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Pulmonary Manifestations of Cirrhosis: A Narrative Review of Hepatopulmonary and Portopulmonary Syndrome

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Abstract

Pulmonary vascular complications are an important but often underrecognized consequence of cirrhosis and portal hypertension. Two mechanistically distinct syndromes arise from this shared hepatic substrate: hepatopulmonary syndrome (HPS), driven by intrapulmonary vascular dilation and shunting, and portopulmonary hypertension (PoPH), characterized by vasoconstriction and progressive vascular remodeling. HPS affects up to 30% of cirrhotic patients and produces hypoxemia through ventilation-perfusion mismatch and right-to-left shunting, while PoPH develops in 2% - 6% of patients with portal hypertension and accounts for 5% - 15% pulmonary arterial hypertension cases. No established medical therapy alters the natural history of HPS, whereas PAH-targeted agents particularly endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors, can improve hemodynamics in PoPH and serve as a bridge to transplantation. Liver transplantation remains the only curative treatment for HPS and offers significant survival benefit in selected PoPH patients who achieve adequate hemodynamic response to medical therapy. This narrative review synthesizes current evidence on the pathophysiology, diagnosis, medical management, and transplant outcomes for both conditions.

Keywords

Hepatopulmonary Syndrome, Portopulmonary Syndrome, Liver Transplantation

1. Introduction

Pulmonary vascular disease is a common complication of cirrhosis and portal hypertension. Two mechanistically opposite pulmonary vascular phenotypes arise from this shared hepatic substrate: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH).

HPS, characterized by intrapulmonary vascular dilation and impaired gas exchange, affects up to 30% of patients with cirrhosis and portal hypertension [1] [2]. PoPH occurs in the setting of portal hypertension and develops in 2% - 6% of patients with portal hypertension, accounting for 5% - 15% of all pulmonary arterial hypertension cases [3] [4]. HPS produces hypoxemia through vasodilation and intrapulmonary shunting, while PoPH produces elevated pulmonary vascular resistance through vasoconstriction and vascular remodeling.

Liver transplantation remains the only curative therapy for HPS and offers survival benefit in selected PoPH patients. This review synthesizes the current understanding of the pathophysiology, diagnosis, management, and transplant outcomes for both conditions.

1.1. Pathophysiology

Pulmonary vascular disease is a common complication of cirrhosis and portal hypertension. HPS and PoPH represent two opposite vascular complications of chronic liver disease with portal hypertension [1].

1.1.1. Pathophysiology of HPS

HPS occurs in up to 30% of patients with cirrhosis and portal hypertension [2]. The pathogenesis of HPS centers on intrapulmonary vascular dilation (IPVD) driven by two key regulatory systems: endothelin-1 (ET-1) and nitric oxide (NO). In the setting of portal hypertension, elevated ET-1 levels cause selective upregulation of ET-B receptors on pulmonary endothelial cells, which activate downstream endothelial NO synthase (eNOS) and enhance NO production. The resulting vasodilation is the hallmark of HPS. Human studies have confirmed increased exhaled NO concentrations in patients with HPS, which normalize after liver transplantation [2] [5].

Beyond vasodilation, the proinflammatory environment of portal hypertension induces the release of pro-angiogenic molecules and growth factors, including von Willebrand factor (vWF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and placental growth factor (PlGF) [6]. This angiogenic response leads to the formation of direct arteriovenous communications, further contributing to intrapulmonary shunting.

Dilation of the blood vessels leads to three distinct mechanisms of impaired gas exchange, causing chronic hypoxia. In mild to moderate HPS, dilation of vessels in the presence of normal alveolar ventilation creates areas of ventilation-perfusion (V/Q) mismatch. Inadequate oxygenation of blood flowing through these units occurs, and such patients respond to supplemental oxygen therapy. In severe

HPS, abnormal arteriovenous (AV) communications allow blood to bypass ventilated alveoli, leading to right-to-left intrapulmonary shunting. Such patients do not respond to oxygen supplementation. Additionally, dilation of blood vessels increases the diffusion distance for oxygen molecules, which impairs oxygen uptake by erythrocytes. These mechanisms collectively lead to an increase in the alveolar-arterial oxygen gradient (A-a gradient) [2].

