Differential diagnosis of hepatopulmonary syndrome (HPS): Portopulmonary hypertension (PPH) and hereditary hemorrhagic telangiectasia (HHT)

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ABSTRACT

Hepatopulmonary syndrome (HPS) is a severe complication of advanced liver disease associated with an extremely poor prognosis. HPS is diagnosed in 4-47% of patients with cirrhosis and in 15-20% of candidates for liver transplantation. In addition, severe hypoxia is associated with a high risk of complications of liver transplantation (a 30% chance during the first 90 days) and increases the gap between transplantation and improving arterial oxygenation. The pathogenesis of HPS is not fully understood, and no effective pharmacological treatment has been developed yet. Currently, the treatment of choice for HPS is orthotopic liver transplantation. Non-specific clinical criteria and the lack of standardized diagnostic criteria for determining HPS can lead to diagnostic errors. Portopulmonary hypertension and hereditary hemorrhagic telangiectasia, also known as Osler–Weber–Rendu syndrome, are pulmonary complications of liver disease which should be differentially diagnosed from HPS.

KEY WORDS: Hepatopulmonary syndrome; differential diagnosis; portopulmonary hypertension; hereditary hemorrhagic telangiectasia; PPH; HPS; HHT; orthotopic liver transplantation; OLT

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INTRODUCTION

In 1884, Fluckiger [1] first described pathological changes occurring in both the liver and lungs, in a young woman with hepatic cirrhosis, nail clubbing, and cyanosis due to syphilis [1]. Snell [2] reported the effects of chronic liver disorder on physical and chemical properties of the blood, in 1935. He observed low capillary oxygen saturation level in patients with hepatic cirrhosis [2].

In 1956, Rydell and Hoffbauer first described the pathophysiology of so-called "hepatic cyanosis" [3]. They reported an 11-year follow-up of a boy (11 years old at the first examination) with progressive dyspnea and pulmonary shunting, corresponding to ejection fraction of 40% and 73% hemoglobin oxygen desaturation. After the patient's death, the autopsy revealed the presence of arteriovenous fistulas, dilatation of pulmonary vessels, and anastomosis between the main arterial trunk and pulmonary veins located close to the diaphragm [3].

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The term "hepatopulmonary syndrome" (HPS) was suggested by Kennedy and Knudson in 1977 [4]. They used HPS to describe exertional dyspnea in patient with alcoholic cirrhosis, which developed after portacaval shunting, in the absence of any signs of respiratory disease. The authors showed an association between acute hypoxemia, due to intrapulmonary arteriovenous shunting, and liver dysfunction. In addition, they pointed out an increase in alveolar-arterial oxygen gradient ($A\text{-}aO_2$) in patients with chronic liver disease.

Today, the HPS term is used to describe the defect in arterial oxygenation caused by pulmonary vascular dilatation and associated with liver disease [5-8].

Morphological changes in HPS include dilatation of the pulmonary pre-capillary and post-capillary vessels (functional shunt) and, less frequently, pleural and pulmonary arteriovenous communications (true shunt). Normally, arteriovenous anastomoses are not functional (less than 10%) [9-11]. Based on pulmonary angiography, HPS is classified as type I lessions that are characterized by a diffuse pattern and type 2 lesions that have discrete, localized arteriovenous communications.

The absence of specific clinical criteria and the lack of standardized diagnostic criteria for determining HPS can lead to diagnostic errors and explain the wide marginal prevalence of

HPS [12]. According to different authors [13-16], HPS is diagnosed in 4-47% of patients with cirrhosis and 15-20% of candidates for liver transplantation. HPS is also often associated with alcohol consumption as well as with primary biliary cirrhosis [17,18]. Some authors pointed out that the development of HPS does not depend on sex and age of patients [9]. On contrary, Lima et al. [12] and Schenket al. [19] found that men are affected with HPS twice as often as women; the patient age range in these studies was 47-56 years. The prevalence of HPS is approximately 10% in patients with chronic viral hepatitis without cirrhosis [20]. Furthermore, no significant correlation with etiology of hepatitis and virus activity was found [21]. In another study [14], among 38 patients with cirrhosis associated with hepatitis C, 11 (28.9%) had HPS; 5 (13.2%) with severe and 6 patients (15.8%) with subclinical HPS.

