

# Hepatopulmonary Syndrome and Liver Transplantation: A Recent Review of the Literature

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## Abstract

A severe and common pulmonary vascular complication of liver disease is hepatopulmonary syndrome (HPS). It is a triad of liver dysfunction and/or portal hypertension, intrapulmonary vascular dilatations, and increased alveolar-arterial oxygen gradient. Prevalence varies according to various study groups from 4%–47%. While the most common presenting symptom of HPS is dyspnea, it is usually asymptomatic, and thus all liver transplant candidates should be screened for its presence. Pulse oximetry is a useful screening method, but arterial blood gas examination is the gold standard. If there is an abnormal P (A-a)O<sub>2</sub> gradient, microbubble transthoracic echocardiography should be done for diagnosis. Outcome is unpredictable, and there is currently no effective medical therapy. The only effective therapy is considered to be liver transplantation. Complete resolution of HPS after liver transplantation is seen within a year in most HPS patients.

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## Introduction

There are three main pulmonary conditions in patients with liver disease and/or portal hypertension. These are hepatopulmonary syndrome (HPS), portopulmonary hypertension (PoPH), and hepatic hydrothorax. Portopulmonary hypertension is a pulmonary hypertension that develops due to portal

hypertension with or without liver disease. Hepatic hydrothorax is a pleural effusion in a cirrhotic patient without cardiac, pulmonary, or pleural disease.

HPS is caused by hyperdynamic circulation, intrapulmonary shunts, and pulmonary vasodilatation. It is a triad of liver dysfunction and/or portal hypertension, intrapulmonary vascular dilatations, and increased alveolar-arterial oxygen gradient (> 15 mm Hg or > 20 mmHg when age ≥ 65 years).<sup>1</sup> Fluckiger first described a relationship between HPS and cirrhosis on a female patient with cyanosis and cirrhosis in 1884, but Kennedy and Knudson named the situation "Hepatopulmonary Syndrome" in 1977.<sup>2</sup> HPS is usually associated with portal hypertension with or without cirrhosis, but it can occur also in patients with acute or chronic hepatitis,<sup>3–5</sup> hypoxic hepatitis,<sup>6</sup> extrahepatic obstruction, Budd-Chiari Syndrome,<sup>7</sup> and cavopulmonary shunts.<sup>8</sup>

The incidence of HPS is higher than PoPH, and both of them are associated with significantly increased morbidity and mortality. Their pathophysiologies, however, are completely different. HPS is characterized by vasodilatation and intrapulmonary shunts, whereas PoPH is caused by pulmonary vasoconstriction and increased pulmonary vascular resistance (PVR). Despite this difference, both can be seen in the same patient, with PoPH developing generally after HPS.<sup>9,10</sup> One theory for this mechanism involves dysregulation of the common vascular signaling pathway for pulmonary dilations and pulmonary arterial remodeling.<sup>10</sup> A second theory involves differences in the expression of the endothelin-1 (ET-1) receptor A, which causes vasoconstriction and increased pulmonary vascular resistance, and receptor B, which leads to upregulation of endogenous nitric oxide synthase and increased nitric oxide production, resulting in pulmonary vasodilation.<sup>11</sup> Medical treatment cannot cure these conditions, so both have serious implications for liver transplantation (LT). After LT, HPS usually resolves, but the response of PoPH is unpredictable.<sup>1</sup> All patients on the LT waiting list should be screened for HPS and PoPH because both are commonly asymptomatic.

In this review, we provide an overview on the prevalence, pathophysiology and pathogenesis, clinical signs, and prognosis of HPS as well as the currently available treatment options for HPS, especially LT.

## Prevalence

The prevalence of HPS varies from 4% to 47%, depending on the population and the criteria used to diagnose.<sup>12–15</sup>

**Keywords:** Hepatopulmonary syndrome; Pulmonary complications of cirrhosis; Liver transplantation.

**Abbreviations:** ABG, arterial blood gas; CBDL, common bile duct ligation; CO, carbon monoxide; CT, computed tomography; ET, endothelin; HPS, hepatopulmonary syndrome; HO, heme oxygenase; iNOS, inducible NOS; IPVD, intrapulmonary vascular dilation; L-NAME, N(G)-nitro-L-arginine methyl ester; LT, liver transplantation; MAA scan, macro-aggregated albumin scan; MELD, model end-stage liver disease; MTTE, microbubble transthoracic echocardiography; NO, nitric oxide; NOS, NO synthase; PoPH, portopulmonary hypertension; PTX, pentoxifylline; PVR, pulmonary vascular resistance; SA, spider angioma; TEE, transesophageal echocardiogram; TGFβ-1, transforming growth factor beta-1; TIPS, transjugular intrahepatic portosystemic shunt; TNFα, tumor necrosis factor alpha; TTE, transthoracic echocardiogram; VEGF, vascular endothelial growth factor; ZnPP, zinc protoporphyrin.

