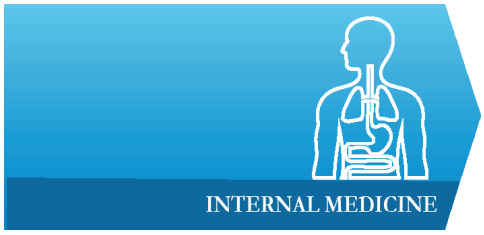
Review



Clinical aspects encountered in patients with portopulmonary hypertension

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Abstract

Portopulmonary hypertension (PoPH) is a condition characterized by the elevation of the arterial pulmonary pressure because of portal hypertension which leads to right heart failure and finally death. The most common cause of PoPH is hepatic cirrhosis, but patients with non-cirrhotic portal hypertension can also develop this complication. It is considered that between 2% and 10% of patients with portal hypertension can develop PoPH, and it is a major determinant factor of prognosis, especially in the context of liver transplantation. Clinically, the symptoms are nonspecific and are usually due to worsening right ventricular dysfunction. The treatment of PoPH consists of vasomodulating therapy, but several future challenges remain in the treatment of PoPH patients. In the absence of medical treatment or liver transplantation, the 1-year survival rate is 35%-46% and 5-year survival rate is 4-14%. Despite advances in understanding this disease, several unresolved questions remain regarding screening, diagnosis, treatment, and liver transplantation.

Keywords: portopulmonary hypertension (PoPH), liver cirrhosis, portal hypertension, right heart failure

Introduction

Portopulmonary hypertension (PoPH) represents a complex and multifaceted condition, and despite significant advancements in the understanding and management of PoPH, numerous challenges remain unresolved, particularly in screening, diagnosis, and treatment selection.

While transthoracic echocardiography (TTE) serves as a widely accepted screening tool, its overestimation of pulmonary pressures leads to unnecessary referrals for right heart catheterization (RHC), an invasive and high-risk procedure in cirrhotic patients. Meanwhile, vasomodulating therapy, although beneficial, raises concerns regarding hepatotoxicity, patient response variability, and long-term safety, particularly in liver transplant candidates. Should all patients with portal hypertension undergo screening, or should we adopt a more selective approach? Is liver transplantation (LT) justified in patients with moderate PoPH, or does the perioperative risk outweigh potential benefits? These unresolved questions underscore the need for a more nuanced approach to PoPH management.

The purpose of this review is to address these pressing clinical uncertainties. We aim to synthesize recent evidence surrounding PoPH screening methods, diagnostic tools, therapeutic strategies, and transplant considerations. By emphasizing both existing limitations and future directions, this review provides a comprehensive yet practical resource for hepatologists, pulmonologists, and transplant teams managing this high-risk population.

Pulmonary hypertension (PH) was described in Geneva, Switzerland, in 1973

at the first World Symposium on PH as a mean pulmonary arterial pressure (mPAP) 25 mmHg at rest, measured on RHC [1,2]. According to the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of PH, pre-capillary PH is defined by:

- a mPAP > 20 mmHg at rest
- pulmonary vascular resistance (PVR) above 2 Wood Units (WU)
- a decrease in pulmonary arterial wedge pressure (PAWP) below 15 mmHg

Portal hypertension can be identified through clinical signs such as ascites, collateral circulation, gastroesophageal varices, portal hypertensive gastropathy, splenomegaly, hepatorenal syndrome, and spontaneous bacterial peritonitis. It can also be confirmed by a hepatic venous pressure gradient (HVPG) ≥ 6 mmHg, which indicates elevated portal pressure [1,3,4].

According to the World Health Organization (WHO), PoPH is classified within Group 1 of pulmonary arterial hypertension (PAH). While hepatic cirrhosis is the most common underlying cause, PoPH can also occur in patients with non-cirrhotic portal hypertension [1,5].

In the most common PAH registries, the most frequently reported form is idiopathic PAH (IPAH), followed by PAH associated with connective tissue diseases and portal hypertension. PoPH accounts for approximately 5.3% to 10% of all PAH cases, reflecting its clinical significance despite its relative rarity [5-7].

Around 20% of patients with cirrhosis exhibit a moderate elevation in pulmonary arterial pressures on echocardiography. However, only a subset of these patients is ultimately diagnosed with PoPH [8]. RHC is the definitive diagnostic tool for PH, however, its invasive nature raises safety concerns in patients with cirrhosis.

Epidemiology

In the United States and Europe, the prevalence of PAH ranges from 15 to 50 per million and PoPH is responsible for 5% to 15% of cases [9,10]. Among liver transplant candidates, PoPH prevalence ranges between 3% and 10% [11-13].

