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# Pulmonary Complications of Liver Cirrhosis: A Concise Review

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<http://dx.doi.org/10.5772/intechopen.68620>

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## Abstract

Pulmonary complications, in the form of hepatopulmonary syndrome (HPS), portopulmonary hypertension (PPH), and hepatic hydrothorax (HH), are rare occurrences in patients with portal hypertension and liver cirrhosis. These complications are associated with high morbidity and mortality. The only effective therapy is liver transplantation in patients who are suitable. In this chapter, each condition will be outlined in detail from clinical presentations to diagnosis and treatment as well as the challenges that clinicians may have encountered in managing patients with these complications.

**Keywords:** hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax, liver transplantation

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## 1. Introduction

Pulmonary complications in patients with chronic liver disease and portal hypertension include hepatopulmonary syndrome (HPS), portopulmonary complications (PPH), and hepatic hydrothorax (HH) (**Figure 1**). They are associated with increased morbidity and mortality and therefore, high suspicion of index is required to make earlier diagnosis and subsequently, to early treatment. The only effective treatment is liver transplantation (LT). All patients suitable for liver transplantation should be screened for potential pulmonary complications because earlier diagnosis gives better survival post liver transplantation. HPS is more common than PPH and HH, and the best chance of survival in these patients is LT. Among all the three conditions, HH carries the best prognosis.

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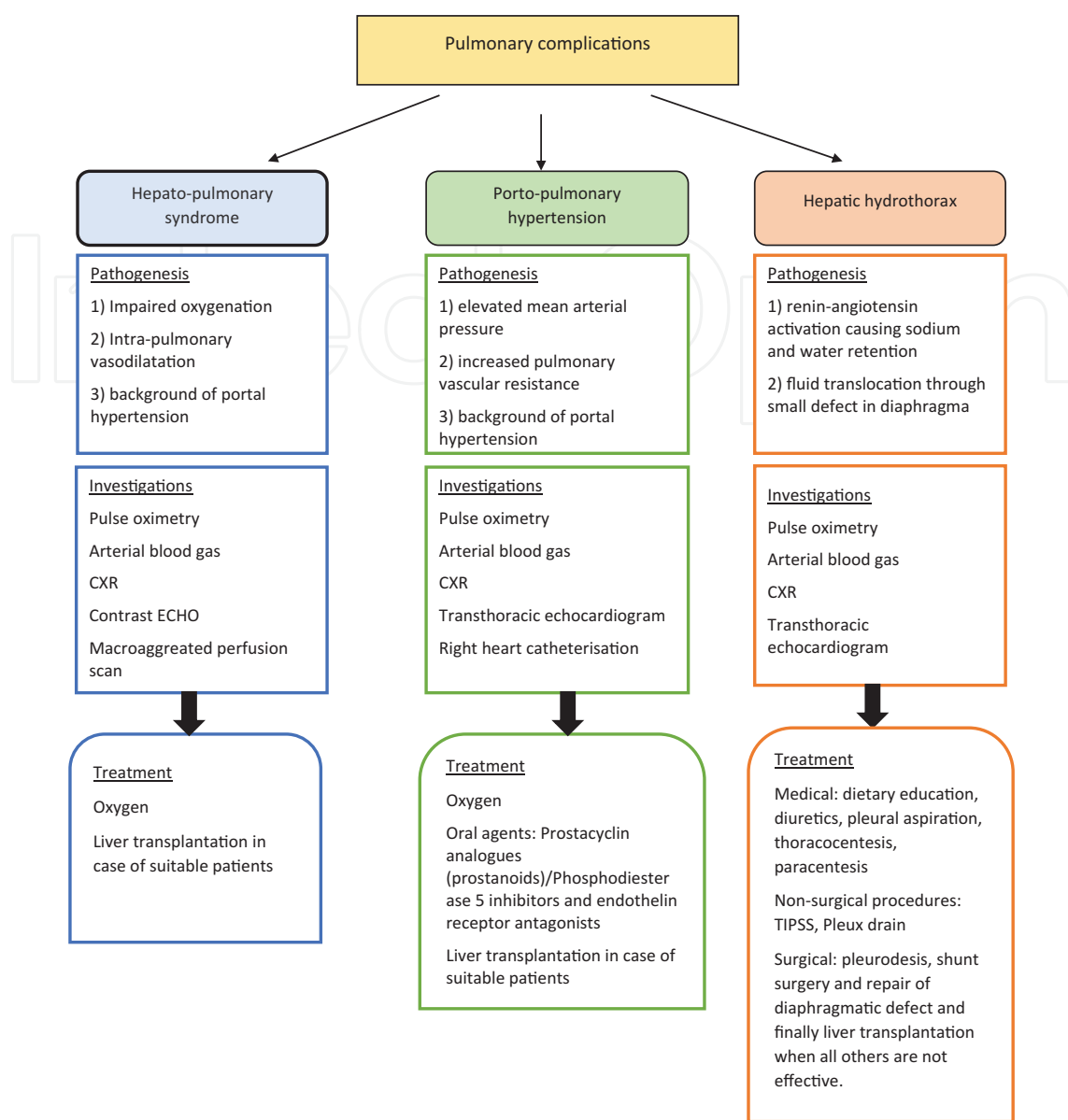
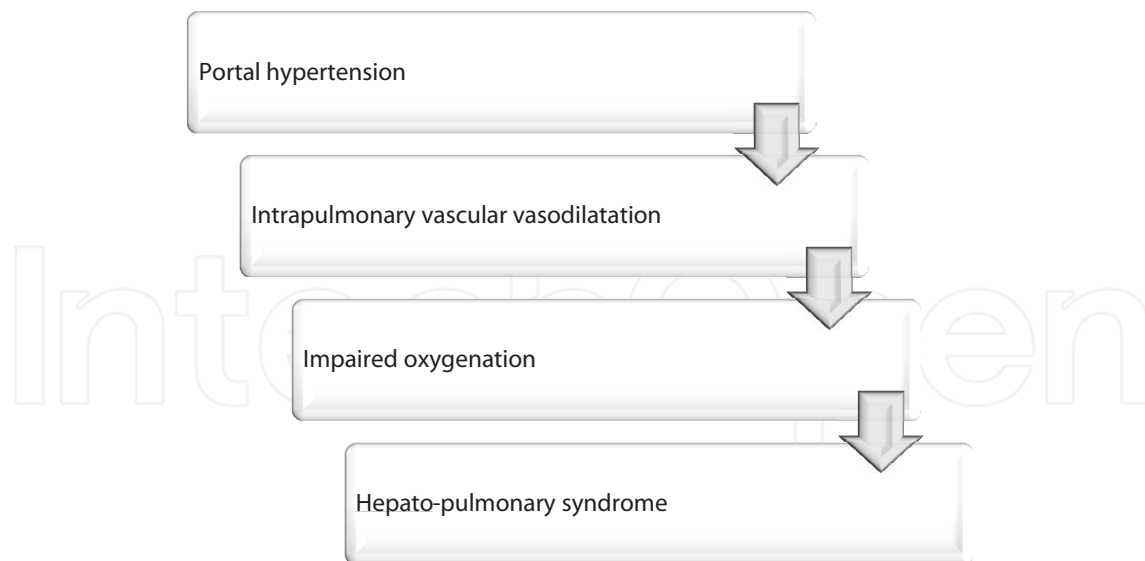