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Intrapulmonary vascular dilatations (IPVD) occur among 13%–80% of LT candidates,<sup>16</sup> but arterial blood gas abnormalities do not develop in all patients. Abrams *et al.*, detected IPVD in 38.0% of cirrhotic patients, however, they reported gas abnormalities among only 17.5% of them.<sup>17</sup> These findings suggest that mild IPVDs do not always cause gas exchange abnormalities. There is no reported association between severity of liver disease and severity of HPS.<sup>17–19</sup>

### Pathophysiology and Pathogenesis

The main mechanism of HPS is impaired gas exchange, ventilation-perfusion mismatch by intrapulmonary capillary vasodilatation, and arteriovenous shunts.<sup>1</sup> Pulmonary blood flow increases due to pulmonary vasodilatation and hyperdynamic circulation in liver disease. These changes also cause a decrease in the transit time of red blood cells in pulmonary capillaries, and oxygen molecules pass a longer distance in a shorter time. Therefore, red blood cells exit from pulmonary capillaries before full oxygenation, and ventilation-perfusion mismatch occurs.<sup>20</sup> Another reason for hypoxemia is arteriovenous shunting due to vasodilatation and angiogenesis.<sup>21</sup>

### Pulmonary vasodilatation

Much of the information on the pathogenesis of HPS is based on studies on an animal model of cirrhosis created by common bile duct ligation (CBDL). Animal and human studies have shown that excess production of pulmonary vasodilators like nitric oxide (NO) and carbon monoxide (CO) cause HPS and that pulmonary arterial vasodilation arises due to the imbalance between vasodilators and vasoconstrictors. In these CBDL animal models, first, cholangiocytes proliferate and then produce and secrete ET-1<sup>22–27</sup> due to stimulation by transforming growth factor beta-1 (TGFβ-1).<sup>28</sup> This increase in ET-1 can cause both vasodilatation and vasoconstriction.<sup>11</sup> When ET-1 binds to its receptor, which is called the ET-1B-receptor, it causes activation of pulmonary endothelial NO synthase (eNOS), and this leads to NO mediated pulmonary vasodilatation.<sup>26,29</sup> Interestingly, the ET-1B receptor has been shown to be selectively upregulated in experimental portal hypertension.<sup>26,29</sup>

ET-1 also initiates the accumulation of pulmonary intravascular monocytes.<sup>30</sup> Selective ET-1B receptor blockade or genetic depletion decreases pulmonary eNOS associated NO activation and prevents the onset of HPS.<sup>31,32</sup> In CBDL animal models, macrophages that adhere to the pulmonary endothelium produce inducible NOS (iNOS), which can also contribute to local NO production.<sup>33</sup> Exhaled levels of NO were measured in different studies, and after LT, these levels were shown to normalize.<sup>34,35</sup> Administration of methylene blue was demonstrated to improve transiently oxygenation by inhibiting the action of NO.<sup>36–38</sup>

Carbon monoxide (CO) is another gas that is responsible for pulmonary artery vasodilatation. Levels of arterial carboxyhemoglobin seem to be elevated in HPS patients,<sup>39</sup> and CO is produced from the degradation of heme by heme oxygenase (HO). HO has two forms, which are called inducible (HO-1) and constitutive (HO-2).<sup>25</sup> Intravascular macrophages that progressively accumulate after CBDL produce HO-1, and they cause vasodilatation.<sup>25,33,40</sup> A specific HO-1 enzyme inhibitor, zinc protoporphyrin IX (ZnPP), decreases intrapulmonary vasodilatation and when it is used in treatment, it improved HPS in animal models of CBDL.<sup>41</sup>