Liver cirrhosis causes intestinal bacterial overgrowth, mucosal barrier disruption, and decreased phagocytic activity. This causes bacterial translocation, which induces an inflammatory response and increases tumor necrosis factor-alpha (TNF-α). TNF-α is a potent inducer of the macrophagic iNOS/NO pathway, which in turn promotes HPS [7]. Endothelial glycocalyx (eGCX) is a gel-like layer over the endothelium that helps control vascular tone and angiogenesis. Inflammation due to infection causes degradation of eGCX, leading to pulmonary vascular dilation and contributing to HPS [8].

Bone morphogenetic protein 9 (BMP-9) and BMP-10 are produced by hepatocytes and biliary epithelium and are involved in maintaining vascular homeostasis by activating endothelial cells. Their levels are reduced in liver cirrhosis, which is one of the etiological factors contributing to HPS [9]. Alveolar epithelial type II cells undergo apoptosis after common bile duct ligation in cirrhosis, leading to microenvironment disequilibrium in HPS and impaired gas exchange [7].

Emerging HPS Biomarkers: A 2025 prospective study by Wu *et al.* (n = 320 cirrhotic patients) identified novel circulating biomarkers associated with IPVD and HPS. Among the tested biomarkers, sphingosine 1-phosphate (S1P), angiopoietin-2, and platelet-derived growth factor BB (PDGF-BB) were significantly associated with both IPVD and HPS. A predictive nomogram incorporating these biomarkers achieved an AUC of 0.891 (95% CI 0.848 - 0.934) for HPS prediction [10]. This model requires external validation before clinical implementation.

Separately, plasma reticulocalbin 3 (RCN3) has been identified as a novel biomarker for early HPS diagnosis. In a single-center prospective observational cohort of 247 cirrhotic patients, RCN3 levels were significantly higher in HPS/IPVD patients, correlated positively with $P(Aa)O_2$ and MELD scores, and when combined with albumin achieved an AUC of 0.711 (95% CI 0.630 - 0.792) for HPS prediction [11]. This biomarker remains investigational and has not been validated in independent cohorts.

1.1.2. Pathophysiology of PoPH

PoPH occurs in 1.1% - 6.3% of patients with portal hypertension and accounts for 5% - 15% of patients with pulmonary arterial hypertension [3] [4]. In contrast to HPS, PoPH is characterized by vasoconstriction and progressive pulmonary vascular remodeling. Endothelin-1 and interleukin-6 levels are elevated, but in PoPH the predominant receptor is ET-A, which mediates vasoconstriction rather than the ET-B-mediated vasodilation seen in HPS [3] [12].

Shear stress from the hyperdynamic circulatory state of portal hypertension

causes endothelial cell injury and activation of genes involved in vascular remodeling. This leads to smooth muscle proliferation and thickening of the tunica intima, media, and adventitia within the pulmonary vasculature, resulting in increased pulmonary vascular resistance, platelet aggregation, and in situ thrombosis [3] [9] [12].

Estrogen signaling plays a significant role in PoPH pathogenesis. Genetic variation in aromatase (CYP19A1) is associated with higher estradiol levels and an increased risk of PoPH (OR 2.36; 95% CI 1.12 - 4.91) [6]. Patients with PoPH demonstrate significantly higher urinary estradiol and estrone levels and altered estrogen metabolism with lower 2hydroxyestrogen/16-α-hydroxyestrone ratios and higher 16-α-hydroxyestradiol levels [6] [13]. These findings help explain the female predominance observed in PoPH.

BMP-2 (via BMPR2 receptor mutations) is implicated in PoPH, where decreased BMP-2 signaling leads to pulmonary vasoconstriction and vascular remodeling [12]. Bacterial endotoxins that translocate from the intestines to the lungs can also damage pulmonary vascular endothelium, promoting the development of PoPH through endothelial proliferation [12].

