Occurrence of hepatopulmonary syndrome in patients with cirrhosis who are candidates for liver transplantation*

Ocorrência de síndrome hepatopulmonar em pacientes cirróticos candidatos a transplante de fígado

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Abstract

Objective: To determine the occurrence of hepatopulmonary syndrome (HPS) in patients with cirrhosis who are candidates for liver transplantation; to compare demographic, clinical, laboratory, and spirometric characteristics, as well as echocardiography results, arterial blood gas analysis, and severity of liver disease between the groups of patients with and without HPS; and to describe the occurrence of HPS in the subgroup of patients with cirrhosis and schistosomiasis mansoni (mixed liver disease). **Methods:** Between January and November of 2007, we evaluated 44 patients under treatment at the Liver Transplant Outpatient Clinic of the Federal University of Pernambuco *Hospital das Clínicas*, in the city of Recife, Brazil. The diagnostic criteria for HPS were intrapulmonary vascular dilatation, identified by transthoracic echocardiography, and an alveolar-arterial oxygen tension difference ≥ 15 mmHg or a PaO_2 < 80 mmHg. **Results:** The mean age of the patients was 52 years, and 31 patients (70%) were males. The most common cause of cirrhosis was alcohol use. Schistosomiasis was present in 28 patients (64%). Of the 44 patients, 20 (45.5%) were diagnosed with HPS. No significant differences were found between those patients and the patients without HPS in terms of any of the characteristics studied. Of the 28 patients with cirrhosis and schistosomiasis, 10 (35.7%) were diagnosed with HPS. **Conclusions:** In the population studied, HPS was highly prevalent and did not correlate with any of the variables analyzed.

Keywords: Hepatopulmonary syndrome; Liver transplantation; Liver cirrhosis; Hypertension, portal; Schistosomiasis mansoni; Echocardiography.

Resumo

Objetivo: Verificar a ocorrência da síndrome hepatopulmonar (SHP) em pacientes cirróticos candidatos a transplante de fígado; comparar as características demográficas, clínicas, laboratoriais e espirométricas, resultados de ecocardiografia, análise de gases arteriais e da gravidade da doença hepática nos pacientes com e sem SHP; e descrever a ocorrência de SHP no subgrupo de pacientes com cirrose associada à esquistossomose mansônica (doença hepática mista). **Métodos:** Entre janeiro e novembro de 2007, foram avaliados 44 pacientes inscritos no Ambulatório de Transplante Hepático do Hospital das Clínicas da Universidade Federal de Pernambuco, em Recife (PE). Os critérios diagnósticos para SHP foram a presença de dilatações vasculares intrapulmonares, identificadas por ecocardiografia transtorácica, assim como diferença alveoloarterial de oxigênio ≥ 15 mmHg ou PaO_2 < 80 mmHg. **Resultados:** A idade média foi 52 anos, e 31 pacientes (70%) eram do sexo masculino. A causa mais frequente de cirrose foi uso de etanol. A esquistossomose esteve presente em 28 pacientes (64%). Dos 44 pacientes, 20 (45,5%) foram diagnosticados com SHP. Não foram observadas diferenças significativas em relação às características estudadas. No subgrupo de pacientes com cirrose associada à esquistossomose, 10/28 (35,7%) receberam o diagnóstico de SHP. **Conclusões:** A SHP apresentou elevada prevalência nesta população estudada, não sendo observadas associações entre a sua ocorrência e as variáveis analisadas.

Descritores: Síndrome hepatopulmonar; Transplante de fígado; Cirrose hepática; Hipertensão portal; Esquistossomose mansoni; Ecocardiografia.

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Introduction

Hepatopulmonary syndrome (HPS) is defined as a triad, represented by intrapulmonary vascular dilatation (IPVD) associated with an alveolar-arterial oxygen tension difference ($A\text{-}aDO_2$) ≥ 15 mmHg or a PaO_2 < 80 mmHg and liver disease.[1] Although HPS is a common complication of liver cirrhosis,[1-4] it has also been reported in patients with non-cirrhotic portal hypertension (PH).[5-7]

In the northeastern region of Brazil, hepatosplenic schistosomiasis (HSS)—the hepatosplenic form of schistosomiasis mansoni—is considered to be a leading cause of PH.[8] It is known that HSS causes presinusoidal PH through increased blood flow from the splenic vein and increased resistance due to liver fibrosis, without significant destruction of hepatocytes, thus preserving the architecture and function of the liver.[9] Liver fibrosis in HSS, also known as Symmers' fibrosis, is not diffuse and is located in the periportal region.[10,11] A study conducted in Brazil reported that 5 (10.2%) of 49 patients with HSS had HPS without cirrhosis.[5]

Due to PH and the formation of collateral circulation, patients with HSS commonly present with digestive bleeding, requiring blood transfusions. Blood transfusions performed some decades ago resulted in infection with the hepatitis B or C virus; currently, many patients present with mixed liver disease (MLD), defined as HSS accompanied by viral hepatitis.[12,13] There have been no studies investigating the occurrence of HPS in this group of patients.

