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Pulmonary Complications in Candidates for Liver Transplantation

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ABSTRACT

The liver plays a pivotal role in maintaining the homeostasis of various organ systems. Also, end-stage liver disease and its complications are major causes of morbidity and mortality among adults. Individuals who develop a chronic liver disease are at increased risk of progression to multi-organ dysfunction, including the pulmonary system. The clinical complications of pulmonary problems related to the presence of liver disease range from mild (such as hypoxemia) to life-threatening diseases (such as portopulmonary hypertension and hepatopulmonary syndrome). Herein, the major pulmonary complications related to liver cirrhosis and considerations for performing liver transplantation are reviewed.

KEYWORDS:

Cirrhosis, Hypoxemia, Liver transplantation, Hepatopulmonary syndrome, Portopulmonary hypertension, Lung diseases

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INTRODUCTION

End-stage liver disease (ESLD) and its associated complications are currently included in the significant causes of death globally among adult population.¹⁻³ Currently, orthotopic liver transplantation (LT) is considered as the only viable option for the management of patients with ESLD.⁴ Patients with advanced liver disease often present with various coexisting organ dysfunction.⁵ In this respect, pulmonary disorders remain one of the major concerns among patients with ESLD who are candidates for LT.⁶⁻¹⁰ Approximately half of the patients with ESLD have been reported to suffer from pulmonary diseases.¹¹ A wide spectrum of pulmonary conditions has been identified to be associated with advanced liver disease regardless of the etiology of liver cirrhosis. The most important pre-existing conditions that compromise lung function in patients with liver disease are concomitant cardiopulmonary disorders, autoimmune disease, and chronic obstructive pulmonary disease (COPD).^{12,13} In this review, we aimed to discuss the most important pulmonary complications related to liver cirrhosis and considerations for performing LT in this group of patients.

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Hypoxemia associated with liver failure

Hypoxemia is the most common pulmonary abnormality in patients with cirrhosis.^{14,15} The severity of chronic liver disease contributes to the development of hypoxemia and worsens the prognosis of these patients.^{16,17} The underlying pathophysiology of hypoxemia in patients with cirrhosis is mainly caused by abnormal pulmonary perfusion pathways.¹⁸ Previous studies suggest that a rightward shift in the oxyhemoglobin dissociation curve seen in patients with cirrhosis may be the primary physiological mechanism that explains this association.¹⁹ Moreover, several studies also have reported an evident increase in 2,3-diphosphoglycerate (2,3-DPG) as a compensatory mechanism for maintaining oxygen consumption in patients with cirrhosis.^{20,21} In a review article,²² it was reported that four factors played a major role in regulating the position of the oxyhemoglobin dissociation curve. These factors were pH, body temperature, carbon dioxide content, and organic phosphates. However, further analysis indicated that a reduction in the affinity of hemoglobin for oxygen did not appear to have the capacity to significantly affect arterial oxygen saturation.²³ In the cohort study done by Clerbaux and colleagues,¹⁹ it was shown that several additional factors contributed to changing the position of oxyhemoglobin dissociation curve such as alteration of the enzymes controlling the phosphoglycerate shunt, hypothyroidism, the type of treatment received by patients (e.g., diuretics and/or propranolol), and acid-base disturbances.

The presence of hypoxemia among patients with cirrhosis suggests that the liver plays a detrimental role in the underlying pathogenesis of this condition. The impact of chronic liver disease on the oxygen saturation of blood may explain the abnormal increase in the alveolar-arterial oxygen gradient among patients awaiting LT.²⁴ In addition, the improvement of cirrhosis-related hypoxemia after performing LT suggests the role of liver disease in causing hypoxemia.

Chronic obstructive pulmonary disease (COPD)

The pre-existing COPD is common among LT candidates.²⁵ In this regard, Ehlers and co-workers²⁶

analyzed the lifetime pre- and post-LT prevalence rates of smoking among 202 LT recipients and found that 60% of these patients had a history of smoking. Similarly, another study reported that the history of smoking existed in approximately 60% of LT candidates and 27% were current smokers. Clinically significant COPD, defined as FEV1/FVC < 70%, was present in only 18% of these patients. Moreover, the prior diagnosis of COPD was not made in 80% of those patients.²⁵ Currently, there is no consensus regarding the safety of patients with COPD who are candidates for LT. One study suggested that the 5-year survival rate of patients with advanced cirrhosis who underwent LT was about 24-30% among those with FEV1 < 30% predicted.^{27,28} It is notable that most of these patients may have a prolonged history of smoking, which may result in an increased risk of lung malignancy.

