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Primary Sclerosing Cholangitis Recurrence After Liver Transplantation: A Systematic Review and Updated Meta-Analysis

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ABSTRACT

Background and Aims: Primary sclerosing cholangitis (PSC) is an immune-mediated cholestatic liver disease. Liver transplantation (LT) remains the only definitive treatment for patients with advanced disease. However, recurrence of PSC (rPSC) after LT is still a significant clinical challenge. The aim of this study was to assess the prevalence and incidence of rPSC following transplantation and to identify factors associated with its occurrence.

Methods: We conducted a systematic review and meta-analysis of observational cohorts by searching PubMed, Embase and Cochrane for studies. Statistical analyses were conducted using R, applying a random-effects model with 95% confidence intervals.

Results: Twenty-nine studies were included, comprising 4682 patients who underwent LT for PSC (63.7% male). Most data originated from Europe (51.7%) and North America (29.2%), with additional cohorts from Asia (13.7%), South America (2.8%) and Oceania (2.6%). The worldwide pooled prevalence of rPSC was 18.66% (95% CI 15.33–22.52; $I^2 = 84\%$) between 1980 and 2024. As for the worldwide pooled incidence, rPSC occurred at 26.04 per 1000 person-years (95% CI 19.30–32.78; $I^2 = 76.1\%$). The continent with the highest rPSC prevalence was Oceania with 30.65% (95% CI 23.17–39.29; $I^2 = 13.8\%$) and South America had the highest incidence with 39.97 per 1000 person-years (95% CI 25.42–54.51). Younger recipient age (mean difference [MD] = 5.16 years, 95%

Abbreviations: AASLD, American Association for the Study of the Liver Diseases; CI, confidence interval; CMV, cytomegalovirus; DDLT, deceased donor liver transplantation; EASL, European Association for the Study of the Liver Diseases; GLMM, generalized linear mixed model; GRADE, grading of recommendations, assessment, development and evaluations; HLA, human leukocyte antigen; HR, hazard ratio; IBD, inflammatory bowel disease; ITBL, ischaemic-type biliary lesions; LDLT, living donor liver transplantation; LT, liver transplantation; MD, mean difference; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; MRCP, magnetic resonance cholangiography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSC, primary sclerosing cholangitis; REML, restricted maximum likelihood; ROBINS-I, risk of bias in non-randomized studies of interventions; rPSC, recurrent primary sclerosing cholangitis; RR, risk ratio.

CI 4.13–6.19; $I^2 = 51.3\%$), male sex (risk ratio [RR] = 0.92, 95% CI 0.87–0.98; $I^2 = 0\%$), post-LT cyclosporine use (RR = 0.56, 95% CI 0.42–0.76; $I^2 = 0\%$), acute rejection (RR = 0.64, 95% CI 0.49–0.83) and de novo IBD (RR = 0.63, 95% CI 0.40–0.99; $I^2 = 0\%$) were associated with an increased risk of recurrence.

Conclusions: Prevalence and incidence of rPSC post-LT varied according to continents. Younger recipient age, male sex, de novo IBD, cyclosporine use post-LT and acute rejection episodes were associated with a higher risk of recurrence.

Trial Registration: PROSPERO ID: CRD420250645485

Lay Summary

Primary sclerosing cholangitis (PSC) is a chronic liver disease that damages the bile ducts and can eventually lead to liver failure. For patients with advanced disease, liver transplantation is currently the only curative treatment. However, PSC can return after transplantation, which may affect long-term outcomes. We analysed data from 29 studies including 4682 patients who received a liver transplant for PSC to determine how often the disease recurs and which factors may increase this risk. Overall, PSC recurred in about 19% of patients worldwide. Recurrence was more common in younger patients, men, those who developed inflammatory bowel disease after transplantation, those treated with cyclosporine and those who experienced episodes of acute rejection.

1 | Introduction

Primary sclerosing cholangitis (PSC) is a rare, chronic, cholestatic liver disease characterized by progressive fibroinflammatory injury to the intrahepatic and extrahepatic bile ducts, likely driven by immune-mediated mechanisms [1, 2]. It is strongly associated with inflammatory bowel disease (IBD), particularly ulcerative colitis, PSC often presents with bile duct strictures that lead to cholestasis, biliary cirrhosis and liver failure [2, 3]. Despite extensive research, no pharmacologic therapy has proven effective in altering disease progression [1, 4]. Liver transplantation (LT) remains the only curative treatment, indicated for advanced liver disease or severe complications such as recurrent cholangitis, intractable pruritus or selected cases of cholangiocarcinoma [5, 6].

Although post-transplant outcomes are generally favourable, recurrent PSC (rPSC) affects approximately 20%–25% of patients, usually within 5–10 years following LT [7]. Diagnosing rPSC can be challenging due to its non-specific presentation and overlap with other post-transplant biliary complications. According to the Mayo Clinic criteria, rPSC requires a confirmed PSC diagnosis prior to LT and the presence of non-anastomotic biliary strictures or characteristic histological features, such as fibrous cholangitis or fibro-obliterative lesions, appearing more than 90 days post-transplant, with exclusion of other causes like ABO incompatibility, cytomegalovirus infection and hepatic artery thrombosis [8].

Recurrent PSC is associated with substantial morbidity and mortality, and may require retransplantation, further straining the limited organ supply [9, 10]. Several factors have been investigated as potential contributors to recurrence, including IBD, colon retention after LT and acute cellular rejection [11–13]. Identifying these risk factors could help improve post-transplant care [12]. However, study findings remain inconsistent, limiting risk stratification and preventive strategies. No pharmacologic therapy has been proven effective in preventing recurrence or altering its progression [9], emphasizing the need for a clearer risk profile before proceeding with LT.

A previous meta-analysis [14] synthesized early evidence on rPSC risk factors, but additional cohort studies have emerged in recent years. We therefore conducted an updated systematic review and meta-analysis to refine current evidence, clarify incidence and prevalence rates globally and identify the most relevant predictors of rPSC, aiming to support clinical decision-making and optimize long-term outcomes.

2 | Methods

2.1 | Search Strategy and Study Selection

Our systematic review and meta-analysis was performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of Interventions [15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [16]. The meta-analysis protocol was registered on PROSPERO.

We systematically searched PubMed (MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to January 31, 2025. To identify newly published eligible studies, an updated search was conducted on December 23, 2025 restricted to publications from 2025. Both searches applied the same predefined eligibility criteria. The search strategy included the terms: 'primary sclerosing cholangitis', 'PSC', 'liver transplant' and 'recurrence'. No search filters or language restrictions were applied. Non-English studies were translated using Google Translate. One author (I.B.S.) removed duplicate references, and two independent reviewers (I.B.S. and I.C.V.) screened titles and abstracts. Full-text reviews were conducted for studies deemed potentially relevant. Reference management was performed using the web application Rayyan [17]. Additionally, we manually reviewed the reference lists of all included studies and relevant systematic reviews or meta-analyses to identify any additional eligible studies. Disagreements were resolved by consensus between the authors. We included studies that met all of the following criteria: (1) enrollment of patients diagnosed with PSC who underwent orthotopic LT; (2) reporting of at least one outcome of interest; (3) classification as either randomized or observational studies; and (4) no restrictions on follow-up duration. rPSC was defined by the Mayo criteria [8],

which is determined by: (1) confirmed diagnosis of PSC before LT; (2) endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiography (MRCP) showing intrahepatic and/or extrahepatic biliary strictures, beading and irregularities at least > 90 days after LT; and histological findings of fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis or biliary cirrhosis on liver biopsy or explant histology at time of transplant; exclusion criteria included the presence of other causes of biliary stricturing such as hepatic artery thrombosis/stenosis, chronic ductopenic rejection, ABO blood type incompatibility and anastomotic bile duct strictures related to surgical reconstruction. While the definition of recurrence varied slightly among the included studies, we accepted descriptions that aligned with the primary outcome, including clinical, endoscopic, MRCP or histological, as defined by each study. rPSC definitions are detailed in Table S1. We excluded studies with overlapping populations, as well as case reports, case series, systematic reviews, meta-analyses and conference abstracts. To minimize the risk of overlapping populations, studies conducted with patient populations from the same period and within the same health institutions were excluded. When these factors could not be precisely determined, geographic location was used as a broader criterion to assess the potential for overlapping populations. In instances where overlap was identified or suspected, we kept the study with the largest or most comprehensive cohort and excluded smaller or partially overlapping reports to avoid double-counting participants. There were no restrictions concerning the date or language of publication. Further details of the search strategy and the reasons for exclusion after full-text review are provided in Data S1 and S2.

2.2 | Data Extraction

Three authors (M.R.T., I.C.V. and M.A.B.C.L.) independently extracted baseline data into a structured spreadsheet, which included the following variables: study title, journal, publication year, first author, study design, geographic region, duration of follow-up, number of patients, patient age and sex, presence and duration of IBD prior to LT, Model for End-Stage Liver Disease (MELD) score at the time of transplantation, median follow-up time, recurrence rate of PSC, median time to recurrence and number of patients requiring retransplantation due to recurrence. The same authors also extracted outcomes data into a second spreadsheet, which captured information across five outcomes domains: prevalence and incidence, patient/donor characteristics, clinical factors, pharmacological factors and operative variables.

2.3 | Endpoints

The outcomes of interest for this study were prevalence and incidence rates of recurrence of PSC following LT with subgroup analysis by: (1) continent and (2) histologic-diagnosed studies. Risk factors associated with rPSC were analysed in terms of risk ratio (RR) and grouped into four domains. Patient and donor factors included: (1) mean age and sex; (2) donor-recipient gender match; and (3) whether the donor was living (LDLT) or deceased (DDLT). Clinical factors included: (1) the presence of IBD prior to transplantation; (2) de novo IBD post-LT; (3) Cytomegalovirus (CMV) positive status of the recipient; (4) acute rejection following transplantation (one or more episodes); (5) colectomy performed before or during transplantation; and (6) the MELD score prior to transplantation. Pharmacological factors considered were: (1) the use of cyclosporine or (2) tacrolimus or (3) mycophenolate mofetil (MMF) as immunosuppressive therapy post-LT. Operative factors included: (1) mean cold ischaemia time; (2) mean warm ischaemia time; and (3) the performance of hepaticojejunostomy. Additionally, where data were available, hazard ratios (HR) were analysed for all endpoints. Acute rejection definition is detailed in Table S2.

