Chapter

Pulmonary Issues in Chronic Liver Disease

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Abstract

Pulmonary complications are important cause for high incidence of mortality in chronic liver disease patients admitted to the intensive care unit. Up to 50–70% of patients report shortness of breath, reflecting the high prevalence of respiratory failure, defined as an arterial pressure of oxygen (PaO_2) of less than 60 mm Hg. The causes of respiratory failure are multifactorial in chronic liver disease. Although much attention is given to the pathologies of pulmonary microcirculation (i.e., portopulmonary hypertension and hepatopulmonary syndrome), these specific conditions are found in <20% of cirrhotic patients. The impact of liver disease on respiratory function extends far beyond these two specific conditions and include micro-aspirations associated with hepatic encephalopathy, fluid overload, hepatic hydrothorax, and basal atelectasis and restriction due to large ascites. The impact of altered bile-acid composition induces a shift in the gut microbiome and this may shed a new light on the molecular basis for the 'gut–liver–lung axis' as the driver for multiple organ failure. This chapter focuses on current evidence surrounding the prevalence, management, and complications from various etiologies of respiratory insufficiency in end-stage liver disease patients.

Keywords: chronic liver disease (CLD), portal hypertension, pulmonary hypertension, portopulmonary hypertension, hepatopulmonary syndrome, hepatic hydrothorax

1. Introduction

Pulmonary disorder in liver disease can broadly be classified into the following 3 groups:

1. Pulmonary disorders which are direct sequelae of liver disease and portal hypertension (hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH), and hepatic hydrothorax (HH)

2. Coexisting common respiratory disease (i.e., asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease) along with pulmonary disease specific to liver disease

3. Disorders that affect both liver and lungs (Alpha-1 antitrypsin deficiency, cystic fibrosis, sarcoidosis, hereditary hemorrhagic telangiectasia)

Chronic liver disease (CLD) and portal hypertension are associated with an imbalance between vasoconstrictors and vasodilators leading to hyperdynamic circulation from splanchnic and systemic vasodilatation. This continued exposure to vasoactive and proliferative mediators leads to remodelling processes in the pulmonary vascular bed, either in the form of diffuse telangiectasia (in HPS) or hyperplastic lesions in terminal pulmonary arterioles (in POPH) [1]. Effect of these pulmonary vascular and parenchymal abnormalities is further augmented by mechanical restriction due to ascites. The spectrum of presentation of these respiratory insufficiencies is varied, with differences in symptoms, signs, pulmonary function tests, ultrasound findings, and gas exchange abnormalities.

Although HPS and POPH are widely discussed in the literature, finding an isolated pulmonary abnormality in end-stage liver disease is rare in real clinical circumstances. There can be multiple diseases (pleural effusion and HPS, or COPD and POPH) coexisting in the same patient. Identifying different contributors, quantifying their severity, and their impact on overall clinical picture is important for patients' symptomatic treatment, optimization before transplantation, and perioperative management.

A comprehensive understanding of potential respiratory pathophysiology that may complicate liver disease and liver transplantation (LT) is essential with the aim of inclusive management. Disorders that affect both the liver and lungs are beyond the scope of this book chapter. This chapter will deal with chronic liver disease's direct and indirect effects leading to respiratory insufficiency.

2. Hepatopulmonary syndrome

HPS is an oxygenation defect occurring in patients with liver disease and/or portal hypertension resulting from intrapulmonary vascular dilatations (IPVDs). HPS may also manifest in acute liver failure, ischemic or viral hepatitis, and portal vein thrombosis. The prevalence of HPS is around 5–30%, while isolated vasodilatation can be found in up to 60% cirrhotic without evidence of arterial hypoxemia [2]. HPS is a progressive disease, and gradual deterioration occurs in 87% of cases with a monthly decline in PaO_2 of 1.1 ± 1.4 mm Hg [3]. Patients with HPS are frequently asymptomatic, resulting in under-recognition of the disease and a delay in diagnosis. This delay in diagnosis and LT is associated with increased mortality [2].

2.1 Suspecting the possibility of HPS

The typical symptom of HPS is dyspnoea on exertion (DOE) and in severe cases Dyspnoea at rest. However, DOE is nonspecific in the case of cirrhosis, and HPS patients may be asymptomatic at mild to moderate severity. This indicates that we should actively screen the patients with cirrhosis for HPS. Clinical signs may include digital clubbing, cyanosis, and diffuse telangiectasias. Although classically described in HPS, **platypnea** (dyspnoea worsening when moving from supine to upright position) and **orthodeoxia** (>5% or >4 mm Hg decrease in SPO_2 or PaO_2, respectively, after changing from supine to upright position) is observed in only in 18–20% of patients with HPS [4]. The coexistence of other pulmonary diseases, such as including COPD, asthma, and interstitial lung disease, should be investigated, as they may exacerbate clinical symptoms and gas exchange abnormalities.

2.2 Screening

Pulse oximetry is easy to use, readily available and is a cost-effective tool to identify hypoxemia. Oxygen saturation < 96% identifies all patients with hypoxemia (PaO_2 < 70 mm Hg) at sea level [5]. In cirrhotic children hyperaemic arterialized capillary blood gas determination found better screening tool than pulse oximetry [6]. A recent study has found that pulse oximetry is an insensitive screening test for severe HPS in LT candidates and showed that a SaO_2 of 94% provides poor sensitivity (22.1%) and specificity (89.8%) to detect severe HPS [7]. However, pulse oximetry seems to be a widely accepted tool to exclude the diagnosis of HPS. To detect all patients with HPS, ABG analysis should be done if oxygen saturation <96%.

2.3 Diagnostic criteria

The hallmark of HPS is intrapulmonary vascular dilatations (IPVDs) which leads to oxygenation defect in the setting of advanced liver disease, portal hypertension, or congenital portosystemic shunts. Abnormal oxygenation is defined by an elevated resting alveolar-arterial oxygen gradient [P(A-a) $O_2 \geq 15$ mm Hg or ≥20 mm Hg if age >64 years] while breathing room air in the sitting position, in the absence of other than mild pulmonary function test abnormalities (**Table 1**) [1, 2]. IVPDs can be demonstrated by contrast-enhanced transthoracic echocardiography (CE-TTE) or Technetium-99 m (Tc99m) labelled macro-aggregated albumin (MAA) lung perfusion scan [8]. **Table 1** enumerates the diagnostic criteria for HPS.

