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REVIEW ARTICLE

Liver Transplantation in Hepatopulmonary Syndrome

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ABSTRACT

Introduction: Hepatopulmonary syndrome (HPS) results from the association between liver disease, intrapulmonary vascular dilations, and hypoxemia, representing a relevant complication of cirrhosis. Liver transplantation (LT) is the only curative treatment; however, patients with HPS present a higher risk of mortality while on the waiting list, which is why they receive exception points in the Model for End-Stage Liver Disease (MELD) score. **Objectives:** To evaluate whether LT improves prognosis and survival in patients with HPS. **Methods:** This is an integrative literature review. The search was conducted in PubMed, LILACS, and Cochrane databases using the descriptors "Liver transplantation," "Hepatopulmonary syndrome," and "Liver." Of the 272 articles identified, 13 met the eligibility criteria and were included in the final analysis. Data extraction included demographic and clinical characteristics, such as mean age, sex distribution, main etiologies of liver disease, mean MELD/Pediatric End-Stage Liver Disease (PELD) score, and mean PaO_2 and $PaCO_2$ values. **Results:** Patients with PaO_2 < 45 mmHg were more likely to be prioritized on the transplant waiting list (hazard ratio [HR] 1.51; p = 0.007), although they also showed lower post-transplant survival compared with those with PaO_2 ≥ 45 mmHg. In the pediatric context, data from an observational study conducted in the United States indicated that children with HPS had a higher risk of mortality after LT compared with those without HPS. In a prospective cohort study, transplanted patients with HPS remained on mechanical ventilation for an average of 19.5 ± 4.3 hours, significantly longer than the 12.5 ± 3.3 hours observed in patients without HPS. **Conclusion:** LT remains the only curative therapy for HPS. The severity of hypoxemia is associated with worse post-transplant outcomes, highlighting the need for proper stratification of HPS. However, although useful for estimating liver-related mortality, the MELD/PELD score does not accurately reflect the severity of this syndrome.

Descriptors: Liver Transplantation; Hepatopulmonary Syndrome; Liver.

Transplante Hepático na Síndrome Hepatopulmonar

RESUMO

Introdução: A síndrome hepatopulmonar [*hepatopulmonary syndrome* (HPS)] resulta da associação entre doença hepática, dilatações vasculares intrapulmonares e hipoxemia, configurando complicação relevante da cirrose. O transplante hepático [*liver transplantation* (LT)] é o único tratamento curativo; no entanto, pacientes com HPS apresentam maior risco de mortalidade na espera, motivo pelo qual recebem pontos de exceção no escore Model for End-Stage Liver Disease (MELD). **Objetivos:** Avaliar se o LT melhora o prognóstico e a sobrevida de pacientes com HPS. **Métodos:** Trata-se de uma revisão integrativa da literatura. A busca foi conduzida nas bases PubMed, LILACS e Cochrane utilizando os descritores "Liver transplantation", "Hepatopulmonary syndrome" e "Liver". Dos 272 artigos identificados, 13 atenderam aos critérios de elegibilidade e foram incluídos na análise final. A extração de dados contemplou características demográficas e clínicas, incluindo média de idade, distribuição por sexo, principais etiologias da doença hepática, escore MELD/Pediatric End-Stage Liver Disease (PELD) médio e valores médios de PaO_2 e $PaCO_2$. **Resultados:** Pacientes com PaO_2 < 45 mmHg apresentam maior probabilidade de serem priorizados na lista de transplante [*hazard ratio* (HR) 1,51; p = 0,007)], embora esses também apresentem menor sobrevida no pós-transplante quando comparados àqueles com PaO_2 ≥ 45 mmHg. No contexto pediátrico, dados provenientes de um estudo observacional realizado nos Estados Unidos indicaram que crianças com HPS apresentaram maior risco de mortalidade após o LT em comparação com aquelas sem HPS. Em um estudo de coorte prospectivo, pacientes transplantados com HPS permaneceram em ventilação mecânica por uma média de 19,5 ± 4,3 horas, significativamente superior às 12,5 ± 3,3 horas observadas em pacientes sem HPS. **Conclusão:** O LT constitui a única terapia curativa para a HPS. A gravidade da hipoxemia está associada a piores desfechos pós-transplante, ressaltando a necessidade de estratificação adequada da HPS. Entretanto, embora útil na estimativa da mortalidade hepática, o escore MELD/PELD não capta de forma precisa a severidade dessa síndrome.

Descritores: Transplante Hepático; Síndrome Hepatopulmonar; Fígado.

INTRODUCTION

Hepatopulmonary syndrome (HPS) is defined by a triad consisting of liver disease and/or portal hypertension, intrapulmonary vascular dilatations (IPVD), and abnormal arterial oxygenation, characterized by an elevated alveolar-arterial (A-a) oxygen gradient (≥ 15 mmHg, or ≥ 20 mmHg in patients over 64 years of age) or a PaO_2 < 80 mmHg.[1]

The pathophysiology of HPS involves impaired hepatic clearance of vascular mediators, leading to an imbalance between vasodilatory and vasoconstrictive agents. As a consequence, abnormal intrapulmonary vasodilation occurs, associated with intrapulmonary shunting, which impairs oxygenation and contributes to the worsening of the clinical condition.[2]

Regarding its classification, HPS can be defined according to severity as follows: mild, when PaO_2 > 80 mmHg with an elevated A-a gradient; moderate, when PaO_2 is between 60 and 80 mmHg; severe, when PaO_2 is between 50 and 60 mmHg; and very severe, when PaO_2 < 50 mmHg.[3-5]