2.4 | Quality Assessment

The risk of non-randomized studies was assessed using version 1 of the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [18], which assesses bias across the following seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. A traffic light plot of bias assessment was generated for both tools. Four reviewers (M.R.T., W.F.O.A., I.B.S. and M.A.B.C.L.) independently conducted the quality assessment of the included studies in pairs, with each study being assessed by two reviewers. Disagreements regarding the overall risk of bias were addressed by a fifth reviewer (I.C.V.) who completed a full ROBINS-I assessment for those studies. For domain-level assessments where disagreement was not formally resolved, the more conservative (higher risk) rating was used to avoid underestimation of bias. Final judgements reflect consensus or the resolved opinion. The quality of evidence for the primary outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [19] that evaluates the certainty of evidence based on risk of bias, inconsistency, indirectness, imprecision and publication bias, with additional domains for upgrading evidence in non-randomized studies including large magnitude of effect, dose–response relationship, and residual confounding. To estimate absolute effects, we selected three plausible baseline risks (10%, 25% and 40%) informed by a range of recurrence rates observed in observational studies and reported in clinical guidelines. These were applied to convert hazard ratios into absolute risk differences using GRADE. In addition, we constructed funnel plots to assess the presence of potential publication bias across the included studies.

2.5 | Statistical Analysis

Pooled prevalence estimates were calculated using a generalized linear mixed model (GLMM) for proportions. Incidence rates were pooled using a random-effects inverse-variance model. Study-specific incidence rates were calculated as the number of events divided by the accumulated person-years of follow-up and expressed as events per 1000 person-years. Between-study variance (τ^2) was estimated using the restricted maximum likelihood (REML) method. Statistical heterogeneity was assessed using Cochran's Q test, the I^2 statistic and the between-study variance (τ^2). Binary outcomes were analysed

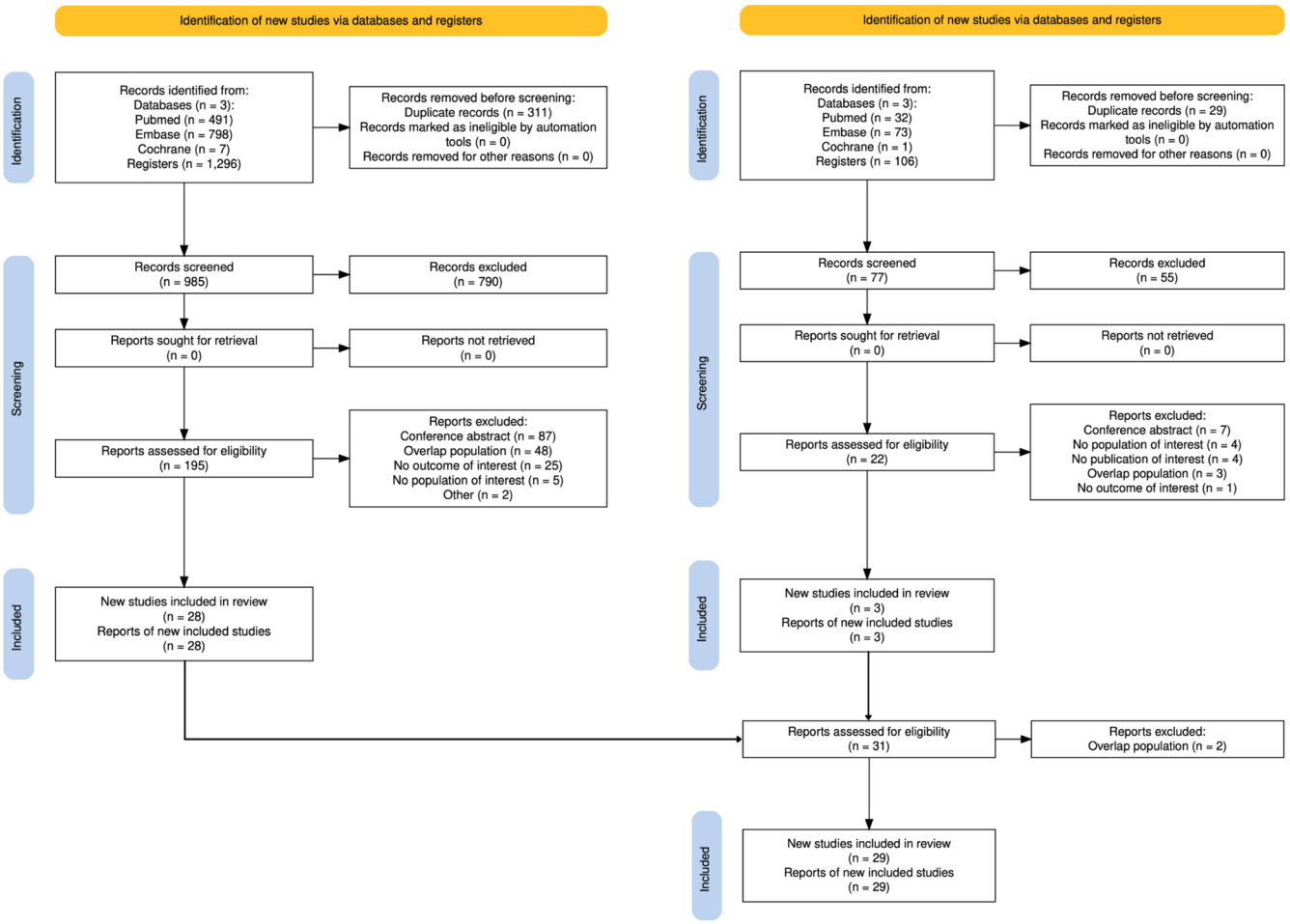

FIGURE 1 | PRISMA 2020 flow diagram of study selection. The diagram reflects results from the initial search (January 2025) and an updated search restricted to 2025 publications (December 2025).

using RR with 95% confidence intervals (CI) calculated using the Mantel–Haenszel method. Continuous outcomes were pooled using mean differences (MDs) with 95% CI, while HR were pooled using the inverse-variance method. In accordance with Cochrane guidelines, random-effects models were applied for all meta-analyses. Geographic distributions of pooled prevalence and incidence were visualized using world maps after aggregating study-level estimates at the country level. Countries without available data were displayed using neutral shading, and continuous colour gradients were used to represent the magnitude of prevalence (%) and incidence (per 1000 person-years). To explore potential sources of heterogeneity, random-effects meta-regression analyses were performed using year of publication as a continuous moderator. All statistical analyses were conducted using R software (version 4.2.1, R Foundation for Statistical Computing) and Review Manager Web (Cochrane Collaboration, Denmark).

3 | Results

3.1 | Study Selection and Baseline Characteristics

Our initial literature search yielded a total of 1296 studies, from which 311 duplicates were manually removed prior to screening. Following title and abstract screening, 790 articles were excluded. Full-text assessment was conducted for the remaining 195 studies, resulting in the inclusion of 28 articles from the initial search. An updated search restricted to 2025 publications identified an additional 106 records, of which 29 duplicates were removed. Following screening of 77 records and full-text assessment of 22 reports, 3 additional studies were included. To prevent double-counting of patients, studies originating from the same institutions and covering overlapping time periods were excluded from the quantitative synthesis, specifically, Cholongitas et al., 2008 [20]; Egawa et al., 2011 [21]; Ravikumar et al., 2015 [22]; Lindström et al., 2018 [23]; Visseren et al., 2022 [24]; and Mouchli et al., 2024 [25]. A total of 29 studies [26–54] were ultimately included in the systematic review and meta-analysis, as patient data from these excluded reports were captured within larger multicentre cohorts (e.g., Akamatsu et al., 2021 [26]; Coelho-Prabhu et al., 2026 [34]; Veyre et al., 2025 [51]; and Visseren et al., 2021 [52]). The study selection process is illustrated in Figure 1. Table S3 further summarizes the assessment of potentially overlapping populations, specifying which studies were included or excluded to ensure cohort independence.

A total of 4682 patients were included across all studies, all of which were retrospective cohort analyses. Among these patients, 2982 (63.7%) were male and the majority of data originated from Europe (51.7%) and North America (29.2%), with additional cohorts reported from Asia (13.7%), South America

(2.8%) and Oceania (2.6%). The rate of retransplantation due to rPSC across these studies was 16.7%. Detailed study characteristics are presented in Table 1.

A world map to illustrate the prevalence and incidence of rPSC after LT per country is exhibited in Figure 2A,B, respectively. The figures show lower prevalence and incidence of rPSC in the United Kingdom. A higher prevalence is seen in Mexico, Canada, Germany, Australia and Japan, with the latter also showing higher incidence, along with Brazil.

3.2 | Prevalence and Incidence of rPSC

A pooled analysis of 29 studies [26–54] comprising 4682 patients showed a recurrence prevalence of 18.66% (95% CI 15.33–22.52; $I^2 = 84\%$). In a subgroup analysis by continent, studies conducted in Asia demonstrated a recurrence prevalence of 17.30% (95% CI 11.72–24.79; $I^2 = 75.7\%$), in Europe of 19.09% (95% CI 13.92–25.61; $I^2 = 83\%$), in North America of 17.83% (95% CI 12.84–24.23; $I^2 = 84.4\%$), in Oceania of 30.65% (95% CI 23.17–39.29; $I^2 = 13.8\%$) and in South America of 18.18% (95% CI 6.71–40.70; $I^2 = 83.7\%$) (Figure 3A).

A pooled analysis of 14 studies [26, 28, 30, 32, 34, 35, 41, 43, 45–47, 49, 51, 54] demonstrated a rPSC incidence of 26.04 per 1000 person-years (95% CI 19.30–32.78; $I^2 = 76.1\%$). A subgroup analysis by continent was also performed, with Asia evidencing an incidence of 34.35 per 1000 person-years (95% CI 25.00–43.70; $I^2 = 0\%$), Europe of 21.81 per 1000 person-years (95% CI 8.51–35.12; $I^2 = 91.3\%$), North America of 24.04 per 1000 person-years (95% CI 11.92–36.17; $I^2 = 79\%$), Oceania of 28.61 per 1000 person-years (95% CI 0.00–68.27) and South America of 39.97 per 1000 person-years (95% CI 25.42–54.51) (Figure 3B).

When analysing 11 studies [26, 28, 32, 35, 41, 43, 45, 46, 48, 51, 54] with histology as rPSC criteria, the pooled prevalence was 21.20% (95% CI 16.03–27.49; $I^2 = 64\%$) (Figure 3C). Across 10 studies [26, 28, 32, 35, 41, 43, 45, 46, 51, 54], the pooled incidence was 28.44 per 1000 person-years (95% CI 20.17–36.72; $I^2 = 76.3\%$) (Figure 3D).