HPS was also documented in patients with rare liver diseases, such as biliary atresia, hemochromatosis, Wilson's disease, primary sclerosing cholangitis, α_1-antitrypsin deficiency, and liver fibrosis [7]. However, the exact prevalence of HPS in patients with rare liver diseases is still unknown. For example, there is limited information regarding its development in patients with Budd–Chiari syndrome [22].

In addition, HPS is reported in patients with acute hepatitis and idiopathic portal hypertension (IPH), without evidence of liver disease [23-26]. In the case of extrahepatic portal hypertension (EPH) HPS was described in patients with portal vein thrombosis, congenital hepatic fibrosis, and IPH. This confirms the importance of portal hypertension in the pathogenesis of intrapulmonary shunting of blood. Development of HPS was also described in a case of the inferior vena cava (suprahepatic) obstruction. However, violation of liver function was not observed and HPS symptoms regressed after the restoration of blood flow [27].

Furthermore, HPS was described in three children with chronic hypervitaminosis A [28] and in a boy who developed transplant rejection after orthotopic liver transplantation (OLT) [29].

Finally, Patil and Cherian [30] described a case of 17-year-old male with Marfanoid habitus who also showed clinical manifestations of HPS, including chronic liver disease with portal hypertension, pulmonary gas exchange abnormalities, and evidence of intrapulmonary shunting [30].

DIAGNOSTIC CRITERIA FOR HPS

Clinical criteria for HPS diagnosis include defective oxygenation, pulmonary vascular dilatation, and presence of chronic liver disease [7].

Oxygenation defect is measured based on the partial pressure of oxygen (PaO_2) in the arterial blood or A-aO_2 while breathing ambient air (Table 1).

TABLE 1. Types of hepatopulmonary syndrome (HPS) in relation to severity of hypoxia

Mild form of HPS	A-aO_2≥15 mmHg, PaO_2≥80 mmHg
Moderate form of HPS	A-aO_2≥15 mmHg, PaO_2<80-60 mmHg
Severe form of HPS	A-aO_2≥15 mmHg, PaO_2<60-50 mmHg
Very severe form of HPS	A-aO_2≥15 mmHg, PaO_2<50 mmHg (<300 mmHg, when the patient breathes 100% oxygen)

A-aO_2: alveolar-arterial oxygen gradient; PaO_2: partial pressure of oxygen

Patients with progressive HPS have respiratory symptoms including, shortness of breath, clubbed fingers, and cyanosis. Although commonly occurs, shortness of breath is a nonspecific symptom of HPS. The most common manifestations of HPS are platypnea (increased shortness of breath when the body is in a vertical position) and orthodeoxia (3-10 mmHg reduction in PaO_2 in capillary blood during transition from horizontal to vertical position) [31]. On contrary, in healthy people and under normal conditions vertical position does not reduce blood oxygenation, but rather leads to an increase in PaO_2. Platypnea is associated with oxygen desaturation and pulmonary arteriovenous malformations (PAVMs), occuring usually in the middle and lower lung fields (i.e., in the base of the lungs). Blood staisis occurs in the upright position of the patient, which impairs blood oxygenation (that is, causes more shunting) [7,32].

According to some authors [7], the use of A-aO_2 gradient in determining arterial hypoxemia is important due to its sensitivity, and because it can increase abnormally before PaO_2 decreases significantly. However, others argue that the value of A-aO_2 gradient normally vary, especially with age [33]. According to Zhang and Yang [34], A-aO_2 gradient ≥20 instead of 15 mmHg should be used for diagnosing HPS in patients older than 64 years. Nevertheless, considering that A-aO_2 gradient varies greatly in healthy people as well, the above-described diagnostic criteria for HPS are still controversial.

