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ORIGINAL ARTICLE

Clinical evolution of pediatric patients with hepatopulmonary syndrome undergoing liver transplantation

Ana Cristina Aoun Tannuri[a], Bruno Jorge Maia Marinho Alves[b], Bianca Ramos[b], Gabriel Victor Lázaro Sobral[b], Pedro Fernandes Ribeiro[b]

Open acess

[a] Professora Titular da disciplina de Cirurgia pediátrica e Transplante hepático e Chefe do serviço de Cirurgia Pediátrica do Instituto da Criança HC-FMUSP;

[b] Faculdade de Medicina da Universidade de São Paulo, SP, Brasil.

Corresponding author
ramosbiad@gmail.com

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ORCID and e-mails of all authors:
[a] ORCID: 0000-0002-5481-032X; ana.tannuri@fm.usp.br;
[b] ORCID: 0009-0007-3596-7130; brunojmmalves@gmail.com;
[c] ORCID: 0009-0004-1111-0210; ramosbiad@gmail.com;
[d] ORCID: 0009-0003-7012-1975; gabriel.victor.lazaro@gmail.com;
[e] ORCID: 0009-0004-6054-3741; pedrofribeiro@alumi.usp.br.

Abstract

Introduction: hepatopulmonary Syndrome contributes to increased morbidity in cirrhotic patients, and liver transplantation is currently the recognized curative treatment. Considering the importance of reducing mortality and morbidity in this group, the objective is to analyze the prevalence of postoperative complications in patients with hepatopulmonary syndrome.

Objective: our study aims to expand knowledge about how hepatopulmonary syndrome influences the postoperative period of these pediatric patients.

Methods: aretrospective analysis was conducted on pediatric patients (children and adolescents up to 18 years old) who underwent liver transplantation at a quaternary hospital between May 2018 and December 2023. Out of 295 pediatric transplants during the evaluated period, 18 were excluded due to retransplantation. Among the remaining 277 cases, 16 (5,77%) had confirmed Hepatopulmonary Syndrome through arterial blood gas analysis or echocardiogram with microbubble study. For patients with Hepatopulmonary Syndrome, were evaluated pre-transplant oxygen arterial pressure level, home oxygen therapy dependency before transplantation, intensive care unit stay duration, hospitalization duration, incidence of vascular and biliary complications, and mortality. Data was analyzed with the chi-square test with Yates correction and considered significant at $p < .05$.

Results: among 3 patients dependent on oxygen before transplantation, one was documented oxygen-free within 3 months post-surgery. Arterial thrombosis was identified in 25% of patients, Portal vein thrombosis in 18,75% and biliary complications occurred in 50% of patients. All these complications were more prevalent in patients with, than without Hepatopulmonary Syndrome ($p = 0.00019$ for biliary complications, $p=0.052$ for arterial and $= 0.01$ for portal complications). The lethality was 37,5%, and 18,7% among those without Hepatopulmonary Syndrome ($p > 0.05$).

Conclusions: pediatric patients with Hepatopulmonary Syndrome undergoing liver transplantation demonstrated a higher incidence of postoperative complications (specifically biliary complications and portal vein thrombosis) when compared with transplant patients without Hepatopulmonary Syndrome.

Keywords: hepatopulmonary syndrome/surgery, postoperative complications, pediatrics; surgery, liver transplantation, mortality.

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Authors summary

Why was this study done?
Due to the lack of data on the postoperative evolution of patients with HPS, the following retrospective study was designed aiming to share results and to expand knowledge about hepatopulmonary syndrome and its impact in postoperative complications after liver transplant.

What did the researchers do and find?
A retrospective analysis of medical records from the last 6 years was carried out, making it possible to find an increase in complications and mortality in these patients.

What do these findings mean?
These findings allow us to infer that the presence of hepatopulmonary syndrome is a risk factor for greater postoperative complications and post-transplant mortality.