When restricting the analysis to studies with low to moderate risk of bias, the pooled prevalence [26–29, 31–34, 39, 43, 46, 50–52] of rPSC was 21.17% (95% CI 16.79–26.34; $I^2 = 91.4\%$). Across the included studies [26, 28, 32, 34, 43, 51], the pooled incidence was 33.55 per 1000 person-years (95% CI 29.82–37.28; $I^2 = 0\%$).

3.3 | Variables Associated With Recurrence

3.3.1 | Patient and Donor Factors

Based on 10 studies [26, 28, 30–32, 37, 38, 41, 51, 52] ($n = 2204$) that reported the mean age and standard deviation for both recurrent and non-recurrent PSC groups, our meta-analysis found that patients with rPSC were significantly younger (MD = 5.16 years, 95% CI [4.13, 6.19], $p < 0.001$), with moderate heterogeneity ($\tau^2 = 0.8048$, $I^2 = 51.3\%$) (Figure 4A). Furthermore, an analysis of six studies [26, 31, 38, 41, 51, 52] ($n = 1890$) showed donor age had no statistical impact on PSC recurrence (MD = −1.53 years, 95% CI −6.95 to 3.89, $p = 0.5796$), with high heterogeneity ($\tau^2 = 37.1494$, $I^2 = 96.6\%$) (Figure 4B).

From 11 studies [26, 28, 30–32, 37, 38, 41, 50–52] ($n = 2563$) that reported the sex of patients, our analysis showed male patients had more frequent rPSC (RR = 0.92, 95% CI 0.87–0.98, $p = 0.0056$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 4C). Regarding donor sex, an analysis of five studies [26, 31, 41, 50, 52] ($n = 1832$) also showed a trend favouring male donors, although this was not statistically significant (RR = 0.93, 95% CI 0.79–1.09, $p = 0.3469$), with moderate heterogeneity ($\tau^2 = 0.0186$, $I^2 = 59.1\%$) (Figure 4D).

Similarly, a pooling of four studies [26, 31, 44, 51] ($n = 762$) showed no statistically significant association between donor-recipient gender match and rPSC (RR = 0.90, 95% CI 0.79–1.03, $p = 0.1416$), with moderate heterogeneity ($\tau^2 = 0.0013$, $I^2 = 5.7\%$) (Figure 4E).

Still regarding donor aspects, our pooled analysis demonstrated no significant difference in rPSC based on whether the donor was living (RR = 1.20, 95% CI 0.65–2.21, $p = 0.5521$) (Figure 4F) or deceased (RR = 0.95, 95% CI 0.86–1.05, $p = 0.3148$) (Figure 4G). The analyses were based on six [26, 29–31, 43, 52] ($n = 2029$) and four [26, 29, 43, 52] ($n = 1864$) studies, respectively. Heterogeneity was high for living donors ($\tau^2 = 0.4624$, $I^2 = 88.5\%$) and low for deceased donors ($\tau^2 = 0.0029$, $I^2 = 9.6\%$).

3.3.2 | Clinical Factors

Considering seven studies [26, 30, 32, 38, 44, 50, 51] ($n = 1267$), our meta-analysis found no statistically significant difference in rPSC among patients with or without IBD before LT (RR = 0.93, 95% CI 0.77–1.13, $p = 0.4748$), with moderate heterogeneity ($\tau^2 = 0.0387$, $I^2 = 33.7\%$) (Figure 5A). Differently, three studies [32, 38, 51] ($n = 425$) showed a statistically significant increased rPSC in patients with de novo IBD (RR = 0.63, 95% CI 0.40–0.99, $p = 0.04300$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 5B). Four studies [26, 28, 50, 51] ($n = 1095$) exhibited no statistically significant association between CMV-positive status and rPSC (RR = 0.79, 95% CI 0.59–1.04, $p = 0.0913$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 5C).

On the other hand, based on seven studies [26, 28, 31, 38, 41, 50, 51] ($n = 1386$), our analysis found that patients who experienced acute rejection after LT had more cases of PSC (RR = 0.64, 95% CI 0.49–0.83, $p = 0.011$), with moderate heterogeneity ($\tau^2 = 0.0643$, $I^2 = 56.2\%$) (Figure 5D).

There was no statistical association between colectomy timing, that is, before or during LT, and rPSC (RR = 1.32, 95% CI 0.44–3.98, $p = 0.6169$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 5E), based on a pooling of three studies [37, 38, 50] ($n = 545$).

An analysis of five studies [26, 30, 38, 41, 51] ($n = 786$), observed a lower mean MELD score in the non-recurrent PSC group (MD = 0.25, 95% CI −2.23 to 2.73, $p = 0.8435$), although this difference was not statistically significant. Substantial heterogeneity was observed ($\tau^2 = 3.7826$, $I^2 = 63.8\%$) (Figure 5F).

TABLE 1 | Baseline characteristics.

Studies	Study design	Region	Years	Number of patients	Age (mean, years)	Male sex (%)	Presence of IBD	Duration of IBD before LT (mean, months)	MELD	Median time of follow-up (mean, months)	Recurrence (%)	Retransplant number recurrence patients	Survival rate patient rate, 1year (%)	Survival rate patient rate, 5years (%)	Survival rate patient rate, 10years (%)
Akamatsu 2021 [26]	Multicentre retrospective cohort	Japan	1998–2016	180	35.2 ± 10.6	111 (56%)	70 (36%)	NA	18.2 ± 5.9	83 ± 69	46 (25%)	23	91%	83%	68%
Al-Judaibi 2018 [27]	Single-centre retrospective cohort	Canada	1990–2014	80	43.3 ± 13.4	53 (66%)	54 (76.5%)	NA	NA	NA	16 (20%)	NA	NA	NA	NA
Alexander 2008 [28]	Single-centre retrospective cohort	USA	1990–2003	69	48.4 ± 10.1	57 (82.6%)	59 (85.5%)	NA	NA	55.2 ± 36.3	7 (10%)	1	NA	NA	NA
Aravinthan 2016 [29]	Single-centre retrospective cohort	Canada	2000–2015	138	40.6 ± 15.7	92 (66.6%)	111 (80.4%)	NA	17.7 ± 9.9	NA	32 (23%)	NA	NA	NA	NA
Astarcioglu 2018 [30]	Single-centre retrospective cohort	Turkey	2005–2013	11	40.6 ± 11.0	6 (54.5%)	4 (36.4%)	NA	17.5 ± 6.32	103.30 ± 45.74	2 (18.1%)	NA	100%	81.8%	81.8%
Aziz 2025 [31]	Single-centre retrospective cohort	Canada	1985–2019	158	41.8	117 (74.1%)	130 (82.3%)	NA	NA	NA	48 (30.4%)	11	NA	NA	NA
Bittencourt 2024 [32]	Multicentre retrospective cohort	Brazil	1991–2022	96	32 ± 13	58 (60.4%)	62 (64.5%)	67.1 ± 23	23.3 ± 6.8	90.7 ± 23.1	29 (30.2%)	7	NA	NA	NA
Campsen 2008 [33]	Single-centre retrospective cohort	USA	1988–2006	130	NA	100 (77%)	92 (70.7%)	NA	NA	NA	22 (16.9%)	7	NA	84%	NA
Coelho-Prabhu 2026 [34]	Multicentre retrospective cohort	USA	1988–2024	320	38.4 ± 13.8	220 (69%)	320 (100%)	NA	NA	NA	131 (41%)	NA	NA	NA	NA
Damrah 2012 [35]	Single-centre retrospective cohort	UK	1988–2008	91	43.5 ± 14	56 (62%)	56 (62%)	NA	18.4 ± 8.5	84 ± 72	6 (6.6%)	16	84.6%	68.1%	64.8%
Emek 2019 [36]	Single-centre retrospective cohort	Turkey	2013–2017	15	46 ± 13	8 (54%)	15 (100%)	NA	NA	NA	2 (13.3%)	NA	NA	NA	NA
Falco 2024 [37]	Single-centre retrospective cohort	Ireland	1993–2019	112	47.9 ± 1.6	83 (74%)	85 (76%)	NA	NA	NA	23 (20.7%)	10	NA	88.9%	70.5%

(Continues)

TABLE 1 | (Continued)

Studies	Study design	Region	Years	Number of patients	Age (mean, years)	Male sex (%)	Presence of IBD	Duration of IBD before LT (mean, months)	MELD	Median time of follow-up (mean, months)	Recurrence (%)	Retransplant number recurrence patients	Survival rate patient rate, 1year (%)	Survival rate patient rate, 5years (%)	Survival rate patient rate, 10years (%)
Gelley 2014 [38]	Single-centre retrospective cohort	Hungary	1995–2011	25	34.7 ± 11	16 (64%)	19 (76%)	112 ± 100	14.2 ± 5	NA	6 (24%)	2	NA	NA	NA
Goss 1997 [39]	Single-centre retrospective cohort	USA	1984–1996	127	46.1 ± 12.2	87 (69%)	92 (72%)	NA	NA	NA	11 (8.6%)	4	90%	85%	NA
Heffron 2003 [40]	Single-centre retrospective cohort	USA	1987–2001	60	NA	NA	NA	NA	NA	NA	5 (8.3%)	NA	NA	NA	NA
Jadaun 2023 [41]	Single-centre retrospective cohort	India	2006–2021	26	42.5 ± 13.8	19 (73%)	1 (3.8%)	NA	18.96 ± 7.1	78.4 ± 65.8	5 (19.2%)	1	88.5%	73.6%	NA
Jeyarajah 1998 [42]	Single-centre retrospective cohort	USA	1985–1995	100	NA	NA	NA	NA	NA	NA	18 (18%)	5	NA	NA	NA
Kashyap 2009 [43]	Single-centre retrospective cohort	USA	1995–2007	58	43.2 ± 11.1	43 (74.1%)	NA	NA	15 ± 8.3	45.2 ± 28.3	11 (19%)	2	96%	88%	NA
Khettry 2003 [44]	Single-centre retrospective cohort	USA	1983–2000	23	NA	NA	29 (56.8%)	NA	NA	NA	6 (26%)	0	NA	NA	NA
Mogl 2013 [45]	Single-centre retrospective cohort	Germany	1988–2010	71	40.6 ± 11.6	49 (69%)	47 (66%)	NA	NA	142.6 ± 54.8	20 (28.2%)	NA	NA	NA	79%
Peverelle 2020 [46]	Multicentre retrospective cohort	Australia	1992–2018	112	46 ± 10	65 (58%)	61 (54%)	204.4 ± 172.2	21.9 ± 6.2	NA	36 (32%)	4	97%	93%	91%
Rabinovitz 1990 [47]	Single-centre retrospective cohort	USA	1985–1987	38	NA	NA	27 (71%)	NA	NA	26.4 ± 10.6	0 (0%)	NA	NA	NA	NA
Salgado-de la Mora 2025 [48]	Single-centre retrospective cohort	Mexico	2015–2021	10	NA	NA	NA	NA	NA	NA	3 (30%)	NA	NA	NA	NA
Schabl 2024 [49]	Single-centre retrospective cohort	USA	1990–2022	55	42.3 ± 12.5	41 (74.5%)	55 (100%)	NA	19.2 ± 7.1	166.6 ± 95.7	13 (23.6%)	3	98.1%	96.2%	91.7%

