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Lung and Heart Disease Secondary to Liver Disease

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Abstract

Patients with chronic liver disease are at risk of extra-hepatic complications related to cirrhosis and portal hypertension, as well organ-specific complications of certain liver diseases. These complications can compromise quality-of-life, while also increasing morbidity and mortality pre- and post-liver transplantation. Patients with chronic liver disease are at risk for pulmonary complications of hepaotpulmonary syndrome and portopulmonary syndrome; the major cardiac complication falls under the general concept of the cirrhotic cardiomyopathy, which can affect systolic and diastolic function, as well as cardiac conduction. In addition, patients with certain diseases are at risk of lung and/or cardiac complications that are specific to the primary disease (i.e., emphysema in alpha-1-antitrypsin deficiency) or occur with increased incidence in certain conditions (i.e., ischemic heart disease associated with non-alcoholic steatohepatitis. This section will focus on the epidemiology, clinical presentation, pathogenesis, treatment options, and role of transplantation for lung and heart diseases secondary to liver disease, while also highlighting select liver diseases that directly affect the lungs and hearts.

INTRODUCTION

Patients with chronic liver disease are at risk of extra-hepatic complications related to cirrhosis and portal hypertension, as well organ-specific complications of certain liver diseases. These complications can compromise quality-of-life, while also increasing

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morbidity and mortality pre- and post-liver transplantation. This section will focus on lung and heart disease secondary to liver disease, focusing on the pulmonary and cardiac complications related to cirrhosis and portal hypertension, while highlighting select liver diseases that directly affect the lungs and hearts.

PULMONARY MANIFESTATIONS OF LIVER DISEASE

Hepatopulmonary Syndrome

Epidemiology—Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilatations (IPVDs) leading to altered gas exchange and right-to-left shunting of blood within the pulmonary vasculature. Although HPS more commonly occurs in patients with cirrhosis and portal hypertension, it can occur with any degree of hepatic dysfunction.[1–5] True HPS is estimated to occur in at least 10% of all patients with cirrhosis and portal hypertension; the disease is more prevalent in those with more advanced liver disease, occurring in approximately one-third of patients evaluated for liver transplantation.[4,6–8]

Pathogenesis—Animal models of advanced liver disease have been used to identify the potential mechanisms underlying the formation of IPVDs, which develop in response to endothelial injury within the pulmonary vasculature. The inciting factors for endothelial injury include: 1) increased bile acids; 2) bacterial translocation and release of endotoxin; and 3) increased cytokines such as tumor necrosis factor α and endothelin-1. The damaged endothelium then releases mediators that direct the pathogenesis of HPS: a) vasodilation due to carbon monoxide and nitric oxide; and b) angiogenesis resulting from activation of p-AKT and p-ERK.[9,10] The intrapulmonary shunting results from pre- and post-capillary dilatation of the pulmonary microvasculature, which is exacerbated by the formation of new blood vessels within the pulmonary microvasculature.[11,12]

Diagnostic criteria and evaluation for HPS—Hypoxemia is required for the diagnosis of HPS, as isolated IPVDs can be seen in up to 60% of patients with cirrhosis.[6] Hypoxemia is caused by the intrapulmonary shunting of blood through the IPVDs, with increasing hypoxemia occurring with more pronounced vasodilation, in addition to a greater size and number of vascular dilatations.

The diagnostic criteria for HPS include clinical and laboratory testing, in the setting of chronic liver disease (with exceptions) and an absence of cardiopulmonary disease (i.e., chronic obstructive pulmonary disease) that could lead to hypoxemia.[7,13] Pulse oximetry is insufficient to diagnose HPS, although it can be a useful screening tool. An oxygen saturation on pulse oximetry (SpO_2) of ≤97% has a 96% sensitivity and positive likelihood ratio of 3.9 for detecting arterial hypoxemia at or near sea level, with a cutoff value ≤94% identifying all subjects with a partial-pressure of oxygen (PaO_2) < 60 mm Hg.[14] Arterial blood gas (ABG) sampling is required for the diagnosis of HPS to calculate the Alveolar-arterial (A-a) gradient. Patients with cirrhosis commonly have central hyperventilation, which leads to exhalation of increased CO_2, and a corresponding increase in PaO_2; this can lead to a normal SpO_2, in the setting of marked intrapulmonary shunting. The HPS A-a

gradient criteria are ≥15 mm Hg in patients <65 years of age, and ≥20 mm Hg for patients ≥65 years of age due to increased baseline shunting with aging.