HPS is one of the complications frequently associated with liver cirrhosis, a condition characterized by diffuse replacement of normal hepatic architecture with regenerative nodules surrounded by fibrous tissue. This structural alteration of the liver leads to architectural disorganization, resulting in hepatic dysfunction that, in turn, promotes the development of the pulmonary vascular changes characteristic of the syndrome.[1,6] When present in patients with cirrhosis, HPS significantly worsens the prognosis, underscoring its clinical relevance.[7]

Currently, studies indicate that there are no effective clinical therapies that provide sustained improvement in oxygenation or reduce mortality in patients with HPS.[3] The only treatment recognized to improve survival in these patients is liver transplantation (LT), which has been shown to reverse the syndrome, fully resolve gas exchange impairment, and increase survival rates in most cases.[8,9]

To establish patient prioritization on the liver transplantation (LT) waiting list, the Model for End-Stage Liver Disease (MELD) was developed. This scoring system assesses the severity of liver disease and estimates short-term mortality in patients with cirrhosis.[10] Based on the same principles, the Pediatric End-Stage Liver Disease (PELD) scoring system was developed specifically for children under 12 years of age.[3]

However, it is believed that the prognosis of HPS is worse than what is predicted by the MELD/PELD scoring systems alone.[3] In this context, patients with HPS who meet established clinical criteria have become eligible for the allocation of exception points within the MELD score system.[5]

Although LT is the only curative treatment for HPS, the presence of this syndrome is associated with reduced quality of life and increased risk of death among transplant candidates, as well as impaired immediate postoperative outcomes and decreased patient survival. Contributing factors include exercise intolerance and deterioration in physical condition, resulting from gas exchange abnormalities caused by HPS.[1,3,6]

Therefore, the objective of this study is to analyze the available evidence in the literature regarding liver transplantation (LT) in patients with HPS, with the aim of evaluating its impact on prognosis and survival in these individuals, considering the severity of HPS, its association with unfavorable clinical outcomes, and the current limitations of available therapeutic options.

METHODOLOGY

This is an integrative literature review aimed at identifying and critically selecting scientific evidence related to liver transplantation (LT) in patients with hepatopulmonary syndrome (HPS). The review was structured according to the following steps: (1) identification of the topic and formulation of the research question; (2) establishment of inclusion and exclusion criteria for studies; (3) definition of the information to be extracted from the selected studies; (4) critical analysis of the included studies based on levels of evidence; (5) discussion of the results; and (6) presentation of the integrative review. In this context, the guiding question was formulated using the PICO strategy—an acronym for Patient, Intervention, Comparison, and Outcomes. Accordingly, the following research question was developed: Does LT improve prognosis and survival in patients with HPS?

Inclusion criteria

The inclusion criteria defined were: articles published from September 2014 to September 2024, available articles, original research articles, articles written in English or Portuguese, and articles related to the topic proposed by the review, taking into account the study population.

Exclusion criteria

The exclusion criteria defined were: articles in which the study population did not include individuals with HPS, non-original articles, animal experiments, review articles, and articles that do not align with the study topic.

Search strategy

The search strategy was based on the verification of Medical Subject Headings (MeSH terms) in the *Descritores em Ciências da Saúde* (DeCS), which were selected and subsequently searched in the data platforms using the following terms: "Liver transplantation," "Hepatopulmonary syndrome," and "Liver." The descriptors were combined using the Boolean operator "AND," and restrictions were applied regarding time frame—articles from the last 10 years were selected—and language, with articles in English and Portuguese being included. The use of descriptors in English was necessary due to the functioning of the databases and the fact that most indexed articles are available in English, which means that searching with Portuguese descriptors limits the results to only those articles available in both Portuguese and English. The bibliographic search was systematically conducted in the following databases: PubMed, LILACS, and Cochrane. These databases were chosen for their extensive literature and their status as references in the health field.

PubMed

Using the aforementioned search strategy, and applying filters that included articles published from September 2014 to September 2024, available articles, and articles in English and Portuguese, a total of 254 articles were found.

LILACS

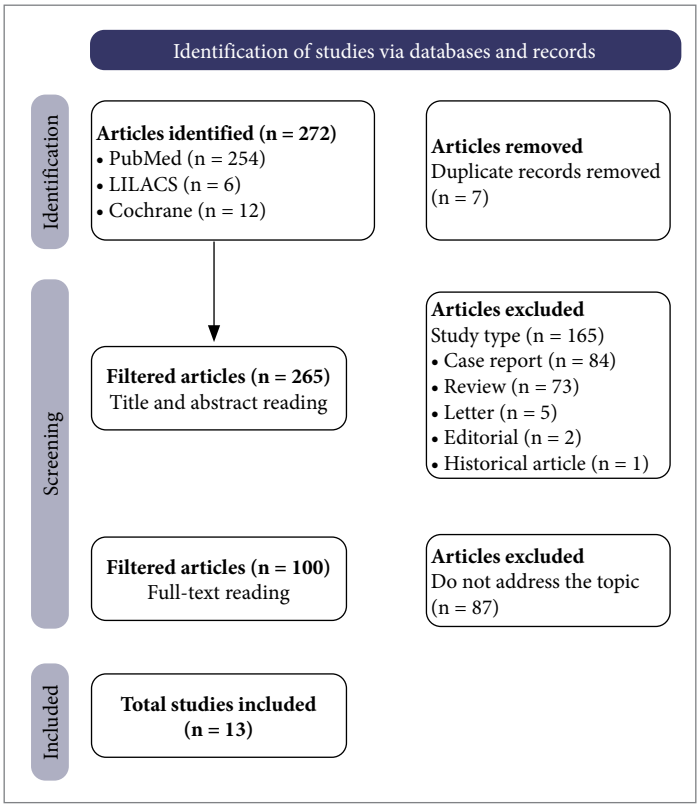
Using the aforementioned search strategy, and applying filters that included articles published from September 2014 to September 2024, available articles, and articles in English and Portuguese, six articles were found.