Two-dimensional transthoracic contrast echocardiography with saline as a contrast agent (shaken to form microbubbles >15 microns in diameter) is recognized as gold standard for detection of pulmonary vasodilation [7,13]. After saline is administered in peripheral vein in the arm, microbubbles appear in the right heart chambers. Because the diameter of microbubbles is larger than the diameter of pulmonary capillaries, microbubbles normally do not reach the left cardiac chambers. A delayed visualization in the left atrium, occurring after the 3rd heartbeat post-injection, indicates intracardiac shunting (i.e., defect of interventricular or interatrial septum). The appearance of microbubbles at the 4th to 6th heartbeat indicates intrapulmonary shunting in HPS.

Furthermore, patients with chronic liver disease and diagnosed HPS showed a significantly greater left atrial volume compared to the control group (55.1 ± 7.5 ml and 37.1 ± 9.3 ml,

respectively, $p < 0.05$); the sensitivity was 86.3% and specificity - 81.2% [35]. These results indicate that left atrial enlargement could be used as diagnostic criteria for HPS [35,36].

The disadvantage of two-dimensional transthoracic contrast echocardiography is the inability to determine the type of vascular anomaly that caused a pulmonary shunt [37].

A more sensitive method is transesophageal contrast echocardiography which directly visualizes the intraatrial septum, identifies the presence of intraatrial right-to-left shunt, and shows the passage of microbubbles in the left atrium through the atrial septal defect or pulmonary veins. However, this method shows significant limitations in the presence of varicose veins of the esophagus in patients with cirrhosis [7,13].

A less sensitive but highly specific (100%) diagnostic method for HPS is lung perfusion scintigraphy with labeled technetium ^{99m}Tc macro aggregated albumin (^{99m}Tc-MAA). ^{99m}Tc-MAA particles have a diameter of 10-90 microns, and normally 95% of the particles get trapped in the pulmonary microvasculature after the intravenous administration. In the case of intrapulmonary vasodilation, up to 60% of ^{99m}Tc-MAA particles passes through the lungs and accumulate in other organs, such as the brain, kidneys, spleen, and thyroid gland. In normal conditions, less than 6% of radioactive albumin is found in the brain. In addition, this method allows quantifying the degree of intrapulmonary shunt [7,13].

Pulse oximetry is a well-established method for noninvasive evaluation of arterial oxygenation [38]; it is accurate and reliable in patients without liver disease, and, recently, similar was demonstrated in cirrhotic patients [38]. In both cases, oxygen saturation measured with arterial blood gas (ABG) analysis might be overestimated with oxygen percent saturation (SpO_2) by 1.5%-3.5%; suggesting that SpO_2 may be of use in patients without liver disease and in cirrhotic patients [38]. One of the important implications of the study of Arguedas et al. [38] is that pulse oximetry provides a practical and widely available method for screening the presence and severity of HPS.

In a study from Germany [39], arterial oxygen saturation (SaO_2) was determined in 316 patients with liver disease using pulse oximetry. SaO_2 was significantly lower in HPS patients compared to those without HPS. The SaO_2 result was also in correlation with the mean PaO_2 and intrapulmonary shunt volume in HPS patients [39].

Recently, Horvatits et al. [40] indicated that von Willebrand factor antigen (vWF-Ag) may be used as a screening tool for early detection of HPS [40]. In their study, vWF-Ag levels were significantly higher in patients with HPS compared to patients without HPS ($p < 0.001$). Furthermore, vWF-Ag correlated significantly with gas exchange in HPS patients ($p < 0.05$) [40]. In another study, Horvatits et al. [41] showed that bilirubin and serum bile acids (BAs) were significantly elevated in patients with HPS contrary to alkaline phosphatase (AP) and gamma-glutamyl transpeptidase (GGT) levels (median total BAs in HPS 83.5 μmol/L, interquartile range (IQR) 43.1-148.9 versus no HPS 26.9 μmol/L, 11-75.6; $p < 0.001$). Total BAs and gas exchange were in correlation by means of $PaO_2/AaPO_2$. Overall, BAs retention was associated with HPS and altered gas exchange abnormalities [41].

In the case of a violation of gas exchange, routine X-ray and pulmonary function tests can help rule out other cardio-pulmonary problems [42]. Among the functional tests, detection of forced expiratory volume in 1 second (FEV1) and overall lung volume by standardized methods are generally used [43,44].

