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Portopulmonary Hypertension: A Systematic Review and Meta-analysis of Diagnostic Strategies, Targeted Therapy, and Transplantation Outcomes

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Article

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Abstract

Background

Portopulmonary hypertension is a life-threatening pulmonary arterial hypertension associated with portal hypertension and complicates liver transplantation.

Aims

To synthesize evidence on screening, targeted pharmacotherapy and transplantation outcomes, quantify diagnostic accuracy, and summarize survival using source-reported time-to-event estimates.

Methods

PubMed, Embase, the Cochrane Library and Web of Science were searched through 31 December 2025. PoPH therapeutic/prognostic studies enrolled adults with right-heart-catheterization (RHC)-confirmed disease; diagnostic-accuracy studies were eligible when RHC-referenced 2×2 data were extractable. TTE accuracy was synthesized using a bivariate random-effects model. Fixed-time survival was summarized descriptively because Kaplan-Meier variance and risk-set information were not consistently reported; baseline cohort size was not treated as a binomial denominator. Certainty was graded with GRADE. Publications first appearing in 2026 were treated as post-search contextual evidence.

Results

Among 3,246 unique citations, 42 records were retained. Across four contemporary treated PoPH cohorts, source-reported survival ranged from 77.0% to 94.7% at 1 year, 52.0% to 88.5% at 3 years, and 34.0% to 80.2% at 5 years. Across three post-LT cohorts with survival measured from transplantation, 1-year survival ranged from 72.0% to 86.9% and 3-year survival from 63.0% to 86.9%. In PORTICO (n = 85), macitentan reduced PVR versus placebo by 35% (between-group geometric mean ratio 0.65, 95% CI 0.59–0.72); improved transplant-risk categorization was post hoc. In the independent validation cohort, plasma BMP9 < 132 pg/mL demonstrated 76.0% sensitivity and 67.0% specificity (low certainty; exploratory combined derivation/validation sensitivity 85.7% and specificity 89.0%). TTE showed summary sensitivity 71.2% and specificity 81.9%. Child-Pugh score independently predicted mortality (adjusted HR 1.53 per point).

Conclusions

Transthoracic echocardiography remains first-line screening, while bone morphogenetic protein 9 is investigational. Macitentan has direct randomized evidence in Child-Pugh A/B disease; evidence in Child-

Pugh C remains sparse. Liver transplantation can provide durable survival in carefully selected patients.

1 Introduction

Portopulmonary hypertension (PoPH) is a distinct pulmonary vascular complication in patients with portal hypertension, classified as Group 1 pulmonary arterial hypertension (PAH) and characterized by obliterative pulmonary arteriopathy, elevated pulmonary vascular resistance (PVR), and progressive RV failure [1–5]. PoPH affects approximately 1%-6% of unselected cirrhotic populations and 5%-10% of patients undergoing liver transplantation (LT) evaluation and is an important determinant of transplant eligibility and perioperative mortality[6, 7]. Distinct from hepatopulmonary syndrome (HPS), which is driven by diffuse pulmonary vasodilation and refractory hypoxemia, PoPH is driven by persistent pulmonary vasoconstriction and vascular obliteration. This divergent pathogenic mechanism mandates distinct diagnostic pathways and management strategies for hepatologists, pulmonologists, and transplant surgeons[8].

Clinically, exertional dyspnea, fatigue, and recurrent ascites overlap substantially with manifestations of decompensated cirrhosis. In the absence of standardized population-level screening protocols, a substantial proportion of PoPH cases remain undiagnosed at early disease stages, contributing to poor long-term survival[9–12]. Historically, severe PoPH was considered a contraindication to LT because of extremely high perioperative mortality in early cohorts. Over the past decade, three major developments have changed PoPH management: (1) the revision of resting hemodynamic diagnostic thresholds in the 2022 ESC/ERS pulmonary hypertension guidelines; (2) broader use of dual oral combination targeted pharmacotherapy; and (3) increasing adoption of structured pre-transplant hemodynamic optimization protocols for PoPH LT candidates[13, 14].

Despite these advances, several critical evidence gaps persist. First, few systematic reviews have stratified the therapeutic efficacy and hepatic safety of endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE5i) across Child-Pugh liver function grades, limiting quantitative guidance for stratified medication selection. Second, the diagnostic and prognostic performance of plasma bone morphogenetic protein 9 (BMP9) as a PoPH-specific biomarker has not been comprehensively synthesized. Third, most available data derive from Western cohorts with liver disease mainly related to hepatitis C virus (HCV) infection and alcohol, raising concerns about generalizability to Asian populations in which hepatitis B virus (HBV)-associated cirrhosis predominates, and post-LT outcomes may differ. Fourth, real-world implementation of unified perioperative multidisciplinary management workflows for PoPH transplant candidates remains heterogeneous across centers and registries.

Circulating BMP9 was selected as an exploratory candidate biomarker because it is synthesized in the liver and acts as a circulating endothelial quiescence factor within the BMP9-ALK1/BMPR2 signaling axis. The available mechanistic literature does not support attributing BMP9 production exclusively to hepatic sinusoidal endothelium; hepatocytes, hepatic stellate cells, and biliary epithelial cells have been

implicated. ALK1 is the high-affinity type-I receptor for BMP9, with BMPR2 participating as a type-II receptor in the signaling complex. Human and experimental data link reduced BMP9 signaling to PoPH, but the available clinical study did not establish validated cutoffs that sequentially classify borderline, mild, moderate, and severe PoPH. Accordingly, BMP9 was evaluated here as an investigational adjunct to guideline-based screening rather than as a replacement for TTE or confirmatory RHC[15, 16].

We therefore hypothesized that circulating BMP9 could serve as a liver-derived investigational screening and prognostic biomarker under the 2022 ESC/ERS hemodynamic thresholds; that PAH-targeted treatment evidence could be stratified by Child-Pugh class while clearly distinguishing direct PoPH evidence from indirect general-PAH combination evidence; and that pre-LT hemodynamic targets and post-LT outcomes could be synthesized using consistent time origins. This systematic review and meta-analysis, conducted in accordance with PRISMA 2020, integrates evidence from randomized controlled trials (RCTs), real-world registries, cohort studies, and international guidelines to: (1) summarize tiered non-invasive screening algorithms aligned with updated hemodynamic definitions; (2) synthesize hemodynamic, functional, survival, and hepatic safety outcomes of PAH-targeted pharmacotherapy; and (3) detail pre-transplant hemodynamic criteria, perioperative care, and long-term post-LT prognostic trajectories.

Prior PoPH evidence syntheses also share two methodological shortcomings that we sought to address. First, nearly all prior pooled analyses focused on isolated diagnostic or therapeutic questions without an integrated liver-lung axis perspective, and few evaluated effect estimates across geographic cohorts and cirrhosis etiologies. Distinct hepatic inflammatory landscapes, baseline BMP9 concentrations, and pulmonary hemodynamic phenotypes have been reported in Western and Asian populations, yet international data remain disproportionately dominated by Western cohorts with hepatitis C virus and alcohol-related liver disease. We therefore formulated an exploratory geographic/etiology-oriented framework to systematically audit evidence availability across Western and Asian populations, with pooling planned only where at least three homogeneous studies per stratum permitted, and narrative tabulation otherwise. Second, published meta-analyses have generally pooled Child-Pugh A/B/C patients without characterizing Child-Pugh C cirrhosis as an exploratory high-risk subgroup, obscuring the severe hepatic decompensation risk of systemic oral PAH-targeted therapy in end-stage liver dysfunction. We therefore evaluated Child-Pugh C as a descriptive high-risk subgroup with dedicated extraction of liver-specific adverse outcomes. No previous review simultaneously integrated BMP9-based diagnostic-accuracy data, the only PoPH-specific randomized trial (PORTICO), Child-Pugh-stratified treatment considerations, and post-liver-transplantation outcomes.

2 Materials and Methods

2.1 Literature Search and Protocol Registration

We systematically searched PubMed, Embase, the Cochrane Library, and Web of Science from database inception to 31 December 2025. The search strategy combined Medical Subject Headings (MeSH) and

free-text keywords, using Boolean operators. Core concepts included “portopulmonary hypertension”, “PoPH”, “portal hypertension”/“cirrhosis”, “pulmonary hypertension”/“pulmonary arterial hypertension”, “BMP9”, “echocardiography”/“screening”, “macitentan”, “tadalafil”, “endothelin receptor antagonist”, “phosphodiesterase 5 inhibitor”, and “liver transplantation”, consistent with the database-specific strategies in the Supplementary Information. Reference lists of international guidelines, landmark trials, and prior systematic reviews were screened manually to identify additional eligible reports and registries, including grey literature with complete clinical data. No language restrictions were imposed at the initial search stage; full-text articles in English or Chinese involving human subjects were retained for formal screening. The review was registered in PROSPERO (ID: CRD420261453868) on 17 July 2026. Study screening and data extraction had been completed before registration, whereas manuscript preparation and final reporting were completed after registration; the registration was therefore retrospective with respect to study selection and data extraction. Two independent reviewers screened titles/abstracts and full texts, resolving disagreements by consensus with a third senior researcher. All procedures followed the PRISMA 2020 recommendations. Because manuscript finalization extended into 2026, a targeted citation update identified newly published reports relevant to prespecified questions; records first published after 31 December 2025 [17–21] are explicitly treated as post-search exploratory/contextual evidence (including the 2026 ILTS guideline update[20] and the 2026 PORTO-DETECT cohort [21]) and were not added to the PRISMA search counts or primary quantitative syntheses. Full per-database search strategies and record counts are provided in the Supplementary Information; the completed PRISMA 2020 checklist is submitted as a separate file. Reliable stage-specific counts separating title/abstract exclusions from full-text exclusions were not preserved in the retained audit files; these intermediate counts and exclusion reasons were therefore not reconstructed or imputed, and only verified aggregate screening counts are reported. The inability to reconstruct intermediate stage-specific exclusion counts between title/abstract screening and full-text retrieval represents a reporting limitation under PRISMA 2020 guidelines. However, aggregate database retrieval counts (n = 3,691), post-deduplication records (n = 3,246), and the final retained synthesis cohorts (n = 42) were strictly cross-verified by two independent reviewers, ensuring that the evidence boundary and qualitative conclusions remain unaffected by intermediate record attrition.