Figure 1. A step-wise approach to pulmonary complications of liver cirrhosis.

2. Hepatopulmonary syndrome

2.1. Background

Hepatopulmonary syndrome (HPS) is first described in 1977 by Kennedy and Knudson [1] and defined as a defect in arterial oxygenation caused by the presence of intrapulmonary vascular dilatation (IVPD) in the context of portal hypertension [2] (**Figure 2**). The estimated prevalence of HPS in liver cirrhosis is 4–32% [3]. In patients who were accessed for LT, the prevalence of HPS is approximately 10–30% [4]. HPS is usually diagnosed during the sixth decade of life and there is no specific association with gender or underlying cause of liver disease or model of end stage liver disease (MELD) [4, 5]. The established 5-year survival rate was 20% for HPS patients versus 32–63% for patients without HPS [5, 6].



**Figure 2.** The sequence in development of HPS in liver cirrhosis.

## 2.2. Clinical features

Most patients with HPS present with dyspnea, orthopnea, platypnea, cyanosis, spider naevi, and finger clubbing [3, 7]. Platypnoea or orthodeoxia is defined as the presence of shortness of breath (dyspnoea) that worsens while sitting or standing and relieved by lying down. It is a common feature described in patients with HPS [7]. When patients with liver cirrhosis present with shortness of breath, the investigations should be done as early as feasible to avoid the delay in the diagnosis. Early diagnosis leads to reduction in patient's morbidity and mortality. The severity of HPS can be distinguished based on the level of hypoxemia as per the European Respiratory Task Force (**Table 1**) [8].

Degree of severity	Level of hypoxaemia (PaO <sub>2</sub> )
Mild	≥80 mmHg
Moderate	≥60–<80 mmHg
Severe	≥50–<60 mmHg
Very severe	<50 mmHg

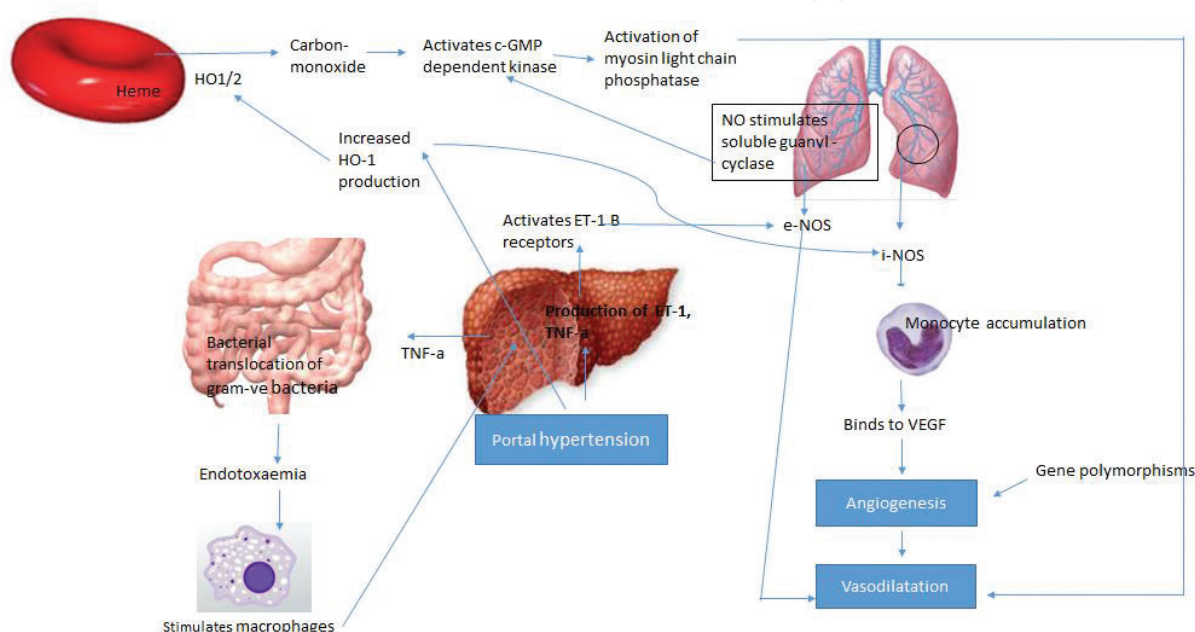
**Table 1.** The severity of HPS as per level of hypoxaemia.

## 2.3. Pathogenesis

The pathogenesis of HPS is still unclear but the hallmark is thought to be due to intrapulmonary vasodilatation (IVPD), especially at the level of pre-capillary and capillary vasodilation [7]. IVPD is mediated by a number of endogenous vasoactive molecules, mainly endothelin-1 (ET-1) and nitric oxide (NO) [3, 9]. Portal hypertension increased the production

of vasoconstrictor ET-1, which stimulates the production of the ETB receptor at the level of the pulmonary microcirculation, with subsequent increase in eNOS activity causing vasodilatation [7, 9]. As a result of IVPD, nearly 20% or more of the cardiac output bypasses the functioning alveoli [2]. IVPD then causes arterial deoxygenation by three mechanisms: ventilation/perfusion mismatch, intrapulmonary shunting, and limitation of oxygen diffusion [7].