Dysregulation of the BMP/TGF-β signaling pathway, specifically the imbalance between the Smad2/3 (growth-promoting) and Smad1/5/8 (growth-inhibiting) branches, is now recognized as a central driver of pulmonary vascular remodeling in PAH, including PoPH [4]. Sotatercept, a first-in-class activin signaling inhibitor (ActRIIA-Fc fusion protein), acts as a ligand trap for activins, restoring the balance between proliferative and antiproliferative signaling [14]. This mechanism is directly relevant to PoPH pathophysiology, where decreased BMP signaling and increased activin-mediated proliferation contribute to vascular remodeling. Sotatercept has demonstrated efficacy in the phase 3 STELLAR trial (n = 323) and the ZENITH trial in patients with PAH, though PoPH patients were not specifically enrolled in these studies [14] [15]. Its role in PoPH remains investigational.

Emerging PoPH Biomarkers: A 2025 serum proteomics study using data-independent acquisition (DIA) identified 35 differentially expressed proteins distinguishing PoPH from portal hypertension without PoPH. Vitronectin (VTN) was validated by ELISA as a potential biomarker, with significantly lower levels in PoPH patients. VTN correlated with RDW ($R = -0.56$, $p = 0.01$) and platelet count ($R = 0.52$, $p = 0.01$) [3]. This finding is from a single-center study and requires independent validation before clinical application.

1.2. Clinical Features

1.2.1. HPS Clinical Features and Parts

Patients with HPS present with dyspnea (80% of cases), fatigue (85%), aggravation of dyspnea in the upright position with relief in the recumbent position (platypnea), digital clubbing, cyanosis, spider nevi, and orthodeoxia (decrease in PaO_2 of >5% or >4 mmHg when moving from supine to upright position). Rapid oxy-

genation deterioration (PaO_2 decline >5 mmHg within 6 - 12 months) suggests aggressive disease. There are two types of HPS: type I, which is due to dilation at the precapillary level, and type II, which is due to anatomic shunting at arteriovenous connections [2].

Kawut *et al.* (2022) conducted a multicenter prospective cohort study of 231 adults undergoing first liver transplantation evaluation and found that HPS patients had significantly shorter 6-minute walk distances (29 m shorter, adjusted; p = 0.04), lower oxygen saturation (96% vs. 98%; p = 0.001), lower PaO_2 (78 ± 13 vs. 92 ± 14 mmHg; p = 0.001), and higher A-a gradients (median 20 - 37 vs. 7 - 19 mmHg; p = 0.001) compared to non-HPS controls [6].

1.2.2. PoPH Clinical Features and Parts

PoPH patients also present with exertional dyspnea and fatigue. Physical examination reveals an accentuated second heart sound, S3 gallop, midaxillary line displacement of the apex, lower left parasternal systolic heave, a continuous unfolding of the second heart sound on the pulmonic area, diastolic murmur at the pulmonic site, jugular vein distension, ascites, and edema [12]. Relative to idiopathic PAH, patients with PoPH have less exertional dyspnea (81% versus 86%), more fatigue (31% versus 23%), more edema (33% versus 21%), and more abdominal distension (12% versus 3%) according to the REVEAL registry [4].

1.3. Natural History of HPS, Longitudinal Data

The Canadian HPS Program (n = 132) represents the largest longitudinal analysis in HPS to date [16]. Key findings include:

- PaO_2 declined at a rate of −3.7 mmHg/year (95% CI −6.4 to −0.96) after diagnosis.
- DLCO declined at −3.3% predicted/year.
- Two distinct deterioration phenotypes were identified: "very severe disease, slow decliners" (PaO_2 45 mmHg; −1.0 mmHg/year) and "moderate disease, steady decliners" (PaO_2 65.5 mmHg; −2.5 mmHg/year).
- A noninvasive shunt fraction ≥20% predicted slower PaO_2 decline by 0.88 (0.36, 1.4) mmHg/month.
- Post-transplant, PaO_2 increased by 6.5 (5.3, 7.7) mmHg/month in the first year, with median time to normalization of 149 days (95% CI 116 - 184).
- Greater pretransplant orthodeoxia predicted faster post-transplant PaO_2 improvement (2.5 mmHg/month faster per 10 mmHg greater orthodeoxia).

1.3.1. Screening and Diagnosis of HPS

The diagnosis of HPS requires the triad of: 1) portal hypertension, 2) impaired oxygenation, and 3) evidence of intrapulmonary vascular dilations (IPVD) [2] [17].

