Prolonged Unexplained Hypoxemia as Initial Presentation of Cirrhosis: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient:	**Male, 43**
Final Diagnosis:	**Hepatopulmonary syndrome**
Symptoms:	**Dyspnea**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Gastroenterology and Hepatology**

Objective:	**Unusual clinical course**
Background:	Hepatopulmonary syndrome (HPS) is a pulmonary complication of advanced liver disease with dyspnea as the predominant presenting symptom. The diagnosis of HPS can often be missed due to its nonspecific presentation and the presence of other comorbidities.
Case Report:	We present an interesting case of an obese 43-year-old man who presented with progressive, unexplained hypoxemia and shortness of breath in the absence of any symptoms or signs of chronic liver disease. After extensive cardiopulmonary investigations, he was diagnosed with severe HPS as a result of non-alcoholic steatohepatitis (NASH) leading to cirrhosis. He subsequently underwent successful hepatic transplantation and continues to improve at 12-month follow-up.
Conclusions:	HPS needs to be considered in the differential diagnosis of unexplained hypoxemia. Given its poor prognosis, early diagnosis is warranted and treatment with liver transplantation is the preferred choice.
MeSH Keywords:	**Anoxia • Hepatopulmonary Syndrome • Liver Transplantation**
Abbreviations:	**AaPO2** – alveolar-arterial oxygen gradient; **CEE** – contrast-enhanced echocardiography; **CT** – computed tomography; **CTPA** – computed tomography pulmonary angiogram; **DLCO** – diffusing capacity for carbon monoxide; **ERS** – European Respiratory Society; **HPS** – hepatopulmonary syndrome; **HRCT** – high-resolution computed tomography; **HVPG** – hepatic venous pressure gradient; **IPS** – intrapulmonary shunt; **IPVD** – intrapulmonary vascular dilatation; **LFT** – liver function tests; **MELD** – Model for End-Stage Liver Disease; **NASH** – non-alcoholic steatohepatitis; **NO** – nitric oxide; **OLT** – orthotopic liver transplant; **PCO2** – partial pressure of carbon dioxide; **PO2** – partial pressure of oxygen; **PFT** – pulmonary function test; **PHD** – pulmonary hepatic vascular disorder; **POPH** – portopulmonary hypertension; **RVSP** – right ventricular systolic pressure; **SPO2** – pulse oximetry oxygen saturation; **VATS** – video-assisted thoracoscopy; **V/Q Scan** – ventilation perfusion scan
Full-text PDF:	http://www.amjcaserep.com/abstract/index/idArt/900530

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Background

Hepatopulmonary syndrome (HPS) is a pulmonary complication of advanced liver disease characterized by intrapulmonary vascular dilatation (IPVD) and arterial hypoxemia. Dyspnea is the predominant presenting respiratory symptom, usually after years of liver disease [1]. There is no clear correlation between severity of HPS and either severity or underlying cause of liver disease [2]. The diagnosis of HPS can often be missed due to nonspecific presentation and presence of other comorbidities. Currently, there is no effective medical therapy for HPS and liver transplantation remains the only option to improve both oxygenation and survival [1,3].

We present the interesting case of a 43-year-old man who presented with progressive, unexplained hypoxemia and shortness of breath in the absence of any symptoms or signs of chronic liver disease. After extensive cardiopulmonary investigations, nodular cirrhosis was incidentally detected on a thoracic computed tomography (CT) scan. He was subsequently diagnosed with severe hepatopulmonary syndrome as a result of non-alcoholic steatohepatitis (NASH)- related cirrhosis and underwent successful orthotopic liver transplantation (OLT) in our unit.

Case Report

After several recordings of oxygen saturation at rest of 85–90% in his GP clinic, a 43-year-old man was referred to the sleep clinic at our institution. Given his anthropometric features, his GP considered sleep-disordered breathing as the probable cause of his hypoxemia. He denied snoring or daytime sleepiness, but he admitted to dyspnea on mild exertion. There was no history of chest pain, cough, weight loss, or excessive bleeding. Of note, his body mass index (BMI) was 37.6 kg/m^2. He had had previous surgery for excision of a pituitary adenoma and was maintained on steroid and thyroid hormone supplementation. He had no history of smoking or alcohol consumption. His cardiovascular and respiratory examinations were unremarkable. At rest, his pulse oximetry oxygen saturation (SPO2) was 89%, remained unchanged with position, and dropped rapidly to 75% after 1 min of normal walking. With supplemental 100% oxygen, SPO2 rose to 100%. On arterial blood gas, pH and partial pressure of carbon dioxide (pCO2) were normal, confirming type 1 respiratory failure with a partial pressure of oxygen (PO2) of 62 mmHg on room air, with age-corrected alveolar-arterial oxygen gradient (AaPO2) of 52 mmHg.