Angiogenesis is also considered to be an important phenomenon in the development of HPS [10] through upregulation of the vascular endothelial growth factor. Other mechanism suggested from experimental studies was vasodilation via increased carbon monoxide production through haem oxygenase [7]. The proposed pathogenesis of HPS was shown in **Figure 3**.



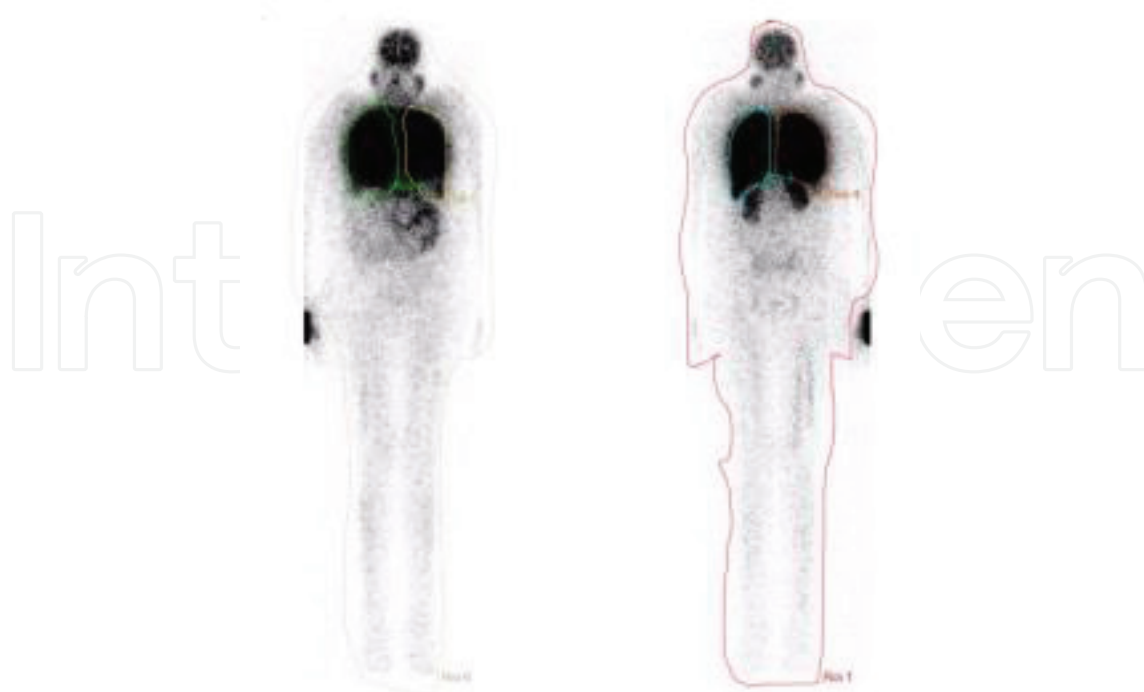
**Figure 3.** The pathogenesis of hepatopulmonary syndrome.

## 2.4. Investigations

In most centers, patients will usually undergo routine cardiopulmonary investigations during LT assessment. Bedside pulse oximetry is the first line screening investigation and oxygen saturation of less than 96%, has a sensitivity of 100% and specificity of 88% to detect  $\text{PaO}_2 < 70$  mmHg [7, 11]. Arterial blood gas (ABG) sampling is required for the diagnosis of HPS to calculate the Alveolar-arterial (A-a) gradient [7]. PA-aO<sub>2</sub> gradient is the most important marker in diagnosing early stage of HPS [7] and the European Respiratory Society Task Force recommends a PA-aO<sub>2</sub>  $\geq 15$  mmHg for the diagnosis of HPS and the level of PaO<sub>2</sub> will determine the severity of the HPS [10] (**Table 1**). In suspected patients with HPS, ABG was performed on room air with patient sitting down first and the procedure is repeated 15 to 20 minutes in the standing up position. Orthodeoxia, which manifests as a decrease in PaO<sub>2</sub> of  $\geq 4$  mmHg or  $\geq 5\%$  from the supine to the upright position [12], and the increase in PaO<sub>2</sub> while breathing 100% oxygen, which should reach above 300 mmHg [7]. Orthodeoxia is a consequence of the increased V/Q mismatch and decreased cardiac output following the change from the supine to the upright position [7].

Chest radiography shows prominent pulmonary vascular markings in bilateral lower lobes, but finding is not specific for HPS [2]. Pulmonary function test should be performed to rule out other associated intrinsic pulmonary disorders. Contrast-enhanced echocardiography is the most sensitive test to demonstrate intrapulmonary shunting disease [2]. It is done using intravenous injections of agitated saline or indocyanine green to produce bubbles of at least 15 microns in diameter [2]. Normally, these microbubbles are trapped in the pulmonary vasculature and absorbed, but in intracardiac right to left shunts, these microbubbles are seen in the left heart within the first three cardiac cycles [7]. In HPS, the bubbles are seen in the left heart after the third heartbeat, usually between the third and sixth heartbeat due to intra-pulmonary shunting [2]. Studies have shown that transesophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting [7].

99 m Technetium-macroaggregated albumin (Tc-99 m MAA) lung perfusion scan is used widely in the diagnosis of HPS (**Figure 4**). Albumin macroaggregates with more than 20  $\mu\text{m}$  in diameter are normally entrapped in the pulmonary vasculature [2]. In patients with intrapulmonary shunts, these albumin macroaggregates escape from the pulmonary vasculature and are taken up by other organs [2]. Normally, less than 5% of isotope reaches brain circulation compared to the lung, but in HPS patients, the fraction is more than 6% [7]. The major disadvantage of Tc-99 m MAA scan is its inability to differentiate intra-cardiac from intrapulmonary shunting. Pulmonary angiography is invasive, and hence, it is only reserved for those who did not have response to 100% oxygen therapy [7]. The baseline investigations and the findings found in HPS are illustrated in **Table 2**.



**Figure 4.** Whole body (Tc-99 m MAA) scan showed an increased uptake in within the lungs and thyroid with well visualization in the brain, kidneys, and liver.