The objective of the present study was to determine the occurrence of HPS in candidates for liver transplantation; to compare demographic, clinical, and laboratory characteristics, as well as echocardiography results, spirometry results, arterial blood gas analysis, and severity of liver disease (Child-Pugh class and Model for End-Stage Liver Disease [MELD] score) between the groups of patients with and without HPS; and to describe the occurrence of HPS in the subgroup of patients with MLD.

Methods

This was a descriptive study that involved intragroup comparisons. We attempted to evaluate all of the 61 patients who were being treated at the Liver Transplant Outpatient Clinic of the *Hospital das Clínicas da Universidade Federal de Pernambuco* (HC-UFPE, Federal University of Pernambuco *Hospital das Clínicas*) and who were on the waiting list for liver transplantation at the beginning of the study. Between January and November of 2007, data were collected in accordance with the following exclusion criteria: having received a liver transplant before the conclusion of the evaluation; having failed to return for follow-up before the final phase of data collection; and having refused to participate in any of the stages of the study.

Patients were evaluated consecutively in accordance with the demand for treatment at the outpatient clinic. After having given written informed consent, patients were interviewed, all by the same physician, in order to gather information regarding age, gender, date of inclusion on the waiting list for liver transplantation (waiting time), and etiology of liver cirrhosis, as well as history of HSS, lung disease, smoking, platypnea, and dyspnea. Dyspnea was measured by the modified Medical Research Council dyspnea scale.[14] In addition, physical examination was performed in order to screen for ascites, encephalopathy, jaundice, telangiectasias (spider veins), and digital clubbing.

The medical charts were analyzed in order to collect data regarding HSS-related liver impairment, which was determined by an abdominal ultrasound showing Symmers' fibrosis accompanied by positive epidemiology for schistosomiasis, which was defined as "having had contact with river water in endemic areas".[10,11,15]

A total of 10 mL of blood was drawn from the peripheral vein in order to determine levels of albumin, aminotransferases, total bilirubin, and creatinine, as well as the international normalized ratio (INR) of prothrombin time, in order to determine the MELD score and the Child-Pugh classification. In addition, 2 mL of blood were drawn from the radial artery, using the puncture and sample handling techniques recommended by the Brazilian Thoracic Association, for the analysis of pH, $PaCO_2$, PaO_2, and $A\text{-}aDO_2$ with a GEM 3000 blood gas analyzer (Instrumentation Laboratory, Bedford, MA, USA).[16] In addition, $A\text{-}aDO_2$ was calculated by applying a standardized equation,[1] with the patient in the sitting position breathing room

air at sea level. All tests were performed at the Central Laboratory of the HC-UFPE using routine methods.

Concurrently with arterial blood gas analysis, pulse oximetry was performed using a pulse oximeter (Onyx II 9550; Nonin, Plymouth, MN, USA) to determine SpO_2. Spirometry was subsequently performed with a Microlab 3300 spirometer (Micro Medical Ltd., Kent, England) in order to measure FEV_1, FVC, and FEV_1/FVC, the predicted values for these maneuvers being adjusted to the Brazilian population.[17]

Chest X-rays were taken in order to rule out other lung diseases.

Contrast transthoracic echocardiography (TTE; contrast agent, 0.9% saline solution) was performed with an HDI 1500 echocardiograph (Philips Medical Systems, Bothell, WA, USA), in accordance with the recommendations of the American Society of Echocardiography.[18] An upper-limb peripheral vein was punctured, and a three-way stopcock was placed. Two 10-mL syringes with 9.5 mL of the solution were connected to the stopcock. Microbubbles were produced manually by agitating the solution between the two syringes 10 times, and the solution was subsequently injected. This procedure was performed three times in each patient, with an interval between injections in order to ensure that the cardiac chambers were completely free of contrast. The images were acquired simultaneously with the injection of the contrast, with the transducer in the apical four-chamber position and the patient in the left lateral decubitus position. Two specialists, who were only aware that the patients had cirrhosis

Table 1 - Univariate analysis of the demographic characteristics, clinical characteristics, liver disease classification and presence of intrapulmonary vascular dilatation in 44 patients with cirrhosis who were candidates for liver transplantation, according to the presence of hepatopulmonary syndrome. Federal University of Pernambuco *Hospital das Clínicas*, 2007.