Pulmonary angiography is an invasive method used in patients who have a poor response to oxygen therapy [44,45]. Both types of HPS can be observed with pulmonary angiography.

Clinical algorithm for evaluating patients with chronic liver disease for HPS was proposed by Fuhrmann et al. [46] (Figure 1).

HPS TREATMENT

The pathogenesis of HPS is not completely understood, and no effective pharmacological treatment has been developed yet. Currently, the treatment of choice for HPS is OLT. Without liver transplatation, the prognosis of HPS is poor. In the case of the development of HPS, the probability of death in the next year is 41% [9]. Although HPS can be an indication for liver transplantation [9,47-49], severe hypoxia in the case of HPS is associated with a high risk of complications of liver transplantation (a 30% chance during the first 90 days) and thus increases the gap between transplantation and improving arterial oxygenation [9,50]. Patients can develop severe posttransplant hypoxemia which means that administration of 100% inspired oxygen is required to maintain an oxygen saturation of ≥85%. This complication is observed in 6-21% of patients, with a mortality rate of 45% [51].

In another study, the strongest predictors of mortality after liver transplatation were preoperative arterial oxygen tension (PaO_2) of ≤50 mmHg alone or in combination with a MAA shunt fraction ≥20% [52,53]. In addition, survival rates between 68% and 80% within one year after liver transplatation were suggested in patients with HPS [53].

A complete regression of HPS symptoms after liver transplantation is observed only in 80% of patients, and may take 6 months or more [9]. Factors that contribute to the regression of HPS after liver transplantation are a young age, minimal hypoxemia, and good response to the therapy with 100% oxygen ($PaO_2 > 200$ mmHg). After liver transplantation, 76% of patients had a 5 year life span [54].