2.2 Inclusion and Exclusion Criteria

PoPH-specific therapeutic and prognostic quantitative studies were eligible if they enrolled adults (≥ 18 years) with PoPH confirmed by right heart catheterization (RHC) and clinical/hemodynamic evidence of portal hypertension. Diagnostic-accuracy studies were eligible when adult participants underwent RHC reference-standard assessment and extractable 2×2 data were available; no minimum number of PoPH-positive cases was imposed for the TTE diagnostic synthesis (full study-level characteristics and reference thresholds are detailed in Supplementary Table S1 and Supplementary References [SR1]-[SR11]). Interventions included PAH-targeted monotherapy or combination therapy, PoPH screening workflows, and pre-LT hemodynamic assessment and perioperative management strategies. Comparators included placebo or active monotherapy, alternative PAH-targeted regimens, LT recipients without PoPH, and conventional cardiac biomarkers for adjunctive assessment. Outcomes of interest

were hemodynamic parameters (mean pulmonary artery pressure [mPAP], PVR, cardiac output), 6-minute walk distance (6MWD), circulating biomarker concentrations, hepatic adverse events, LT eligibility, perioperative cardiovascular complications, and short- and long-term all-cause survival. General-PAH RCTs, international guidelines, and systematic reviews were retained only when they informed indirect treatment, safety, or policy context; they were not pooled as PoPH-specific efficacy evidence.

Exclusion criteria for PoPH-specific quantitative synthesis included preclinical animal experiments, isolated case reports, conference abstracts without extractable quantitative data, editorial letters, narrative reviews without pooled clinical results, studies focused on other pulmonary hypertension subtypes without a separate PoPH subgroup, duplicate or overlapping cohorts reporting identical datasets, and reports lacking accessible full-text English/Chinese versions. Historical studies using pre-2022 hemodynamic definitions were not excluded solely because of older thresholds; eligibility required extractable hemodynamics sufficient for interpretation under the prespecified contemporary framework.

2.3 Risk of Bias and Methodological Quality Assessment

Risk of bias was appraised using design-specific tools: RCTs were evaluated using the Cochrane RoB 2.0 instrument, covering randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results (Fig. 1A). Among the 14 RCTs assessed, PORTICO is the only PoPH-specific randomized trial; the remaining trials enrolled general pulmonary arterial hypertension populations and provide indirect evidence only. Observational cohorts and real-world registries were assessed with the Newcastle-Ottawa Scale (NOS), with scores of 7–9, 5–6, and 0–4 indicating high, moderate, and low quality, respectively (Fig. 1B). Guidelines were evaluated with the AGREE II instrument across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (Fig. 1C). Figure 1 illustrates the design-specific assessment framework, while complete study-level domain ratings for all 14 RCTs and individual NOS item scores for all 24 observational studies are detailed in Supplementary Tables S2 and S3, respectively. Studies were not excluded solely because of risk-of-bias concerns; such evidence was interpreted cautiously within the GRADE hierarchy.

The certainty of key evidence was graded using the GRADE framework (high, moderate, low, very low), taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.4 Data Extraction and Statistical Analysis

Two independent reviewers extracted baseline characteristics, intervention details, and outcomes into standardized electronic forms. Extracted data included demographics, liver disease etiology, duration of portal hypertension, Child-Pugh grade, PoPH severity, treatment regimens, hemodynamic and functional endpoints, hepatic adverse events, and survival outcomes.

For diagnostic-accuracy meta-analysis, potential small-study effects were assessed with the Deeks funnel-plot asymmetry test, weighted by effective sample size. In the 11-study transthoracic

echocardiography (TTE) analysis, Deeks regression did not show statistically significant asymmetry (P = 0.501); this result was interpreted cautiously because only 11 studies were available. Conventional Egger or Begg tests were not used for diagnostic-accuracy data. Survival outcomes were synthesized descriptively rather than subjected to funnel-plot regression because fixed-time Kaplan-Meier variance and risk-set information were not consistently available and fewer than 10 cohorts contributed. These assessments are summarized in Supplementary Table S1.

For continuous outcomes, mean differences (MDs) with 95% confidence intervals (CIs) were planned, but formal pooling was restricted to comparisons with at least three study-level data points; otherwise, results were summarized narratively. For time-to-event outcomes, pooled hazard ratios (HRs) were calculated only where study-level HR data permitted. For TTE diagnostic accuracy, the 11 study-level 2×2 datasets were synthesized jointly with a bivariate random-effects model on the logit sensitivity and specificity scales, with between-study variance-covariance estimated by restricted maximum likelihood. All statistical syntheses were performed in R (version 4.3.2) using the mada package for bivariate diagnostic meta-analysis and the metafor package for meta-analytic modeling and Deeks regression. A 0.5 continuity correction was applied to all four cells only when a study contained a zero cell for likelihood-ratio and diagnostic-odds-ratio calculations. Summary positive and negative likelihood ratios (LR + and LR-), diagnostic odds ratio (DOR), and post-test probabilities at clinically relevant pre-test probabilities were derived from the joint summary estimates. Because the BMP9 derivation and validation data originated from a single translational study, those subsets were reported separately and combined using the underlying 2×2 counts rather than treated as independent studies in a meta-analysis. Leave-one-out sensitivity analysis was performed for the TTE bivariate synthesis. Fixed-time survival proportions were treated as source-reported Kaplan-Meier estimates. Because time-specific standard errors/95% CIs and numbers at risk were not consistently reported, baseline cohort size was not used as a binomial denominator and survival proportions were not meta-analyzed; cohort-specific estimates were summarized descriptively by time origin and follow-up horizon.

Predefined exploratory subgroup analyses by geographic region and cirrhosis etiology (Western versus Asian cohorts) and by Child-Pugh class were outlined in the PROSPERO protocol. Stratum-specific estimates were planned for pooling where at least three studies per stratum permitted; otherwise, results were summarized descriptively. Treatment-by-geography interaction testing was explored but could not be performed for most outcomes because of sparse per-stratum study counts, so geographic comparisons are considered descriptive and hypothesis-generating. Restricted maximum likelihood meta-regression was considered exploratory and was not applied given sparse per-stratum data. Descriptive cohort characteristics, hemodynamics, and survival outcomes stratified by Child-Pugh class and geographic region are tabulated in Supplementary Table S4.

For the Child-Pugh hepatic function-stratified synthesis, three discrete hepatic function subgroups (Child-Pugh A, B and C) were predefined, and Child-Pugh C was evaluated as an exploratory descriptive high-risk subgroup rather than pooled with compensated cirrhosis cohorts, with dedicated extraction of liver-specific adverse outcomes: acute hepatic decompensation, 6-month all-cause mortality, and treatment

discontinuation secondary to hepatotoxicity. Because fewer than three cohort-level datasets met the eligibility criteria, formal pooling for Child-Pugh C was not performed; the subgroup is summarized descriptively with cohort data17. Geographic subgroup analyses (Western vs Asian) were summarized descriptively when fewer than three studies per stratum precluded pooling. All stratified estimates are considered exploratory (GRADE certainty: very low).

3 Results

3.1 Study Selection and Baseline Characteristics

The prespecified search yielded 3,246 unique records after deduplication. After title/abstract screening and full-text assessment, 42 records were retained in the review framework: 38 original studies and 4 international guidelines used as reference evidence (Fig. 2). The descriptive baseline/diagnosis-origin survival synthesis included four contemporary treated PoPH cohorts (Savale 2020; Sithamparanathan 2017; Tamura 2022; Aggarwal 2022), with REVEAL and other registries retained as contextual or sensitivity evidence; three cohorts provided post-LT survival measured from transplantation (Supplementary Table S5). Geographic representation remained imbalanced: the Japanese JAPHR registry [22] was part of the prespecified evidence base, whereas the Korean [17] and Taiwanese [18] reports were 2026 post-search exploratory updates and were not included in the PRISMA counts or primary quantitative syntheses.

Baseline characteristics reflected a middle-aged adult population with predominantly viral (HCV- and HBV-related) and alcoholic cirrhosis; non-cirrhotic portal hypertension accounted for a substantial minority. For descriptive presentation, PoPH was grouped into conventional mPAP severity strata adapted to the contemporary > 20-mmHg diagnostic threshold (Table 1); these categories are not formal 2022 ESC/ERS risk strata. Pooled demographic proportions were not reported because the underlying datasets could not be traced to the cited primary studies; study-level data are provided in the Supplementary Information.

Table 1
PoPH mPAP severity strata used for descriptive analyses

PoPH Severity	mPAP (mmHg)	Clinical Interpretation
Mild	21–34	Descriptive review stratum below historical moderate-disease threshold; interpret with PVR, RV function, symptoms, and liver status.
Moderate	35–44	Higher transplant-related risk; requires integrated assessment of PVR and RV function and treatment response.
Severe	≥ 45	High-risk hemodynamic phenotype; transplant candidacy depends on treatment response, PVR, and RV function.

Note: These mPAP categories are pragmatic descriptive strata adapted from conventional PoPH severity grading to the contemporary > 20-mmHg diagnostic threshold; they are not formal 2022 ESC/ERS risk categories.

