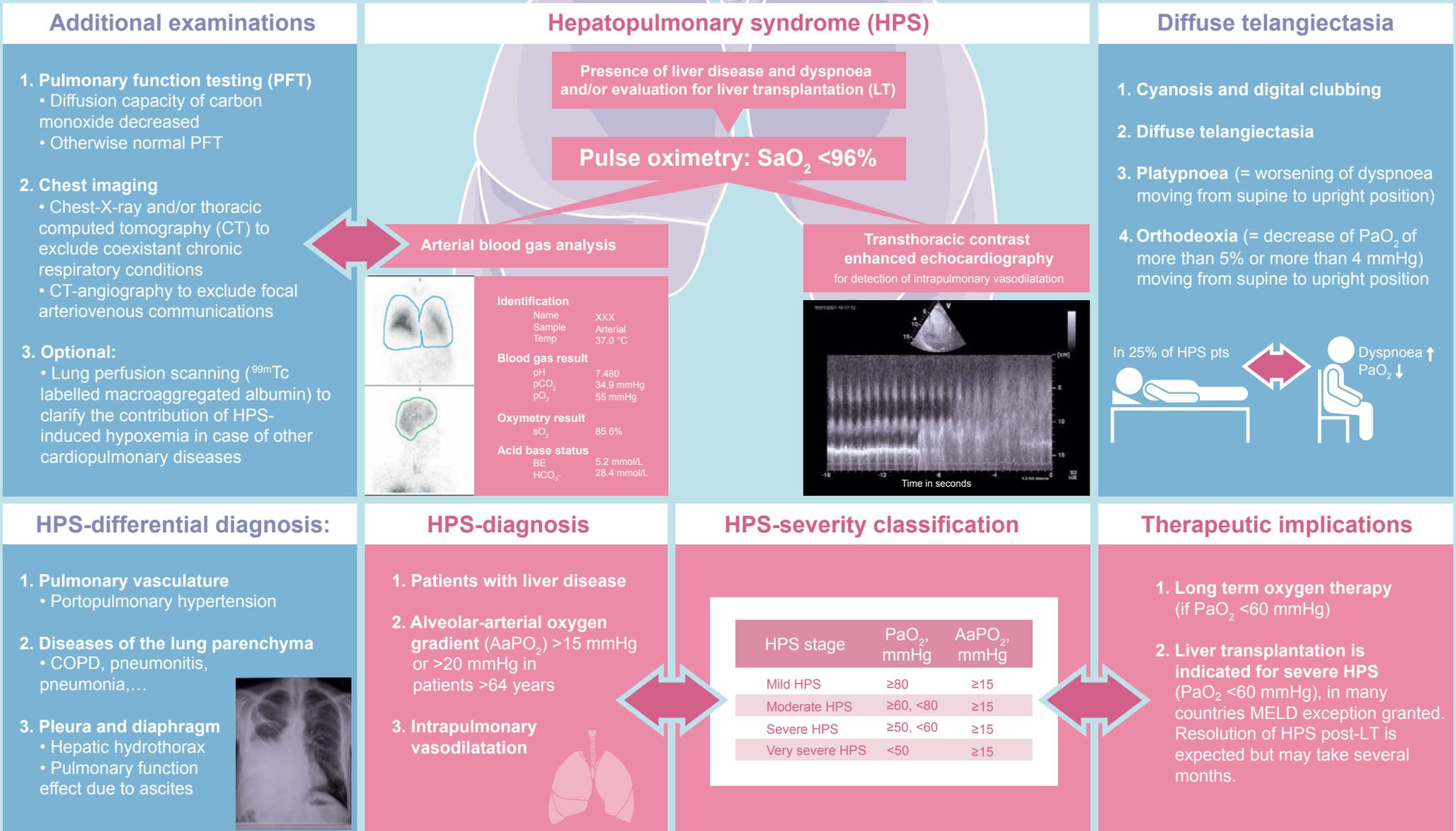


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Hepatopulmonary syndrome (HPS) is the most common cause of respiratory insufficiency in patients with chronic liver disease. It is characterised by a gas exchange abnormality caused by intrapulmonary vascular dilatations (IPVD) in patients with liver diseases. It occurs in 5–32% of liver transplant candidates.<sup>1</sup> Abnormal oxygenation is defined by elevated alveolar-arterial oxygen gradient (>15 mmHg or >20 mmHg in patients >64 years, respectively) while breathing room air in the sitting position at rest. IPVD is usually diagnosed by contrast-enhanced transthoracic echocardiography. The severity of HPS is classified according to the degree of hypoxemia.<sup>2</sup>

Every patient with advanced liver disease that is undergoing evaluation for liver transplantation or suffers from dyspnoea should be screened for the presence of HPS. An established screening tool is pulse oximetry as it can identify all patients with PaO<sub>2</sub> <70 mmHg using an oxygen saturation cut-off <96%.<sup>1,3</sup> Genetic testing or other screening tools are not yet established for routine clinical purposes.<sup>1,3,4</sup> In case of positive screening results, arterial blood gas analysis is warranted for diagnosis of HPS.