Cochrane

Using the aforementioned search strategy, and applying filters that included articles published from September 2014 to September 2024, available articles, and articles in English and Portuguese, a total of 12 articles were found.

Selection procedure

After retrieving articles from the databases, a screening process was conducted for the 272 articles found. During this phase, the articles were uploaded to the Rayyan Intelligent Systematic Review application, following the search strategy outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020, in accordance with the CARE Guidelines from the Equator Network for systematic reviews, as illustrated in Fig. 1.



Source: Elaborated by the authors.

Figure 1. Screening of articles using the PRISMA Statement 2020 flowchart for systematic reviews.

The application identified duplicated texts, and after careful analysis and exclusion of these copies, 265 unique articles remained. In the next stage, six independent reviewers individually read the title and abstract of each article to assess their relevance to the review topic, identifying those that clearly diverged from the previously established inclusion criteria. In the third stage, following the selection of 100 articles within the application that met the criteria, it was necessary to read the introduction, results, and discussion sections of each article to determine which were truly suitable for the study. As a result, 87 articles were excluded after full-text review, leaving 13 articles that were used in the development of this review paper.

Data Extraction Procedure

In the fourth phase, following the selection of articles, six independent reviewers conducted the data extraction. During this stage, the reviewers used a document file created in the free application Google Docs, accessed through the institutional account @upe.br. This document was used to record, first, general information from each study, including the journal of publication, year, location, authors, study design and level of evidence, sample size, duration, objective, main findings, and conclusions. Subsequently, clinical data of the patients were recorded, such as mean age, sex distribution, main etiologies of liver disease, average MELD/PELD score, as well as mean values of PaO_2 and $PaCO_2$.

RESULTS

Table 1 summarizes the characteristics of the studies included in the review. The publication years of the studies ranged from 2014 to 2023, with five published between 2010 and 2020, and seven in the last five years. Regarding methodological design, 10 articles (83.3%) were retrospective studies, while two (16.7%) were prospective studies, which offer a higher level of evidence. In terms of geographic distribution, two studies were conducted in Europe, five in North America, three in Asia, and two in South America, both in Brazil.

Table 1. Summary of the studies included in the integrative review.

Author	Journal/year	Location	Study design/ level of evidence	Sample	Objective	Results
Pereira et al.[1]	Arquivos de Gastroenterologia/ 2020	Federal University of Health Sciences of Porto Alegre, Brazil	Prospective cohort observational study (Level III evidence)	90 patients with cirrhosis who underwent liver transplantation (42 with hepatopulmonary syndrome)	To evaluate exercise capacity, complications, and survival after LT in cirrhotic patients with HPS, and to compare these outcomes with those of cirrhotic patients without this diagnosis.	The HPS group showed a lower peak oxygen consumption (VO_2peak) (14.2 ± 2.3 vs. 17.6 ± 2.6, $p < 0.001$) and a shorter distance covered in the 6-minute walk test (340.8 ± 50.9 vs. 416.5 ± 91.4, $p < 0.001$) prior to LT. Transplanted patients with HPS required more hours of mechanical ventilation (19.5 ± 4.3 vs. 12.5 ± 3.3, $p = 0.02$), had a greater need for NIV (12 vs. 2, $p = 0.01$), and showed lower survival two years after the procedure ($p = 0.01$).
Orozco-Delgado et al.[2]	Revista Colombiana de Anestesiologia/ 2016	La Fe University and Polytechnic Hospital, Valencia, Spain	Observational, descriptive, and retrospective study (Level III evidence)	8 patients with hepatopulmonary syndrome who underwent LT	To evaluate the importance of early diagnosis of HPS and identify predictors of mortality in patients undergoing LT.	Pre-LT PaO_2 was the only significant predictive factor for mortality ($p = 0.002$). The mean PaO_2 in patients who died was 51.5 ± 2.49 mmHg, significantly lower than in survivors (70.5 ± 5.86 mmHg). None of the variables were statistically significant for HPS reversibility. The survival rate of patients diagnosed with HPS after LT was 62.5%.

Continue...

Table 1. Continuation...