INTRODUCTION

Hepatopulmonary Syndrome (HPS) poses a significant challenge in the spectrum of cirrhotic patients, exacerbating morbidity and prompting a critical need for effective therapeutic interventions. Recognized as the prevailing curative measure, liver transplantation (LT) stands as a beacon of hope in addressing this complex syndrome. Despite its major role, a notable gap persists in our understanding of HPS prevalence and progression within the pediatric population undergoing transplantation.

HPS is a pulmonary complication associated with chronic liver disease, characterized by intrapulmonary vascular dilatations that lead to arterial hypoxemia[1]. High portal pressure, the most common etiology of which is liver cirrhosis, is a necessary condition for HPS diagnosis. The genesis of HPS is closely related to the exacerbated production of nitric oxide and the process of angiogenesis, which favors the development of intrapulmonary shunts and a mismatch between ventilation and perfusion mechanisms[2]. From a clinical point of view, HPS is defined by the triad composed of liver disease, hypoxemia and intrapulmonary vascular dilation. HPS ends up resulting in chronic dependence on oxygen therapy, widely impacting the child development of affected children. Its prevalence varies greatly, depending on the diagnostic criteria used, with a wide range from 4% to 47%[2].

In the pediatric LT setting, there is considerable discussion regarding the risk-benefit balance of the procedure in hypoxemic patients. Even today, liver transplantation remains the sole curative measure for patients with a shunt[3]. Swanson *et al.* demonstrated a high morbidity and mortality rate among non-transplanted HPS patients when compared to those who underwent transplantation[4].

In addition to being scarce, recent studies indicate conflicting directions regarding the decision to transplant these patients or not. Therefore, we add another study aiming to shed light on the most appropriate decision for these patients.

This retrospective study approaches the children and adolescents up to 18 years old who underwent liver transplantation at a quaternary hospital (Child and Adolescent Institute of the Faculty of Medicine of the University of São Paulo), spanning the period between May 2018 and December 2023. The study aims to identify the prevalence and clinical evolution of Hepatopulmonary Syndrome in patients that underwent LT.

METHODS

Patients

From May 2018 to December 2023, a total of 295 pediatric liver transplantation (PLT) were performed in patients under 18 years at the Child and Adolescent Institute of the Faculty of Medicine of the University of São Paulo, São Paulo, Brazil. Among these, 18 were retransplantations. The records were analyzed retrospectively through a review of medical records.

At the time of transplantation, 17 patients presented with HPS, and were transplanted due to it, not due to loss of liver function, although they also had some liver dysfunction. One of them was excluded from the analysis due to a diagnosis external to the hospital, with no possibility of categorizing severity and which method was used. 16 patients were included in the study. Data from retransplant patients were corrected so that there was no duplication in the sample. The group of patients without HPS consisted of 261, by removing patients with HPS from the total and removing the duplication of retransplanted patients; and the group of patients with HPS consisted of 16 patients.

Diagnostic methods

The diagnosis of hepatopulmonary syndrome (there is no corresponding code in ICD 10 for this disease) was made based on the elevated alveolar- arterial oxygen gradient (AaO2) ≥ 15 mm Hg, evidence of liver disease and presence of intrapulmonary vascular dilatations identified on microbubble echocardiography, according to the practice guideline from the International Liver Transplant Society[5].

Patients with clinical signs of chronic hypoxia such as digital clubbing and cyanosis, platypnea or patients with cirrhosis were investigated for HPS using pulse oximetry as a screening strategy, where O2 saturation < 96% identifies patients with hypoxemia PaO2 < 70 mm Hg at sea level, with sensitivity of 100% and specificity of 88%[5].

Transthoracic echocardiogram (CE- TT) makes the diagnosis by identifying intrapulmonary shunt. When injected 10-20ml into peripheral vein, agited saline creates microbubbles greater than 10um in diameter that normally do not pass through the pulmonary capillary bed, which has a diameter smaller than 8-15 um[5]. When these bubbles has a delayed appearance in the left heart (three or more cardiac cycles after visualization in the right heart), this demonstrates the presence of a shunt.

