95%-CI:0.60-1.41; P=0.70), higher odds of diarrhoea (OR=12.39; 95%-CI: 5.67-27.07; P<0.00001) and abnormal liver-function tests (OR=2.98; 95%-CI:1.92-4.61; P<0.00001), and lower odds of photosensitivity (OR=0.06; 95%-CI:0.01-0.25; P=0.0001), and skin-rash (OR=0.17; 95%-CI:0.08-0.34; P<0.00001). *Conclusions:* While both treatment groups had similar overall survival and all-cause mortality, the safety profiles of nintedanib and pirfenidone differed significantly, with nintedanib being associated with greater odds of liver toxicity and diarrhoea, and pirfenidone with photosensitivity and skin rash, suggesting that they could be favoured in slightly different population groups. Further research is necessary to refine the current comprehension of these drugs and their optimal utilisation in IPF treatment, particularly considering factors such as disease stage and sequential therapy.

Key words: idiopathic pulmonary fibrosis, nintedanib, pirfenidone, anti-fibrotic therapy, safety profile

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe restrictive lung disease affecting approximately 3 million people worldwide, with a prognosis worse than that of some cancers (1). It is classified as a diffuse parenchymal lung disease and is characterised by the histologic pattern of usual interstitial pneumonia (UIP), including patchy areas of fibrosis, proliferation of type II alveolar pneumocytes, and the presence of fibroblastic foci composed of fibroblasts and myofibroblasts (1–3). A possible mechanism leading to this pattern could be repetitive microinjuries that can cause damage to the alveolar epithelium, which triggers the proliferation of type II pneumocytes (AEC2) and fibroblasts (1). Furthermore, since other fibrosing interstitial lung diseases (ILFs), especially familial pulmonary fibrosis (FPF), are associated with mutations in telomere- and

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surfactant-related genes, there could also be a genetic predisposition to IPF, highlighting the potential role of genetic screening in early diagnosis (4). These genetic mutations and ageing drive these cells towards a pro-fibrogenic phenotype, with hyperproliferating AEC2 cells responding to type I pneumocyte injury by secreting elastin, whereas fibroblasts, which differentiate into myofibroblasts via transforming growth factor-beta (TGF-β) signalling, and producing collagen, leading to the formation of the fibroblastic foci observed upon histology (1,5,6). Given the pathogenesis of idiopathic pulmonary fibrosis (IPF), targeting key pathways with antifibrotic drugs appears to be a promising approach for treatment. Currently, only two such drugs, nintedanib and pirfenidone, are available for use in IPF (7). Nintedanib is a non-selective tyrosine kinase inhibitor (TKI) that primarily targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) (8). By inhibiting these growth factor receptors, nintedanib prevents the proliferation and migration of fibroblasts, which are responsible for parenchymal fibrosis, thus inhibiting the progression of pulmonary fibrosis (8). In contrast, pirfenidone exhibits multiple mechanisms of action, including anti-inflammatory, antioxidant, and gene function modulation (9). The most relevant and extensively studied mechanism for early-stage IPF is the inhibition of key mediators in the transforming growth factor-beta (TGF-β) signalling pathway (10). This inhibition prevents the conversion of fibroblasts into myofibroblasts, which are crucial in driving pulmonary fibrosis (9,10). In the later stages of IPF, myofibroblasts often become senescent, making the anti-inflammatory and antioxidant properties of pirfenidone potentially more significant (11). The landmark trials of nintedanib and pirfenidone have demonstrated their efficacy in improving pulmonary function in patients with IPF. The INPULSIS trials, which compared nintedanib to placebo, showed a significant reduction in the annual rate of decline in forced vital capacity (FVC) and extended the time to the first exacerbation (12). Similarly, the CAPACITY and ASCEND trials for pirfenidone demonstrated comparable efficacy in reducing the decline in FVC (13,14). Pooled analyses from these trials also indicated that both drugs significantly lower the risk of mortality (15,16). Similar reductions in FVC decline, in addition to improved health-related quality of life (HRQOL), were highlighted in a systematic review (17) and were also shown to have some efficacy in treating ILFs other than IPF (18). Furthermore, both drugs are reported to have slightly different associated adverse effects; Gastrointestinal effects, e.g., diarrhoea, are more common with nintedanib, and dermatologic effects, e.g., rashes and photosensitivity, with pirfenidone (17, 18). Despite the comparable efficacy of nintedanib and pirfenidone as evidenced by randomised controlled trials (RCTs), current guidelines do not favour one drug over the other (7,19). However, several considerations are important in this regard. First, no RCT has conducted a direct head-to-head comparison of these two drugs. Second, RCTs typically have strict patient selection criteria, often excluding patients with comorbidities or advanced fibrosis, making it difficult to apply the findings to these patient groups. Third, adherence to therapy, including treatment discontinuations and switches, was not thoroughly reported in these RCTs (12,13,15). Finally, as IPF is a chronic illness, long-term survival is a more meaningful endpoint than those evaluated by the RCTs, such as improvements in pulmonary function tests and acute exacerbations. Keeping these limitations in view, this meta-analysis aimed to supplement the available data from these RCTs with pooled analysis of longer-term outcomes including survival, mortality, and treatment tolerance from real-world evidence (non-RCT) studies in order to provide a more clearer comparison of the efficacy and safety profiles of nintedanib and pirfenidone, that could provide valuable information to guide the choice between these two drugs.

Methodology

This systematic review and meta-analysis followed a pre-registered protocol and was reported in accordance with the guidelines of "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA). The eligibility criteria for the selection of studies, the search strategy for each database, primary and secondary outcomes, and the expected strategy for the data synthesis and analysis of this review were registered on the PROSPERO website (CRD: 42024580201).

Outcome assessment

The primary outcomes of this review were "overall survival" and "all-cause mortality". The overall

survival was compared using hazard ratios representing the risk of death from any cause for patients for any specified period of time. If multiple time points were reported, the data at the earliest time point was used in the analysis. The secondary outcomes were "treatment adjustments" and "adverse events". The treatment adjustments were defined as instances where: (1) the initial dose was reduced due to any reason (dose reduction); (2) the primary antifibrotic drug was replaced with any other drug (drug switch); and (3) the therapy was discontinued due to any reason (discontinuations). Furthermore, the adverse events were separately analysed in subgroups based on the most commonly reported types of adverse events.

Study selection

All the original studies that were deemed eligible were included. The inclusion criteria were defined as (1) Human studies; (2) Controlled trials and cohorts (both prospective and retrospective); (3) Studies reporting patients with a confirmed diagnosis of Idiopathic pulmonary fibrosis of any age or stage; (4) Studies with patients receiving Antifibrotics: pirfenidone or nintedanib as the primary treatment regimen for any specified period of time. The selected studies were deemed ineligible if they met at least one of the following exclusion criteria: (1) Studies only with patients receiving combination therapy regimens of pirfenidone OR Nintedanib with any other antifibrotics (steroids for instance); (2) Studies not reporting any of the outcomes or number of participants separately for both pirfenidone and nintedanib group; (4) Ongoing trials without any reported outcomes or meeting abstracts without available data for analysis; (5) Studies not reporting any of the outcomes of interest of this review. If a study involved some of the participants fulfilling the exclusion criteria, separate data was collected for only the included participants. Otherwise, the study was excluded. Also, if two (or more) studies were found to have included the same or overlapping cohort of patients, the latest one was selected to avoid the analysis of duplicated data.

Search strategy

The following two databases: (1) PubMed; (2) Cochrane, and two trial registers: (1) WHO ICTRP; and (2) Clinicaltrial.gov, were systematically searched without any language or publication restrictions for studies reporting both pirfenidone and Nintedanib as the primary antifibrotic treatment for idiopathic pulmonary fibrosis until 02, August 2024. Search terms for identification of studies from these sources included both the text words (synonyms and word variations) and database-specific subject controlled-vocabulary for "Pulmonary fibrosis and idiopathic pulmonary fibrosis", "pirfenidone", and "Nintedanib" were used. The exact search strategy for each source is given in Table S1. Titles and abstracts were examined by two independent authors. The full texts of the identified studies were further verified by at least two authors to finalise eligibility. Disagreements were resolved by the consensus of the corresponding authors. To identify possible additional studies, the reference lists of all the included articles were searched (ancestry approach). Finally, the studies citing our included were also searched via Web of Science and Google Scholar (descendency approach).

Data collection and management

For each included study, two reviewers independently extracted data in a standardized form, and inconsistencies were resolved by reviewing the full text of the articles. We extracted the following data: The first author's name, year of publication, study design, duration and type, study country and setting, patients' clinical characteristics (age, sex, treatment span and dosage), and the reported data of the outcomes of interest of this review for each treatment. When study cohorts included patients who experienced drug switches, the patient data for each independent treatment block was collected separately. If the outcome was not reported at the time of the drug switch, the data of those participants were excluded from that outcome analysis.

Quality assessment and estimation of risk of bias

The quality of each included study was independently assessed by two reviewers, and a consensus was reached. The quality of included cohorts was assessed on the study level using the Newcastle-Ottawa scale (NOS) for cohort studies. The scale applies a semi-quantitative star system (0 – 9 stars, with more stars indicating higher quality) to estimate study quality in three domains: subject selection (up to four stars), comparability of cohorts (up to two stars), and

assessment of outcome (up to three stars) (20). The summary and traffic-light plots summarising the results of the quality assessment were constructed using Robvis (a visualisation tool). Moreover, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was employed for the assessment of the overall quality of evidence for each outcome of this review, and the results were presented in the form of a summary of outcomes table (21).

Data analysis

All the statistical analysis for the meta-analysis was done using "RevMan Web" developed by Cochrane. The comparison of the survival impact of nintedanib and pirfenidone was made by calculating pooled Hazard ratios (HR) alongside 95%-confidence intervals (CIs) from the summary data statistics for each outcome, while all-cause mortality and safety profile (treatment adjustments and adverse events) were compared using pooled Odds ratios (OR). The Mantel-Haenszel (M-H) statistical method was used for the analysis of all the dichotomous outcomes. The Cochrane Q test and I^2 test were used to measure the overall heterogeneity across the included studies, where a p-value of <0.1 or an I^2 value of >50%, respectively, was considered a significant heterogeneity. Either a random- or fixed-effects model was used to pool the effect measures based on this heterogeneity assumption, i.e., a fixed-effects model was utilised in the case of non-significant heterogeneity (P>0.1, and I^2<50%); otherwise, the random-effects model was utilised. To explore the effects of individual studies on the overall result, sensitivity analyses were conducted for the primary outcomes by sequentially removing each study and evaluating the effect on the overall results (ORs and 95%-CI), heterogeneity (I^2), and statistical significance. In addition to this, the outcomes that were initially analysed using a fixed-effects model were re-run using the random-effects model. The funnel plots for each outcome were constructed using RevMan Web to assess the possible publication bias in the included studies.