A transthoracic echocardiogram (TTE) with agitated saline ('bubble echo') is the standard imaging test to identify IPVDs. In the absence of IPVDs (and intra-atrial shunting), the microbubbles created by agitating saline get trapped within the pulmonary microvasculature capillaries. By contrast, in patients with HPS and IPVDs, these bubbles are visualized in the left atrium on a four-chamber TTE as they are shunted through the IPVDs.[15] The timing of visualization of the microbubbles is important, as intra-atrial shunts can lead to right-to-left shunting of these microbubbles within the first three cardiac cycles after injection of the agitated saline.[15] In HPS however, there is a delay in the shunting of the microbubbles as they first must pass through the right ventricle; thus they are not seen until four to six cardiac cycles after injection of agitated saline. For patients whose body habitus precludes high-quality four-chamber views needed to visualize IPVDs, an alternative imaging techniques is trans-esophageal echocardiography. Although a radiolabeled macroaggregated albumin (MAA) scan was historically used as an alternative to echocardiographic testing, its major limitation is its inability to distinguish between intracardiac versus intrapulmonary shunting.[16]

There are no specific guidelines dictating the testing needed to exclude other cardiopulmonary conditions such as intrinsic lung disease (i.e. chronic obstructive pulmonary disease). It is recommended that minimal testing include pulmonary function tests (PFT), especially in patients with a history of cigarette smoking. Other testing should be dictated by a patient's symptoms and/or risk factors for cardiopulmonary diseases, and can include high-resolution CT scanning, exercise stress testing, and PFTs after thoracentesis in patients with a substantial hepatic hydrothorax.[6]

Clinical manifestations—Patients with HPS may be asymptomatic, but commonly have some degree of dyspnea, impairments in quality of life (QOL) and lower functional capacity as measured by the New York Heart Association (NYHA) functional class.[6] The symptoms of dyspnea may be more pronounced in the upright position (platypnea) because the intrapulmonary vascular dilations are more prominent in the lung bases, leading to preferential shunting of blood to the bases in the upright position. This shunting causes pronounced V/Q mismatch and subsequent hypoxemia.[12] This change in gas exchange in the upright position manifests with a decrease in the SpO_2 (orthodeoxia), the objective correlate of platypnea.

Notable physical exam findings include distal cyanosis, clubbing, and/or spider angiomata. Spider angiomata, defined as dilated blood vessels on the surface of the skin, can be seen in patients with cirrhosis of any etiology, but are more in patients with HPS.[6] All of these findings however are of low sensitivity in patients with HPS.[6]

Prognosis—Cirrhotic patients with HPS have a significantly increased mortality in comparison to cirrhotic patients without HPS. In a multi-center cohort of cirrhotic patients being evaluated for liver transplantation at seven US liver transplant centers, patients with HPS had a 2–2.4 times increased risk of mortality compared to all other patients being

evaluated for transplantation.[6] These findings have been replicated in an Austrian cohort of cirrhotic patients evaluated for liver transplantation, with a median survival of 10.6 months from evaluation for liver transplantation for patients with HPS, compared with 40.6 months in those without HPS.[8]

Treatment—There are no Federal Drug Administration (FDA) approved medical treatments for HPS, and the only proven treatment is liver transplantation. Although animal studies and small case series initially suggested potential benefits of pentoxifylline[17,18] and garlic,[19,20] neither has provided durable improvement in PFTs in human clinical trials. Management of symptoms has been the mainstay of therapy, including supplemental oxygen as needed, and vaccination for pneumococcus and influenza.[15] There have been several reports of placement of a transjugular intrahepatic portosystemic shunt (TIPS) as a treatment for HPS, but these data are limited.[21–23] Based on animal data, sorafenib, a multi-kinase inhibitor that is FDA-approved for the treatment of hepatocellular carcinoma, is a potential treatment for HPS. This is being explored in an ongoing National Institutes of Health sponsored multi-center phase II clinical trial of sorafenib for hepatopulmonary syndrome (ClinicalTrials.gov identifier NCT02021929).

