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Efficacy and safety of PPAR agonists in primary biliary cholangitis: a systematic review and meta-analysis of Randomized Controlled Trials

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Abstract

Background and aims Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease. Some patients with PBC do not adequately respond to Ursodeoxycholic acid (UDCA) as a first-line treatment, putting them at an increased risk of disease progression. Peroxisome Proliferator-Activated Receptor (PPAR) agonists are emerging as promising therapeutic options for PBC. We aim to investigate the efficacy and safety of PPAR agonists in treating PBC patients.

Methods PubMed, EMBASE, Cochrane Library, and Clinicaltrials.gov were searched for Randomized Controlled Trials (RCTs) investigating the use of PPAR agonists in combination with UDCA in patients with PBC, compared to UDCA alone. Mean differences (MD) for continuous variables and risk ratios (RR) for dichotomous variables were calculated to compare treatment response endpoints.

Results A total of 17 studies with 1219 PBC cases were included in the current review. Alkaline phosphatase (ALP) levels had a significantly greater decline in PPAR and UDCA arms than in UDCA alone (MD − 131.15, 95% CI − 155.95 to − 106.36). Furthermore, in combination therapy arms, gamma-glutamyl transferase (GGT) (MD − 55.69, 95% CI − 76.26 to − 35.13) and total bilirubin (MD − 0.08, 95% CI − 0.14 to − 0.03) were significantly lower than in the UDCA alone group.

Conclusions The current study demonstrates that combining UDCA and PPAR agonists effectively reduces ALP, GGT, and Bilirubin levels, crucial markers for effective therapy in PBC patients.

Keywords Autoimmune liver disease, Fibrate, Meta-analysis

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Background

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease primarily affecting middle-aged women. It is characterized by the gradual destruction of small intrahepatic bile ducts, leading to cholestasis, fibrosis, and potentially cirrhosis if left untreated [1]. PBC is relatively rare, with a prevalence ranging from 1.76 to 14.60 per 100,000 individuals worldwide, and its etiology involves a complex interplay of genetic predisposition and environmental factors [2]. According to the European Association for the Study of the Liver (EASL), the diagnosis of PBC can be established when two out of three criteria are met: (1) elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), with exclusion of extrahepatic biliary obstruction; (2) presence of antimitochondrial antibodies (AMA) or PBC-specific antinuclear antibodies (ANA) such as anti-sp100 or anti-gp210; and (3) histologic evidence of non-suppurative destructive cholangitis affecting interlobular bile ducts [3]. Patients with PBC may also show increased alanine transaminase (ALT) and aspartate transaminase (AST), reflecting liver cell injury. However, these elevations are usually less pronounced than the rise in ALP and GGT [3].

Ursodeoxycholic acid (UDCA) is the first-line pharmacological treatment for PBC. It helps by altering the bile acid pool, protecting cholangiocytes against toxic bile acids, increasing bile acid secretion, and reducing the accumulation of toxic bile acids within hepatocytes [4]. However, only two-thirds of patients respond to UDCA, and those with an incomplete response have a worse prognosis [5]. For patients who exhibit an incomplete response to UDCA or are intolerant to it, obeticholic acid (OCA), a farnesoid X receptor agonist, was previously the only licensed second-line therapy [6]. Despite that, its utilization has recently faced limitations by the FDA in severe cirrhosis cases, as reported incidents of liver injury have resulted in hepatic decompensation or, in some cases, liver failure [7].

Peroxisome Proliferator-Activated Receptor (PPAR) agonists show promise as a potential treatment for PBC and are currently under investigation [8]. PPARs are nuclear receptor proteins that regulate gene expression related to metabolism, cellular differentiation, and inflammation [8]. There are three main subtypes: PPARα, PPARγ, and PPARβ/δ, each with distinct tissue distributions and functions. Fibrates, such as Bezafibrate (a pan-PPAR agonist) and Fenofibrate (a PPARα agonist), are employed off-label in various countries as adjunctive or alternative treatments for PBC and demonstrated efficacy in improving biochemical markers and symptoms in PBC patients [8–11]. With limited data available, Ciprofibrate and Pemafibrate (both PPARα agonists) have shown potential in enhancing response to UDCA in a few studies, some of which were uncontrolled [11–13]. Elafibranor (a dual PPARα/δ agonist) and Seladelpar (a PPARδ agonist) have both been granted accelerated approval by the FDA in 2024 for treating PBC in combination with ursodeoxycholic acid (UDCA) or, in the case of Elafibranor, as monotherapy in patients intolerant to UDCA [14]. In addition, Saroglitazar (a dual PPARα/γ) has shown promising results in reducing alkaline phosphatase levels in PBC patients [8, 15]. These emerging PPAR-targeted therapies offer new hope for PBC patients, particularly those with an inadequate response or intolerance to standard UDCA treatment.

This systematic review and meta-analysis aims to comprehensively evaluate the efficacy and safety of PPAR agonists, including PPARα, PPARβ/δ, and PPARγ subtypes, in the treatment of PBC. By synthesizing the available evidence from randomized controlled trials, this review seeks to determine the potential benefits of PPAR agonists as combination therapy with UDCA. We focus on improving biochemical markers, alleviating symptoms, and safety outcomes for PBC patients, particularly those with an inadequate response or intolerance to UDCA.

Methods

Eligibility criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. Randomized Controlled Trials (RCTs) reporting the use of a drug from the PPAR agonists class in patients with Primary Biliary Cholangitis (PBC) were eligible for inclusion. Abstracts, case reports, review articles, trial design protocols, non-comparative studies, and conference abstracts were dismissed.

Search strategy

We systematically searched the following electronic databases: PubMed, EMBASE, Cochrane Library, Clinicaltrials.gov, and WHO's International Clinical Trials Registry Platform (ICTRP) until June 14, 2024. No language restrictions or search filters were applied. Keywords and search terms were: "Peroxisome Proliferator Activted Receptor", "PPAR", "Bezafibrate", "Fenofibrate", "Elafibranor", "Seladelpar", "Saroglitazar", "Primary Biliary Cholangitis", and "PBC. We also screened the reference list of eligible studies and relevant reviews on the topic. The complete search strategy can be seen in the supplementary Table 1.

Study selection

The results of the systematic search were imported into Endnote software version 21.2 (Clarivate PLC, London, United Kingdom). Two independent authors (BS, NB)

screened them using the title and abstract of the studies. Disagreements were resolved by a third reviewer (MP).

Data collection

Full texts of selected studies were retrieved, and data were extracted according to a predesigned sheet. One of the reviewers (BS) did the data extraction, while a second reviewer (NB) cross-checked it. If information was unavailable or they were reported as a different effects measure, we contacted the authors of the trial publications. From each trial, the following information was extracted: the first author's name, study year, country of origin, trial design, trial duration, population and baseline characteristics, type of the drug and dosage, the sample size of each comparison group, and outcomes at the end of treatment. Our primary outcomes included (1) changes from baseline or final values of serum alkaline phosphatases (ALP), serum gamma-glutamyl transferase (GGT), and serum total bilirubin, and (2) pruritus, defined as the number of patients experiencing pruritus throughout the study. Secondary outcomes included (1) changes from baseline or final values of serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST), (2) the number of patients experiencing at least one adverse event (AE), and (3) the number of patients experiencing at least one serious adverse event (SAE). Definitions of pruritus, prespecified adverse events, and serious adverse events varied across the included studies.

Risk of Bias assessment

The quality of the included randomized controlled trials (RCTs) was assessed using version 2.0 of the Cochrane Risk of Bias Assessment Tool for Randomized Trials (RoB2) [17, 18]. Two authors (TB, FOS) rated each domain as "Low", "High", or "Some concerns", and consensus resolved conflicts. The five evaluated domains according to RoB2 were: (1) the randomization process, (2) deviations from the intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. One of the included studies used a version of RoB2 for crossover trials.

Data synthesis and statistical analysis

We performed all statistical analyses using R Programming language (R for Mac, version 4.2.2, Vienna, Austria) and R Studio version 2023.12.1 + 402 (Posit PBC, Boston, MA, United States) utilizing the "meta" and "dmetar" statistical packages. The random-effects model for the meta-analysis used the inverse-variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes. Mean and standard deviation (SD) were used to calculate the mean difference (MD) with a 95% confidence interval (CI) for continuous variables or risk ratios (RR) with a 95% CI for dichotomous variables. Reported median and interquartile range (IQR) or mean and range were converted to the mean and SD using the methods developed by Luo et al. [19] and Wan et al. [20]. We combined change from baseline values with final measurement values in the meta-analysis, as suggested by Cochrane, stating that mean differences based on changes from baseline can usually be assumed to address the same underlying intervention effects as analyses based on final measurements [21]. In studies including multiple intervention groups with different drug dosages and a shared control group, we combined the mean and SD of intervention groups into one [21]. Some studies reported least-squares mean (LS mean) instead of arithmetic average. In these cases, we combined them with other studies to perform a pooled analysis and later assessed the impact of including them with a sensitivity analysis. The restricted maximum likelihood (REML) model estimated the between-study variance. Heterogeneity was evaluated using Higgin's I^2 test, with thresholds defined as ≤ 25% for low, 26–75% for moderate, and > 75% for high [22]. Meta-regression, subgroup, and leave-one-out sensitivity analyses were conducted to identify sources of heterogeneity. Publication Bias was evaluated using funnel plot visual assessment. Later on, Egger's test [23] was performed to check continuous variables reported in more than ten studies to confirm publication bias.