The severity of HPS is determined by the degree of hypoxemia on arterial blood gas. Based on the European respiratory society (ERS) Task Force, severity is graded as mild ($PaO_2 \geq 80$ mm Hg), moderate (PaO_2 = 60–79 mm Hg), severe (PaO_2 = 50–59 mm Hg), and very severe (PaO_2 < 50 mm Hg) [8]. So PaO2 is not essential to diagnose HPS, it is required to classify for severity of HPS.

Despite well-defined criteria for its diagnosis, HPS is often inaccurately diagnosed because of the lack of use of standard diagnostic criteria, or attempt to diagnose and classify during acute illness, and sometimes from diagnostic confusion with POPH and

	Diagnostic criteria	Investigations
1	Abnormal oxygenation defined by elevated alveolar-arterial oxygen gradient (≥15 mm Hg or ≥20 mm Hg if age >64 years), in the **absence of other than mild pulmonary function test abnormalities**[a]	Arterial blood gas analysis while patient breathing room air, in sitting position at rest
2	Presence of liver disease and or portal hypertension/ portosystemic shunts	Clinical diagnosis (ascites, gastroesophageal varices, splenomegaly) or portal pressure
3	Demonstration of Intrapulmonary vasodilatations	Positive CE-TTE or >6% brain uptake on Tc99m MAA lung perfusion scan

[a]*Other than mild pulmonary function test abnormalities: A forced vital capacity <70% of predicted for restrictive ventilatory defect. The obstructive ventilatory defect can be defined by a forced expiratory volume in 1 second/forced vital capacity ratio <0.70 together with forced expiratory volume in 1 second percent predicted <80%. CE-TTE (contrast-enhanced transthoracic echocardiography).*

Table 1.
Diagnostic criteria for HPS.

other associated respiratory diseases. Therefore, it is important that diagnostic criteria be carefully applied whilst simultaneously demonstrating the absence or only presence of mild form of coexisting pulmonary disease [9].

The response to 100% inspired oxygen is much better in patients with HPS alone as compared to HPS with an additional pulmonary disease and it should be used whenever in doubt [9]. The response to 100% oxygen may also have prognostic importance as it demonstrates significant scope of improvement in oxygenation.

2.4 HPS vascular patterns

On the basis of pulmonary angiographic findings, HPS can be divided into Type I and II (**Table 2** describe pulmonary angiographic patterns of HPS). On the basis of, response to 100% inspired oxygen (PaO_2 < 300 mm Hg) and presence of discrete abnormalities on high-resolution chest computed tomography, subgroup of patients can be identified who should proceed to get pulmonary angiography [10]. Rarely coil embolization can be successfully used to improve hypoxemia in type I (diffuse) and type II (discrete) HPS [11].

2.5 Demonstration of IPVDs

IPVDs can be demonstrated non-invasively by saline contrast enhanced transthoracic echocardiography or invasively by 99mTc labelled macro-aggregated albumin (MAA) lung perfusion scan.

2.5.1 Contrast-enhanced transthoracic echocardiography (CE-TTE)

The normal diameter of pulmonary capillaries is less than 8 to 15 μm [12]. The size of microbubbles created by saline agitation is more than 10 μm in diameter, which due to greater size, does not cross through the normal pulmonary capillary vasculature after intravenous injection. The delayed appearance of these microbubbles in the left heart after 3 or more cardiac cycles after visualization in the right heart demonstrates IPVDs. CE-TTE can differentiate between IPVDs and intracardiac shunts (i.e., due to persistent foramen ovale or atrial septal defect). In intracardiac shunts microbubbles appear early in the left heart (i.e., within 1–2 cardiac cycles) [13]. It is minimally invasive, radially available and highly sensitive examination and is gold standard for demonstrating IPVDs. CE-TTE also has some limitations. For example, positive detection rate is 40%, in patients who have normal arterial blood gas content. Therefore, demonstrating IPVDs, using CE-TTE alone is not sufficient for the diagnosis of HPS [9].

	Angiographic finding	**Symptoms**	**Response to 100% Oxygen**
Type 1 minimal	Finely diffuse, spidery vascular abnormality	Hypoxemia	Excellent
Type 1 advanced (evolves from type 1 minimal	Diffuse spongy or blotchy appearance	Severe hypoxemia	Limited response
Type 2	Discrete, direct arteriovenous communications	Severe hypoxemia	Extremely poor response

Table 2.
Pulmonary angiographic patterns of HPS [10].

2.5.2 Nuclear/invasive testing

Another method to demonstrate IPVDs is lung perfusion scanning (peripheral venous injection of 20 μm 99mTechnetium labelled macro-aggregated albumin [MAA] with brain uptake >6%). Although this can quantify the IPVDs, it does not differentiate between intracardiac and intrapulmonary shunting and has lower sensitivity as compared to CE-TTE for the detection of mild or moderate HPS in adults. In children, MAA lung perfusion scans may have favourable sensitivity for detecting mild degrees of IPVD relative to CE-TTE. In HPS patients with coexisting respiratory problems abnormal brain uptake of 99mTcMAA after lung perfusion (uptake >6%) helps to distinguish and quantify the degree of hypoxemia caused by IPVDs versus hypoxemia due to nonvascular lung parenchymal abnormalities [13]. Although sensitivity of 99mTc-MAA is lower than that of CE-TTE, its specificity is higher for the diagnosis of HPS [9]. Whole-body uptake (>42.5%) of 99mTc-MAA was found superior to simple brain uptake (>5.8%) for demonstrating IPVDs [14].

2.6 Pathogenesis

The oxygenation defect in HPS has been ascribed to 3 mechanisms resulting from alterations in the alveolar microcirculation

i. Diffusion limitation

ii. Presence of direct arteriovenous communications

iii. Ventilation perfusion (V/Q) mismatch

Diffusion limitation occurs because oxygen needs to travels a more distance to bind hemoglobin due to vascular dilation. Direct arteriovenous communications bypass the alveolar microcirculation, resulting in the direct mixing of venous and arterial blood. V/Q mismatch is consequence of increased pulmonary blood flow due to microvascular alterations as compared to unchanged ventilation [15].