Screening methods	Findings
Pulse oximetry	Oxygen saturation <96%
Chest radiograph	Increased vascular markings
Lung function tests	Normal or reduction FVC or FEV1 Reduction in diffusing capacity of the lungs for carbon monoxide (DLCO-co)
Diagnostic tests	Findings
Arterial blood gas analysis	AaO <sub>2</sub> ≥ 15 mmHg or AaO <sub>2</sub> ≥ 20 mmHg (in patients above 64 years of age)
Contrast echocardiography	Bubbles in the left cavities between the fourth and sixth beat
99 m Tc-MAA	Cerebral uptake ≥6%

**Table 2.** Screening and investigative methods used in HPS.

## 2.5. Treatment

### 2.5.1. Medical treatment

Patients who experience severe dyspnea at rest and evidence of hypoxemia clinically should receive oxygen therapy [10]. Many studies have looked into treatment of HPS with nitric oxide inhalation, low consumption of L-arginine using methylene blue, aspirin, antibiotic usage to reduce intestine's bacterial translocation, somatostatin, indomethacin, garlic, and transjugular intrahepatic portosystemic shunt (TIPS), but none of them have not shown any particular benefit as long-term treatment of HPS [7].

Recent pilot randomized controlled study with norfloxacin did not show any improvement in gas exchange of HPS patient [13]. Initial studies suggested that garlic may have a role in the treatment of HPS by altering nitric oxide production [7]. A recent randomized controlled trial showed garlic supplementation, which was associated with a 24.66% increase in baseline arterial oxygen levels and 28.35% decrease in alveolar-arterial oxygen gradient [14]. It also shown that garlic supplementation may be beneficial in patients with HPS for the reversal of intrapulmonary shunts as well as for reducing hypoxemia and mortality, although study with higher number of patients are required to show clinical effectiveness [14].

One of the factors involved in the pathogenesis of HPS was tumor necrosis factor-alpha (TNF-a) and overproduction of TNF-a cause vasodilatation [4]. Hence, treatment with pentoxifylline (an inhibitor of TNF-a) although in recent pilot study [15] showed that pentoxifylline did not improve arterial oxygenation in advanced HPS, and tolerance was limited by gastrointestinal toxicity.

Enhanced pulmonary production of nitric oxide (NO) has been implicated in the pathogenesis of HPS, and NO inhibition with N(G)-nitro-L-arginine methyl ester (L-NAME) in both animals and humans with HPS has improved arterial hypoxemia [16]. A study [16] investigating the effect of nebulized L-NAME in patients with HPS showed that

the treatment decreased exhaled NO, mixed venous nitrite/nitrate, and cardiac output although systematic and pulmonary vascular resistance were increased. In contrast, ventilation-perfusion mismatching, intrapulmonary shunt, and, in turn, arterial deoxygenation remained unchanged [16].

#### 2.5.2. Transjugular intrahepatic portosystemic shunt (TIPSS)

Recent systematic reviews of 10 studies with 12 patients showed that TIPSS is technically feasible to perform in patients with HPS, but overall benefit is unclear [17]. The current management did not advise TIPSS in patients with HPS.

#### 2.5.3. Liver transplantation (LT)

The only effective treatment available for HPS is liver transplantation (LT), although LT is invasive and carries a high risk. Hence, patients should be assessed thoroughly prior to consideration of LT. After LT, 85% patients had significant improvement in gas exchange, although it can take up to 1 year for the abnormalities to normalize [2]. The mortality is higher for patient with HPS who underwent LT than those without HPS and the mortality is higher for those with marked hypoxemia ( $\text{PaO}_2 < 50$  mmHg) and intrapulmonary shunting (shunt fraction  $> 20\%$ ) [2]. The established 5-year survival rate was 23% for HPS patients and 67% for patients without HPS [18]. For patients with HPS who are on LT waiting list should be monitored closely to prevent worsening of the conditions. The most challenging post LT is severe hypoxemia post-operative period with prolonged respiratory weaning that often resulted in death. Ten-year survival after LT in HPS patients stands at 64% [10] and post LT mortality rates obtained in these studies range between 7.7 and 33% [10].

Recent study showed that patients with HPS presented higher cardiac output, lower systemic vascular resistance, and higher progesterone and estradiol levels than patients without HPS [19]. The study showed that LT produced normalization of intrapulmonary vasodilatation in all patients as well as hyperdynamic circulation and hence, is a useful therapeutic option in patients with HPS [19]. Normalization of sex hormone levels after LT suggests that they could play a pathogenic role in the development of HPS [19].

#### 2.5.4. Other treatment options

One of the recent management options for life-threatening hypoxemia in HPS patients is extracorporeal membrane oxygenation (ECMO) [20]. Monsel et al. reported the use of ECMO in preparation of LT in patients with refractory hypoxemia caused by a combination of acute respiratory distress syndrome (ARDS) and HPS [21]. The preliminary data showed that ECMO allowed the performance of successful LT by controlling gas exchange [3]. Auzinger et al. also reported the successful case of using ECMO for severe refractory hypoxemia after LT in HPS patients [20]. It could facilitate early ventilator weaning, thus prevented the need for the prolonged use of sedation and reduced complication associated with interventions [20]. However, the effectiveness of ECMO still has to be proven by future randomized trials.

3. Portopulmonary hypertension

3.1. Background

Portopulmonary syndrome (PPH) was first described in 1951 by Mantz and Craig [22]. PPH is characterized by the presence of elevated mean pulmonary hypertension in patients with portal hypertension due to increased pulmonary vascular resistance [4]. It is found in 2–10% of patients with cirrhosis [2] and reported among 5–8% of the patients with CLD who have undergone liver transplantation [23].

A recent retrospective review conducted in treatment-naïve patients with PPH within the United Kingdom national registry showed that patients with PPH had survival rates of 85, 60, and 35% at 1, 3, and 5 years [24]. The study mentioned that the prevalence of PPH was found to be 0.85 cases per 1 million and the mean age of diagnosis was 53 years [24]. Alcohol and hepatitis C were found to be the most common causes of PPH [24].

PPH results from arterial vasoconstriction linked to remodeling of the vasculature of the lung caused by prolonged portal hypertension and subsequently lead to pulmonary arterial hypertension (PAH) [9]. The condition is more common in females and in patients with autoimmune hepatitis [7, 25]. PPH can occur at any age but more common in fourth or fifth decade of life [4]. PPH occurs 4–7 years after patients are diagnosed with portal hypertension [26]. The severity of liver disease does not correlate with the severity of PPH. Without treatment, estimated 1-year survival in PPH is around 60% [23, 27].