Certainty of evidence assessment

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the overall evidence quality of our primary outcomes [24–26]. The evidence was rated as high, moderate, low, or very low in five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality of each outcome may be downgraded for 1 or 2 levels due to either 'serious' or 'very serious' risks in these domains. Two reviewers (BS and TB) assessed each domain for each outcome. All decisions regarding downgrading the certainty of evidence were documented in the supplementary Table S2.

Results

Study characteristics

Our search resulted in 1062 records from PubMed ($n = 295$), Embase ($n = 628$), Cochrane Library ($n = 125$), Clinicaltrials.gov ($n = 5$), and WHO's International Clinical Trials Registry Platform ($n = 9$). A PRISMA flow chart is available in Fig. 1. After removing duplicate studies and excluding reports not eligible for this study, 17 studies were included in this review [9, 15, 27–41]. Details of these included studies are presented in Table 1.

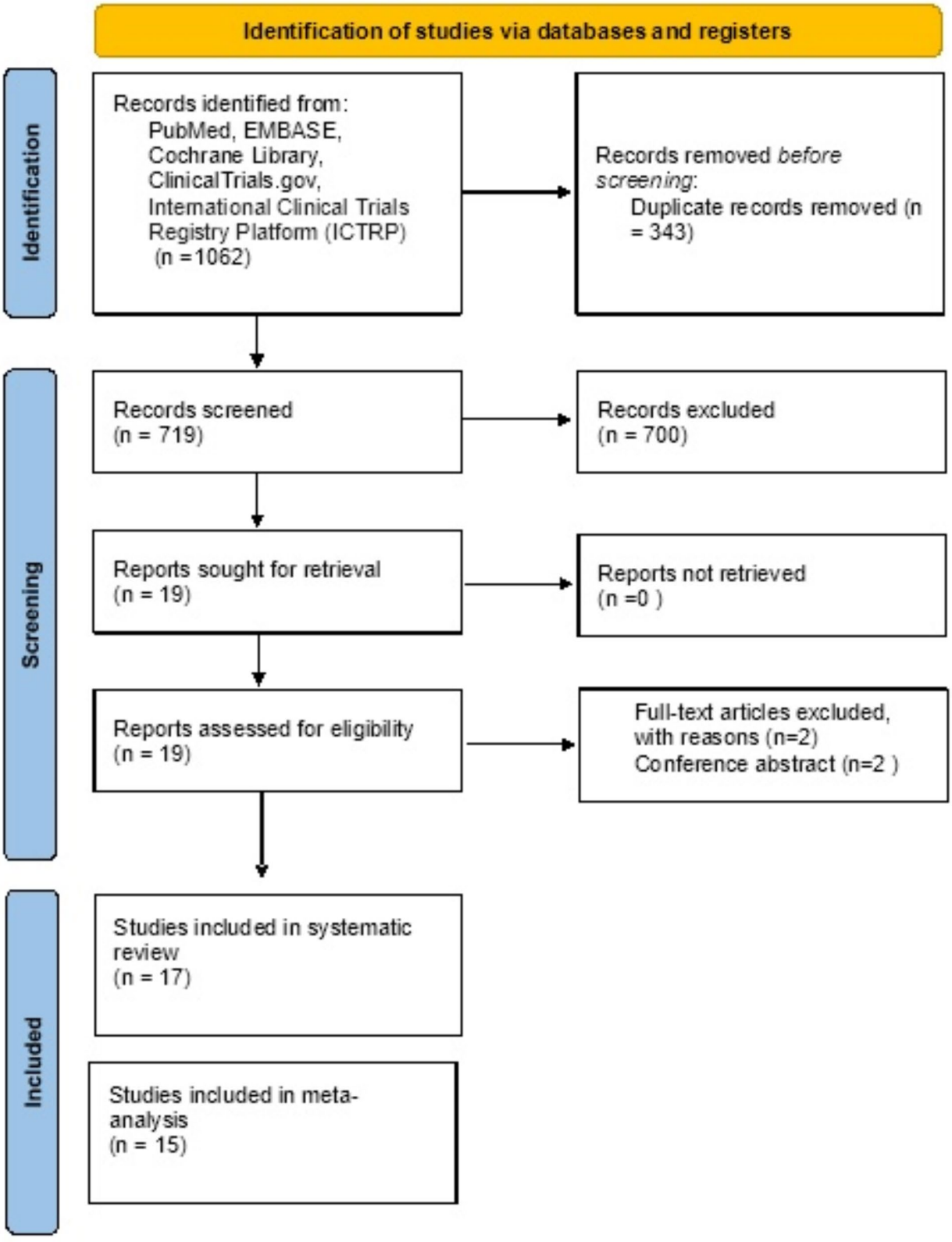

Fig. 1 The PRISMA flow diagram of included articles in the current systematic review

Table 1 Characteristics of studies evaluating PPAR drugs in PBC patients

Author	Year	Country	Design	Duration	Population (% of cases intolerant or irresponsive to UDCA)	Combination Therapy[†] (Number)	Monotherapy[‡] (Number)	Baseline liver biochemistry (ALP[1]/TBill)	Biochemical Response Definition	Biochemical Response Combination (%)	Biochemical Response Monotherapy (%)	Age	% Female	Main Findings
Nakai et al.	1999	Japan	randomized, open, controlled	12 months	Patients diagnosed with PBC using a positive AMA and a compatible liver biopsy, who had been treated with UDCA for 1–5 years (NR)	UDCA 600 mg daily + Bezafibrate 400 mg daily (10)	UDCA 600 mg daily (13)	179 ± 48 / –	–	–	–	57 ± 10	–	Results suggest that the combination therapy of Bezafibrate and UDCA improves levels of ALP, GGT, and IgM; thereby, the combination therapy may lead to the improvement of clinical outcome.
Kurihara et al.	2000	Japan	randomized, open, controlled	12 months	Patients diagnosed with PBC by liver biopsy (NR)	Bezafibrate 400 mg daily (12)	UDCA 600 mg daily (12)	188.9 ± 32.3 / –	–	–	–	60.1 ± 9	96	Patients in the Bezafibrate group showed more highly significant reductions than those in the UDCA group for ALP, GGT, IgM and ALT at 1, 3, 6, and 12 months.
Kanda et al.	2003	Japan	randomized, open, controlled	6 months	Patients who had been diagnosed histologically as having PBC, and who had been treated with 600 mg/day of UDCA for at least 6 months, and had elevated serum ALP (100)	UDCA 600 mg daily + Bezafibrate 400 mg daily (11)	UDCA 600 mg daily (11)	400.2 ± 124.4 / –	–	–	–	56 ± 10.4	86	Changes in ALP levels were greater in the Bezafibrate group than in the control group ($P < 0.01$) and serum ALP levels were significantly lower than those before treatment in patients receiving UDCA plus Bezafibrate ($P < 0.05$). At the end of the 6 months, normalization of serum ALP was observed in 45.4% patients given Bezafibrate and in 18.1% patients in the control group ($P < 0.16$). Bile acid proportions during the combination therapy did not change.
Itakura et al.	2004	Japan	randomized, crossover trial	12 months	Patients diagnosed with PBC. Thirteen patients were diagnosed with PBC at entry, and three patients received treatment with UDCA for 2–11 years (18.75)	first half: UDCA 600 mg daily + Bezafibrate 400 mg daily second half: UDCA alone (9)	first half: UDCA alone second half: UDCA 600 mg daily + Bezafibrate 400 mg daily (7)	618 ± 183 / 0.73 ± 0.1	–	–	–	57.1 ± 7.6	75	The combination therapy with UDCA + Bezafibrate significantly improves the laboratory data that specific for PBC in comparison with UDCA alone.

Table 1 (continued)