Spirometry is the most frequently performed lung function test. A recently developed lung function measurement tool showed better prognostic capabilities, compared with spirometry, for patients with COPD. The BODE index, which is based on Body mass index (BMI), airway Obstruction, Dyspnea scale, and Exercise capacity, could predict the risk of mortality from any respiratory causes regardless of the FEV1-based classification. The BODE index assesses several additional risk factors, such as the evidence of hypoxemia, severe dyspnea, body-mass index, and 6-minute walking test. Thus, this grading system should be used more widely among LT candidates with COPD because of its better risk assessment.²⁹

Hepatopulmonary syndrome (HPS)

Hepatopulmonary syndrome (HPS) is defined by portal hypertension with or without concomitant liver cirrhosis, pulmonary gas exchange abnormalities, and arterial hypoxemia caused by intrapulmonary vascular dilatations.³⁰⁻³⁴ (Figure 1). Approximately, 4-47% of patients with documented liver cirrhosis and 4-32% of candidates for LT are diagnosed with HPS.³⁵⁻³⁸ The most prominent clinical feature of HPS is progressive dyspnea and low oxygen saturation levels.³⁹ The progressive decline of lung function

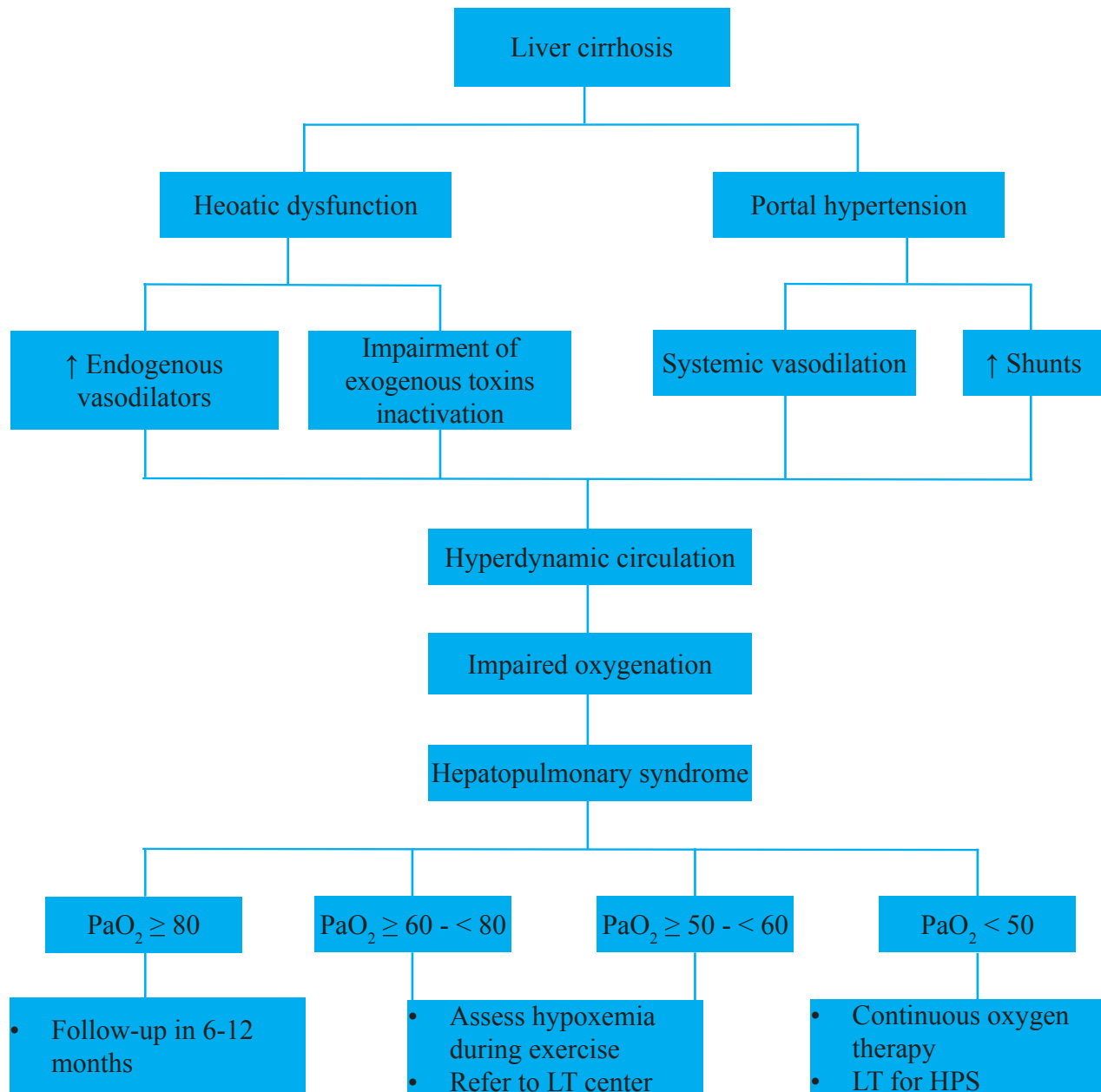


Fig.1: Algorithm depicting the diagnostic and pathophysiology approach to hepatopulmonary syndrome³⁴

