European Review for Medical and Pharmacological Sciences 2022; 26: 8411-8424

The efficacy and safety of pirfenidone in the treatment of HPS-related pulmonary fibrosis and Idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Y.-J. MA[1,2], Q. ZHANG[1], C.-X. WANG[3], W. WU[1]

[1]Department of Respiratory and Critical Care Medicine, the Second Affiliated Hospital of Xi'an Medical University, Xi'an, China
[2]Department of Respiratory Medicine, Zhenba County People's Hospital, Shaanxi, China
[3]Department of Traditional Chinese Medicine, Baoji Vocational & Technical College, Baoji, China

Abstract. – OBJECTIVE: The incidence of idiopathic pulmonary fibrosis is increasing year by year in the world, which has a greater impact on the quality of life of patients. In the past, symptomatic treatment was used in clinical practice, but the overall effect is still not good. Multiple clinical studies have demonstrated the efficacy of pirfenidone in the treatment of idiopathic pulmonary fibrosis; however, adverse reactions have been reported. We, therefore, systematically evaluated the effectiveness and safety of pirfenidone in patients with idiopathic pulmonary fibrosis.

PATIENTS AND METHODS: Relevant studies were retrieved from the Embase, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature (CBM), Wanfang and Weipu databases between January 1999 and May 2020, including the keywords "pirfenidone" and "idiopathic pulmonary fibrosis", were included in our systematic review. Review Manager 5.4 software was used for data synthesis, and analyses of publication bias and sensitivity.

RESULTS: Our systematic review included 13 studies involving a total of 13,247 patients with idiopathic pulmonary fibrosis. Pirfenidone was associated with reduced declines in vital capacity (VC) and forced vital capacity (FVC) from baseline in patients with hermansky-pudlak syndrome (HPS)-related pulmonary fibrosis and to moderate idiopathic pulmonary fibrosis (IPF). Pirfenidone treatment was associated with lower reductions in FVC, lower reductions in 6-minute walking test distance, lower decreases in minimum oxygen saturation during the 6-minute walking test, lower all-cause death, lower relative risk of IPF-related death and increased progression-free survival compared to placebo. Progression-free survival was significantly longer in the pirfenidone group. The incidence of gastrointestinal, skin, nervous system, and liver function-related adverse events was significantly higher in the pirfenidone group compared to the control group.

CONCLUSIONS: Pirfenidone has efficacy in delaying the progression of idiopathic pulmonary fibrosis. Pirfenidone is well-tolerated by the majority of patients; however, mild adverse reactions related to the gastrointestinal tract, skin, nervous system, and liver function are common. Overall, Pirfenidone may be an effective and well-tolerated treatment option for idiopathic pulmonary fibrosis.

Key Words:
Pirfenidone, HPS-related pulmonary fibrosis, Idiopathic pulmonary fibrosis, Randomized controlled trials, Systematic review.

Introduction

Interstitial lung disease (ILD) is a large group of diseases characterized by diffuse alveolar inflammation and diffuse pulmonary fibrosis at an advanced stage. The pathogenesis of ILD remains unclear and causative agents are diverse, including industrial inorganic dust, chemical, physical, organic antigens, drugs, and microbial infections. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia of unknown origin that occurs in adults. Imaging and histology findings are typically consistent with usual interstitial pneumonia. IPF is associated with high morbidity and mortality, with a median survival time of 3-5 years[1]. Idiopathic pulmonary fibrosis represents a substantial public health concern, with increasing worldwide interest in determining the pathogenesis of idiopathic pulmonary fibrosis and methods of prevention.

Corresponding Author: Wei Wu, MD; e-mail: wwatp@163.com

Pirfenidone, 5-methyl-1-phenyl-2-(1hydro)-pyridone, is a pleiotropic pyridine compound with antifibrotic, anti-inflammatory, and antioxidant effects. *In vitro* experiments have demonstrated a regulatory role for pirfenidone in important profibrotic and proinflammatory cytokine cascades, with animal studies demonstrating reduced fibroblast proliferation and collagen synthesis in response to pirfenidone[1]. Pirfenidone can inhibit fibrosis in various organs, including lungs, liver, heart, kidney, small intestine, and skin[2,3]. Pirfenidone has been approved for the treatment of idiopathic pulmonary fibrosis in multiple countries, with a number of large clinical trials ongoing. Given the low incidence and prevalence of IPF, sample sizes may be limited and inclusion and exclusion criteria, study time, pirfenidone treatment dose, and primary and secondary endpoints may differ between studies. Systematic reviews are therefore required to fully evaluate the safety and efficacy of pirfenidone. While many systematic reviews[23,24] have reported the efficacy and safety of pirfenidone in the treatment of idiopathic pulmonary fibrosis using randomized controlled trials (RCTs) from developed countries, there is a lack of real-world research and date from developing countries. In China, pirfenidone has been approved for the treatment of idiopathic pulmonary fibrosis, and a number of clinical randomized controlled studies have been conducted. We, therefore, conducted a meta-analysis of high-quality studies to evaluate the effectiveness and safety of pirfenidone in the treatment of idiopathic pulmonary fibrosis.

Patients and Methods

Data Sources and Searches

A literature search was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. We systematically searched the bibliographic databases PubMed, Embase, and Cochrane databases for randomized controlled studies of pirfenidone for idiopathic pulmonary fibrosis published between January, 1999 and May, 2020. Search keywords used were: "pirfenidone", "idiopathic pulmonary fibrosis" and "randomized controlled trial". The same terms were used to search Wanfang Medical, China HowNet, and Weipu Medical. The two authors independently searched and screened the full texts that met the selection criteria and resolved differences through discussion.

Study Selection

Inclusion criteria were: (i) randomized controlled studies of oral pirfenidone monotherapy compared to placebo or conventional treatment as controls; (ii) subjects were all patients with idiopathic pulmonary fibrosis and hermansky-pudlak syndrome (HPS)[4]; (iii) outcomes included vital capacity (VC), forced vital capacity (FVC), mortality, 6-minute walking test shortening distance and rate of change in minimum oxygen saturation, disease-free survival, and adverse reactions; (iv) measurable data were presented as mean (MD), standard deviation (SD), relative risk (RR), or risk ratio (HR). We excluded reviews and repeated publications of previous studies.

Data Extraction

One reviewer (MYJ) performed data extraction according to a standard protocol, including author, publication time, country, subject disease, intervention measures, number of patients, average age, and outcome measures. Data extraction was appraised by a second reviewer (ZQ) using a random subsample of included studies.

Quality Assessment

The methodological quality of the included studies was evaluated according to the Cochrane bias risk assessment tool[5]. The main points of the evaluation included: whether the random method is adopted and described in detail; whether the randomized allocation scheme is well hidden; whether the blind method is adopted and described in detail; and whether the lost follow-up and withdrawal are described in detail. Scoring was independently conducted by two researchers, and differences were resolved through discussion.

Statistical Analysis

Statistical analysis was performed using RevMan5.3 software. Numerical data are expressed by RR or HR with 95% CI (confidence interval). Measurement data were expressed as MD and 95% CI. A heterogeneity test was performed using I^2 statistic and χ^2 test. A fixed-effects model was used where heterogeneity was small, defined as $I^2 \leq 50\%$ or $p > 0.1$. Random effects models were used where heterogeneity was large, defined as $I^2 > 50\%$ or $p < 0.1$. Qualitative data were analyzed using a random effect model. p-values < 0.05 were considered statistically significant. Publication bias was evaluated using a funnel chart. Random effect and fixed effect models were used for sensitivity analyses.