Clinical characteristics of patients with HPS are mainly consequences of hypoxemia, the leading symptom, like cyanosis and digital clubbing.<sup>5</sup> Furthermore, platypnoea and orthodeoxia are observed in up to 25% of the patients with HPS.<sup>6</sup> However, clinicians should be aware that chronic pulmonary comorbidities can coexist in HPS. In particular, chronic obstructive pulmonary disease, bronchial asthma, idiopathic pulmonary fibrosis and restriction of the lung following extrapulmonary complications like ascites or hepatic hydrothorax can contribute to and aggravate dyspnoea.<sup>7</sup>

Both spirometry and static lung volumes are usually within the normal range in HPS. However, diffusion capacity of carbon dioxide is frequently decreased in pulmonary function testing in HPS.<sup>2</sup>

The primary tool for detection of IPVD is transthoracic contrast-enhanced echocardiography. Agitated saline is commonly used as a contrast agent as it creates microbubbles of >10 µm diameter that are usually not able to pass the normal pulmonary vascular bed. However, in case of IPVD and HPS, microbubbles appear in the left chambers of the heart three or more cardiac cycles following visualization in the right heart. Lung perfusion scanning can detect and quantify IPVD. Lung perfusion scanning determines the extrapulmonary tracer accumulation, but is not able to distinguish between intracardiac and intrapulmonary shunting. It is mainly used to distinguish the degree of hypoxemia caused by intrapulmonary vasodilatation vs. other potential contributing factors like non-vascular pulmonary or extrapulmonary factors. Lung imaging techniques like chest X-ray or thoracic computed tomography are useful for excluding other coexistent chronic respiratory conditions.<sup>1,2</sup>

Patients with HPS have more than twofold increased mortality.<sup>8,5</sup> Therapeutic options in HPS include initiation of long term oxygen therapy in patients with severe HPS (PaO<sub>2</sub> <60 mmHg). Liver transplantation is the only therapeutic approach that is able to cause resolution of HPS. Patients with severe HPS have MELD exception granted in many countries around the world.<sup>1</sup> Post-liver-transplant survival rates in expert centres are excellent, even in cases of severe HPS.<sup>9</sup>

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### Conflict of interest

Dr. Fuhrmann reports grants from Actelion outside the submitted work. Dr Krowka has nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jhep.2018.01.002>.

### References

- [1] Krowka MJ, Fallon MB, Kawut S, Fuhrmann V, Heimbach JK, Ramsay M, et al. International Liver Transplant Society Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation* 2016;100:1440–1452.
- [2] Rodriguez-Roisin R, Krowka M, Herve Ph, Fallon MB. Pulmonary-Hepatic vascular disorders (PHD). *Eur Respir J* 2004;24:861–880.
- [3] Arguedas M, Singh H, Faulk D, Fallon M. Utility of pulse oximetry screening for hepatopulmonary syndrome. *Clin Gastroenterol Hepatol* 2007;5:749–754.
- [4] Horvatits T, Drolz A, Roedl K, Herkner H, Ferlitsch A, Perkmann T, et al. Von Willebrand factor antigen for detection of hepatopulmonary syndrome in patients with cirrhosis. *J Hepatol* 2014;61:544–549.
- [5] Fallon MB, Krowka MJ, Brown RS, Trotter JF, Zacks S, Roberts K, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology* 2008;135:1168–1175.
- [6] Gomez FP, Martinez-Palli G, Barbera JA, Roca J, Navasa M, Rodriguez-Roisin R. Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. *Hepatology* 2004;40:660–666.
- [7] Rodriguez-Roisin R, Krowka M. Hepatopulmonary syndrome—a liver-induced lung vascular disorder. *N Engl J Med* 2008;358:2378–2387.
- [8] Schenk P, Schöniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Müller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042–1052.
- [9] Iyer VN, Swanson KL, Carin-Ceba R, Dierkhsing RA, Rosen CB, Heimbach J, et al. Hepatopulmonary syndrome: favorable outcomes in the MELD exception era. *Hepatology* 2013;57:2427–2435.