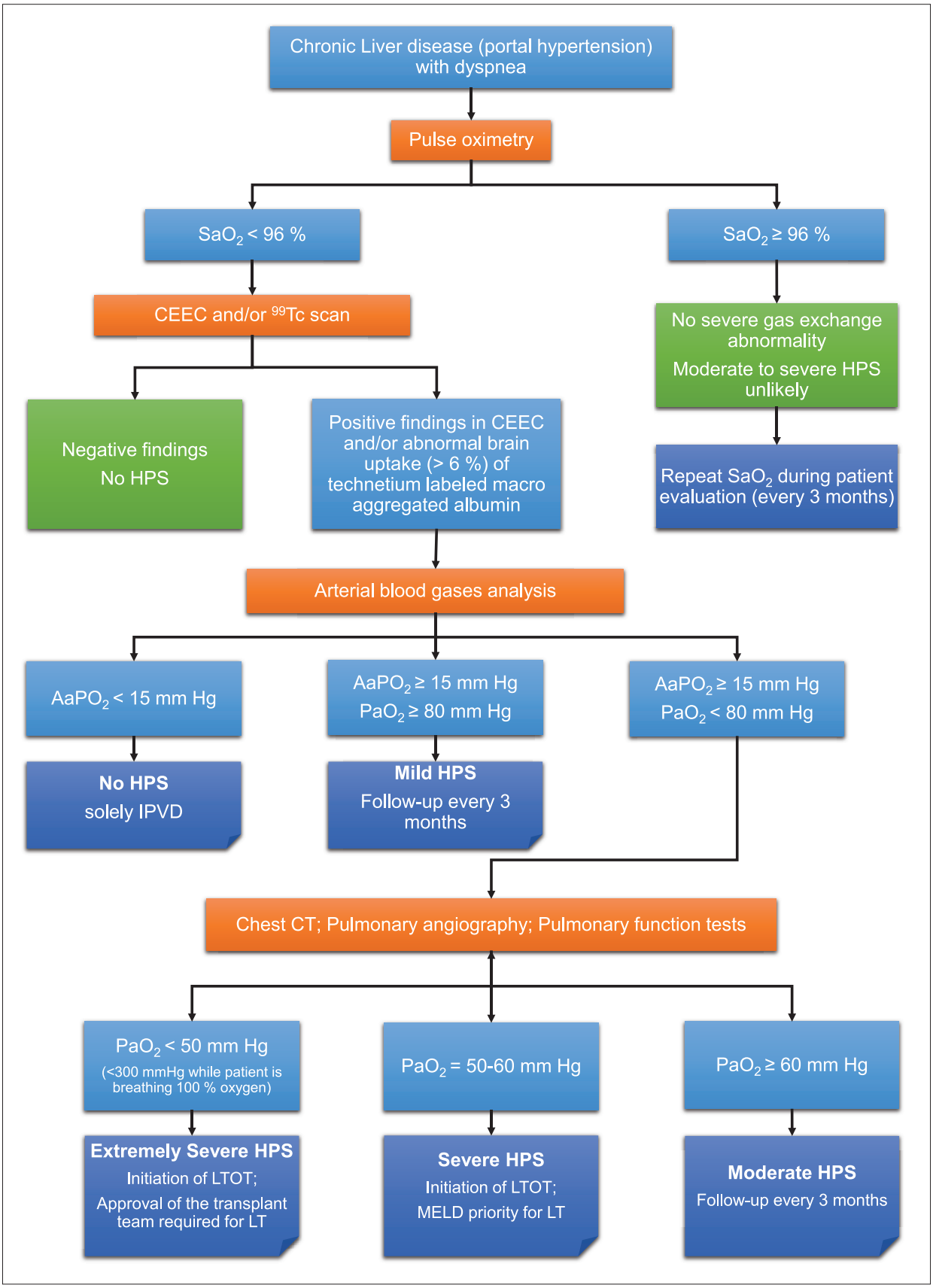

FIGURE 1. Clinical algorithm for screening patients with chronic liver disease for hepatopulmonary syndrome (HPS). SaO_2: arterial oxygen saturation; CEEC: contrast enhanced echocardiography; ^{99m}Tc scan: lung perfusion scintigraphy with technetium ^{99m}Tc labeled macro aggregated albumin; $AaPO_2$: alveolar-arterial oxygen tension difference; PaO_2: partial pressure of oxygen; IPVD: intrapulmonary vasodilatation; CT: computed tomography; LTOT: long term oxygen therapy; MELD: Model for End-Stage Liver Disease; LT: liver transplantation.

Swanson et al. [55] investigated long-term survival in 61 HPS patients diagnosed at Mayo Clinic between 1985 and 2002 compared to case controls, and they assessed the impact of OLT on survival in HPS and control group. Overall, HPS patients who did not undergo transplantation had worse 5-year survival compared to their matched controls (p = 0.0003). The authors indicated that the effect of comorbidity on the survival difference cannot be underestimated, and that baseline PaO_2 at the time of diagnosis was also associated with worse survival in HPS patients [55]. Gupta et al. [56] evaluated mortality, complications, and gas exchange in 21 HPS patients who underwent liver transplantation between 2002 and 2008 (11/21 patients were with severe HPS and 5/21 had living donor liver transplantation). Oxygenation improved in 19 patients for which PaO_2 or SaO_2 were recorded. Survival of liver transplant HPS and severe HPS patients was higher in their study compared to previous reports and the authors indicated that severity of HPS should not be the reason to deny a transplant [56].

DIFFERENTIAL DIAGNOSIS OF HPS

General criteria [6,27] for differential diagnosis of pulmonary vascular disorders associated with liver disease are presented in Table 2.

Portopulmonary hypertension (PPH)

PPH is a pulmonary complication of liver disease, which should be differentially diagnosed from HPS. According to the classification adopted in 1998 at the World Conference on the Problems of Primary Pulmonary Hypertension in France, PPH is defined as pulmonary hypertension associated with chronic liver disease or portal hypertension. It is characterized by increased pressure in the pulmonary artery, i.e., more than 25 mmHg at rest and more than 30 mmHg during exercise, as well as increased pulmonary vascular resistance (PVR), i.e., more than 240 dynes/sec/sm^{-5} [57-59].