Transplantation for HPS—Liver transplantation is the only curative option for HPS. There is well-documented normalization of pulmonary function and resolution of hypoxemia within a short time period after transplantation.[5,6,24–26] Because of the significantly increased risk of mortality among patients with HPS,[6,8] in the US, patients with HPS meeting specific criteria are eligible to receive Model for End-Stage Liver Disease (MELD) exception points to increase their prioritization on the waitlist. This policy has allowed for expedited transplantation of these patients, without compromising overall long-term post-transplant outcomes. In fact, the long-term post-transplant survival of transplant recipients with HPS is excellent, and is as good, if not better than many patients with other indications for liver transplantation.[27,28] The challenge is identifying those patients in need of a liver transplantation for HPS, and among those, whether there is a subset that can be considered too ‘high-risk.’ Early data on transplantation for HPS suggested that the risk of post-transplant mortality was higher in those patients with a $PaO_2 < 50$ mm Hg on room-air.[8,24] More recent data has challenged this, and demonstrated very good post-transplant survival in patients with HPS, irrespective of the pre-transplant impairment in gas-exchange, with complete resolution of pre-transplant lung abnormalities within one-year of transplantation.[25,26] These data stand in contrast to analyses of ten years of national transplant in the US that included >700 transplant recipients with HPS. In this analysis, the largest published in the literature, there was a significant association between pre-transplant gas-exchange abnormalities, and post-transplant survival, with patients with a $PaO_2 \leq 44.0$ mm Hg at the time of waitlisting having three-year post-transplant survival of 68%, compared with 84% and 86% in transplant recipients with PaO_2 levels of 44.1–54.0 and 54.1–61.0 mm Hg, respectively.[28] While further data are needed to reconcile the findings from these different cohorts, it remains clear that transplantation for HPS can be curative and lifesaving for many patients.

Portopulmonary Hypertension

Epidemiology—The epidemiology, evaluation, and clinical parameters of portopulmonary hypertension (POPH) and HPS differ substantially (Table 2). Pulmonary hypertension is a disorder characterized by elevated pressures within the pulmonary arteries or veins. Pulmonary arterial hypertension (PAH) represents a subset of pulmonary hypertension that is essentially limited to the arterial component of the pulmonary vasculature. PAH that occurs in the setting of portal hypertension without other identifiable causes is deemed POPH.[29] It is estimated that approximately 5% of all patients with cirrhosis and portal hypertension have POPH, with an even higher prevalence among patients evaluated for liver transplantation.[30]

Diagnostic criteria and evaluation for POPH—The diagnostic criteria for POPH are the presence of portal hypertension (almost always in the setting of cirrhosis), exclusion of other etiologies of PAH, and corresponding hemodynamic criteria that define all forms of PAH. Although a TTE can be used to screen for POPH, the diagnosis rests on hemodynamic parameters that can only be obtained via a right-heart catheterization. The TTE can serve as a screening tool to identify which patients should undergo a right-heart catheterization, with the estimated systolic pulmonary artery pressure (sPAP) serving as a marker of true PAH. Traditionally, transplant centers use cutoffs ranging from 30–40 mm Hg on TTE to triage patients for a right-heart catheterization. However, recent data on 152 patients undergoing pre-transplant echocardiography showed that a cutoff value of 30 mm Hg is associated with a specificity of 54%, resulting in unnecessary right-heart catheterizations, while a cutoff of 38 mm Hg yields a specificity of 82% and a sensitivity of 100%.[31]

The hemodynamic parameters for PAH (and POPH) include: 1) mean pulmonary artery pressure (mPAP) > 25 mm Hg; 2) pulmonary vascular resistance (PVR) >3 Wood units (or 240 dynes·s/cm^5); and 3) normal left sided filling pressure (pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) ≤15 mm Hg.[29] However, because patients with cirrhosis may have marked volume overload, POPH can still be diagnosed in the setting of an elevated PCWP (>15 mm Hg) if the difference between the mPAP and the PCWP is ≥12 mm Hg (deemed the trans-pulmonary gradient, TPG).[29,30,32] These parameters can only be measured by right heart catheterization, and are needed to differentiate POPH from volume overload and left-sided heart failure, both commonly seen in patients with cirrhosis (Table 3). In addition to hemodynamics consistent with PAH, POPH cannot be diagnosed without ruling out other potential etiologies of pulmonary hypertension, including chronic obstructive pulmonary disease,[33] sleep-disordered breathing, and left ventricular systolic or diastolic dysfunction.