3.2 Pathophysiology: Liver–Lung Axis Dysregulation

PoPH arises from complex liver-lung axis dysregulation rather than a single dominant pathway. Four partially overlapping mechanisms are consistently implicated across translational studies. Impaired hepatic clearance and portosystemic shunting lead to systemic accumulation of vasoactive and pro-inflammatory mediators, including endothelin-1 (ET-1), serotonin, and cytokines, which promote sustained pulmonary vasoconstriction and irreversible pulmonary artery smooth muscle cell (PASMC) vascular remodeling[23–30]. Cirrhosis-related hyperdynamic circulation with increased cardiac output (CO), reduced systemic vascular resistance, and splanchnic vasodilation augments pulmonary blood flow and shear stress, further driving endothelial injury[31–33]. Emerging evidence supports a central role for dysregulated BMP9/BMPR2 signaling, with reduced circulating BMP9 levels associated with higher mPAP, elevated PVR, and adverse outcomes, suggesting an acquired, liver-driven deficiency state[15, 16, 34–36]. Clinical risk factors such as female sex, autoimmune liver disease, large or multiple portosystemic shunts, and long-standing portal hypertension appear to increase susceptibility. However, they are insufficient as standalone predictors[37, 38]. Detailed correlations between circulating mediators, hemodynamics, and outcomes from individual mechanistic studies are summarized in Supplementary Table S6.

3.3 Updated Hemodynamic Criteria and Tiered Screening

3.3.1 2022 ESC/ERS Hemodynamic Diagnostic Criteria

The 2022 ESC/ERS pulmonary hypertension guidelines lowered the resting mPAP diagnostic threshold to > 20 mmHg. Formal PoPH diagnosis requires simultaneous fulfillment of the following criteria: presence of portal hypertension, resting mPAP > 20 mmHg, PVR > 2 WU, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and exclusion of alternative Group 1 PAH etiologies and other pulmonary hypertension subgroups[13, 14]. Application of the updated threshold can identify patients with previously borderline

mPAP 21–24 mmHg[13, 14]. For descriptive analyses, we used conventional PoPH mPAP severity categories adapted to the > 20-mmHg threshold (Table 1); these are pragmatic review strata rather than formal ESC/ERS risk categories.

3.3.2 Tiered Screening Algorithm and BMP9 Performance

International guidance recommends TTE screening for LT candidates and other patients with portal hypertension at increased risk of PoPH[39–42]. TTE is the established first-line non-invasive test; BNP/NT-proBNP may provide adjunctive right-ventricular risk information, whereas BMP9 remains an investigational biomarker. We therefore evaluated an exploratory tiered framework in which BMP9 augments, rather than replaces, guideline-based TTE screening. Two published TTE meta-analyses reported pooled sensitivity of 0.85–0.86 and specificity of 0.83-0.87[43, 44]; our bivariate random-effects synthesis of the 11 study-level 2×2 datasets yielded summary sensitivity 71.2% (95% CI 59.2–80.8%) and specificity 81.9% (95% CI 71.8–89.0%), corresponding to LR + 3.94 (95% CI 2.49–6.24), LR- 0.35 (95% CI 0.24–0.51), and DOR 11.2 (95% CI 5.7–22.2). In a standardized screening cohort of 152 consecutive Polish LT candidates, only 0.7% had high echocardiographic probability of pulmonary hypertension, underscoring the low pre-test probability that makes invasive screening of all candidates inefficient[42]. Positive screening results require confirmatory RHC with standardized hemodynamic measurement and, when necessary, repeat RHC for borderline values[43, 44]. Study-level TTE results, reference thresholds, and the joint summary are presented in Fig. 3, Supplementary Table S1 and Supplementary Table S7; the exploratory TTE/BMP9 framework is summarized in Supplementary Table S8.

In the derivation cohort, plasma BMP9 < 132 pg/mL alone identified PoPH with 100% sensitivity and 96% specificity (AUC 0.999); in the validation cohort, sensitivity was 76% and specificity 67% (AUC 0.827) (Fig. 3C). Combining the two subsets at the 132-pg/mL threshold (24 true positives, 28 false positives, 4 false negatives, 226 true negatives) yielded sensitivity 85.7% (95% CI 68.5–94.3%) and specificity 89.0% (95% CI 84.5–92.3%), with LR + 7.8, LR- 0.16, and DOR approximately 48; the original pooled patient-level ROC analysis reported AUC 0.956[16]. In the validation cohort alone, sensitivity was 76.0% and specificity was 67.0% (LR + 2.30), yielding a post-test probability of ~ 11% at 5% pre-test probability (compared with 29% from combined data), indicating that investigational biomarker cutoffs warrant prospective multicenter validation. At a pre-test probability of 5%, a positive BMP9 result raises the post-test probability of PoPH to approximately 29%, and a negative result lowers it to below 1%; corresponding post-test probabilities for TTE are approximately 17% and 2%. In the original report, BMP9 predicted transplant-free survival in group 1 PAH (HR 0.74 per 50-pg/mL increase; 95% CI 0.56–0.97), and BMP9 ≥ 176 pg/mL was associated with a 76% reduced hazard for death or transplantation[16]. The study did not establish validated BMP9 cutoffs for sequential PoPH severity stages. BNP/NT-proBNP and endothelial markers (vWF, VCAM-1) provide adjunctive prognostic information. A standardized screening flow chart and complete biomarker threshold data are provided in Supplementary Table S8.

3.4 PAH-Targeted Pharmacotherapy Stratified by Child-Pugh Liver Function Grade

3.4.1 Drug Classes Efficacy and Hepatic Safety

Three primary drug classes are currently applied for PoPH treatment: endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5i), and prostacyclin pathway agents, with distinct hepatic safety profiles stratified by Child-Pugh classification. Macitentan has demonstrated favorable hemodynamic efficacy with relatively low hepatotoxicity in Child-Pugh A/B populations[45–47], whereas bosentan is associated with higher rates of transaminase elevation and is generally avoided in Child-Pugh B/C patients[45–47]. Ambrisentan provides comparable hemodynamic improvement but is associated with approximately 18% fluid retention and is usually reserved for macitentan-intolerant patients[45–47]. Preferred PDE5i partners include tadalafil and sildenafil, and prostacyclin agents (intravenous epoprostenol, inhaled treprostinil, selexipag) are mainly reserved for moderate–severe PoPH and LT bridging[48, 49].

3.4.2 PoPH-Specific Evidence for Macitentan and Indirect Evidence for Dual Oral Combination Therapy

No completed randomized trial has directly compared dual oral combination therapy with monotherapy in PoPH. In the only PoPH-specific randomized trial (PORTICO; 85 patients with Child-Pugh A/B cirrhosis, MELD < 19, and PVR ≥ 320 dyn·s·cm^{-5}), the prespecified week-12 between-group treatment effect for PVR was a geometric mean ratio of 0.65 (95% CI 0.59–0.72; P < 0.0001), corresponding to a 35% reduction with macitentan versus placebo (95% CI 28%-41%). Arm-specific week-12/baseline geometric mean ratios were 0.63 (95% CI 0.58–0.67) with macitentan and 0.98 (0.91–1.05) with placebo, without a hepatic safety signal[50] (Fig. 4A). Week-12 6-minute walk distance did not differ significantly between arms in PORTICO, consistent with the short double-blind treatment window and the predominant vasodilatory mechanism captured by invasive hemodynamics rather than by functional testing[50]. A post hoc analysis demonstrated improved LT perioperative mortality risk categorization (OR 4.9, 95% CI 1.6–17.7) and wait-list mortality risk categorization (OR 10.5, 95% CI 2.4–66.8), with MELD exceptions granted in 6/43 versus 2/42 patients (Fig. 4B)[51]. Macitentan-tadalafil fixed-dose combination data from general-PAH studies (OPUS/OrPHeUS[48]; A DUE[19]) and bioequivalence data[52] provide indirect rationale for combination therapy, but do not establish PoPH-specific comparative efficacy; observational PoPH cohorts support targeted therapy broadly[22, 53–55]. Formal pooling of dual-versus-monotherapy hemodynamic and survival outcomes was not performed because no PoPH-specific head-to-head datasets met the prespecified three-study criterion. Evidence-informed treatment considerations by mPAP severity and Child-Pugh class are summarized in Table 2.

Table 2
Evidence-informed PAH-targeted treatment considerations by PoPH severity and Child-Pugh liver function grade

Child-Pugh class	Mild	Moderate	Severe
Child-Pugh A	Macitentan has direct PoPH RCT evidence; other ERA/PDE5i choices should be individualized by PAH risk and hepatic status.	Combination therapy may be considered according to PAH risk, but PoPH-specific head-to-head evidence is lacking.	Escalation including parenteral prostacyclin may be considered in expert centers, including as LT bridging when appropriate.
Child-Pugh B	Macitentan may be considered with close hepatic/volume-status monitoring; combination evidence remains indirect.	Individualized combination therapy in expert centers with serial hepatic and RV assessment.	Escalation/bridging therapy only with intensive hepatic and hemodynamic monitoring.
Child-Pugh C	Evidence insufficient for routine systemic oral therapy; expert-center individualized decisions.	Avoid extrapolating Child-Pugh A/B combination data; consider only exceptional cases with predefined stopping rules.	Highly selected rescue/bridging decisions only; transplant candidacy depends on RV/hemodynamic response and liver status.

Note: LT = liver transplantation; RHC = right heart catheterization; TTE = transthoracic echocardiography; RV = right ventricle. Treatment choices are evidence-informed considerations rather than prescriptive algorithms and require prospective validation. Monitoring principles: Serial liver function tests, symptoms/functional status, and TTE; repeat RHC when clinically indicated or required for LT eligibility. Monitoring intervals should be individualized by disease severity, therapy changes, and transplant status; no PoPH-specific randomized evidence establishes a fixed monitoring interval or a preferred ERA-PDE5i combination.

Small-study-effect assessment for the primary quantitative analysis is provided in Supplementary Table S9 (TTE 11-study diagnostic meta-analysis: Deeks P = 0.501, with no statistically significant funnel-plot asymmetry). Survival outcomes were synthesized descriptively and were not subjected to funnel-plot regression.