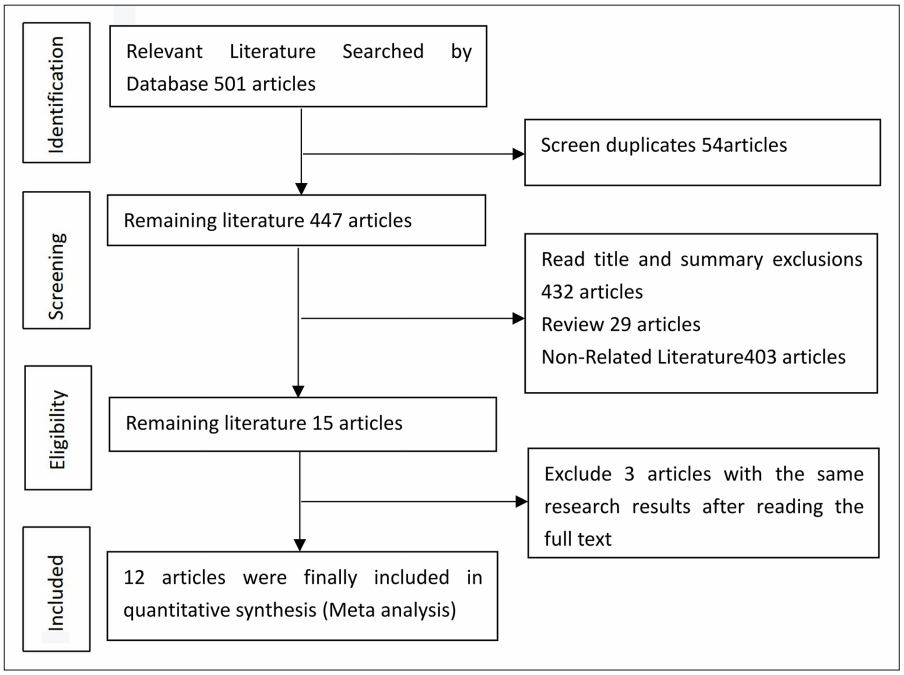

Figure 1. The literature screening process.

Results

Literature Search Results

A total of 501 articles were identified by our database search. A total of 12 articles were included after reading the article title, abstract, and full-text screening. The literature screening process is shown in Figure 1.

Basic Characteristics and Quality Evaluation of Included Studies

The basic characteristics of the included studies are shown in Table I. Baseline data were similar between experimental and control groups in each study. The bias risk assessments of included studies are shown in Figure 2A and B. The overall bias risk assessments of each study demonstrated low bias and high methodological quality. All included studies were randomized, placebo-controlled studies. There were five studies that did not describe a randomization protocol and five studies that did not describe a blinding method in detail.

Efficacy Analysis of Pirfenidone

Absolute change in Vital Capacity (VC)

Two studies[5,6] were included comprising 176 patients in the pirfenidone group and 138 patients in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 0%, p = 0.55), a fixed effect model was used demonstrating a combined MD of 0.08 (95% CI = 0.03, 0.13) and a combined effect amount, Z, of 3.41 (p = 0.0006; Figure 3). Absolute decrease in VC from baseline was significantly lower in the pirfenidone group compared to the placebo group.

Change in Forced Vital Capacity (FVC) as a percentage of predicted values

Five studies[7,8,11,12,20] were included comprising 836 patients in the pirfenidone group and 662 patients in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 26%, p = 0.24), a fixed effect model was used demonstrating a combined MD of 4.92 (95% CI = 3.71, 6.13) and a combined effect amount, Z, of 7.97 (p < 0.00001; Figure 4A). The percent change in FVC from baseline was significantly lower in the pirfenidone group compared to the placebo group.

Absolute change in Forced Vital Capacity (FVC)

Three studies[12,13,21] were included comprising 133 patients in the pirfenidone group and 136 patients in the placebo group. As the heterogeneity test demonstrated high heterogeneity (I^2 = 88%, p = 0.0003), a random effects model analysis was used demonstrating a MD of 0.25 (95% CI = 0.00, 0.50), and a combined effect, Z, of 1.97 (p

Table I. Real time PCR primers.

Study	Years	Country	Disease	Study type	Drug intervention (mg/d)	People	Male	Age
Gahl et al[4]	2002	USA	HPS	RCT-II	2400	11	5	41.5 ± 12.1
					Placebo	10	4	34.0 ± 9.2
Azuma et al[5]	2005	Japan	IPF	RCT-II	1800	73	62	64.0±7.1
					Placebo	36	33	64.3 ± 7.6
Taniguchi et al[6]	2010	Japan	IPF	RCT-II	1800	109	85	65.4 ± 6.2
					Placebo	107	81	64.7 ± 7.3
O'Brien et al[7]	2011	USA	IPF	RCT-II	2403	23	8	39.2 ± 10.8
					Placebo	12		643.4 ± 7.7
CAPACITY004[8]	2011	Multicenter	IPF	RCT-III	2403	174	118	65.7± 8.2
					Placebo	174	128	65.7 ± 8.2
CAPACITY006[8]	2011	Multicenter	IPF	RCT-III	2403	171	123	66.8 ± 7.9
					Placebo	173	124	67.0 ± 7.8
ASCEND[9]	2014	Multicenter	IPF	RCT-III	2403	278	222	68.4 ± 6.7
					Placebo	277	213	67.8 ± 7.3
Alhamad et al[10]	2015	Saudi	IPF	RCT	2400	33	22	63.3 ± 13.3
					Placebo	25	11	62.4 ± 15.1
Huang et al[12]	2015	China	IPF	RCT-II	1800	38	33	59.03 ± 5.9
					Placebo	38	38	61.6 ± 6.4
Huiping et al[13]	2015	China	IPF	RCT-II	1200	43	36	61.9 ± 6.0
					Placebo	44	39	62.6 ±6.9
Yan et al[20]	2018	China	IPF	RCT	1800	47	44	66.0 ± 9.0
					Placebo	47	47	67.0 ± 8.0
Zurkova et al[11]	2019	Czech	IPF	RCT	2403	383	281	$p = 0.52$
					Placebo	218	150	
Fenli et al[21]	2019	China	IPF	RCT	1200	55	30	57.92 ± 4.81
					Placebo	55	31	59.83 ± 12.5

= 0.05; Figure 4B). Absolute change in FVC from baseline was reduced in the pirfenidone group compared to control group.

Forced Vital Capacity (FVC) change from baseline

Four studies[8-11] were included comprising 1038 patients in the pirfenidone group and 867 in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 30%, p = 0.22), a fixed effect model was used demonstrating a combined RR of 0.61 (95% CI = 0.52, 0.71) and a combined effect amount, Z, of 6.20 ($p < 0.00001$; Figure 5). A significantly lower proportion of patients had a ≥ 10% decrease in FVC in the pirfenidone group compared to the placebo group. No significant difference was seen in the number of patients with a ≥5% in FVC between the pirfenidone group and the placebo group.

Rate of change in lowest oxygen saturations (ΔSPO2) during the 6-minute walking test (6 MWD)

Two studies[5,12] were included comprising a total of 110 patients in the pirfenidone group and 73 patients in the placebo group. As the heterogeneity test demonstrated low heterogeneity ($I^2 = 0$, $p = 0.58$), a fixed effect model was used for analysis demonstrating a combined MD of 2.27 (95% CI = 1.02, 3.51) and a combined effect amount, Z, of 3.57 ($p = 0.0004$; Figure 6A). The rate of change in minimum oxygen saturation during the 6-minute walking test compared to baseline was significantly lower in the pirfenidone group compared to the control group.

6-minute walking test distance compared to baseline

Three studies[8-10] were included comprising a total of 649 patients in the pirfenidone group and 640 in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 41%, p = 0.17), a fixed effect model was used demonstrating a combined RR = 0.71 (95% CI = 0.61, 0.82) and a combined effect amount, Z, of 4.59 ($p < 0.00001$; Figure 6B). A significantly lower proportion of patients had a 6 MWD 50 m or 30 m shorter than at baseline in the pirfenidone group compared to the placebo group. Compared with the placebo group, the RR of