Results

A total of 3,321 studies were identified through the initial search, and 66 duplicates were removed in total. Out of 2,655 remaining records, 2,583 were excluded during the title and abstract screening, and 72 were selected for the secondary screening. A total of 52 records were removed during the secondary screening, and 20 records were eventually included. Moreover, a total of 9 records were selected for the full-text review after an extensive grey literature search, and 3 of these were eventually included in this review. The whole selection process is summarised in the PRISMA 2020 flow diagram, Figure 1. The reasons for the exclusion of the excluded studies are described within the PRISMA Flowchart.

Characteristics and quality assessment of the included studies

The 23 cohorts were eventually included, which were published between 2017 and 2024. Out of these 23 cohorts, 19 were retrospective (11,22–39) and only 4 were prospective (40–43). These cohorts consisted of two groups of participants who received Nintedanib and Pirfenidone as the primary antifibrotic drug, respectively, did not receive any other concomitant treatment directly related to IPF, and had no history of previous antifibrotic therapy (drug switch). No RCT was included, and two reports, Khan 2023a and Khan 2023b, presented the data from a single cohort. The characteristics of the included studies are summarised in Table 1. Using the NOS scale, studies with a cumulative score of ≥7, 4-6, and <4 were considered as high, fair, and low quality, respectively. Among 23 cohorts, only 9 were deemed to have high quality, while the remaining 14 studies were determined to have fair quality. The summary of the quality assessment is presented in Figure 2.

Survival and all-cause mortality

6 cohorts (11,23,26,35,40,42) consisting of a total of 4,891 participants were included in the survival analysis described in Figure 3. Using the IV method, the pooled HR was 1.12 (95%-CI:0.99, 1.27) with a statistically non-significant difference (P=0.07), i.e., the treatments did not have any significant difference in their impact on overall survival. A fixed-effect model was used due to low overall heterogeneity (I^2=0%).

A total of 7 cohorts (25,31,32,35,38,40,43) consisting of 1189 and 1386 participants in the Nintedanib and pirfenidone therapy group, respectively,

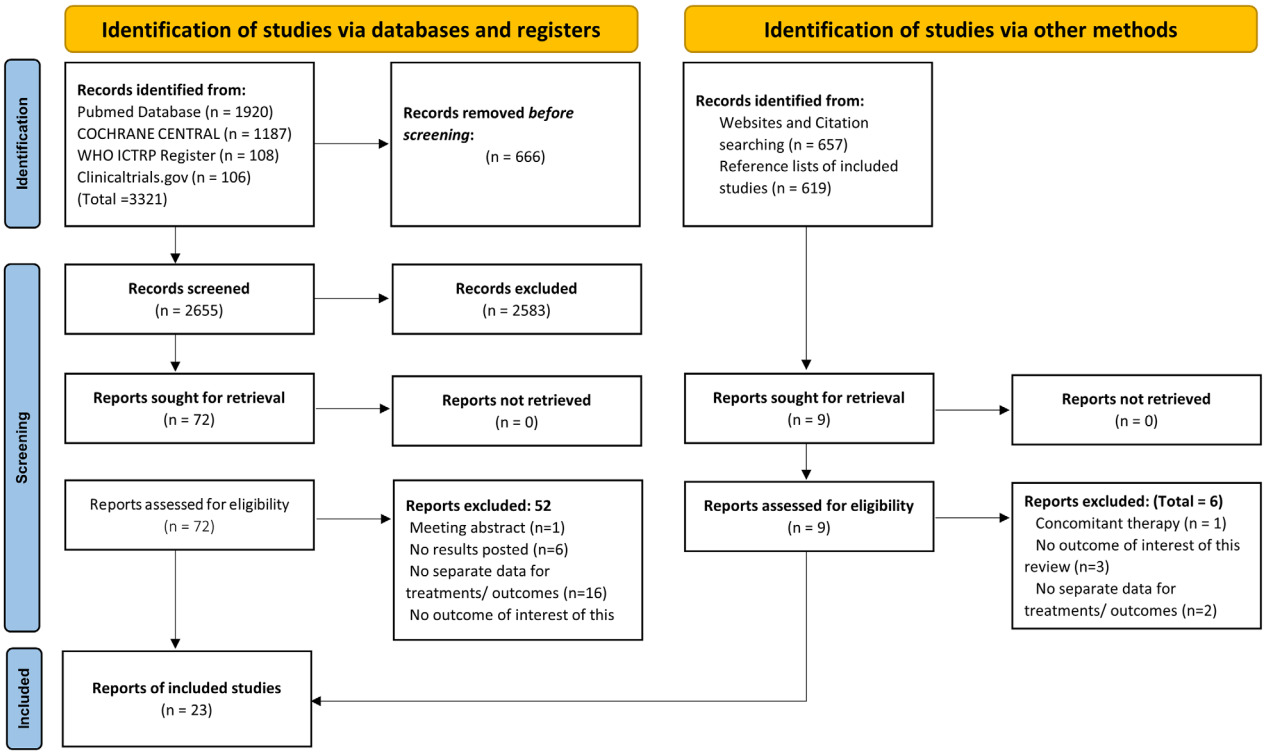

Figure 1. PRISMA 2020 flow diagram summarising the literature search, which included searches of databases, registers and other sources.

reported summary data statistics of All-cause mortality. The pooled OR of the reported data, using the M-H method, revealed a statistically non-significant difference (P=0.22) with OR= 1.11 (95%-CI:0.94, 1.31) (Figure 4). A fixed-effect model was used due to low overall heterogeneity (I^2=15%).

Lastly, four of the included cohorts reported the median survival of the participants on these two therapies. Both treatment groups had relatively similar median survival periods, which are summarised in Table 2.

Safety profile

The reported summary data statistics for treatment adjustments were analysed in three different subgroups, i.e., dose reductions, drug switches and treatment discontinuations, using the M-H method and a random-effects model due to the high amount of heterogeneity (I^2= 89% in drug switch, and I^2= 83% in treatment discontinuations). The odds of having a dose reduction were significantly higher in the nintedanib group (P=0.02) with OR = 1.56 (95%-CI:1.07, 2.27) and I^2=0% (Figure 5). There was no significant difference for the instances of drug switches (OR=1.82; 95%-CI: 0.69, 4.78; P=0.22) and treatment discontinuations (OR=0.92; 95%-CI: 0.60, 1.41; P=0.70) between the two treatment groups.

Furthermore, 7 cohorts (24,27,33,34,38,40,43) consisting of 483 and 853 participants in the Nintedanib and pirfenidone therapy group, respectively, reported summary data statistics of individuals with reported adverse events per group. The pooled OR, using the M-H method, revealed a statistically significant difference (P=0.02) with OR= 1.35 (95%-CI: 1.06, 1.71), i.e., the odds of an individual having an adverse event were 1.35 times with nintedanib therapy compared to pirfenidone as described in Figure 6. A fixed-effects model was used due to low overall heterogeneity (I^2=15%).

Lastly, a total of 11 cohorts report summary data statistics based on the specific type of adverse events reported. The pooled ORs using the M-H method and random-effects models revealed that, compared to the pirfenidone group, the nintedanib group had

Table 1. Characteristics of the included cohorts based on the data extracted from full-text manuscripts

Study ID	Type of cohort	Duration and period of follow-up	Participants	Eligibility Criteria	Dosing in		Outcomes reported
					Pirfenidone group	Nintedanib group	
Galli 2017 (28)	Retrospective	52 ±17 and 41 ±15 weeks for pirfenidone and nintedanib, respectively. (Between 2014 and 2016)	186 in the treated cohort (129 in the pirfenidone group and 57 in the nintedanib group)	1) At least 30 years old, therapy with either pirfenidone or nintedanib and a diagnosis of pulmonary fibrosis (any aetiology) as determined by each subject's primary pulmonologist; 2) Subjects with pulmonary fibrosis from IPF, in addition to those with pulmonary fibrosis from other etiologies were included; 3) Patients were excluded if lung transplantation, transition to hospice or death occurred before starting therapy.	Not specified	Not specified	Adverse events and treatment discontinuations
Barratt 2018 (22)	Retrospective	423.6 ± 362 and 320.9 ± 220.9 days for pirfenidone and nintedanib, respectively (Between 2012 and 2017)	167 (115 in the pirfenidone group and 49 in the nintedanib group)	1) IPF patients with prescribed anti-fibrotic therapy by the Northern hub (North Bristol NHS Trust) of the Southwest of England regional ILD network; 2) Diagnosis of IPF confirmed by a multidisciplinary team (MDT), following the ATS/ERS/JRS/ALAT consensus guidelines.	801 mg (3 times a day)	150 mg (2 capsules a day)	Treatment Discontinuations
Cerri 2019 (43)	Prospective	24 months.	106 in the treated cohort (78 in the pirfenidone group and 28 in the nintedanib group)	1) Patients aged 40–80y, with IPF diagnosis based on the ATS/ERS/JRS/ALAT 2015 guidelines; 2) Naïve to both drugs tested, and had received only low doses of oral steroids in the past and/or at the start of this study; 3) Percent predicted Forced Vital Capacity (FVC % pred.) > 50%, with a Forced Expiratory Volume at 1 s (FEV1)/Forced Vital Capacity ratio >70%, and a % predicted diffusing capacity of the lung for carbon monoxide (DLCO %pred.) >30% at screening; 3) Exclusion criteria were: alanine aminotransferase, aspartate aminotransferase or bilirubin levels higher than 1.5 times the upper limit of normal; bleeding risk or thrombosis; planned major surgery within the next 3 months including lung transplantation, major abdominal, or major intestinal surgery; myocardial infarction within the previous 6 months, or unstable angina within the last month.	801 mg (3 times a day)	150 mg (2 capsules a day) eventually decreased to 100mg twice daily	Mortality and adverse events.