3.4.3 Hepatic Safety Stratified by Child-Pugh Class

Macitentan demonstrated acceptable hepatic tolerability in Child-Pugh A/B patients in PORTICO, with no clinically significant worsening of liver function over 12 weeks[50]. General-PAH combination studies provide indirect safety information for macitentan-tadalafil[19, 48], but PoPH-specific combination safety has not been established in randomized comparisons. Child-Pugh C cirrhosis carries the highest clinical concern for hepatic decompensation during systemic oral PAH-targeted therapy. In the 2026 Korean post-search cohort (n = 43), Child-Pugh score was an independent mortality predictor (adjusted HR 1.53 per 1-point increase; P = 0.005), and five of seven non-transplanted high-risk Child-Pugh C patients died (71.4%)[17]. Formal pooling of Child-Pugh C safety outcomes was not feasible because fewer than three

cohort-level datasets were available; the evidence is therefore summarized descriptively (GRADE certainty: very low). PDE5 inhibitors warrant particular caution in advanced hepatic dysfunction because sildenafil and tadalafil are CYP3A4 substrates and hepatic impairment can elevate their plasma exposure; dose reduction and closer monitoring are advisable when PDE5i are used in Child-Pugh B/C disease[47, 48]. Routine systemic oral therapy in Child-Pugh C should therefore be individualized in expert centers rather than inferred from Child-Pugh A/B data (Table 2). Child-Pugh-stratified cohort details and geographic context are provided in Supplementary Table S4.

3.4.4 Emerging Investigational Therapies

Preliminary efficacy and safety data for sotatercept derive from general pulmonary arterial hypertension trials (PULSAR, STELLAR, and their open-label extensions) and have not yet been verified in PoPH-specific populations[56–58]. Recombinant BMP9 replacement remains a translational concept motivated by BMP9/BMPR2 biology[16], whereas the rationale for SGLT2 inhibitors derives from broader cardiovascular and renal literature[59, 60]; neither strategy had PoPH-specific prospective clinical efficacy evidence in the reviewed dataset. These concepts are therefore presented only as investigational context and were not included in quantitative efficacy synthesis. Their evidence status and translation considerations are summarized in Supplementary Table S10.

3.5 Liver Transplantation: Pre-Transplant Eligibility, Perioperative Management and Long-Term Outcomes

3.5.1 Pre-transplant Hemodynamic Eligibility Targets

LT can normalize portal pressure and improve pulmonary hemodynamics, but carries a substantial perioperative risk of right ventricular (RV) failure without adequate pre-LT optimization. The 2026 ILTS practice guideline update recommends LT consideration when mPAP is < 35 mmHg with acceptable PVR, and conditional listing in selected patients with mPAP 35–45 mmHg when PVR is < 3 WU, with PVR ≥ 5 WU and severe RV dysfunction identified as high-risk features[20]. These thresholds are consistent with the 2022 ESC/ERS pulmonary hypertension recommendations for post-capillary threshold and RV risk stratification[61]. In the PORTICO post hoc analysis, macitentan treatment improved the LT perioperative mortality risk category (OR 4.9, 95% CI 1.6–17.7) and the wait-list mortality risk category (OR 10.5, 95% CI 2.4–66.8)[51]. Repeat RHC after treatment optimization is used to document transplant eligibility[39, 62, 63]. Refractory severe PoPH without adequate hemodynamic or RV response remains a major contraindication to LT.

3.5.2 Multidisciplinary Perioperative Management

Perioperative protocols emphasized continuity of PAH-targeted therapy, use of inhaled nitric oxide (NO, 20–40 ppm) or treprostinil, intraoperative transesophageal echocardiography (TEE)-guided monitoring, strict hemodynamic control, and early postoperative weaning of inhaled vasodilators with prompt resumption of oral agents [20, 61, 63, 64].

3.5.3 Long-term Post-LT Survival and Hemodynamic Remission Outcomes

Across included cohorts, LT was associated with durable survival and frequent hemodynamic improvement. Post-LT survival was 80%, 77%, and 77% at 6 months, 1 year, and 3 years in the French cohort[65]; 86.9% at 1, 3, and 5 years when survival was measured from transplantation in the US moderate-severe cohort[7]; and 72%, 63%, and 60% at 1, 3, and 5 years in the three-center US cohort[66]. The 95.8%, 90.9%, and 90.9% values reported by Sadd et al. refer to survival from PoPH diagnosis and were therefore not used as post-LT estimates. Among four contemporary treated PoPH cohorts with survival measured from cohort baseline/diagnosis (Savale 2020[53]; Sithamparanathan 2017[67]; Tamura 2022[22]; Aggarwal 2022[54]), reported survival ranged from 77.0% to 94.7% at 1 year, 52.0% to 88.5% at 3 years, and 34.0% to 80.2% at 5 years (Fig. 5A). Tamura 2022 reported Kaplan-Meier 95% CIs of 84.5%-98.3%, 76.0%-94.7%, and 64.8%-89.3% at 1, 3, and 5 years, respectively[22]; comparable time-specific variance estimates were not consistently available for the other cohorts. Accordingly, survival proportions were not meta-analyzed and no binomial CIs were reconstructed from baseline sample sizes. Additional nontransplanted or historical cohorts are shown descriptively in Fig. 5B and Supplementary Table S5, including Mayo Clinic (77%, 51%, and 38% at 1, 3, and 5 years[68]), REHAP (5-year 49.3%[69]), REVEAL (5-year 40%[70]), and untreated natural history (5-year 14%[71]). Post-LT survival measured from transplantation ranged from 72.0% to 86.9% at 1 year, 63.0% to 86.9% at 3 years, and 60.0% to 86.9% at 5 years among cohorts reporting those horizons (Fig. 5C). Cohort characteristics and time origins are detailed in Supplementary Table S5; In addition to survival, post-transplant hemodynamic remission is common but variably quantified: repeat right-heart catheterization in the French post-LT cohort documented normalization of pulmonary hemodynamics in most surviving recipients[65], and approximately half of the three-center US cohort underwent reassessment with substantial improvement or resolution of PoPH after transplantation[66]. Certainty ratings for these endpoints are provided in Supplementary Table S11.

3.6 Prognostic Factors

Multivariable prognostic analyses were limited. In the Korean cohort (n = 43), Child-Pugh score independently predicted mortality (adjusted HR 1.53 per 1-point increase; P = 0.005), and five of seven non-transplanted high-risk Child-Pugh C patients died[17]. In the US REVEAL registry, PoPH carried significantly lower survival than idiopathic PAH (2-year survival 67% versus 85%; 5-year 40% versus 64%; both $P < 0.001$)[70]. In the French national cohort, the presence and severity of cirrhosis and baseline cardiac index were major independent prognostic factors[55]. In the PORTICO post hoc analysis, macitentan improved LT perioperative and wait-list mortality risk categorization[51]. Plasma BMP9 predicted transplant-free survival in group 1 PAH (HR 0.74 per 50-pg/mL increase; BMP9 ≥ 176 pg/mL associated with a 76% reduced hazard)[16]. Prognostic and outcome data are summarized in Table 3.

Analyses were restricted to estimates that could be traced to the cited primary sources; estimates without traceable source support were excluded.

Table 3
Prognostic factors and outcomes in PoPH

Predictor / outcome	Contrast or cutoff	Estimate (95% CI)	P	Source (verified)
Child-Pugh score	Per 1-point increase	aHR 1.53 (1.14–2.05)	0.005	Kwak 2026 [17]
Non-transplanted Child-Pugh C high-risk	7 patients	5/7 (71.4%) deaths	-	Kwak 2026 [17]
Macitentan vs placebo: LT perioperative mortality risk category	-	OR 4.9 (1.6–17.7)	0.004	Krowka 2020, PORTICO post hoc [51]
Wait-list mortality risk category	-	OR 10.5 (2.4–66.8)	0.001	Krowka 2020, PORTICO post hoc [51]
PoPH vs IPAH, 2-year survival	-	67% vs 85%	< 0.001	REVEAL [70]
PoPH vs IPAH, 5-year survival	-	40% vs 64%	< 0.001	REVEAL [70]
Cirrhosis severity / baseline cardiac index	-	Independent prognostic factors (descriptive)	—	Le Pavec 2008 [55]
Plasma BMP9 (group 1 PAH)	Per 50-pg/mL increase	HR 0.74 (0.56–0.97); BMP9 ≥ 176 pg/mL: 76% reduced hazard	0.03; <0.0001	Nikolic 2019 [16]

3.7 Certainty of Evidence

Using the GRADE framework, certainty was rated as follows: BMP9 diagnostic accuracy, low (single-study derivation/validation setting and indirectness to routine screening); TTE diagnostic accuracy, low (between-study threshold/verification heterogeneity and limited study count); PORTICO treatment effects, moderate (single randomized trial, precise hemodynamic effect, short follow-up, and no PoPH-specific dual-therapy comparison); survival evidence, very low (observational cohorts, variable time origins/case mix, and incomplete reporting of time-specific Kaplan-Meier variance); Child-Pugh C safety, very low (single post-search observational cohort with a small high-risk subgroup). Summary-of-findings tables with explicit downgrading reasons are provided in Supplementary Table S11. Deeks funnel-plot asymmetry testing for the 11-study TTE analysis (P = 0.501) is shown in Fig. 6. TTE leave-one-out analyses are provided in Supplementary Table S12; survival-cohort characteristics in Supplementary Table S5; study-level TTE diagnostic data in Supplementary Table S7; robustness and small-study-effect results in Supplementary Table S13; and GRADE certainty assessments in Supplementary Table S11; and complete study-level RoB 2.0 and NOS scores in Supplementary Tables S2 and S3.

3.8 Clinical Management Considerations and Transplant Policy

Several practical issues relevant to transplant programs are summarized here on the basis of the included guidelines and expert practice, with data limitations noted. In the United States, PoPH can qualify for MELD exception points when specified hemodynamic criteria are met; serial invasive reassessment remains part of current policy, while the optimal role of non-invasive surveillance requires further study[20]. Non-selective beta-blockers, commonly used for variceal prophylaxis, may attenuate cardiac output and should be individualized in PoPH. Transjugular intrahepatic portosystemic shunt placement increases preload and right ventricular strain and is generally avoided in moderate-to-severe PoPH. Anticoagulation decisions must balance in-situ pulmonary thrombosis risk against portal hypertension-related bleeding; dedicated PoPH data are lacking. Management of right heart failure centers on diuresis, afterload reduction, and avoidance of volume overload; pregnancy is contraindicated in moderate-to-severe PAH and requires structured counseling. These points are presented as expert-practice context, not as pooled quantitative findings.