In a study conducted by Anany Gupta, the prevalence of PoPH in patients with hepatic cirrhosis was 9.3% [14]. Similarly, Jian Li's study of 223 liver transplant recipients found that 6.3% (14 patients) were diagnosed with PoPH. Alarmingly, 57% (8 of 14) of those patients died post-transplant, primarily due to pulmonary infections [15]. As cirrhosis becomes more prevalent and populations continue to age, the incidence of PoPH is expected to rise [10].

Risk factors are illustrated in table I.

Pathophysiology

The pathophysiology of this condition is not yet fully understood, being a pathology still under study (figure 1).

Liver cirrhosis and portal hypertension favor splanchnic vasodilatation, and the formation of portosystemic shunts that allow the liver to metabolize blood, which causes both a decrease in peripheral vascular resistance and indirect vasodilation through intestinal vasoactive molecules causing a hyperdynamic status [1,26-28].

Vasoactive imbalances occur between:

- **Vasodilators**: nitric oxide, prostacyclin
- **Vasoconstrictors**: endothelin-1, serotonin, thromboxane A2

This imbalance promotes pulmonary vasoconstriction and increases PVR, ultimately contributing to right ventricular overload and failure [1,29,23,30,31].

Plasmatic levels of serotonin and endothelin 1 increase due to altered metabolism of substances following cirrhosis and portosystemic shunts. This can ultimately cause vascular damage at the level of the smooth muscles in the pulmonary arteries.

These changes cause endothelial cell damage, intimal proliferation, tunica media, and adventitia, which decreases pulmonary blood flow causing thrombus formation.

Table I. Risk factors for PoPH.

Risk factors	
Portal hypertension	Hepatic cirrhosis, portal vein thrombosis, autoimmune disorders, granulomatous disorders, infections, congenital abnormalities [16-18]
Demographic factors	Feminine sex [19]
Genetic factors	Mutations of the genes that codify BMPR2 [16,20,21], the risk allele rs7175922 of the CYP19A1 gene [24], single nucleotide polymorphisms of the genes involved in estrogen metabolism (estrogen receptor-1, aromatase) [22,23]
Systemic factors	Autoimmune hepatitis, anemia [19,25]
Splenic factors	Splenomegaly, hypersplenism
Drugs and toxins	Alcohol consumption, hepatotoxic medication

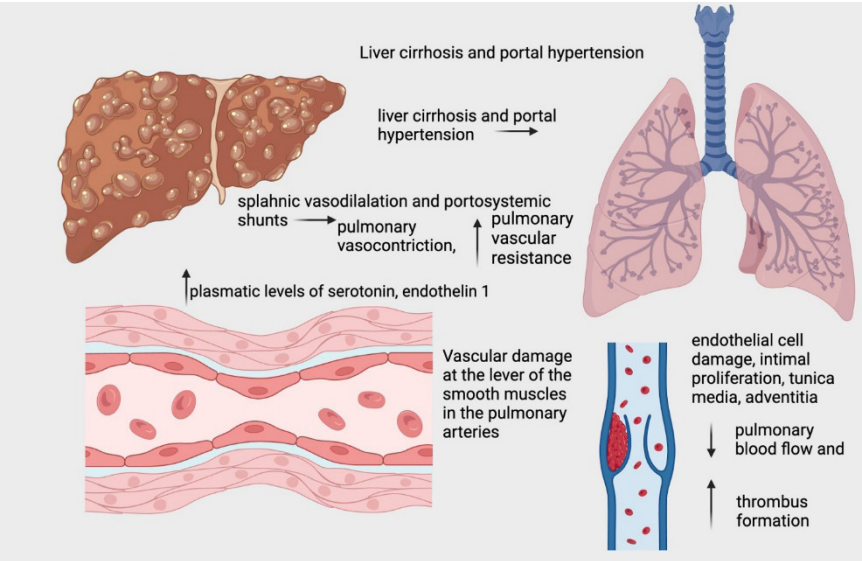

Figure 1. PoPH pathophysiology.