Dempsey 2019 (26)	Retrospective	24 months. (Between 2014 and 2018)	1255 in the treated cohort (692 in the pirfenidone group and 593 in the nintedanib group)	(For the treated cohort) 1) Adult patients (>18) who filled a prescription for either pirfenidone or nintedanib; 2) have a diagnosis of IPF using the International Classification of Diseases, Ninth Edition (ICD-9) and International Classification of Diseases, 10th Edition (ICD-10), 180 days before their first fill for either drug.	Not specified	Not specified	Survival
Cameli 2020 (24)	Retrospective	885 ± 559.5 days (Between 2011 and 2019)	263 (124 in the pirfenidone group and 139 in the nintedanib group)	1) All IPF patients treated with pirfenidone and nintedanib at the Regional Referral Centre for Rare Lung Diseases, Siena.	Not specified	Not specified	Mortality and Adverse events
Corral 2020 (25)	Retrospective	Median 403 and 383 days for pirfenidone and nintedanib, respectively. (Between 2014 and 2018)	1455 (799 in the pirfenidone group and 656 in the nintedanib group)	1) At least 40 years old on the index date; 2) have continuous enrollment with medical and prescription coverage for at least 12 months before the index date (baseline period); 3) have at least one non-diagnostic inpatient or outpatient claim with a diagnosis code for IPF between the baseline period and June 30, 2018 and 4) no evidence of other interstitial lung diseases (hypersensitivity pneumonitis, diffuse connective tissue disease, rheumatoid arthritis, sarcoidosis, etc.) between the index date and June 30, 2018.	Not specified	Not specified	Treatment adjustments.
Holtze 2020 (29)	Retrospective	Up to 24 months. (Between 2016 and 2018)	703 in the single antifibrotic-treated cohort (312 in the pirfenidone group and 391 in the nintedanib group)	1) IPF diagnosis confirmed at the registry site with evaluation including a medical history, physical exam, pulmonary function test (PFT), and computerised tomography scan of the chest (CT) at a minimum; 2) no history of lung transplants before enrollment.	Not specified	Not specified	Treatment adjustments.
Sadon 2020 (41)	Prospective	12 months. (Between 2016 and 2018)	50 (25 in the pirfenidone group and 25 in the nintedanib group)	1) Clinically stable patients diagnosed as having IPF (according to ATS/ERS/JRS/ALAT* guidelines) with Age >40 years; 2) FVC >50% of predicted and DLCO >30% of predicted value; 3) Duration since IPF diagnosis within 5 years; 4) No planned high oxygen requirement (≥15 h/day) or lung transplantation; 5) No indications of rapidly deteriorating disease or life expectancy of less than 3 months; 6) No history of coexisting respiratory infection, lung cancer, or IIP other than IPF;.7) No history of previous pirfenidone or nintedanib therapy (for proper evaluation of the drug efficacy).	267mg three times per day (days 1-7), then 2 tablets three times per day (days 8-14), and then 3 tablets three times per day (day 15 onwards),	300mg per day.	Treatment adjustments and adverse events

Table 1 (*Continued*)

Study ID	Type of cohort	Duration and period of follow-up	Participants	Eligibility Criteria	Dosing in		Outcomes reported
					Pirfenidone group	Nintedanib group	
Belhassen 2021 (23)	Retrospective	Up to 3 years. (Between 2015 and 2017)	1313 in the treated cohort (804 in the pirfenidone group and 509 in the nintedanib group)	1) Patients with IPF, newly treated with pirfenidone or nintedanib; 2) only patients continuously covered by the French NHS during the study period; 3) Patients older than 50; 4) Patients who had previously received a lung transplant were excluded. 5) Those who had received pirfenidone or nintedanib in the five years before the inclusion period were excluded.	Not specified	Not specified	Survival
Marijic 2021 (35)	Retrospective	Up to 2 years. (Between 2013 and 2018)	1553 in the treated cohort (840 in the pirfenidone group and 713 in the nintedanib group)	1) Patients with IPF and antifibrotic treatment; 2) age > 40 years; 3) Excluded patients, who were not continuously insured with the AOK and those with a baseline period (pre-observational) or an outcome period (post-observational) of less than one year.	Not specified	Not specified	Mortality and survival
Noor 2021 (36)	Retrospective	21.8 ±15.9 and 24.3 ±16.1 months for pirfenidone and nintedanib, respectively (Between 2007 and 2018)	110 in the single antifibrotic-treated cohort (24 in the pirfenidone group and 86 in the nintedanib group)	1) Patients with a multidisciplinary diagnosis of idiopathic pulmonary fibrosis (IPF) and an FVC[†] greater than 80%.	Not specified	Not specified	Median survival, treatment discontinuations and adverse events
Wright 2021 (39)	Retrospective	Up to 3 years. (Between 2011 and 2017)	104 in the treated cohort (62 in the pirfenidone group and 42 in the nintedanib group)	1) Patients with definite and probable usual UIP[‡] with no identifiable cause diagnosed with IPF, following ATS/ERS/JRS/ALAT guidelines; 2) Patients with IPF eligible for antifibrotic treatment; 3) FVC percentage predicted between 50% and 80%.	Not specified	Not specified	Treatment adjustments and adverse events.
Fournier 2022 (27)	Retrospective	20.0 ± 16.8 months. (Between 2011 and 2020)	176 (115 in the pirfenidone group and 61 in the nintedanib group)	1) Started on pirfenidone or nintedanib; 2) "Treated for IPF.", and "Followed up at the Rennes University Hospital throughout."; 3) IPF patients included in pirfenidone or nintedanib clinical trials/ followed-up at another health care facility were excluded.	Not specified	Not specified	Adverse events

Levra 2022 (34)	Retrospective	27 ± 17 and 17 ± 14 months for pirfenidone and nintedanib, respectively (Between 2011 and 2020)	310 (192 in the pirfenidone group and 89 in the nintedanib group)	1) Only patients who started the antifibrotic treatment for the first time; 2) Patients older than 50; 3) Patients with a new diagnosis of pulmonary fibrosis other than IPF during the study period were excluded.	801 mg (3 times a day) After the induction period	150 mg (2 capsules a day) After the induction period	Adverse events and treatment discontinuations
Takehara 2022 (37)	Retrospective	390 days. (Between 2009 and 2018)	283 (134 in the pirfenidone group and 50 in the nintedanib group)	1) Patients diagnosed with IPF and treated with pirfenidone or nintedanib at six regional core facilities in Gunma prefecture, Japan; 2) Excluded if a drug switch or addition of another drug occurred within 1 year	1153 ± 420 mg (daily)	249 ± 59.69 mg (daily)	Median survival and treatment discontinuations
Bocchino 2023 (11)	Retrospective	4.2y (median) (Between 2012 and 2019)	235 (133 in the pirfenidone group and 102 in the nintedanib group)	1) Patients aged >18y diagnosed with IPF according to established criteria at the time of the patient's assessment; 2) No history of acute exacerbation at disease onset, any reason against the initiation of any anti-fibrotic drug (i.e., not eligibility or patient decision), permanent therapy discontinuation or lung transplantation, or therapy switch; 3) Patients starting therapy with a delay >12 months from the first diagnosis were excluded.	Not specified	Not specified	Survival and median survival.
Honda 2023 (30)	Retrospective	Variable. (Between 2008 and 2019)	91 (37 in the pirfenidone group and 54 in the nintedanib group)	1) Patients with IPF who were treated with antifibrotic agents (pirfenidone or nintedanib); 2) Excluded patients administered both antifibrotic medications.	600-1800 mg (daily)	200-300 mg (daily)	Median survival.
Khan 2023a (32)	Retrospective	35 ± 16.5 months. (Between 2014 and 2020)	81 (45 in the pirfenidone group and 36 in the nintedanib group)	1) Patients diagnosed with IPF according to international guidelines (ATS/ERS/ JRS/ALAT 2011) and confirmed by pathologists with subspecialty training in ILD.	801 mg (3 times a day)	150 mg (2 capsules a day)	All-cause mortality
Khan 2023b (32)	Retrospective	Same as Khan 2023	Same as Khan 2023	Same as Khan 2023	Same as Khan 2023a	Same as Khan 2023a	All-cause mortality and adverse events
Uzer 2023 (38)	Retrospective	28.9 ± 20.5 and 22.5 ± 17 months for pirfenidone and nintedanib, respectively (Between 2014 and 2020)	227 (167 in the pirfenidone group and 60 in the nintedanib group)	1) Patients receiving at least one dose of antifibrotic medication were included in the study; 2) Those with incomplete data in their electronic files, and patients diagnosed with progressive pulmonary fibrosis were excluded.	Not specified	Not specified	All-cause mortality, treatment discontinuations and adverse events

Table 1 (*Continued*)

Study ID	Type of cohort	Duration and period of follow-up	Participants	Eligibility Criteria	Dosing in		Outcomes reported
					Pirfenidone group	Nintedanib group	
Romero 2024 (40)	Prospective	Mean = 716 days. (Between 2015 and 2021)	232 (147 in the pirfenidone group and 85 in the nintedanib group)	1) Patients diagnosed with IPF according to European Respiratory Society/ American Thoracic Society guidelines, with no age limit; 2) Started antifibrotic treatment for >10 days; 3) Signed the informed consent form; 4) No other interstitial lung diseases other than IPF; 5) Excluded participants with refusal to be contacted for follow-up and those who had not taken the medication within the specified number of days.	801 mg (3 times a day)	150 mg (2 capsules a day)	All-cause mortality, survival, treatment discontinuations and adverse events.
Iwasaki 2024 (31)	Retrospective	22.9 ± 20.1 months. (Between 2008 and 2021)	103 (32 in the pirfenidone group and 81 in the nintedanib group)	1) Patients diagnosed with IPF through a medical expense assistance program and treated with antifibrotic drugs; 2) No history of acute exacerbation at the initiation of therapy or with concurrent lung cancer.	Not specified	Not specified	All-cause mortality, treatment discontinuations and adverse events.
Zhao 2024 (42)	Prospective	593 ± 478 and 357 ± 259 days for pirfenidone and nintedanib, respectively. (Between 2017 and 2022)	303 (205 in the pirfenidone group and 98 in the nintedanib group)	1) Adult patients (>18 years) with the diagnosis of IPF, confirmed after multidisciplinary team discussion, according to the IPF consensus criteria of the ATS/ERS/JRS/ALAT; 2) Treated with antifibrotic drugs, i.e., either pirfenidone or nintedanib, based on the guidance for the treatment of IPF, taking into account the patient's economic status and the presence of drug contraindications; 3) Patients were excluded if combination is used or a drug change occurred during the observation period; 4) Patients were excluded for missing baseline data, such as lung function or blood gas analysis.	1800mg per day (after an induction period)	300mg per day	Survival, adverse events and treatment discontinuations

*American Respiratory Society, European Respiratory Society Japanese Respiratory Society and Latin American Thoracic Association.
†Forced Vital Capacity.
‡Usual interstitial Pneumonia.