He underwent extensive pulmonary and cardiac investigations. An overnight sleep study revealed no sleep-disordered breathing, but abnormal oximetry with average SPO2 of 88%. Pulmonary function tests (PFT) revealed normal spirometry and lung volumes but a very low diffusing capacity for carbon monoxide (DLCO) of 31%. Results of chest X-ray, computed tomography pulmonary angiogram (CTPA), and high-resolution thoracic computed tomography (HRCT) were normal. A pulmonary ventilation perfusion (VQ) scan showed no evidence of VQ mismatch.

A transthoracic echocardiogram showed normal right and left ventricular function with right ventricular systolic pressure (RVSP) of 20 mmHg. A bubble contrast echocardiography test (CEE) at this stage was attempted but was inconclusive. Cardiac catheterization showed normal coronaries and pulmonary artery pressures and absence of any intracardiac shunt.

In the absence of any detectable pulmonary or cardiac etiology, video-assisted thoracoscopic (VATS) lung biopsy was planned to rule out other primary pulmonary pathology. He tolerated this procedure well and significant macroscopic venous dilatation was noted at surgery. CTPA had been repeated as a part of preoperative investigations (Figure 1), this time revealing mild main pulmonary artery dilatation and normal intrapulmonary vessels with no peripheral dilatation, but there was incidental detection of features suggestive of liver cirrhosis on upper abdominal cuts.

His liver function tests (LFTs) were normal (Table 1). Coagulation profile showed thrombocytopenia with a count of 60 000 per microliter. Four-phase CT liver revealed cirrhosis with portal hypertension and splenomegaly. Hepatic venous pressure gradient measurement showed HVPG of 10 mmHg, further confirming portal hypertension. Upper gastrointestinal endoscopy revealed gastric varices. HPS was suspected at this point and confirmed through a repeat bubble test, which was positive for intrapulmonary shunt (IPS). VATS lung biopsy showed histological features compatible with HPS and pulmonary artery hypertension with extensive vascular remodeling (Figure 2). His oxygenation was gradually deteriorating, with cyanosis and room air PO2 of 53.2 mm Hg. He was listed for orthotopic liver transplantation, with severe hepatopulmonary syndrome and mild portopulmonary hypertension (POPH) from NASH-related cirrhosis as the indication, confirmed on pathological examination of the explanted liver (Figure 3). His model for end-stage liver disease (MELD) score was 7 at the time of listing and he remained on continuous home oxygen therapy at 2 l/min while waiting for transplantation. He was successfully transplanted 1 year after listing. His intraoperative and postoperative periods were uneventful and he was discharged home after 14 days. At 12-month follow-up, our patient remains asymptomatic with normal resting oxygen saturation and requiring 2 l/min of supplemental oxygen for mobilization.
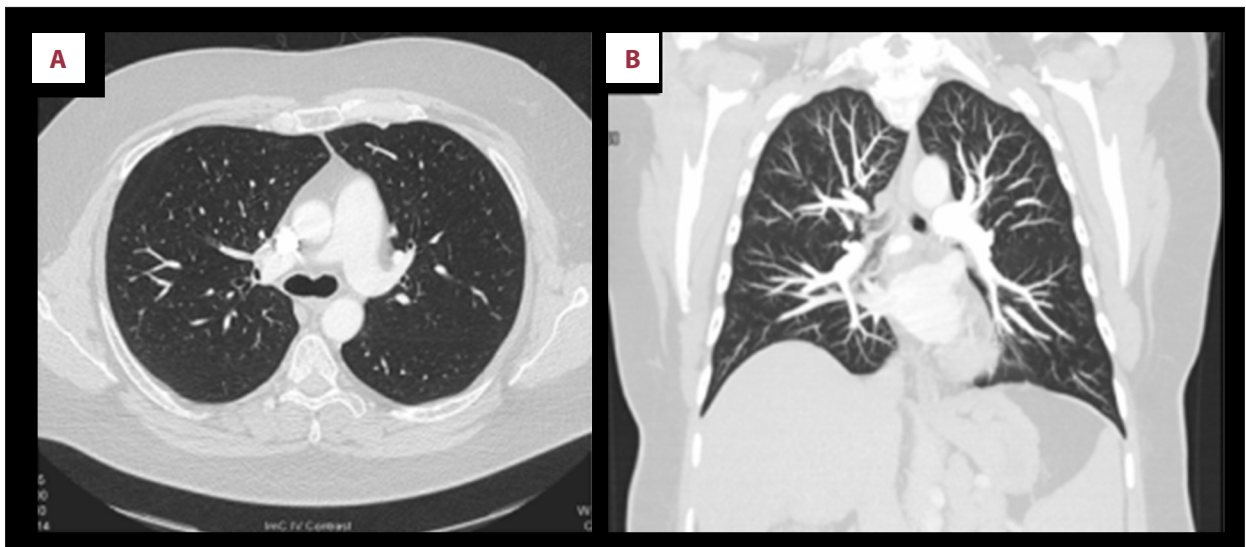
Figure 1. CT Thorax (**A** – Axial, **B** – Coronal) showing mild main pulmonary artery dilatation, normal intrapulmonary vessels with no peripheral dilatation.