Author	Journal/year	Location	Study design/ level of evidence	Sample	Objective	Results
Raza et al.[3]	Liver Transplantation/ 2022	Scientific Registry of Transplant Recipients, USA	Retrospective observational study (Level III evidence)	3,082 patients under 18 years of age with MELD/PELD exception requests who underwent LT	To evaluate the impact of the MELD/PELD exception policy for children with HPS on post-LT survival in the United States.	Most patients (87.9%) were listed with laboratory MELD/ PELD scores < 15. Waitlist mortality among patients with HPS exception points was rare and not significantly different from patients without HPS. When stratified by pre-LT PaO_2, the severity of hypoxemia was not associated with differences in 1-, 3-, or 5-year post-LT survival rates ($p = 0.13$). However, patients with HPS showed a slightly lower 5-year survival rate compared to those without HPS.
Kawut et al.[4]	European Respiratory Journal/2022	University of Pennsylvania, Mayo Clinic, and University of Texas at Houston, United States	Multicenter prospective cohort study (Level II evidence)	231 patients eligible for LT (85 with HPS)	To evaluate the impact of HPS on the survival of LT candidates and explore the role of angiogenesis in the pathogenesis of HPS.	Patients with HPS showed a shorter distance in the 6-minute walk test, worse functional class, and a higher risk of death (HR 1.80, $p = 0.04$). HPS was associated with elevated levels of pro-angiogenic biomarkers such as angiopoietin-2 and von Willebrand factor.
Jose et al.[5]	Respiratory Medicine/2021	University of Cincinnati, United States	Retrospective cohort observational study (Level III evidence)	60,110 patients who underwent LT (656 with HPS)	To use Accelerated Failure Time models with multivariable competing risks and propensity score matching to analyze the relationship between pre-LT hypoxia and post-transplant outcomes in patients with HPS.	Pre-LT PaO_2 was significantly associated with post-LT mortality in patients with HPS, with each 1 mmHg increase in PaO_2 leading to a significant reduction in post-LT mortality risk (coefficient 0.039, HR = 0.95, $p = 0.001$). Patients with HPS and pre-LT $PaO_2 < 54$ mmHg had higher post-transplant mortality compared to matched cirrhotic patients without HPS.
Pereira et al.[6]	Einstein/2017	Santa Casa de Misericórdia Hospital Complex of Porto Alegre, Brazil	Prospective cohort study (Level II evidence)	178 patients with cirrhosis (92 with HPS)	To compare mechanical ventilation time, need for NIV, ICU length of stay, and hospitalization duration in cirrhotic patients with and without HPS.	Patients with HPS had: longer mechanical ventilation time (19.5 ± 4.3 h vs. 12.5 ± 3.3 h; $p = 0.02$), greater need for NIV (12 vs. 2; $p = 0.01$), longer ICU stay (6.7 ± 2.1 days vs. 4.6 ± 1.5 days; $p = 0.02$), and longer hospitalization duration (24.1 ± 4.3 days vs. 20.2 ± 3.9 days; $p = 0.01$).
Koc et al.[7]	Clinical Transplantation/ 2023	University Hospitals KU Leuven, Belgium	Retrospective cohort observational study (Level III evidence)	32 patients with HPS who underwent LT	To compare the characteristics and outcomes of patients with HPS who underwent LT, with or without concomitant respiratory disease.	Patients with concomitant respiratory disease required prolonged oxygen therapy after transplantation. The oxygen therapy resolution rate was 63% at both 12 and 18 months in patients with respiratory disease, compared to 91% and 100%, respectively, in those without the condition. The estimated 5-year survival was lower in patients with respiratory disease (50% vs. 23%).

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Table 1. Continuation...

Author	Journal/year	Location	Study design/ level of evidence	Sample	Objective	Results
Al-Harbi et al.[8]	Annals of Transplantation/ 2016	King Abdulaziz Medical City, Riyadh, Saudi Arabia	Retrospective observational study (Level III evidence)	524 patients with end-stage liver disease evaluated for LT (57 with HPS)	To determine the prevalence of HPS in LT candidates and assess its impact on survival with or without the procedure.	Twelve percent of patients evaluated for transplantation had HPS, with most cases classified as mild to moderate in severity (88%). The 1- and 3-year survival rates were 95% and 92% in patients with HPS, and 96% and 91% in those who underwent transplantation. Post-transplant survival did not differ significantly between patients with and without HPS (HR = 0.489, $p = 0.228$).
Yi et al.[9]	Journal of Thoracic Disease/2014	The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China	Prospective cohort observational study (Level III evidence)	31 patients with HPS, of whom 26 underwent LT and 5 did not, plus 10 healthy volunteers as a control group	To investigate the role of LPS, TLR2, iNOS, TNF-α, and ET-1 in HPS, as well as changes in the levels of these factors after LT.	Patients with HPS exhibited higher pre-transplant levels of TLR2 mRNA, iNOS mRNA, LPS, TNF-α, and ET-1 compared to the control group. Following orthotopic liver transplantation (LT), levels of TLR2 mRNA, TNF-α, and ET-1 decreased in HPS patients relative to their pre-transplant values. Additionally, both PaO_2 and PaO_2/FiO_2 improved significantly, with the intrapulmonary shunt returning to normal levels after LT.
Kadry et al.[10]	JHEP reports/2021	Penn State College of Medicine, Hershey, USA	Retrospective observational study (Level III evidence)	1,152 patients with HPS listed for LT with approved MELD exception	To evaluate pre- and post-LT outcomes in patients with HPS, considering different levels of PaO_2 prior to transplantation.	Patients with $PaO_2 < 45$ mmHg had a higher likelihood of undergoing transplantation (HR = 1.51, $p = 0.007$), but lower post-transplant survival compared to those with $PaO_2 \geq 45$ mmHg. Median survival was 11.5 years for $PaO_2 < 45$ mmHg and 14.1 years for PaO_2 between 45–50 mmHg. The survival difference became significant after 2.6 years. Cardiac arrest was a significant cause of death ($p = 0.025$) among patients with $PaO_2 < 50$ mmHg.
Khositseth et al.[11]	Annals of Hepatology/2016	Ramathibodi Faculty of Medicine, Mahidol University, Thailand	Retrospective cohort observational study (Level III evidence)	18 children with chronic liver disease listed for LT	To evaluate the presence of IPVD in children with chronic liver disease before and after LT.	Eighty-nine percent of children showed evidence of IPVD on contrast-enhanced saline bubble testing prior to transplantation, with 67% presenting grade III shunting (> 20 bubbles). No child exhibited hypoxemia or met diagnostic criteria for HPS. After transplantation, the bubble test became negative in all surviving children (n = 16, $p = 0.0001$).
Sabang et al.[12]	Annals of Transplantation/ 2021	Westchester Medical Center, USA	Retrospective observational study (Level III evidence)	39 patients with cirrhosis who underwent LT (14 with HPS)	To evaluate the impact of LT on arterial HbCO levels as a marker of carbon monoxide production in patients with cirrhosis, comparing those with and without HPS.	Mean arterial HbCO levels decreased significantly after LT (2.6% vs. 1.8%, $p = 0.0002$). This reduction occurred in both patients with HPS (79%) and without HPS (64%), with no significant difference between the groups ($p = 0.48$).