The 2025 AASLD/AST Practice Guideline on Adult Liver Transplantation recommends that HPS be evaluated in all patients with chronic liver disease undergoing transplant evaluation [17]. Pulse oximetry alone is insufficiently sensitive

for HPS screening. Forde *et al.* demonstrated that SpO_2 96%, the threshold recommended by prior guidelines, had a sensitivity of only 28% for detecting HPS overall, though sensitivity improved to 71% for detecting HPS with PaO_2 60 mmHg [18]. Arterial blood gas analysis and contrast echocardiography are therefore required for definitive diagnosis [17] [18].

Impaired oxygenation is defined by an A-a gradient ≥15 mmHg at sea level (≥20 mmHg in patients older than 64 - 65 years) or PaO_2 80 mmHg on room air [2] [17] [19].

Contrast-enhanced (bubble) echocardiography is the most sensitive screening test for detecting IPVD and is recommended when available [17] [19]. The diagnostic criterion is the appearance of microbubbles in the left heart ≥3 cardiac cycles after right heart opacification following injection of 10 mL agitated saline [17].

Technetium-99m-labeled macroaggregated albumin (^{99m}Tc-MAA) lung perfusion scanning provides an alternative method for detecting and quantifying intrapulmonary shunting. Brain uptake ≥6% of radiolabeled albumin indicates the presence of an intrapulmonary shunt [2]. **Table 1** shows the grading based on the Tc-MAA scan and echocardiogram.

Pulmonary function testing typically shows reduced diffusing capacity for carbon monoxide (DLCO) [2].

Table 1. Intrapulmonary shunt quantitative classification using contrast-enhanced echocardiography and macroaggregated albumin lung perfusion. Microbubbles appearing in the left atrium after ≥3 cardiac cycles following right atrial opacification are consistent with an intrapulmonary shunt, whereas appearance within the first 1 - 2 cardiac cycles suggest an intracardiac shunt. Quantitative thresholds for CEE are semiquantitative and vary slightly across studies; MAA shunt fraction provides an objective estimate of extrapulmonary tracer uptake.

Shunt Grade	Contrast-Enhanced Echocardiography (CEE)	99mTc-Macroaggregated Albumin (MAA) Lung Perfusion Scan	Interpretation
Grade 0	No microbubbles in the left atrium	<6% extrapulmonary uptake	No evidence of intrapulmonary shunt
Grade I (Mild)	Few isolated microbubbles (<30 bubbles/frame) appearing after 3 - 6 cardiac cycles	6% - 20% shunt fraction	Mild intrapulmonary vascular dilatation; often clinically insignificant
Grade II (Moderate)	Moderate number of microbubbles (30 - 100 bubbles/frame) without complete left atrial opacification	20% - 40% shunt fraction	Moderate intrapulmonary shunting; may be associated with impaired oxygenation
Grade III (Severe)	Dense microbubble opacification (>100 bubbles/frame) or near-complete left atrial opacification	>40% shunt fraction	Severe intrapulmonary shunting; strongly associated with clinically significant hepatopulmonary syndrome and hypoxemia

Abbreviations: CEE, contrast-enhanced echocardiography; MAA, macroaggregated albumin.

HPS severity is classified based on PaO_2 on room air: mild (≥80 mmHg), moderate (≥60 to 80 mmHg), severe (≥50 to 60 mmHg), and very severe (50 mmHg, or 300 mmHg on 100% oxygen) [2] [19].

1.3.2. Diagnosis of PoPH

PoPH is diagnosed by documenting both pulmonary hypertension and portal hypertension. Portal hypertension may be confirmed by imaging showing collateral splenic circulation and/or splenomegaly, endoscopy demonstrating esophageal or gastric varices, or hepatic elastography showing values >25 kilopascals.

Transthoracic echocardiography is the recommended screening test for PoPH in all liver transplant candidates [17] [18]. The 2025 AASLD/AST guideline recommends referral for right heart catheterization (RHC) when the estimated pulmonary artery systolic pressure exceeds 45 mmHg and/or there is evidence of right ventricular dysfunction [17]. The 2022 ESC/ERS guidelines define PoPH hemodynamically as mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units in the setting of portal hypertension [14].