The second mechanism of pulmonary vasodilatation is bacterial translocation and endotoxemia, which trigger recruitment and activation of macrophages in the pulmonary vascular network.<sup>42–44</sup> These macrophages produce pro-inflammatory cytokines, like tumor necrosis factor alpha (TNFα), leading to NO mediated vasodilatation.<sup>45</sup> Pentoxifylline (PTX) is a non-specific TNFα, iNOS, and angiogenesis inhibitor. Administration of pentoxifylline has been shown to improve HPS in a rat model of cirrhosis.<sup>46,47</sup>

### Pulmonary angiogenesis

Although vasodilatation is an important factor for HPS, inhibition of NO failed to improve gas exchange in some patients, so it cannot be the only mechanism for HPS.<sup>48</sup> Vascular endothelial growth factor (VEGF)-mediated angiogenesis<sup>49</sup> and increased pulmonary capillary density in the CBDL animal model contribute to collateral formation.<sup>50</sup> These findings suggest that angiogenesis plays a role in HPS pathogenesis. Inflammatory cells accumulate in the lungs by bacterial translocation, endotoxemia, and increased circulating TNF-α due to decreased liver function and inflammation post-CBDL.<sup>46,50,51</sup> Abnormal intrapulmonary accumulation of monocytes and activated macrophages trigger activation of VEGF signaling pathways, and this causes pulmonary angiogenesis.<sup>51</sup> It was shown that CD68+ macrophages accumulate in the lungs from rats with HPS and that the histological and hemodynamic features of HPS get better when these macrophages deplete.<sup>50</sup> In addition, it was demonstrated that there was a decrease in intrapulmonary shunt fraction and a decrease in the P(A-a)O<sub>2</sub> gradient by TNF-α neutralization.<sup>46,52</sup> Endothelial activation of the circulating chemokine ligand 1 (fractalkine, CX3CL1) in the lung may play a role in mediating intrapulmonary accumulation of monocytes and induction of angiogenesis in experimental HPS.<sup>53,54</sup> Some studies showed that anti-angiogenesis therapy reduced the severity of HPS<sup>55</sup> and improved gas exchange and intrapulmonary shunting.<sup>22</sup>

### Clinical signs

HPS is usually asymptomatic, but the most frequent symptoms of HPS are progressive dyspnea and cyanosis.<sup>56–57</sup> Fatigue, spider naevi, digital clubbing, platypnea, and orthodeoxia are other symptoms of HPS.<sup>58</sup> None of these signs are specific for HPS; and if a liver disease patient presents with both hypoxemia and digital clubbing, HPS should be eliminated.<sup>59</sup> Dyspnea and hypoxemia worsen in the upright position due to vasodilatation in the basal parts of the lung, leading to an increase in ventilation-perfusion mismatch.<sup>58</sup> Orthodeoxia is defined as a decreased partial pressure of arterial oxygen (PaO<sub>2</sub>) from supine to upright position, and it is related with increased intrapulmonary shunting and vascular dilatations in HPS.<sup>60</sup> Spider angioma (SA) can be a skin marker of HPS, since patients with SA are more hypoxemic in comparison to those who do not have SA. This can be due to the same imbalance between vasodilators and vasoconstrictors.<sup>61</sup> Usually, oxygen desaturation occurs during sleep in HPS patients, and the degree of hypoxemia correlates with the severity of HPS.<sup>62</sup> Other physical signs, such as cirrhosis and portal hypertension, can be seen in patients with HPS.

## Diagnosis

When there is a patient with liver disease who shows clinical manifestations of HPS, arterial oxygenation and pulmonary dilatation should be assessed. Pulmonary function tests and imaging should also be done to investigate concomitant lung disease because HPS can coexist with other pulmonary or cardiac diseases and exacerbate symptoms and hypoxemia.<sup>63</sup> HPS is usually asymptomatic, so all liver transplant centers should routinely screen patients for HPS.

HPS diagnosis consists of a triad (Table 1): the presence of liver disease and/or portal hypertension, elevated room air alveolar-arterial oxygen gradient [P(A-a)O<sub>2</sub> gradient] > 15 mmHg or > 20 mmHg when age ≥ 65 years], and evidence of IPVD, especially in the basal parts of the lungs. The European Respiratory Society Task Force in 2004 classified HPS according to stage.<sup>1</sup> The importance of staging is discussed below.