Source: Elaborated by the authors.

Table 2 summarizes the sample characteristics of the studies included in the analysis, such as the average patient age (ranging from 50 to 60 years), sex distribution (75% of the studies reported a predominance of males), main etiologies of liver disease (most commonly hepatitis C and alcohol-related liver disease), MELD/PELD scores (with MELD averaging between 13 and 19), and pre-transplant blood gas parameters (PaO_2 and $PaCO_2$), when available — with PaO_2 typically reduced and $PaCO_2$ often within normal limits.

Table 2. Summary of the sample of studies included in the integrative review.

Author	Age	Gender	Etiology of Liver Disease	MELD score	PaO_2	$PaCO_2$
Pereira et al.[1]	HPS (+) = 61.2 ± 6 and HPS (–) = 59.2 ± 7	55M/35F	Hepatitis C virus (HCV) and alcohol-related	HPS (+) = 18.4 ± 0.6 e HPS (-) = 18.6 ± 3.2	HPS (+) = 68.2 ± 6.3 e HPS (-) = 91.5 ± 3.1	Not specified
Orozco-Delgado et al.[2]	49.4 ± 10.3	7M/1F	HCV (12.5%), alcohol use (37.5%), alcohol use + HCV (25%), non-cirrhotic portal hypertension (12.5%), cryptogenic (12.5%)	18 ± 5.9	63.4 ± 11.5	35.5 ± 4.6
Raza et al.[3]	9 (median)	1,505 M/1,577 F	Hepatocellular (19.4%), chronic cholestatic (46%), others (34%)	11 (median)	< 60 mmHg	Not specified
Kawut et al.[4]	HPS (+) = 55.2 ± 9.4 and HPS (–) = 57.6 ± 8.9	158M/73 F	Alcohol use (35.5%), HCV (42.8%), autoimmune hepatitis (4.3%), nonalcoholic fatty liver disease (22.9%), hepatitis B virus (HBV) (3%), primary biliary cholangitis (6.5%), primary sclerosing cholangitis (5.2%)	HPS (+) = 15 (median) e HPS (-) = 14 (median)	HPS (+) = 78 ± 13 mmHg e HPS (-) = 92 ± 14 mmHg	HPS (+) = 33 ± 5 mmHg e HPS (-) = 35 ± 5 mmHg
Jose et al.[5]	55 years (median)	341M/315F	HCV (33.2%), alcoholism (25%), nonalcoholic steatohepatitis (NASH) (14.5%), others (27.3%)	14 (12-17)	52 mmHg (mediana)	Not specified
Pereira et al.[6]	HPS (+) = 60.4 ± 7.10 and HPS (–) = 58.7 ± 8.20	Not specified	Alcoholic cirrhosis or HCV	HPS (+) = 17.2 ± 2.1 e HPS (-) = 17.0 ± 3.0	HPS (+) = 67.9 ± 9.3 e HPS (-) = 89.1 ± 10.1	Not specified
Koc et al.[7]	57 ± 11.0	20M/12F	Alcohol use (53.1%), NASH (18.8%), HCV (3.1%), others (25%)	14 ± 7.0	65 ± 19.8	34 ± 9.8
Al-Harbi et al.[8]	HPS (+) = 54 ± 10 and HPS (-) = 54 ± 10.4	HPS (+) = 35M/22F and HPS(-) = 246M/162F	HPS (+) = HCV (47%), HBV (28%), cryptogenic cirrhosis (7%), others (18%) HPS (–) = HCV (55%), HBV (18%), cryptogenic cirrhosis (15%), hepatocellular carcinoma (17%), others (13%)	HPS (+) = 18 ± 6 // HPS (-) = 16 ± 5	HPS (+) = 71 ± 10 e HPS (-) = 90 ± 8 mmHg	HPS (+) = 33 ± 5 // HPS (-) = 35 ± 5 mmHg
Yi et al.[9]	48.8 ± 10.9	24M/2F	HBV (88.5%), HCV (6.5%), alcoholic cirrhosis (3.2%)	Not specified	≤ 70 mmHg (inclusion criteria)	33,6 ± 4,5 mmHg
Kadry et al.[10]	55 years (median)	573M/ 579F	Viral (34.7%), alcohol-related (20.4%), NASH (16.4%), autoimmune (7.1%), others (21.4%)	13 (median)	55 mmHg (median)	Not specified
Khositseth et al.[11]	1.9 (0.7-9)	8M/ 10F	Biliary atresia (77.8%), Alagille syndrome (11.1%), progressive familial intrahepatic cholestasis (5.6%), unknown (5.6%)	PELD score = 19 (12-25)	Not specified	Not specified
Sabang et al.[12]	59 ± 8 years	28M/ 11F	Hepatocellular carcinoma (49%), HCV (44%), alcohol-related (28%), NASH (11%), others (8%)	19 ± 10	84 ± 16 mmHg	Not specified

Source: Elaborated by the authors.