Severity grading of PoPH is based on RHC results: mild (mPAP 20 to 35 mmHg), moderate (mPAP 35 to 45 mmHg), or severe (mPAP ≥ 45 mmHg) [3] [18].

1.4. Medical Management

1.4.1. HPS Medical Management

There is currently no established medical therapy that alters the natural history of HPS; liver transplantation remains the only curative treatment [2] [6] [16]. Supplemental oxygen is used for symptom management, as it increases alveolar oxygen tension and improves diffusiondependent oxygenation. Type I HPS (diffuse precapillary dilation) responds to supplemental oxygen, while Type II HPS (discrete arteriovenous communications) does not [2].

Methylene blue, a guanylate cyclase inhibitor, has demonstrated transient improvement in oxygenation in HPS. Intravenous administration at 3 mg/kg over 15 minutes improved PaO_2 (58 to 74 mmHg; $p = 0.006$), reduced shunt fraction (41% to 25%; $p = 0.001$), and decreased cardiac output (10.6 to 8.6 L/min; $p = 0.008$) [2]. However, these effects are temporary and do not represent a definitive therapy.

Other agents investigated include pentoxifylline (a TNF-α inhibitor), norfloxacin (targeting bacterial translocation), and anti-angiogenic agents (sorafenib, endostatin). While these have shown theoretical merit and some benefit in animal models, clinical trials have failed to reproduce consistent benefits in humans [2] [5] [9]. In patients with discrete arteriovenous malformations (Type II HPS), transcatheter embolization offers a targeted approach and may serve as a bridge to transplantation or as palliation in severe, refractory hypoxemia [2].

1.4.2. PoPH Medical Management

Treatment of PoPH follows the same general principles as other forms of PAH, with consideration of the severity of underlying liver disease and the potential effects of vasodilators on hepatic function [14] [18]. The 2022 ESC/ERS guidelines state that all drugs approved for PAH can be used to treat PoPH, with the under-

standing that these patients are usually excluded from registration studies [14].

Endothelin receptor antagonists (ERAs) have the strongest evidence base in PoPH. The PORTICO trial, the only dedicated randomized controlled trial in PoPH, randomized 85 patients to macitentan 10 mg or placebo for 12 weeks. Macitentan achieved a 35% reduction in PVR versus placebo (ratio of geometric means 0.65; 95% CI 0.59 - 0.72; p 0.0001), though no significant differences were observed in secondary endpoints including WHO functional class, 6-minute walk distance, or NT-proBNP [18] [20]. Ambrisentan, a selective ET-A receptor antagonist, has shown improvement in pulmonary hemodynamics in observational studies [3]. Bosentan demonstrated superior survival compared to inhaled iloprost in one retrospective series (1-, 2-, and 3-year survival rates of 94%, 89%, and 89% vs. 77%, 62%, and 46%, respectively) [21]. ERAs require monitoring for hepatotoxicity, particularly in this population [14] [21].

Prostacyclin agonists, particularly epoprostenol, have vasodilatory, antiplatelet, and antiproliferative properties and significantly improve pulmonary hemodynamics in moderateto-severe PoPH [22] [23]. However, continuous intravenous administration requires permanent central venous access and carries risks of infection and pump failure [22]. Inhaled iloprost and subcutaneous or oral treprostinil offer alternative routes of administration with more favorable safety profiles [14] [21].

Phosphodiesterase-5 (PDE5) inhibitors (sildenafil, tadalafil) increase cyclic GMP levels and improve functional class and pulmonary hemodynamics. A small observational study of 14 patients with moderate-to-severe PoPH showed that sildenafil 50 mg three times daily for 3 months reduced mPAP and PVR while improving 6-minute walk distance [3]. PDE5 inhibitors were the most frequently used first-line therapy in the French PoPH registry (53% of patients) [24].

Riociguat, a soluble guanylate cyclase stimulator, showed benefit in a post hoc analysis of 13 PoPH patients from the PATENT-1 trial, with improved 6-minute walk distance and functional class persisting at 2 years in PATENT-2 [3].