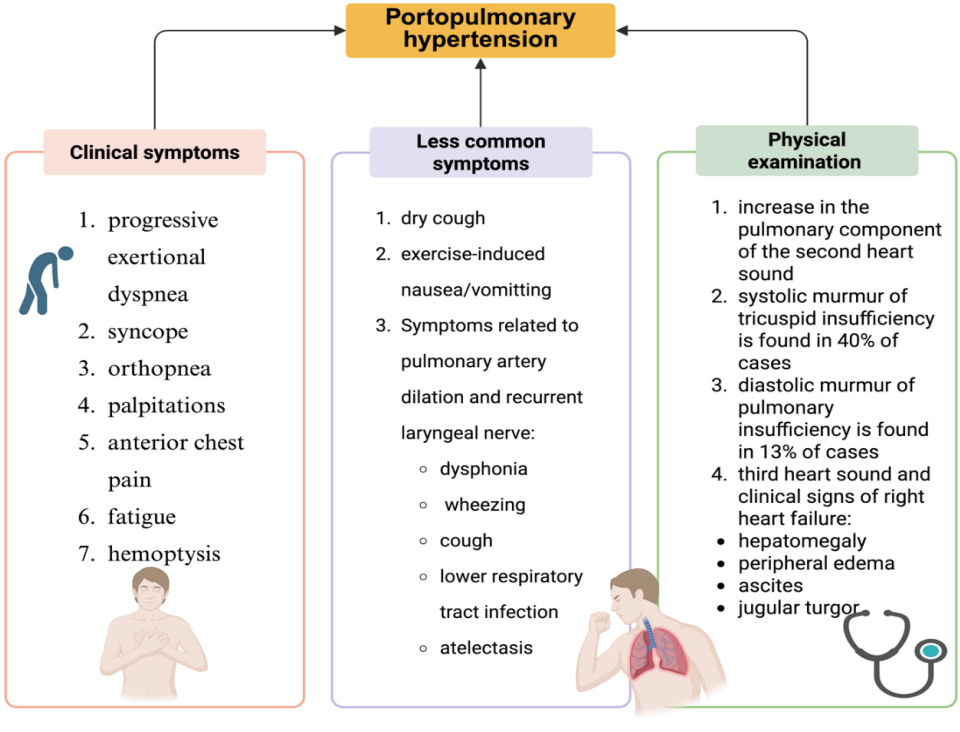

Figure 2. Clinical symptoms and physical examination.

The increase in pulmonary vascular resistance causes the loading of the right heart, which will cause right ventricular (RV) hypertrophy, right heart failure, and death.

Pathological changes in the final stage of this condition include intimal and medial proliferation, plexiform lesions, and fibrotic venular obstruction [16].

Clinical presentation

Clinically, the symptoms are nonspecific and are usually due to worsening right ventricular dysfunction [5,32,33]. The clinical symptoms and physical examination are presented in figure 2.

The six-minute walk test (6MWD) is a test that plays a key role for the evaluation and management of PAH patient, exercise capacity measured by 6MWD and hemodynamic parameters (right atrium pressure gender and cardiac output) were significant markers of survival in the French Registry [5,34].

Screening strategies

The International Liver Transplant Society recommends TTE screening for all patients with symptomatic cirrhosis suspected of having PoPH, as well as those being evaluated for Transjugular intrahepatic portosystemic shunt (TIPS) or LT [35]. However, TTE has several limitations in screening for PoPH:

- it often overestimates or underestimates pulmonary arterial systolic pressure (sPAP), which may result in unnecessary referrals for RHC or missed diagnoses
- the diagnostic accuracy is compromised in patients with obesity or poor acoustic windows, making it less reliable in certain populations

Echocardiography is the preferred screening tool for PoPH, with 85% sensitivity and 83% specificity [11]. Therefore, it should be recommended for all patients with chronic liver disease experiencing dyspnea or unexplained hypoxemia and those undergoing LT evaluation [1,36,37]. A study of 152 LT candidates found that raising sPAP cut-off above 30 mmHg could reduce unnecessary RHC by minimizing false positives [38].

According to ESC/ERS, it is recommended to use the peak tricuspid regurgitation velocity (TRV) and not the estimated sPAP in order to assign the echocardiographic probability of PH. Other echocardiographic signs include:

- RV dilation,
- increased RV/LV ratio > 1
- flattening of the interventricular septum (IVS)
- increased inferior vena cava (IVC) diameter with decreased inspiratory collapse
- right ventricular outflow tract tachycardia (RVOT) < 105 ms
- tricuspid annular systolic excursion (TAPSE) < 18 mm
- fractional change in RV area (RV-FAC) <35%
- tissue Doppler index at the tricuspid annulus, with assessment of S wave velocity < 9.5 cm/s
- RV area > 18 sq.cm
- TRV > 2.8 m/s
- pericardial effusion

The TAPSE/sPAP ratio can be a useful tool for diagnosing PH [5,39-41].

According to a study conducted on a group of 86 patients with liver cirrhosis, PoPH was found in 8 patients, presenting the following ultrasound signs: dilation of the right atria and ventricles, increased systolic pressure at the level of the RV, increased diameter of the left ventricle, tricuspid insufficiency, increased maximum pulmonary velocity, pulmonary insufficiency, increased atrial volume, increased diameter of the IVC, increased collapse of the IVC [14].