Clinical manifestations—Patients with POPH may range from being asymptomatic, to having signs and symptoms of right heart failure which include dyspnea on exertion, lower extremity edema, and difficult to control ascites. Because POPH may be asymptomatic in the early stages of disease, TTE should be used to screen for elevated pulmonary arterial pressures, especially in those with cirrhosis being evaluated, or currently waitlist for liver transplantation.

Prognosis and Treatment—POPH is associated with significant morbidity and mortality. Among cirrhotic patients diagnosed with POPH, the estimated 1-year survival without treatment is 60%.[29,30,34] The medical treatments that can be used for patients with POPH are similar to those offered to patients with PAH, and include: endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin analogues. However, there are limited data evaluating the long-term survival of patients with POPH managed with medical therapy alone, as POPH occurs in the setting of cirrhosis and portal hypertension, which influences long-term patient survival. As a result, liver transplantation is seen as a potential option for patients with POPH, although it does come with risks of increase peri- and post-operative mortality. Among those patients evaluated for liver transplantation, the optimal medical therapy remains unknown. Most commonly, these patients are treated aggressively with intravenous prostacyclin therapy. Yet case series of patients suggests that oral therapy alone, even in those with severe POPH pre-transplantation, may serve as a sufficient bridge to liver transplantation.[35]

Transplantation for POPH—The first large series of transplant recipients was published in 2002, and aggregated center-level data, in combination with published case reports and case series. Among 43 transplant recipients with POPH, 15 (35%) died after transplantation, with 14 of the deaths related to cardiopulmonary dysfunction.[36] The post-transplant deaths occurred exclusively in patients with a mPAP ≥35 mm Hg,[36] which led to widespread adoption of this cutoff for determining transplant eligibility. However, due to concerns about the inclusion criteria for patients included in this cohort, notably the large proportion diagnosed with POPH in the operating room at the time of transplantation, individual transplant centers adopted individualized policies for transplantation.[36] Between 2006 and 2012, three U.S. centers published small case series of successful transplantation in patients with POPH, however there were small sample sizes at each of these centers with short-term follow-up.[37–39] One of these case series has recently been updated, and with long-term follow-up (median 7.8 years), has shown 85.7% patient and graft survival of their seven transplant recipients with POPH. These results are tempered by the fact though that 4/6 of the surviving patients still require oral vasodilator therapy for persistent PAH.[40]

In contrast to these small case series, a recent analysis of UNOS data from 2006–2013 identified 100 transplant recipients with POPH MELD exception points who had hemodynamic criteria consistent with POPH. The unadjusted three-year post-transplant patient survival in this cohort was 64.3%, which is dramatically lower than the overall transplant population, with 9/12 deaths occurring within the first 35 days of transplantation, independent of pre-transplant mPAP.[41] While these data require further validation, they do suggest that even with pre-transplant medical treatment of POPH, transplant outcomes may not be acceptable in these patients. However, despite these discouraging data, there have been several case reports and case series demonstrating successful living donor liver transplants for POPH.[42–44] Most of these patients had normalization of their pulmonary arterial pressures following transplantation, despite requiring intravenous therapy pre-transplantation. Despite these successes though, transplant physicians must still exercise caution in evaluating patients with POPH for transplantation given the increased risk of post-transplant morbidity and mortality. Future multicenter collaborative studies are needed

to better define selection criteria for transplantation that integrate both pulmonary hemodynamics as well as residual cardiac function.