(Continues)

TABLE 1 | (Continued)

Studies	Study design	Region	Years	Number of patients	Age (mean, years)	Male sex (%)	Presence of IBD	Duration of IBD before LT (mean, months)	MELD	Median time of follow-up (mean, months)	Recurrence (%)	Retransplant number recurrence patients	Survival rate patient rate, 1year (%)	Survival rate patient rate, 5years (%)	Survival rate patient rate, 10years (%)
Taghavi 2024 [50]	Single-centre retrospective cohort	Iran	2011–2021	408	NA	247 (60.5%)	86 (21%)	NA	NA	NA	49 (12%)	NA	NA	NA	NA
Veyre 2025 [51]	Multicentre retrospective cohort	France	1985–2019	571	42±3.4	389 (68%)	301 (56.7%)	154.7±28.43	14.18±1.45	92.9±67.42	141 (25.9%)	62	NA	NA	NA
Visseren 2021 [52]	Multicentre retrospective cohort	Europe	1980–2015	1549	42.5±5.9	1045 (67.5%)	NA	NA	NA	NA	259 (16.7%)	NA	89%	80%	73%
Wiederkehr 2023 [53]	Multicentre retrospective cohort	Brazil	2011–2021	37	40.6±14.9	20 (54%)	17 (46%)	NA	23±4.22	NA	3 (8.1%)	NA	83.8%	80.6%	NA
Yusoff 2002 [54]	Multicentre retrospective cohort	Australia	1985–1999	12	42	NA	NA	NA	NA	69.9±52	2 (17%)	1	NA	NA	NA

3.3.3 | Pharmacological Factors

With six studies [26, 31, 38, 44, 50, 51] included ($n = 1256$), a significantly higher recurrence rate was seen among patients using cyclosporine post-LT (RR = 0.56, 95% CI 0.42–0.76, $p = 0.0002$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 6A). As for the use of tacrolimus post-LT, the analysis of seven studies [26, 30, 31, 38, 44, 50, 51] ($n = 1268$) showed no statistical significance (RR = 0.99, 95% CI 0.88–1.12, $p = 0.8837$), with substantial heterogeneity ($\tau^2 = 0.013$, $I^2 = 63\%$) (Figure 6B). Similarly, the use of mycophenolate mofetil (MMF), reported in three studies [31, 50, 51], was not associated with rPSC (RR = 1.35, 95% CI 0.41–4.50; $p = 0.62$), although the estimate showed considerable heterogeneity ($\tau^2 = 1.10$, $I^2 = 98.6\%$) (Figure 6C).

3.3.4 | Operative Factors

Considering five studies [28, 31, 38, 41, 51] ($n = 802$), the mean cold-ischaemia time was not meaningfully different between groups (MD = 8.06, 95% CI −27.36 to 43.47, $p = 0.6556$), with high heterogeneity ($\tau^2 = 934.733$, $I^2 = 79\%$) (Figure 7A). Similarly, according to four studies [28, 31, 38, 41] ($n = 243$), no difference in warm ischaemia time was observed (MD = −1.69, 95% CI −8.68 to 5.29, $p = 0.6351$), with low heterogeneity ($\tau^2 = 14.0923$, $I^2 = 26.8\%$) (Figure 7B). Analysing three studies [26, 38, 41] ($n = 231$), hepaticojejunostomy was not associated with recurrence (RR = 1.01, 95% CI 0.91–1.11, $p = 0.9021$), with no heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$) (Figure 7C).

3.4 | Variables Associated With Time-to-Recurrence

Hazard ratio analyses were performed for mean age and sex of patient, donor sex, donor-recipient gender match, presence of IBD prior to LT, acute rejection, cyclosporine use and LDLT to evaluate their association with PSC recurrence following LT. None of the examined factors demonstrated a statistically significant effect, which may be attributable to the limited number of studies providing sufficient data for these analyses. Detailed results are presented in Figures S1–S8.

3.5 | Risk of Bias Assessment

Of the 29 non-randomized studies, 15 studies [30, 35–38, 40–42, 44, 45, 47–49, 53, 54] were judged to have a serious risk of bias, while 14 studies [26–29, 31–34, 39, 43, 46, 50–52] were assessed as having a moderate risk of bias (Figure S9).

Using the GRADE system, the certainty of the evidence was rated as moderate for most outcomes with a MDs or RRs as relative effect (Table S3A) and high for most outcomes with HR as relative effect (Table S3B). Downgrades were most commonly due to serious risk of bias and inconsistency.

As part of the GRADE assessment, we calculated anticipated absolute effects to contextualize the clinical relevance of our findings. Using baseline risks derived from representative

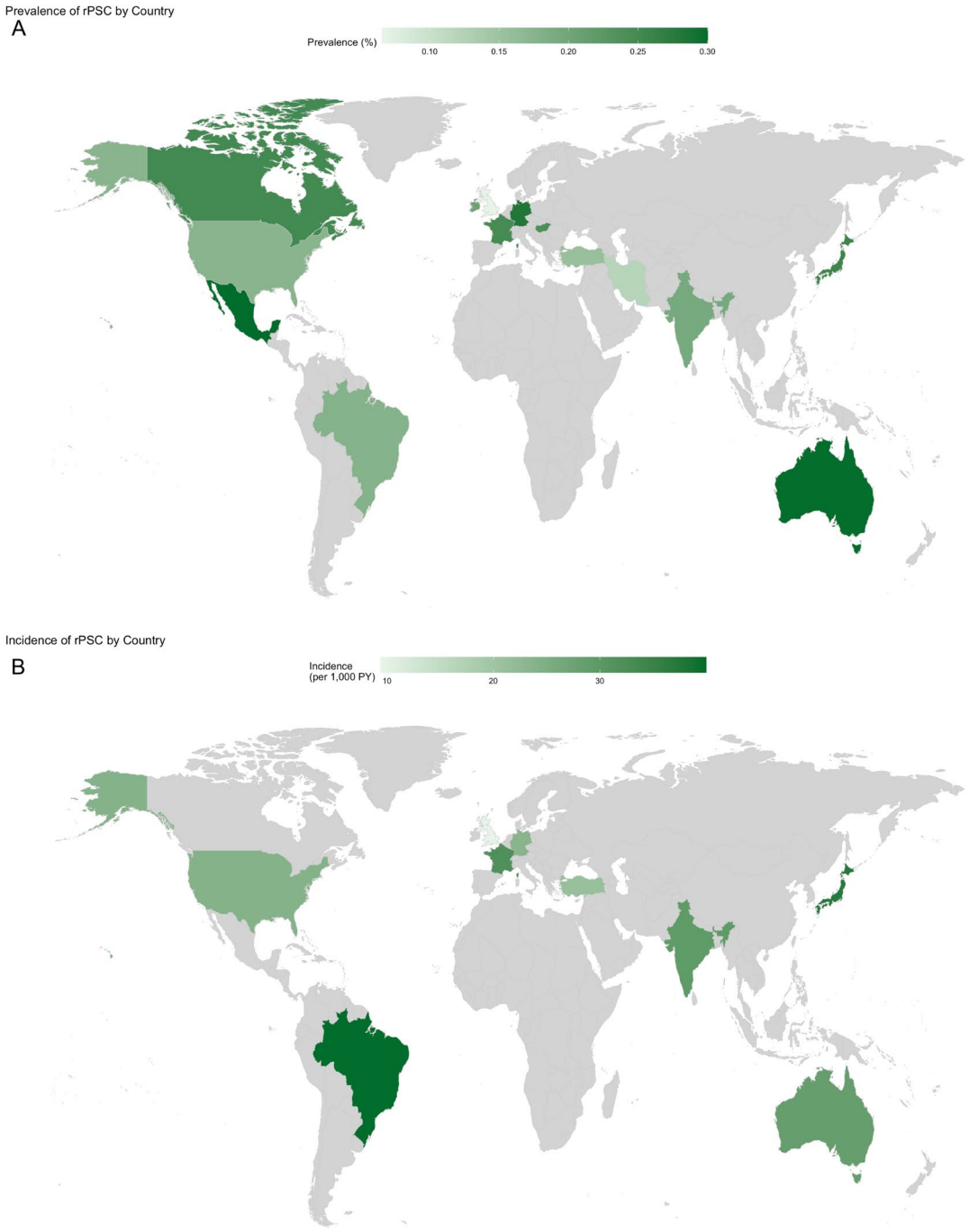

FIGURE 2 | (A) Prevalence of rPSC by country: The geographical heat map presents country-level pooled prevalence estimates, weighted by study size and standardized per percentage (%). (B) Incidence of rPSC by country: The geographical heat map presents country-level pooled incidence estimates, weighted by study size and follow-up duration, and standardized per 1000 person-years.

control groups, we observed that male sex was associated with 56 more recurrences per 1000 patients (95% CI: 91 more to 14 more; moderate-certainty evidence). Non-recurrent patients experienced fewer episodes of acute rejection than recurrent patients, corresponding to 165 fewer events per 1000 (95% CI: 233 fewer to 78 fewer) based on a baseline risk of 458 per 1000 (low-certainty evidence). Similarly, considering cyclosporine use, rPSC resulted in 90 more recurrences per 1000 patients (95% CI: 119 more to 49 more), according to a baseline risk of 205 per 1000 (moderate-certainty evidence).

Further anticipated absolute effects and corresponding certainty ratings are summarized in Tables S4A and S4B.