3.2. Clinical features

Most patients are asymptomatic but clinical features of liver disease will be apparent. Patients usually present with features of right-sided heart failure such as dyspnea, orthopnea, chest pain, fatigue, and syncope [9]. On clinical examination, patient may present with tricuspid regurgitation murmur, loud pulmonary (P2) sound, diastolic murmur of pulmonary regurgitation, and features of right-sided heart failure evident by the presence of elevated jugular venous pressure, pulsatile liver, peripheral edema, and ascites [9]. The severity of PPH is classified based on degree of MPAP values: mild (25–35 mmHg), moderate (35–50 mmHg), and severe (>50 mmHg) [9].

The European Cardiologic Society and the European Respiratory Society Task Force have defined the diagnostic criteria for PPH as follow in **Table 3** [28]. According to the World Health Organization classification, PPH is located within PAH group 1 [29].

Diagnostic criteria for PPH

- Mean pulmonary arterial pressure (mPAP) >25 mmHg
- Pulmonary vascular resistance (PVR) >240 dyn s cm<sup>-5</sup>
- Pulmonary capillary wedge pressure <15 mmHg

Table 3. Diagnostic criteria for portopulmonary hypertension (PPH).

### 3.3. Pathogenesis

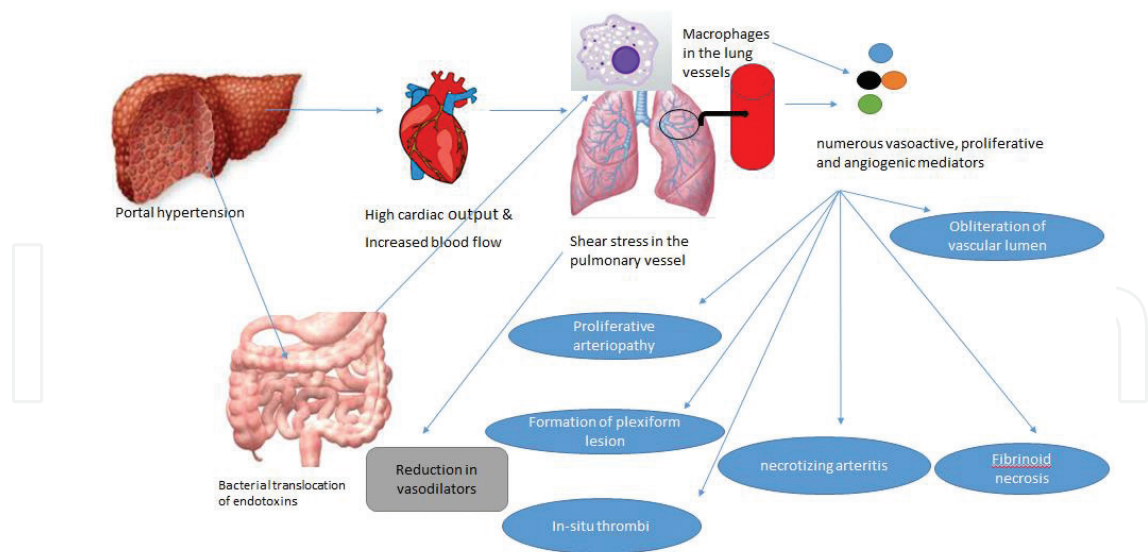
The exact pathophysiology behind PPH is poorly understood but histologically, it is thought to be similar to the pathogenesis of idiopathic pulmonary arterial hypertension (PAH) [29]. Hyperdynamic circulatory state and high cardiac output are the hallmarks in most of the patients with PPH leading to increased shear stress on the pulmonary circulation [29]. Due to vascular shear stress, vasoactive, proliferative, and angiogenic mediators (including endothelin 1 (ET-1), vasoactive intestinal peptide, serotonin, thromboxane A<sub>2</sub>, interleukin 1, glucagon, and secretin) were released which lead to arterial changes seen in PPH [2, 4, 23, 27]. The main pathological abnormalities include proliferate arteriopathy, obliteration of the vascular lumen by endothelial and smooth muscle cells, formation of plexiform lesions, necrotizing arteritis, fibrinoid necrosis, and *in-situ* thrombi [23, 27]. Due to portosystemic shunts, bacterial endotoxins were found in pulmonary circulation from gastrointestinal tract and the recruitment of interstitial macrophages to clear those endotoxins also contribute to the development of PPH [30].

Genetic polymorphisms may play a role in the development of PPH. Finally, vasodilating mediators, such as nitric oxide (NO) and prostaglandin I<sub>2</sub> (prostacyclin), may be decreased in PPH [29]. Prostacyclin synthase, the enzyme responsible for prostacyclin synthesis, has been demonstrated to be deficient in the pulmonary endothelium of patients with PPH [4]. The illustration pathogenesis of PPH is shown in **Figure 5**.

### 3.4. Investigations

Since patient can be asymptomatic, high suspicion is required to diagnose this condition earlier, which can lead to earlier treatment and better prognosis. All baseline investigations such as ECG, CXR, blood gas analysis, and lung function tests have poor prognostic yield and did not reflect severity of PPH. In patient with PPH, CXR might show a prominent main pulmonary artery, cardiomegaly due to enlarged right cardiac chambers, and increased vascularity in the upper lobes [2, 4, 9]. Pulmonary function tests in patients with PPH would show decreased lung diffusion capacity and reduced lung volume [2, 4]. In arterial blood gas analyses, hypoxemia and hypocapnia associated with an elevated alveolar-arterial oxygen gradient would be seen [2].