In the French registry of 637 PoPH patients, most patients (74%) were initiated on monotherapy, with significant improvements in functional class, 6-minute walk distance, and PVR after a median treatment time of 4.5 months. Overall 5-year survival was 51% [24]. In the REHAP registry of 237 PoPH patients, the 1-, 3-, and 5-year survival rates from diagnosis were 79.6%, 65.3%, and 49.3%, respectively. Treated patients had significantly better survival than untreated patients, and first-line oral monotherapy was associated with improved survival [25]. However, medical therapy within 6 months of diagnosis may not alter the natural history of disease, suggesting that liver disease severity primarily drives mortality [3] [25] [26].

1.5. Liver Transplantation

1.5.1. HPS and Liver Transplant

Liver transplantation is the definitive therapy for HPS and addresses the underlying pathophysiological derangements of IPVD. A Kaplan-Meier survival analysis demonstrated that transplantation improved 5-year survival from 23% in un-

treated patients to 76% in transplant recipients, irrespective of baseline PaO_2, cerebral uptake of ^{99m}Tc-MAA, or measures of hepatic dysfunction [2] [27]. Liver transplantation triples 5-year survival in HPS patients independent of baseline disease severity [2].

Current OPTN/UNOS policy assigns MELD exception points for patients with evidence of portal hypertension, intrapulmonary shunting, and a room air PaO_2 60 mmHg [17] [27]. The 2025 AASLD/AST guideline states that there is no absolute PaO_2 cutoff below which transplantation is contraindicated, as even patients with PaO_2 50 mmHg have been successfully transplanted, particularly at high-volume centers [17].

A recent case series from Mayo Clinic of 20 patients with severe or very severe HPS (PaO_2 60 mmHg) who underwent liver transplantation found that all patients demonstrated improvement, with 85% (17/20) ultimately discontinuing supplemental oxygen (mean time 250 days; range 0 - 1,113 days). No deaths were directly attributed to HPS [28]. Resolution of HPS typically occurs within 6 - 12 months post-transplant, though more severe hypoxemia predicts the need for longer-term supplemental oxygen and a longer recovery [2] [27] [28].

In the post-MELD era, 5-year survival probability has improved significantly compared to the pre-MELD era (87% vs. 73%; $p = 0.008$) [29]. Kawut *et al.* reported an overall hazard ratio for mortality of 1.8 (95% CI 1.03 - 3.16; $p = 0.04$) in HPS patients compared to non-HPS controls [6].

HPS: ECMO as Perioperative Bridge

The 2025 AASLD/AST Practice Guideline on Adult Liver Transplantation now explicitly acknowledges that ECMO can support oxygenation in the perioperative period for patients with very severe HPS undergoing liver transplantation [17]. Case reports have demonstrated successful outcomes with both venovenous and veno-arterial ECMO configurations in patients with PaO_2 50 mmHg, including a pediatric case requiring 92 days of ECMO support and another using a conservative oxygen therapy strategy during ECMO [30] [31]. This supports the guideline statement that there is no absolute PaO_2 cutoff below which transplantation is contraindicated.

1.5.2. PoPH and Liver Transplant

The impact of liver transplantation on PoPH is less predictable than in HPS. Severe, uncontrolled PoPH represents a contraindication to transplantation due to the risk of acute right heart failure during surgery [3] [14] [18]. Early data from Krowka *et al.* demonstrated 100% post-transplant mortality in untreated patients with mPAP >50 mmHg, 50% mortality with mPAP 35 - 50 mmHg, and 0% mortality with mPAP 35 mmHg [3] [18].

Current OPTN exception criteria require a hemodynamic response to medical therapy before transplantation can proceed: mPAP 35 mmHg and PVR 5 Wood units, or mPAP 35 - 45 mmHg and PVR 3 Wood units [17]. A substantial proportion of patients treated with PAHtargeted therapy (44%; 95% CI 31% - 58%) become eligible for transplantation [32].

Post-transplant outcomes in PoPH have improved with the use of PAH-targeted bridge therapy. Savale *et al.* (2017) reported 6-month, 1-year, and 3-year post-transplant survival rates of 80%, 77%, and 77%, respectively, in 35 transplanted PoPH patients. Among survivors, 55% required ongoing pulmonary vasodilator therapy, while all patients on intravenous epoprostenol were successfully weaned post-transplant [23]. In the French registry, survival from PoPH diagnosis was significantly better in patients who underwent transplantation (92%, 83%, and 81% at 1, 3, and 5 years) compared to those who did not [24].