3.6 | Sensitivity Analysis

Due to variable outcome heterogeneity, we performed a leave-one-out sensitivity analysis. Overall removal of each study from the pooled analysis did not affect the endpoint of rPSC prevalence. For recipient age, removal of Falco et al., 2024

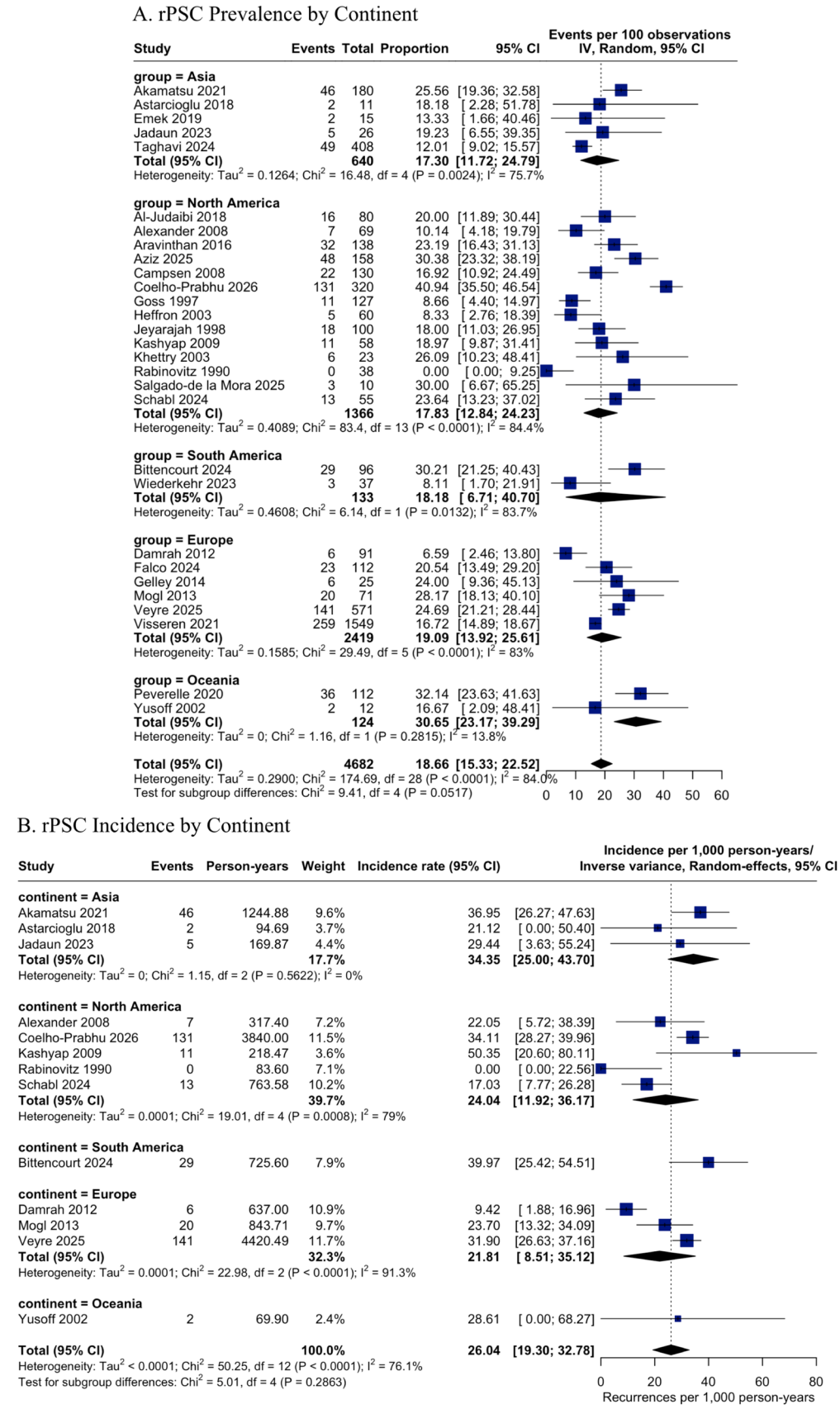

FIGURE 3 | (A) Prevalence of rPSC by continent: Continent-level pooled prevalence estimates of rPSC derived from included studies, weighted by sample size and presented as percentages. (B) Incidence of rPSC by continent: Continent-level pooled incidence estimates of rPSC derived from included studies, weighted by sample size and presented as percentages. (C) Subgroup analyses of rPSC prevalence: Pooled prevalence of rPSC among studies with histologically confirmed diagnosis, weighted by study size and expressed as percentages. (D) Subgroup analyses of rPSC incidence: Pooled incidence of rPSC among studies with histologically confirmed diagnosis, weighted by study size and expressed as percentages.

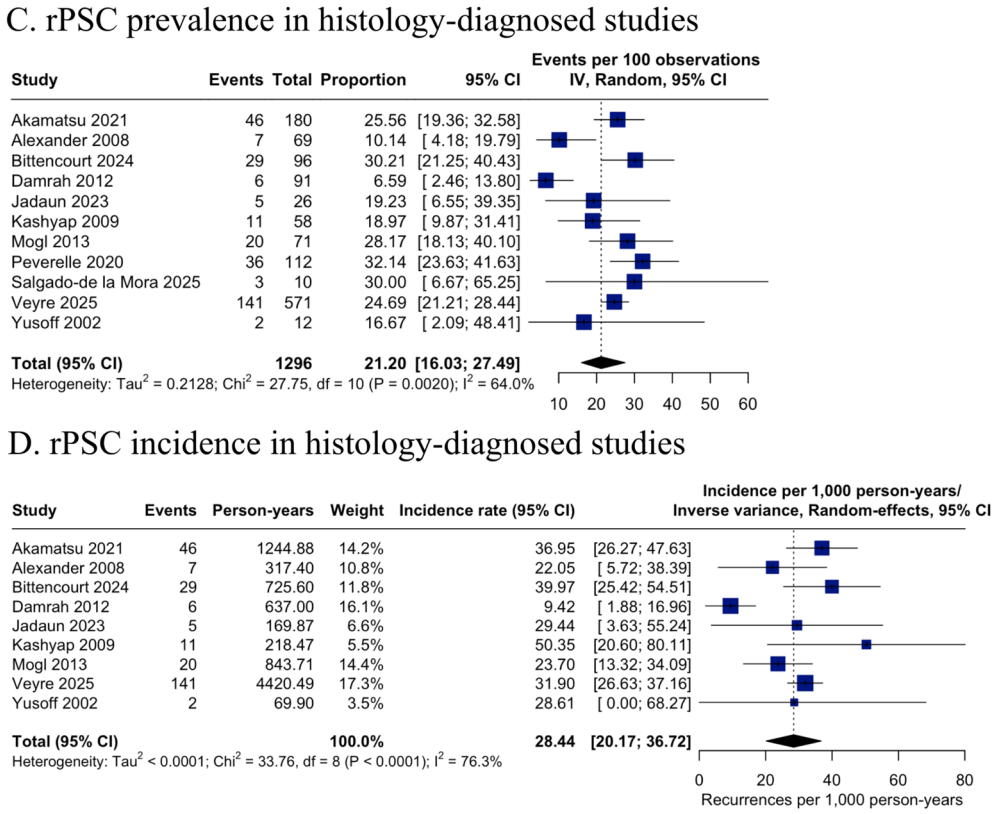

FIGURE 3 | (Continued)

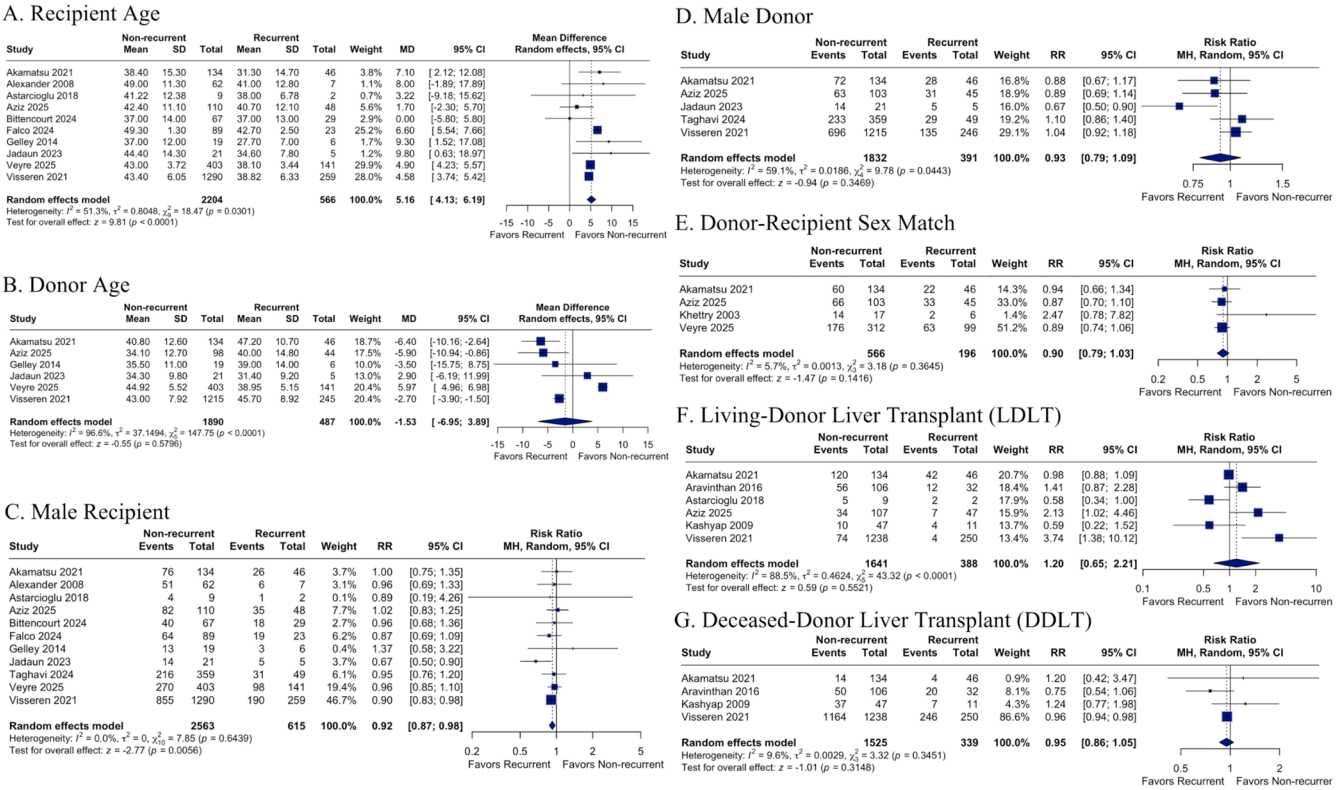

FIGURE 4 | Risk factor analysis for rPSC after liver transplantation: Forest plots showing pooled effect estimates for recipient-related factors (A–C), donor-related factors (D–E) and transplant-related factors (F–G). (A) Recipient age; (B) donor age; (C) male recipient; (D) male donor; (E) donor-recipient sex match; (F) living donor liver transplantation (LDLT); (G) deceased-donor liver transplantation (DDLT). Effect estimates are presented as risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals, calculated using a random-effects model.