occurs regardless of stable liver function.⁴⁰ These patients often experience cyanotic nail beds and clubbed fingers. Supplemental oxygen therapy is often needed for managing hypoxemia in more advanced HPS cases. Currently, the only viable option for the management of HPS is liver transplantation, which is followed by an improved lung function within about 1 year.⁴¹ Despite advances in post-liver transplantation care and monitoring of the recipi-

ents, the presence of HPS is still associated with extremely poor prognosis. In a cohort study, Schenk and colleagues reported that the presence of HPS before transplantation was an independent risk factor for higher mortality rate in patients with cirrhosis.⁴² The median survival time among patients with cirrhosis and concomitant HPS was significantly lower compared with patients with cirrhosis but without HPS (10.6 months vs. 40.8 months, re-

spectively). Moreover, the overall mortality incidence among patients with HPS was about 63% during 2.5 years of follow-up duration. The major cause of death was due to gastrointestinal bleeding leading to hemorrhagic shock.⁴² Another study reported that the mortality rate among 22 patients with HPS was 41% after the establishment of the diagnosis. In addition, Swanson and others showed that arterial hypoxemia was a major risk factor that influences survival outcome.¹⁶ According to these previous reports, the survival rates following LT are markedly lower in HPS cases when compared with those without HPS. Hence, an in-depth individual analysis is required for those HPS cases that have severe hypoxemia ($\text{PaO}_2 \leq 50$ mmHg) prior to the final acceptance as LT candidates. At the same time, it should be noted that severe HPS cases have an extremely poor survival rate without transplantation, and therefore, it is considered as a criterion for prioritizing organ allocation. Accordingly, a great debate still remains whether the allocation of scarce life-saving resources should include patients with HPS or that should be allocated to potentially more clinically stable candidates.^{16,43-45}

Portopulmonary hypertension (POPH)

Portopulmonary hypertension (POPH) is defined as the coexistence of intrapulmonary vasoconstriction in the setting of portal hypertension (caused by chronic liver disease or extrahepatic causes).⁴⁶ Patients must meet the following diagnostic criteria including elevated resting mean pulmonary artery pressure more than 25 mmHg at right heart catheterization, evidence of pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and a pulmonary vascular resistance greater than 240 dynes/s/cm-5.^{47,48} Although POPH is a relatively rare condition, it is most commonly seen in patients with ESLD. Overall, this condition is found in approximately 2-8.5% of patients with liver cirrhosis and liver transplant candidates.⁴⁹⁻⁵² Based on the French National Center for pulmonary artery hypertension, POPH comprises nearly 10% of referred patients as a consequence of cirrhosis severity and poor cardiac function.⁵³

POPH is generally asymptomatic and is usually detected with suspicious changes on screening echocardiography with evidence of elevated right ventricular systolic pressure (RVSP). In high-volume transplantation centers, liver transplant candidates undergo contrast-enhanced echocardiography to identify pre-existing POPH. Moreover, the suspected cases should be followed with right heart catheterization if elevated RVSP is detected on echocardiogram. RVSP can be calculated from the tricuspid regurgitant (TR) jet velocity using the modified Bernoulli equation ($[\text{RSVP} = 4 \times (\text{TR})^2 + \text{RAP}]$), in which the mean right atrial pressure (RAP) remains constant at 10 mm Hg.⁵⁴⁻⁵⁶ Right heart catheterization is performed if the RSVP is greater than 50 mm Hg. The 50-mm Hg threshold for RSVP is associated with 97% sensitivity and 77% specificity for the diagnosis of POPH.^{57,58} The most common presenting symptom among LT candidates is fatigue and exertional dyspnea and is not easily differentiated from general signs and symptoms of liver problems. Although syncope or chest pain is usually found in LT candidates with severe POPH and right heart failure, the lack of these symptoms should not rule out the possibility of POPH.