Alpha-1-antitrypsin and lung disease

Alpha-1-antitrypsin (AAT) deficiency involving the liver can manifest as abnormal liver enzymes, and in a subset of patients, advanced fibrosis and cirrhosis, while in others it can lead to features of chronic obstructive pulmonary disease (COPD).[45] Deficiency in alpha-1-antitrypsin leads to alveolar septal destruction and airspace enlargement, which on gross pathology reveals basilar panacinar emphysema.[45] Not all patients with AAT deficiency will develop emphysema, however. The risk of developing pulmonary complications is partly dependent on the molecular genotype of an individual patient, and may exist in the absence of overt liver disease. The presence of secondary factors risk factors for COPD also augments the risk of developing emphysema in patients with AAT deficiency, most notably a history of cigarette smoking.[45] Unlike hepatic complications of AAT deficiency, which are related solely to the deposition of the abnormal AAT protein, pulmonary disease derives from lack of the enzymatic action of AAT. As a result, pulmonary AAT deficiency can be managed with intravenous augmentation therapy that contains high concentrations of AAT.[46]

Liver transplantation is curative for hepatic complications of AAT deficiency. Recent data suggest that liver transplantation can also help the pulmonary complications of AAT deficiency. An initial analysis of seven liver transplant recipients with pre- and post-transplant pulmonary function tests available showed essentially no change in lung function following liver transplantation, despite an expected decrease over time without liver transplantation.[47] A more recently analysis of 17 liver transplant recipients with AAT demonstrated that despite a statistically significant decrease in the FEV_1/FVC ratio pre- versus post-liver transplantation, this value was numerically similar, while all other PFT parameters were not significantly different following liver transplantation.[48] More importantly, post-transplant survival in these patients was excellent. Together, these recent data highlight liver transplantation likely slows the progression of lung disease in these patients.

CARDIAC MANIFESTATIONS OF LIVER DISEASE

Vascular response to cirrhosis and portal hypertension

Cardiac manifestations of liver disease involve aspects of both the cardiac and vascular systems. Portal hypertension leads to a state of marked peripheral arterial vasodilation as a result of release of vasodilatory mediators such as nitric oxide[49], carbon monoxide[50], and prostacyclin.[51] This peripheral arterial vasodilation leads to a lowering of the systemic vascular resistance (SVR), activation of the renin-angiotensin-aldosterone system, and consequently sodium retention and volume overload.

Left ventricular systolic function

Peripheral arterial vasodilation leads to a progressive decrease in the SVR, thus reducing the cardiac afterload. In response, the cardiac output must increase in order to maintain an

adequate blood pressure to sustain end-organ tissue perfusion (blood pressure=cardiac output * SVR). This increase in cardiac output manifests as a hyperdynamic left ventricle, with estimated ejection fractions that are above 'normal' relative to patients without cirrhosis, and an increased cardiac index on right heart catheterization. This state may persist indefinitely until death or liver transplantation, but in a subset of patients, progresses to impaired systolic function.[52] This decrement in systolic function frequently occurs in the setting of decreased renal perfusion, impaired renal function, and ultimately the hepatorenal syndrome. This cardio-renal failure is associated with increased mortality, and reflects the end-stage of cirrhosis and portal hypertension.[52]

Diastolic dysfunction

It is estimated that over 50% of patients with cirrhosis may have abnormal diastolic function measured by TTE.[53] This abnormal stiffening of the ventricular wall leads to inadequate ventricular filling, and when severe, overt heart failure. The diastolic dysfunction is usually mild (grade 1), but in approximately 25% of those with diastolic dysfunction, can be more severe (grade 2).[53] Patients who progress to having diastolic dysfunction are those with more advanced liver disease, evidenced by higher MELD and Child-Pugh scores, lower values of serum albumin, and a greater prevalence of ascites.[53] The exact pathophysiological mechanisms underlying the cardiac remodeling and increased stiffness is unknown.

QT Prolongation

The QT interval on an electrocardiogram reflects myocardial depolarization and repolarization, and its prolongation is associated with cardiac arrhythmias that can be potentially life-threatening.[54,55] Several case series have clearly demonstrated an increased prevalence of QT interval prolongation in patients with chronic liver disease, independent of other known risk factors for this condition.[54,55] The mechanism underlying this conduction abnormality remains unknown, although one hypothesis focuses on increased autonomic dysfunction.[56]