Work in the common bile duct model (CBDL) has identified underlying pathophysiologic triggers for 3 mechanisms that contribute to the development of hypoxemia in the HPS [16]:

1. Relaxation of blood vessels leading to vasodilation,

2. Angiogenesis leads to shunt formation, and

3. Alveolar dysfunction.

Endothelin-1 (ET-1) induced pulmonary vascular relaxation: Circulating ET-1 levels which increases in cirrhosis, has differential action on the sinusoidal and pulmonary vasculature. Although it acts as a potent vasoconstrictor for sinusoidal vasculature and increases sinusoidal and presinusoidal pressure, it causes nitric oxide (NO) mediated pulmonary vasodilatation [15].

Bacterial translocation, endotoxemia, and pulmonary inflammation: Due to portosystemic shunts bacterial translocation products and endotoxins reach the pulmonary circulation, where they induce the local release of chemotactic factors, which

then recruit immune cells. Pulmonary vascular monocytes in experimental HPS models have been found to increase production of inducible nitric oxide synthase and heme-oxygenase 1, leading to NO-mediated vasodilation and, increased production of the vasodilator carbon monoxide [15].

Angiogenesis and intrapulmonary shunt formation and Alveolar dysfunction: Increased pulmonary expression of proangiogenic factors occurs in HPS, which leads to angiogenesis and formation of intrapulmonary shunts [15].

2.7 HPS and liver transplantation

Liver transplantation (LT) is only definitive therapeutic option for HPS. Previously very severe hypoxemia (PaO_2 < 50 mm Hg) due to HPS was considered an absolute contraindication for LT [17]. However, further evidence showed that LT improves IPVDs, oxygenation, and even leads to complete resolution of HPS. HPS with PaO_2 < 60 mm Hg is eligible for MELD exception points to facilitate early transplant [18].

Hypoxemia associated with HPS is progressive and with worsening severity the risk of pre- and post-LT mortality increase [19]. In HPS patients with similar baseline PaO_2, brain uptake of 99mTcMAA and liver dysfunction, 5-year survival associated with LT found to be 76% versus 23% without LT [17]. Improvement in PaO_2 can be seen in all patients after LT by 12 months and subsequent normalization of the 99mTcMAA brain scan [17]. Once MELD exception points were implemented, both survival rates and post-transplant oxygenation improved in adults whereas only post-transplant oxygenation improved in children after LT [13].

A multivariate analysis of United Network for Organ Sharing (UNOS) data regarding MELD exception points granted to HPS patients found no association between waitlist mortality and severe hypoxemia, but a pre-LT PaO_2 < 45 mm Hg was associated with increased post-LT mortality [20]. In analysis of 1152 HPS patients listed for liver transplantation, there was high likelihood of getting transplanted if patient PaO2 < 45 mm Hg. After LT, patients with a PaO_2 < 45 mm Hg had lower long-term survival, however this difference became significant only after 2.6 years. The median survival was 11.5 years in this subgroup. This suggests that in patients with very severe HPS transplant may not provide long term survival benefit but they do benefit from LT [21].

In experienced centres, HPS patients with very severe hypoxemia ($PaO_2 \leq 50$ mm Hg) and oxygen dependence showed an overall survival of 86%, comparable to non-HPS patients undergoing LT. PaO_2 improved in all patients from a mean of 65.1 to 90.9 mm Hg, and all patients dependent on ambulatory oxygen were able to discontinue oxygen therapy [3].

2.8 Salient management points

Perioperative and intensive care management concerns in HPS patients who are going for LT are mainly related to hypoxemia. Following are some general guidelines that can be used during managing HPS patients:

i. Restrictive fluid therapy should be done to avoid fluid overload and pulmonary congestion.

ii. The choice of volatile anesthetic agents does not affect oxygenation

iii. Continuous monitoring of mixed venous oxygen saturation (SvO_2) should be carried out. If the mixed venous saturation falls below 65% on hepatic vascular exclusion, veno-venous bypass may be beneficial [22].

iv. Low tidal lung protective ventilation in a supine position should be employed

v. Early extubation should be done to prevent ventilator-associated pneumonia

vi. O_2 saturation should be maintained ≥85% with supplemental oxygen

vii. Due to chronic hypoxia, HPS patients develop an increase in hemoglobin, so their hemoglobin targets should be kept higher.

viii. Inhaled pulmonary vasodilators (nitric oxide) can be used to improve post-LT oxygenation

ix. ECMO can be used as a bridge to LT

x. Supplemental oxygen should be discontinued when O_2 saturation remains greater than 88% (rest, exercise, and sleep)

xi. High frequency nasal cannula and non-invasive ventilation should also be utilized to improve oxygenation

2.9 Severe post-transplant hypoxemia

Severe post-transplant hypoxemia is defined as need of 100% oxygen to maintain a saturation of ≥85% and this hypoxemia is out of proportion to any concurrent lung process. It occurs in 6–21% of patients with HPS after liver transplantation. It is associated with a peri-transplant mortality rate of 45% in patients with pretransplant $PaO_2 < 70$ mm Hg. Due to impaired hypoxic vasoconstriction in the dilated pulmonary vasculature and disproportionately increased vasoconstriction in normal pulmonary vasculature there is increased blood flow through the dilated vessels which results in enhanced worsening of V/Q mismatch is proposed mechanism for severe post-transplant hypoxemia. Trendelenburg position, pulmonary vasodilators, inhaled nitric oxide, intravenous methylene blue, and beta-blockers can be used to maintain oxygenation [23]. Non-invasive ventilation and high frequency nasal cannula can also be used to maintain oxygenation. Extracorporeal membrane oxygenation (ECMO) showed good outcomes in patients with HPS either as a bridge to LT or to aid recovery after LT with a median ECMO duration of 13 days and survival of 82.4%. ECMO is found to improve outcome in severe HPS as compared to other indications in LT [24].

3. Pulmonary hypertension (PH) and portopulmonary hypertension (PoPH)

3.1 Definition

Pulmonary arterial hypertension (PAH) which is secondary to portal hypertension is termed portopulmonary hypertension (PoPH). The elevation of mean pulmonary artery pressures (mPAP) is because of an increase in pulmonary vascular resistance

(PVR) with normal pulmonary artery wedge pressure (PAWP). PoPH hemodynamic diagnostic criteria are derived from Right heart catheterization (RHC) enumerated in **Table 3**. To diagnose PoPH all hemodynamic criteria should be met.