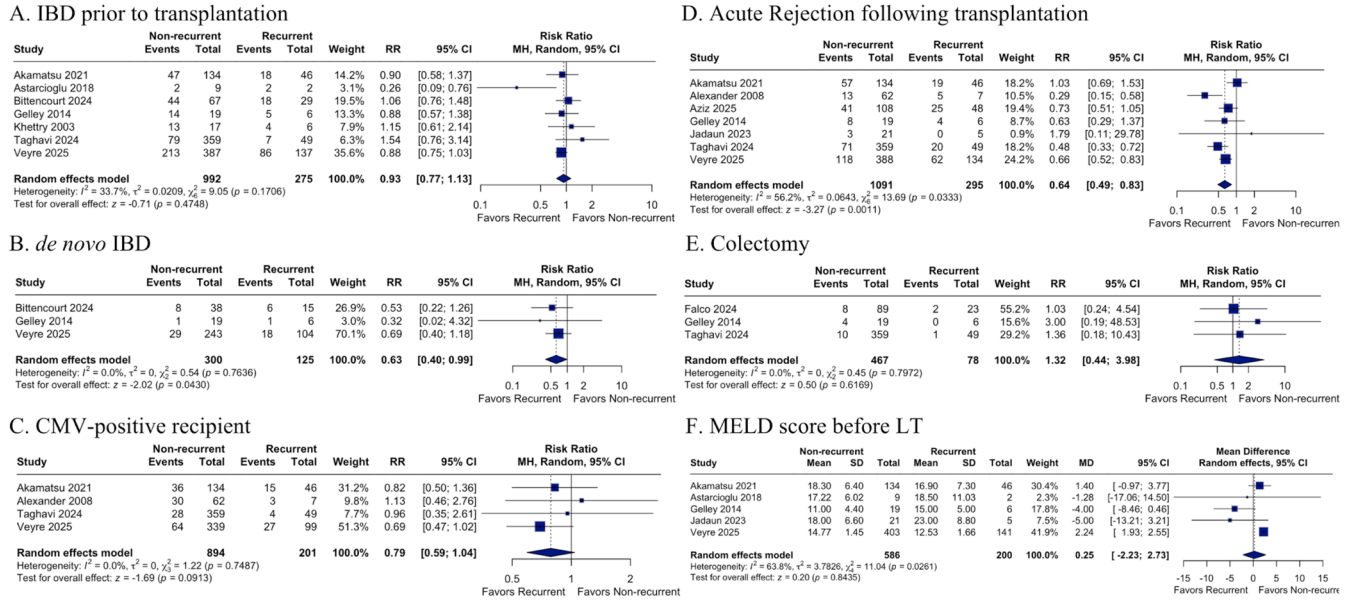

FIGURE 5 | Risk factor analysis for rPSC after liver transplantation: Forest plots showing pooled effect estimates for pre- and post-transplant clinical factors (A–E) and disease severity at transplantation (F). (A) IBD prior to transplantation; (B) de novo IBD after transplantation; (C) CMV-positive recipient; (D) acute rejection following transplantation; (E) colectomy; (F) MELD score before liver transplantation. Effect estimates are presented as risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals, calculated using a random-effects model.

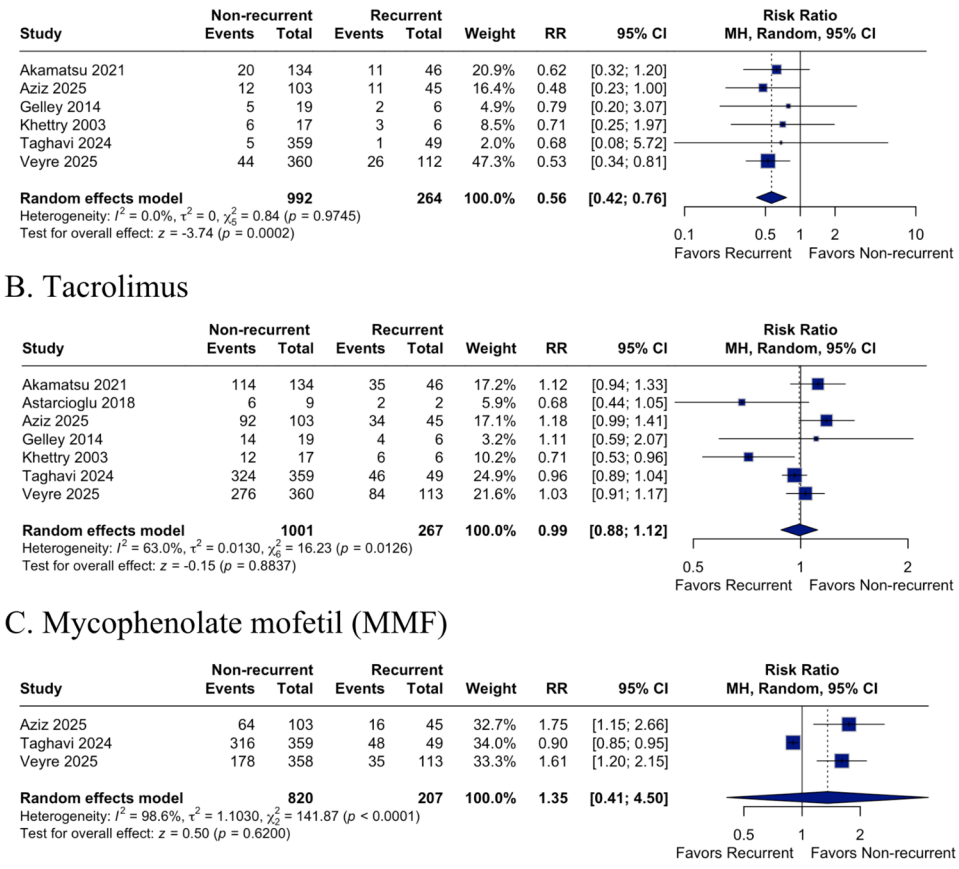

FIGURE 6 | Association between immunosuppressive therapy and rPSC after liver transplantation: Forest plots showing pooled effect estimates for immunosuppressive regimens: (A) cyclosporine; (B) tacrolimus; (C) mycophenolate mofetil (MMF). Effect estimates are reported as risk ratios (RRs) with 95% confidence intervals using a random effects model.

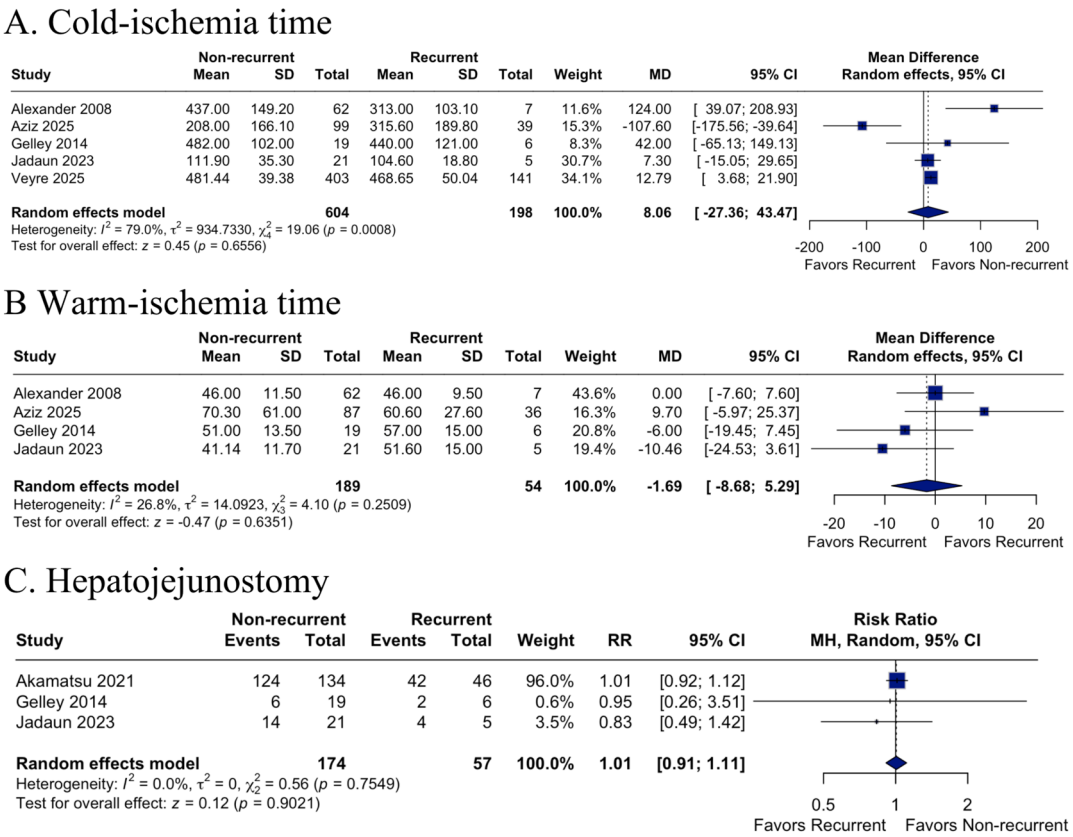

FIGURE 7 | Perioperative factors associated with rPSC after liver transplantation: Forest plots showing pooled effect estimates for perioperative variables. (A) Cold-ischaemia time; (B) warm-ischaemia time; (C) hepaticojejunostomy. Effect estimates are presented as mean differences (MDs) for continuous variables and risk ratios (RRs) for categorical variables, with 95% confidence intervals, calculated using a random-effects model.

[37] led to a decrease in heterogeneity from 51.3% to 10.8% (Figure S10); for donor age, omission of Veyre et al., 2025 [51] reduced I^2 from 96.6% to 36% (Figure S11); for male donor, removal of Jadaun et al., 2023 [41] dropped I^2 from 59.1% to 0% (Figure S13); for LDLT, heterogeneity remained substantial ($I^2 > 75\%$) even upon removal of Visseren et al., 2021 [52]. On the other hand, for presence of IBD, removal of Astarcioglu et al., 2018 [30] led to a decrease in heterogeneity from 33.7% to 0% (Figure S17); for acute rejection, omitting Alexander et al., 2008 [28] reduced heterogeneity from 56.2% to 35.4%; for MELD score, withdrawal of Gelley et al., 2014 [38] reduced I^2 from 63.8% to 17.4% (Figure S22); and for tacrolimus use, removal of Khettry et al., 2003 [44] led to a discrete I^2 reduction from 63% to 53.3%. And for warm and cold-ischaemia time, the omission of Aziz et al., 2025 [31] dropped I^2 from 26.8% to 0% (Figure S27), and from 79% to 57.7% (Figure S28), respectively. Other leave-one-out sensitivity analyses are detailed in the Figures S10–S28.