The incidence of PPH is relatively low; according to different studies [60-64] it is from 2-8.5% in patients with portal hypertension and 16-20% in patients with cirrhosis. However, diagnostics of PPH needs to be improved due to extremely poor prognosis of the disease (without proper treatment a 5-year survival rate is observed in 14% cases) and high mortality rate (up to 35%) even in the case of successful liver transplantation [65,66]. Risk factors previously determined for PPH include: female sex, autoimmune hepatitis, and genetic variation in estrogen signaling and cell growth regulators [67,68], while hepatitis C infection was associated with a decreased risk of PPH [67].

It appears that the development of PPH is not associated with the causes of portal hypertension. Although a majority of PPH patients have liver cirrhosis as the primary disorder, PPH has been found in patients with portal hypertension due to reasons other than liver, such as portal vein thrombosis without chronic liver disease [61]. Therefore, portal hypertension could likely be an etiology of pulmonary hypertension [69,70].

The mechanism by which portal hypertension causes pulmonary hypertension remains unclear. In the early stages of the disease, almost all patients with PPH have hyperdynamic circulation. However, high cardiac output and hyperdynamic circulation are also the main clinical features in almost all patients with progressive liver disease who develop portal hypertension [70].

Predisposing factors of pulmonary hypertension include: blood volume overload in the splanchnic circulation and congestion in the intestine that leads to the release of endotoxins and cytokines into the splanchnic circulation. The increased cardiac output generates shear stress on the pulmonary

TABLE 2. Differential diagnosis of pulmonary vascular disorders associated with liver disease

	Hepatopulmonary syndrome	Portopulmonary hypertension	Hereditary hemorrhagic telangiectasia
Type of disease	acquired	acquired	hereditary
Age group	children, adults	children, adults	children, adults
Documented genetic predisposition	–	–	+
Type of dilatation of pulmonary vessels	diffuse	in rare cases diffuse	in rare cases diffuse, and descrete
Morphological changes	pre-capillary and capillary dilatation	obstructive arteriopathy	vascular malformations in the lungs, liver, brain and spinal cord, and digestive tract
Clinical symptoms	progressive dyspnea, cyanosis	progressive dyspnea	epistaxis, telangiectasia
Detection of lung pathology using contrast-enhanced echocardiography	+	+	+
Pulmonary vascular resistance	normal or low	elevated	normal or low
Acute hypoxemia	+	in rare cases	+
Normalization of hypoxemia during inhalation of 100% oxygen	+	+	–
Relationship with severity of liver disease	yes	no	–
Resolution with liver transplantation	+	–	+

circulation. This can result either in maintaining adequate PVR which prevents development of related syndromes or in abnormal pulmonary vascular dilatation that causes an abnormal decrease in vascular resistance and leads to the development of HPS. In contrast, increased vascular resistance due to vasoconstriction and remodeling of pulmonary vessels leads to pulmonary hypertension. In the cases of PPH and HPS, altered vascular resistance is probably more due to remodeling of pulmonary vasculature and less due to vascular tone changes [58,70].

A prominent histological feature of PPH is proliferative pulmonary arteriopathy with obliteration of the vascular lumen by endothelial cells and smooth muscle cells and formation of plexiform lesions identical to those observed in primary pulmonary hypertension [57,70,71,72].

Factors affecting the development of proliferative vasculopathy are still not clear. Among these factors may be mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*), which belongs to the transforming growth factor β (TGF-β) superfamily. These mutations have been associated with proliferative pulmonary vasculopathy and identified in patients with primary pulmonary hypertension, but no PPH case has been described with *BMPR2* mutations. Mutations of activin receptor-like kinase 1 (*ALK-1*), another member of the TGF-β family, have been associated with pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia (HHT). Nevertheless, uninvestigated genetic mechanisms may also contribute to the development of proliferative pulmonary vasculopathy, that are specific only to patients with pulmonary hypertension [70,73,74].

Increased cardiac output may lead to mild pulmonary hypertension if PVR is normal or close to normal, resulting in an overestimation of the incidence rate of PPH [70].

In most patients diagnosed with PPH of mild and moderate severity, vasoconstriction and moderate hypertrophy of pulmonary arteries are predominant clinical features [72]. However, in some people, mild or moderate PPH progresses to severe disease and becomes a complication in chronic liver disease or portal hypertension. Patients with progressive PPH tend to deteriorate rapidly and have right heart failure [70].