Variables	Total	Hepatopulmonary syndrome		OR (95% CI)	p
	n (%)	Positive, n (%)	Negative, n (%)		
Patients	44 (100)	20 (45)	24 (55)		
Age					
≤ 50 years	16 (36)	10 (63)	6 (37)		
> 50 years	28 (64)	10 (36)	18 (64)	0.33 (0.09-1.19)	0.09
Gender					
Male	31 (71)	15 (48)	16 (52)		
Female	13 (30)	5 (38)	8 (62)	0.67 (0.19-2.49)	0.55
Waiting time[a]					
≤ 24 months	20 (46)	8 (40)	12 (60)		
> 24 months	24 (55)	12 (50)	12 (50)	1.50 (0.45-4.98)	0.51
Smoking	8 (18)	5 (63)	3 (37)	2.33 (0.48-11.29)	0.44
HSS	28 (64)	10 (36)	18 (64)	0.33 (0.09-1.19)	0.08
Dyspnea	15 (34)	8 (53)	7 (47)	1.62 (0.46-5.68)	0.45
Ascites	15 (34)	7 (47)	8 (53)	1.08 (0.31-3.76)	0.91
Encephalopathy	10 (23)	4 (40)	6 (60)	1.33 (0.32-5.58)	0.69
Jaundice	7 (16)	3 (43)	4 (57)	0.88 (0.17-4.51)	0.99
Spider veins	6 (14)	4 (67)	2 (33)	2.75 (0.45-16.89)	0.39
Digital clubbing	2 (5)	1 (50)	1 (50)	1.21 (0.07-20.76)	0.99
Child-Pugh class					
A	17 (39)	10 (59)	7 (41)		
B + C	27 (61)	10 (37)	17 (63)	0.41 (0.12-1.43)	0.16
MELD score					
< 15	29 (66)	16 (55)	13 (45)		
≥ 15	15 (34)	4 (27)	11 (73)	0.43 (0.09-1.94)	0.11
IPVD[b]	23 (52)	20 (87)	3 (13)		< 0.001

HSS: hepatosplenic schistosomiasis; MELD: Model for End-Stage Liver Disease; and IPVD: presence of intrapulmonary vascular dilatation. [a]Waiting time for liver transplantation. [b]Diagnostic criterion for hepatopulmonary syndrome.

Table 2 - Mean age, waiting time for liver transplantation, spirometric parameter values, pulse oximetry values, arterial blood gas values and liver disease classification for 44 liver transplant candidates, according to the presence of hepatopulmonary syndrome. Federal University of Pernambuco *Hospital das Clínicas*, 2007.

Variables	Total	Variation	Hepatopulmonary syndrome		p
			Positive	Negative	
	mean ± SD		mean ± SD	mean ± SD	
Age, years	51.77 ± 9.03	29-67	51.15 ± 9.80	52.29 ± 8.51	0.69
Time,[a] months	26.64 ± 11.97	10-63	28.75 ± 13.77	24.87 ± 10.19	0.29
FVC, L	2.95 ± 0.81	1.03-4.74	3.07 ± 0.74	2.85 ± 0.86	0.38
FEV_1, L	2.39 ± 0.59	0.97-3.57	2.53 ± 0.54	2.30 ± 0.63	0.18
SpO_2, %	98.07 ± 1.40	94-100	97.60 ± 1.60	98.45 ± 1.10	0.04[b]
PaO_2, mmHg	87.66 ± 9.28	60-100	83.55 ± 9.48	91.08 ± 7.72	0.006[b]
$PaCO_2$, mmHg	32.15 ± 4.77	21-43	30.60 ± 4.64	33.45 ± 4.56	0.05[b]
A-aDO_2, mmHg	22.07 ± 11.98	0-63	27.87 ± 11.39	17.25 ± 10.37	0.002[b]
Child-Pugh, n	7.55 ± 2.20	5-14	7.20 ± 2.04	7.83 ± 2.33	0.35
MELD, n	14.10 ± 3.56	8-25	13.34 ± 2.95	14.73 ± 3.95	0.20