The pathophysiology of HPS involves a complex interplay between hepatic dysfunction, systemic inflammation, and dysregulation of pulmonary vascular homeostasis. A study conducted in 2014 demonstrated that patients with HPS, in the pre-transplant period, exhibit significantly elevated levels of lipopolysaccharides (LPS), toll-like receptor 2 (TLR2), tumor necrosis factor alpha (TNF-α), and endothelin-1 (ET-1). Notably, following liver transplantation (LT), there was a marked reduction in these inflammatory markers, accompanied by significant improvement in oxygenation parameters, including increased PaO_2 and PaO_2/FiO_2 ratio, as well as normalization of the previously identified intrapulmonary shunt.[9]

Similarly, data from a cohort analysis demonstrated that a pre-transplant PaO_2 below 54 mmHg is associated with higher postoperative mortality when compared to patients with cirrhosis without HPS.[5] Additionally, an investigation conducted at Hospital La Fe in Spain reinforces this association: patients who died after liver transplantation (LT) had a mean preoperative PaO_2 of 51.5 ± 2.49 mmHg, whereas survivors had a mean of 70.5 ± 5.86 mmHg. The survival rate of patients with HPS who underwent LT in this study was 62.5%.[2]

HPS has also been associated with an abnormal systemic angiogenesis profile, impaired exercise tolerance and functional capacity, and an increased risk of death in patients without liver transplantation (hazard ratio = 1.84). However, in this group, it did not affect the likelihood of receiving a liver transplant or post-transplant mortality.[4]

Four studies included in this review primarily focused on evaluating LT outcomes in patients diagnosed with HPS. A survival analysis based on pre-transplant PaO_2 levels showed that patients with $PaO_2 < 50$ mmHg (hypoxemia) had a 5-year survival rate of 89.4%, while those with PaO_2 between 60–69 mmHg had a survival rate of 76.5%. Furthermore, a linear relationship was observed between PaO_2 levels and median survival time: 11.5 years for $PaO_2 < 45$ mmHg, 13.3 years for PaO_2 between 45–60 mmHg, and longer than the study follow-up period for $PaO_2 > 60$ mmHg. It is important to note that although patients with $PaO_2 < 45$ mmHg are more likely to be prioritized on the transplant waiting list [hazard ratio (HR) 1.51; $p = 0.007$], they also exhibit lower post-transplant survival compared to those with $PaO_2 \geq 45$ mmHg.[10]

Three articles included in this review addressed the mechanisms and impacts of HPS in relation to liver transplantation (LT). In the pediatric context, data from an observational study conducted in the United States indicated that children with HPS had a higher risk of post-transplant mortality compared to those without HPS (adjusted HR = 1.75; $p = 0.043$). However, no differences were observed in mortality while on the waiting list ($p = 0.69$), nor in post-transplant survival in relation to pre-transplant PaO_2 levels ($p = 0.13$).[3] Corroborating these findings, another study—also conducted in a pediatric population—reported 1-, 3-, and 5-year survival rates of 93.5%, 88.7%, and 88.7%, respectively, in patients with HPS, in contrast to 95.7%, 94.4%, and 93.7% in patients without HPS.[11]

In line with this reasoning, adult patients with concomitant respiratory disease had a pre-transplant $PaCO_2$ of 38 mmHg, whereas those without respiratory disease had 33 mmHg. Post-transplant, the rate of resolution of oxygen therapy dependence was 63% at 12 and 18 months in the group with respiratory disease, compared to 91% and 100%, respectively, in the group without associated pulmonary disease. Additionally, factors such as smoking, pre-existing respiratory disease, and a shunt fraction ≥ 20%, assessed by technetium-99m-labeled macroaggregated albumin scintigraphy (^{99}mTc-MAA), were significantly associated with persistent oxygen therapy requirements. Notably, 5-year mortality was 50% in patients with respiratory disease, compared to 23% in those without this condition.[7]

Regarding biomarkers, a study evaluated the mean fraction of carboxyhemoglobin (HbCO) as an indirect marker of carbon monoxide production in patients with HPS undergoing liver transplantation (LT). The results showed a mean pre-transplant HbCO fraction of 2.7 ± 0.7% in the HPS group and 2.5 ± 1.1% in the control group, with no statistically significant difference (Δ = 0.2%; 95% CI: –0.4 to 0.8; p = 0.48).[12]