The American Association for the Study of Liver Diseases (AASLD) recommends routine echocardiographic monitoring for all patients awaiting liver transplantation. Given the coagulation risks in cirrhotic patients, right heart catheterization (RHC) is not suitable as a screening tool in this population [11,42].

However, RHC is advised when right ventricular systolic pressure exceeds 45 mmHg, according to AASLD guidelines. In comparison, the European Respiratory Society (ERS) and the Mayo Clinic recommend RHC at a slightly higher threshold of 50 mmHg [1].

Screening for PoPH remains challenging due to limitations in current methodologies. While TTE is the most practical initial screening tool, its limitations necessitate confirmatory RHC in suspected cases.

Biomarker-based screening approaches

Several biomarkers have been studied and could prove to be potent diagnostic and prognostic indicators and a solution for evaluating the response to therapies. Using circulating biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) has been proposed to enhance PoPH screening [43]. Bone morphogenetic protein-9 (BMP9) is a highly sensitive and specific biomarker for PoPH, accurately predicting transplant-free survival and the occurrence of PAH in liver disease [44]. DuBrock et al. demonstrated that macrophage migration inhibitory factor (MIF) shows promise as a screening tool for detecting PoPH in high-risk patients with liver disease and portal hypertension. Additionally, it may serve as a valuable prognostic indicator [45].

While these biomarkers offer a promising solution, standardized thresholds, validation in large cohorts, and cost-effectiveness studies are needed before they can replace invasive diagnostics. Future research should focus on integrating echocardiographic parameters with biomarker-based screening algorithms to improve diagnostic accuracy in resource-limited settings.

Diagnostic challenges

Early diagnosis of PoPH remains challenging due to the **nonspecific nature of symptoms,** overlap with other cardiopulmonary conditions, and **limited availability of RHC** in resource-limited settings. **While TTE is widely used as an initial screening tool, its limitations result in both false positives and missed diagnoses**.

RHC remains the gold standard for diagnosing PoPH, yet its invasive nature, cost, and need for specialized expertise render it impractical in resource-limited settings.

This raises an important question: how can clinicians accurately diagnose PoPH without access to RHC? Beyond its diagnostic role RHC provides critical insights into the severity of hemodynamic impairment, assesses response to PAH-specific therapies, and helps establish prognosis, guiding clinical decision-making in PAH management [46].

In a study of 335 patients with portal hypertension, only 2 (1.1%) met the older diagnostic criteria for PoPH, while 6 (3.3%) were diagnosed under the newer, lower mPAP threshold, highlighting the impact of updated definitions on case detection [47].

To confirm the diagnosis mPAP and PVR must remain increased while maintaining PAWP within normal limits. However, patients with decompensated liver disease may show elevated mPAP, PVR, and PAWP due to other hemodynamic changes like hyperdynamic circulation or fluid overload, making interpretation more complex) [16,48,49].

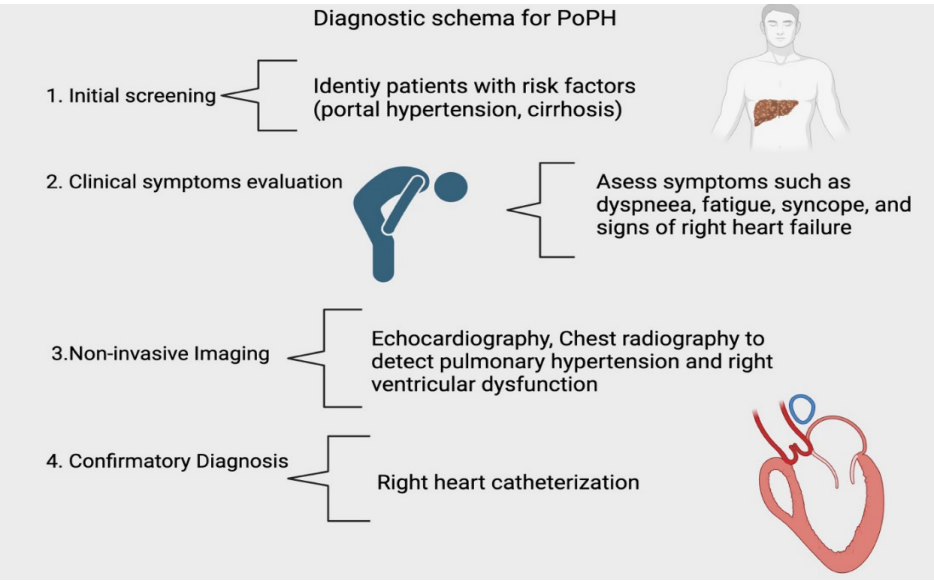

Figure 3. A diagnostic schema.