Author	Year	Country	Design	Duration	Population (% of cases intolerant or irresponsive to UDCA)	Combination Therapy† (Number)	Monotherapy‡ (Number)	Baseline liver biochemistry (ALP¶/TBill)	Biochemical Response Definition	Biochemical Response Combination (%)	Biochemical Response Monotherapy (%)	Age	% Female	Main Findings
Iwasaki et al. (study A)[2]	2008	Japan	randomized, open, controlled	52 weeks	Non-cirrhotic PBC patients who had been not treated within the previous 4 weeks with UDCA or bezafibrate (0)	Bezafibrate 400 mg daily (20)	UDCA 600 mg daily (25)	764.0 ± 401.3 / 0.6 ± 0.2	–	–	–	55.2 ± 10.5	82	Study 1 showed that Bezafibrate monotherapy is equally as effective as UDCA in the treatment of PBC. Study 2 showed that combination therapy of Bezafibrate and UDCA improved biliary enzymes in patients with PBC refractory to UDCA.
Iwasaki et al. (study B)[2]	2008	Japan	randomized, open, controlled	52 weeks	Non-cirrhotic PBC patients. They were treated with UDCA for more than 26 weeks before the study and their ALP levels had remained > 1.5 x ULN (100)	UDCA 600 mg daily + Bezafibrate 400 mg daily (12)	UDCA 600 mg daily (10)	643 ± 262 / 0.8 ± 0.4	–	–	–	51.4 ± 11.6	86	
Hosonuma et al.[2]	2015	Japan	randomized, open, controlled	median of 107–110 month	PBC patients with dyslipidemia. PBC diagnosis was made according to AASLD. Patients were treated with UDCA for more than 24 weeks before the study and their ALP levels had remained > 350 IU/l (100)	UDCA 12–15 mg/kg/day + Bezafibrate 400 mg daily (13)	UDCA 12–15 mg/kg/day (14)	423 [359–798] / 0.7 [0.3–2.1]	–	–	–	61 ± 9.7	81	The ALP levels and the Mayo risk score in the UDCA + Bezafibrate group were significantly lower than those in the UDCA monotherapy group at 8 years after the beginning of the study ($P < 0.05$).
Corpechot et al. (BEZURSO trial)[3]	2018	France	randomized, double-blind, placebo-controlled	24 months	Patients diagnosed with PBC according to established criteria of EASL. Patients were treated with UDCA for more than 6 months before the study and had an inadequate biochemical response according to the Paris 2 criteria (100)	UDCA 15 (IQR, 13–16) mg/kg/day + Bezafibrate 400 mg once-daily (50)	UDCA 15 (IQR, 14–16) mg/kg/day + Placebo once-daily (50)	244 [211–308] / 14.0 ± 7.6	Normal serum levels of ALP, AST, ALT, total bilirubin, and albumin, as well as a normal prothrombin index	31	0	53 ± 10	95	31% of the patients in the Bezafibrate group reached biochemical response, compared to 0% in the control group ($P < 0.001$). The rate of biochemical response in the Bezafibrate group rised progressively until month 15, until it reached a plateau of 30 to 35%.
de Vries et al. (FITCH trial)	2020	Netherlands and Spain	randomized, double-blind, placebo-controlled	21 days	Patients with moderate to severe pruritus (> 5 out of 10 on VAS) due to PSC, PBC and SSC as defined by EASL (NR)	UDCA + Bezafibrate 400 mg once-daily (38, 11 PBC)	UDCA + Placebo once-daily (36, 15 PBC)	–/–		–	–	48.3 ± 13.9	74	55% of the PBC patients in the Bezafibrate group had a > 50% reduction of severe or moderate pruritus, compared to 11% of all the patients in the placebo group ($p = 0.003$).
Liberopoulos et al.[2]	2010	Greece	randomized, open, controlled	8 weeks	Patients with histologically confirmed PBC. Patients were treated with 600 mg/day UDCA for more than 8 months before the study and their ALP levels had remained > 3 x ULN (100)	UDCA 600 mg daily + Fenofibrate 200 mg daily (6)	UDCA 600 mg daily (4)	195 ± 73 / 0.70 ± 0.14		–	–	55.1 ± 5.4	80	Fenofibrate plus UDCA seems to be well tolerated and may improve lipid and liver indices in patients with PBC who do not respond fully to UDCA monotherapy.

Table 1 (continued)

Author	Year	Country	Design	Duration	Population (% of cases intolerant or irresponsive to UDCA)	Combination Therapy† (Number)	Mono-therapy‡ (Number)	Baseline liver biochemistry (ALP[1]/TBill)	Bio-chemical Response Definition	Biochemical Response Combination (%)	Biochemical Response Monothera-py (%)	Age	% Female	Main Findings
Li et al.[3]	2022	China	randomized, open, controlled	12 months	Patients diagnosed with PBC according to AASLD. Patients were treated with UDCA for more than 6 months before the study (100)	UDCA 13–15 mg/kg/day + Fenofibrate 200 mg daily (24)	UDCA 13–15 mg/kg/day (24)	174 (137- 253.5) / 15.45 (10.75-23.525)	Normal serum levels of ALP, GGT, and total Bilirubin levels	20.8	0	51 ± 11.3	90	Combinaition therapy with Fenofibrate and UDCA can improve biochemical indices of PBC patients who had an incomplete response to UDCA. Reversible elevation of serum creatine and transaminases is observed in some patients.
Liu et al.[3]	2023	China	randomized, open, controlled	12 months	Patients diagnosed with PBC were recruited based on the AASLD criteria. Patients had never received UDCA before (0)	UDCA 13–15 mg/kg/d + Fenofibrate 200 mg daily (57)	UDCA 13–15 mg/kg/d (60)	277 (202–426) / 15.7 (11.5–25.6)	Barcelona criteria: Decrease in ALP > 40% or a return to normal levels after 1 year of treatment	81.4 [69.9–92.9]	64.3 [51.9–76.8]	52 ± 8.5	86	The combination therapy with Fenofibrate and UDCA resulted in a significantly higher biochemical response rate (81.4% vs. 64.3%, $P = 0.048$) and the treatment seemed to be well tolerated.
Schat-tenberg et al.[3]	2021	Global	randomized, double-blind, placebo-controlled	12 weeks	Patients with PBC diag-nosed based on the AASLD criteria. Patients were treated with UDCA for more than 12 months before the study and their ALP levels had remained > 1.67 x ULN (100)	UDCA 14.30 ± 4.01 mg/kg/day + Elafibranor 80 mg once-daily (15)	UDCA 13.50 ± 3.05 mg/kg/day + Elafibranor 120 mg once-daily (15)	UDCA 14.80 ± 2.14 mg/kg/day + Placebo (15)	80 mg: 350.6 ± 152.1 120 mg: 263.7 ± 137.6 / 80 mg: 9.9 ± 6.7 120 mg: 9.7 ± 5.3	Com-posite Response: ALP < 1.67 x ULN, de-crease of ALP > 15% and total biliru-bin < ULN	80 mg: 67 120 mg: 79	6.7	59.1 ± 8.1	96	Elafibranor was generally well tolerated and significantly reduced levels of ALP and other markers of disease activity and resulted in a higher biochemical response in patients with PBC and an incomplete response to ursodeoxycholic acid.
Kowdley et al. (ELATIVE trial)[3]	2024	Global	randomized, double-blind, placebo-controlled	52 weeks	Patients with a diagnosis of PBC and an inadequate response to or unaccept-able side effects with UDCA (100)	UDCA (94% of patients) + Elafibranor 80 mg once-daily (108)	UDCA (96% of patients) + Placebo (53)	321.3 ± 121.9 / 9.7 ± 5.1	Com-posite Response: ALP < 1.67 x ULN, de-crease of ALP > 15% and total biliru-bin < ULN	51	4	57.1 ± 8.7	96	51% of the patients in the Elafi-branor group reached biochemi-cal response, compared to 4% in the control group ($P < 0.001$).
Jones et al.[2]	2017	Global	randomized, double-blind, placebo-controlled	12 weeks	Patients with a diagnosis of PBC with AASLD criteria. Patients were treated with UDCA for more than 12 months before the study and their ALP levels had remained > 1.67 x ULN (100)	UDCA 15 ± 3 mg/kg/day + Seladelpar 50 mg daily (13)	UDCA 14 ± 2 mg/kg/day + Seladelpar 200 mg daily (12)	UDCA 16 ± 2 mg/kg/day + Placebo (13)	50 mg: 312 ± 95 200 mg: 248 ± 89 / 50 mg: 0.73 ± 0.27 200 mg: 0.75 ± 0.38	Com-posite Response: ALP < 1.67 x ULN, de-crease of ALP > 15% and total biliru-bin < ULN	50 mg: 100 (of 3 patients) 200 mg: 100 (of 2 patients)	0 (of 4 patients)	55.8 ± 9.2	95	Seladelpar normalised ALP levels in patients who completed 12 weeks of treatment. However, treatment was associated with grade 3 increases in amino-transferases and the study was stopped early. The effects of seladelpar should be explored at lower doses.

Table 1 (continued)

Author	Year	Country	Design	Duration	Population (% of cases intolerant or irresponsive to UDCA)	Combination Therapy† (Number)		Monotherapy‡ (Number)	Baseline liver biochemistry (ALP[1]/TBill)	Biochemical Response Definition	Biochemical Response Combination (%)	Biochemical Response Monotherapy (%)	Age	% Female	Main Findings
Hirschfield et al. (ENHANCE trial)[2]	2023	Global	randomized, double-blind, placebo-controlled	3 months	Patients diagnosed with PBC accoridng to AASLD criteria. Patients were treated with UDCA for more than 12 months before the study, unless they were UDCA intolerant. Their ALP levels had remained > 1.67 x ULN, and total bilirubn ≤ 2 x ULN (100)	UDCA (93% of patients) 15.6 ± 4.4 mg/kg/day + Seladelpar 5 mg once-daily (89)	UDCA (91% of patients) 15.3 ± 3.7 mg/kg/day + Seladelpar 10 mg once-daily (89)	UDCA (98% of patients) 15.0 ± 2.6 mg/kg/day + Placebo (87)	5 mg: 290.5 ± 104.2 10 mg: 290.8 ± 109.1 / 5 mg: 0.76 ± 0.35 10 mg: 0.72 ± 0.32	Composite Response: ALP < 1.67 x ULN, decrease of ALP > 15% and total bilirubin < ULN	5 mg: 57.1 10 mg: 78.2	12.50	55.4 ± 9	94	Patients with PBC with inadequate response or intolerance to UDCA had significant improvements in liver biochemistry and pruritus when they were treated with seladelpar 10 mg. The treatment appeared safe and well tolerated.
Hirschfield et al. (RESPONSE trial)[2]	2024	Global	randomized, double-blind, placebo-controlled	12 months	PBC patients who were treated with UDCA for more than 12 months before the study, unless they had a history of unacceptable side effects. All patients had an incomplete biochemical response (100)	UDCA (93.8% of patients) 15.0 ± 3.1 mg/kg/dat + Seladelpar 10 mg daily (128)		UDCA (93.8% of patients) 14.9 ± 3.3 mg/kg/day + Placebo (65)	314.6 ± 123.0 / 0.77 ± 0.3	Composite Response: ALP < 1.67 x ULN, decrease of ALP > 15% and total bilirubin < ULN	61.7	20.0	56.7 ± 9.7	95	61.7% of the patients in the Seladelpar group reached biochemical response, compared to 20% in the control group ($P < 0.001$).
Vuppalanchi et al. (EPICS trial)[2]	2021	USA	randomized, double-blind, placebo-controlled	16 weeks	Patients who had a diagnosis of PBC based on the AASLD and EASL criteria. Patients were treated with UDCA for more than 12 months before the study and their ALP levels had remained > 1.67 x ULN (100)	UDCA (85.7% of patients) 15.0 ± 6.5 mg/kg/day + Saroglitazar 2 mg daily (14)	UDCA 11.6 ± 4.0 mg/kg/day + Saroglitazar 4 mg daily (13)	UDCA 14.0 ± 4.3 mg/kg/day + Placebo (10)	2 mg: 351.3 ± 161.3 4 mg: 323.2 ± 111.0 / 2 mg: 0.6 ± 0.2 4 mg: 0.7 ± 0.2	Composite Response: ALP < 1.67 x ULN, decrease of ALP > 15% and total bilirubin < ULN	2 mg: 71 4 mg: 69	10	57 ± 8.4	97	Saroglitazar was well tolerated and significantly reduced levels of ALP and other markers of disease activity and resulted in a higher biochemical response in patients with PBC.