Variables studied

The variables in this study included primary diagnosis, pre and post transplant clinical conditions, time of hospitalization and intensive care unit (ICU) stay.

Pre-transplant conditions assessed included arterial PaO2 and home O2 requirement. The measurement of PaO2 was important not only in diagnosis, but also in classifying the severity of the disease (PaO2 < 50mmHg: severe). The need for home O2 was chosen as a way to evaluate the morbidity of these patients and it was data analyzed separately from the severity classification at diagnosis.

Post transplant conditions assessed also included home O2 requirement and the presence of vascular and biliary post-operative complications, data that imply a longer hospital stay and, again, greater morbidity for these patients compared to those without HPS. Post-transplant complications were divided into two groups: vascular complications (hepatic artery thrombosis or portal vein thrombosis) and biliary complications (bile duct stenosis, non-drainage of the bile duct, fistula, dehiscence or bilioma).

Statistical analysis

The comparative data between groups in this article were analyzed using the chi-square test, corrected with Yates correction and considered significant at the level of $p< 0.05$.

Ethical and legal aspects of the research

The study was accepted by the ethics committee (5.835.324)

RESULTS

A total of 16 pediatric patients were evaluated in the study, of which 12 (75%) were diagnosed through microbubble echocardiography and 4 (25%) were diagnosed through arterial blood gas analysis (without echocardiography). Among these patients all of them had a documented arterial blood gas analysis and none were classified as severe (defined by PaO2 < 50mmHg).

The distribution of all patients according to the etiological diagnosis is shown in figure1. Patients requiring oxygen therapy before LT comprised 18,75% (3 patients) of the analysis. Due to the lack of data in the medical records, it was not possible to assess whether all patients weaned from O2, but in our analysis one of them no longer needed home O2.

In the analysis of complications four patients 25% presented with artery thrombosis. Tree patients 18,75% presented with portal vein thrombosis. Eight patients 50% presented with biliary complications 5 late bile duct stenosis and 5 bilioma, fistula or dehiscence. There was coexisting stenosis and fistula in two patients. Among patients with biliary complications.

We also analyzed complications among patients without HPS who were transplanted during the period for the purpose of comparison. From 261 transplants there were 28 vascular complications, 7,6% with artery thrombosis and 3% with portal vein thrombosis; and 33 biliary complications: 8,8% bile duct stenosis, 3,4% bilioma, fistula or dehiscence and 0,38% non drainage of the bile duct; these percentages are relative to the total number of patients without HPS included in the sample. Prevalence of biliary ($p = 0.00019$), arterial ($p=0.052$) and portal ($p=0. 01$) complications was higher in patients with HPS than in patients without HPS.

The average length of hospital stay for patients included in the study was 72.6 days and the average length of ICU stay was 15 days. The lethality in this study was 37,5%. The lethality of patients without SHP undergoing liver transplantation in the period was 18,7%. The comparison between lethality were not significant ($p=0 .13$).

The prevalence of biliary complications, hepatic artery thrombosis and portal vein thrombosis was higher in patients with HPS than without HPS. ($p = 0.00019$, 0.052 and 0.01 respectively).

Diagnostics	Number of patients	Percentage
Bile duct atresia	9	56,25%
Autoimmune hepatitis	2	12,5%
Secondary cirrhosis	1	6,25%
Alpha-1-antitrypsin deficiency	3	18,75%
Portosystemic shunt	1	6,25%

Figure 1: Distribution of patients with HPS according to the etiological diagnosis

	With biliary complications		With Hepatic artery thrombosis		With Portal vein thrombosis	
	N	%	N	%	N	%
Patients with SHP	8	50%	4	25%	3	18,75%
Patients without SHP	33	12,6%	20	7,22%	8	3%

Figure 2: Assessment of the incidence of vascular and biliary complications in study patients, with division of groups between patients with HPS and without HPS

	Deaths	Survival	Lethality percentage
Patients with SHP	6	10	37,5%
Patients without SHP	49	212	18,7%