Transthoracic echocardiogram showed right ventricular hypertrophy and right atrium dilatation, which is not usually specific to PPH [23, 27]. Transthoracic echocardiogram (TTE) is the screening tool used initially and it can identify patients with elevated pulmonary arterial systolic pressure (PASP). In those patients with elevated PASP, the next investigation is right heart catheter which can confirm the diagnosis of PPH. Usually, RV systolic pressure <30 mmHg was used to exclude PPH and if it is >50, patient is highly likely to have PPH [23]. Cardiac output (CO), mean pulmonary arterial pressure (mPAP), mean pulmonary arterial occlusion pressure (mPAOP), and pulmonary vascular resistance (PVR) can help to determine the nature and severity of the PPH [2, 27]. There are three main causes of elevated mPAP in liver disease patients and those are cirrhotic cardiomyopathy due to left ventricular dysfunction, the typical high-output state of cirrhosis, and PPH [27]. **Table 4** illustrates the difference findings noted in each condition.



**Figure 5.** The pathogenesis of portopulmonary hypertension.

	Cardiac output	mPAP	mPAPOP	PVR
Hyperdynamic state	Elevated	Elevated	Normal	Decreased
LV dysfunction	Low	Elevated	Elevated	Elevated
PPH	Low	Elevated	Low	Elevated

**Table 4.** The difference findings for each conditions.

The severity of PPH and the progression of disease during the course of disease in patients with portal hypertension can only be investigated through invasive right heart catheterization. Hence, it will be useful to develop a sensitive biomarker which can detect disease presence, predict the severity, and treatment response. A recent prospective multicentre case-control study which studied the plasma level of macrophage migration inhibitory factor (MIF) in PPH patients seemed to show promising results [31]. It showed that MIF was higher in both the systemic and pulmonary circulations of patients with PPH compared with controls and correlated with hemodynamic indices of disease severity [31]. High levels of MIF were associated with an increased risk of death and MIF production may play a role in disease pathogenesis of PPH [31]. MIF can be an ideal novel biomarker in detecting disease presence and severity [31].

**3.5. Treatment**

Treatment strategies for PPH are derived from studies of idiopathic PAH and the aim of therapy is to provide symptomatic relief, to improve the quality of life and exercise capacity, and to facilitate liver transplant [23]. The only effective treatment in patients with PPH is liver transplantation in patients who are suitable after careful assessment. Medical therapies that have

been tried for PPH include endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin analogs [2, 23, 27]. There are limited data evaluating the long-term survival of patients with PPH managed with medical therapy alone. Recent study from UK showed that phosphodiesterase 5 inhibitors were the most frequently used targeted therapy (63%) followed by prostacyclin analogs (12.7%), and endothelin receptor antagonists (10%) [32].

#### *3.5.1. General medical treatment*

In patient with significant hypoxemia, oxygen therapy is needed for improvement of symptoms. For those with significant edema and ascites, diuretics should be initiated. In patients with PPH, they are at risk of thrombosis and hence anticoagulation is recommended. However, in patients with liver cirrhosis had increased risk of variceal bleeding due to underlying portal hypertension and clinical judgment is required prior to starting anticoagulation in these group of patients.

Calcium channel blockers can be used due to their acute vasoreactive properties in PAH but can be dangerous in patients with PPH since it can result in worsening of portal hypertension because of their mesenteric dilatation properties [2, 23, 27]. TIPSS are not recommended in PPH since it can deteriorate PPH because of acute increase in preload causing increased cardiac output and mPAP, and then leads to worsening right ventricular strain and dysfunction [29].

#### *3.5.2. Specific therapies for PPH*

The therapies specific for PPH targeted to improve pulmonary vasoconstriction and vascular remodeling by altering three pathways: Prostacyclin analogs (prostanoids), phosphodiesterase 5 inhibitors, and endothelin receptor antagonists [2, 9, 27, 33]. Pulmonary vasodilators treatment should be employed with the aim of lowering mPAP < 35 mmHg, to minimize the risk of graft failure and to improve the overall outcome [42].

#### *3.5.3. Prostacyclin derivatives*

They are potent pulmonary as well as systemic vasodilators, and have antiplatelet aggregating and antiproliferative effects [27]. The most commonly used prostacyclin is epoprostenol and it is the only treatment that has been shown to improve survival in idiopathic PAH [27].

#### *3.5.4. Endothelin receptor antagonists*

Bosentan is an oral dual effective, nonselective receptor antagonist that blocks both endothelin A and B receptors [27], and it has been shown to be effective in the treatment of PPH showing clinical, functional, and hemodynamic benefits without significant hepatotoxicity in some small retrospective case series [29]. Bosentan is probably the therapy of choice for patients with PPH as it potentially improves pulmonary as well as portal hypertension [29]. It is potentially hepatotoxic and may cause deterioration in liver enzymes in about 10% of patients, and hence, close monitoring is needed [29]. A recent study showed that Child-Pugh B cirrhosis with PPH had significantly larger hemodynamic improvement with bosentan treatment [34].

It was also found that plasma concentrations of bosentan were higher in patients with child B cirrhosis than those observed in idiopathic PAH [34].

### 3.5.5. Phosphodiesterase 5 inhibitors

Phosphodiesterase-5 inhibitor therapy is efficacious in other causes of WHO group I pulmonary arterial hypertension [32]. They inhibit the growth of pulmonary vascular smooth muscle cells and lower mean pulmonary artery pressure and pulmonary vascular resistance by mediating vasodilation through guanosine monophosphate [2, 27]. Sildenafil is commonly used in PPH and reported to be effective in reducing mPAP and PVR [29]. Sildenafil is approved in a dose of 20 mg three times a day for treatment of PPH [35], and it should be considered as a bridging therapy before liver transplant for patients with PPH to delay the progression of the disease.

A recent single center retrospective study showed that sildenafil therapy resulted in improvement of WHO functional class with significant decrease in PVR, mPAP, and increase in cardiac output but no change in 6-min walk test over the period of 6 months treatment [32]. A recent retrospective study of all patients with PPH treated by oral pulmonary vasoactive drugs (PVD) (bosentan, ambrisentan, sildenafil, tadalafil) showed that oral PVD improved MPAP, PVR, and 6-min walk distance [36]. The study showed that oral PVD are safe, better tolerated in patients with cirrhosis, and did not show any worsening of cirrhosis and these treatments improved hemodynamic conditions allowing patients access to liver transplantation eligibility [36].