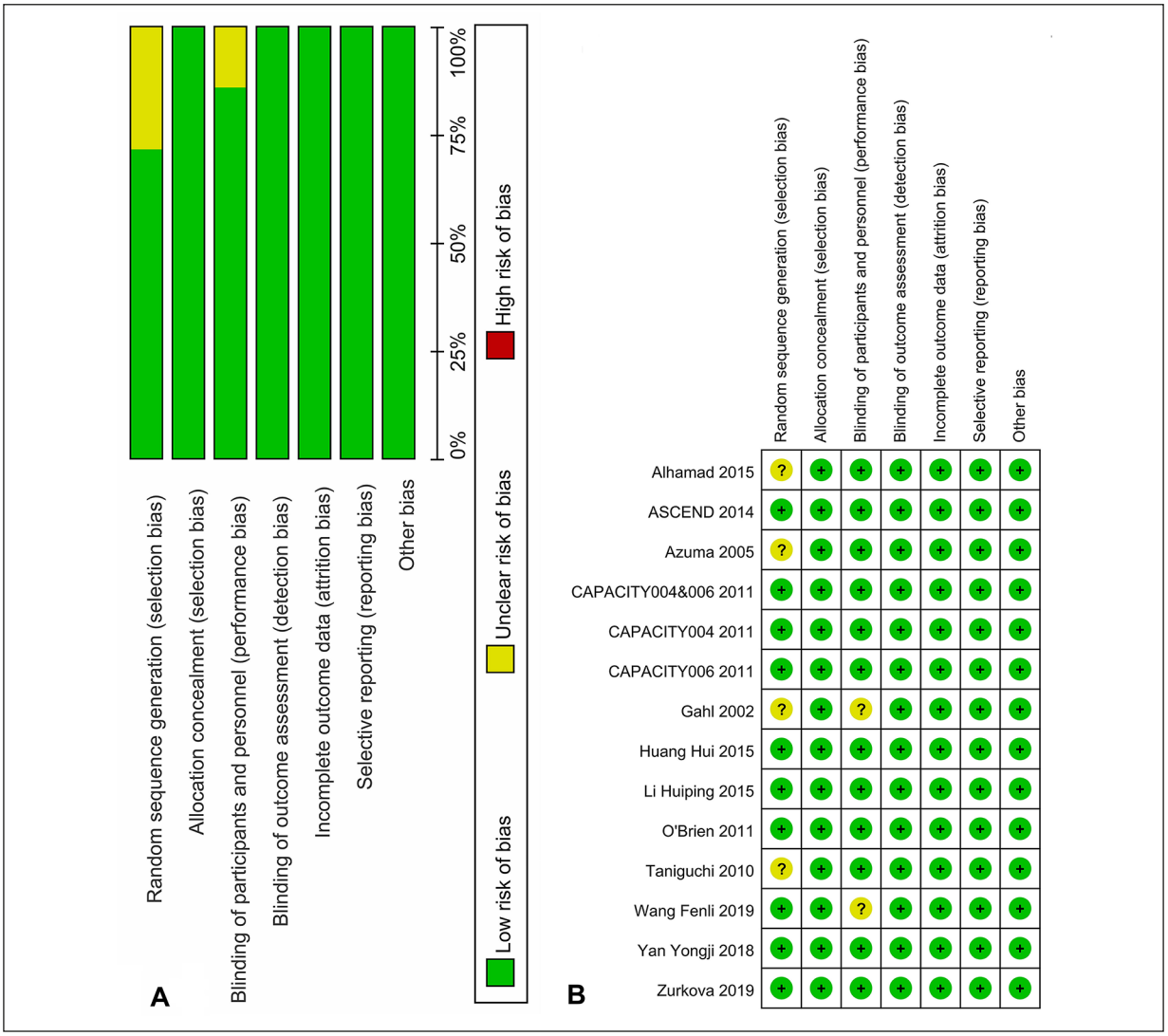

Figure 2. Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies (**A**); Risk of bias summary review authors' judgements about each risk of bias item for each included study (**B**).

a 6 MWD reduction of ≥50 m and 30 m from baseline in the pirfenidone group was reduced by 27% and 76%, respectively, during the study period.

All-cause mortality

Ten studies[4-12,20] were included, of which CAPACITY 004 and CAPACITY 006 were combined into CAPACITY 004 & 006 2011 in this

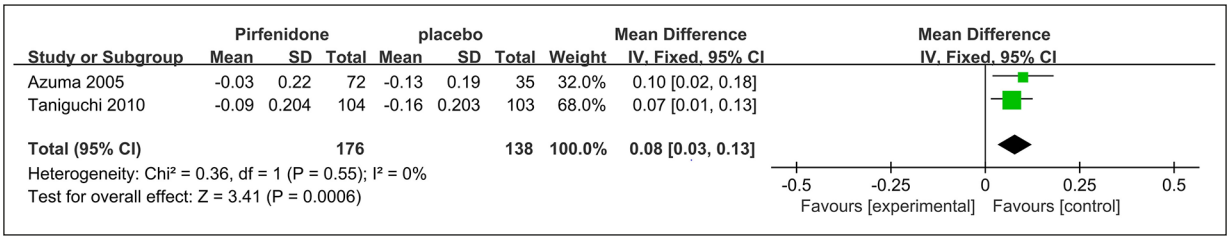

Figure 3. Analysis data of absolute change in vital capacity (VC).

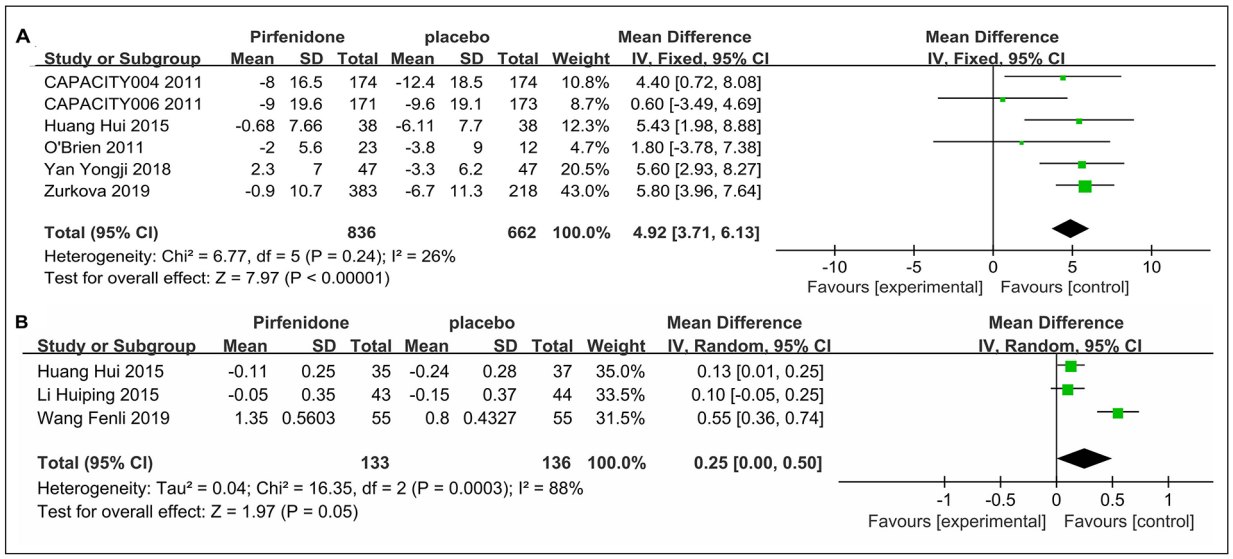

Figure 4. Analysis of the change in forced vital capacity (FVC). FVC as a percentage of the predicted value (**A**); Analysis of Absolute Change in FVC (**B**).

analysis, comprising a total of 1338 patientΔΔΔs in the pirfenidone group and 1113 patients in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 0%, p = 0.91), a fixed effect model was used for analysis demonstrating a combined RR of 0.52 (95% CI = 0.43, 0.63) and a combined effect amount, Z, of 6.88 (p < 0.00001; Figure 7A). The RR of all-cause death was 48% lower in the pirfenidone group during the trial period compared to the placebo group.