PPAR = Peroxisome Proliferator-activated Receptor, PBC = Primary Biliary Cholangitis, UDCA = Ursodeoxycholic Acid, AASLD = American Association for the Study of Liver Diseases, VAS = Visual Analogue Scale, PSC = Primary Sclerosing Cholangitis, ALP = Alkaline Phosphatase, AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase, TBill = Total bilirubin, ULN = Upper Limit Normal, NR = Not reported

Continuous values are represented in: Mean ± SD / Median [Minimum-Maximum] / Median (IQR1-IQR3)

† Combination therapy with PPAR agonists + UDCA

‡ Monotherapy with UDCA alone

[1] Baseline ALP is reported as (Unit/L)

[2] Baseline TBill is reported as (mg/dl)

[3] Baseline TBill is reported as (μmol/L)

These trials were published between 1999 and 2024. A total of 1219 PBC patients with a mean age of 55.1 ± 10 years comprising 1100 female patients were included. Seven hundred thirty-one patients were treated with the combination therapy of a PPAR agonist and UDCA, while 488 patients were treated with placebo and UDCA. Bezafibrate was evaluated in eight [9, 27–33], Fenofibrate in three [34–36], Elafibranor in two [37, 38], Seladelpar in three [39–41], and Saroglitazar in one study(s) [15]. Almost all of the studies included patients who were previously treated with UDCA and had an inadequate biochemical response, except two studies by Nakai et al. [27] and Liu et al. [36] that included patients regardless of their biochemical response to UDCA, and three studies by Kurihara et al. [28], Itakura et al. [29], and de Vries et al. [33], which included patients who had never received UDCA before [28, 29, 33]. Most studies either did not enroll cirrhotic patients or included only a small number. None of the included studies reported a significant difference in the number of cirrhotic patients between the combination therapy and monotherapy groups.

Pruritus was defined differently across studies, such as the Numerical Rating Scale (NRS) ≥ 4 [38, 40, 41] and the Visual Analog Scale (VAS) ≥ 30 [39] or > 0 [37], while some studies did not specify a definition. SAEs were defined as adverse events that resulted in death, were life-threatening, required in-patient hospitalization, prolonging an existing hospital stay, or led to persistent or significant disability or incapacity. However, not all studies provided specific definitions for SAEs.

Risk of Bias in studies

According to RoB2, seven of the 17 included studies [15, 32, 33, 37, 38, 40, 41] had an overall low risk of bias (Fig. 2). Nine studies received a "Some concerns" rating in Domain 4, which pertains to bias in measuring the outcome [9, 27–31, 34–36]. This was due to these studies being open randomized trials, raising the possibility that the outcome assessors' knowledge might influence their assessments of some outcomes. Two studies lacked a prespecified analysis plan, leading to concerns in Domain 5 regarding bias in selecting the reported result [27, 28]. Lastly, the study by Jones et al. exhibited baseline imbalance, particularly in ALP levels, indicating issues with the randomization process and leading to concerns in Domain 1 [39].

Meta-analysis and subgroup analysis of primary outcomes

Fifteen studies were used for the meta-analysis to compare the combination therapy of a PPAR agonist and UDCA with UDCA alone. Twelve studies included patients previously treated with UDCA who had an inadequate biochemical response. In contrast, one study included patients regardless of their biochemical responses [27], and two included patients who had not received UDCA before [29, 36]. The study by Kurihara et al. [28] was not included in the meta-analysis because the intervention arm was Bezafibrate without UDCA. Itakura et al. [29] conducted a randomized crossover trial in which we used the data from the first half of the study. Iwasaki et al. [30] published a paper comprising two studies, one of which (study A) had an intervention arm of Bezafibrate without UDCA and was not used for the meta-analysis. Lastly, the FITCH trial [33] included both primary sclerosing cholangitis (PSC) and PBC patients but did not provide separate data for PBC patients. Although no SAEs were reported among PBC patients in this trial, we excluded the study from the SAEs analysis due to its relatively short 21-day treatment period compared to other studies.

The meta-analysis found that ALP level had a significantly greater decline in patients taking the combination therapy compared to those taking UDCA alone (MD − 131.15, 95% CI − 155.95 to − 106.36, $I^2 = 78\%$, Fig. 3). GGT and total bilirubin levels were also significantly lower in the PPAR + UDCA group (MD − 55.69, 95% CI − 76.26 to − 35.13, $I^2 = 67.8\%$, Fig. 4; and MD − 0.08, 95% CI − 0.14 to − 0.03, $I^2 = 53\%$, Fig. 5; respectively). There was a statistically significant difference in levels of ALT in favor of combination therapy with PPAR and UDCA (MD − 8.70, 95% CI − 13.42 to − 3.97, $I^2 = 71\%$, Supplementary Figure S1), although AST showed no difference (MD − 1.40, 95% CI − 4.90 to 2.09, $I^2 = 65\%$, Supplementary Figure S2). Incidence of pruritus, adverse events (AEs), and serious adverse events (SAEs) were also comparable between the two groups (RR 0.69, 95% CI 0.47 to 1.02, $I^2 = 11\%$, Fig. 6; RR 1.01, 95% CI 0.95 to 1.07, $I^2 = 0\%$. Supplementary Figure S3; and RR 1.08, 95% CI 0.71 to 1.64, $I^2 = 0\%$, Supplementary Figure S4; respectively).

A subgroup analysis was conducted based on the type of PPAR agonist. Combination therapy with all types of PPAR agonists (Bezafibrate, Fenofibrate, Elafibranor, Seladelpar, and Saroglitazar) showed a significantly greater reduction in ALP levels compared to UDCA alone (Fig. 2). Combination therapy with Bezafibrate, Seladelpar, and Saroglitazar were the only drug regimens that significantly lowered the GGT levels more effectively compared to UDCA monotherapy (MD − 53.81, 95% CI − 95.55 to − 120.07, $I^2 = 65.7\%$; MD − 72.52, 95% CI − 109.85 to − 35.18, $I^2 = 60.8\%$; MD − 72.03, 95% CI − 98.90 to − 45.16; respectively; Fig. 3). Bezafibrare was the only PPAR agonist that caused a more significant reduction in total bilirubin levels when used in combination with UDCA compared to UDCA alone (MD − 0.20, 95% CI − 0.28 to − 0.12, Fig. 4). Unlike other PPAR agonists, Seladelpar and Saroglitazar combined with UDCA decreased ALT levels to a greater extent than UDCA alone (MD − 9.31, 95% CI − 12.77 to − 5.86, $I^2 = 0\%$; MD − 12.64, 95%