PPH symptoms

A typical clinical symptom of PPH is breathlessness during exercise. Other symptoms such as fatigue, palpitations, loss of consciousness due to a fall in blood pressure, or chest pain occur less frequently. Clinical findings indicating pulmonary hypertension may even be completely absent. The emphasis of the second tone on the pulmonary artery and systolic heart murmur, suggesting failure of tricuspid valve, are more common. Enlarged jugular veins, edema, and ascites are clinical features associated with decompensated liver cirrhosis and right ventricular failure [70].

Hypoxemia and increased alveolar-arterial (A-a) gradient are observed in the arterial blood of patients with PPH. Signs of right ventricular hypertrophy, right atrial enlargement and displacement of the heart to the right can be observed in electrocardiogram (ECG). X-ray of the lungs is usually normal or with signs of enlarged pulmonary arteries and cardiomegaly [67]. Pulmonary function tests may be normal or indicate lower lung diffusion capacity [60].

Clinical features that support the diagnosis of PPH in patients with liver cirrhosis or portal hypertension include increased pulmonary artery pressure and PVR (Table 3), when other possible causes are excluded such as left ventricular failure, pathology of heart valves, and interstitial and obstructive lung diseases. Although electrocardiography, vectorcardiography, phonocardiography, and pulmonary function tests can be useful for diagnosing PPH, the most accurate method for PPH diagnosis is echocardiography [70].

According to the recommendations of the American Association for the Study of Liver Diseases [60,75] the primary diagnostic method for screening patients suspected of having PPH is transthoracic echocardiography, i.e. estimation of the right ventricular systolic pressure (>50 mmHg indicates PPH in about 65% of patients). Diagnosis confirmation is based on pulmonary artery (right heart) catheterization which includes the measurement of pulmonary arterial pressure, cardiac output, and PVR [11,64].

In addition, vasoreactivity testing with nitric oxide or epoprostenol (prostacyclin) is performed to determine if a patient may benefit from an oral calcium channel blocker. The mean pulmonary arterial pressure >35 mmHg is a risk factor of increased mortality after liver transplantation and requires adequate therapy in the perioperative period [76,77].

There are only a few reports on the co occurrence of HPS and PPH [78,79]. HPS usually develops before PPH [76], although Ioachimescu et al. [80] reported a patient in whom HPS developed following PPH [80].

Hereditary hemorrhagic telangiectasia (HHT)

Another condition which should be differentially diagnosed from HPS is HHT, also known as Osler–Weber–Rendu syndrome. HHT is a relatively common, under-recognized autosomal dominant genetic disorder that results from

TABLE 3. Classification of portopulmonary hypertension (PPH)

Mild form of PPH	Pressure in the pulmonary artery 25-34 mmHg, pulmonary vascular resistance 240-500 dynes/sec/sm^{-5}
Moderate form of PPH	Pressure in the pulmonary artery 35-44 mmHg, pulmonary vascular resistance 500-800 dynes/sec/sm^{-5}
Severe form of PPH	Pressure in the pulmonary artery>45 mmHg, pulmonary vascular resistance>800 dynes/sec/sm^{-5}

multisystemic vascular dysplasia and is characterized by mucocutaneous telangiectases and arteriovenous malformations (AVMs) [81].

HHT was first described by Sutton in 1864; the author reported a case of a man with vascular malformations and recurrent hemorrhage. In 1896, Rendu reported the complex of hereditary epistaxis and telangiectases in a 52-year-old patient, who suffered anemia and epistaxis since the age of 12. In 1901, Osler presented three cases of the disease and highlighted its hereditary nature using the phrase «family recurrent nasal bleeding, associated with multiple telangiectasia» [82,83]. Weber (1907) recognized Osler-Weber-Rendu Syndrome (OWRS) as a clinical entity distinct from hereditary hemophilia. The term "hereditary hemorrhagic telangiectasia" was coined by Hanes [84] in 1909.