Table 1. Liver function tests, creatinine, and platelets.

	Initial presentation	9 months	18 months	24 months*	30 months	36 months**	6 months post-transplant	12 months post-transplant
Bilirubin	1.2	0.87	N/A	1.46	0.87	0.76	0.46	0.58
PT	13.6	N/A	12.5	13.5	13.2	13.1	12	12.7
Creatinine	0.99	0.86	0.87	0.82	0.89	0.89	1.49	1.23
Platelets	111	78	69	60	76	75	144	156

* At the time of diagnosis of HPS; ** prior to hepatic transplant. PT – prothrombin time in seconds (range 10–14 s); Bilirubin – total bilirubin in mg/dl; Creatinine in mg/dl; Platelets ×10^9/L; N/A – not available.

Discussion

HPS is a life-threatening condition characterized by the triad of hepatic disease, arterial deoxygenation, and IPVD. In patients with cirrhosis undergoing evaluation for LT, the prevalence of HPS is estimated at 5–30% [1,4]. There are no reported multicenter prevalence studies, and the wide range in prevalence is partly a result of the range of definitions used for deoxygenation [1,3]. Though most commonly seen in patients with portal hypertension and cirrhosis, HPS has been reported in association with acute and chronic hepatitis without portal hypertension or cirrhosis and in patients with noncirrhotic portal hypertension [3,5,6].

The arterial oxygen tension (PO2) can be deceptively normal in the early stages of HPS. Hyperventilation and associated decreased arterial carbon dioxide often occurs in the setting of cirrhosis, and alveolo-arterial oxygen gradient (AaPO2) is a more sensitive indicator of deoxygenation in this setting [1,3,7].

The recommended diagnostic cut-off for deoxygenation is AaPO2 ≥15 mmHg on room air or AaPO2 ≥20 mmHg for patients older than 64 years [8]. Using PO2, HPS can be classified as mild (PO2 ≥80 mmHg), moderate (PO2 ≥60 mmHg to <80 mmHg), severe (PO2 ≥50 mmHg to <60 mmHg), or very severe (PO2 <50 mmHg or <300 mmHg on 100% oxygen) [8]. Defective oxygenation results from ventilation perfusion mismatch caused by microvascular dilatation within pulmonary arterial circulation. With disease progression, increased intrapulmonary shunt and/or impaired diffusion may contribute further to the severity of hypoxemia [1,9].