### 3.5.6. Liver transplantation

LT is the definitive therapy for patient with PPH when medical therapy fails. LT should be considered in patients with mean pulmonary artery pressure (MPAP)  $<35$  mmHg or MPAP between 35 and 50 mmHg with pulmonary vascular resistance (PVR)  $<250$  dyn s cm<sup>-5</sup> [23, 37]. PPH is diagnosed in 2–6% of liver transplantation (LT) candidates [38]. Without LT, the survival rate for patients with PPH was found to be 38% at 3 years and 28% at 5 years [37]. Due to the severity of the condition and high mortality associated with it, patient with PPH should be assessed carefully before considering LT. Perioperative mortality in patients with mean PAP  $>35$  mmHg is significantly higher compared to those with mPAP  $<35$  mmHg [4, 23]. The outcome is worse in patients with moderate to severe PPH [mean pulmonary artery pressure (MPAP)  $\geq 35$  mm Hg] and associated with a perioperative mortality rate of 50% [37, 38].

Therefore, patient should be treated with medical therapy while awaiting LT to delay the progression of disease as well as to improve perioperative risk. The goal of therapy in patients with PPH, who are candidates for liver transplants, is to reduce mPAP  $<35$  mmHg and the PVR  $<400$  dyn s cm<sup>-5</sup> before proceeding to liver transplant [29].

Patients on liver transplant waiting list are prioritized based on the model of end-stage liver disease (MELD) score but in patients with PPH, potentially important factors such as severity of PPH is not included which may affect survival. Recent retrospective cohort study of patients in the Organ Procurement Transplantation Network (OPTN) database with hemodynamics consistent with PPH [defined as mean pulmonary arterial pressure (mPAP)  $>25$  mmHg and

pulmonary vascular resistance (PVR)  $\geq 240$  dynes.sec.cm<sup>-5</sup> who were approved for a PPH-MELD exception between 2006 and 2014 showed that initial native MELD score and initial PVR were the only significant univariate predictors of waitlist mortality and remained significant predictors in a multivariate model [39]. The study showed that PVR and mPAP were not significant predictors of post-transplant mortality [39].

According to the European Respiratory Society Task Force, patients with mean pulmonary artery pressure  $< 35$  mmHg can undergo a liver transplant, patients with mean pulmonary artery pressure of 35–45 mmHg should receive vasodilator therapy before transplant, and patients with mean pulmonary artery pressure  $> 45$  mmHg should receive vasodilator therapy only [4, 7].

## 4. Hepatic hydrothorax

### 4.1. Background

Hepatic hydrothorax (HH) is a more common clinical entity compared to HPS and PPH and carries the best prognosis [9]. HH accounts for 2–3% of total pleural effusions [40]. However, in patients with portal hypertension, HH occurred in 5–10% of cases [41].

HH is caused by the accumulation of transudative effusion in patients who did not have underlying cardiopulmonary disease [42]. Majority of HH was noted on right side in 79.5% of cases followed by left sided and bilateral in 17.5 and 3%, respectively [40].

Since the pleural space is relatively small compared to the abdominal cavity with low compliance of the thoracic cavity, patients can become symptomatic with as little as 500 ml accumulation of fluid [42]. Like ascites, HH can become spontaneously infected, a condition known as spontaneous bacterial empyema (SBEM), which carries a mortality of up to 20% [42]. The incidence of SBEM was noted to be 13% in a prospective study [43] and interestingly, up to 40% of SBEM patients are not associated with incidence of spontaneous bacterial peritonitis (SBP) [43].

### 4.2. Clinical features

The clinical presentation is usually found in patients with cirrhosis and portal hypertension, i.e., ascites, spider naevi, asterixis, hepatosplenomegaly, and caput medusa. Patients with HH can present with pulmonary symptoms as in shortness of breath, cough, hypoxemia, or respiratory failure associated with large pleural effusions [40]. SBEM should always be suspected when patients develop fever, pleuritic chest pain, or features of liver decompensation.

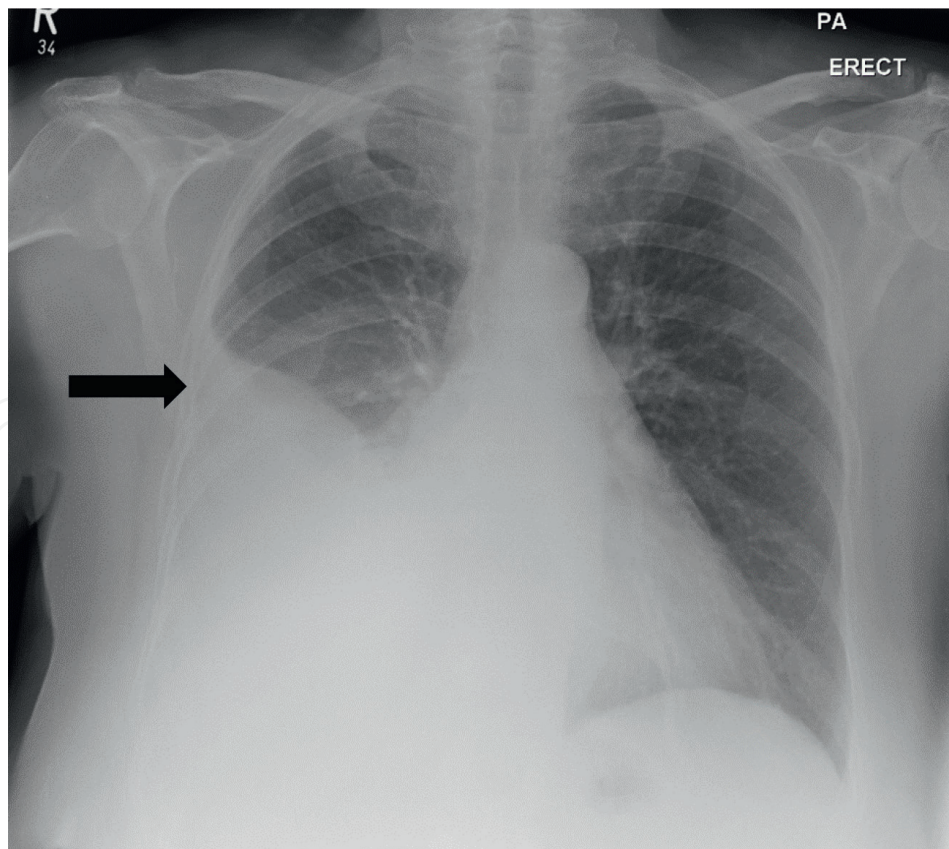
### 4.3. Pathogenesis

The pathogenesis of HH is similar to those leading to ascites in portal hypertension [40, 41]. Portal hypertension and splanchnic vasodilatation are the main pathways leading to fluid accumulation as a result of decrease in effective blood volume which then activate renin-angiotensin system leading to sodium and water retention [9]. Particularly in HH, it is thought to be a