3.2 Severity of PoPH

Based on the mean values of pulmonary artery pressure on RHC, PoPH is classified as mild (25 ≤ mPAP < 35 mm Hg), moderate (35 ≤ mPAP < 45 mm Hg), and severe (MPAP ≥ 45 mm Hg). In contrast to HPS, there is no association between the severity of PoPH with the disease state of CLD [13].

3.3 New developments in pulmonary hypertension

Since 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, PH has been defined as mPAP ⩾ 25 mm Hg measured by RHC [25]. It was recognized that this upper limit of normal mPAP of 25 mm Hg was empirical and arbitrarily defined [26]. This definition remained unchanged and was adapted by liver transplant societies [13].

Recently, 6th World Symposium on Pulmonary Hypertension (WSPH) has reconsidered the hemodynamic definition of PH and decreased the threshold for PH (mPAP≥20 mm Hg) but kept PVR > 3 WU for precapillary PH [25]. This reconsideration was based upon a systemic review finding that mPAP at rest is 14.0 ± 3.3 mm Hg [27]. Two standard deviations of this, would suggest mPAP ≥ 20 mm Hg as upper limit of normal. This new cut-off (mPAP ≥ 20 mm Hg) to define PH is evidence based [25].

The new definitions of PH have been endorsed and expanded in guidelines proposed by the European Respiratory Society/European Society of Cardiology, including a revised cut-off mPAP but they also reduced the PVR cut off to >2 WU [28]. (New definition of PH shown in **Figure 1**.) These hemodynamic definitions are currently not adapted by liver transplant societies. Till this update is incorporated into liver transplantation assessment, we should use the definition adapted by International liver transplant society (ILTS) and shown in **Table 3**. However hemodynamic characterization into precapillary, isolated postcapillary, and combined post-precapillary PH can be done in CLD patients using cut-off given in **Table 3**.

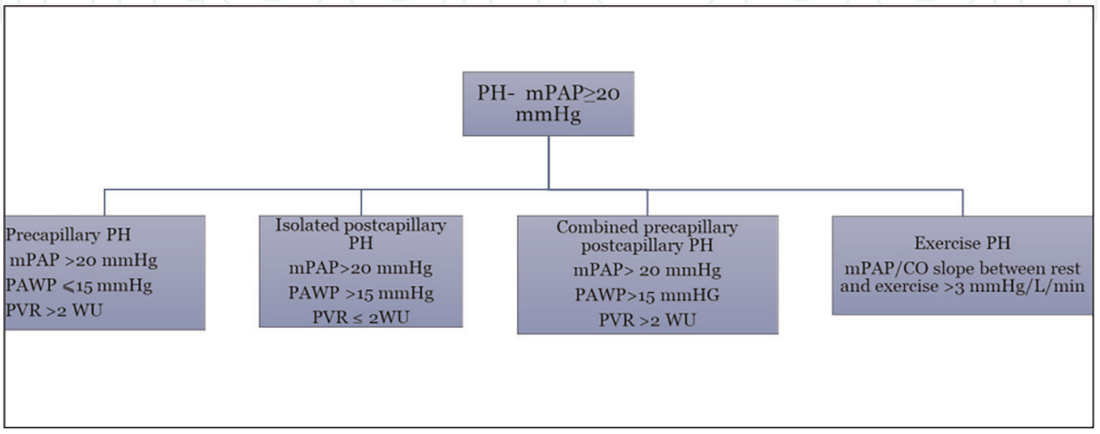

Figure 1.
New Hemodynamic definitions of pulmonary hypertension.

Portal hypertension (clinical diagnosis by gastroesophageal varices, splenomegaly, ascites) or portal pressure measurement	
mPAP >25 mm Hg	Hemodynamic parameters on Right heart catheterization with patient supine and at rest
PVR > 3 wood units (240 dynes/s per cm^{-5})	
PAWP < 15 mm Hg	

Table 3.
Diagnostic criteria for portopulmonary hypertension.

3.4 Classification of PH

PoPH is a type of precapillary PH. However, other forms of PH, such as PH due to left-sided heart disease, lung disease, and chronic hypoxemia, may coexist in chronic liver disease patients. So, understanding the other hemodynamic definition of PH is pertinent to the workup of PoPH.

Group 1: Pulmonary arterial hypertension (PAH). It includes Idiopathic PAH, POPH, connective tissue disease, HIV-associated PAH, congenital heart disease, and drug/toxin-induced PAH (Primarily precapillary).

Group 2 PH associated left-sided heart disease (both HF with preserved EF and reduced EF) Valvular heart disease (Primarily postcapillary).

Group 3 PH associated with lung disease and chronic hypoxia-related.

Group 4 Mostly includes chronic thromboembolic PH (CTEPH) (Primarily pre capillary).

Group 5 PH associated with the unclear or multifactorial mechanism.

3.5 Prevalence of PoPH

The prevalence of PoPH is assumed to be between 2% and 10% [29]. Up to 20% of patients undergoing LT have elevated pulmonary pressures; however, only 4% of patients have true PoPH [30]. More recent evidence shows the overall incidence of PH in patients undergoing LT is around 5.8%; of this, 73% are postcapillary PH, 14% PoPH, and 11.8% PH because of high cardiac output [31].

mPAP should not be used in isolation to characterize PoPH, as it does not define different pathological process. In cirrhosis PAP elevation may be caused by various chronic and/or acute pathological process and they have different management strategies and outcomes. Apart from primary pulmonary hypertension an increase in cardiac output (CO), left-to-right cardiac shunts, left heart disease (LHD), respiratory diseases, and various drugs may lead to elevated PAP [25]. Postcapillary PH is more common in CLD and it is characterized by elevated PAP and pulmonary artery wedge pressure (>15 mm Hg) and normal pulmonary vascular resistance (PVR) (<3 WU) [30]. This occurs due to volume overload because of secondary hyperaldosteronism and left ventricular dysfunction [32]. Unlike true PoPH, other types of PH do not seem to negatively affect the post-transplant outcome.