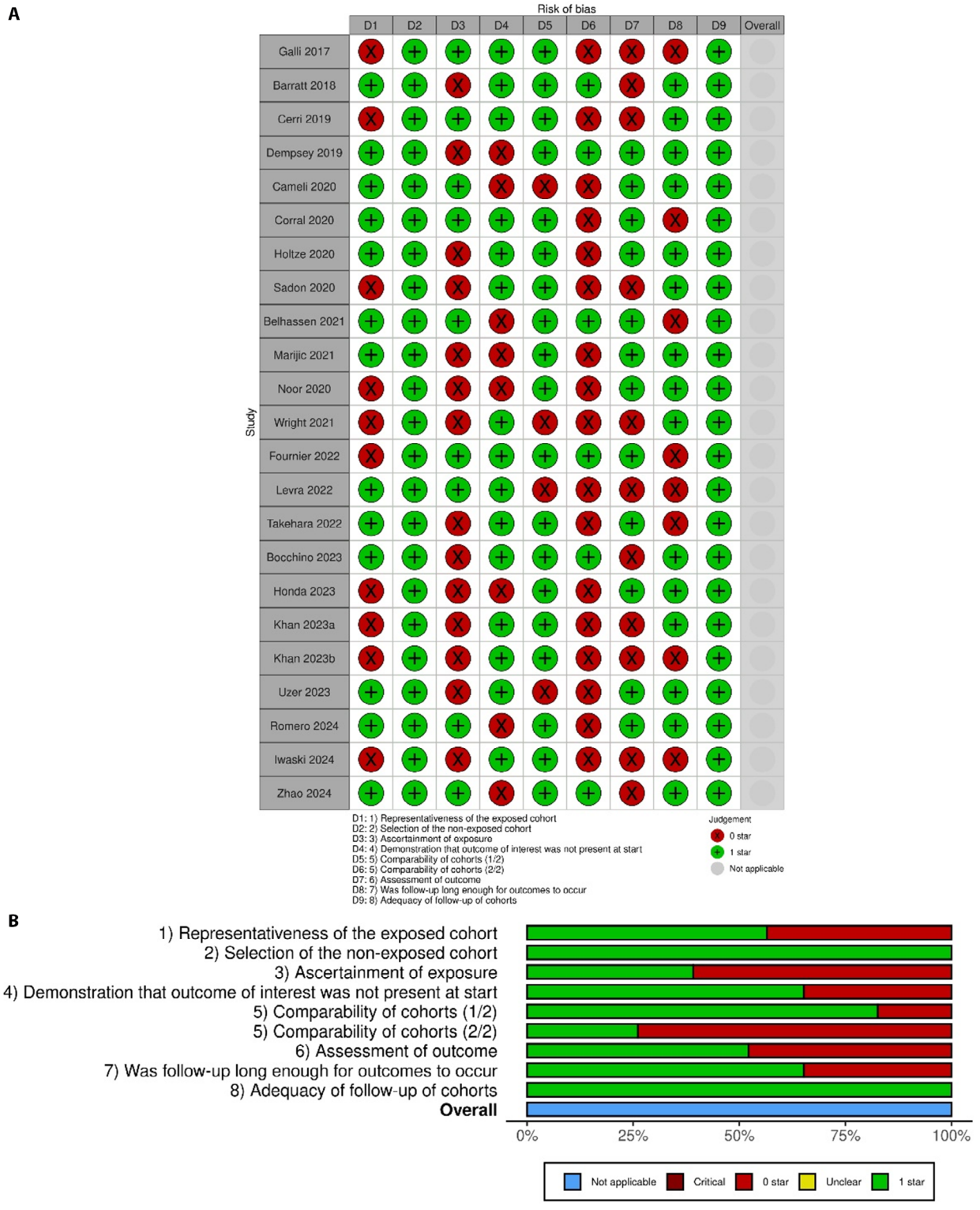

Figure 2. Summary of the quality assessment of the included studies using the NOS; (A) traffic-light plot showing the assessment of each study, and (B) Summary plot representing the sum for each point of scale.

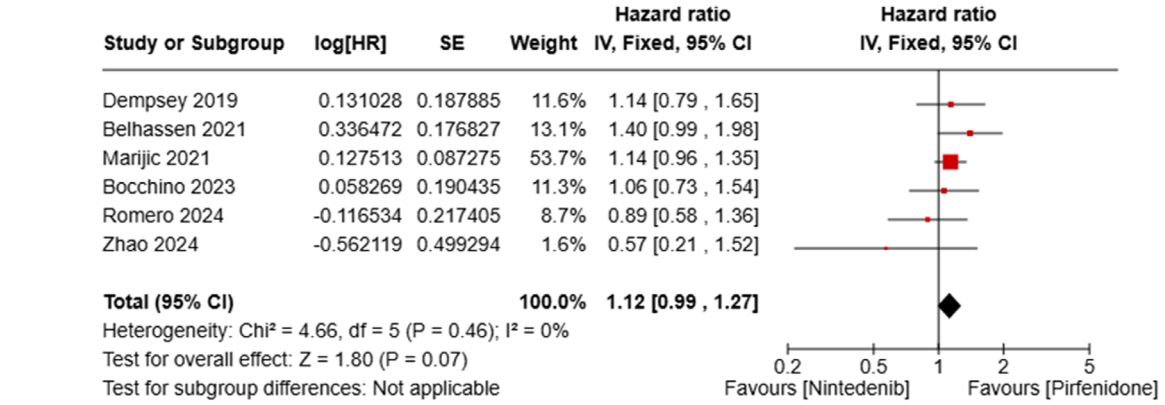

Figure 3. The forest plot of survival analysis using the hazard ratios (HR).

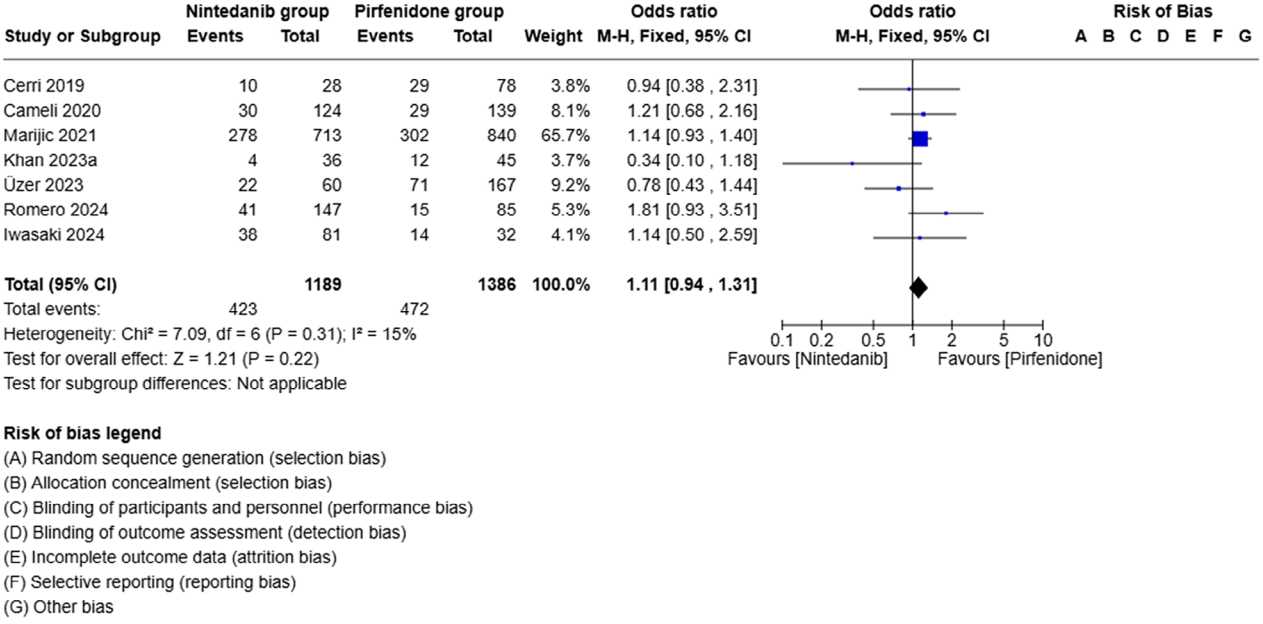

Figure 4. The forest plot of all-cause mortality analysis using the pooled odds ratio (OR).

Table 2. Reported median Survival times for Idiopathic pulmonary fibrosis patients

	Median Survival		Significance of the difference (P value)
Study ID	**Pirfenidone Group**	**Nintedanib Group**	
Honda 2023	40.3 months (elderly) 53.2 months (non-elderly)	51.0 months (elderly) 52.6/24 (non-elderly)	-
Takehara 2022	19 months (95%-CI: 12-28)	20 months (95%-CI: 9-26)	0.439
Bacchino 2023	4.6 months (95%-CI: 3.6-5.3)	4.3 months (95%-CI: 3.8- not estimable)	
Noor 2021	3.5 years	3 years	0.33

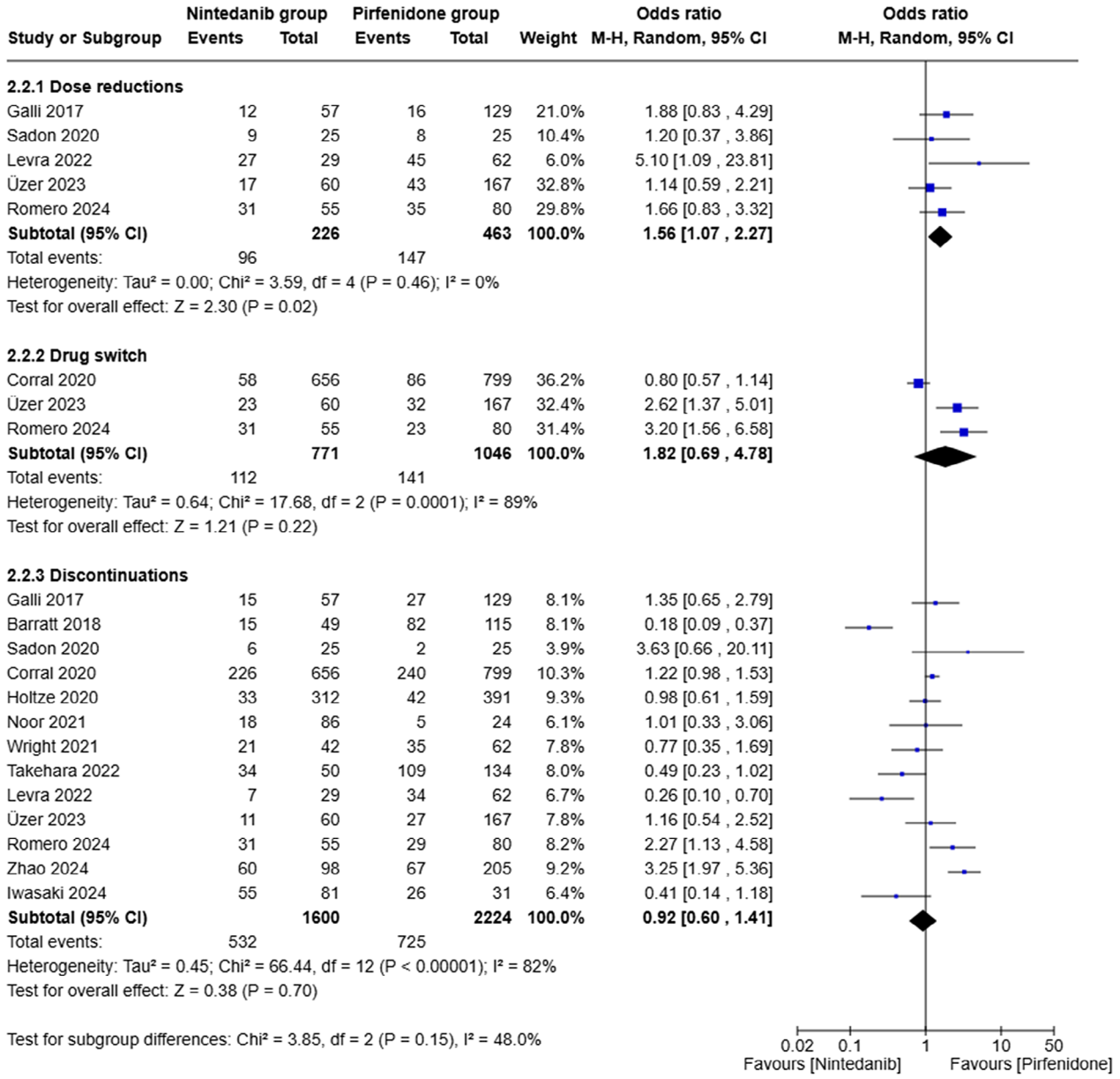

Figure 5. The forest plot of Treatment adjustments using the pooled odds ratio (OR).