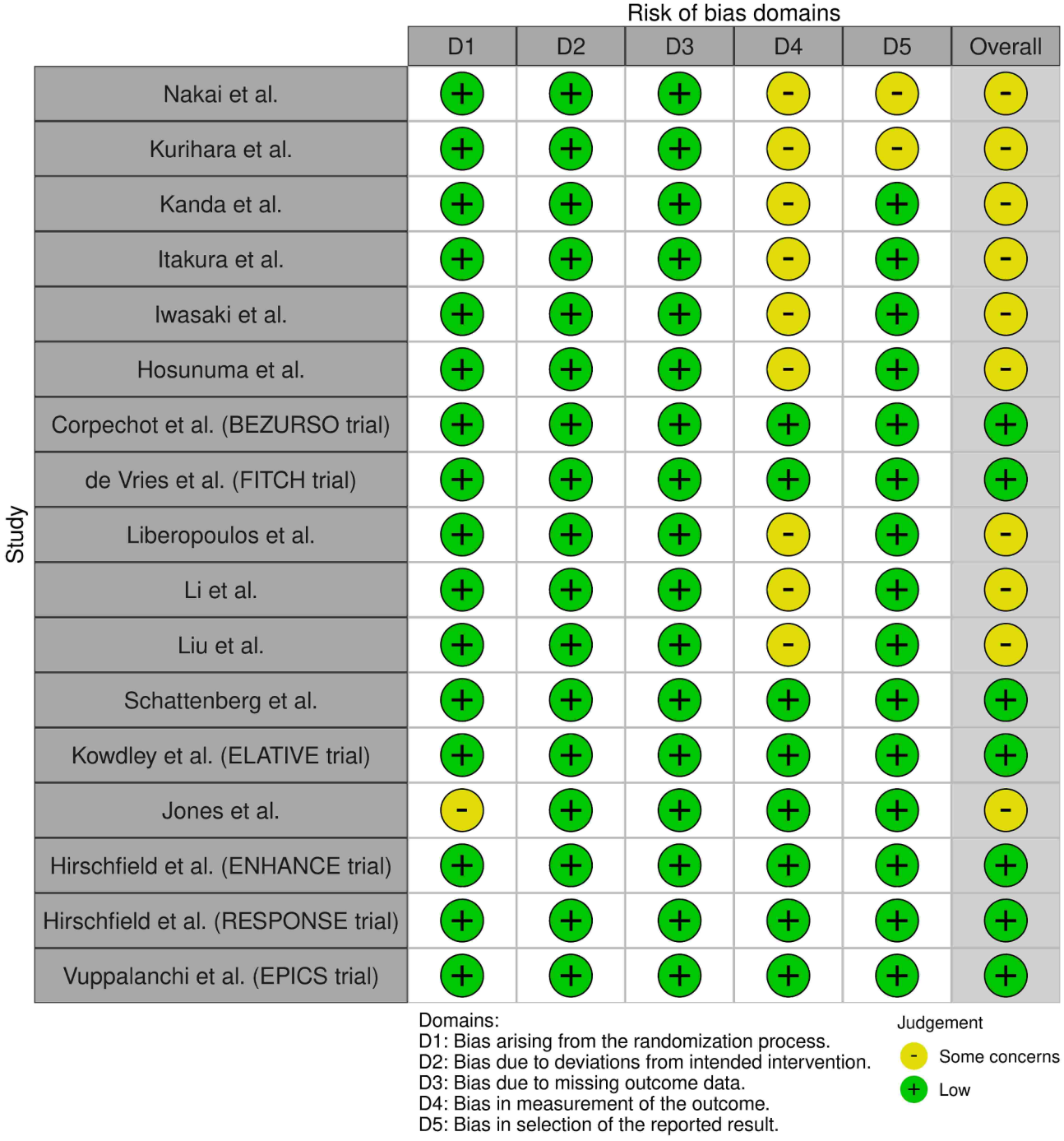

Fig. 2 Risk of bias assessment for included studies across five domains using the Cochrane risk of bias tool (RoB 2). Each study is evaluated for bias arising from the randomization process (D1), deviations from the intended intervention (D2), missing outcome (D3), bias in measurment of the outcome (D4), and in selective reporting (D5)

CI −16.63 to −8.65; respectively; Supplementary Figure S1). Sarolitazar was the only PPAR agonist that caused a more significant reduction in AST levels when combined with UDCA compared to UDCA monotherapy (MD −6.56, 95% CI −9.46 to −3.66, Supplementary Figure S2). There was no significant difference between combination therapies with different PPAR agonists and UDCA monotherapy while analyzing the incidence of pruritus, AEs, and SAEs (Fig. 6, Supplementary Figures S3 and S4). We also performed a subgroup analysis comparing double-blind and open-label studies (Supplementary Figures S21–S28). Except for pruritus and ALT, all other outcomes showed effect sizes in the same direction across both study designs and aligned with the overall analysis.

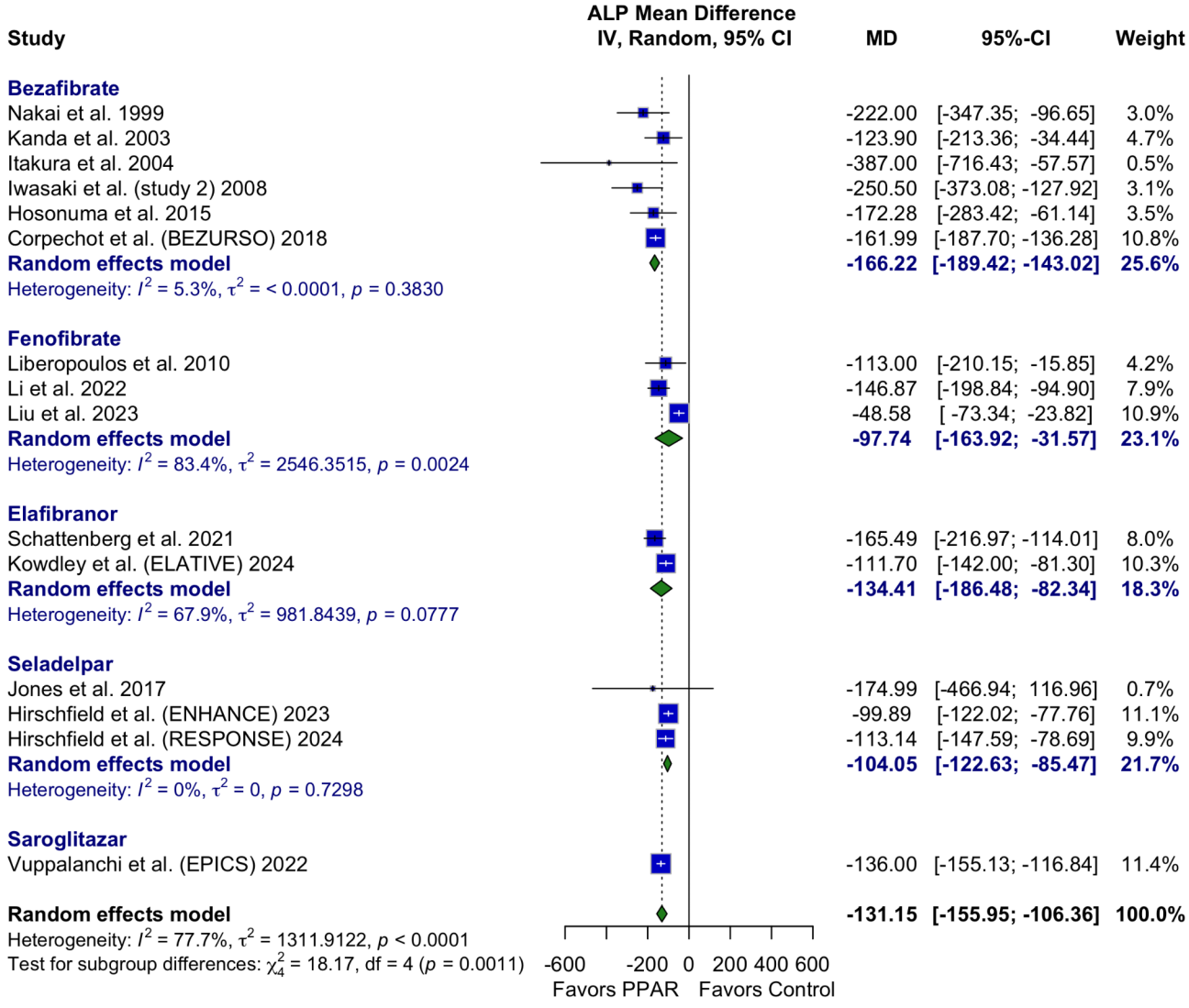

Fig. 3 Forest Plot of Mean Difference in ALP Levels in Groups of UDCA + PPAR Agonist Recipients vs. UDCA Alone Recipients

For ALT, double-blind studies followed the direction of the overall estimate (MD −10.13, 95% CI −15.48 to −4.78, Supplementary Figure S24), whereas open-label studies did not. Unlike the overall estimate, double-blind studies demonstrated a significant difference in favor of PPAR agonists for pruritus (MD 0.59, 95% CI 0.38 to 0.92, Supplementary Figure S26).

Meta-regression, sensitivity analysis, and publication bias

We conducted a meta-regression analysis to assess the impact of baseline ALP differences on the estimated effect sizes. None of the regression models yielded significant p-values for the primary and secondary outcomes (all p-values > 0.05), indicating that baseline ALP levels did not influence our findings.

Sensitivity leave-one-out analysis was conducted by omitting each of the individual studies for all of the primary outcomes. The reduction in ALP, GGT, total bilirubin, and ALT levels were still significantly different regardless of the removal of each study (Supplementary Figures S5, S6, S7, and S8). However, removing any study in the analysis for AST levels, the incidence of AEs and SAEs did not result in a significant difference between the two groups (Supplementary Figures S9, S11, and S12). On the other hand, the incidence of pruritus changed towards favoring combination therapy with the removal of studies, with the second [9] and fourth [39] having the most contributed heterogeneity (Supplementary Figures S10).