3.7 | Publication Bias

Publication bias was assessed for patient age and sex, the only outcomes with at least 10 studies included. Visual inspection of the funnel plot, along with Egger's regression test, showed symmetry, and no evidence of small-study effects for both patient age ($t = 0.19$, df = 8, $p = 0.85$) and sex ($t = 0.40$, df = 9, $p = 0.70$), suggesting no evidence of publication bias, although the analysis was limited by the small number of included studies (Figures S29 and S31). Other publication bias analyses are detailed in the Figures S29–S46.

3.8 | Meta-Regression

A meta-regression analysis of the incidence of rPSC demonstrated a statistically significant increase in recurrence incidence over time ($\beta = 0.0007$ per year; 95% CI 0.0001–0.0012; $p = 0.0206$). Year of publication accounted for approximately 45% of between-study heterogeneity, although substantial residual heterogeneity remained ($I^2 = 63.3\%$) (Figure S47).

As for the pharmacological outcomes, and considering we allocated the 'Non-recurrent' group as intervention and the 'recurrent' group as control, a meta-regression for the use of cyclosporine, using year of publication as a moderator suggested a decreasing trend in RRs over time ($\beta = -0.017$ per year; 95% CI −0.037 to 0.002), although this association did not reach statistical significance ($p = 0.067$) and no residual heterogeneity was observed ($I^2 = 0\%$) (Figure S48). This trend indicates progressively lower relative cyclosporine use among non-recurrent patients compared with recurrent patients in more recent studies.

As for tacrolimus, meta-regression suggested an increasing trend in RRs over time ($\beta = +0.017$ per year; 95% CI −0.004 to 0.038), although this association did not reach statistical significance ($p = 0.089$). Year of publication explained

a substantial proportion of between-study heterogeneity ($R^2 = 62.5\%$), with moderate residual heterogeneity remaining ($I^2 = 43.6\%$) (Figure S49). This indicates an increased tendency in more recent publications indicating a reduced contrast between non-recurrent and recurrent patient groups across study years.

4 | Discussion

In this systematic review and meta-analysis, we evaluated commonly reported factors associated with rPSC following liver transplantation. Older recipient age was associated with a decreased risk of rPSC, while male sex, de novo IBD, use of cyclosporine and the occurrence of acute rejection were identified as statistically significant risk factors for rPSC.

Reported rates of rPSC vary widely across studies, ranging from less than 10% to over 50% [55]. According to the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on Sclerosing Cholangitis, the overall prevalence is estimated between 20% and 30% [56], while the American Association for the Study of Liver Diseases (AASLD) reports a range of 10%–37% [1]. Our findings are consistent with these estimates, with a pooled recurrence prevalence of 18.66%. As for incidence, recurrence varies from 8.6% to 47% [57] in reports from different centres. Our analysis found a worldwide incidence rate of 26.04 events per 1000 person-years and, in a meta-regression, year of publication was significantly associated with recurrence incidence. Each additional year was associated with an increase of 0.7 events per 1000 person-years. Publication year explained approximately 45% of between-study heterogeneity, although the absolute magnitude of the increase was modest. This temporal trend likely reflects changes in survival, diagnostic sensitivity, disease definitions and post-treatment surveillance across decades, although substantial residual heterogeneity remained, suggesting that recurrence risk is influenced by additional study and population-level factors beyond calendar time. In light of these findings, subgroup analyses restricted to studies that incorporated histologic evaluation for rPSC diagnosis demonstrated higher prevalence and incidence estimates compared with the overall analysis. These discrepancies raise concern regarding the definition of rPSC, as the absence of a biopsy for confirmation leads to underdiagnosis of recurrence. Upon later diagnosis, patients face an increased risk for fibrotic complications. However, repeated biopsy after LT does not necessarily improve this scenario and may soon be replaced by the implementation of quantitative MRCP, which has the potential to improve the detection and diagnosis of PSC and might be incorporated into clinical protocols over time [58]. Moreover, a second subgroup analysis, restricted to studies classified as low or moderate risk of bias, also yielded slightly higher estimates, suggesting that methodological differences, outcome definitions and reporting practices across studies may also influence reported outcomes.

Furthermore, pooled rPSC prevalence and incidence may be influenced by broader epidemiological factors. Current European data indicate a post-LT rate of 16.7% [52], which likely reflects intercountry variability. For example, Germany has reported a cumulative incidence of 36% at 10 years following LT [59] whereas the United Kingdom reported an incidence of 15% over a comparable follow-up period [31], a pattern of variation also observed in this meta-analysis. In the American continent, Canadian data demonstrate similar findings, with reported rates comparable to the approximately 25% rPSC over a 10-year period described in the literature [31]. In Japan, the frequency of recurrence identified in this meta-analysis exceeded previous published cohort data, which have reported rates of approximately 27% of recurrence [21]. In Latin America, substantial rPSC prevalence and incidence were noted in this study, regarding Mexico and Brazil, respectively. There is limited data for both countries, with Brazilian data reported estimates ranging from 8.1% to 30.2% rPSC [32, 53]. A similar scarcity of data was noted in Oceania, where available values were derived from a small number of studies already included in our analysis [46, 54]. These intercontinental disparities likely reflect heterogeneity in patient demographics, including racial and ethnic composition, healthcare systems, and transplant practices, as well as differences in diagnostic approaches and reporting over time [60, 61]. In particular, historical under-recognition of rPSC and the more recent adoption of advanced imaging modalities (e.g., MRCP) may have influenced case ascertainment across regions [58, 60]. Moreover, variation in the distribution of established risk factors may further contribute to the observed differences and limit the ability to distinguish country-specific effects from broader intercontinental patterns. Accordingly, the available data do not allow definitive attribution of these geographic differences to specific causes.

There is no clear consensus in the literature regarding the factors associated with rPSC. Current clinical practice guidelines do not include age as a determinant of rPSC risk [1, 56]. Nevertheless, this meta-analysis found that older patients had a lower risk of recurrence post-LT, a finding initially reported by Ravikumar et al., 2015 [22], then later confirmed by Lindstrom et al., 2018 [23]. The underlying mechanisms for this association remain uncertain. Immunogenetic factors have been proposed as potential contributors, with earlier onset possibly reflecting a more aggressive disease phenotype [62]. Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimates. The observed heterogeneity was largely driven by a single study that also favoured non-recurrence [37].

Older donor age has been reported as a risk factor for rPSC in a previous meta-analysis [14] and has been hypothesized to contribute to the development of ischaemic-type biliary lesions (ITBL) following LT [63]. However, we did not obtain comparable results. Leave-one-out sensitivity analysis indicated the observed high heterogeneity was primarily driven by Veyre et al., 2025 [51], and its exclusion resulted in older age emerging as a significant risk factor. This suggests the pooled estimate was largely influenced by study-level characteristics rather than reflecting a consistent effect across studies, warranting cautious interpretation of the overall association.

The impact of recipient sex on PSC recurrence also remains controversial. While some studies have reported no significant association between sex and rPSC [64], others have suggested that male patients are less [41, 52] and more [65] likely to experience recurrence. In our analysis, male sex emerged as a factor associated with increased risk of rPSC. Furthermore, the funnel plot

demonstrated a low likelihood of substantial publication bias, strengthening the credibility of this finding.

Calcineurin inhibitors are the cornerstone of immunosuppressive therapy following LT for PSC [56], and their potential role in rPSC has been extensively investigated. In our meta-analysis, cyclosporine exhibited an increased risk for rPSC, contrasting with previous cohorts in which no clear statistical significant benefit was observed [23, 66]. As for tacrolimus, another calcineurin inhibitor, no clear impact in preventing recurrence was seen across three cohorts where it was the first-line immunosuppressant [22, 38, 64]. One study evidenced higher risk with tacrolimus use [23] and another reported it as a significant risk factor for worsening IBD post-LT, which could explain the non-benefit of the medication [67]. An important consideration is the temporal shift in immunosuppressive protocols following LT. Tacrolimus has increasingly been adopted as a first-line agent in recent years, supported by the 2006 Cochrane review demonstrating superior patient and graft survival, as well as improved acute rejection prevention, compared to cyclosporine, more commonly prescribed until the early 2000s [68]. These changes represent a plausible explanation for the temporal patterns observed in the meta-regression analyses. Cyclosporine showed a decreasing relative use among non-recurrent patients in more recent studies, although this trend did not reach statistical significance and was not associated with residual heterogeneity. In contrast, tacrolimus demonstrated an increasing relative use over time, with publication year explaining a substantial proportion of between-study heterogeneity. Together, these findings suggest that temporal changes in prescribing practices [68] have diminished exposure contrasts between recurrent and non-recurrent patients, limiting the ability of pooled analyses to detect true associations. Accordingly, the observed relationship with cyclosporine and the lack of effect for tacrolimus may be driven by calendar-time confounding rather than genuine differences in recurrence risk. Given these elements, randomized controlled trials evaluating the best immunosuppressive strategy after LT for PSC are warranted.

Acute rejection is another established risk factor for rPSC [14, 50] and our findings are consistent with this association. From a mechanistic perspective, it has been hypothesized that rejection may contribute to recurrence either through biliary injury or through shared immunopathogenic pathways underlying both conditions, such as the presence of more reactive lymphocytes in the graft [55]. In our analysis, moderate heterogeneity was observed across studies ($I^2 = 56.2\%$). Sensitivity analysis showed that exclusion of one study reduced heterogeneity to 35.4% without materially altering the pooled estimate, suggesting that the variability was primarily related to differences in effect magnitude rather than direction and supporting the stability of the observed association.

Consistent with previous analyses [14], recipient CMV seropositivity was not associated with an increased risk of rPSC. Similarly, donor/recipient gender matching was also not linked to rPSC.