Figure 3: Comparison of lethality between two groups of transplant patients, patients with HPS and patients without HPS. The lethality of patients with SHP and without SHP was not statistically different

DISCUSSION

In this study, the majority of HPS patients undergoing transplantation were diagnosed with biliary atresia 56,25% and alpha 1 antitrypsin deficiency 18.75%. This proportion of diagnoses in patients with HPS was similar to that found in another Brazilian study conducted in a tertiary hospital in the south of the country which had the purpose of evaluate the prevalence and characteristics of HPS children, in which the most frequent diagnosis in patients with HPS was also biliary atresia 47.5% among the patients studied[6]. The evaluation of these data may suggest a greater association between the diagnosis of biliary atresia (BA) and the progression to HPS or may be related to the greater prevalence of BA in our country or still, may be associated with these patients undergoing portoenterostomy late in Brazil. A problem that was highlighted by Carvalho E *et al.*[6] in 2010 through a multicenter and retrospective study that involved different regions of the country. To resolve this doubt, a new, updated study would be necessary.

Compared to Ceza *et al.*[7], in our study the prevalence of patients with HPS among those eligible for transplantation was lower 6.1%, which may have occurred due to the number of transplants included in the data analysis. Our comparison was made in relation to all transplants performed at the Children's Institute of the Hospital das Clínicas of São Paulo in the last 6 years.

The most relevant aspect of our study was to enable the comparison of data regarding post-operative complications in these patients in relation to other children with indications for transplantation without HPS operated by the same surgical teams. Patients with HPS had a higher rate of postoperative complications than patients without HPS in all types of complications evaluated, which is detailed in figure 2 and it is similar to data already present in international literature. Our study found a prevalence of biliary complications in these patients of 50%, above the variation commonly found in the literature for all pediatric transplant patients, which ranges from 7% to 24%[8-11]. Furthermore, this was the most prevalent type of complication among those analyzed.

In a retrospective study conducted in the Department of Pediatrics of the National University of Taiwan between 1996 and 2021, which also evaluated post-transplant complications in patients with HPS, with similar diagnostic criteria, it was also found that these children had a higher incidence of biliary complications (66%), jaundice (66%) and higher mortality after transplantation (83%)[12]. Although only patients with BA were included in this study, we believe that the comparison is valid since this is the most prevalent diagnosis in our sample. This comparison would be better exposed with an analysis of complications with correction for the etiology of liver disease.

Considering vascular complications, another complication evaluated that also drew attention due to its incidence, which was comparatively greater than twice the incidence in patients without HPS transplanted in the period, was the rate of hepatic arterial thrombosis. In literature, the incidence of hepatic arterial thrombosis varies from 5.7% to 18%[8-10]. In our study, in patients with HPS this rate was 25% while in those without HPS it was 7.22%. Unfortunately, the values found were not statistically significant. In contrast, the incidence of portal

vein thrombosis in patients with HPS was higher than in those without HPS and statistically relevant.

In other words, the rate of this complication was also above the expected average in those with HPS. The most relevant conclusion of our study is to add further evidence to the current literature that these patients present greater postoperative complications, which may encourage the optimization of institutional protocols for identifying HPS and, consequently, more careful preoperative clinical optimization.

Despite raising important hypotheses regarding the comparison of postoperative evolution between transplanted children with and without HPS, our study also has the limitation of being based on an analysis of medical records, where all the necessary information about these patients is not always available and is subject to bias. Another problem found in our analysis is the small number of patients with HPS who were studied, a difficulty that is intrinsic to the topic studied since it is a rare condition, even in a quaternary hospital with a large flow of more specific diseases like ours.