Hepatic-function-stratified treatment considerations should distinguish direct PoPH evidence from extrapolation. Macitentan has direct randomized PoPH evidence in Child-Pugh A/B patients[50]; bosentan is generally avoided in moderate-to-severe hepatic impairment because of hepatotoxicity concerns; ambrisentan can cause fluid retention; PDE5 inhibitors and prostacyclin-pathway agents are used according to PAH risk, hepatic function, and transplant-bridging needs[45–47, 49]. No PoPH-specific randomized evidence establishes a preferred ERA-PDE5i combination or fixed monitoring interval. Evidence-informed considerations are summarized in Table 2.

3.9 Sensitivity Analyses

Sensitivity/context analyses additionally included the largest US single-institution nontransplanted PoPH registry (n = 160; 6-month to 5-year survival 89%, 77%, 51%, and 38%[68]) and the Spanish REHAP national registry (n = 237; age/sex-adjusted 5-year survival 49.3%[69]). Cartin-Ceba 2021 (n = 50; 1/3/5-year post-LT survival 72%, 63%, and 60%[66]) expanded the descriptive post-LT evidence base. Real-world macitentan safety in PoPH was confirmed in the combined OPUS/OrPHeUS analysis (n = 206; median exposure 11.9 months) [72], and the PORTO-DETECT cohort showed that early PoPH (mPAP 20.5–24.5 mmHg, PVR > 2 WU) predicts mortality in cirrhosis (3-year survival 49.5% versus 76.7% in patients with normal mPAP)[21], supporting the clinical relevance of the 2022 ESC/ERS threshold. For the 11-study TTE diagnostic meta-analysis, bivariate leave-one-out analyses yielded summary sensitivity ranging from 68.6% to 76.5% and specificity from 79.3% to 83.9%, indicating that no single study determined the joint result. Deeks regression showed no statistically significant funnel-plot asymmetry (P = 0.501), although power was limited by the small number of studies (Supplementary Tables S7, S12 and S13; Fig. 6).

4 Discussion

4.1 Main Findings and Methodological Contributions

This systematic review and meta-analysis synthesizes evidence from 42 records in the prespecified review framework (38 original studies and 4 international guidelines) and provides an overview of pathophysiology, non-invasive screening, Child-Pugh-stratified treatment considerations, and LT outcomes. Relative to previous reviews [3, 4, 6, 61], this work adds five contributions: (1) a quantitative diagnostic-accuracy synthesis of BMP9 and TTE; (2) a structured synthesis of pharmacotherapy evidence that distinguishes the PoPH-specific PORTICO trial from indirect general-PAH combination data; (3) survival data from European, US, and Asian cohorts summarized using source-reported time-to-event estimates rather than reconstructed binomial proportions, with post-search Asian reports labeled separately; (4) standardized LT-related hemodynamic thresholds and correction of post-LT survival time origin; and (5) explicit characterization of the geographic evidence gap.

A key methodological contribution is the explicit separation of pooled from descriptive subgroup evidence. Prespecified geographic/etiologic pooling required at least three sufficiently homogeneous studies per stratum; this criterion was not met for most outcomes, so treatment-by-geography interaction testing was not performed. Western and Asian cohort characteristics were therefore summarized descriptively in Supplementary Table S4. The available data were insufficient to estimate region-specific BMP9 diagnostic cutoffs or macitentan-tadalafil response magnitudes. Any apparent regional differences should be regarded as hypothesis-generating and require prospective validation rather than interpreted as quantified treatment-effect modification[9, 17, 18, 53].

Second, unlike prior reviews that pooled all Child-Pugh grades into a single cohort, our analysis isolates Child-Pugh C as an independent high-risk subgroup. Evidence from the Korean cohort supports a strong risk signal in decompensated cirrhosis (adjusted HR 1.53 per 1-point Child-Pugh score increase; 71.4% mortality among seven non-transplanted high-risk patients)[17], and PORTICO showed no hepatic safety signal in Child-Pugh A/B patients[50]. These data support the prevailing practice of avoiding routine systemic oral regimens in Child-Pugh C, while underscoring the need for dedicated prospective safety cohorts.

Taken together, the descriptive geographic summary and Child-Pugh stratification provide a more transparent account of evidence gaps than unstratified pooling. Mechanistic studies support a broadly shared liver-lung framework involving portal hypertension, portosystemic shunting, endothelial dysfunction, vasoactive mediators, and BMP9/BMPR2 signaling[29, 31–35]. However, the present clinical dataset does not demonstrate equivalent biomarker thresholds, treatment effects, or hepatic safety across geographic or etiologic subgroups. Accordingly, BMP9-augmented screening and hepatic-function-stratified treatment strategies should be viewed as investigational frameworks requiring region-specific prospective validation, particularly in Asian populations.

4.2 Clinical Translational Implications

The stratified evidence in this review is primarily descriptive and hypothesis-generating. It may help define variables that should be prespecified in future region-specific PoPH screening studies and hepatic-function-stratified treatment trials, but it does not establish population-specific treatment effects or validated regional biomarker cutoffs.

For hepatologists, TTE should remain the routine non-invasive screening test for LT candidates and other at-risk patients; plasma BMP9 may be studied as an investigational adjunct to refine risk before confirmatory RHC[13, 14, 16, 43, 44]. For pulmonary vascular specialists, macitentan has direct PoPH randomized evidence in Child-Pugh A/B patients[50], whereas adding tadalafil is supported by general-PAH combination data and should not be presented as an established PoPH-specific first-line regimen[19, 48, 52]. In Child-Pugh C cirrhosis, evidence is sparse and post-search observational data identify a high-risk subgroup[17]; treatment decisions should be individualized in expert centers with intensive hepatic and hemodynamic monitoring. Evidence from other PAH populations can inform general treatment principles but remains indirect for PoPH[73].

For transplant teams, adherence to standardized hemodynamic thresholds and multidisciplinary perioperative management can mitigate perioperative RV risk in carefully selected patients[7, 20, 65, 66]. Additional multicenter transplant series provide complementary outcome context[74]. Dynamic RV assessment is clinically relevant, whereas BMP9-based risk stratification for listing or post-LT surveillance remains investigational and requires prospective validation[16, 51].

4.3 Study Limitations

This systematic review and meta-analysis has several important methodological and clinical limitations. In addition, PROSPERO registration occurred on 17 July 2026, after study screening and data extraction had been completed; the registration was therefore retrospective for those review stages, although manuscript preparation and final reporting were completed after registration. The inability to reconstruct stage-specific exclusion counts separating title-abstract and full-text screening represents a reporting limitation under PRISMA 2020 guidelines. We did not impute or invent intermediate screening numbers; only cross-verified aggregate retrieval, post-deduplication, and final included study counts are reported. This shortcoming affects reporting granularity of the screening workflow rather than the internal validity of the quantitative syntheses and qualitative conclusions derived from the retained study cohort. Only one PoPH-specific randomized trial (PORTICO, n = 85) has been completed, so most treatment and outcome evidence is observational and prone to confounding[50]. Survival estimates varied materially across baseline/diagnosis-origin registry cohorts, and time-specific Kaplan-Meier standard errors/95% CIs and risk-set information were not consistently reported. We therefore did not meta-analyze fixed-time survival proportions or reconstruct binomial CIs from baseline sample sizes; the survival synthesis is descriptive[22, 53, 54, 67, 68, 70]. Geographic and etiologic representation remains imbalanced. The Korean and Taiwanese reports[17, 18] and the full A DUE publication[19] first appeared after the prespecified 31 December 2025 search cutoff; they were therefore treated as post-search exploratory/contextual

evidence and did not enter the PRISMA counts or primary quantitative syntheses. No included study reported sex- or gender-stratified estimates, precluding sex-based analyses in accordance with SAGER expectations. Analyses were restricted to study-level estimates traceable to cited primary sources. Our bivariate TTE summary sensitivity (71.2%) was lower than the 85%-86% reported in two previous meta-analyses[43, 44], plausibly reflecting differences in eligibility, echocardiographic thresholds, disease spectrum, and RHC verification procedures. The pooled TTE estimates therefore represent an average operating point across heterogeneous study thresholds rather than a universal screening threshold. Deeks testing did not identify statistically significant funnel-plot asymmetry, but its power was limited with 11 studies. Post-LT survival evidence is based on only three principal cohorts and remains very low-certainty; the Sadd cohort required correction because diagnosis-origin survival had previously been conflated with survival measured from transplantation[7].

Given these constraints, the precision-oriented stratified clinical framework proposed in this analysis should be regarded as hypothesis-generating rather than definitive prescriptive guidance. It requires validation in large multinational real-world registries and stratified RCTs before it can be translated into firm guideline recommendations. The subgroup and meta-regression analyses were further limited by the relatively small number of studies per comparison, and their findings should therefore be considered exploratory signals of potential effect modification rather than definitive evidence.