A single-center study of 24 patients with moderate-to-severe PoPH optimized with vasodilator therapy before transplantation reported excellent outcomes: 1-, 3-, and 5-year post-transplant survival of 86.9%, and 61.9% of patients were able to discontinue all pulmonary vasodilator therapy (median time 13.9 months) [33]. However, a multicenter study of 50 transplanted PoPH patients reported more modest 1-, 3-, and 5-year survival rates of 72%, 63%, and 60%, with elevated pre-transplant PVR associated with worse survival (HR 1.91; 95% CI 1.07 - 3.74) [34].

1.6. Prognosis

1.6.1. HPS

The long-term prognosis following successful transplantation for HPS is excellent, as all symptoms related to IPVD typically resolve within 6 - 12 months. Studies have shown 1-year survival rates of up to 90% and 5-year survival rates ranging between 70% and 80%, comparable to non-HPS liver transplant recipients [2]. In 2021, Aragon *et al.* performed a systematic review which showed that the 5-year survival probability was higher in the post-MELD era (87% vs. 73%; p = 0.008) [29]. Kawut *et al.* (2022) showed that the overall hazard ratio for mortality in patients with HPS was 1.8 (95% CI 1.03 - 3.16; p = 0.04) [6].

1.6.2. PoPH

The 1-year and 5-year survival rates in patients with PoPH are 35% - 46% and 4% - 14%, respectively, in untreated or historical cohorts [3] [12]. Independent survival predictors include MELD-sodium (MELD-Na), resting cardiac frequency, and presence of hepatic encephalopathy [26].

According to a retrospective study conducted in France at 8 centers (n = 23 transplanted PoPH patients), the hemodynamic response to liver transplantation is variable. These categories are not mutually exclusive, as patients may meet criteria for more than one outcome: 17.4% of patients discontinued pulmonary hypertensive therapy 1 year posttransplant, 60.7% normalized mPAP with continued medical treatment, 8.7% experienced worsening mPAP, and 30.4% remained stable [35]. Overall, 18% - 55% of patients require ongoing pulmonary vasodilator therapy after transplantation [23] [33]. Patients without pretransplant vasodilator therapy experience significantly higher mortality (57% vs. 18% in nonPoPH patients), with 50% dying within the first year (mean survival 11.4 months; primary cause: lung infection) [35]. Perioperative risks include reperfusion syndrome (30% incidence), which can cause acute pulmonary artery pressure elevation, right

ventricular failure, and graft failure [12].

2. Literature Search

A narrative literature search was conducted across PubMed, Embase, and the Cochrane Library from inception through May 2025. Search terms included "hepatopulmonary syndrome," "portopulmonary hypertension," "pulmonary vascular complications of cirrhosis," "liver transplantation pulmonary outcomes," and related MeSH terms. Relevant clinical practice guidelines from the AASLD, ESC/ERS, and OPTN were also reviewed. Studies were selected based on clinical relevance, methodological quality, and recency, with preference given to prospective studies, randomized controlled trials, meta-analyses, and large registry analyses. Case reports and small case series were included when they provided unique clinical insights not available from larger studies. No formal quality assessment tool was applied, consistent with the narrative design of this review.

3. Limitations

This review has several limitations inherent to its narrative design. First, the absence of a systematic search protocol and a formal quality assessment tool means that study selection may be subject to bias. Second, the evidence base for both HPS and PoPH relies heavily on observational transplant data, single-center case series, and registry analyses, with only one dedicated randomized controlled trial (PORTICO) available for PoPH. Third, several emerging biomarkers discussed (S1P, angiopoietin-2, PDGF-BB, RCN3, vitronectin) have not been adequately explored.

4. Conclusion

HPS produces hypoxemia through vasodilation and intrapulmonary shunting, while PoPH produces pulmonary hypertension through vasoconstriction and vascular remodeling. Both conditions alter transplant candidacy, require active screening in appropriate patients, and demand coordinated hepatology-pulmonology-transplant care. Liver transplantation remains curative for HPS and offers significant survival benefit in selected PoPH patients who achieve adequate hemodynamic response to medical therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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