3.6 Screening and diagnosis

Dyspnea on exertion in the absence of gross ascites or pleural effusion, dyspnea when bending forward (Bendopnoea), chest pain, weakness, easy fatigability, peripheral edema, and syncope are symptoms of PoPH. However, these symptoms are

common in chronic liver disease. On clinical examination jugular venous distension, an accentuated and split P2, right-sided S3 gallop, and right ventricular heave may hint towards PoPH. Electrocardiograms may display right axis deviation, right bundle branch block, and right ventricular strain. Chest radiographs may show enlarged right-sided chambers and dilatation of the pulmonary arteries. Pulmonary function tests may show decreased diffusion capacity, and the ventilation/perfusion lung scan is usually normal except in cases of chronic thromboembolic PH. Arterial blood gases (ABGs) may show an increased alveolar-arterial oxygen gradient (PA-a, O_2), mild-to-moderate hypoxemia, and decreased arterial carbon dioxide tension (<30 mm Hg) [27].

3.6.1 Transthoracic echocardiography

The single most important screening tool for PoPH is transthoracic echocardiography (TTE), and it is recommended in all patients getting evaluated for LT [33]. In the absence of right ventricular (RV) outflow tract obstruction, the RV systolic pressure (RVSP) estimated by tricuspid regurgitation velocity (TRV) is equal to pulmonary artery systolic pressure (PASP).

A PASP cut-off of >38 mm Hg was reported as the most accurate PASP cut off value to detect all forms of PoPH (specificity of 83%, negative predictive value of 100%). Diagnostic accuracy further increases by adding the presence of right ventricular dilatation to PASP cut-off (sensitivity of 100%, specificity of 93%, and negative predictive value of 100%) [34]. As only moderate to severe PoPH affect outcome post-transplant, liver transplant units have differed on when to investigate further with RHC. Mayo clinic suggesting PASP cut-off of 50 mm Hg whilst [35], The American Association for the Study of Liver Diseases (AASLD) has recommended a value of PASP >45 mm Hg [34].

Using the modified Bernoulli equation, PASP can be estimated from the tricuspid regurgitant jet velocity (TRV) [PASP = $4V^2$ + right atrial pressure (RAP)]. PASP measurement is considered the standard for estimating PAP [36]. However, in Bernoulli equation square of velocity is used so even a slight measurement error will get amplified, further RAP estimations are often inaccurate. Due to these two reasons, recent guidelines for pulmonary hypertension recommend using the peak TRV (>2.8 m/s) in place of estimated PASP, for the echocardiographic probability of PH [27].

Other echocardiography parameters which should be assessed alongside of PASP are measures of RV function, including the tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (<35%), RV free-wall strain, and tricuspid annulus velocity (S′ wave). To differentiate between postcapillary (group 2) PH and other forms of PH both LV systolic function (LA size, LV hypertrophy, LV ejection fraction) and diastolic functions (e.g., E/A ratio, E/E′) should be assessed [27].

3.6.2 Right heat catheterization

Patients with liver disease frequently have volume overload and increased cardiac output, thus TRV tends to overestimate PASP. Hence, RHC is essential to confirm the diagnosis of PH and to distinguish true PoPH (with elevated PVR) from other types of PH (with a normal PVR). For a comprehensive assessment all measures listed in **Table 4** should be performed. All pressure measurements, including PAWP, should be taken at the end-expiration (without breath-holding manoeuvre) and should be averaged over at least three respiratory cycles [27].

Right atrial pressure, mean (RAP)
Pulmonary artery pressure, systolic (sPAP)
Pulmonary artery pressure, diastolic (dPAP)
Pulmonary artery pressure, mean (mPAP)
Pulmonary arterial wedge pressure, mean (PAWP)
Cardiac output (CO)
Pulmonary vascular resistance (PVR)
Mixed venous oxygen saturation (SvO2)
Systemic blood pressure

Table 4.
Parameters to be noted on RHC.

3.7 Differential diagnosis

PH is hemodynamically classified in precapillary PH, isolated postcapillary, and combined precapillary and postcapillary. As PH in chronic liver disease patients with multiple comorbidities can be due to PoPH or a combination of other precapillary and postcapillary causes it would be important to rule out a simple hyperdynamic state (PVR < 240 dynes/cm^5) or volume overload (PCWP >15 mm Hg), and more commonly postcapillary PH due to LV systolic or diastolic dysfunction. Some patients have elevated mPAP but low PVR and low PAWP. These patients do not fulfil the criteria for pre-, post-, or combined PH. This subgroup is described as unclassified PH and frequently characterized by elevated pulmonary blood flow which can be seen in patients with liver disease, airway disease, lung disease, or hyperthyroidism. Etiological workup for elevated pulmonary blood flow should be done [27] (**Table 5** showing differential diagnosis of PH in CLD).

3.8 Risk assessment

The severity of PoPH is based on resting mean PAP determined via RHC. It is graded as mild (25 ≤ mPAP < 35 mm Hg), moderate (35 ≤ mPAP <45 mm Hg), and severe (mPAP ≥ 45 mm Hg) [8].

		mPAP	PVR	PAWP	CO		Probable patologies
Diagnostic	POPH	↑	↑	↔	Mild ↑	Severe ↓	True POPH
Probable diagnosis	Hyperdynamic circulation and volume overload	↑	↔	↑	↑		Gross ascites AKI Albumin infusion
	PH with left heart disease	↑	↔	↑	HEpEF ↔	HFrEF ↓	Diastolic or Systolic dysfunction
	Unclassified PH	↑	↓	↓	↑↔↓		Congenital heart disease (CHD), liver disease, airway disease, lung disease, or hyperthyroidism

Table 5.
Hemodynamic pattern in chronic liver disease on right heart catheterization.

Signs of RV retrograde failure	Signs of RV forward failure
Distended and pulsating jugular vein	Peripheral cyanosis
Abdominal distension	Dizziness
Hepatomegaly	Pallor
Ascites	Cool extremities
Peripheral edema	Prolong capillary refill

Table 6.
Signs of right heart failure.