Dyspnea on a background of chronic liver disease is a common presentation of HPS. Platypnea (increased shortness of breath while sitting up from prone position), orthodeoxia (decrease in arterial saturation by more than 5% or 4 mmHg in erect position), spider nevi, and clubbing are more common in patients with HPS but are not specific to the condition [3,10,11]. Apart from progressive dyspnea, none of these features were
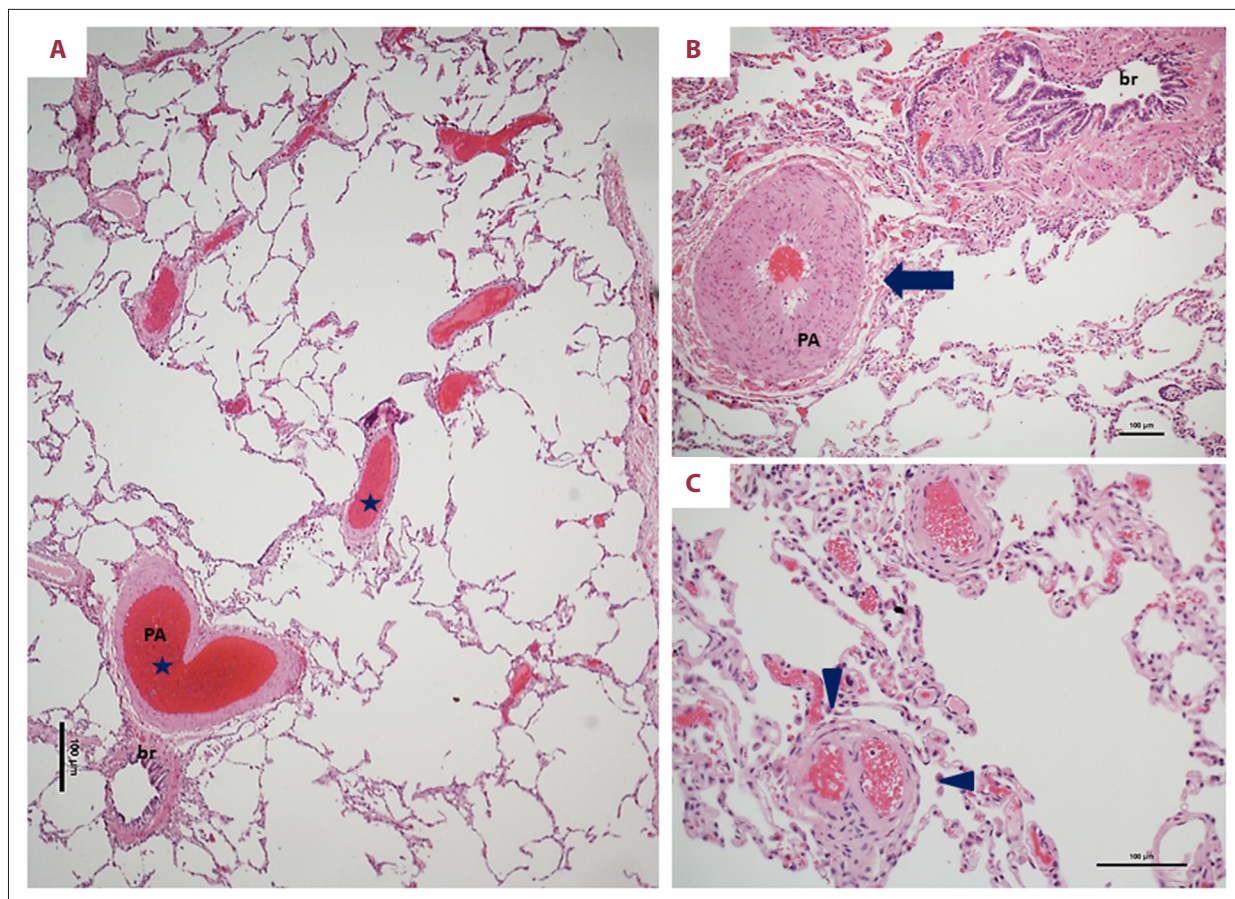
Figure 2. Pathological changes in the lung from VATS biopsy. The branches of the pulmonary arteries are dilated (stars, **A**), or show medial hypertrophy (arrow, **B**). Plexiform lesions are also present (arrow heads, **C**) (PA – pulmonary artery; br – bronchiole) (hematoxylin and eosin stain, magnification ×40 (**A**), ×100 (**B**), ×200 (**C**), scale bar 100 μm).

present on initial presentation in our patient, which contributed to the delay in diagnosis. In a retrospective study of 22 patients, Krowka et al. [12] reported the mean duration of respiratory symptoms (primarily dyspnea) before the diagnosis of HPS as 4.8 years (range 1–10 years).