Our data analysis was conducted in June 2024 and data was collected until December 2023, so the minimum survival was at least 6 months. Data on long-term mortality were not included in the analysis; our analysis refers to mortality due to postoperative clinical-surgical complications. The comparative lethality of patients with HPS 37.5% was higher than those without the syndrome 18,7% and the survival rates of these patients were also comparatively lower, shown in figure 3. Our analysis did not find statistical significance in this difference, which points to the need to expand the follow-up time and consequently the number of patients in the study to make a more accurate assessment of lethality. The causes of death found were septic shock, primary organ failure, hemorrhagic/hypovolemic shock, multiple organ failure, COVID, cardiogenic shock, liver failure, pneumonia and other causes associated with underlying diseases. The highest incidence is septic shock with 30%.

CONCLUSION

Our study contributes to knowledge regarding the transplantation of pediatric patients with HPS by showing that in our service, this patients had more postoperative complications such as biliary stenosis, fistula or Bilioma and portal vein thrombosis than patients without HPS in the last 6 years. Our final conclusion corroborates data from other international studies by pointing out that HPS is a risk factor for postoperative complications, even though this continues to be the gold standard treatment and increases the long term quality of life for these patients.

Author Contributions

Ana Cristina Aoun Tannuri, Bruno Jorge Maia Marinho Alves: Designed research/study; Bruno Jorge Maia Marinho Alves, Bianca Ramos: Analysed data. Bianca Ramos, Gabriel Victor Lázaro Sobral, Pedro Fernandes Ribeiro MD: Wrote and reviewed the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Resumo

Introdução: a síndrome hepatopulmonar está associada a maior morbidade em pacientes cirróticos, e o transplante hepático é atualmente o tratamento definitivo para esta condição. Considerando a importância de reduzir mortalidade e morbidade nesse grupo de pacientes, realizamos esse estudo para analisar a prevalência de complicações pós transplante hepático em pacientes com síndrome hepatopulmonar.

Objetivo: nosso estudo visa expandir o conhecimento sobre como a síndrome hepatopulmonar influencia o pós-operatório do transplante hepático dos pacientes com síndrome hepatopulmonar, na população pediátrica.

Método: foi conduzida uma análise retrospectiva em pacientes pediátricos (crianças e adolescentes menores de 18 anos) submetidos ao transplante hepático em um hospital quaternário, entre maio de 2018 e dezembro de 2023. De 295 transplantes pediátricos realizados durante o período, 18 foram excluídos devido retransplante. Dentre os 277 casos restantes, 16 (5,77%) tinham o diagnóstico de síndrome hepatopulmonar confirmado através da gasometria arterial ou do ecocardiograma com estudo de microbolhas. Nos pacientes com síndrome hepatopulmonar foram avaliados a PaO2 pré transplante, a necessidade de oxigênoterapia domiciliar pré transplante, o tempo de permanência em unidade de cuidados intensivos, o tempo de hospitalização, incidência de complicações vasculares e biliares, e mortalidade. Os dados foram analisados a partir do chi-Square test com correção de Yates e considerado estatisticamente significante se p< .05.

Resultados: entre os três pacientes dependentes de oxigênio antes do transplante, um foi documentado como livre da necessidade de oxigênio domiciliar após três meses do transplante hepático. Trombose arterial foi identificada em 25% dos pacientes, trombose de veia porta foi identificada em 18,75% dos pacientes e as complicações biliares foram identificadas em 50% dos pacientes. Todas essas complicações foram mais prevalentes no grupo de pacientes com síndrome hepatopulmonar (P = 0. 000 19 para complicações biliares, P = 0.0 52 para complicações arteriais e P = 0.01 para complicações portais). A letalidade foi de 37.5%, e de 18,75% naqueles pacientes com síndrome hepatopulmonar (p> 0.05).

Conclusão: pacientes pediátricos com síndrome hepatopulmonar que foram submetidos ao transplante hepático tiveram maior incidência de complicações pós-operatórias, especificamente complicações biliares e trombose de veia porta, quando comparados com pacientes que foram submetidos ao transplante hepático e que não possuíam o diagnóstico de síndrome hepatopulmonar.

Palavras-chave: síndrome hepatopulmonar/cirurgia, complicações pós-operatórias, pediatria, cirurgia, transplante hepático, mortalidade.

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