In accordance with previous a meta-analysis [14], no significant association between pre-LT IBD and the risk of rPSC was observed. In contrast, following known evidence [1, 22], de novo IBD stands as a statistically significant factor for recurrence in this analysis, suggesting that post-LT activity may represent a more relevant risk marker for rPSC [26]. From a mechanistic perspective, the well-established association between PSC and ulcerative colitis, as well as between post-LT colitis and rPSC, has been hypothesized to relate to bacterial endotoxin release from an inflamed colon [20]. Nevertheless, rPSC has also been reported in patients who have undergone colectomy, possibly due to long-lived memory T cells initially activated in the gut, later reactivated in the liver and perpetuating inflammation and disease progression [69]. Although an earlier study suggested a potential protective effect of the intervention [66], our pooled analysis showed that colectomy is not a factor that lowers the risk for rPSC with a $I^2 = 0\%$, highlighting the uniformity of the findings. Additionally, colectomy prior to LT is not standard practice and is generally reserved for IBD patients with either persistent inflammation or high-grade dysplasia [70].

Another factor with uncertain relevance to rPSC in the literature is the pre-transplant MELD score. While previous studies have reported an association between higher MELD scores and increased risk of recurrence [59, 64], our meta-analysis did not identify a significant effect. This finding underscores the limitations of MELD in capturing the complexity of PSC and highlights the need for a PSC-specific prognostic model that more accurately reflects the unique clinical course and recurrence risk in this patient population.

Similarly, the type of donor had no impact on rPSC. The literature has been conflicting on this matter, as higher recurrence has been stated for the LDLT group [21], potentially related to biliary complications, including biliary leak and anastomotic and non-anastomotic strictures [63]. In contrast, other investigators have observed comparable rPSC rates between living and deceased donors [64], whereas a recent meta-analysis reported different results [71]. However, this variation in findings should be interpreted with caution given the difference in the populations included. In addition, neither the type of biliary reconstruction (e.g., hepaticojejunostomy) nor the type of ischaemia had a measurable impact on recurrence.

This study has several limitations. Immunogenetic characteristics of PSC were not explored in this meta-analysis, due to heterogeneous reporting across studies. Consequently, recipient and donor human leukocyte antigen (HLA) classes were excluded, despite well-established genetic associations between PSC and specific alleles such as HLA-B08 and HLA-DRB1*03, *04, *07 and *13:01 [72]. In addition, assessing the impact of a prior diagnosis of cholangiocarcinoma on rPSC could elucidate the role of this factor; however, the included studies did not report sufficient data to enable such analysis. Regarding epidemiology, some prevalence and incidence estimates were derived from a limited number of studies, reflecting the scarcity of region-specific data, with certain geographic areas represented by only a single cohort. Consequently, these estimates may have reduced precision and limited external validity. Additionally, immunosuppressive regimens varied across centres and were incompletely reported. While most studies described the use of calcineurin inhibitors, 26 [26–30, 32–49, 52–54] of 29 [26–54] (90%) did not report detailed information on additional immunosuppressive agents, and only a minority reported specific

adjunctive therapies. Although current evidence does not support a clear role for basiliximab, rituximab, antithymocyte globulin, MMF or mTOR inhibitors in the prevention of rPSC, interpretation remains limited by the heterogeneous and often incomplete reporting of immunosuppressive strategies, including insufficient detail regarding specific agents, combination regimens and treatment modifications over time. These findings should therefore be interpreted cautiously and considered exploratory [1]. Another important consideration is the paediatric population, which was not included in the present analysis. Paediatric recipients were underrepresented in the available literature, with existing evidence primarily derived from retrospective, single-centre cohorts with relatively small sample sizes and shorter follow-up, which limits the precision and robustness of reported recurrence estimates [13, 73, 74]. For example, multicentre cohorts such as the Paediatric PSC Consortium have reported rPSC rates of approximately 10%–30% within 2–5 years after transplantation and identified potential risk factors including younger age at transplantation, IBD, and rejection episodes [75]. However, these findings remain based on comparatively limited datasets. Therefore, given that our analyses predominantly reflect adult populations, and the relative scarcity of paediatric data, extrapolation of these results to paediatric recipients should be undertaken with caution.

Finally, most of the studies included in this meta-analysis reported their findings as RR, hindering assessment of time-to-event outcomes, which would be more informative considering that rPSC usually occurs within the first 5 years post-LT.

Our findings are largely consistent with the current AASLD [1] guideline particularly by placing male recipients and de novo IBD as risk factors and LDLT as not directly associated with recurrence. Acute rejection has been stated as a risk in both AASLD and EASL [56]. However, our analysis sheds light in several key areas. Notably, we found no association between colectomy and rPSC, which provides updated evidence on prior assumptions of its protective role. Furthermore, recipient older age and cyclosporine were also found to be associated with diminished and increased risk of rPSC, respectively—associations not currently acknowledged in either guideline. These findings highlight the need for updated evidence-based recommendations that incorporate emerging data on risk factors for rPSC following liver transplantation.

Although this analysis focused on the prevalence and incidence of rPSC, it is important to acknowledge the potential clinical implications of this endpoint. For instance, recurrence can adversely reduce graft survival, as early rPSC (i.e., within 5 years) leads to graft loss in about 30% of transplanted patients over 15 years, thus needing a second LT [56]. The rate of retransplantation for rPSC has been reported as 12.4% at 10 years [1], which is lower in comparison with our included studies that indicate a 16.7% overall absolute retransplantation rate.

Overall, this meta-analysis synthesized data from a diverse cohort of over 4000 patients across four continents, offering a comprehensive global perspective on rPSC after LT. In order to avoid double counting of patients, single-centre studies originating from institutions later incorporated into larger multicentre cohorts (e.g., Akamatsu et al., 2021 [26]; Coelho-Prabhu et al., 2026 [34]; Veyre et al., 2025 [51]; and Visseren et al., 2021 [52]) were excluded from the quantitative synthesis, as inclusion of overlapping populations would have artificially inflated sample size and biased pooled effect estimates. Notably, eight of the 29 included studies originated from multicentre collaborative initiatives, further strengthening the representativeness of the data. Given the sample size and the overall low to moderate heterogeneity observed across outcomes, it is reasonable to draw inferences regarding the potential impact of both pre- and post-transplant factors on rPSC. These findings may inform future updates to clinical guidelines. Nonetheless, additional large-scale, multicentre studies are needed to generate more robust evidence and support the development of refined clinical approaches and recommendations for managing rPSC.

5 | Conclusion

This meta-analysis demonstrates that older recipient age is associated with a decreased risk of rPSC, whereas male sex, de novo IBD, acute rejection and the use of cyclosporine after LT are associated with a significantly increased risk of recurrence. These findings provide valuable insights that may inform clinical practice and contribute to guideline development in the management of PSC. However, further high-quality, multicentre studies are needed to strengthen the evidence base and support more definitive recommendations for clinical decision-making.

Author Contributions

I.C.V.: conception and design of the work, data acquisition, data analysis, interpretation of data, writing the manuscript. M.R.T.: data acquisition, interpretation of data, writing the manuscript. W.F.O.A.: data acquisition, data analysis, interpretation of data. I.B.S., M.A.B.C.L., P.R.C.P., V.O.C.F., M.M.N. and Y.I.R.: data acquisition, interpretation of data. G.G.L.C. and R.V.M. conception and design of the work, interpretation of data, writing the manuscript, final approval of the version of the manuscript to be published.

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Artificial intelligence tools were used solely to assist in English language refinement and for wording/grammar suggestions. All scientific content, study design, data analysis and interpretations were developed independently by the authors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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The authors have nothing to report.

Conflicts of Interest

All authors report no relationships that could be construed as conflicts of interest. Rodrigo Vieira Motta has previously received a research grant from PSC Support. Guilherme Grossi Lopes Cançado has received

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Forest plot for patient age. **Figure S2:** Forest plot for male patient. **Figure S3:** Forest plot for male donor. **Figure S4:** Forest plot for donor-recipient gender match. **Figure S5:** Forest plot for presence of IBD prior to transplantation. **Figure S6:** Forest plots for acute rejection following transplantation. **Figure S7:** Forest plot for cyclosporine. **Figure S8:** Forest plot for LDLT. **Figure S9:** Risk of bias in the included studies. **Figure S10:** Sensitivity analysis for patient age. **Figure S11:** Sensitivity analysis for donor age. **Figure S12:** Sensitivity analysis for male patient. **Figure S13:** Sensitivity analysis for male donor. **Figure S14:** Sensitivity analysis for donor-recipient gender match. **Figure S15:** Sensitivity analysis for LDLT. **Figure S16:** Sensitivity analysis for DDLT. **Figure S17:** Sensitivity analysis for pre-LT IBD. **Figure S18:** Sensitivity analysis for de novo IBD. **Figure S19:** Sensitivity analysis for CMV-positive patient. **Figure S20:** Sensitivity analysis for acute rejection. **Figure S21:** Sensitivity analysis for colectomy. **Figure S22:** Sensitivity analysis for MELD. **Figure S23:** Sensitivity analysis for cyclosporine. **Figure S24:** Sensitivity analysis for tacrolimus. **Figure S25:** Sensitivity analysis for mycophenolate mofetil (MMF). **Figure S26:** Sensitivity analysis for hepaticojejunostomy. **Figure S27:** Sensitivity analysis for warm-ischaemia time. **Figure S28:** Sensitivity analysis for cold-ischaemia time. **Figure S29:** Funnel plot for patient age. **Figure S30:** Funnel plot for donor age. **Figure S31:** Funnel plot for male patient. **Figure S32:** Funnel plot for male donor. **Figure S33:** Funnel plot for donor-recipient gender match. **Figure S34:** Funnel plot for LDLT. **Figure S35:** Funnel plot for DDLT. **Figure S36:** Funnel plot for pre-LT IBD. **Figure S37:** Funnel plot for CMV-positive patient. **Figure S38:** Funnel plot for acute rejection. **Figure S39:** Funnel plot for colectomy. **Figure S40:** Funnel plot for MELD. **Figure S41:** Funnel plot for cyclosporine. **Figure S42:** Funnel plot for tacrolimus. **Figure S43:** Funnel plot for mycophenolate mofetil (MMF). **Figure S44:** Funnel plot for hepaticojejunostomy. **Figure S45:** Funnel plot for warm-ischaemia time. **Figure S46:** Funnel plot for cold-ischaemia time. **Figure S47:** Meta-regression for incidence. **Figure S48:** Meta-regression for cyclosporine use. **Figure S49:** Meta-regression for tacrolimus use. **Table S1:** Definition of recurrent PSC in each study included. **Table S2:** Definition of acute rejection in each study included. **Table S3:** Characteristics of studies reviewed and decision to include or not. **Table S4A:** GRADE assessment. **Table S4B:** GRADE assessment.