A-aDO_2: alveolar-arterial oxygen tension difference; and MELD: Model for End-Stage Liver Disease. [a]Waiting time for liver transplantation. [b]Diagnostic criterion for hepatopulmonary syndrome.

and were liver transplant candidates, analyzed the images simultaneously. The images were recorded for reviewed in cases of uncertainty. The test was considered to be indicative of IPVD when contrast was observed in the left atrium after four to six cardiac cycles, after contrast had been observed in the right atrium, during any of the injections, in the absence of intracardiac communication. Intracardiac communication was considered to be present when the contrast was observed in the left atrium for three cardiac cycles following the opacification of the right atrium.[19]

In order to diagnose HPS, we used a criterion that is currently recommended by guidelines published in 2004; the criterion consists of identifying IPVD through TTE, together with changes in arterial blood gases, which were defined as an A-$aDO_2 \geq 15$ mmHg or a $PaO_2 < 80$ mmHg (both adjusted for age).[1] The severity of HPS was classified according to the degree of hypoxemia: mild ($PaO_2 \geq 80$ mmHg); moderate (60 mmHg $\leq PaO_2 < 80$ mmHg); severe (50 mmHg $\leq PaO_2 < 60$ mmHg); or extremely severe HPS ($PaO_2 < 50$ mmHg).[1]

All of the data were submitted to statistical analysis with the program Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). For the quantitative variables, mean, standard deviation, and range were used in order to indicate the variability of the data. The Student's t-test was used in order to compare the means between the groups of patients with and without HPS. For the qualitative variables, we used Pearson's chi-square test or Fisher's exact test, ORs and 95% CIs being calculated.

The study design was approved by the Research Ethics Committee of the Federal University of Pernambuco Health Sciences Center.

Results

Of the 61 patients with cirrhosis who were on the HC-UFPE waiting list for liver transplantation,

Table 3 - Distribution of the etiology of liver disease in 44 patients with cirrhosis who were candidates for liver transplantation. Federal University of Pernambuco *Hospital das Clínicas*, 2007.

Etiology	All patients	Patients with HSS
	n (%)	n (% of the total)
Alcohol	18 (40.9)	10 (22.7)
Alcohol + HCV	3 (6.8)	2 (4.5)
HCV	7 (15.9)	5 (11.4)
HBV	4 (9.1)	2 (4.5)
HCV + HBV	2 (4.5)	2 (4.5)
NASH	2 (4.5)	2 (4.5)
Secondary biliary cirrhosis	2 (4.5)	0 (0.0)
Cryptogenic	5 (11.4)	5 (11.4)
Autoimmune	1 (2.2)	0 (0.0)
Total	44 (100)	28 (64.0)

HCV: hepatitis C virus; HBV: hepatitis B virus; and NASH: nonalcoholic steatohepatitis.

17 were excluded: 6 because they died before undergoing echocardiography; 5 because they declined to participate in the study; 3 because they failed to appear at the outpatient clinic before the final phase of data collection; and 3 because they were transferred to other facilities. Of the remaining 44 patients, 31 (70%) were male (Table 1). The mean age was 52 years (range, 29-67 years), and the mean waiting time for liver transplantation was 27 months (range, 10-63 months; Table 2).

The etiology of cirrhosis in the sample as a whole and in the subgroup of patients also presenting with HSS are shown in Table 3.

Of the 44 patients under study, 20 (45.5%) met the criteria for the diagnosis of HPS (positive TTE results for IPVD and an A-aDO_2 ≥ 15 mmHg or a PaO_2 < 80 mmHg). All 7 of the patients with a PaO_2 < 80 mmHg and IPVD presented an A-aDO_2 ≥ 15 mmHg (Table 4). The classification according to the degree of hypoxemia demonstrated that 13 (65%) of the patients had mild HPS (PaO_2 ≥ 80 mmHg) and 7 (35%) had moderate HPS (60 mmHg ≤ PaO_2 < 80 mmHg). None of the patients had severe or extremely severe HPS.

In order to facilitate comparisons with other studies, other A-aDO_2 cut-off points were used in order to diagnose the syndrome. Those cut-off points can be seen in Table 5.

No significant differences were found between the groups of patients with and without HPS in terms of clinical history or physical examination (Table 1). In addition, no significant differences were found between the groups of patients with and without HPS in terms of the mean age, waiting time for transplantation, or classification of liver disease (Table 2).