significantly higher odds of having diarrhoea (OR= 12.39; 95%-CI: 5.67, 27.07; P<0.00001) and abnormal liver function tests (OR= 2.98; 95%-CI: 1.92, 4.61; P<0.00001), while having significantly lower odds of having photosensitivity (OR= 0.06; 95%-CI: 0.01, 0.25; P=0.0001), and skin rash (OR= 0.17; 95%-CI: 0.08, 0.34; P<0.00001). No statistically significant difference was observed for odds of other gastrointestinal adverse events (OR=1.00; 95%-CI: 0.58, 1.74; P=0.99), and anorexia (OR=1.23; 95%-CI: 0.39, 3.84; P=0.72). The forest plots are presented in Figure 7.

Sensitivity analysis

Similar results were observed for overall survival and all-cause mortality when a random-effects model was used instead. However, the results became statistically insignificant when a random-effects model was used for total adverse events (OR=1.33; 95%-CI:

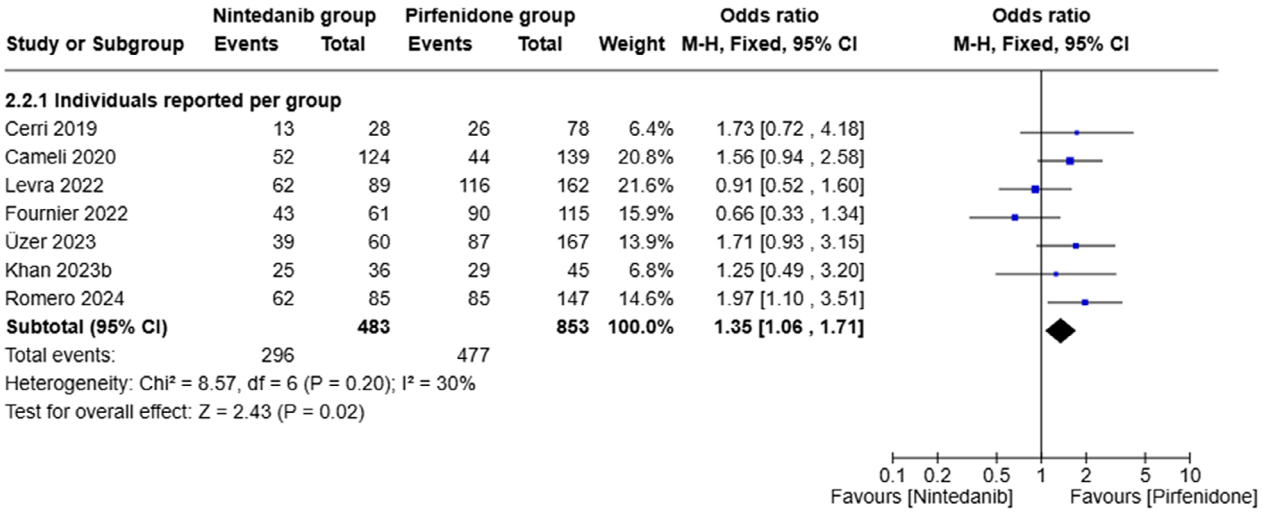

Figure 6. The forest plot of individuals affected by adverse events, using the pooled odds ratio (OR).

0.99-1.79; P=0.06). Removing individual studies in the outcome analysis of "all-cause mortality", "Dose reductions subgroup", and "treatment discontinuations subgroup" gave similar results. The results became statistically significant in "Overall survival" after removing one cohort, Romero 2024 (OR=1.15; 95%-CI: 1.01-1.31; P=0.04) and in "Drug switch subgroup" after removing Corral 2020 (OR=2.87; 95%-CI: 1.77, 4.64; P<0.0001). Lastly, the results of "total adverse events" became statistically insignificant when either Cameli 2020 or Uzer 2023 were removed (P=0.07; P=0.06). The detailed results of the sensitivity analysis are provided in Table S2.

Publication bias and grading of outcomes

The funnel plot of the "treatment discontinuations subgroup" could not rule out the possibility of publication bias and the assessment of "overall survival", "all-cause mortality", "dose reductions subgroup", "drug switch subgroup" and "total adverse events" was not possible due to an inadequate (less than 10) number of studies. Nonetheless, the funnel plots of all the outcomes are given in Figures S1-S6. Using the GRADE scale, the certainty of evidence was evaluated as moderate for "overall survival", "all-cause mortality", and three specific adverse events subgroups (photosensitivity, skin rash, and abnormal liver function tests) due to the data being completely from cohorts. On the other hand, "treatment adjustments", "total adverse events" and "the remaining 3 specific adverse event subgroups (Diarrhoea, other GI symptoms, and anorexia)" were deemed to have low certainty due to imprecision, (the CI was wide enough to allow for the possibility of more than one conclusion, i.e., no effect and an important effect), and/or significant heterogeneity within the reported outcomes. The "Summary of Outcomes table" for the results assessed using the GRADE tool is given in Table 3.

Discussion

This review aimed to determine the comparative survival impact, in terms of hazard ratios and all-cause mortality, and safety profile, in terms of adverse effects and treatment adjustments, for the antifibrotics nintedanib and pirfenidone. Acute exacerbations, along with the rapid FVC decline, are the major contributors to overall mortality in IPF patients (44). A previous meta-analysis that pooled data for nintedanib and pirfenidone individually found that nintedanib reduced the risk of acute exacerbations by 5% compared to placebo, whereas pirfenidone did not show a significant reduction (45). Petnak et al. reported a similar statistically significant acute exacerbation risk reduction compared to non-treatment in only the nintedanib subgroup and not the pirfenidone subgroup (46). Kou et al. reported acute exacerbation incidence rates of 14.4% and 12.5% for

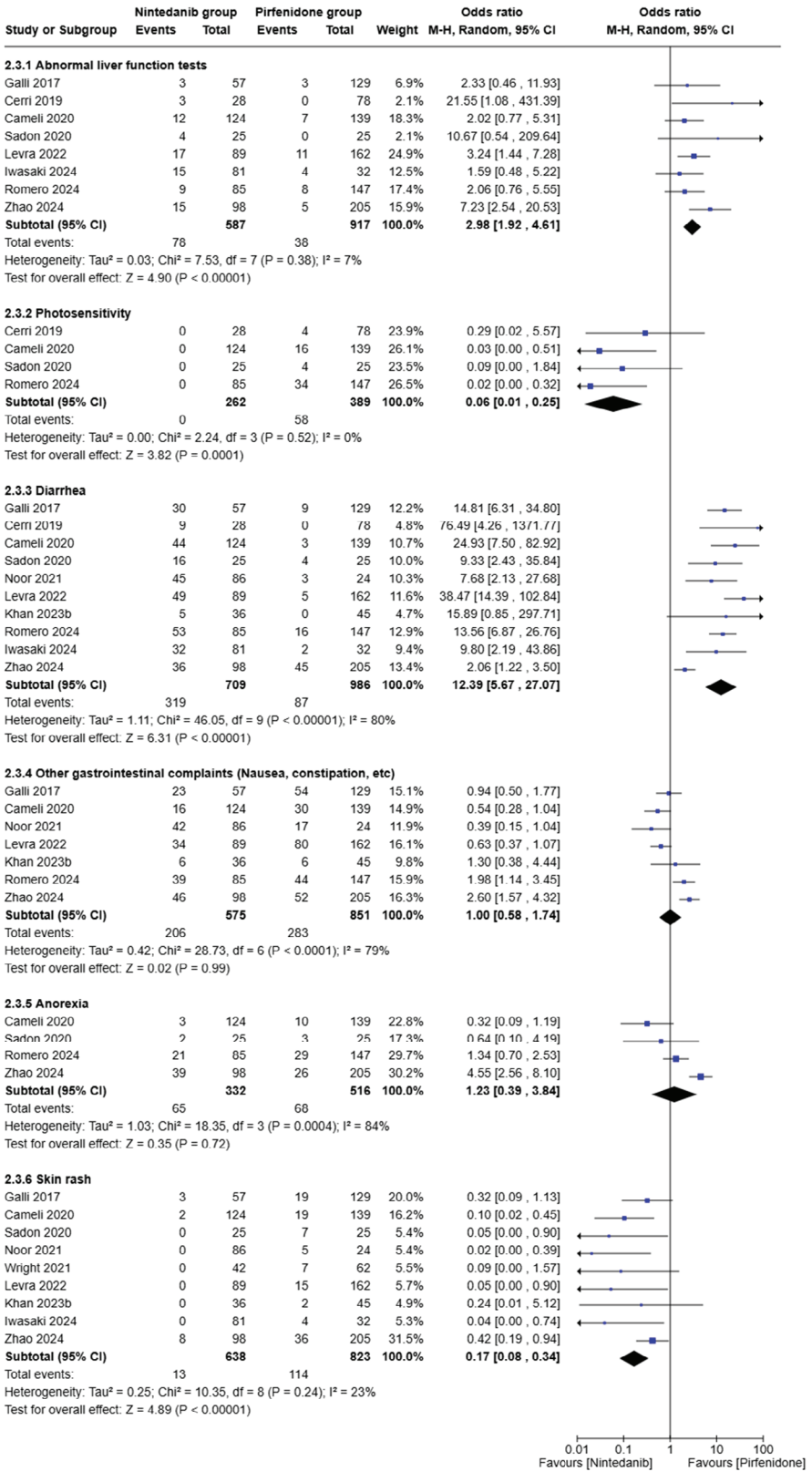

Figure 7. The forest plots commonly reported adverse events for antifibrotic treatment, using the pooled odds ratio (OR).