Baseline clinical assessment is an important benchmark for the assessment of disease severity and in determining whether it is improving, deteriorating, or getting stabilized. The appearance of physical signs of RV failure also indicates disease severity (Signs of RV failure enumerated in **Table 6**). The World Health Organization functional class (WHO-FC) at diagnosis and follow-up is one of the strongest predictors of survival [37], and worsening WHO-FC is an indicator of disease progression [38, 39]. According to estimated 1 year mortality and patients can be divided in to low, intermediate, and high risk. Other risk assessment parameters are pulmonary hemodynamics, 6-minute walk distance, biomarkers, and other echocardiographic parameters. (Risk assessment parameters are described in **Table 7**).

3.9 Pathophysiology and therapeutic targets

Medial hyperplasia, intimal proliferation and plexiform lesions formation leads to progressive pulmonary vasculopathy of PoPH. This vasculopathy leads to increase in pulmonary vascular resistance and gradual right ventricular failure. (**Figure 2** describe various pathophysiology and current therapeutic targets for PAH).

Patients with unclassified PH and isolated postcapillary PH should be followed up regularly, or liver transplant should be performed if there is significant liver dysfunction. They do not need PAH-specific therapy.

In patients with an established diagnosis of PoPH, PAH specific therapy should be started keeping following considerations:

- The severity of liver disease and urgency for LT
- PoPH specific indication and contraindication for LT.

PoPH patients are usually excluded from PAH treatment studies, but in principle, all drugs approved for PAH can be used to treat patients with PoPH. 5-year survival on PAH-specific therapy is 51% and reaches 81%, if patients underwent LT as well. In patients presenting with mild liver disease, the main causes of death were PAH progression and malignancy, whereas complications of liver disease were the most common causes of death in patients with advanced liver disease [40]. The only RCT dedicated to the treatment of PoPH, Macitentan, demonstrated a significant reduction in PVR from baseline [41].

3.10 Prognosis without LT

Analysis of a US registry data showed a median survival from time of diagnosis to be 27.5 months. Overall survival was 89%, 77%, 51%, and 38% at 6 months, 1 year, 3 years,

The prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Hemodynamics	RAP < 8 mm Hg	RAP 8–14 mm Hg	RAP > 14 mm Hg
	CI ⩾ 2.5 l/min/m^2	CI 2.0–2.4 l/min/m^2	CI < 2.0 l/min/m^2
	SVI > 38 ml/m^2	SVI 31–38 ml/m^2	SVI < 31 ml/m^2
	SvO2 > 65%	SvO2 60–65%	SvO2 < 60%
Signs of right HF	Absent	Absent	Present
History of syncope	No	Occasional[a]	Frequent[b]
Progression of symptoms and signs	No	Slow	Rapid
WHO-FC	I, II	III	IV
6 MWD	>440 m	165–440 m	<165 m
BNP	<50 ng/l	50–800 ng/l	>800 ng/l
NT-proBNP	<300 ng/l	300–1100 ng/l	>1100 ng/l
Echocardiography	RA area < 18 cm^2	RA area 18–26 cm^2	RA area > 26 cm^2
	TAPSE/ PASP > 0.32 mm/mm Hg	TAPSE/PASP 0.19–0.32 mm/mm Hg	TAPSE/PASP <0.19 mm/mm Hg
	No pericardial effusion	Minimal pericardial effusion	Moderate or large pericardial effusion
cMRI	RVEF > 54%	RVEF 37–54%	RVEF < 37%
	SVI > 40 ml/m^2	SVI > 26–40 ml/m^2	SVI < 26 ml/m^2
	RVESVI<42 ml/m^2	RVESVI-2-54 ml/m^2	RVESVI>54 ml/m2

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class. Adapted and reproduced with permission of the © European Society of Cardiology & European Respiratory Society 2023: European Respiratory Journal ***61****(1):2200879; DOI: 10.1183/13993003.00879-2022. Published 6 January 2023 (from Ref. [28]).*
[a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.[b]Repeated episodes of syncope even with little or regular physical activity.

Table 7.
Risk assessment in pulmonary artery hypertension.

and 5 years, respectively. Patients with PoPH who did not undergo LT had a poor prognosis [27]. United Kingdom National Pulmonary Hypertension Service registry reported 3-year survival of 60% and survival of patients with PoPH remained poor despite targeted therapy and worse than patients with idiopathic PAH [42]. However, in both studies, most of the patients were on monotherapy and recent use of combination therapy has shown improved outcomes (3- and 5-year survival, 88.5% and 80.2%, respectively) [43].

3.11 Liver transplantation and prognosis after LT

Postcapillary PH does not negatively affect post-liver transplant survival, and a higher cardiac output (11 l/min in patients who lived, as compared with 8 l/min in