IPF-related mortality

Three studies[8,9,12] were included, of which CAPACITY 004 and CAPACITY 006 were combined into CAPACITY 004 & 006 2011 in this analysis. There were 661 cases in the pirfenidone group and 662 in the placebo group. As the heterogeneity test demonstrated low heterogeneity (I^2 = 0%, p = 0.75), a fixed effect model was used demonstrating a combined RR of 0.50 (95% CI = 0.28, 0.89) and a combined effect amount, Z, of

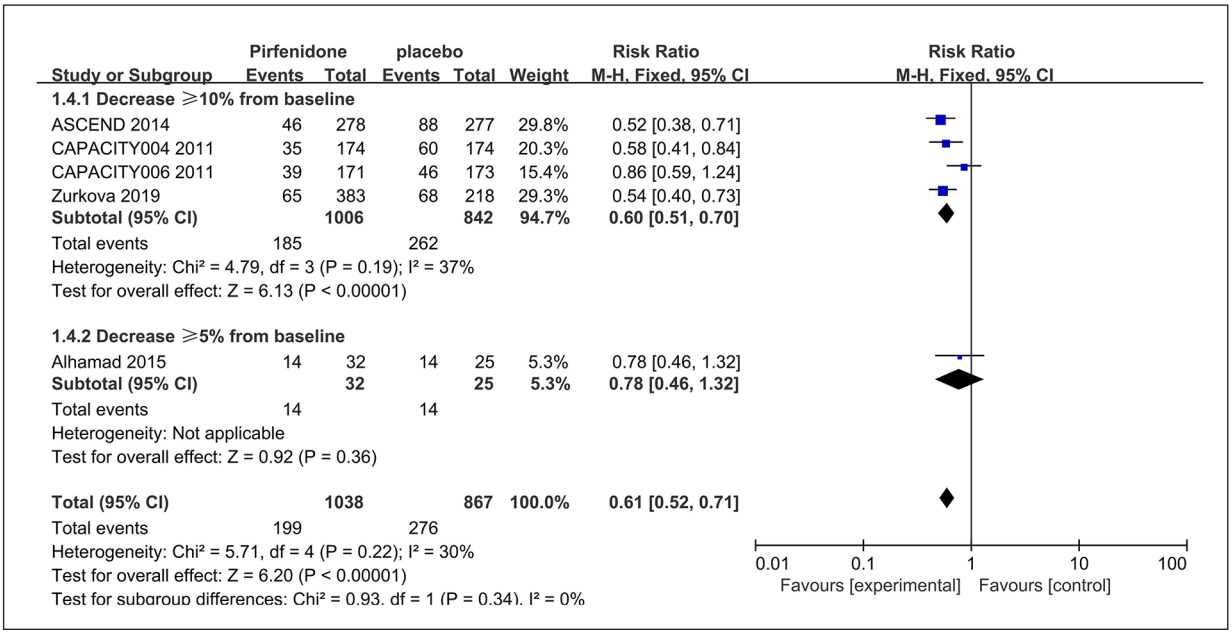

Figure 5. Forced vital capacity (FVC) decreased from baseline by ≥10% or ≥5% analysis.

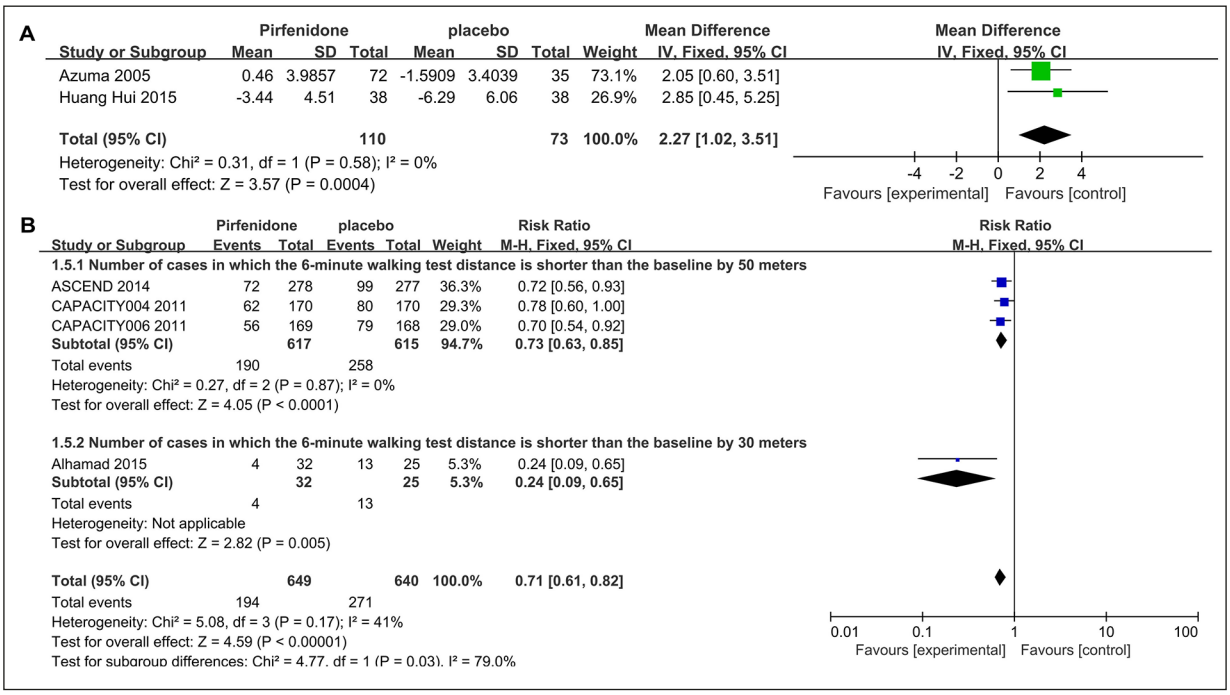

Figure 6. Analysis of the 6-minute walking test distance (6MWD). The rate of change of the lowest oxygen saturation (ΔSpO_2) (**A**); The number of cases in 6MWD is ≥50 or 30 meters shorter than the baseline (**B**).

2.37 (p = 0.02; Figure 7B). The RR of IPF-related deaths in the pirfenidone group was reduced by 50% during the trial period compared to the placebo group.

Disease progression-free survival

Four studies[6,8,9,12] were included. As the heterogeneity test demonstrated large heterogeneity (I^2 = 75%, p = 0.003) a random effect model was

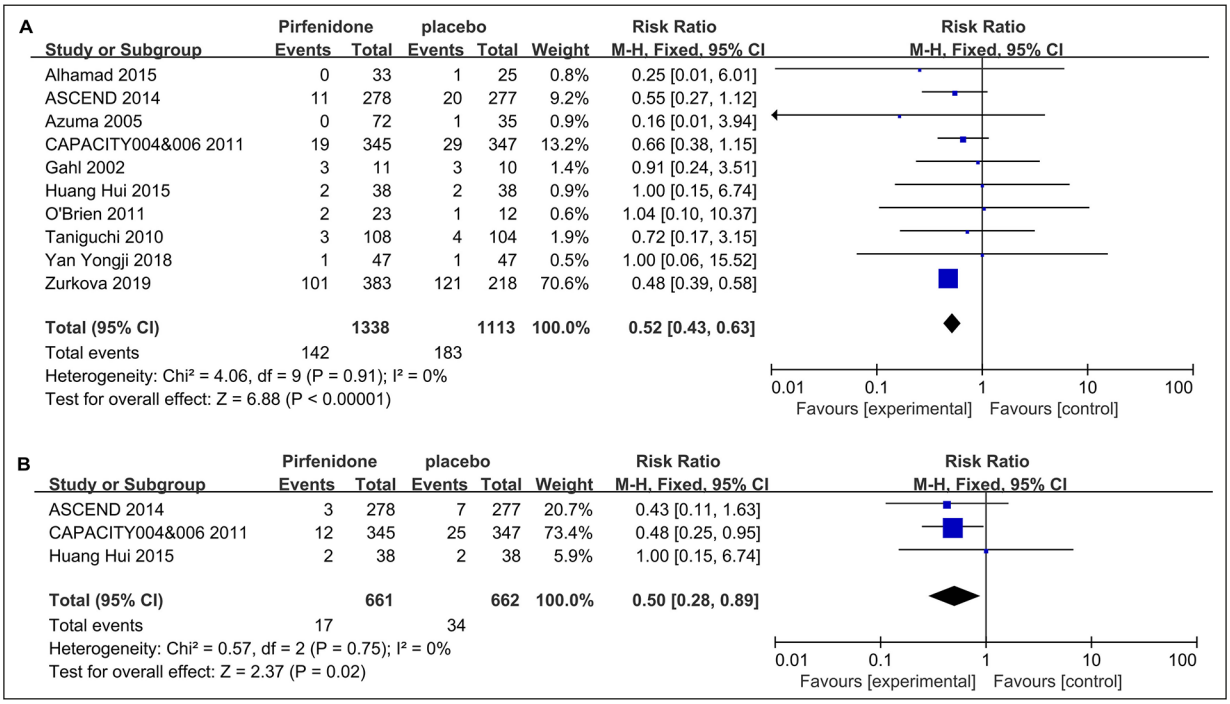

Figure 7. All-cause mortality analysis (**A**); IPF-related mortality analysis (**B**).

used demonstrating a HR of 0.79 (95% CI = 0.56, 1.11) and a combined effect amount, *Z*, of 1.37 ($p = 0.17$; Figure 8), $p > 0.05$, there was no significant difference in progression-free survival between the two groups.