Severity of HPS has no consistent correlation with the severity of hepatic dysfunction [2, 13], as demonstrated in our patient, who had a PO2 <60 mmHG (indicating severe HPS) but normal synthetic liver function tests. Very low carbon monoxide diffusion was the only abnormal respiratory result observed in our patient that was consistent with previous reports [10].

Pulse oximetry saturation of ≤97% is a simple screening test for HPS, with sensitivity of 100% and specificity of 65% [3,14]. To make a diagnosis, however, ABG determination of oxygenation is necessary [4]. A positive bubble test result with contrast-enhanced echocardiography (CEE) is a recommended diagnostic criterion [4,8]. CEE using agitated saline is simple and inexpensive and is the most sensitive test for detecting intrapulmonary shunt [3,15]. Saline is agitated to produce bubbles

>10 microns in size, injected through a peripheral vein, and the right atrium and right ventricle are observed for presence of bubbles. Normally, with pulmonary vascular diameters of <10 microns, bubbles are absorbed within the pulmonary circulation. Appearance of bubbles in left heart chambers within 3 cardiac cycles indicates intracardiac shunt. Delayed appearance of bubbles in left heart chambers (3–6 cardiac cycles after appearance in right heart chambers) suggests intrapulmonary shunt.

HPS may coexist with other cardiopulmonary comorbidities, which may contribute to impaired gas exchange, such as chronic obstructive pulmonary disease, restrictive lung disease, and hepatic hydrothorax. In addition to a careful history-taking and physical examination, a lung perfusion scan with technetium-labeled macroaggregates of albumin (99 mTcMAA) may help to distinguish the degree of hypoxemia caused by IPVD (abnormal brain uptake >6%) in the setting of coexistent intrinsic cardiopulmonary disease [4]. The MAA lung-brain perfusion scan does, however, have limitations, being less sensitive than CEE and unable to distinguish intracardiac from intrapulmonary shunting [3,4].
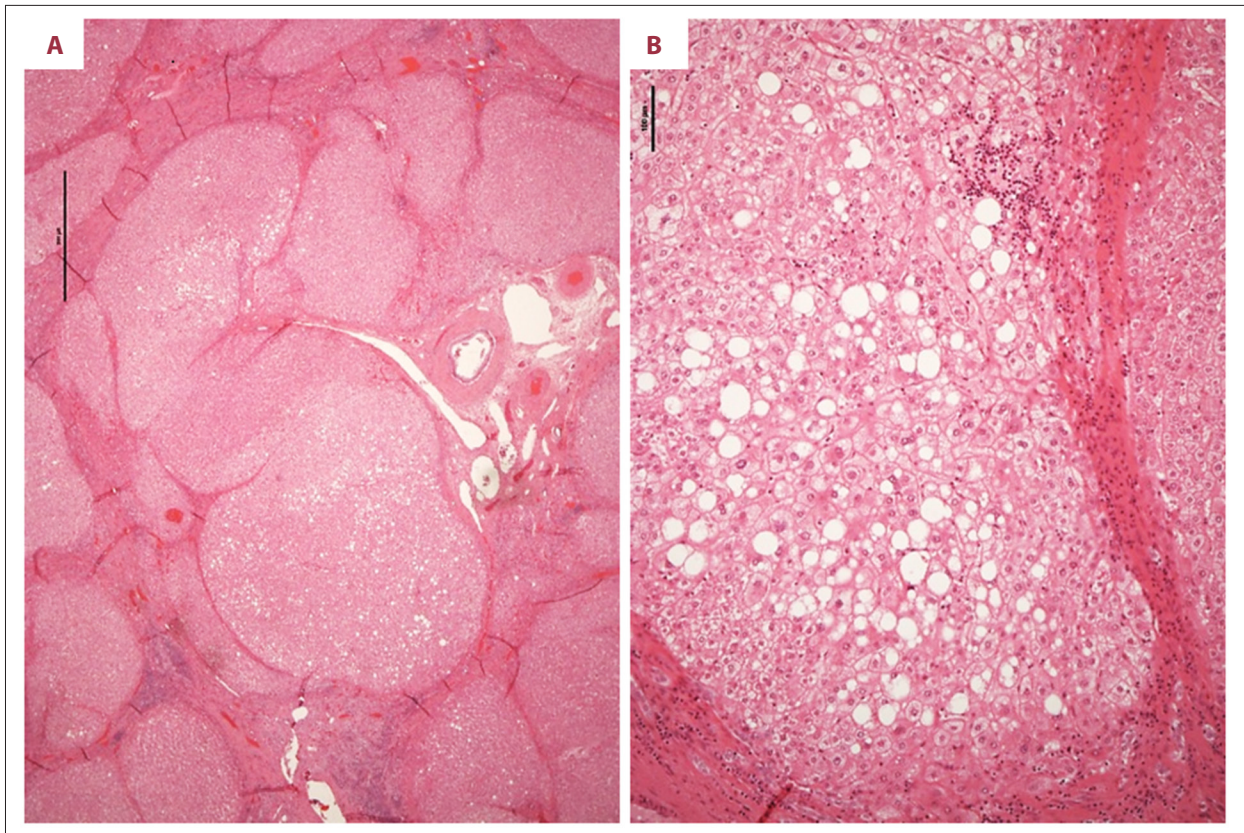
Figure 3. Histology of the explanted liver show cirrhosis (**A**) and steatosis (**B**) (hematoxylin and eosin stain, magnification ×20 (**A**), ×100 (**B**), scale bar 1000 μm (**A**) and 100 μm (**B**)).