### Intrapulmonary Vasodilatation

Microbubble transthoracic echocardiography (MTTE), nuclear lung scanning (99m-Technetium-labelled macro-aggregated albumin scan, MAA scan), and rarely pulmonary angiography and high-resolution computed tomography (CT) can be used for detection of IPVD. MTTE is considered for the diagnosis of HPS.<sup>1,17,64</sup> For MTTE, agitated saline with microbubbles with a diameter > 10 μm are injected into peripheral vein in the arm.<sup>65,66</sup> Normally, these microbubbles are absorbed by alveoli and trapped by the pulmonary capillary bed (8–15 μm). In HPS, bubbles cannot stay in lung, and they transverse to the lung circulation and enter the left atrium. If microbubbles are seen in left atrium in three to six cardiac cycles after they are seen in right atrium, it is indicative of intrapulmonary shunting; but if it happens within three cardiac cycles, this indicates intracardiac shunting.

Transthoracic echocardiogram (TTE) is not as sensitive as transoesophageal echocardiogram (TEE) because TEE can show bubbles in the pulmonary veins.<sup>64,67</sup> TEE requires sedation, has more risk because of esophageal varices in cirrhotic patients, and has a higher cost, so it is not usually used in practice.<sup>1</sup>

MAA is a more invasive method that uses the signal of 99mTc-radiolabelled MAA (> 20 μm in diameter). In this method, Technetium-99m-labelled albumin is injected, and this larger radionuclide is normally trapped in the pulmonary capillaries. However, in HPS patients with intracardiac or intrapulmonary shunts, these aggregates pass through the pulmonary vasculature and are retained in the brain and kidneys.<sup>68</sup> Radionuclide uptake to the brain and kidneys is studied in this method, but it is not very sensitive and cannot differentiate between intracardiac and intrapulmonary shunts.<sup>17,65</sup> Pulmonary angiography is an invasive method, so it is not commonly used in diagnosis of HPS. According to the angiographic patterns and underlying pathophysiology,

HPS can be classified into two types. Type 1 HPS is associated with an increase in the number of visible vessels, and vascular dilatation is more severe in the basal part of lung. Patients with type 1 usually have normal or near normal PaO<sub>2</sub> responses to breathing pure oxygen. In contrast, the type 2 pattern of HPS, which is less common, does not respond to 100% oxygen.<sup>69</sup> Another method used for embolization when large arteriovenous shunts are suspected is pulmonary angiography.<sup>58</sup> High-resolution CT can show intrapulmonary vasodilatation. Additional methods are used to exclude other pulmonary diseases. Chest radiographs are usually normal, but they sometimes show evidence of severe intrapulmonary vasodilatation.<sup>1,58,67,68,70</sup>

### Hypoxemia

Pulse oximetry is a quick, noninvasive, inexpensive, and useful method to determine arterial oxygenation.<sup>71–73</sup> It can be used as a screening test for the detection of pulmonary arterial blood oxygenation deficits by measuring the difference between supine and standing oxygen saturation.<sup>71–73</sup> Nevertheless, oxygenation measured by arterial blood gas (ABG) in the sitting position with room air is the gold standard for diagnosis of HPS.<sup>15,71,72,74,75</sup> SaO<sub>2</sub> is not sufficient to diagnose HPS,<sup>72,73</sup> so when SaO<sub>2</sub> levels are < 97%, an ABG should be considered.<sup>75</sup> The recommended cutoff value for the diagnosis of HPS is P(A-a)O<sub>2</sub> gradient > 15 mmHg, and for patients who are older than 64 years, the cutoff is P(A-a)O<sub>2</sub> gradient > 20 mmHg.<sup>1</sup> The European Respiratory Society Task Force in 2004 classified HPS according to stage: mild (PaO<sub>2</sub> ≥ 80 mmHg), moderate (PaO<sub>2</sub> 60 to < 80 mmHg), severe (PaO<sub>2</sub> 50 to < 60 mmHg), and very severe (PaO<sub>2</sub> < 50 mmHg) (Table 2).<sup>1</sup> Staging is important to determine prognosis and timing of LT.<sup>1,76</sup> Abnormal diffusing capacity of CO can be measured with a lung function test as well.<sup>77</sup> Biomarkers, such as vascular cell adhesion molecule 1, intercellular cell adhesion molecule 3, and von Willebrand factor, are new markers to detect HPS, but these markers have not yet been tested in large groups.<sup>78,79</sup>