Further exploring the mechanisms and impacts of HPS, functional capacity and post-transplant rehabilitation parameters were assessed in two studies. In a prospective cohort study, transplant recipients with HPS remained on mechanical ventilation for an average of 19.5 ± 4.3 hours, significantly longer than the 12.5 ± 3.3 hours observed in patients without HPS. Two-year survival was also lower in the HPS group. Additionally, patients with HPS showed a reduced peak oxygen consumption (VO_2peak) after transplantation (14.2 ± 2.3 mL/kg/min) compared to pre-transplant values (17.6 ± 2.6 mL/kg/min), as well as a shorter distance in the six-minute walk test (6MWT), averaging 340.8 ± 50.9 meters post-LT versus 416.5 ± 91.4 meters preoperatively.[1] Complementarily, another study observed that patients with HPS walked, on average, 29 meters less in the six-minute walk test (6MWT) compared to patients without the syndrome, even after adjustment for age, sex, and MELD-Na score, reinforcing the impact of the syndrome on functional capacity even after transplantation.[4]

DISCUSSION

HPS is a condition characterized by the presence of intrapulmonary vascular dilations that lead to arterial hypoxemia in individuals with chronic liver disease. In addition to these vascular abnormalities, to which the pathophysiology has traditionally been attributed, systemic inflammation and intestinal bacterial translocation appear to play an equally fundamental role in the pathogenesis of HPS. demonstrated that patients with HPS had significantly elevated levels of LPS, TNF-α, ET-1, and nitric oxide (NO) prior to liver transplantation (LT), suggesting that HPS is not merely a hemodynamic phenomenon but an inflammatory condition mediated by innate immune response. The deterioration of the intestinal barrier in cirrhosis allows bacterial endotoxins to translocate into the systemic circulation, activating TLR2 and TLR4 receptors and triggering an inflammatory cascade that leads to NO overproduction and uncontrolled pulmonary vasodilation. These findings are consistent with other studies showing that HPS often improves after LT, as the recovery of hepatic and intestinal function reduces inflammation and restores pulmonary vascular homeostasis. In this context, LT not only halts the progression of underlying liver disease but also targets the pathophysiological mechanisms of HPS, currently representing the only intervention with proven curative potential.[9]

HPS is associated with an increased risk of overall mortality, especially among those who do not undergo liver transplantation (LT). The study by Kawut et al.[4] identified that patients with HPS had a higher risk of death compared to those without the syndrome, regardless of the degree of hypoxemia. This relationship underscores the importance of early identification of HPS and appropriate prioritization for LT, as the procedure can reverse pulmonary vascular abnormalities and improve survival. The severity of HPS and the pre-transplant clinical condition may influence postoperative outcomes and are considered in eligibility criteria.[4] In this context, among patients with advanced liver disease, the MELD scoring system is used to assess the severity of hepatic insufficiency in order to estimate short-term mortality risk and determine prioritization on the liver transplant (LT) waiting list. However, the system may not fully reflect the mortality risk of patients with HPS, as it does not directly capture the presence or severity of the syndrome through its parameters. This highlights that MELD alone may not ensure appropriate transplant prioritization for these patients, and that revising exception points for HPS within the MELD framework may be crucial to optimizing post-transplant outcomes.[5]

The study by Jose et al.[5] identified a strong association between ambient air PaO_2 prior to transplantation and post-transplant mortality, with increased risk for values below 54 mmHg. Each 5 mmHg decrease was associated with an approximate 40% reduction in time to death following the procedure. These findings are consistent with those of Goldberg et al. (2014, as cited in Jose et al.[5]), who reported significantly lower survival in patients with pre-transplant PaO_2 values below 44 mmHg.[10] The study by Kadry et al.[10] indicates that differences between PaO_2 groups are significant for transplant prioritization, but not for pre-transplant mortality or removal from the waiting list. The analysis showed that patients with ambient air $PaO_2 < 45$ mmHg were more likely to undergo transplantation, suggesting that transplant centers prioritized advanced HPS cases to prevent decompensation and worsening hypoxemia. Therefore, it is evident that MELD criteria help prevent mortality on the waiting list but promote delayed intervention due to the absence of parameters that account for HPS, ultimately offering lower post-transplant survival for these patients.[10]

In contrast, regarding pediatric patients, the study by Raza et al.[3] found that the PELD exception system reduces waitlist mortality for children with HPS. Patients who meet the criteria for exception points show good post-transplant survival, although it remains lower than that observed in children without HPS. This pattern was also identified in adults in the study by Jose et al.[5], which demonstrated lower survival in patients with HPS.[3] The study demonstrated that pediatric patients with PaO_2 between 60 and 69 mmHg had worse outcomes than those with even lower PaO_2 levels, indicating a distinct pattern between adult and pediatric patients regarding pre-transplant PaO_2 and post-transplant outcomes.[3]

Continuing the pediatric approach, the study by Khositseth et al.[11] showed that 89% of children with HPS evaluated for liver transplantation (LT) had a positive intrapulmonary shunt on contrast-enhanced saline bubble testing, indicating significant intrapulmonary vascular dilatation (IPVD) prior to the clinical onset of HPS. After transplantation, all bubble tests were negative, suggesting that IPVD is fully reversible with restoration of hepatic function. This finding supports the hypothesis that IPVD may represent an early stage of HPS, highlighting the importance of early recognition to optimize LT indication and prevent long-term complications.[11]

Al-Harbi et al.[8] demonstrated that most patients with HPS evaluated for liver transplantation (LT) presented with mild to moderate forms of the syndrome, without significant impact on post-transplant survival. This suggests that mild HPS may not compromise post-LT recovery, whereas more severe cases may be associated with increased morbidity and poorer prognosis. These findings highlight that the lack of clear stratification of HPS severity in many studies limits the ability to accurately assess its long-term impact on survival.[8] The survival rate of patients with HPS after liver transplantation (LT) indicates that, although it is a crucial therapeutic option, these patients still face considerable postoperative mortality. This further reinforces the notion that

severe hypoxemia is an important risk indicator.[2,10] It is also worth noting that there appears to be a significant decline in survival around three years after liver transplantation (LT).[10]