Portopulmonary hypertension (POPH) is another condition that may coexist in patients with HPS. In a retrospective review of 80 patients, Fussner et al. [16] reported that IPVD was present in 59% of patients with POPH and was associated with decreased survival. POPH results from obstructed pulmonary arterial flow in the setting of portal hypertension and requires right heart catheterization (RHC) measurement for diagnosis. Diagnostic criteria include: mean pulmonary artery pressure (mPAP) >25 mm Hg, pulmonary vascular resistance (PVR) >3 Wood units (240 dynes/s per cm^{-5}), and normal pulmonary artery wedge pressure (PAWP) [4]. Dyspnea is commonly present in POPH but is not specific [17]. AaPO2 may be elevated, but hypoxemia is usually mild, even in the setting of moderate-to-severe POPH [17,18]. In contrast to HPS, targeted medical therapy for pulmonary hypertension in POPH may be beneficial in improving functional capacity [4,17].

Currently, there is no established medical therapy for HPS [4]. Supplemental oxygen to maintain oxygen saturation >88% is frequently recommended, but there are no data to confirm clinical benefits [3,4,17]. Pharmacotherapies directed at possible humoral mediators of IPVD have shown inconsistent benefits [3,4]. Nitric oxide (NO) inhibition with methylene blue, garlic supplementation, nebulized L-NAME, and norfloxacin have

shown conflicting results [19–22]. Pentoxifylline improved experimental HPS in rats by inhibiting tumor necrosis factor alpha (TNF-alpha), but not in human studies [23,24]. Portal decompression with transjugular intrahepatic portosystemic shunt (TIPS) has been suggested, but the benefit is uncertain and it may in fact increase the severity of HPS by exacerbating the hyperkinetic circulatory state [3,4].

OLT remains the only effective therapy in improving oxygenation and survival. Our patient remained on continuous oxygen therapy until OLT. There was no further hepatic decompensation. His PO2 on room air decreased from 62 mmHg at initial presentation to 53.2 mmHg at diagnosis of HPS 2 years later, but did not decrease further in the year waiting for transplantation. Swanson et al. [25] observed a decline in mean PO2 of 5.2 mmHg per year in patients with HPS awaiting OLT. HPS patients who did not undergo transplantation had worse 5-year survival compared with the matched control group who underwent transplantation (23% vs. 63%, respectively). A baseline PO2 of 50 mmHg or less is associated with worse survival.

Following OLT, complete resolution of hypoxemia is observed but is slow, often taking up to 12 months and sometimes longer [3,26,27]. Considering the poor prognosis without OLT [25]

and favorable post-OLT outcome even for patients with severe hypoxemia [26,27], allocation of exception points in MELD score is recommended [4,28].

Conclusions

Hepatopulmonary syndrome (HPS) is an important vascular complication of hepatic disease and significantly affects survival. HPS may occur without overt clinical manifestations of liver disease and needs to be considered in the differential diagnosis of unexplained hypoxemia. Due to the limited understanding of its pathophysiology, no effective pharmacotherapy is currently available to treat HPS. Improvement in oxygenation is seen in most patients after hepatic transplantation, even in patients with severe pre-transplant oxygenation defects.

Conflict of interest

None declared.

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