Safety analysis of pirfenidone gastrointestinal adverse reactions

All nine studies[4-10,12,21] included adverse gastrointestinal reactions, including abdominal discomfort, nausea, vomiting, indigestion, diarrhea, and anorexia. CAPACITY 004 and CAPACITY 006 were merged into CAPACITY 004 & 006 2011 in this analysis. A total of 4,777 patients in the pirfenidone group and 4565 patients in the placebo group were tested. As the heterogeneity of each study was large ($I^2 = 47\%$, $p = 0.002$), a random effect model was used to demonstrate that a combined RR was 2.02 (95% CI = 1.69, 2.41), with a combined effect size, *Z*, of 7.85 ($p < 0.00001$; Figure 9). The incidence of gastrointestinal-related adverse reactions was significantly higher in the pirfenidone group compared to the placebo group.

Adverse skin reactions

Adverse skin reactions were reported in nine included studies[4-10,12,21], most of which are photosensitivity and rash. CACAPITY 004 and CAPACITY 006 were merged into CAPACITY 004 & 006 2011 in this analysis comprising a total of 1835 patients in the pirfenidone group and 1765 patients in the placebo group. As the heterogeneity was small ($I^2 = 27\%$, $p = 0.16$), a fixed effect model was used demonstrating a combined RR of 2.99 (95% CI = 2.47, 3.62) and a combined effect amount, *Z*, of 11.24 ($p < 0.00001$; Figure 10). The incidence of skin-related adverse reactions (including photosensitivity and rash) was significantly higher in the pirfenidone group compared to the placebo group.

Nervous system adverse reactions

Seven included studies[4-10] reported neurological adverse effects including dizziness, fatigue, insomnia, and lethargy. CACAPITY 004 and CAPACITY 006 were merged into CAPACITY 004 & 006 2011 in this analysis comprising 2292 patients in the pirfenidone group and 2167 patients in the placebo group. As heterogeneity was small ($I^2 = 0\%$, $p = 0.79$), a fixed effect model was used demonstrating a combined RR of 1.57, 95% CI (1.33, 1.84), and the combined effect amount *Z* = 5.45 ($p < 0.00001$) (Figure 11). The incidence of neurological-related adverse reactions in the pirfenidone group was significantly higher than in the placebo group.

Incidence of upper respiratory tract infections

Upper respiratory tract infections were reported in five included studies[4,5,6,9,12] comprising 509 patients in the pirfenidone group and 468 patients in the placebo group. As heterogeneity was small ($I^2 = 37\%$, $p = 0.17$), a fixed effect model was used demonstrating a combined RR of 1.02 (95% CI = 0.76, 1.36) and a combined effect amount, *Z*, of 0.12 ($p = 0.90$; Figure 12A). There was no significant difference in the incidence of upper respiratory tract infections between the pirfenidone group and the placebo group.

Incidence of liver dysfunction

All seven included studies[5-10,12] reported liver dysfunction, typically mild elevation of transaminases. CACAPITY 004 and CAPACITY 006 were merged into CAPACITY 004 & 006 2011 in this analysis comprising 899 patients in the pirfenidone group and 842 patients in the placebo group. As heterogeneity was small ($I^2 = 0\%$, $p = 0.46$), a fixed effect model was used demonstrating a combined RR of 2.45 (95% CI = 1.62, 3.70) and a combined effect amount, *Z*, of

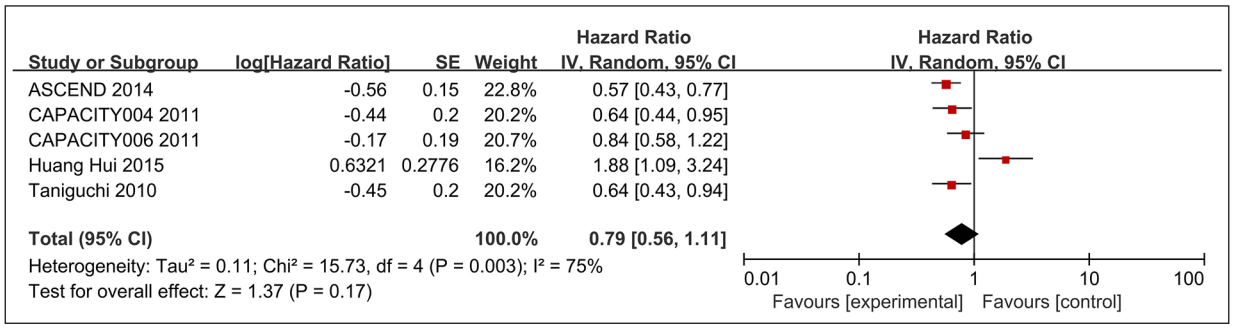

Figure 8. Analysis of disease progression-free survival.

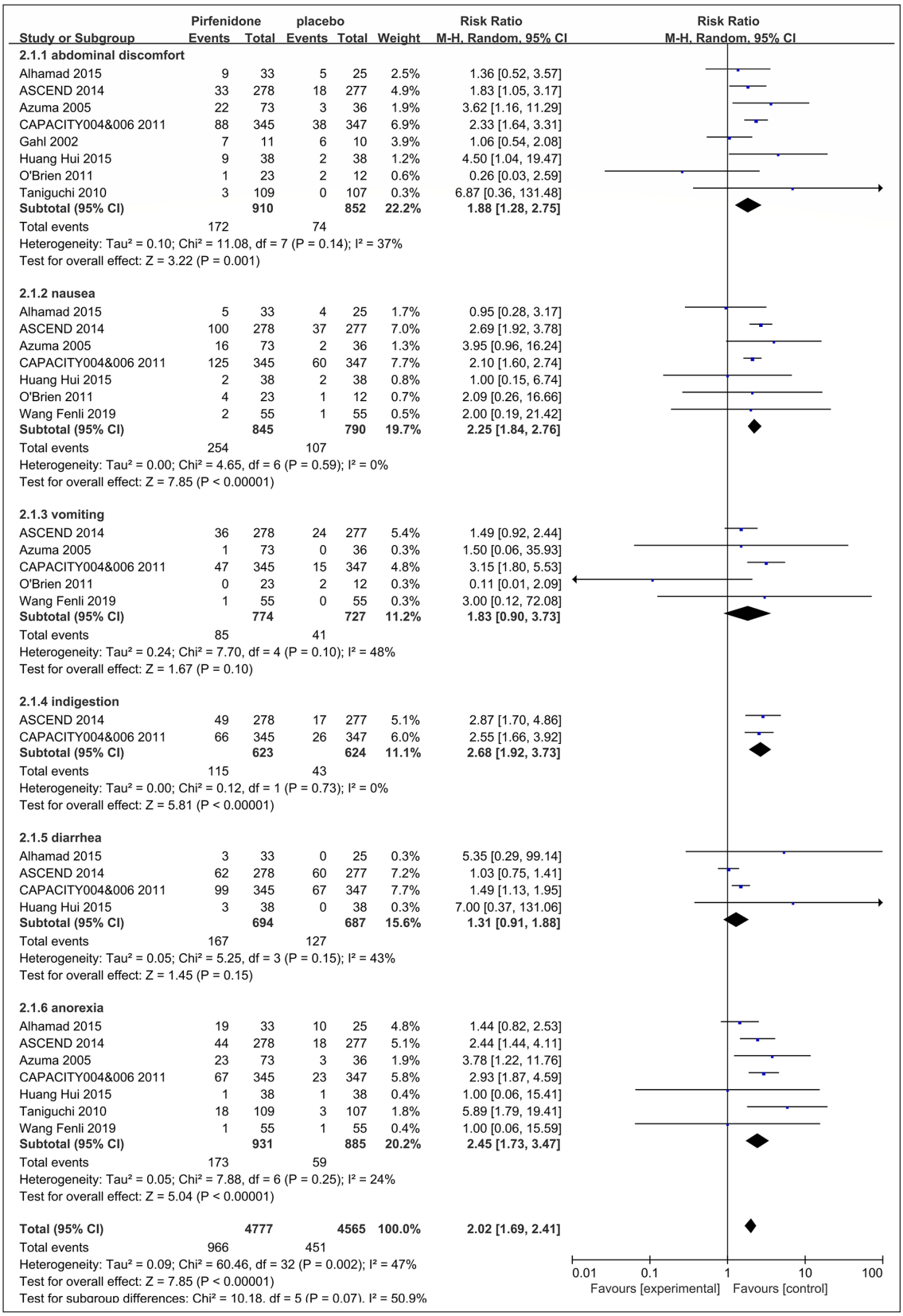

Figure 9. Analysis of gastrointestinal adverse reactions (abdominal discomfort, nausea, vomiting, indigestion, diarrhea, anorexia).