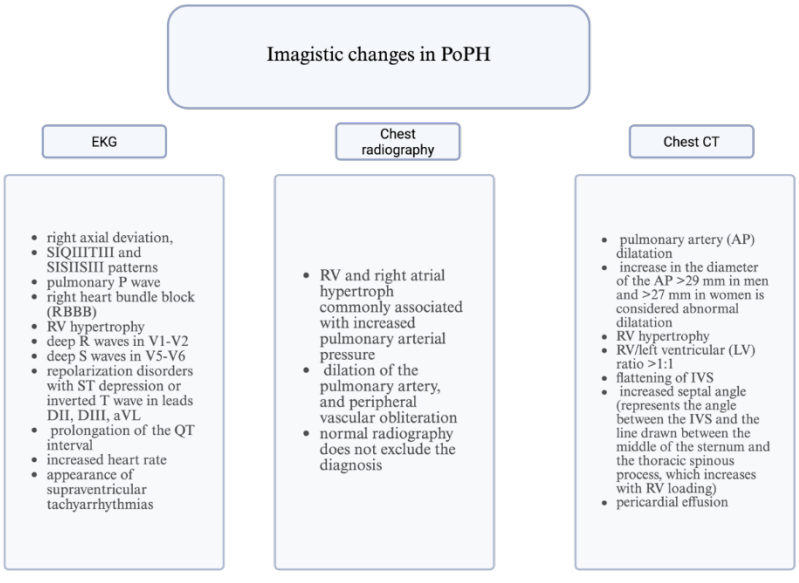

Figure 4. Imagistic changes in PoPH.

RHC remains the gold standard for diagnosing pulmonary hypertension but it remains an invasive procedure, raising concerns in cirrhotic patients with coagulopathy, with potential complications sush as bleeding, infection, arrythmias. Barriers to performing RHC may include limited physician knowledge or training, financial constraints, and concerns regarding the risks associated with its invasive nature [50].

In low-resource settings where RHC is unavailable, alternative screening strategies, such as echocardiographic risk scores combined with biomarker panels, could help bridge the diagnostic gap. However, the lack of guideline recommendations on noninvasive screening protocols continues to hinder their implementation. Addressing these gaps is crucial to improving equitable access to diagnosis and care for patients worldwide.

The characteristic signs of PH that appear on the ECG, chest radiography and chest computer tomography (CT) are illustrated in figure 4 [5,41,50-55].

The differential diagnosis is made with other causes of PH (heart failure, collagen diseases, HIV infection, primary forms of PH, and medication-induced PH) and with pulmonary diseases (thromboembolism, chronic lung diseases) [56].

Hepatopulmonary syndrome (HPS) is the most common pulmonary hemodynamic condition in these patients and is characterized by the triad of liver damage or portal hypertension accompanied by pulmonary vascular abnormalities and gas exchange disorders, leading to hypoxemia. It affects 5-32% of those with end-stage liver disease and significantly increases mortality [52].

Intrapulmonary vasodilation is the main factor that determines the alteration of gas exchange in patients with liver cirrhosis, but the exact mechanism of vasodilation is not fully elucidated. The primary mechanism is intrapulmonary vasodilation, largely driven by excess nitric oxide production, endothelin imbalances, and bacterial translocation associated with portal hypertension [57,58]. This leads to arteriovenous shunting and ventilation-perfusion mismatch. While symptoms are often nonspecific, dyspnea being the most common, HPS may coexist with PoPH [3,59,60]. Relief of elevated pulmonary vascular pressures and improvement of cardiac function from PoPH patients may worsen the symptoms of underlying HPS [3,61-63]. Major causes of death include right heart failure, sepsis, gastrointestinal bleeding, and hepatocellular carcinoma, especially in patients with low cardiac output and high right atrial pressure [35,64,65].

Treatment approach and future directions

Currently, there is limited knowledge regarding the treatment of PoPH patients. Several factors contribute to this gap, including the exclusion of PoPH patients from clinical trials due to concerns about hepatotoxicity, the rarity of the condition, and the tendency to group PoPH patients with those who have idiopathic PAH to achieve adequate sample sizes. Except for one, all randomized studies leading to Food and Drug Administration (FDA) approval of PAH-specific therapies excluded PoPH patients, with evidence for their use in PoPH derived mainly from small observational studies [66-69]. Additionally, PoPH may be underdiagnosed due to its lower prevalence compared to more common complications of liver disease [70].