Funnel plots showed some apparent asymmetry for ALP, GGT, and total bilirubin levels (Supplementary Figures S13, S14, and S15). Egger's statistical tests suggested the presence of asymmetry only for total bilirubin levels (p-value = 0.048). Utilizing the trim-and-fill method demonstrated that the two groups did not significantly

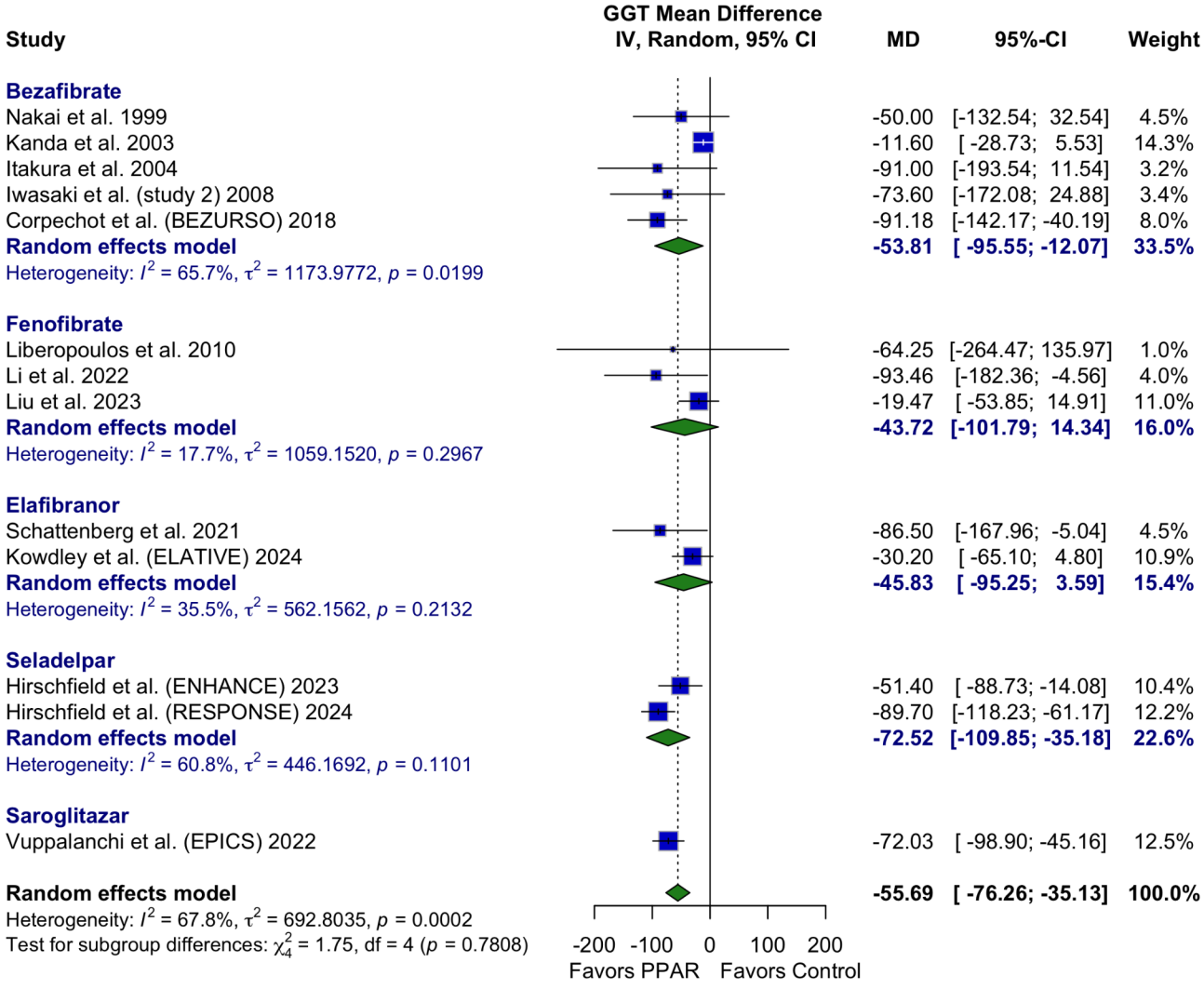

Fig. 4 Forest Plot of Mean Difference in GGT Levels in Groups of UDCA + PPAR Agonist Recipients vs. UDCA Alone Recipients

differ in total bilirubin level reduction (MD − 0.04, 95% CI − 0.10 to 0.02).

Biochemical response and other biomarkers

The most common definition of biochemical response through included studies was a composite of 1) > 15% reduction of ALP from baseline, 2) ALP < 1.67 x upper limit of normal (ULN), and 3) total bilirubin ≤ ULN. Several studies indicated that the prevalence of biochemical response was significantly higher in treatment groups than in the control arm [15, 32, 35–41].

Nine studies reported changes in immunoglobulin M (IgM) levels before and after treatment in PBC cases. Most studies revealed a significantly larger reduction in IgM levels within the treatment group [27–29, 37, 38, 40, 41], while some articles showed no significance [30, 32].

All included studies that investigated the effect of PPAR agonists on cholesterol levels showed a more significant decrease in the treatment group than in the patients who only received UDCA [15, 29, 30, 32, 34, 36, 40]. Furthermore, in all studies that reported the changes in triglyceride levels, cases in the treatment group experienced a significantly more reduction [15, 29, 30, 34, 37, 40].

Liver stiffness and fibrosis

Four articles studied the change in liver stiffness and the enhanced liver fibrosis (ELF) score in PBC patients treated with PPAR agonists [32, 36, 38, 41]. Three studies used the Fibroscan system to measure the stiffness [32, 38, 41], while one used the Fibrotouch system [36]. All studies except for one [32] demonstrated no significant difference in liver stiffness and ELF score changes between patients administered with combination therapy of PPAR agonists and UDCA and those who received UDCA monotherapy. The BEZURSO trial [32] demonstrated that combination therapy was superior in reducing liver stiffness and ELF score in PBC.

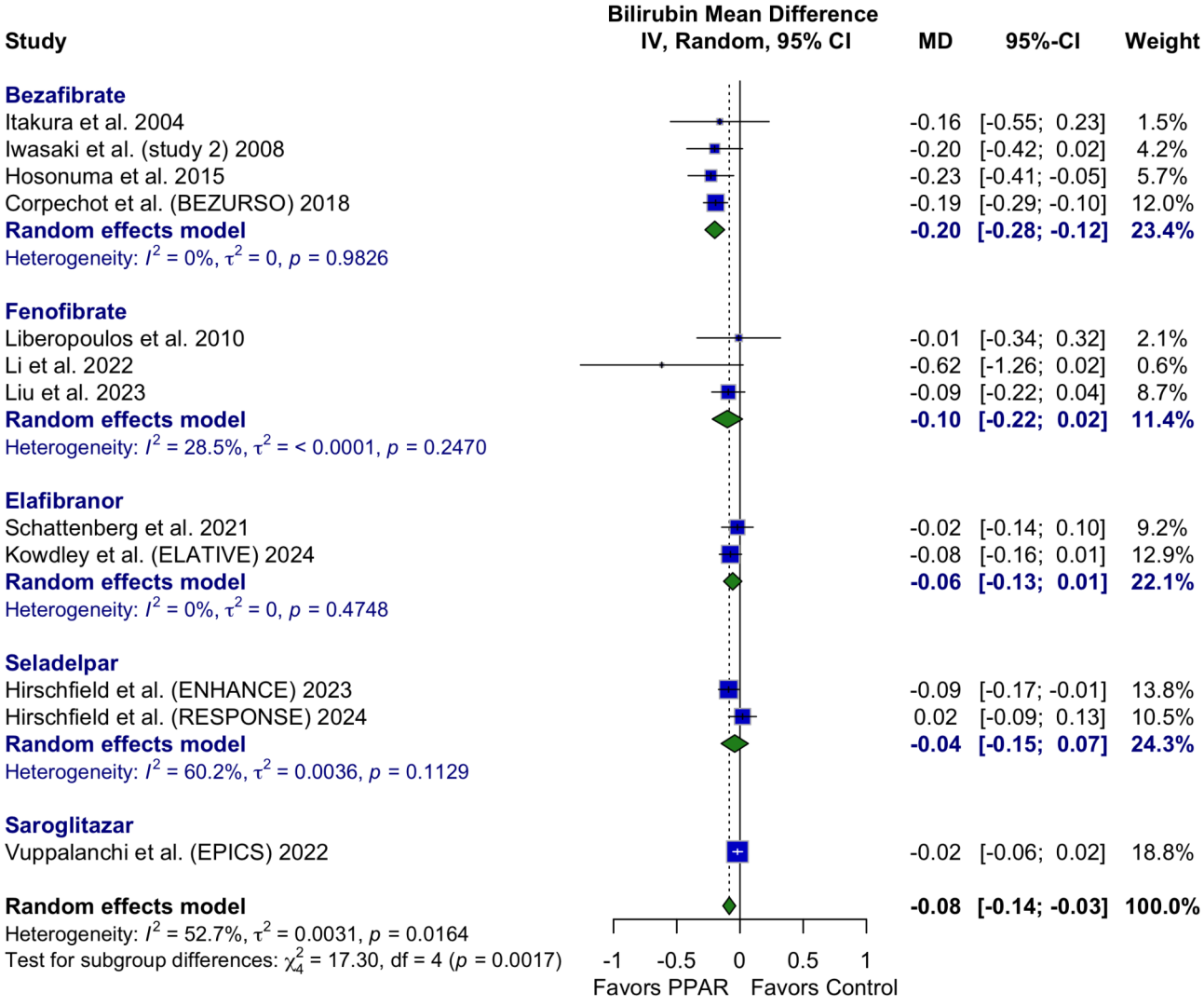

Fig. 5 Forest Plot of Mean Difference in Total bilirubin Levels in Groups of UDCA + PPAR Agonist Recipients vs. UDCA Alone Recipients

Quality of life and adverse events

Various tools were utilized in studies to evaluate pruritus in PBC patients. The visual analog scale (VAS) [42] appeared in four studies [32, 33, 37, 39], the PBC-40 quality of life questionnaire [43] was employed in four studies [15, 37, 39, 41], and the 5 D-itch questionnaire [44] was used in two articles [37, 39]. The numerical rating scale (NRS) [41] and the worst itch NRS (WINRS) [38] were also used to assess pruritus. The findings regarding the changes in pruritus intensity after the treatments were debatable. Some articles [15, 33, 37, 38, 41] showed a significantly greater decrease in pruritus intensity in treatment groups, while some studies [32, 39] did not. The FITCH trial [33] was conducted to specifically evaluate the fibrate's effect on pruritus in patients with PBC and primary sclerosing cholangitis (PSC) following 21 days of treatment. They defined their primary outcome as at least a 50% reduction of the pruritus VAS score. This outcome was achieved in 55% of the bezafibrate-treated PBC patients, compared to 13% in the placebo-treated PBC group (p-value = 0.04).