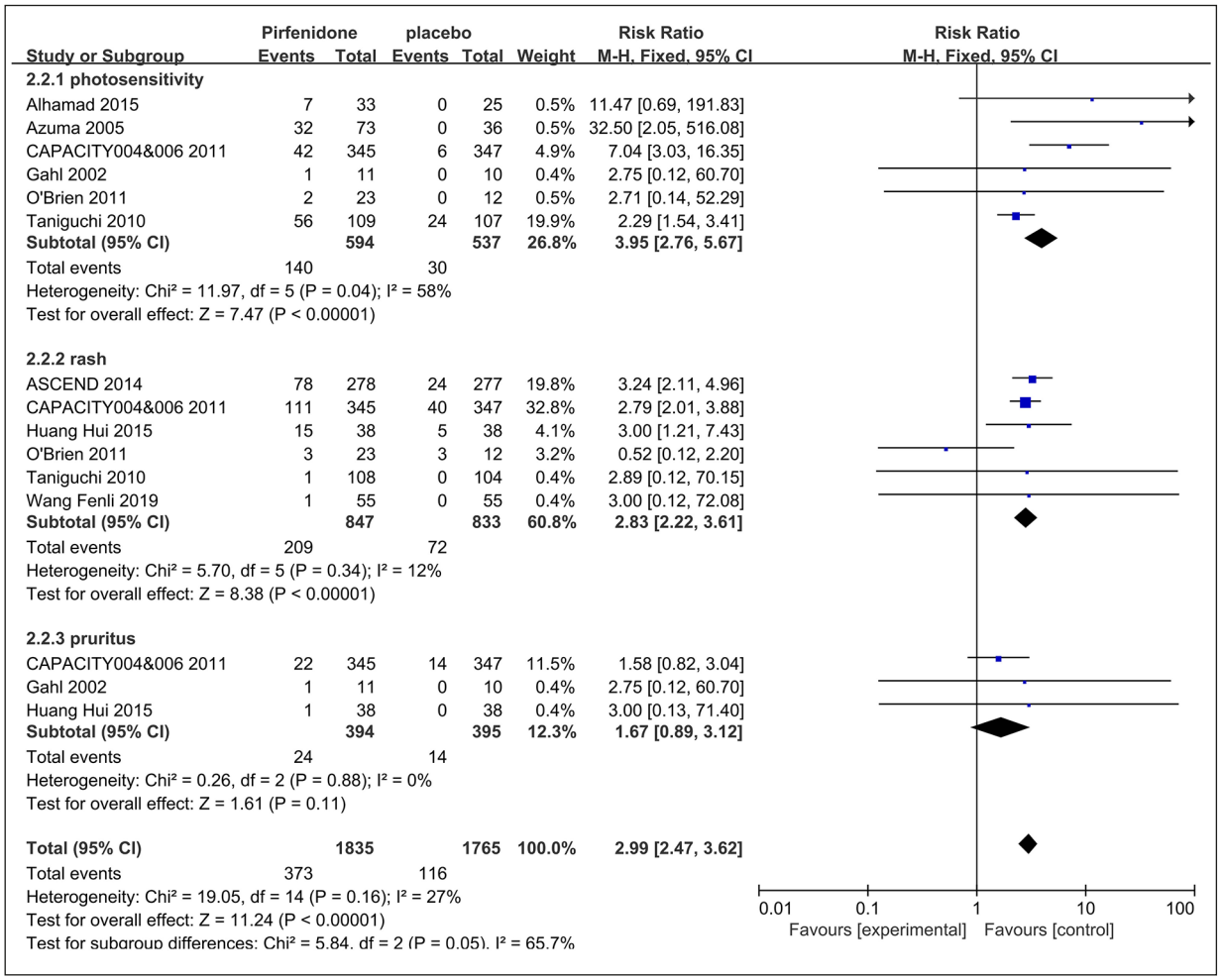

Figure 10. Analysis of skin adverse reactions (photosensitivity, rash, pruritus).

4.24 ($p < 0.0001$; Figure 12B). The incidence of liver dysfunction was significantly higher in the pirfenidone group compared with the placebo group.

Discussion

The Efficacy of Pirfenidone in the Treatment of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a chronic progressive disease with an unclear pathogenesis. There are currently no specific therapeutic drugs. Several studies[5-13,20,21] have indicated that pirfenidone may reduce the rate of decline in lung function and delay the progression of idiopathic pulmonary fibrosis. In 2002, Gahl et al[4] reported a lower annual decline in FVC with pirfenidone compared to placebo indicating pirfenidone may slow the rate of lung function decline in patients with HPS-related pulmonary fibrosis.

Azuma et al[5] conducted a randomized, double-blind, placebo-controlled, phase II clinical trial of pirfenidone for IPF in Japan in 2005 demonstrating higher blood oxygen saturations at 6 and 9 months following pirfenidone treatment. Further, decline in VC and the incidence of acute exacerbations were significantly lower in the pirfenidone group compared to the placebo group. Taniguchi et al[6] conducted a phase III clinical study in 267 IPF patients, reporting a significantly reduced decrease in FVC and improved progression-free survival after 52 weeks of pirfenidone treatment compared with placebo. O'Brien et al[7] reported no statistical difference in rate of FVC decline with pirfenidone compared to placebo, indicating pirfenidone is unable to delay the progression of HPS-1 and type 4 related pulmonary fibrosis.