4.4 Priorities for Future Translational and Clinical Research

To further validate the stratified subgroup findings that address Western/Asian etiology disparities and Child-Pugh C safety limitations, several tiered research priorities emerge. Large prospective multinational real-world registries with mandatory stratification by cirrhosis etiology (HBV, HCV, alcohol, autoimmune liver disease) and geographic region are needed to validate differential BMP9 screening performance and therapeutic response magnitudes across Asian and Western populations[75]. Dedicated prospective observational safety cohorts exclusively enrolling Child-Pugh C PoPH patients, with standardized serial liver function testing and longitudinal hemodynamic monitoring, are required to refine stratified risk-prediction models for oral PAH-targeted therapy. Stratified RCTs should be prespecified by both Child-Pugh grade and underlying cirrhosis etiology, enabling head-to-head comparisons of combination-therapy efficacy and hepatic safety across high-risk subgroups. Composite multivariable risk models integrating geographic etiology, Child-Pugh score, hemodynamics, RV function and plasma BMP9 should be developed and externally validated. Additional priorities include multicenter validation of BMP9-based screening (alone and in combination with BMP10 and endoglin as a multi-marker panel to compensate for the attenuation of single-marker performance in validation settings[15]) and prognostication across diverse etiologies; prospective Asian and non-cirrhotic PoPH registries; scalable echocardiographic and point-of-care biomarker tools; and careful preclinical clarification of BMP9-pathway modulation before human therapeutic translation. Comparative treatment syntheses should be undertaken only when a sufficiently connected PoPH-specific evidence network becomes available. Prospective evaluation of echocardiography-guided surveillance for PoPH MELD exceptions is also warranted given the imperfect TTE-RHC correlation[20].

5 Conclusion

PoPH is a unique Group 1 pulmonary vascular complication associated with portal hypertension and liver-lung vascular dysregulation[3, 11, 31, 32]. The 2022 ESC/ERS hemodynamic threshold supports recognition of earlier precapillary disease, while BMP9 is a promising investigational biomarker rather than a guideline-endorsed screening test[13, 14, 32]. In the only PoPH-specific randomized trial, macitentan improved hemodynamics and LT risk categorization in Child-Pugh A/B patients[50, 51]; general-PAH combination data provide indirect rationale for adding a PDE5 inhibitor, while observational PoPH cohorts support targeted therapy broadly[19, 22, 48, 53, 54]. In the three principal cohorts included in the corrected post-LT descriptive synthesis, 1-year survival ranged from 72% to 86.9% and 3-year survival from 63% to 86.9%[7, 65, 66]. However, the evidence base remains disproportionately Western, and the long-term safety and effectiveness of intensive combination regimens, particularly in Asian and Child-Pugh C populations, remain incompletely characterized.

This systematic review and meta-analysis addresses two major limitations of the global PoPH evidence base: it provides a quantitative diagnostic-accuracy synthesis of BMP9 and TTE, and it isolates Child-Pugh C as a high-risk subgroup while clearly labeling the relevant 2026 cohort as post-search exploratory evidence. The evidence base incorporates the only PoPH-specific randomized trial (PORTICO) and limited Asian data, but substantial geographic and treatment-evidence gaps remain. The proposed BMP9 augmentation and hepatic-function-stratified treatment framework should therefore be viewed as hypothesis-generating rather than prescriptive and should be tested prospectively.

Future translational and clinical research focusing on BMP9-targeted therapies, AI-assisted screening platforms, and underrepresented populations, particularly in Asia and in non-cirrhotic portal hypertension, will be essential to establish and validate a multi-ethnic precision medicine framework for PoPH management.

Abbreviations

6MWD
6-minute walk distance
BMP9
Bone morphogenetic protein 9
CI
confidence interval
CO
cardiac output
ERA
endothelin receptor antagonist
ET-1
Endothelin-1

HBV
Hepatitis B virus
HCV
Hepatitis C virus
HR
hazard ratio
HPS
hepatopulmonary syndrome
IPAH
idiopathic PAH
LT
liver transplantation
mPAP
mean pulmonary artery pressure
NO
nitric oxide
NOS
Newcastle-Ottawa Scale
PAH
pulmonary arterial hypertension
PASMC
pulmonary artery smooth muscle cell
PDE5i
phosphodiesterase 5 inhibitors
PoPH
portopulmonary hypertension
PVR
pulmonary vascular resistance
RCT
randomized controlled trial
RHC
right heart catheterization
RV
right ventricle.

Declarations

Ethics approval and consent to participate

Not applicable. This systematic review and meta-analysis was based exclusively on previously published, de-identified aggregate data and did not involve the recruitment of human participants or the collection

of individual-level patient data.

Consent for publication

Not applicable.

Use of generative artificial intelligence

Generative artificial intelligence tools were used solely for language editing and formatting during manuscript preparation. They were not used for study selection, data extraction, statistical analysis, or scientific interpretation. All manuscript content, extracted data, analyses, and interpretations were reviewed and verified by the authors, who take full responsibility for the content of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

PY: Conceptualization, data curation, formal analysis, investigation, methodology, writing—original draft, and writing—review and editing. YX: Formal analysis, investigation, methodology, and writing—original draft. YL: Data curation, formal analysis, and validation. DY: Investigation, methodology, and visualization. XM: Methodology and visualization. CD: Conceptualization, visualization, supervision, and writing—review and editing. CS: Conceptualization, methodology, project administration, validation, and writing—review and editing. CD and CS served as guarantors of the review. All authors read and approved the final manuscript.

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Data Availability

The datasets analysed during the current systematic review and meta-analysis are included in the revised manuscript and its supplementary information files (Supplementary Tables S1-S13), containing study-level extracted data including diagnostic 2 × 2 tables, survival data, and Child-Pugh-stratified data.

Full literature-search strategies and the completed PRISMA 2020 checklist are also provided within the supplementary materials. The custom analysis code used for meta-analyses is available from the corresponding authors upon reasonable request.

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Figures

Figure 1. Risk-of-bias and methodological quality assessment framework

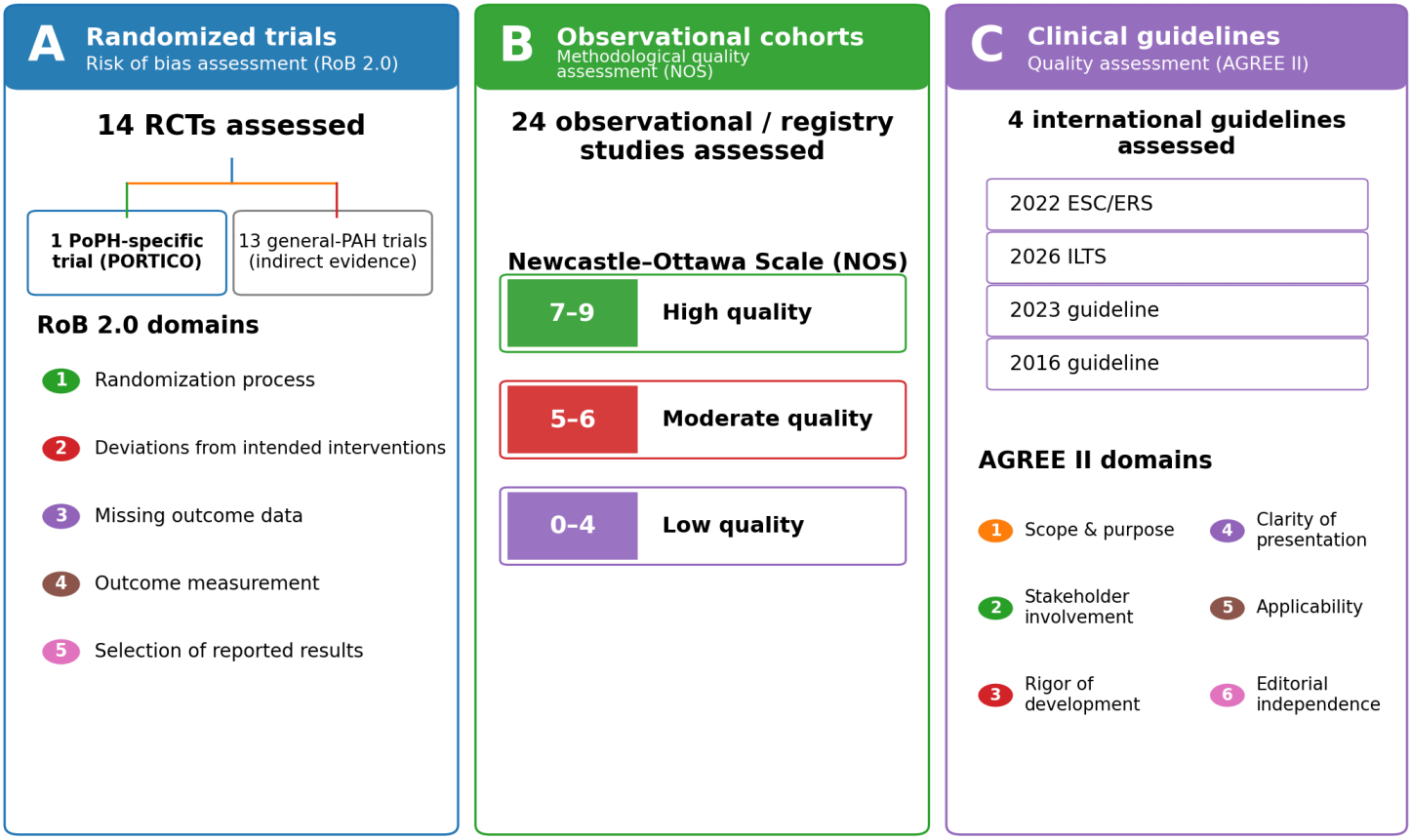


Figure 1

Risk-of-bias and methodological quality assessment framework. (A) Cochrane RoB 2.0 domains applied to 14 randomized controlled trials; PORTICO is the only PoPH-specific RCT and the remaining trials provide indirect general-PAH evidence. (B) Newcastle-Ottawa Scale (NOS) interpretation thresholds used for 24 observational cohort and registry studies (7-9 high quality, 5-6 moderate quality, 0-4 low quality). (C) Six AGREE II domains applied to four international clinical guidelines. The figure illustrates the conceptual appraisal framework; complete study-level RoB 2.0 domain evaluations for 14 RCTs and itemized NOS scores for 24 observational cohorts are provided in Supplementary Tables S2 and S3.