Treatment-related adverse events (TRAEs) were rare in the included articles. However, some side effects were common in multiple studies. The significant (> 3 x ULN) elevation in creatine phosphokinase (CPK) in a limited number of patients was observed in four studies [30–32, 41]. Myalgia was another muscle-related TRAE in several studies [31, 32, 39, 41]. Additionally, eight articles found a considerable rise in ALT levels [15, 32, 35–39, 41]. Furthermore, a change in renal function as a marked elevation in creatinine or decrease in glomerular filtration rate (GFR) was reported in a few cases in seven studies [31–33, 35, 36, 38, 41]. SAEs included renal dysfunction [31]; aminotransferase elevation [32, 36, 37]; liver morbidity such as jaundice, ascites, and esophageal varices [32, 41]; pruritus aggravation [32, 35]; rhabdomyolysis [32]; and

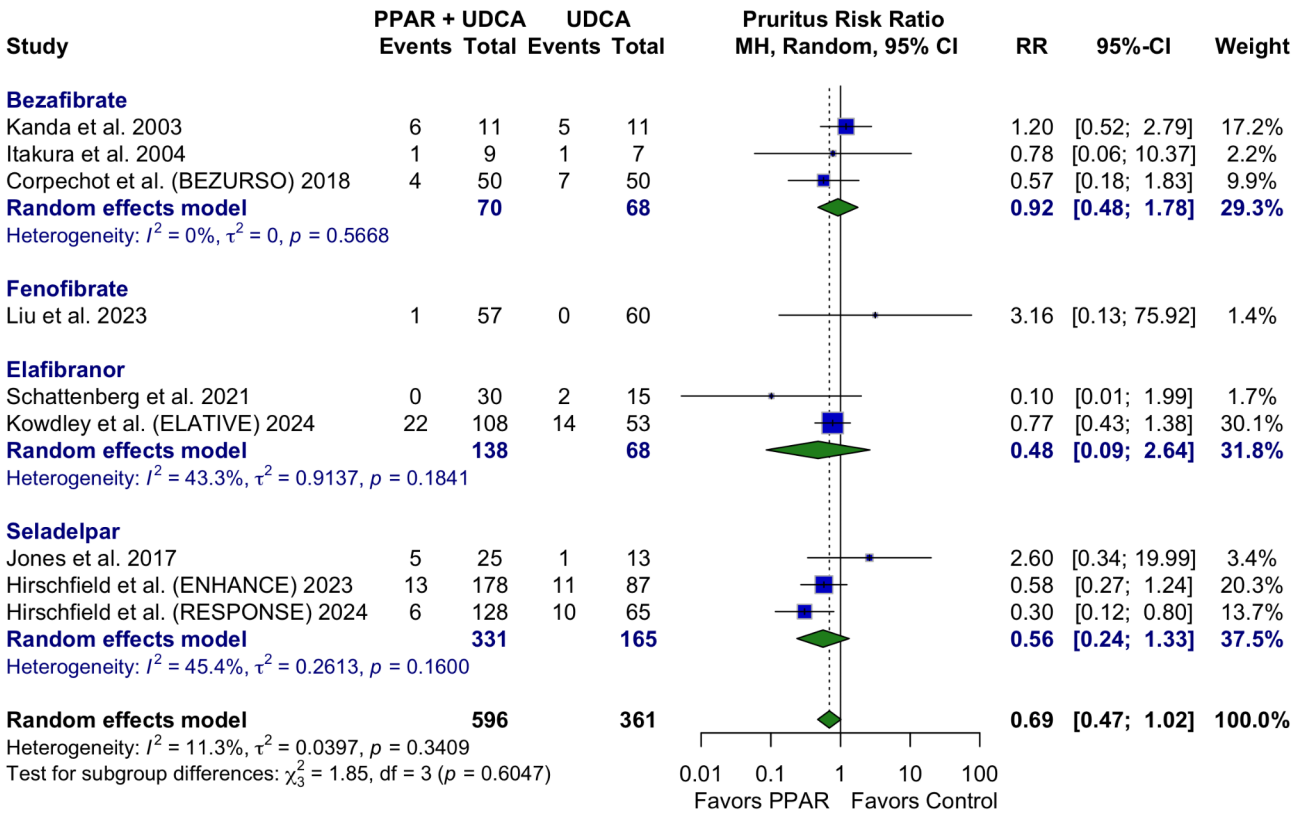

Fig. 6 Forest Plot of Relative Risk of Pruritus in Groups of UDCA + PPAR Agonist Recipients vs. UDCA Alone Recipients

respiratory-related problems [15, 41]. A summary of AEs and SAEs is available in Supplementary Table S3.

Certainty of evidence

Among the eight outcomes assessed for evidence certainty with the GRADE tool, ALP, GGT, Pruritus, and AEs were rated as high quality (Supplementary Table S2). Total Bilirubin, ALT, AST, and SAEs were rated moderate. None of the outcomes had a low quality. ALT and AST had serious inconsistencies because of the high heterogeneity. ALP also showed a high heterogeneity, but since nearly all effect sizes and their CIs were on the same side of the null effect line, the differences were only between small and large treatment effects. As a result, the heterogeneity did not reduce our confidence regarding the benefit of combination therapy with PPAR agonists in reducing ALP levels. Bilirubin had serious publication bias, suggested by its funnel plots and confirmed by Egger's test. (Supplementary Table S15). Moreover, SAEs had serious imprecision risk due to the broad 95% CI and the inability to estimate the absolute effect accurately.

Discussion

We identified studies assessing the effects of combination therapy with PPAR agonists in patients with primary biliary cholangitis (PBC). Our analysis found that add-on therapy with PPAR agonists could significantly enhance the biochemical response, including ALP, serum total bilirubin, ALT, and GGT levels. However, there was no improvement in pruritus and AST levels. Additionally, there was no meaningful difference in the number of adverse events and serious adverse events. We could not analyze the changes in triglyceride (TG), IgM, and cholesterol levels, as some trials did not report the relevant data. However, when evaluating the treatment response to second-line therapies, it is recommended to assess not only the normalization of ALP and total bilirubin levels but also the GLOBE and UK-PBC Risk Scores [45]. Only a few of our included studies reported these scores.

Ursodeoxycholic acid (UDCA) is the first-line medication for PBC. It is a hydrophilic bile acid with choleretic and hepatoprotective effects. UDCA effectively reduces ALP, TBIL, GGT, ALT, AST, and cholesterol [3, 46]. However, only about two-thirds of people with PBC respond to this treatment [5]. Since approximately 40% of patients exhibit an inadequate biochemical response to UDCA, there is a significant need for additional or alternative therapies for UDCA-refractory PBC patients. The FDA approved Obeticholic Acid (OCA) as a second-line therapy, a farnesoid X receptor (FXR) agonist with bile acid transport regulation and anti-inflammatory effects [47, 48]. OCA has been shown to successfully decrease

ALP and bilirubin levels in patients with PBC [49, 50]. However, this drug also has its side effects, including pruritus and elevated low-density- lipoprotein (LDL) levels. More importantly, in patients with advanced cirrhosis, liver injury leading to hepatic decompensation and even liver failure has been reported. Consequently, the FDA restricted its administration [8]. Peroxisome Proliferator-Activated Receptors (PPARs) comprise three isotypes: PPAR-α, PPAR-γ, and PPAR-β/δ, each with distinct tissue distribution and functions related to inflammation, bile acid regulation, liver fibrosis, and metabolism [8, 51]. PPAR-α mitigates acute and chronic inflammation by promoting fatty-acid oxidation, reducing plasma triglycerides, increasing HDL levels, and suppressing pro-inflammatory cytokines [52, 53]. It also regulates bile acid metabolism through four fundamental mechanisms: 1- downregulating CYP7A1 expression to inhibit bile acid production, 2- upregulating BSEP and MRP2 to enhance bile acid secretion, 3- increasing MDR3 expression to reduce bile acid toxicity, and 4- upregulating CYP3A4 to facilitate bile acid detoxification [54–56]. Fibrates, such as Bezafibrate (a weak pan-PPAR ligand) and Fenofibrate, are PPAR- α agonists. Compared to OCA add-on therapy, fibrates show better results in normalizing the ALP levels, whereas OCAs are more effective in reducing transaminase levels [57]. PPAR-γ exerts immunomodulatory and anti-inflammatory effects by suppressing tumor necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β). Saroglitazar is a dual PPAR-α and PPAR-γ activator [58, 59]. The effects of PPAR-β/δ on lipid metabolism are controversial. This nuclear receptor, as well as PPAR-δ, are known to have anti-inflammatory effects. PPAR-δ also plays a role in the regulation and absorption of bile compounds, leading to therapeutical uses such as Seladelpar (a PPAR-δ agonist) and Elafibranor (a PPAR- α /δ agonist) [60], both of which have been recently approved by the FDA as a second-line therapy for patients with PBC [14].