The first morphological change of HHT is a focal dilatation of postcapillary venules. As the venules increase in size they become folded and connect to dilating arterioles through capillary segments, forming eventually arteriovenous communication [85,86]. The disease occurs at different geographical areas and the frequency varies between 1-2 cases per 10000-100000 people. Different symptoms are associated with HHT such as hematological, neurological, pulmonary, skin and gastrointestinal tract symptoms. In many cases, clinical symptoms are limited only to nasal bleeding.

The diagnosis of HHT is considered if at least three of the four diagnostic criteria are met: spontaneous, recurrent epistaxis, multiple telangiectases at different sites (lips, oral cavity, fingers, and nose), visceral lesions including gastrointestinal telangiectasia, pulmonary PAVMs, hepatic, cerebral and spinal AVMs, as well as family history of HHT [87].

HHT is particularly associated with mutations in two genes, and classified into two types accordingly: HHT1 and HHT2 [88,89]. In HHT1, the related gene *ENG* is located on the chromosome 9 and encodes protein endoglin, found on the surface of the cells that line the interior of the blood vessels. The gene *ACVRL1* (chromosome 12) is associated with HHT2 and produces the enzyme activin receptor-like kinase 1 (ACVRL1 or ALK1). This protein is also found on the surface of cells, especially on the cells lining developing arteries.

Clinical manifestations of disease vary depending on the genotype [90]. PAVMs are associated with mutations in the *ENG* gene, while altered *ACVRL1* gene is related to the occurrence of liver disease [91]. In some cases HHT phenotype was not associated with these two mutations, suggesting that other genes may be involved in the pathogenesis of HHT.

HHT symptoms

Spontaneous, recurrent epistaxes are due to telangiectasias in the nasal mucosa, and occur in more than 90% of patients with HHT. The severity of the disease can range from mild, requiring no treatment, to severe when patients need repeated blood transfusions. Usually, nasal bleeding occurs in early childhood, and becomes more frequent and prolonged later in life.

Vascular malformations in the lungs are found in 15-35% of patients with HHT, and they are common after 30 years of age [86]. Clinically, they may be asymptomatic when shunt fraction is less then 25%. Large AVMs may manifest by acute intolerance to physical activity, respiratory insufficiency, secondary polycythemia, and even pulmonary bleeding. It should be noted that vascular malformations in the lungs may be also complicated by neurological factors. In normal physiological conditions, pulmonary capillaries provide a filter system for blood, i.e., gas exchange occurs, removing carbon dioxide and adding oxygen to the blood. In the case of PAVMs, which are anatomical right-to-left shunts between pulmonary arteries and pulmonary veins, small clots can bypass the pulmonary capillaries and eventually reach the brain which causes transient ischemic attack (TIA) [92]. In some patients, these complications may indicate the beginning of HHT.

Using multislice computed tomography, Memeo et al. [93] showed that liver is affected in 41-78% of patients with HHT. In most of these patients, there were no clinical symptoms of the liver disease [93]. Abnormalities of the blood vessels connected to the liver vary in size greatly, from microscopic to large arteriovenous shunts and portal venous shunts. Portal hypertension in HHT patients is due to shunting of blood from the hepatic artery to the portal vein [86].

Liver transplantation reduce the possibility of sepsis of the biliary tract and prevents the development of cardiopulmonary failure, greatly improving the quality of patient life. The long-term survival rate was 75% in patients undergoing OLT (i.e., 9 patients from 12 that underwent the transplantation). These patients experienced improvements in epistaxis and quality of life and had more physical activity [94,95].

CONCLUSION

HPS is a severe complication of advanced liver disease associated with an extremely poor prognosis. The pathogenesis of HPS is not fully understood, and no effective pharmacological treatment has been developed yet. Currently, the treatment of choice for HPS is OLT. However, additional studies are necessary to identify the optimal criteria for the selection of patients for liver transplantation. Furthermore, the mechanism of pulmonary vasodilatation, associated humoral factors, and the reversal of symptoms after liver transplantation require further investigation. Finally, because HPS is still an under-recognized complication of end-stage liver disease, it should be considered in every patient with advanced liver

disease showing symptoms of dyspnea and hypoxemia. Also, modern diagnostic methods should be used for early identification of pulmonary vascular complications and their differential diagnostics.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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