Of the 28 patients with MLD, 10 (35.7%) had HPS (A-aDO2 ≥ 15 mmHg and positive TTE results for IPVD; Table 4). Of those, 7 had mild HPS (PaO_2 ≥ 80 mmHg), and 3 had moderate HPS (60 mmHg ≤ PaO_2 < 80 mmHg). When an A-aDO_2 cut-off point of 20 mmHg was used, the frequency of HPS was 25%, compared with 28.6% when the cut-off point was 15 mmHg.

Discussion

Until recently, the diagnostic criteria for HPS were not standardized, which resulted in a wide variation in the reported prevalence of the syndrome, as well as in difficulties in comparing

Table 4 - Demonstration of the alveolar-arterial oxygen tension difference and PaO_2 in 44 patients with cirrhosis who were candidates for liver transplantation and in the subgroup of patients with mixed liver disease. Federal University of Pernambuco *Hospital das Clínicas*, 2007.

Patient	Cirrhosis		Mixed liver disease	
	A-aDO_2, mmHg	PaO_2, mmHg	A-aDO_2, mmHg	PaO_2, mmHg
1			30	80
2[a]	20	90		
3	16	95		
4[a]			34	72
5[a]			28	83
6			24	87
7			4	98
8			2	100
9[a]			33	78
10			24	79
11			12	98
12	27	84		
13[a]	15	90		
14	15	86		
15			11	100
16			22	83
17			14	88
18			22	81
19[a]			37	74
20[a]	20	95		
21[a]	36	76		
22	14	93		
23			14	99
24[a]	38	72		
25[a]	26	77		
26[a]			15	92
27			24	91
28			21	94
29[a]			20	88
30			45	75
31[a]			36	87
32[a]	17	93		
33[a]			22	84
34	5	100		
35			15	97
36	4	97		
37[a]			27	91
38[a]	25	95		
39			0	99
40			26	94
41[a]	30	82		
42			23	88
43[a]			15	92
44[a]	63	60		

A-aDO_2: alveolar-arterial oxygen tension difference. [a]Presence of hepatopulmonary syndrome, defined as an A-aDO_2 ≥ 15 mmHg and positive transthoracic contrast-enhanced (0.9% saline solution) echocardiography results for intrapulmonary vascular dilatation.

Table 5 - Comparison between the present study and others in terms of the frequency of hepatopulmonary syndrome, according to the cut-off point for the alveolar-arterial oxygen tension difference.

$A\text{-}aDO_2$	Present study		Lima et al.[4]		Ferreira et al.[5]	
Cut-off point	n/n	%	n/n	%	n/n	%
20 mmHg	13/44	29.5	9/56	16.0		
16 mmHg	17/44	38.6	15/56	26.8	19/125	15.0
15 mmHg	20/44	45.5				

$A\text{-}aDO_2$: alveolar-arterial oxygen tension difference.

studies.[20] According to the 2004 arterial blood gas standards for the diagnosis of HPS,[1] the frequency of the syndrome in the present study was 45.5%.

A study involving liver transplant candidates and using an $A\text{-}aDO_2$ of 20 mmHg as a cut-off point reported that the occurrence of HPS was 16% (9/56); however, when the $A\text{-}aDO_2$ cut-off point was lowered to 15 mmHg, the frequency of HPS was 27% (15/56).[4] In another study involving liver transplant candidates and using an $A\text{-}aDO_2$ cut-off point of 15 mmHg, the prevalence of HPS was reported to be 15% (19/125).[21]

In the present study, the occurrence of HPS was 45.5% (20/44), 38.6% (17/44), and 29.5% (13/44) when $A\text{-}aDO_2$ cut-off points of 15 mmHg, 16 mmHg, and 20 mmHg, respectively, were used. For all of the different $A\text{-}aDO_2$ parameters analyzed, the occurrence of HPS was greater than that reported in other studies (Table 5).[4,21] The occurrence of MLD in 64% of the patients (Table 1) is one of the factors in which the present study differs from other studies investigating the prevalence of HPS in liver transplant candidates. However, the number of patients was too small to demonstrate that there was an association between this variable and the occurrence of HPS.

In the present study, the diagnosis of the HSS-cirrhosis combination was based on an abdominal ultrasound showing Symmers' fibrosis, together with positive epidemiology for schistosomiasis.[15] The use of liver ultrasound in the diagnosis of HSS has recently increased, since it is a noninvasive method that evaluates practically the entire organ.[10,11] This is superior to needle liver biopsy, which can result in sampling error because it allows the analysis of only a small liver fragment. In the present study, however, we were unable to quantify Symmers' fibrosis in this subgroup of patients due to the concomitant cirrhosis, which leads to a reduction in liver volume and distortion of the liver architecture.[15] The diagnostic, epidemiologic, and ultrasound criteria adopted in the present study allowed us to suggest but not confirm the presence of HSS. Therefore, the presence of HSS can only be confirmed after transplantation, by means of anatomopathological analysis of the liver.