All included studies and subgroups, including Bezafibrate, Fenofibrate, Elafibranor, Seladelpar, and Saroglitazar, demonstrated a significant difference in ALP reduction between UDCA monotherapy and combinational therapy of UDCA + PPAR. This parameter strongly correlates with disease prognosis and the need for a liver transplant and is a crucial element in various treatment response definitions and scores [5, 61–65]. Similar favorable results were observed in other systematic reviews and meta-analyses conducted on the efficacy of fibrates [7, 66–72].

GGT is another biomarker indicating biochemical response to treatment in patients with PBC. The GGT levels showed a significant reduction in patients receiving PPAR agonist and UDCA compared to UDCA alone. Based on subgroup analysis, Bezafibrate, Seladelpar, and Saroglitazar significantly reduced GGT levels. Studies conducted by Rudic et al. and Yin et al. also demonstrate the therapeutic effect of bezafibrate on GGT levels in patients with PBC [71, 73]. However, a meta-analysis of randomized and non-randomized control trials by Guoyun et al. demonstrated a therapeutic benefit of fenofibrate add-on therapy on GGT levels compared to UDCA monotherapy [66]. This finding may be attributed to the longer average treatment duration and differences in baseline GGT levels in the included studies. The therapeutic effect of fenofibrate on GGT levels is also supported by the study conducted by Zhang et al. [70].

Bilirubin reduction is another important indication of biochemical response to treatment [74]. It is also considered a key biomarker in Paris-1 [61], Paris-2 [62], and Rotterdam biochemical response definitions [75], as well as the GLOBE score [64] and UK-PBC risk score [65]. Our meta-analysis indicates that bilirubin concentrations in PPAR + UDCA patients were lower than those receiving UDCA alone. This result remains the same, excluding any of the articles included based on the sensitivity analysis. This favorable outcome is primarily attributable to the Bezafibrate subgroup, demonstrating a significant reduction in bilirubin levels. In contrast, Fenofibrate, Elafibranor, Seladelpar, and Saroglitazar subgroup analyses revealed no meaningful changes. The considerable reduction in total bilirubin levels in patients receiving Bezafibrate compared to other PPAR agonists may be due to its unique pharmacological profile. Bezafibrate targets all three PPAR isoforms (α, δ, and γ), unlike more selective PPAR agonists, such as Fenofibrate (PPAR-α) or Seladelpar (PPAR-δ), providing a broader spectrum of action that possibly enhances bilirubin metabolism. While bezafibrate's broader pharmacological profile offers a mechanistic rationale, further research comparing isoform-specific potencies and standardizing study parameters is needed to elucidate these differences fully. Additionally, the studies evaluating bezafibrate had longer treatment durations, allowing more time for meaningful changes to develop. There was also evidence of publication bias in the analysis of total bilirubin using Egger's tests. The trim-and-fill method indicated no significant difference between the two groups for total bilirubin levels. This suggests that the efficacy of combination therapy in lowering bilirubin levels may have been overestimated due to the underreporting of studies with non-significant results. However, the moderate to high heterogeneity observed among studies warrants a cautious interpretation of the corrected effect estimates from the trim-and-fill method [76, 77]. This substantial between-study heterogeneity could also contribute to funnel plot asymmetry, which might be misinterpreted as publication bias.

Our meta-analysis demonstrated that UDCA combination therapy with PPAR agonists resulted in a significant reduction in ALT levels but did not meaningfully affect AST levels. The only notable change in AST levels was observed in the Saroglitazar subgroup. However, this finding is based on a single study with a limited sample size, as Saroglitazar is a relatively novel treatment. Studies by Yin et al. and Zhang et al. also reported significant changes in ALT levels but not in AST [67, 71]. The systematic review and meta-analysis by Yin et al. focused exclusively on bezafibrate and included not only RCTs but also self-controlled trials. Similarly, Zhang et al. conducted a meta-analysis examining the effects of bezafibrate and fenofibrate on liver biochemical parameters in patients with PBC. This could be attributed to the fact that while AST is present in the liver, as well as in cardiac and skeletal muscle and erythrocytes, ALT is predominantly liver-specific. As such, ALT is considered a more specific marker for liver damage, supporting the notion that ALT is more sensitive to these therapies than AST in patients with PBC [78]. Subgroup analysis based on study design (double-blind vs. open-label) revealed that the significant changes in ALT were primarily supported by double-blind studies.

The common-effect meta-analysis suggested that using fibrates could help with pruritus in patients with PBC, although this finding was not confirmed by using the random-effects meta-analysis. We performed a common-effect meta-analysis due to the low observed heterogeneity. Moreover, the subgroup analysis of double-blind studies confirmed the beneficial effect of combination therapy for pruritus. A sensitivity analysis, excluding the second-most heterogeneous study by Kanda et al., also confirmed the meaningful effect of PPAR agonist combination therapy on pruritus. Kanda et al. reported the prevalence of pruritus at the beginning of the trial and the number of patients whose pruritus was resolved by the end [9]. However, other trials documented the incidence of pruritus among the participants throughout the trial. Additionally, the pruritus assessment tools and their threshold definition varied between studies. Shen et al. conducted a systematic review and meta-analysis focusing on PBC-induced pruritus, concluding that fibrates could improve PBC-associated pruritus [79].

Serious adverse events following PPAR-agonist use mainly include an increase in hepatic enzymes and creatinine levels. Some also reported respiratory-related problems [15, 41]. However, according to our study, this medication is still safe under monitoring. Other reviews on this subject support this conclusion [67, 68]. The systematic review and meta-analysis conducted by Carrion et al. also revealed the safety of fibrate use in patients with PBC [80]. Nevertheless, this finding does not align well with observations from daily clinical practice. This discrepancy may be attributed to differences between controlled clinical trial settings and broader clinical practice, such as the shorter duration or smaller sample sizes of clinical trials.

Strengths and limitations

To our knowledge, this study is the first systematic review and meta-analysis evaluating fibrate and non-fibrate PPAR agonists as an add-on therapy to UDCA. We faced some limitations during this study. First, only some relevant data regarding the outcomes we would consider to analyze could be obtained. Second, trials reported their outcomes in different statistical effect estimates, like changes from baseline or final values. Third, we encountered a wide between-study heterogeneity, including the treatment or follow-up durations, dosage variations, the UDCA-response status before the trial, and the study designs. There was variability in patient exposure and response to UDCA across the included trials. Specifically, some studies included patients who were resistant to UDCA, others who had responded to it, and some who had no prior exposure to UDCA. Fourth, there were limited RCTs in the Seladelpar, Elafibranor, and Saroglitazar subgroups. Lastly, most of the included studies in the Bezafibrate and Fenofibrate groups were unblinded. These limitations highlight the need for further research on newer PPAR agonist subtypes and the importance of conducting blinded trials on Bezafibrate and Fenofibrate.

Conclusion

In conclusion, our study demonstrates the efficacy of combining UDCA with PPAR agonists in reducing ALP, Bilirubin, and GGT levels, crucial markers for effective treatment in PBC patients. Importantly, we found no significant increase in adverse events compared to UDCA alone. Future investigations should prioritize non-fibrate PPAR agonists, examining optimal dosing and treatment duration. Including patients with advanced liver disease in these studies could further clarify treatment efficacy.

Abbreviations

PBC	Primary Biliary Cholangitis
UDCA	Ursodeoxycholic Acid
PPAR	Peroxisome Proliferator-Activated Receptor
ALP	Alkaline Phosphatase
GGT	Gamma-Glutamyl Transferase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
TBIL	Total Bilirubin
PSC	Primary Sclerosing Cholangitis
CI	Confidence Interval
MD	Mean Difference
RR	Risk Ratio
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
DTA	Diagnostic Test Accuracy
RoB2	Cochrane Risk of Bias Assessment Tool for Randomized Trials Version 2

GRADE	Grading of Recommendations Assessment, Development, and Evaluation
SE	Standard Error
SROC	Summary Receiver Operating Characteristic
LS Mean	Least-Squares Mean
SAE	Serious Adverse Event
TRAEs	Treatment-Related Adverse Events
VAS	Visual Analog Scale
NRS	Numerical Rating Scale
WINRS	Worst Itch Numerical Rating Scale
FDA	Food and Drug Administration
ELF	Enhanced Liver Fibrosis
FXR	Farnesoid X Receptor
IQR	Interquartile Range
REML	Restricted Maximum Likelihood
IgM	Immunoglobulin M

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03821-2.

Supplementary Material 1

Author contributions

Study concept and design: BS. and NB. Data acquisition: TB., FOS., and SMP. Data analysis and interpretation: BS and NB. Drafting of the manuscript: BS., NB., TB., FOS., and SMP; critical revision of the manuscript for important intellectual content: BS. and NB.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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