Figure 2. Study identification and selection (PRISMA 2020-aligned summary)

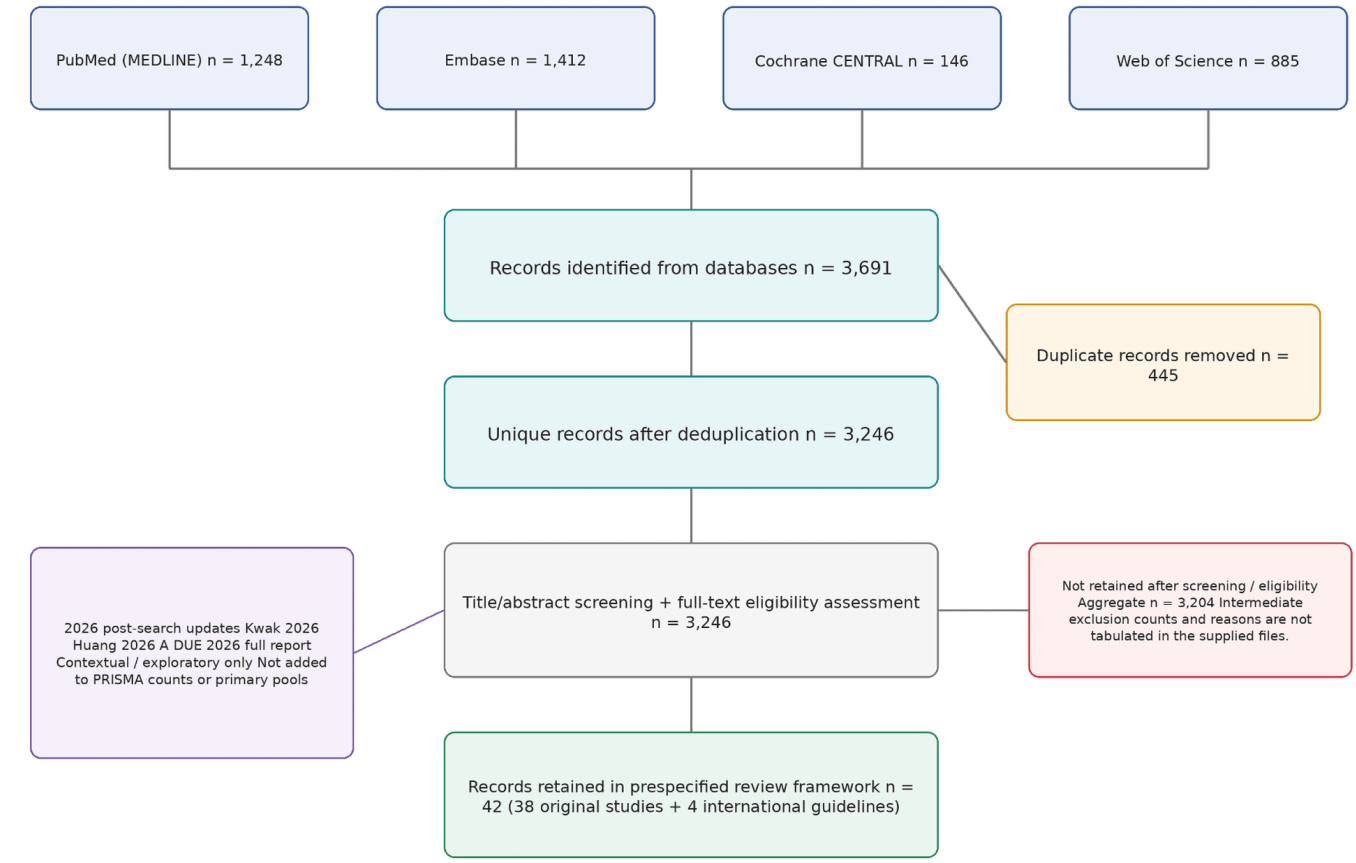


Figure 2

PRISMA 2020 flow diagram for literature identification, screening, eligibility assessment, and final study inclusion. The database searches retrieved 3,691 records; after deduplication, 3,246 unique citations underwent screening, and 42 records were retained in the prespecified review framework. Publications first appearing after 31 December 2025 were treated as post-search exploratory/contextual evidence and were not added to the PRISMA counts. Reliable stage-specific title/abstract and full-text exclusion counts could not be reconstructed from the retained audit files and were therefore not imputed; the diagram reports verified aggregate counts only.

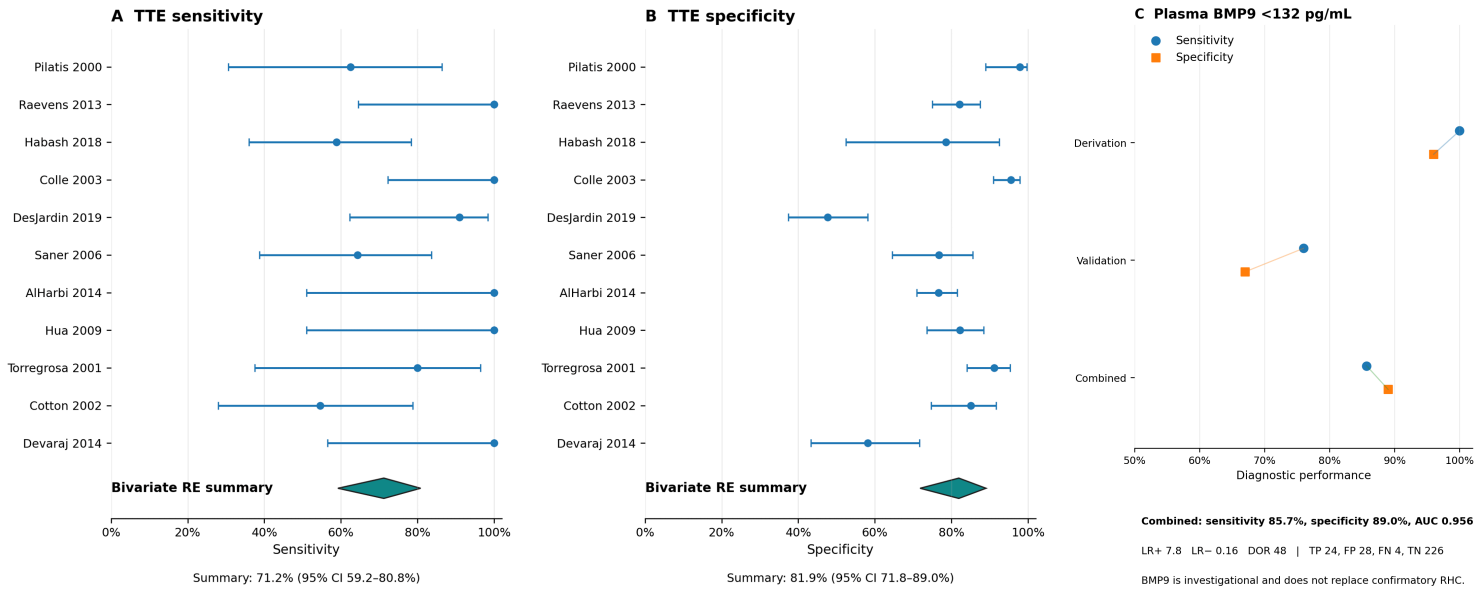


Figure 3

Diagnostic accuracy of transthoracic echocardiography (TTE) and plasma BMP9 for PoPH. (A-B) Study-level TTE sensitivity and specificity from 11 right-heart-catheterization-controlled studies. The bivariate random-effects summary was sensitivity 71.2% (95% CI 59.2-80.8%) and specificity 81.9% (95% CI 71.8-89.0%), with LR+ 3.94 (95% CI 2.49-6.24), LR- 0.35 (95% CI 0.24-0.51), and DOR 11.2 (95% CI 5.7-22.2). Forest plots show study-level raw proportions with confidence intervals; the joint bivariate model provides the summary operating point. (C) Plasma BMP9 <132 pg/mL: derivation cohort 100% sensitivity/96% specificity; validation cohort 76%/67%; combined 2×2 counts 85.7% sensitivity, 89.0% specificity, LR+ 7.8, LR- 0.16, and DOR approximately 48. AUC 0.956 is the original pooled patient-level ROC result, not a quantity derived from the single combined 2×2 table.

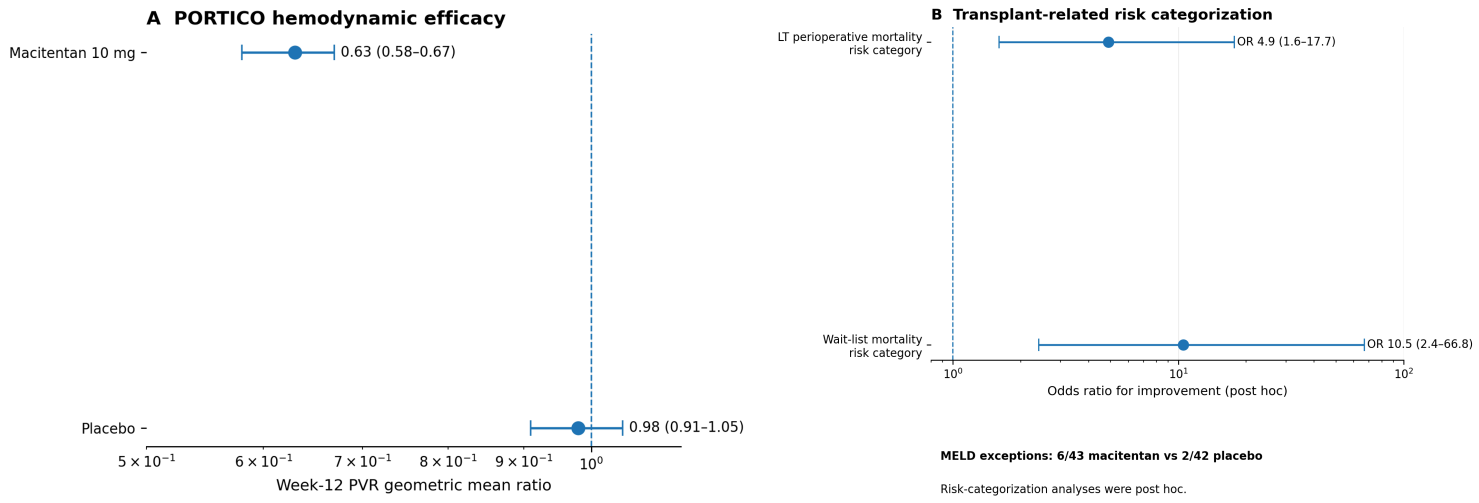


Figure 4

Macitentan in the PORTICO trial: hemodynamic efficacy and risk categorization for liver transplantation. (A) The prespecified between-group PVR treatment effect at week 12 was a geometric mean ratio of 0.65 (95% CI 0.59-0.72; P<0.0001), corresponding to a 35% reduction with macitentan versus placebo (95% CI 28%-41%). Arm-specific week-12/baseline ratios were 0.63 (95% CI 0.58-0.67) for macitentan and 0.98 (0.91-1.05) for placebo. (B) Post hoc risk categorization: improvement in transplantation perioperative mortality risk category, OR 4.9 (95% CI 1.6-17.7); wait-list mortality risk category, OR 10.5 (95% CI 2.4-66.8); MELD exceptions granted in 6 of 43 macitentan-treated versus 2 of 42 placebo patients.