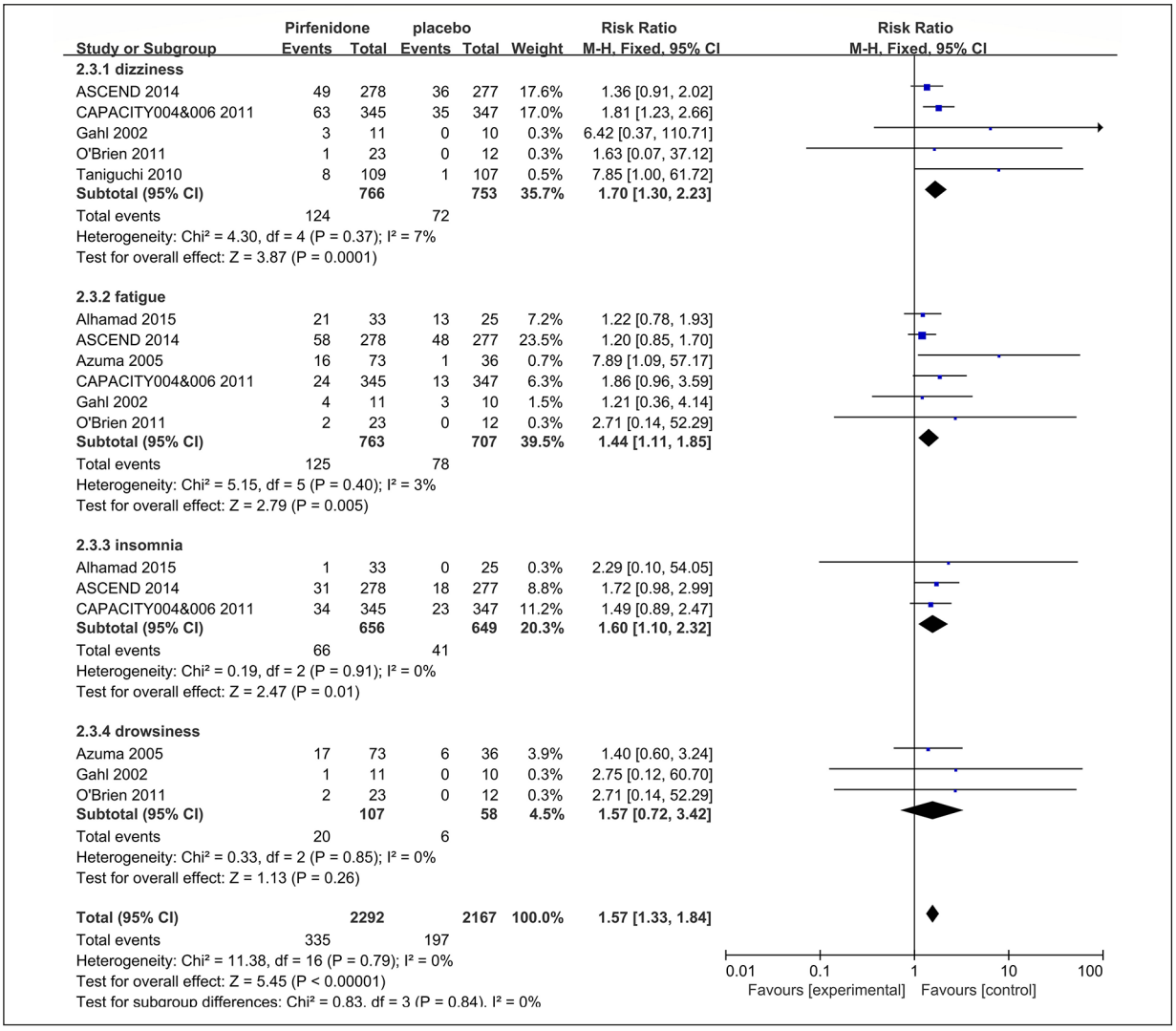

Figure 11. Analysis of neurological adverse reactions (dizziness, fatigue, insomnia, drowsiness).

Two pirfenidone III clinical trials (CAPACITY 004 and 006) were conducted in 110 centers in Australia, Europe, and North America comprising 435 and 344 patients with mild to moderate IPF treated for 72 weeks. CAPACITY 004 demonstrated reduced decreases in FVC as a percentage of the predicted value with pirfenidone compared to placebo; however, CAPACITY 006 failed to reach the primary endpoint and did not observe a significant difference in FVC reductions[8]. Due to the differing results between the two studies, the ASCEND study was conducted in order to further clarify the effectiveness and safety of pirfenidone in the treatment of IPF. The study included 555 patients with IPF and demonstrated pirfenidone for 52 weeks can significantly delay FVC decline, reduce 6 MWD shortening, and increase disease progression-free survival (p<0.001)[9].

Alhamad et al[10] conducted a study of pirfenidone in Saudi Arabia comprising 58 patients with IPF. This study reported patients in the pirfenidone group were less likely to shorten their 6-minute walking distance (p = 0.001). Zurkova et al[11] conducted a real-world cohort study of 601 IPF patients in the Czech Republic reported increased 5-year overall and disease-free survival in the pirfenidone group compared to the placebo group. Hui et al[12] conducted a randomized, double-blind, placebo-controlled phase II clinical trial of pirfenidone treatment for 21 weeks and demonstrated reduced declines in FVC and ΔSpO2 during the 6-minute walk test with pirfenidone compared to control. Huiping et al[13]

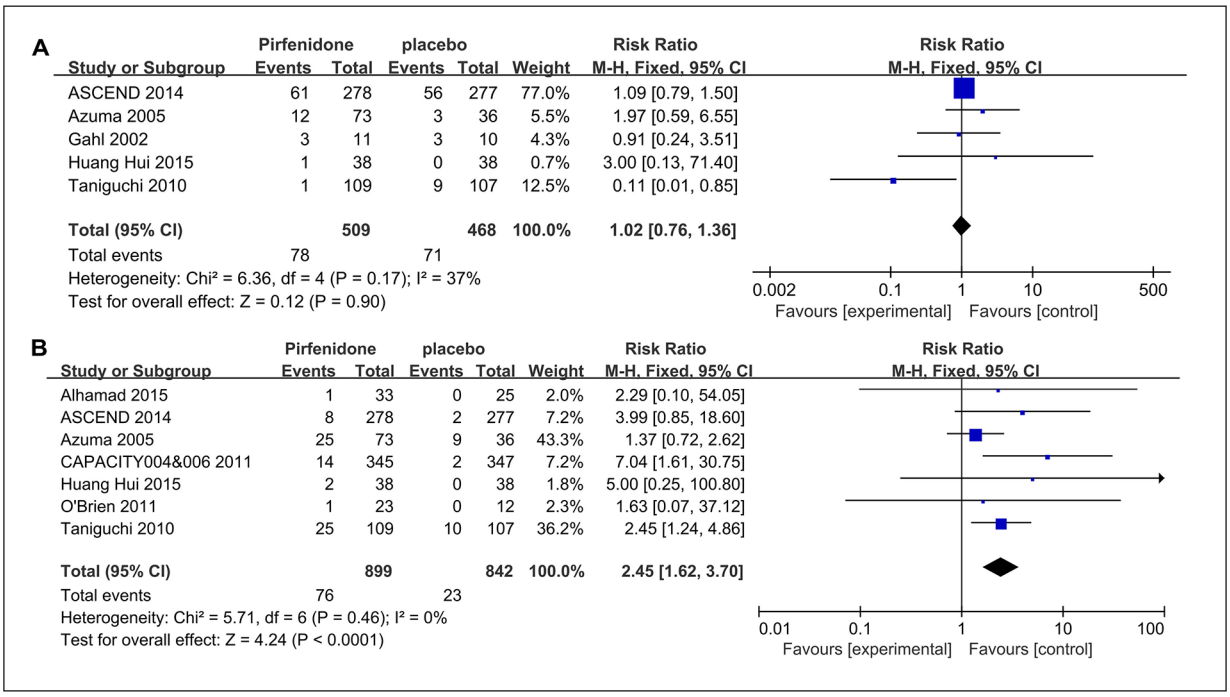

Figure 12. Analysis of other side effects. The incidence of upper respiratory infections (**A**); The incidence of abnormal liver function (**B**).

conducted a further multi-center, randomized, double-blind, placebo-controlled phase II clinical trial reporting statistically significant differences in changes in FVC, Forced Expiratory Volume In 1s (FEV_1), and walking distance in the 6-minute walk test. A real-world study indicate pirfenidone can only delay decline in lung function during the first six months of treatment[14]. A 48-week controlled study showed that pirfenidone did not delay the decline of FEV_1[15]. However, another study[16] showed the pulmonary function of patients treated with pirfenidone remained largely stable over up to 24 months of follow-up.

Our systematic review and meta-analysis demonstrate that although pirfenidone was failed to significantly delay the decline of FEV_1, it was associated with lower reductions in FVC, lower reductions in 6-minute walking test distance, lower decreases in minimum oxygen saturation during the 6-minute walking test, lower all-cause death, lower RR of IPF-related death and increased progression-free survival compared to placebo. Evidence-based medicine guidelines for the treatment of IPF updated in 2015 conditionally recommend oral pirfenidone and nidanib treatment for IPF patients with mild to moderate pulmonary dysfunction[1]. Real-world studies[17] have demonstrated pirfenidone can reduce cough symptoms and improve quality of life among patients with severe IPF. However, there is currently a lack of studies of pirfenidone in patients with severe pulmonary dysfunction in IPF. Further large-scale, multi-center studies are required to determine whether pirfenidone can delay the progression of lung function, prolong progression-free survival, and reduce mortality.

The Safety of Pirfenidone in the Treatment of Pulmonary Fibrosis

The present systematic review and meta-analysis demonstrates the incidence of gastrointestinal, skin, nervous system and liver function-related adverse reactions is increased with pirfenidone. However, studies[15,18-21] have found pirfenidone is well-tolerated by the majority of patients with IPF and common gastrointestinal, skin, nervous system, and liver function-related adverse reactions are typically reversible and of mild to moderate severity, of which a decreased appetite and a photosensitivity reaction were the most frequent ones. Recommendations to reduce the adverse reactions of pirfenidone include a stepwise increase in drug dose and administration with meals to protect the skin and avoid rapid absorption leading to supratherapeutic levels[22].