### Prognosis

There are varying results about prognosis in HPS. It was reported in a multicenter prospective study that a higher overall mortality rate was present in patients with HPS who were candidates for LT. Similar results were found for pre- and post-LT periods, and this mortality was independent of age, sex, race, model end-stage liver disease (MELD) score, the probability of receiving an LT, and hypoxemia.<sup>80</sup> In another study, median survival was demonstrated to be 10.6 months, and only 25% of patients who have PaO<sub>2</sub> < 60 mmHg lived for 6 months.<sup>81</sup> In a different study that compared survival rates in HPS and non-HPS patients who had similar liver function, it was shown that median survival was 24 months

**Table 1. Diagnostic Criteria of hepatopulmonary syndrome (HPS) (The European Respiratory Society Task Force in 2004)<sup>1</sup>**

|    |  |
|----|--|
| 1- | Presence of liver disease and/or portal hypertension   |
| 2- | Elevated room air alveolar-arterial oxygen gradient [P(A-a)O <sub>2</sub> gradient] > 15 mmHg or > 20 mmHg when age ≥ 65 years |
| 3- | Evidence of intrapulmonary vascular dilation (IPVD)  |

**Table 2. Staging of HPS (The European Respiratory Society Task Force in 2004)<sup>1</sup>**

|                    |                              |
|--------------------|------------------------------|
| <b>Mild</b>        | PaO <sub>2</sub> ≥ 80 mm Hg  |
| <b>Moderate</b>    | PaO <sub>2</sub> 60–79 mm Hg |
| <b>Severe</b>      | PaO <sub>2</sub> 50–59 mm Hg |
| <b>Very severe</b> | PaO <sub>2</sub> < 50 mm Hg  |

(5-year survival of 23%) in HPS group and 87 months (5-year survival of 63%) in non-HPS group.<sup>57</sup> The level of oxygenation reflecting the severity of HPS was not correlated with severity of liver disease, which was determined by Child-Pugh or MELD score.<sup>57,63,82</sup> However, there are newer studies that have shown no reduction in survival in patients with HPS who are on the LT waiting list.<sup>83</sup>

## Treatment

The only known effective therapy for HPS is LT,<sup>82,84-89</sup> with an improvement in oxygenation at 1 year.<sup>85-87</sup> After LT in HPS patients, the 5-year survival rate was shown to be approximately 76%, which is similar to patients with non-HPS.<sup>57</sup> In Swanson *et al.*, 80% of all HPS patients showed complete resolution after LT,<sup>57</sup> and the mortality rate was 16% in the whole group, 30% in the severe HPS group at 3 months.<sup>57</sup> Some studies showed worse survival in patients who have PaO<sub>2</sub> ≤ 50 mmHg alone or with MAA shunt fraction ≥ 20%.<sup>84,88</sup> However, some other studies showed that there were no significant differences in survival between any HPS and non-HPS patients.<sup>86,89</sup> Iyer *et al.* reported that there was no association between PaO<sub>2</sub> levels at diagnosis and survival rates after transplantation.<sup>85</sup> Post-transplantation early death predictors are pretransplantation PaO<sub>2</sub> ≤ 50 mmHg and a lung scan with brain uptake of 20% or more.<sup>84</sup> Patients with advanced HPS (PaO<sub>2</sub> < 60 mmHg) are eligible for MELD exception points to increase priority for transplantation. In a recent study, US MELD-era data were analyzed, and it was found that the present system of allocating HPS MELD exception points provides a survival advantage to wait listed patients with HPS compared to patients without HPS exception.<sup>90,91</sup> In the same study, patients with a pretransplantation PaO<sub>2</sub> < 44 mmHg had significantly lower post-transplantation survival rates compared with those with a PaO<sub>2</sub> between 44 and 54 mmHg.<sup>90</sup> It may come to mind that living donor LT (LDLT) may be more suitable than deceased donor LT (DDLT) because of the advantages of immediate availability of graft and opportunity to stabilize patient before LT.<sup>86</sup> However, some reports have shown that complication rates are the same between LDLT and DDLT patients.<sup>92-95</sup> To improve survival after LT, patients who are on the waiting list should be screened properly, and adequate oxygen should be given.<sup>89</sup> It should be remembered that HPS patients who are not candidates for LT may be candidates for localized resection or coil embolization of the dilated pulmonary vessels as a palliative treatment.<sup>70</sup> This is especially true for patients with type 2 lesions who would not respond to LT.<sup>96</sup>