Nonspecific treatment

Anticoagulation is not recommended in patients with PoPH, especially in patients with severe hepatocellular insufficiency, thrombocytopenia, or untreated esophageal varices [71,72]. Diuretics can also be used in patients with ascites or edema. The use of beta-blockers in the treatment of esophageal varices, it is controversial, as they decrease exercise capacity in these patients. Thus, treatment with angiotensin-converting enzyme (ACE) inhibitors or sartans is recommended.

Use of PAH-specific therapies

The treatment of PoPH consists of vasomodulating therapy and the main classes are represented by prostacyclin agonists, endothelin receptor antagonists, phosphodiesterase V inhibitors, and guanylate cyclase stimulators [1]. Before initiating treatment, it is crucial to evaluate the patient's living conditions, social support, treatment adherence, ability to manage PAH-specific therapies, and financial aspects [73].

Unfortunately, these treatment decisions are limited to one randomized control trial (RCT) and case series and small observational cohort studies, remaining unclear the optimal choice of vasomodulating therapy, administration route, and escalation strategy [3].

Another challenge is treatment response variability. Some patients exhibit dramatic hemodynamic improvements with PAH-targeted therapy, enabling successful LT, while others experience minimal benefit. Are genetic factors influencing drug metabolism responsible for these differences? Should treatment regimens be personalized based on biomarker-driven therapy selection? The lack of clear answers to these questions highlights the need for precision medicine approaches in PoPH.

The strongest evidence for targeted therapy in PoPH is from the PORTICO RCT, where 85 patients were randomly assigned to macitentan (n=43) or placebo (n=42) and after 12 weeks there was a 35% reduction in pulmonary vascular resistance with macitentan versus placebo [74].

Prostacyclin agents are considered the most effective therapy for PAH

In a study of 15 PH patients, intravenous epoprostenol significantly improved PVR, mPAP, and cardiac output ($p < 0.01$). Long-term use further reduced PVR, though 6 out of 10 patients on this therapy died [75]. In contrast, inhaled iloprost showed no improvement in

hemodynamic measures in PoPH, and the effectiveness of prostacyclin therapy in PoPH may depend on the delivery method [3,76].

Endothelin receptor antagonists are used for patients with functional class II or III (according to WHO), either as monotherapy or combined with phosphodiesterase inhibitors [1]. A non-selective antagonist of endothelin A and B receptors (Bosentan) is effective in a study conducted by Savale et al. with the improvement of hemodynamic impairment. In the short term, improvements were observed in the degree of heart failure, 6MWD exercise test, right atrial and AP pressure, cardiac index, PVR, and O_2 saturation. These improvements were more significant in patients with Child-Pugh class B liver cirrhosis compared to those with Child-Pugh class A [77].

Ambrisentan is a selective antagonist of the endothelin A receptor. A study of 13 patients with Child-Pugh class A liver cirrhosis demonstrated significant hemodynamic improvement, similar to Bosentan [78]. Macitentan significantly improved PVR in the PORTICO study of 85 patients (42 of whom received a placebo) with PoPH, without hepatic adverse effects. Patients receiving Macitentan had a 35% reduction in PVR compared to those receiving placebo [74].

Sotatercept over a fusion protein that captures activins and differentiation factors involved in PH is used for patients with functional class II or III (according to WHO), which causes improvement in the 6MWD exercise test [79].

Another class of drugs, phosphodiesterase V inhibitors, Silfenafil, and Tadalafil, which inhibit the hydrolysis of cyclic guanosine monophosphate in endothelial cells, which determines the potentiation of the vasodilatory effect of nitric oxide, has proven to be useful in improving the hemodynamics of these patients. In a study conducted by F Reichenberger [80] on a group of 14 patients with moderate/severe PoPH treated with oral Sildenafil, improvement in exercise test results and decreased natriuretic peptide levels were observed after 3-12 months of treatment with Sildenafil.

Riociguat, soluble guanylate cyclase activator (sGC), that is approved in two separate PH indications (PAH and inoperable or persistent/recurrent chronic thromboembolic PH) significantly improved exercise capacity and functional class (FC) and delayed clinical worsening in patients with PAH in a 12-week randomized placebo-controlled PATENT-1 trial, and 6MWD and WHO FC improvements were sustained over two years in the open-label extension, PATENT-2 [81].

Many of these specific therapies undergo hepatic metabolism, heightening the risk of drug toxicity in cirrhotic patients. Therefore, there is an urgent need to develop new agents with minimal hepatic metabolism to enhance safety and efficacy

Patients with advanced liver disease and PoPH often experience symptoms such as fatigue, dyspnea, dizziness, ascites, and edema, which can overlap with side effects of PAH-specific therapies (e.g., nausea, vomiting, anorexia, and fluid retention), complicating the differentiation between disease-related manifestations and medication effects [73,82-84].