Analysis of the cause of death revealed a higher incidence of cardiovascular-related deaths compared to respiratory causes in patients with $PaO_2 < 50$ mmHg, suggesting that prolonged pre-transplant hypoxemia may impact cardiac function over time. It is understood that vasodilation and intrapulmonary shunting in HPS may contribute to a hyperdynamic circulatory state, leading to increased cardiac output and long-term left ventricular dysfunction.[10] In contrast, for pediatric recipients with HPS, data analysis from a study revealed that hypoxemia—although associated with more severe clinical status—does not translate into worse post-transplant outcomes in this population.[3]

Another relevant point is the influence of concomitant pulmonary diseases on clinical outcomes in patients with HPS undergoing liver transplantation (LT). Although these conditions did not affect immediate outcomes, their long-term impact was significant. Koc et al.[7] observed that these patients required prolonged oxygen therapy, suggesting a reduced capacity to resolve hypoxemia. Moreover, they exhibited lower survival rates, reinforcing the need for individualized management and intensive monitoring. Therefore, the presence of respiratory comorbidities should be considered in the therapeutic approach, including adjustments in oxygen therapy, pulmonary function monitoring, and specific transplant and immunosuppression strategies to reduce post-transplant pulmonary complications.[7]

Previous studies have explored peak oxygen consumption in patients with cirrhosis, such as the one by Dharancy et al. (2008, as cited in Pereira et al.[1]), which found that most transplanted patients had peak VO_2 values below a critical threshold, associated with higher mortality. Furthermore, the study by Galant et al. (2013, as cited in Pereira et al.[1]) reported a high mortality rate in patients with alcoholic cirrhosis and peak oxygen consumption below 14 mL/kg, reinforcing its potential value as a clinical marker of disease severity.

Regarding HbCO levels, the study by Sabang et al.[12] demonstrated that liver transplantation (LT) significantly reduced the fraction of HbCO measured by arterial co-oximetry in a sample of non-smoking patients with end-stage liver disease and no chronic pulmonary disease, from a single transplant center. However, when cases with and without HPS were compared, no differences were found in HbCO levels before or after transplantation, nor in the absolute or relative variation of these levels throughout the process. In other words, the change was similar for both groups, regardless of HPS status. This reduction, observed in both groups, suggests that lower CO production may contribute to improved vascular tone, resulting in increased systemic blood pressure and resolution of HPS. Despite the small sample size, the study's findings may indicate that the reduction in HbCO after transplantation enhances the accuracy of pulse oximetry.[12]

Physical inactivity and loss of functional capacity—common conditions in patients with advanced liver disease—may be exacerbated by HPS, compromising post-transplant recovery.[6] Pereira et al.[1] reinforced this hypothesis by showing that patients with cirrhosis exhibit reduced functional capacity, exercise tolerance, and respiratory muscle strength, with even poorer performance observed in the group with HPS. In this context, another study by Pereira et al.[6] demonstrated that patients with cirrhosis and HPS required longer durations of mechanical ventilation, extended stays in the ICU, and prolonged hospitalization following liver transplantation.[6] Moreover, Pereira et al.[1] also observed a greater need for non-invasive ventilation (NIV) in the group of cirrhotic patients with HPS. One explanation for these findings is the difficulty in diagnosing HPS, which may lead to a lack of prior awareness of the condition among ICU professionals. Thus, following extubation, reduced arterial oxygenation may prompt a conservative decision to maintain ventilatory support, delaying weaning in anticipation of oxygenation normalization that does not occur immediately. Additionally, this delay in weaning may be related not only to hypoxemia but also to functional and muscular impairment. Therefore, it is evident that these patients arrive for LT in poorer physical condition, which may lead to increased postoperative complications.[1,6]

CONCLUSION

Liver transplantation (LT) remains the only therapeutic approach with proven curative potential, promoting significant improvement in arterial oxygenation, reversal of pulmonary vascular abnormalities, and restoration of inflammatory homeostasis. The severity of hypoxemia is associated with poorer post-transplant outcomes, underscoring the importance of stratifying HPS when prioritizing candidates for LT. In the pediatric population, however, this relationship differs from that observed in adults.

Although the MELD/PELD system is effective in predicting hepatic mortality, it proves limited in assessing the true severity of HPS. Additionally, patients with HPS exhibit reduced preoperative functional capacity and greater complexity in post-transplant clinical management, with longer hospital stays and prolonged need for ventilatory support.

Finally, strategies aimed at early identification of HPS, appropriate prioritization of patients on the transplant waiting list, and individualized management should be implemented to optimize clinical outcomes and improve post-transplant results—especially in light of the existing gaps in specific knowledge about the syndrome.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Santini MC, Lucena O; **Conception and design:** Santini MC, Schwambach B, Barbosa L, Cardoso L, Ribeiro L, Andrade S, Lucena O; **Data analysis and interpretation:** Santini MC, Schwambach B, Barbosa L, Cardoso L, Ribeiro L, Andrade S; **Article writing:** Santini MC, Schwambach B, Barbosa L, Cardoso L, Ribeiro L, Andrade S; **Critical revision:** Santini MC, Lucena O; **Final approval:** Santini MC.

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