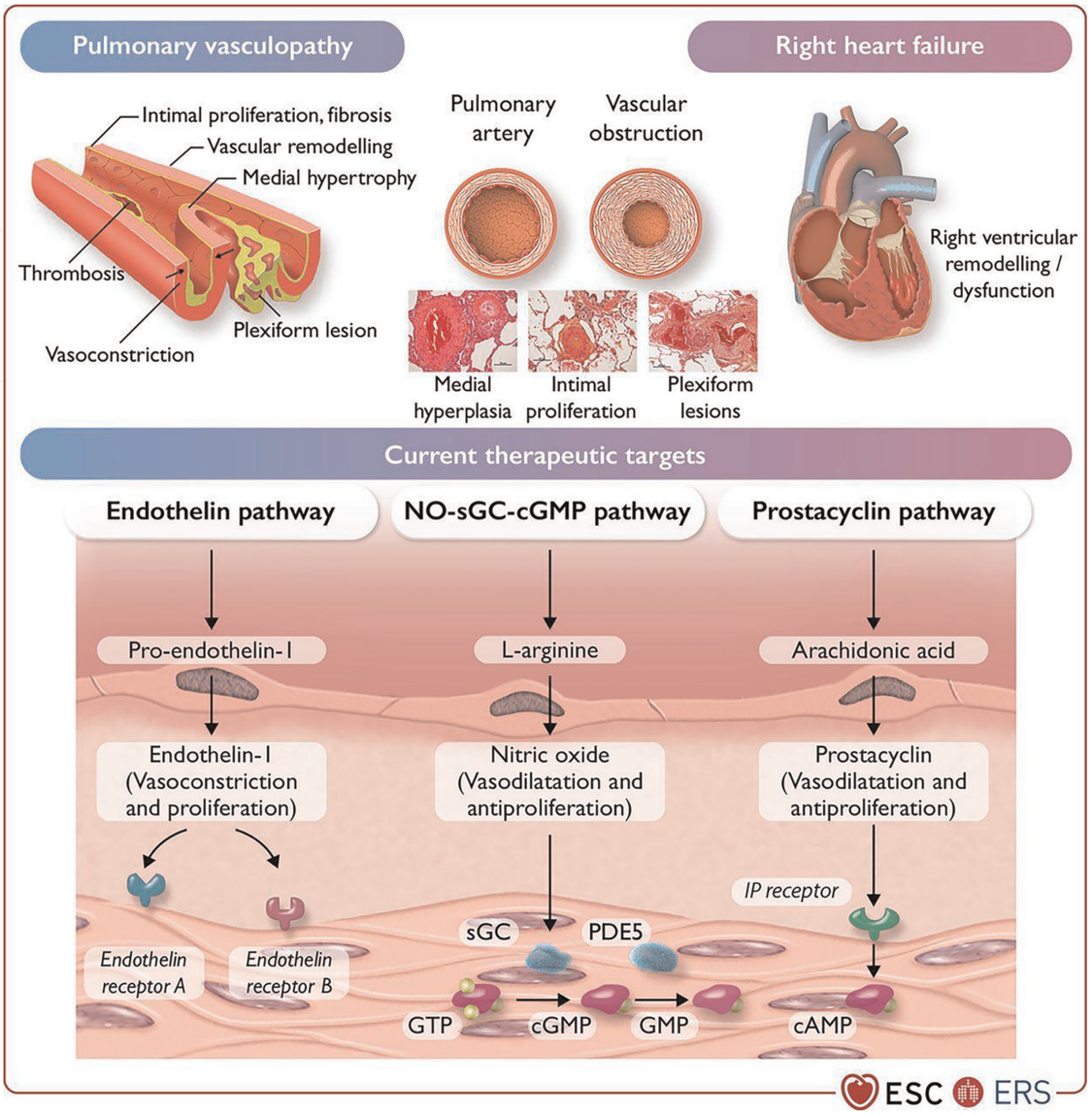

Figure 2.
Pathophysiology and current therapeutic targets of pulmonary arterial hypertension (group 1). cAMP, cyclic adenosine monophosphate; (c)GMP, (cyclic) guanosine monophosphate; GTP, guanosine-5'-triphosphate; IP receptor, prostacyclin I2 receptor; NO, nitric oxide; PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase. Reproduced with permission of the © European Society of Cardiology & European Respiratory Society 2023: European Respiratory Journal ***61****(1):2200879; DOI: 10.1183/13993003.00879-2022. Published 6 January 2023 (from Ref. [28]).*

patients who died) may be protective against mortality in patients with postcapillary PH [30]. Mortality rate after LT according to severity stood 100%, 50%, and 0% in patients with mPAP >50 mm Hg, 35–50 mm Hg, and <35 mm Hg, respectively [44]. Patients in whom mPAP was ≤35 mm Hg, both the graft and patient survival rates were found to be 85.7% after a median follow-up of 7.8 years [45]. Achieving reduction in PVR < 250 dynes/s per cm^{-5} by PAH specific therapy, even if mPAP remains ≥35 mm Hg before LT has shown 69% 1-year post-transplant survival and PAH specific therapy can be discontinued in majority of patients [46]. This shows importance of reduction of PVR before proceeding for LT.

Patients with mild PoPH do not possess an increased risk for LT, so they should be considered for LT. Patients with an mPAP between 35 and 45 mm Hg should undergo PAH-specific treatment, and who reach a reduction of mPAP to ≤35 mm Hg and PVR

<400 dynes/s per cm^{-5} should be offered LT [34]. The ILTS practice guideline further added LT could also be considered if treated PoPH does not reduce mPAP to <35 mm Hg, but there is a normalization of PVR (<240 dynes/s per cm^{-5}), as it does not seems to be associated with adverse outcomes [13].

4. Hepatic hydrothorax

A transudative pleural effusion in a patient with chronic liver disease with portal hypertension or cirrhosis in the absence of other etiological factors is termed hepatic hydrothorax (HH) [47]. A median survival of 8–12 months is reported once it is diagnosed [48].

Usually, ascites is a precursor of hydrothorax. Ascites coexists in 80% of cases but are not mandatory for diagnosis [49]. The hypothesis based on the trans-diaphragmatic shift of fluid vial defects in the diaphragm is commonly accepted and this theory is endorsed by evidence of macro- and microscopic diaphragmatic defects [50]. HH has a predilection for the right side as the right diaphragm is thinner and less muscular with frequent defects as compared to the left. Radiolabelled 99mTc-sulfur colloid or 99mTc-albumin transmigration from the peritoneal to the pleural cavity has been demonstrated earlier to support the theory [51]. As per the studies, overall, the prevalence is 70% right sides, 18% bilateral, and 12% left-sided HH [52]. In HH with ascites, negative intrathoracic pressures in during inspiration promotes fluid accumulation in the pleural space [53].

Patients usually present with severe but nonspecific complaints of dyspnoea at rest (4%), dyspnoea on exertion (7%), non-productive cough (22%), pleuritic chest pain (8%), dizziness or fatigue (7%). In extreme cases, respiratory failure and subsequent heart failure is also reported [54]. Once established on radiological evidence, the nature of effusion (exudative or transudative) is determined by diagnostic thoracocentesis.

HH is characterized by a total cell count of polymorphonucleocytes <250/μl, a total protein concentration < 2.5 g/dl, a serum to pleural albumin gradient >1.1 g/dl, or a pleural fluid to serum albumin quotient <0.6. Other parameters indicating HH are an LDH gradient <0.6 (serum—pleural fluid) and similar pH value, as well as glucose concentration in serum and pleural fluid [55]. Other supportive investigations are to be performed to rule out the differentials in consideration, including pleural effusion of other etiology, pancreatitis, thoracic or abdominal malignancies, etc. complimentary abdominal sonography is helpful in diagnosis or prognostication of already diagnosed underlying CLD.

The treatment principle of treatment is essentially on parallel lines with that of the treatment of ascites, which includes sodium restriction, diuresis, and large-volume paracentesis for respiratory insufficiency. The invasive procedure of therapeutic thoracocentesis should be performed only if symptoms persist. Precautions in the form of pleural puncture volume up to 2 l/Puncture, and substitution of 6–8 gm albumin/litre can be taken to avoid re-expansion pulmonary edema. Continuous thoracic drainage is not recommended in view of the loss of proteins and increased rate of infections [56].