Table 3. Summary of the grading of outcomes using the GRADE tool

Nintedanib Compared to Pirfenidone for Idiopathic Pulmonary Fibrosis.					
Patient or population: Idiopathic Pulmonary Fibrosis					
				Anticipated absolute effects	
Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Risk with Pirfenidone**	**Risk difference with Nintedanib**
Survival	(6 non-randomised studies)	⨁⨁⨁◯ Moderate	**HR 1.12** (0.99 to 1.27)	0 per 1,000	-- **per 1,000** (-- to --)
All-cause Mortality	2575 (7 non-randomised studies)	⨁⨁⨁◯ Moderate	**OR 1.11** (0.94 to 1.31)	341 per 1,000	**24 more per 1,000** (14 fewer to 63 more)
Treatment Adjustments - Dose Reductions	689 (5 non-randomised studies)	⨁⨁◯◯ Low[a]	**OR 1.56** (1.07 to 2.27)	317 per 1,000	**103 more per 1,000** (15 more to 196 more)
Treatment Adjustments - Drug Switch	1817 (3 non-randomised studies)	⨁◯◯◯ Very low[b,c]	**OR 1.82** (0.69 to 4.78)	135 per 1,000	**86 more per 1,000** (38 fewer to 292 more)
Treatment Adjustments - Discontinuations	3824 (13 non-randomised studies)	⨁◯◯◯ Very low[b,c]	**OR 0.92** (0.60 to 1.41)	326 per 1,000	**18 fewer per 1,000** (101 fewer to 79 more)
Total Adverse Events (Individuals reported per group)	1336 (7 non-randomised studies)	⨁⨁◯◯ Low[c]	**OR 1.35** (1.06 to 1.71)	559 per 1,000	**72 more per 1,000** (14 more to 125 more)
Adverse Events - Abnormal Liver Function Tests	1504 (8 non-randomised studies)	⨁⨁⨁◯ Moderate	**OR 2.98** (1.92 to 4.61)	41 per 1,000	**73 more per 1,000** (35 more to 125 more)
Adverse Events – Photosensitivity	651 (4 non-randomised studies)	⨁⨁⨁◯ Moderate	**OR 0.06** (0.01 to 0.25)	149 per 1,000	**139 fewer per 1,000** (147 fewer to 107 fewer)
Adverse Events – Diarrhoea	1695 (10 non-randomised studies)	⨁⨁◯◯ Low[b]	**OR 12.39** (5.67 to 27.07)	88 per 1,000	**457 more per 1,000** (266 more to 635 more)
Adverse Events - Other Gastrointestinal Complaints (Nausea, constipation, etc.)	1426 (7 non-randomised studies)	⨁⨁◯◯ Low[c]	**OR 1.00** (0.58 to 1.74)	333 per 1,000	**0 fewer per 1,000** (108 fewer to 132 more)
Adverse Events - Anorexia	848 (4 non-randomised studies)	⨁◯◯◯ Very low[b,c]	**OR 1.23** (0.39 to 3.84)	132 per 1,000	**26 more per 1,000** (76 fewer to 236 more)
Adverse Events - Skin rash	1461 (9 non-randomised studies)	⨁⨁⨁◯ Moderate	**OR 0.17** (0.08 to 34.00)	139 per 1,000	**112 fewer per 1,000** (126 fewer to 707 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimated effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimated effect.
Explanations
a. The sample size of the included studies does not meet the optimal information size.
b. There is significant heterogeneity in the overall result.
c. The 95% CI is wide enough to allow for the possibility of more than one conclusion, i.e., no effect and an important effect.

pirfenidone and nintedanib, respectively (47). Ideally, this difference in exacerbation rates between the two groups should translate into a difference in overall survival and reduced mortality. However, our meta-analysis of these outcomes revealed no significant survival benefit of nintedanib over pirfenidone with HR=1.12 (95%-CI:0.99, 1.27) and OR=1.11 (95%-CI:0.94, 1.31) for all-cause mortality. This finding aligns with a network meta-analysis that indirectly compared the two drugs and found no significant difference in all-cause mortality (48). Petnak et al. showed that all-cause mortality was significantly lower for both nintedanib and pirfenidone subgroups compared to non-treatment (46), while Kou et al. reported all-cause mortality rates of 16.6% and 20.1% for nintedanib and pirfenidone, respectively, even though acute exacerbations were more frequent with the former (47). This may be attributed to the fact that survival in IPF is also influenced by several factors other than exacerbations, such as age, hospitalisations, and baseline FVC (49). As a result, the direct effect of reducing acute exacerbations might not significantly impact overall survival when compared to pirfenidone. Furthermore, the drugs' effects on slowing lung function decline may be insufficient to counteract these stronger predictors of mortality, which play a more decisive role in patient outcomes. Another important consideration when comparing survival outcomes between therapies for IPF is the great variability in IPF pathogenesis across patient groups. For instance, a recent study utilizing single-cell RNA sequencing identified two distinct subsets of IPF patients, i.e., one subset exhibited a myeloid-enriched phenotype with high levels of macrophage and fibroblast activation, while the other demonstrated a ciliated epithelium-enriched phenotype with elevated B cells and plasma cells (50). The study revealed that the ciliated epithelium-enriched subset had significantly higher expression of genes known to respond to pirfenidone treatment, suggesting that these patients may experience a better therapeutic response to pirfenidone, potentially leading to greater survival benefits compared to nintedanib (50). IPF pathogenesis also exhibits variability over the course of disease progression. For example, fibroblasts from IPF patients have been shown to exhibit different characteristics depending on how long they've been in culture, i.e., fibroblasts initially display a strong pro-fibrotic phenotype, with increased collagen production, myofibroblast differentiation, and ROS generation, but this behaviour diminishes over time leading to their senescence (51). This suggests that nintedanib may be more effective in the early stages of IPF due to its targeted inhibition of fibroblast proliferation and growth factor signalling, which are more prominent in the early disease stages while pirfenidone may be better suited for later stages, where fibrosis is driven by other mechanisms, such as inflammation associated with myofibroblast senescence (11,51). These findings also raise the possibility of using sequential therapy, i.e., starting with pirfenidone in the early stages and transitioning to nintedanib in the later stages (11). However, some authors argue that nintedanib might be more beneficial in the later stages of IPF due to its ability to reduce acute exacerbations, while pirfenidone's efficacy may decline over time, as observed in previous trials (26). Regardless of the sequence, the concept of sequential therapy is worth exploring in future studies to optimise treatment for IPF. Our meta-analysis is the first to provide comprehensive statistics on the comparative safety profiles of nintedanib and pirfenidone. The pooled summary data revealed that a statistically higher proportion of individuals experienced adverse events with nintedanib compared to pirfenidone (61.3% vs. 55.9%; OR=1.35, 95%-CI:1.06-1.71; P=0.02). This is in line with the findings of Kou et al., who reported adverse event incidence rates of 69.7% and 56.4% for nintedanib and pirfenidone, respectively (47). However, the I^2 statistic in our analysis suggests that 30% of the variance between studies may be attributable to differences among the studies themselves rather than random variability, which means the results might not be fully generalizable to the overall population. Although the overall rate of adverse events may only differ by 5.4% between the two drugs, there are notable differences in the nature of adverse events experienced. Patients taking nintedanib had significantly higher odds of experiencing liver function abnormalities and diarrhoea. Conversely, pirfenidone was more commonly associated with cutaneous manifestations, including skin rash and photosensitivity. Understanding the underlying mechanisms of these adverse events is crucial to effectively manage them. Drug-induced liver injury (DILI) is an idiosyncratic reaction observed with many medications, including TKIs like nintedanib (52). While mechanisms such as the inhibition of mitochondrial oxidative metabolism and hepatocyte apoptosis have been proposed to

explain DILI associated with other TKIs, the most likely underlying cause of elevated liver enzymes with nintedanib is direct hepatocyte injury (53–56). This effect was more pronounced with nintedanib compared to pirfenidone (OR= 2.98; 95%-CI:1.92-4.61), likely due to differences in their pharmacokinetics (53): Nintedanib's higher lipophilicity results in greater deposition in the liver, and its interaction with various hepatic transporters can exert more metabolic stress on the liver than pirfenidone (53). Diarrhoea is another well-known adverse effect of antifibrotic therapy, with data from our analysis (OR=12.39; 95% CI: 5.67-27.07) agreeing with previous trials indicating that it most commonly occurs with nintedanib (8). Although the exact mechanism is unclear, several hypotheses have been proposed (57). First, VEGFR inhibition by nintedanib may lead to ischemic colitis, resulting in bowel mucosal damage (57). Second, FGFR inhibition may disrupt EGF signalling, which is important in IPF fibroblasts where EGFR is overexpressed (57,58). While speculative, this suggests that indirect inhibition of the EGF pathway via FGFR inhibition in the intestinal epithelium could impair normal mucosal repair, contributing to diarrhoea. Lastly, nintedanib may directly cause inflammation, leading to mucosal damage (57). An interesting observation regarding nintedanib-induced diarrhoea from the INPULSIS trial is that patients who experienced diarrhoea while on nintedanib tended to preserve their baseline FVC (forced vital capacity) better than those who did not experience diarrhoea (8,12). This positive correlation between clinical efficacy and adverse events with nintedanib suggests a potential link that warrants further investigation (8). On the other hand, pirfenidone is associated with a higher incidence of cutaneous adverse events, including photosensitivity (OR=0.06; 95%-CI:0.01-0.25) and skin rash (OR=0.17; 95%-CI:0.08-0.34), compared to nintedanib. This might be explained by the pharmacokinetic murine studies that have demonstrated that pirfenidone accumulates more in the skin and eyes at higher doses (160 mg/kg), where it absorbs UVA and UVB radiation, generating reactive oxygen species (ROS) that cause lipid peroxidation in cell membranes (59). This results in cellular damage, leading to increased sensitivity to sunlight and potentially causing skin rashes during oral therapy (59). Sometimes, such adverse effects necessitate treatment adjustments. In our analysis, while the overall treatment adjustments showed no significant difference between nintedanib and pirfenidone, the odds of dose reductions were significantly higher with nintedanib compared to pirfenidone (OR = 1.35; 95%-CI:1.06-1.71). This is because lowering the dose of nintedanib does not significantly reduce the time to treatment failure but does notably decrease the rate of adverse events, most importantly for diarrhoea (60). This aligns with the INPULSIS trials, where 10.7% of patients had to lower their doses because of diarrhoea (8,12). Regarding treatment discontinuations, the pooled effect size did not reveal any significant differences between the two drugs. This parallels the findings of Kou et al., who reported a treatment discontinuation rate of 16.2% for nintedanib,which was very close to the 16.6% reported for pirfenidone (47). However, an interesting finding from two of the included studies, Belhassen 2021 and Romero 2024, is that female gender was significantly associated with treatment discontinuation across any therapy group (23,40). Although no specific cause for this finding can be identified, future studies on treatment discontinuations should ensure equal representation of women in both therapy groups to avoid confounding their results. As previously mentioned, analysing RWE data is crucial for diseases like idiopathic IPF, but it comes with its own limitations and challenges. First, many studies had small sample sizes, with significantly fewer patients in the nintedanib group compared to the pirfenidone group. Second, the effect sizes in the studies were highly variable, as evidenced by the wide confidence intervals throughout our analysis, which raises concerns about the reliability of the available data. Third, none of the studies employed propensity score matching to address baseline imbalances between the two groups. Finally, some of the included studies, such as Belhassen 2021, Corral 2020, and Dempsey 2019, based their results on claims data, which may not be representative of the general population, as these data often include only patients who have accessed specific healthcare services (23,25,26).