consequence of ascitic fluid translocation through congenital diaphragmatic defects into the pleural cavity [42]. These defects, normally covered with pleuroperitoneum, were most frequently seen in the right hemi-diaphragm and usually smaller than 1 cm in size [42]. Ascites accumulation increases the intraperitoneal pressure which causes rupture of the pleuroperitoneal membrane and as a result, ascitic fluid can move into the low pressure pleural space [42]. This explanation for the appearance of hepatic hydrothorax is supported by studies showing intraperitoneal-injected radiotracer activity in the pleural fluid of such patients [44]. HH can happen due to hypoalbuminemia resulting in decreased colloid osmotic pressure [45] and lymphatic leakage from the thoracic duct [46].

#### 4.4. Investigations

Patients with portal hypertension with pulmonary clinical features should be investigated thoroughly to rule out other causes of pulmonary and cardiac disorders. HPS and PPH should be investigated as part of differential diagnosis. The presence of pleural effusions is usually detected by thorough respiratory examination with findings of dullness to percussion, mediastinal shift, diminished or inaudible breath sounds, and pleural friction rub. In clinically suspected patients, pleural effusions can be confirmed with one of the imaging modalities such as chest X-ray (**Figure 6**), ultrasound scan, or CT chest. Echocardiogram should be performed to rule out underlying cardiac causes of effusions.



**Figure 6.** Chest X-ray showed the presence of right-sided pleural effusion.

Pleural fluid should be examined to rule out other causes leading to pleural fluid such as infection, inflammation, and malignancy. Pleural fluid should be aspirated using ultrasound and the sample should be sent for cell count, gram stain, culture, cytology, pH, total protein, albumin, lactate dehydrogenase (LDH), and amylase. Diagnosis of transudate is based on Light’s criteria, which is shown in **Table 5** [47], since HH is transudate in nature.

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*Light’s criteria*

Pleural fluid total protein/serum total protein ratio <0.5

Pleural fluid LDH/serum LDH <0.6

Pleural fluid LDH < two thirds of the upper limit of normal serum LDH

*Other investigative parameters*

Total protein <2.5 g/dl

Pleural fluid lactic dehydrogenase (LDH) <200 IU

Serum pleural to fluid albumin gradient >1.1 g/dl

Glucose level similar to that of serum

pH 7.4–7.55

Polymorphonuclear count <250 cells/mm<sup>3</sup>

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**Table 5.** Characteristics of pleural fluid in HH.

In patients with SBEM, pleural fluid has high Polymorphonuclear cell counts >250 cells/mm<sup>3</sup> with positive culture or >500 cells/mm<sup>3</sup> in patients with negative culture without any evidence of underlying chest infection/pneumonia or exudative features of infection [40].

## 4.5. Treatment

### 4.5.1. Medical therapy

The role of medical therapies is to relieve symptoms and prevent the complications of HH in patients awaiting liver transplantation or to palliate symptoms in those who are not transplant candidate [42]. Treatment is similar to the treatment of ascites which include dietary salt restriction, diuretic therapy, and drainage of fluid either from abdomen or pleural space.

The management of dietary sodium is important to prevent re-accumulation of fluids and dietary education should be given to patients. Diuretic therapies with furosemide 40–80 mg once daily with or without addition of spironolactone 50–400 mg OD are used in patients who are tolerant of diuretic therapy. Urinary sodium should be checked before and during therapy to adjust diuretic dosage as per clinical response. In patients with refractory ascites, the other treatment modalities can be used. These include paracentesis, thoracentesis, insertion of chest drain tube, indwelling tunneled pleural catheter (PleurX) insertion, insertion of transjugular intrahepatic portosystemic shunt (TIPSS), pleurodesis, shunt surgery, and repair

of diaphragmatic defect [40, 41, 48–51]. Each treatment has its own advantages and disadvantages and should be selected as per patient's clinical condition.

In patients with HH and large volume ascites, ascites should be drained before draining pleural fluid to prevent the rapid accumulation of fluid in the pleural space after thoracentesis due to decreased intrathoracic pressure [40]. Thoracentesis is used for large pleural effusion in patient with significant dyspnea. Pleural fluid should be drained not more than 2 L of fluid at any time point to prevent expansion pulmonary edema. If patients required regular thoracentesis, they should be considered for therapies that provide long term symptom relief. Indwelling tunneled pleural catheter (PleurX) insertion is usually considered for patients in palliative setting.

TIPSS is effective in controlling ascites and hepatic hydrothorax, although the procedure did not improve the prognosis of patients with end-stage liver cirrhosis [40, 51]. TIPSS should be considered in patients with compensated liver cirrhosis and the factors associated with increased mortality in patients who had TIPSS are age >60 years, Child Pugh class C, presence of pre-TIPSS high model for end-stage liver disease (MELD) score >15 and high pre-TIPS creatinine levels >2 mg/dl [51]. Patients whose had high risk features described above should be considered for LT.

In patients with SBEM, the management is to treat underlying infection with broad spectrum antibiotics with or without inserting large bore chest drain tube.

#### 4.5.2. Liver transplantation

In patients with refractory ascites who are Child Pugh C cirrhosis, LT should be considered first prior to other therapies. The presence of HH does not lead to more post-operative complications, and long-term survival is similar to other indications of liver transplantation [40, 41]. Patient should be managed conservatively with medical therapy while awaiting LT.

## 5. Conclusion

Pulmonary complications (HPS, PPH, and HH) are rare occurrence in patients with liver cirrhosis and portal hypertension. In patients with these conditions carry a significant morbidity and mortality and therefore, strong clinical suspicion is required to make earlier diagnosis. There are multiple medical therapies available for each condition in literature but most of the treatments are not effective. The only effective treatment that alters the clinical prognosis is liver transplantation and hence, patients with these conditions should be screened and assessed for the suitability of LT.

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