Limitations

The present study has certain limitations. First, our search criteria may not have identified all relevant studies. For example, some studies may not be published in the searched database. Second, the research subjects included in this meta-analysis are limited to patients with HPS-related pulmonary fibrosis and IPF, and there is a lack of randomized controlled trials of other types of pulmonary fibrosis using pirfenidone. Furthermore, ILD encompasses many heterogeneous diseases with differing pathophysiology, pathogenesis, and treatments. Third, disease severity may differ between studies. The included studies include patients with idiopathic pulmonary fibrosis with mild and moderate pulmonary dysfunction, without stratification, and lack patients with severe and very severe pulmonary dysfunction. Fourth, heterogeneity was observed in some studies, which is related to the differences in the inclusion criteria, exclusion criteria, duration of the study, and time nodes for the selection of observation indicators. We searched relevant domestic and foreign literature, included multiple randomized controlled trial (RCT) studies, real-world research data, and some studies from developing countries, and found that the efficacy and safety of pirfenidone was similar to the results of previous systematic reviews[23,24].

Conclusions

Pirfenidone delays the progression of HPS-related pulmonary fibrosis and IPF as measured by FVC, PFS, 6-minute walk test, and all-cause mortality. The majority of study subjects tolerate pirfenidone well, with most common side effects being mild and related to the gastrointestinal tract, skin, nervous system or liver function indicating pirfenidone is generally safe and side effects are acceptable. Therefore, pirfenidone is a suitable treatment option for patients with IPF. Further multi-center, large sample, double-blind, prospective randomized controlled trials are required to further define the safety profile and effects of pirfenidone on overall survival and lung function in patients with IPF and other different etiologies of pulmonary fibrosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

Not required.

Funding

Neither financial support nor any sort of sponsorship was received for this study.

Authors' Contribution

Yu-jiong Ma performed the literature search, study selection, data extraction, quality assessment and data synthesis, and drafted the manuscript, tables and figures. Qian Zhang performed study selection and quality assessment, assessed data extraction and made major revisions to the manuscript. Chun-xia Wang provided support in design and execution of the review and meta-analyses. Wei Wu provided support in design and execution of the systematic review and meta-analyses, and made major revisions to the manuscript, is the guarantor of this work and takes responsibility for the integrity of the work and analyses.

References

1) Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schünemann HJ; American Thoracic Society; European Respiratory society; Japanese Respiratory Society; Latin American Thoracic Association. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015; 192: e3-e19.

2) Schaefer CJ, Ruhrmund DW, Pan L, Seiwert SD, Kossen K. Antifibrotic activities of pirfenidone in animal models. Eur Respir Rev 2011; 120: 85-97.

3) Meier R, Lutz C, Cosín-Roger J, Fagagnini S, Bollmann G, Hünerwadel A, Mamie C, Lang S, Tchouboukov A, Weber FE, Weber A, Rogler G, Hausmann M. Decreased Fibrogenesis After Treatment with Pirfenidone in a Newly Developed Mouse Model of Intestinal Fibrosis. Inflamm Bowel Dis 2016; 22: 569-582.

4) Gahl WA, Brantly M, Troendle J, Avila NA, Padua A, Montalvo C, Cardona H, Calis KA, Gochuico B. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab 2002; 76: 234-242.

5) Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, Sato A, Kudoh S. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171: 1040- 1047.

6) Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nuki-

wa T; Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821-829.

7) O'Brien K, Troendle J, Gochuico BR, Markello TC, Salas J, Cardona H, Yao J, Bernardini I, Hess R, Gahl WA. Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. Mol Genet Metab 2011; 103: 128-134.

8) Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377: 1760-1769.

9) King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2083-2092.

10) Alhamad EH. Pirfenidone treatment in idiopathic pulmonary fibrosis: A Saudi experience. Ann Thorac Med 2015; 10: 38-43.

11) Zurkova M, Kriegova E, Kolek V, Lostakova V, Sterclova M, Bartos V, Doubkova M, Binkova I, Svoboda M, Strenkova J, Janotova M, Plackova M, Lacina L, Rihak V, Petrik F, Lisa P, Bittenglova R, Tyl R, Ondrejka G, Suldova H, Lnenicka J, Psikalova J, Snizek T, Homolka J, Kralova R, Kervitzer J, Vasakova M; ILD section; IPF registry. Effect of pirfenidone on lung function decline and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry. Respir Res 2019; 20: 16.

12) Huang H, Dai HP, Kang J, Chen BY, Sun TY, Xu ZJ. Double-Blind Randomized Trial of Pirfenidone in Chinese Idiopathic Pulmonary Fibrosis Patients. Medicine (Baltimore) 2015; 94: e1600.

13) Huiping L, Siqin W, Jianying Z, Huanyin W, Limin W, Guangfa W, Peiji Y. Clinical Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. Chinese Journal of Respiratory and Critical Care Medicine 2015; 14: 229-235.

14) Tzouvelekis A, Ntolios P, Karampitsakos T, Tzilas V, Anevlavis S, Bouros E, Steiropoulos P, Koulouris N, Stratakos G, Froudarakis M, Bouros D. Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: A real-world observational study. Pulm Pharmacol Ther 2017; 46: 48-53.

15) Chung MP, Park MS, Oh IJ, Lee HB, Kim YW, Park JS, Uh ST, Kim YS, Jegal Y, Song JW. Safety and Efficacy of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis: A Nationwide Post-Marketing Surveillance Study in Korean Patients. Adv Ther 2020; 37: 2303-2316.

16) Majewski S, Białas AJ, Buchczyk M, Gomółka P, Górska K, Jagielska-Len H, Jarzemska A, Jassem E, Jastrzębski D, Kania A, Koprowski M, Krenke R, Kuś J, Lewandowska K, Martusewicz-Boros MM, Roszkowski-Śliż K, Siemińska A, Sładek K, Sobiecka M, Szewczyk K, Tomczak M, Tomkowski W, Wiatr E, Ziora D, Żołnowska B, Piotrowski WJ. A multicentre retrospective observational study on Polish experience of pirfenidone therapy in patients with idiopathic pulmonary fibrosis: the PolExPIR study. BMC Pulm Med 2020; 20: 122.

17) Ogura T, Azuma A, Inoue Y, Taniguchi H, Chida K, Bando M, Niimi Y, Kakutani S, Suga M, Sugiyama Y, Kudoh S, Nukiwa T. All-case post-marketing surveillance of 1371 patients treated with pirfenidone for idiopathic pulmonary fibrosis. Respir Investig 2015; 53: 232-241.

18) Costabel U, Bendstrup E, Cottin V, Dewint P, Egan JJ, Ferguson J, Groves R, Hellström PM, Kreuter M, Maher TM, Molina-Molina M, Nordlind K, Sarafidis A, Vancheri C. Pirfenidone in idiopathic pulmonary fibrosis: expert panel discussion on the management of drug-related adverse events. Adv Ther 2014; 31: 375-391.

19) Cottin V, Koschel D, Günther A, Albera C, Azuma A, Sköld CM, Tomassetti S, Hormel P, Stauffer JL, Strombom I, Kirchgaessler KU, Maher TM. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. ERJ Open Res 2018; 4: 00084.

20) Yongji Yan, Yali Fan, Shiwen YU, Ye Qiao.Efficacy and safety of pirfenidone in the treatment of idiopathic pulmonary fibrosis: a single-center real world study. Chinese journal of tuberculosis and respiration 2018; 41: 327-332.

21) Fenli W, Wei F, Jian L, Yanbin L. Clinical efficacy of pirfenidone in the treatment of idiopathic pulmonary fibrosis. Clin med research practice 2019; 4: 32-34.

22) Rahaghi FF, Safdar Z, Brown AW, de Andrade JA, Flaherty KR, Kaner RJ, King CS, Padilla ML, Noth I, Scholand MB, Shifren A, Nathan SD. Expert consensus on the management of adverse events and prescribing practices associated with the treatment of patients taking pirfenidone for idiopathic pulmonary fibrosis: a Delphi consensus study. BMC Pulm Med 2020; 20: 191.

23) Aravena C, Labarca G, Venegas C, Arenas A, Rada G. Pirfenidone for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. PLoS One 2015; 10: e0136160.

24) Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, Kardatzke DR, Daigl M, Kirchgaessler KU, Lancaster LH, Lederer DJ, Pereira CA, Swigris JJ, Valeyre D, Noble PW. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med 2017; 5: 33-41.