Several future challenges remain in the treatment of PoPH patients. These include the lack of long-term treatment data, the need for further studies on long-term survival and quality of life in PoPH patients receiving PAH-specific therapies, and the limited available data on cirrhotic patients. Additionally, there is a growing need for personalized treatment strategies tailored to disease severity, as well as further exploration of the potential role of genetic and biomarker-driven therapies.

Management of portal hypertension

Treatment of PH includes the prevention of variceal hemorrhage, the treatment of the acute bleeding episode, and preventing rebleeding in patients who survived a first bleeding episode. The prevention of the first bleeding from the esophageal varices is made by screening through endoscopy [85]. The use of beta-blockers in the treatment of esophageal varices is controversial, as they decrease exercise capacity in these patients. Thus, treatment with ACE inhibitors or sartans is recommended. TIPS is an intervention that increases the filling pressure in the RV, increases CO, increases PVR and pressure or volume of the right atrium, therefore heart failure and severe PoPH are absolute contraindications, while moderate PoPH is a relative contraindication [35,86-88].

Liver transplantation eligibility

The role of LT in PoPH remains one of the most debated issues in hepatology and pulmonary medicine. Unlike HPS where transplantation is a clear indication, PoPH presents a high perioperative risk due to increased pulmonary vascular resistance and right ventricular dysfunction.

In 1991, LT had a fatal outcome in patients with severe PoPH. Subsequent case reports suggested that PoPH was non-reversible and posed an unacceptably high risk for LT in patients who did not respond to pulmonary vasodilators [35,89]. However, the use of effective PAH-specific therapy has led to successful LT in some individuals, allowing for discontinuation of PAH-specific treatment post-transplant [65]. Echocardiographic monitoring of patients who received pre-transplant therapy and LT revealed normal right heart function and domains, suggesting successful treatment of PoPH [35,90-92].

Unlike HPS, where LT is an indication, in PoPH the indications for OLT are controversial due to the unpredictable posttransplant hemodynamic response, but LT should be considered in patients with moderate PoPH or those with mPAP values between 35 and 35 mm/Hg who

can successfully lower mPAP below 35 mm Hg following post-vasodilator therapy [1]. An mPAP value above 50 mmHg (45 mmHg in some centers) represents an absolute contraindication for LT, and exceptionally patients with mPAP above 50 mmHg may survive LT, in the absence of specific pulmonary treatment, if the cardiac index is preserved [35,81,93-95].

In the post-liver transplant period, treatment of PH should be continued, unless it contributes to hemodynamic instability [96].

Since 2006, PoPH patients have been eligible for Model for End-Stage Liver Disease (MELD) exception-based priority listing under Organ Procurement and Transplantation Network guidelines [65]:

1. Moderate to severe PoPh diagnosis confirmed by RHC (mPAP of 35 mmHg or grater, PVR of 3 WU or 240 dynes*sec/cm $^{-5}$ or greater, and PAWP 15 mmHg or less).
2. PAH-specific therapy initiated (mPAP of less than 35 mmHg, PVR of less than 5 WU or 400 dynes*sec/cm $^{-5}$, satisfactory RV function by TTE)
3. MELD exception updated every 3 months (grant additional MELD exception if RHC satisfies criteria 2)

Should MELD exception points be granted to PoPH patients if transplant success is uncertain? A study analyzing data from the Organ Procurement and Transplantation Network database found that 504 unique PoPH MELD exception points were granted between 2006 and 2019. Over time, researchers observed an increase in patient age, a rise in MELD scores, and worsening liver disease severity at the time of listing for LT. However, there was no significant difference in unadjusted waitlist survival over time. Similarly, among those who underwent LT, unadjusted post-transplant survival remained unchanged [97].

Based on the recommendations of the International Liver Transplant Society Practice Guidelines it is suggested that PAH-targeted therapy should be initiated in PoPH when the mean pulmonary arterial pressure (mPAP) is ≥35 mmHg. Patients should be informed that a pre-LT mPAP of ≥35 mmHg, along with elevated PVR is associated with increased morbidity and mortality. TTE screenings are advised while patients await LT, although the optimal screening interval remains uncertain [8]. Additionally, PoPH with an mPAP between 45 and 50 mmHg or higher should be considered an absolute contraindication to LT [35]. This raises questions of fairness—should transplantation policies be standardized globally to avoid disparities in access?