Cardiac manifestations of specific liver diseases

Hemochromatosis—Hereditary hemochromatosis is a multi-systemic disease, and can affect organs such as the heart and pancreas. Iron deposition within the heart can lead to congestive heart failure, conduction abnormalities, and rarely a restrictive cardiomyopathy.[57,58] The prevalence of heart failure symptoms in patients with hereditary hemochromatosis is variable, with estimates ranging from 0–35%.[59–63] Despite these risks of congestive heart failure, cardiac function in patients with hereditary hemochromatosis can improve in response to therapeutic phlebotomy.[58] However, cardiac complications following liver transplantation are higher in patients transplanted for hereditary hemochromatosis compared to other transplant recipients, thus these patients require close evaluation pre- and post-transplantation, with imaging that can include a TTE, MRI, and/or PET scan.[64]

Non-alcoholic steatohepatitis (NASH)—Although there are several theories as to the exact pathophysiologic mechanism leading to the development of fatty liver disease in patients with NASH, insulin resistance and altered fatty acid metabolism are supported by

the most robust data. As a result, non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of the metabolic syndrome,[65] with NAFLD being considered an independent risk factor for coronary artery disease.[65] This risk is amplified in patients with NASH, as compared to those with NAFLD and bland steatosis. To date, there are limited medical therapies to decrease the inflammation and fibrosis related to NASH. Yet, there are data to suggest that in patients with abnormal liver enzymes attributable to NAFLD, statin therapy can reduce cardiovascular morbidity.[66]

Hepatitis C—Early data was unclear about the relationship between chronic HCV and coronary heart disease, yet new data has emerged from a cohort of nearly 15,000 HCV-negative controls, 8,000 isolated HCV antibody positive patients, and 1,400 patients with active viremia. Those with isolated HCV antibody positivity had a 32% increased risk of coronary artery disease when compared to controls, while patients with detectable HCV RNA had nearly a 60% increased risk, independent of factors such as hypertension and diabetes.[67]

Screening for cardiac complications in patients with liver disease

The cardiac evaluation of patients with chronic liver disease should focus on detecting complications that can impact their mortality pre- and post-liver transplantation, in addition to specific screening for patients with liver disease associated with cardiac complications. TTE should be performed routinely in patients being evaluated for, and awaiting a liver transplant. The optimal timing of such TTE screening has not been defined, although most centers perform yearly TTEs to identify patients with echocardiographic parameters suggestive of PAH.[31] Furthermore, the performance of routine TTEs can identify patients with cirrhotic cardiomyopathy complicated by decreased left- and/or right-ventricular systolic function. Despite the sensitivity however of TTE to identify depressed cardiac function which places patients at risk of overt heart failure post-transplantation, there still is a risk for post-operative heart failure despite a normal pre-transplant TTE.[68]

Patients being evaluated for liver transplantation are routinely evaluated for coronary artery disease due to the risk of peri- and post-operative cardiac events which may impact mortality. There are no clear data on the optimal testing strategy for asymptomatic patients who are low-risk for coronary artery disease. In patients with non-hepatic cardiac risk factors for coronary disease (i.e., diabetes), pre-transplant assessment for coronary artery disease is recommended, although there are no clear data identifying the ideal mechanism to screen patients (stress echocardiography, nuclear imaging, and or routine left heart catheterization).[69] Patients with NASH should be evaluated for coronary artery disease as this is considered a risk equivalent for coronary artery disease.[69] In those with coronary artery disease or significant risk factors (i.e., hyperlipidemia), statin therapy is safe, indicated, and can decrease morbidity and mortality.[66,70]

CONCLUSIONS

In summary, chronic liver disease is associated with the development of potentially severe pulmonary and cardiac complications. HPS and POPH are common in patients with advanced liver disease, and may adversely influence quality of life and survival. While HPS

is an indication for liver transplantation, severe POPH is generally considered a contraindication. Those with POPH who respond to medical therapy can tolerate transplantation, but consistent reversal has not been found. Cirrhotic cardiomyopathy manifests with systolic, diastolic, and conduction abnormalities, and is a manifestation of end-stage cirrhosis and portal hypertension. The role of liver transplantation in this setting is not fully defined. Individuals with AAT deficiency are at increased risk for emphysema, while those with chronic HCV and NASH are at risk, for coronary disease; each of these complications has the potential to influence transplant candidacy. Understanding the pathogenesis of these unique consequences of liver disease and defining the precise role of liver transplantation in therapy is needed to optimize outcomes in these individuals.