Conclusions

This meta-analysis is one of the first to pool data from RWE studies to conduct a direct, head-to-head comparison between the efficacies and safety profiles of nintedanib and pirfenidone. While nintedanib has been shown to reduce the risk of acute exacerbations,

both drugs appear to have similar effects on overall survival and all-cause mortality. This may be due to the complex nature of IPF, which is influenced by various factors beyond acute exacerbations. However, a novel finding from the direct comparison of safety profiles of nintedanib and pirfenidone was that they differed significantly, with nintedanib being associated with greater odds of liver toxicity and diarrhoea, and pirfenidone with photosensitivity and skin rash. Furthermore, these drugs could be favoured in slightly different population groups based on individual patient characteristics and preferences. Nevertheless, due to the substantial heterogeneity in IPF pathogenesis and presentation, further research is necessary to refine the current comprehension of these drugs and their optimal utilisation in IPF treatment, particularly taking into account factors such as disease stage and sequential therapy.

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Annex

Table S1. Search strategies used for each source

Source	Search Strategy
PUBMED	((((((((((((("Idiopathic Pulmonary Fibrosis"[Mesh]) OR (Idiopathic Pulmonary Fibroses)) OR (Cryptogenic Fibrosing Alveolitis)) OR (Cryptogenic Fibrosing Alveolitides)) OR (Pulmonary Fibrosis, Idiopathic)) OR (Fibrosing Alveolitis, Cryptogenic)) OR (Fibrocystic Pulmonary Dysplasia)) OR (Fibrocystic Pulmonary Dysplasias)) OR (Idiopathic Fibrosing Alveolitis, Chronic Form)) OR (Familial Idiopathic Pulmonary Fibrosis)) OR (Usual Interstitial Pneumonia)) OR (Interstitial Pneumonia, Usua)) OR (Usual Interstitial Pneumonias)) OR (Pneumonitides, Usual Interstitial)) OR (Pneumonitis, Usual Interstitial)) OR (Usual Interstitial Pneumonitis) AND (((((("pirfenidone" [Supplementary Concept]) OR (5-methyl-1-phenyl-2-(1H)-pyridone)) OR (Deskar)) OR (Esbriet)) OR (deupirfenidone)) OR (1-phenyl-5-(trideuteriomethyl)-1,2-dihydropyridin-2-one) AND ((((((("nintedanib" [Supplementary Concept]) OR (BIBF 1120)) OR (BIBF-1120)) OR (BIBF1120)) OR (Vargatef)) OR (Nintedanib esylate)) OR (Ofev)
Cochrane CENTRAL	#1 Pulmonary Fibrosis OR Idiopathic Pulmonary fibrosis OR Cryptogenic Fibrosing Alveolitis OR Fibrocystic Pulmonary Dysplasias OR Familial Idiopathic Pulmonary Fibrosis #2 MeSH descriptor: [Pulmonary Fibrosis] explode all trees #3 MeSH descriptor: [Idiopathic Pulmonary Fibrosis] explode all trees 603 #4 MeSH descriptor: [Antifibrotic Agents] explode all trees #5 Anti-fibrotic drug OR Antifibrotics OR Pirfenidone OR Nintedanib #6 #1 OR #2 OR #3 #7 #4 OR #5 #8 #6 AND #7
WHO ICTRP	In condition: Pulmonary fibrosis OR Idiopathic pulmonary fibrosis In intervention: Antifibrotics OR pirfenidone OR Nintedanib
Clinicaltrials.gov	Condition/Disease: Pulmonary fibrosis OR Idiopathic pulmonary fibrosis Intervention/treatment: Antifibrotics OR pirfenidone OR Nintedanib

Table S2. Summary of the results of the sensitivity analysis for each outcome

Survival impact			
	Fixed-effects		
Study ID removed from the analysis	**HR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	1.12 (0.99, 1.27)	0%	0.07
All with the Random-effects model	1.12 (0.99, 1.27)	0%	0.07
Dempsey 2019	1.12 (0.98, 1.28)	14%	0.10
Belhassen 2021	1.09 (0.95, 1.24)	0%	0.23
Marijic 2021	1.11 (0.92, 1.33)	13%	0.29
Bocchino 2023	1.13 (0.99, 1.29)	12%	0.07
Romero 2024	**1.15 (1.01, 1.31)**	**0%**	**0.04**
Zhoa 2024	1.13 (1.00, 1.29)	0%	0.05
All-cause Mortality			
	Fixed-effects		
Study ID removed from the analysis	**OR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	1.11 (0.94, 1.31)	15%	0.22
All with the Random-effects model	1.09 (0.87, 1.37)	15%	0.43
Cerri 2019	1.10 (0.84, 1.43)	28%	0.50
Cameli 2020	1.06 (0.79, 1.41)	29%	0.70

Marijic 2021	1.04 (0.73, 1.49)	28%	0.23
Khan 2023a	1.14 (0.96, 1.35)	0%	0.14
Uzer 2023	1.15 (0.91, 1.44)	12%	0.25
Romero 2024	1.08 (0.90, 1.28)	0%	0.42
Iwasaki 2024	1.08 (0.82, 1.42)	29%	0.59
Dose Reductions			
	Random-effects		
Study ID removed from the analysis	**OR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	1.56 (1.07, 2.27)	0%	0.02
Galli 2017	1.50 (0.95, 2.38)	10%	0.08
Sadon 2020	1.63 (1.06, 2.51)	11%	0.03
Levra 2022	1.44 (0.98, 2.13)	0%	0.06
Uzer 2023	1.81 (1.14, 2.88)	0%	0.01
Romero 2024	1.56 (0.94, 2.59)	16%	0.09
Drug switches			
	Fixed-effects		
Study ID removed from the analysis	**OR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	1.82 (0.69, 4.78)	89%	0.22
Corral 2020	**2.87 (1.77, 4.64)**	**0%**	**<0.0001**
Uzer 2023	1.55 (0.40, 5.97)	91%	0.53
Romero 2024	1.41 (0.44, 4.47)	89%	0.22
Treatment discontinuations			
	Random-effects		
Study ID removed from the analysis	**OR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	0.92 (0.60, 1.41)	82%	0.70
Galli 2017	0.89 (0.56, 1.41)	83%	0.62
Barratt 2018	1.08 (0.75, 1.56)	73%	0.69
Sadon 2020	0.87 (0.56, 1.34)	83%	0.53
Corral 2020	0.89 (0.52, 1.52)	83%	0.67
Holtze 2020	0.91 (0.56, 1.47)	83%	0.71
Noor 2021	0.91 (0.58, 1.43)	83%	0.70
Wright 2021	0.93 (0.59, 1.47)	83%	0.77
Takehara 2022	0.97 (0.62, 1.52)	82%	0.90
Levra 2022	1.01 (0.66, 1.54)	81%	0.97
Uzer 2023	0.90 (0.57, 1.43)	83%	0.66
Romero 2024	0.85 (0.54, 1.33)	82%	0.47
Zhao 2024	0.81 (0.54, 1.22)	77%	0.31
Iwasaki 2024	0.97 (0.63, 1.51)	83%	0.90

Table S2 (*Continued*)

Adverse Events			
	Fixed-effects		
Study ID removed from the analysis	**OR (95% CI)**	**I^2**	**Test of significance (P value)**
All included	1.35 (1.06, 1.71)	30%	0.02
All with the Random-effects model	**1.33 (0.99, 1.79)**	**30%**	**0.06**
Cerri 2019	1.32 (1.03, 1.70)	39%	0.03
Cameli 2020	**1.29 (0.98, 1.70)**	**39%**	**0.07**
Levra 2022	1.47 (1.12, 1.91)	21%	0.005
Fournier 2022	1.48 (1.14, 1.91)	0%	0.003
Uzer 2023	**1.29 (0.99, 1.67)**	**36%**	**0.06**
Khan 2023b	1.35 (1.06, 1.74)	41%	0.02
Romero 2023	1.24 (0.95, 1.62)	24%	0.11

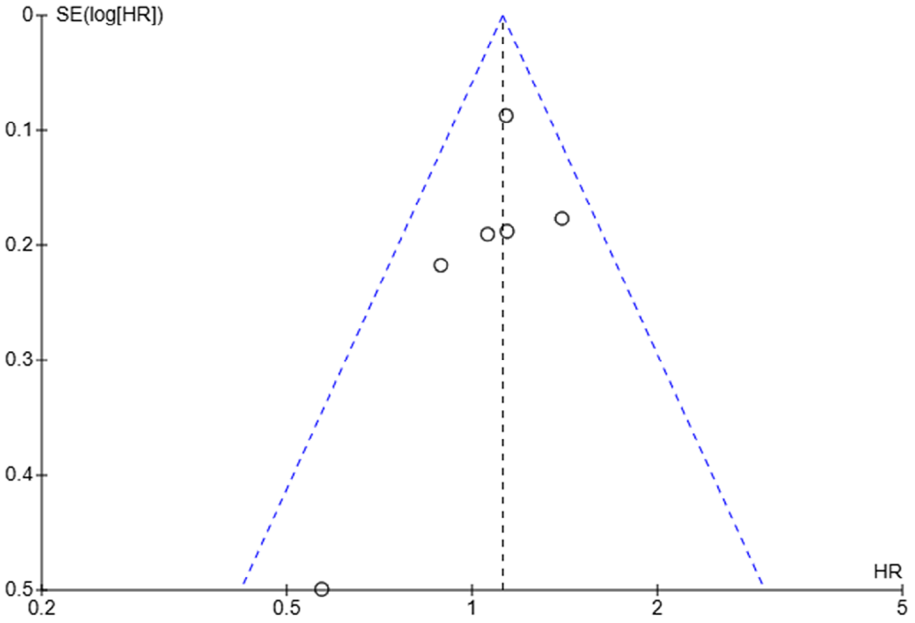

Figure S1. Funnel plot for overall survival.