In this context, when the subgroup of patients with MLD was analyzed separately, the occurrence of HPS was 35.7% (10/28), 28.6% (8/28), and 25% (7/28), respectively, when $A\text{-}aDO_2$ cut-off points of 15 mmHg, 16 mmHg, and 20 mmHg were used. To date, there have been no studies investigating HPS in patients presenting with combinations of various PH mechanisms. However, the analysis of studies that evaluated PH patients without cirrhosis reveals that the occurrence of HPS is lower than is that described in patients with cirrhosis. In fact, a study investigating patients with noncirrhotic portal fibrosis and using an $A\text{-}aDO_2$ cutoff of 20 mmHg showed the frequency of HPS to be 8% (2/25).[7] In another study, in which patients with HSS were evaluated and an $A\text{-}aDO_2$ cut-off point of 15 mmHg was used, the occurrence of HPS was 10.2% (5/49).[5]

Taking into consideration that the pathophysiology of PH in HSS differs from that observed in cirrhosis (increased blood flow being a relevant factor in the former and increased resistance being a relevant factor in the latter), the combination of the two conditions might increase the pressure in the portal vein and result in a higher occurrence of HPS. In the present study, the PH triggered by HSS might have been an additional factor for the development of the syndrome, although we were unable to demonstrate differences between the groups of patients with and without HPS in terms of the occurrence of this helminthiasis (Table 1). Underscoring the role of schistosomiasis-related PH (without associated cirrhosis) in the etiology

of HPS, this syndrome has been diagnosed only in patients with the hepatosplenic form, not in those with the hepatointestinal form.[5]

In the present study, no differences were observed between the groups of patients with and without HPS in terms of the demographic and clinical characteristics (Table 1), which is in accordance with the findings reported by other authors.[2,4,22] However, in studies investigating larger samples, digital clubbing, spider veins, and ascites were reported to be associated with HPS.[23,24] It is possible that the number of patients involved in the present study was not sufficient to demonstrate differences that were more significant.

Studies using TTE with saline solution as the contrast agent, together with second harmonic imaging, obtained conflicting results regarding the occurrence of IPVD. This can be explained by differences in the underlying diseases investigated and by variations in echogenicity or in the interpretation of test results.[19] In the present study, the TTE results were suggestive of IPVD in 52% of the patients, which is in accordance with the results of other studies, in which rates ranging from 30 to 56% were reported.[4,25-27]

It is of note that, in the present study, the waiting time for transplantation was long (mean, 27 months). This is similar to that reported for other liver transplant centers before the MELD score came into use as a means of determining the position on the waiting list.[28] It should be highlighted that before the introduction of the MELD scale in Brazil in mid-2006, the position on the waiting list was determined on a chronological (first-come, first-served) basis. A longer waiting time translated to a potential advantage for receiving a transplant, since patients with early-stage liver disease were included in the list.[29]

The present study was the first pulmonary evaluation of these patients after the introduction of MELD, and the sample originally comprised those who were on the chronological waiting list (Table 2). We believe that a longer waiting time would have naturally selected patients with less impaired liver function (although associated with the worsening of PH), and this might have resulted in a higher occurrence of portasystemic shunt, development of IPVD, and, consequently, HPS. However, shunting would have resulted in a reduction in PH, leading to a lower occurrence of cirrhosis complications, such as ascites and digestive bleeding, which are generally associated with death. A recent survey revealed an association between HPS and severe liver disease (MELD) without increased short-term mortality, indirectly suggesting that the syndrome does not lead to death.[21]

Regarding liver function impairment, whether defined by the Child-Pugh class or the MELD score), we found no differences between the groups of patients with and without HPS, which is in accordance with the findings of another study.[4] In fact, HPS has been shown to be more common in patients with milder liver dysfunction (Child-Pugh class A).[30] In contrast, HPS has also been shown to be more common in patients with hepatic changes that were more severe (Child-Pugh classes B and C).[3,21]

In summary, the frequency of HPS in the liver transplant candidates analyzed in the present study was high, even when different A-aDO_2 cut-off points were used. In addition, we found no association between the occurrence of HPS and the variables analyzed. Studies involving larger numbers of patients with cirrhosis, HSS (without cirrhosis), and MLD could confirm these findings.

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