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Abbreviations

HPS	Hepatopulmonary syndrome
IPVDs	Intrapulmonary vascular dilatations
SpO_2	Pulse oximetry
PaO_2	Partial-pressure of oxygen
ABG	Arterial blood gas
(A-a) gradient	Alveolar-arterial
TTE	Transthoracic echocardiogram
MAA	Macroaggregated albumin
PFT	Pulmonary function tests
QOL	Quality of life
NYHA	New York Heart Association
FDA	Federal Drug Administration
TIPS	Transjugular intrahepatic portosystemic shunt
MELD	Model for End-Stage Liver Disease
POPH	Portopulmonary hypertension
PAH	Pulmonary arterial hypertension
mPAP	Mean pulmonary artery pressure
sPAP	Systolic pulmonary artery pressure
PVR	Pulmonary vascular resistance

PCWP	Pulmonary capillary wedge pressure
LVEDP	Left ventricular end-diastolic pressure
TPG	Trans-pulmonary gradient
AAT	Alpha-1-antitrypsin
SVR	Systemic vascular resistance
NASH	Non-alcoholic steatohepatitis
NAFLD	Non-alcoholic fatty liver disease
HCV	Hepatitis C virus

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Table 1

Diagnostic criteria for hepatopulmonary syndrome

Physiologic abnormality	Diagnostic criteria
Impaired gas exchange	Arterial blood gas sampling while breathing ambient air with:
	1 PaO_2 <80 mm Hg **or**
	2 Alveolar-arterial oxygen gradient ≥15 mm Hg if age <65 years, or ≥20 mm Hg if age ≥ 65 years*
Intrapulmonary shunting	**1** Transthoracic echocardiogram with agitated saline demonstrating “late passage” (after >3 cardiac cycles) of bubbles into left atrium
	2 Radiolabeled macro-aggregated albumin scan with a brain shunt fraction of >6%
Liver disease	Cirrhosis and/or portal hypertension†
Liver disease	No specific defined testing required, but other causes of hypoxemia must be ruled out ‡

*$AaPO_2 = (FiO_2 [P_{atm} – PH_2O] – [PCO_2/0.8]) – PaO_2$, where PaO_2 represents partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, P_{atm} atmospheric pressure, PH_2O partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest)

†Patients may have acute and/or chronic hepatitis in the absence of cirrhosis and/or portal hypertension, although nearly all patients with HPS have cirrhosis

‡Testing may include high-resolution pulmonary CT scanning to assess for parenchymal abnormalities, or pulmonary function testing to evaluate for obstructive or restrictive defects.

Table 2

Comparison of hepatopulmonary syndrome and portopulmonary hypertension

	Hepatopulmonary syndrome	Portopulmonary hypertension
Prevalence in cirrhotic patients	10–33%	5–10%
Portal hypertension	Usually present	Always present
Pulmonary vasculature changes	Vasodilation and angiogenesis in alveolar regions	Arterial thickening and remodeling in resistance vessels
Hypoxemia	Always present	Sometimes present
Echocardiographic findings	Left atrial bubbles 4–6 cardiac cycles after injection of agitated saline	Elevated pulmonary artery systolic pressure
Indication for transplantation	Indication; increased prioritization for patients meeting specific criteria	Increased prioritization for patients with mild disease controlled by POPH therapy; contraindication if severe,
Improves with transplantation	Always	Variable

Table 3

Examples of hemodynamic parameters seen in cirrhotic patients with POPH, left-sided heart failure, and volume overload

Diagnosis	Mean pulmonary arterial pressure*	Pulmonary capillary wedge pressure*	Cardiac output*	Pulmonary vascular resistance†
Portopulmonary hypertension	45 mm Hg	10 mm Hg	7 L/min	5 Wood units
Left-sided heart failure	40 mm Hg	30 mm Hg	4 L/min	2.5 Wood units
Volume overload	40 mm Hg	15 mm Hg	10 L/min	2.5 Wood units

*Values obtained at the time of right heart catheterization

†Calculation: [(mean pulmonary artery pressure) - (pulmonary capillary wedge pressure)] / (cardiac output)