Without treatment or LT, PoPH prognosis is poor, with 1-year survival at 35–46% and 5-year survival at just 4–14% [1]. Patients with severe or uncontrolled PH face high perioperative risk during LT. In a study of 43 untreated PoPH patients evaluated for OLT, 35% (15 patients) died, with 93% of deaths caused by cardiopulmonary complications. Mortality varied by mPAP: 100% for mPAP >50 mmHg, 50% for 35–50 mmHg, and 0% for <35 mmHg. In another study by Savale et al., 35 of 49 PoPH patients underwent LT; 8 died post-transplant, 5 due to PoPH. Among survivors, intravenous epoprostenol was discontinued, and 5 to 15 continued treatment with endothelin receptor antagonists or phosphodiesterase inhibitors. Post-transplant survival was 80% at 6 months and 77% at both 1 and 3 years [98].

Echocardiographic monitoring of patients who received pre-transplant therapy and LT revealed normal right heart function and domains, suggesting successful treatment of PoPH [35,90-92].

Although OLT improves clinical outcomes in many patients, the precise impact of LT on ameliorating/reversing pulmonary vascular disease is not well established [3].

Ethical dilemmas in liver transplantation

The decision to offer LT to patients with PoPH presents significant ethical challenges. Unlike HPS, where LT is a clear indication, PoPH carries substantial perioperative risks, particularly in patients with mPAP exceeding 50 mmHg. The question arises: should these patients be prioritized for transplantation, knowing their elevated perioperative mortality rates, or should scarce donor organs be allocated to patients with better survival prospects?

Table II. Treatment approach.

Treatment approach	
General measures	Avoid anticoagulants in cirrhotic patients, use beta-blockers cautiously, manage edema with diuretics.
Vasomodulating therapy	Prostacyclin agonists (e.g. epoprostenol, endothelin receptor antagonists (e.g. macitentan) and PDE-5 inhibitors (e.g. sildenafil).
Portal hypertension management	Endoscopic variceal screening and management, TIPS for the suitable patients.
Advanced interventions	For the eligible patients, liver transplantation with pre-transplant optimization of the pulmonary pressures.

LT, whether from a live or deceased donor, is lifesaving but faces significant barriers to equitable access, especially in critically ill patients and those with acute-on-chronic liver failure. LT rates vary globally, with the lowest rates in lower-income countries due to resource limitations, late disease presentation, and low donor awareness [99]. While the role of LT in PoPH remains controversial, recent studies highlight its survival benefits and potential for discontinuing PAH-specific therapy, but due to the limited availability of donors, further research is needed to identify the patients who would benefit most.

Patient perspective

Patients with PH suffer both physical and mental health challenges, being a high morbidity and having high mortality rates. A cross-sectional study of 155 patients with PAH showed that greater 6MWD correlated with better health-related quality of life score, however hemodynamic measurements did not correlate with health-related quality of life scores [100]. Another study of 559 patients with PH showed that these patients suffered more impairments in both physical and emotional domains than the U.S. population normative values [101].

Prognosis

Generally, the prognosis is poor and PAH therapy and LT are the only effective treatment for PoPH [1]. Although from a hemodynamic point of view, patients with PoPH are more stable than patients with IPAH/ Heritable PAH, the mortality rate is similar or even greater. The REVEAL study shows that patients with PoPH have a worse survival rate than IPAH / Heritable PAH, respectively 67% versus 85% in 2 years and 40% versus 64% in 5 years [102]. For a better survival rate, patients with PoPH need LT, but a study reported a mortality rate of 36% in patients with PoPH after LT [12,31]. Amelioration of clinical outcome has been shown by different treatment modalities of targeting pulmonary vascular remodeling and portal hypertension therapies, but the optimal choice of vasomodulating therapy, administration route, and escalation strategy remain unclear.

Conclusion

In conclusion, portal hypertension is an almost unavoidable complication of cirrhosis, which is responsible for additional complications such as PoPH. Despite advancements in screening, diagnosis, and targeted therapies, major challenges persist, including the need for optimized treatment approaches, better-defined transplant eligibility criteria, and improved long-term outcomes. Echocardiography is a valuable screening tool, but RHC remains the gold standard for diagnosis. PAH-specific therapies have improved pulmonary hemodynamics and transplant eligibility, yet concerns regarding hepatic metabolism, response variability, and long-term outcomes persist. LT may offer a potential cure in selected patients, but careful evaluation and pre-transplant hemodynamic optimization are crucial. The high risk of death and the poor survival rate make this a lethal disease. These patients are in need of a multidisciplinary team with the involvement of hepatologists, pulmonologists, cardiologists and liver transplant specialists. Further research is needed to better understand the pathophysiology of the disease, improve screening strategies, develop individualized treatment plans, optimize patient outcomes, and explore innovative therapeutic targets. Collaborative research efforts are essential to advance our understanding and treatment of this multifaceted severe condition.

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Figures 1, 2, 3, 4, were created with BioRender.com.

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