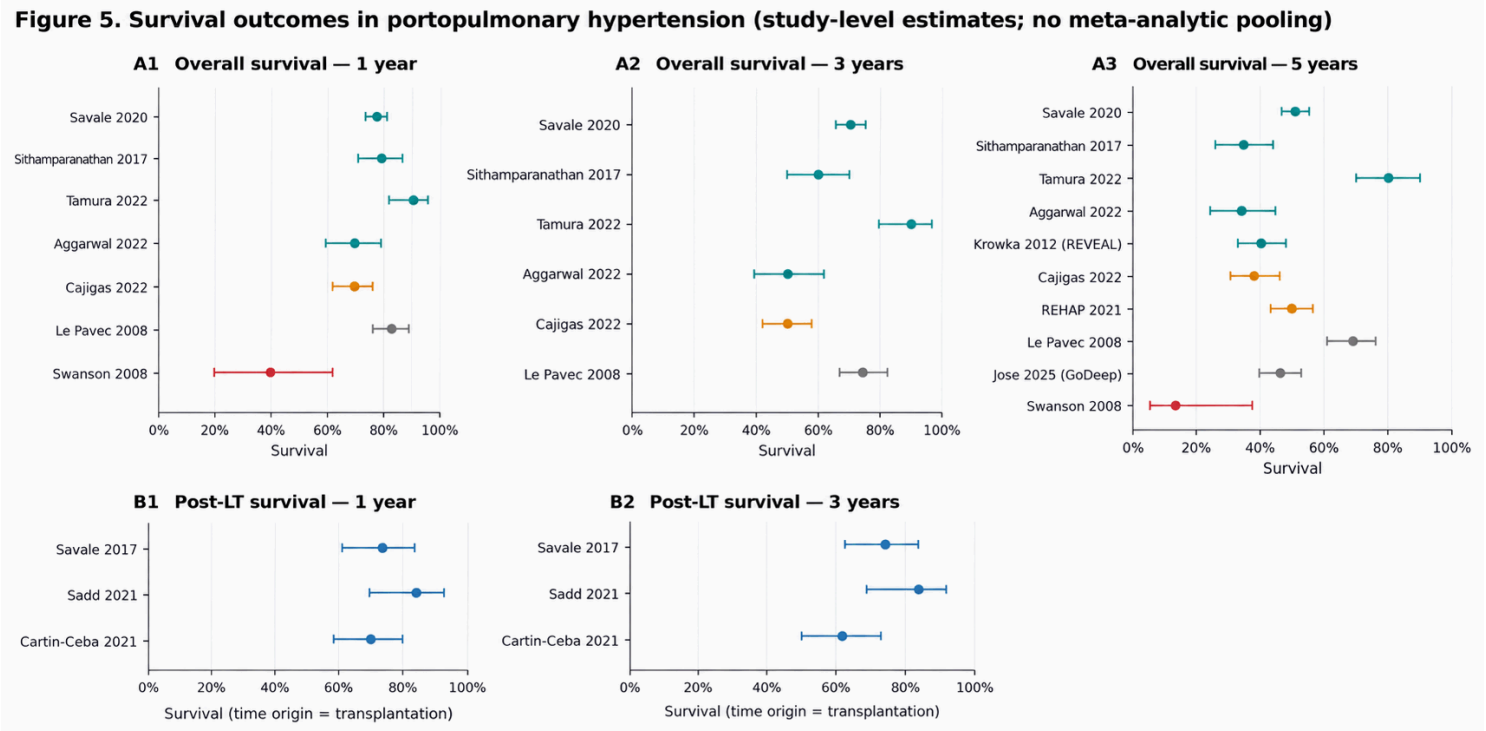


Figure 5

Source-reported survival outcomes in PoPH. (A) Contemporary treated cohorts with survival measured from cohort baseline/diagnosis. (B) Contextual, sensitivity, historical, and untreated cohorts. (C) Post-liver-transplantation cohorts with survival measured from transplantation. No meta-analytic pooling of fixed-time survival proportions was performed because time-specific Kaplan-Meier variance and risk-set information were not consistently reported; baseline cohort size was not treated as a binomial denominator. Error bars are shown only where the source publication reported time-specific 95% CIs (Tamura 2022: 1 year 94.7% [84.5%-98.3%], 3 years 88.5% [76.0%-94.7%], 5 years 80.2% [64.8%-89.3%]). Sadd diagnosis-origin survival estimates were not used as post-LT values.

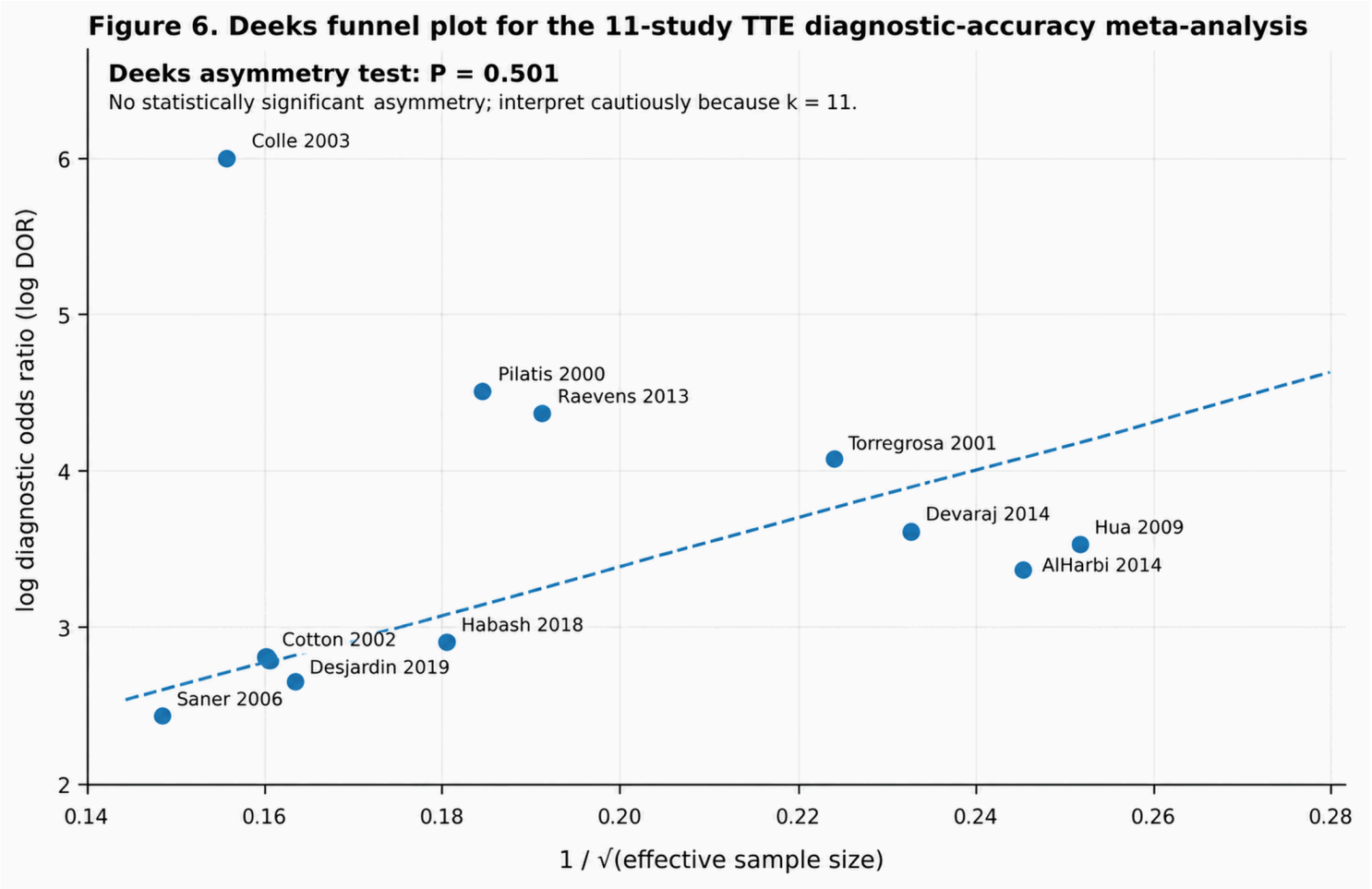


Figure 6

Deeks funnel plot for small-study-effect assessment in the 11-study TTE diagnostic-accuracy meta-analysis. The prespecified model regressed log diagnostic odds ratio on 1/√effective sample size (ESS), weighted by ESS; the figure therefore places 1/√ESS on the x-axis and log(DOR) on the y-axis. Deeks P=0.501 indicated no statistically significant funnel-plot asymmetry; interpretation remains cautious because only 11 studies were available.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.docx