Autoimmune diseases

Autoimmune diseases can affect various parts of the body, most often the lung and liver.⁵⁹ It has been estimated that nearly half of the patients with rheumatoid arthritis develop lung diseases such as chronic pleural effusion, pulmonary parenchymal disease (e.g., interstitial pneumonitis), pulmonary fibrosis, and pulmonary vasculature (e.g., pulmonary hypertension).^{60,61} In addition, the therapeutic regimen used for controlling inflammation and symptoms related to these autoimmune conditions is independently associated with the development of liver disease. Liver damage caused by the widespread use of anti-inflammatory drugs, including high dose non-steroidal anti-inflammatory drugs, antirheumatic drugs (e.g. methotrexate), and tumor necrosis factor inhibitors have shown to significantly accelerate the process of liver and lung injury.^{62,63}

Pulmonary manifestations of autoimmune disorders

are complex and may be associated with the involvement of airway and/or lung parenchyma.⁶⁴ Although non-specific symptoms of pulmonary involvement may occur in the early stages of autoimmune disorders, the diagnosis of liver involvement precedes or is diagnosed concurrently with pulmonary manifestation.⁶⁵ The most common indications for autoimmune-related LT include primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis.^{66,67} Pulmonary complications, including lymphocytic interstitial pneumonia, bronchiolitis obliterans, obstructive airway disease, and pulmonary hypertension, are frequently seen in these groups of patients.^{68,69} Moreover, these patients are at increased risk of autoimmune hepatitis development and also parenchymatous liver diseases such as nodular regenerative hyperplasia.⁷⁰ Other autoimmune disorders, including dermatomyositis, scleroderma, and systemic lupus erythematosus, can also cause both liver and lung damages.⁷¹ The high incidence and widely diverse presentation of lung involvement in patients with autoimmunity indicate the need for a rigorous preoperative assessment of pulmonary function in LT candidates.

Hepatic hydrothorax

Hepatic hydrothorax (HH) is defined as a large accumulation of fluid (more than 500 mL) within the pleural space in the setting of liver cirrhosis and in the absence of other etiologies related to pleural effusion, such as cardiac, pulmonary, or pleural diseases.^{72,73} This complication occurs in about 5-10% of patients with cirrhosis. Patients with HH can be presented with severe symptoms (e.g. dyspnea, hypoxemia, and cough) with only 500 mL accumulation of fluid. Although the exact underlying mechanisms of HH development have not been well understood, studies suggest that the passage of ascitic fluid to the peritoneal cavity may be due to small diaphragmatic defects. Several diagnostic factors have been suggested to assist physicians in determining the causes of effusion demonstrated by thoracentesis (table 1).^{72,74,75} The management of HH is similar to those of ascites. Alcohol consumption should be extremely avoided in patients who continue active drinking.⁷⁶ Moreover, dietary sodium

Table 1: Characteristics of Hepatic Hydrothorax in patients undergoing thoracentesis

Location
Right side (73-85%)
Left side (13-17%)
Bilateral (2-10%)
Fluid characteristics
Cell count < 250 polymorphonuclear cells per mm ³
pH > 7.4
Protein < 2.5 g/dL
Pleural fluid/serum total protein ratio < 0.5
Glucose level similar to that of serum
Serum-to-pleural fluid albumin gradient > 1.1 g/dL
Pleural fluid/serum bilirubin ratio < 0.6
Pleural fluid/serum lactate dehydrogenase ratio < 0.6

restriction, along with diuretic usage, should be considered in these patients. Finally, evaluation for liver transplantation should be considered in those patients with refractory HH.⁷⁷

Spontaneous bacterial empyema

Spontaneous bacterial empyema is referred to as the infected pleural fluid as the secondary complication of HH.⁷⁸ Notwithstanding the term implying the presence of bacterial infection, no evidence of pus or abscess is observed in most of the cases, and therefore, its management strategy is distinct from those of empyema secondary to pneumonia. This complication has been reported to occur in approximately 13-30% of HH cases.⁷⁹ Spontaneous bacterial empyema is associated with poor outcome and a relatively high mortality rate of more than 20%.⁸⁰ The exact pathogenesis of this complication is not fully understood. However, it may be due to the spread of bacteria throughout the peritoneal cavity. Moreover, this condition could also occur even in the absence of an obvious ascites.⁸¹

CONCLUSION

Pulmonary complications related to liver cirrhosis is associated with distinct clinical features. The early recognition of these complications among patients with cirrhosis is mandatory for enhancing

the prognosis and reducing post-liver transplantation complications. Currently, the proposed pharmacological and nonsurgical treatments have not shown promising results. However, results from prospective studies suggest the beneficial role of early LT in the reversal of pulmonary symptoms. In this regard, further clinical investigations are warranted to elucidate the mechanisms and predictors of this pulmonary involvement and possibly new treatment modalities.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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