## Medical therapy

Since the main disease mechanism involves vasodilation and angiogenesis mediated by NO and CO, treatment studies have targeted this pathway but with disappointing results. Some of the agents used in these studies are methylene blue, N(G)-nitro-L-arginine methyl ester (L-NAME), curcumin, terlipressin, somatostatin analogues, NOS inhibitors, cyclooxygenase inhibitors, antibiotics, chemotherapeutics, glucocorticoids, and beta blockers.<sup>1,36,76</sup>

Pentoxifylline (PTX) is a nonspecific phosphodiesterase inhibitor that also inhibits TNF- $\alpha$ ,<sup>97</sup> monocyte chemoattractant protein-1 (MCP-1), macrophage inhibitory protein-1 (MIP-1), interleukin-6, and interleukin-8 and decreases the expression of adhesion molecules and activation and

proliferation of neutrophils.<sup>98-101</sup> It is used in HPS patients because of its inhibitory effect on iNOS, leading to a subsequent decrease in NO production and downregulation of angiogenesis.<sup>102</sup> A few studies have shown that improving oxygenation prevents development of HPS in both animal models and humans.<sup>51,103</sup> However, in a different study, Tani-kella *et al.* administered a lower dose of PTX (400 mg once daily by mouth for 7 days, followed by 400 mg twice daily for 7 days, and then 400 mg thrice daily for 42 days) because of side effects and did not find any improvement after PTX therapy in cirrhotic patients with HPS. TNF- $\alpha$  levels were not decreased significantly before and after treatment with PTX.<sup>104</sup> To date, there have been no randomized, placebo, controlled trials regarding the use of PTX in patients with HPS.

Garlic (*Allium sativum*) is thought to decrease NO synthesis, and although it has the potential to be a therapy for HPS, it has also been reported to cause an increase in NO synthesis.<sup>105</sup> There are a few studies showing improvement in oxygen levels with garlic therapy.<sup>106,107</sup>

Methylene blue (MB) is an oxidizing agent and has a vasoconstrictor effect by blocking the stimulation of soluble guanylate cyclase by NO.<sup>36,38</sup> Although some have found favorable results,<sup>36,38</sup> no randomized, placebo-controlled trials has been performed on the use of MB in HPS patients.<sup>108</sup>

Norfloxacin is an active quinolone antibiotic against gram negative bacteria. Norfloxacin decreases pulmonary intravascular macrophage accumulation and reduces HPS by decreasing bacterial translocation.<sup>109</sup> It is used for its potential to prevent bacterial translocation in cirrhosis patients.<sup>110</sup> There is a case report that showed improvement in HPS after administration of 400 mg oral norfloxacin two times per day.<sup>111</sup> Gupta *et al.* showed that there was no major effect of norfloxacin on gas exchange in patients with hepatopulmonary syndrome.<sup>112</sup> However, there should be more randomized studies to discuss the effect of norfloxacin in improvement of HPS.

Transjugular intrahepatic portosystemic shunt (TIPS) placement is a medical intervention that has been associated with improvement of HPS in several case reports,<sup>113-114</sup> but there is also a risk that TIPS may worsen HPS by increasing the hyperkinetic state, leading to more pulmonary vasodilatation, shunting, and hypoxemia. The American Association for the Study of Liver Disease guidelines do not recommend TIPS placement for the treatment of HPS.<sup>115</sup>

## Conclusion

HPS is a severe pulmonary vascular complication of liver disease. As it is usually asymptomatic, all patients should be screened for its presence prior to LT since it can affect survival after LT. There is no medical therapy described to date, and LT is considered to be the only effective therapy. Complete resolution of HPS after LT is usually seen within a year in most HPS patients. The correlation between pre-LT PaO<sub>2</sub> levels and the long term post-LT survival of patients with HPS needs to be studied further.

## Conflict of interest

None

## Author contributions

Writing the article (CC, AMC, MG, NND, AG).

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