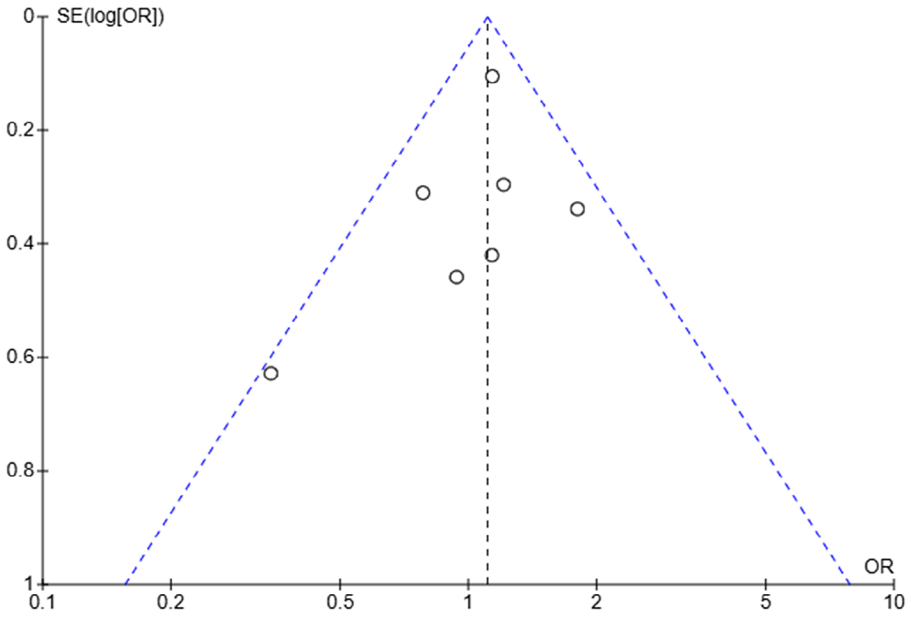

Figure S2. Funnel plot for all-cause mortality.

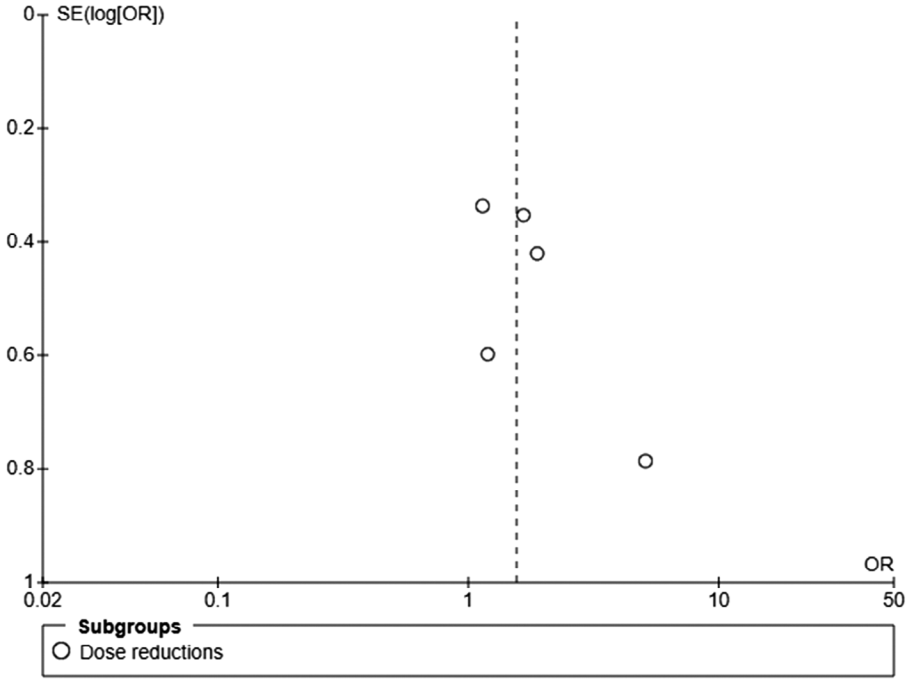

Figure S3. Funnel plot for dose reduction.

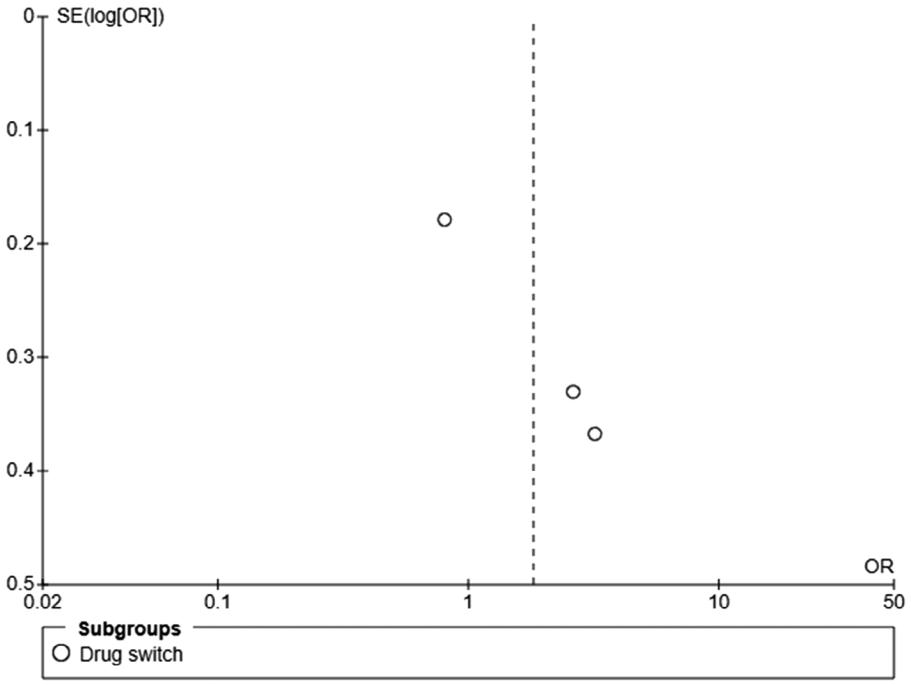

Figure S4. Funnel plot for drug switches.

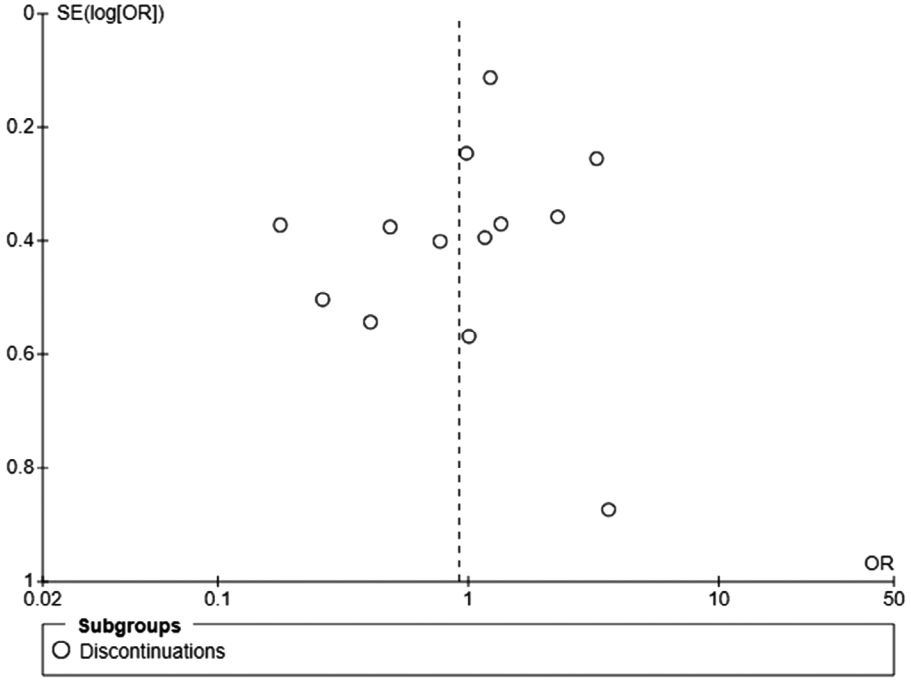

Figure S5. Funnel plot for treatment discontinuations.

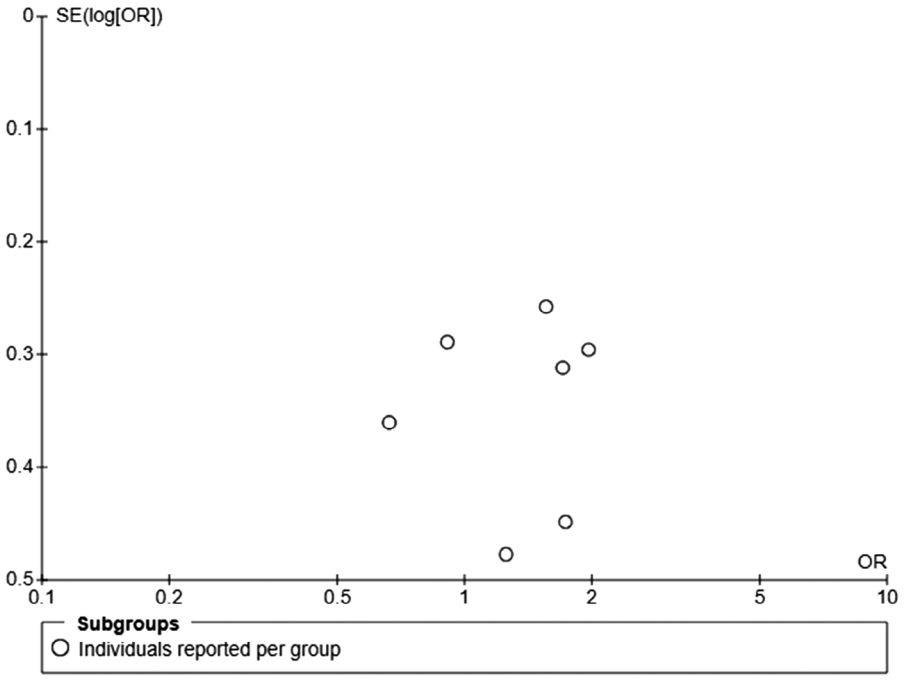

Figure S6. Funnel plot for total individuals with adverse events.