Trans-jugular intrahepatic portosystemic shunt (TIPS) may be beneficial for rare intractable cases. Attempts in reduction of portal hypertension, the recovery was seen in 56% and improvement in 18% [57]. Pleurodesis may be performed; having said that, it has a high relapse of 25% and complications in 80% [58]. Surgical treatment in the form of pleural flaps or mesh reinforcement has been described [59].

Refractory hepatic hydrothorax (RHH) is defined by the failure to control symptomatic HH with sodium restriction (<2 g/day), tolerable amounts of diuretic (160 mg/day furosemide and 400 mg/day spironolactone, or repeated thoracentesis) [60].

Liver transplantation is the only curative therapeutic option [61]. The patients with preoperative HH have higher rates of postoperative infections, emphasizing the relevance of HH as an adverse prognostic factor [62]. HH persisted in one-third of patients till 1-month post-LT but resolved completely in all patients within 3 months of transplant [63].

5. Spontaneous bacterial empyema

Analogous to spontaneous bacterial peritonitis, spontaneous bacterial empyema (SBE) is a specific complication of HH [64]. The overall prevalence of SBE is 2.4% of CLDs, the incidence increases to 10–16% in the decompensated state of HH, and the mortality associated with SBE is 38% [65]. Half of the patients with concomitant HH and SBP develop SBE [66]. Pleural fluid examination typically suggests low total proteins and albumin, C3 compliments [67, 68].

The patient may present with nonspecific symptoms and sometimes with worsening in liver function. The diagnosis should be based on thoracocentesis with a total polymorphonucleocytes >250/microlitres with cultures growing the organisms or >500 per microlitres with no growth on culture. The most common organisms growing are *Escherichia coli*, Klebsiella, Streptococcus, or Enterococcus. Although 2/3rd of the patients remains culture negative and most of the patients have a history of multiple hospital admissions, such are at risk of multidrug-resistant bacteria [69, 70].

The treatment consists of intravenous antibiotics as per local antibiogram immediately after the pleural fluid sampling [21]. Streptokinase and, in extreme, video-assisted thoracoscopic surgery may be the only options [71].

6. Restrictive lung disease

Restrictive lung diseases are group of varied lung disorders defined by restrictive patterns (forced vital capacity (FVC) <70% predicted) on spirometry. Restrictive lung diseases may be caused by intrinsic conditions (interstitial lung disease, ILD) or by extrinsic conditions (limitations in neuromuscular function and chest wall movements, obesity). In CLD prevalence of restrictive lung disease is 18.4%, and it is associated with lower 6-minute walk distances, dyspnea, worse quality of life, and increased risk of death [72]. Restrictive abnormalities correlate with prolonged after LT ventilation and length of stay. Efforts to identify and minimize the impact of restrictive abnormalities on PFTs might improve outcomes [73].

ILD defines progressive inflammatory and fibrotic diseases targeting the pulmonary interstitial tissue. It has an affinity to be associated with primary biliary cirrhosis, autoimmune hepatitis, or hepatitis [74]. It leads to progressive hypoxemia and may contribute to hypoxia caused by HPS [75]. 99mTcMAA lung perfusion scan can differentiate between ILD and HPS as brain uptake is normal (<6%) in ILD. Patients with ILD characteristically have a restrictive pattern and a decrease in DLCO. The most common radiographic feature observed is a reticular pattern. However, nodular or mixed patterns can be seen. High-resolution computed tomography

(HRCT) shows coarse crosslinking in basal regions in early stage and honeycombing in later stages. LT should be avoided in moderate to severe restrictive lung disease due to ILD [76].

7. Asthma and chronic obstructive pulmonary disease (COPD)

Asthma is a reversible airway obstructive disease with bronchial hyperreactivity. There is no evidence regarding the influence of asthma on outcomes after liver transplant.

COPD is a progressive lung disease characterized by non-reversible airflow limitation caused by chronic inflammation and mucus hypersecretion. Severity classification done on basis of FEV1% predicted. For mild COPD FEV1% predicted ≥80%, moderate as FEV1% predicted ≥50% and <80%, severe as FEV1% predicted ≥30% and <50% and very severe as FEV1% predicted <30% [77]. Around 18% of new patients undergoing LT evaluation have COPD particularly if they are older and have history of smoking. 80% patients had the diagnosis of COPD made for the first time during their LT evaluation. Despite the impact of COPD on functional status and quality of life, the risk of death and post-LT outcomes were not affected by the existence or severity of COPD [78]. However, in this study, only 11% of patients had severe COPD (30% < FEV1% predicted <50%), and no patient had FEV1% < 30%. Long-term post-LT outcomes in COPD are poorly characterized. Very severe COPD should be considered a contraindication for LT, and in severe COPD, detailed evaluation and risk stratification should be done before considering LT.

8. Conclusion

HPS and POPH are pulmonary complications of liver disease and portal hypertension. All pulmonary manifestations of liver disease, except uncontrolled moderate and Severe POPH, are treatable with liver transplantation with a good outcome. LT not only halts the progression of these diseases but also leads to complete resolution. As both CLD-specific pulmonary disorders and chronic liver disease in itself are progressive diseases, the gradual worsening of both has a dual, negative effect on the outcome. The increasing severity of these pulmonary manifestations increases waitlist mortality and inferior survival after liver transplants. Early identification and optimization of these manifestations and the timely liver transplant are reasonable. Dyspnea on exertion and sometimes at rest is a common index symptom of respiratory insufficiency; however, in liver disease due to ascites, pleural effusion, poor nutrition, sarcopenia, and chronic illness, dyspnea is otherwise a very common presentation. So high index of suspicion is required in CLD for asymptomatic as well as symptomatic respiratory symptoms. The approach must focus on determining whether the etiology is pre-existing, CLD-specific (HPS, POPH), or a combination of both. The accurate identification of the primary pulmonary issue, quantifying its severity, and assessment of additional abnormalities becomes important for patients' symptomatic treatment, optimization before transplantation, and perioperative management.

Conflict of interest

The authors declare no conflict of interest.

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