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ORIGINAL PAPERS

Hepatopulmonary syndrome: which blood gas analysis criteria and position should we use for diagnosis?

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ABSTRACT

Introduction: Different blood gas criteria have been used in the diagnosis of hepatopulmonary syndrome (HPS).

Patients and methods: Arterial blood gases were prospectively evaluated in 194 cirrhotic candidates for liver transplantation (LT) in the supine and seated position. Three blood gas criteria were analyzed: classic (partial pressure of oxygen [PaO_2] < 70 mmHg and/or alveolar-arterial gradient of oxygen [A-a PO_2] ≥ 20 mmHg), modern (A-a PO_2 ≥ 15 mmHg or ≥ 20 mmHg in patients over 64) and the A-a PO_2 ≥ threshold value adjusted for age.

Results: The prevalence of HPS in the supine and seated position was 27.8% and 23.2% (classic), 34% and 25.3% (modern) and 22.2% and 19% (adjusted for age), respectively. The proportion of severe and very severe cases increased in a seated position (11/49 [22.4%] *vs* 5/66 [7.6%], p = 0.02). No difference was observed in the pre-LT, post-LT and overall mortality in patients with HPS, regardless of the criteria used.

Conclusion: Obtaining blood gas measurements in the supine position and the use of modern criteria are more sensitive for the diagnosis of HPS. Blood gas analysis with the patient seated detects a greater number of severe and very severe cases. The presence of HPS was not associated with an increase in mortality regardless of blood gas criterion used.

Key words: Cirrhosis. Ascites. Contrast echocardiography. Pulmonary vascular diseases. Macro-aggregated albumin lung perfusion scan and perioperative care.

INTRODUCTION

The hepatopulmonary syndrome (HPS) is characterized by the presence of changes in blood oxygenation levels caused by the presence of intrapulmonary vascular dilations (IPVD) in the setting of a liver disease, usually hepatic cirrhosis (1,2). A decrease in blood oxygenation and the presence of IPVD are diagnostic criteria for this syndrome. HPS prevalence varies widely in the literature between 4 and 32%. This is likely due to the use of different criteria for the diagnosis of decreased blood oxygenation, the method used for the demonstration of IPVD (transthoracic or transesophageal contrast echocardiography or macroaggregated albumin lung scan) and the characteristics of the study population (6-12).

A decreased blood oxygenation is demonstrated by performing an arterial blood gas analysis, although pulse oximetry is also used, especially in HPS screening (3-5). Blood gas criteria with different cutoffs and assessment using both the PaO_2 and A-a PO_2 methods have been used for the diagnosis of HPS. The position of the patient when obtaining blood gas levels has also changed; it is often performed in both the supine and seated/upright position (6-12). Finally, for the diagnosis of HPS, arterial blood gas analyses are usually performed with the patient seated using A-a PAO_2 ≥ 15 mmHg or ≥ 20 mmHg in patients over 64 years of age, while the PaO_2 value was used to stratify HPS severity (1). There is only one previous study that has assessed the influence of different blood gas criteria in estimating HPS prevalence (13). There is no study to date that has analyzed the role of the physical position of the patient when arterial blood gas is extracted in HPS prevalence.

It is important to know the influence of HPS on survival, especially in cirrhotic patients who are candidates for LT. This fact is highlighted in a recent publication that recommended the revaluation of the exception policy of Model for End-Stage Liver Disease (MELD) points in HPS, as previously described (14,15). Existing studies addressing this issue are scarce and have a relatively small sample size (11,12,16). Our group has recently published the results of

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a prospective study in a large group of LT candidates using PaO_2 < 70 mmHg and/or ≥ 20 mmHg PO_2 A-a (17) blood gas diagnosis as a criteria of HPS (1).

The objectives of this study were: a) to analyze the effects of using different blood gas criteria and the position in which arterial blood gases are obtained (supine or seated/upright) in estimating HPS prevalence; and b) to evaluate the influence of the presence of HPS (with different criteria) in pre- and post-LT survival.

PATIENTS AND METHODS

Selection of patients

All adult patients with cirrhosis who were evaluated for a first case of LT at the Hospital Universitario Virgen del Rocío in Seville (Spain) over a period of five years were prospectively included in the study. Candidates evaluated for re-transplantation were excluded. Patients signed an informed consent for inclusion into the study. The study was conducted according to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the hospital. The results presented here are part of a larger study and some of these results have been published previously (17).

Hepatopulmonary syndrome

Blood gas studies

Patients underwent an arterial blood gas analysis while in the supine and seated position; the sample was taken after spending at least 20 minutes in each position. The samples were then analyzed in a gasometer (Gasometer ABL-500, Radiometer, Copenhagen, Denmark) and the A-a PO_2 was calculated using the following formula: A-a PO_2 = [(BP - 47) FIO_2 - $PaCO_2$ / 0.8] - PaO_2 (BP is the barometric pressure, FIO_2 is the fraction of inspiratory oxygen, $PaCO_2$ is the partial pressure of carbon dioxide and PaO_2 is the partial pressure of arterial oxygen). The existence of orthodeoxia was considered when the PaO_2 with the patient seated was reduced by ≥ 5% or ≥ 4 mmHg when compared to supine values.

Transthoracic contrast echocardiography

A transthoracic contrast echocardiogram was performed in patients with an arterial blood gas analysis compatible with the diagnosis of HPS. This included any of the criteria and both the supine and seated positions. The tests were performed by two specialists in cardiology and echocardiography from our hospital using the following method. Two syringes with 10 ml of saline serum were shaken and connected to a three-way valve. This was injected through a 20 G catheter into a vein of the upper limb. An apical four-chamber image was obtained using a variable frequency transducer (2.1-4.2 MHz) with a Philips model E-33 echocardiograph (Royal Philips Electronics, Amsterdam, the Netherlands) for the detection of bubbles at the intra-cardiac level. The result was considered as positive when bubbles were detected in the left chambers between the fourth and sixth beat.

HPS criteria

HPS was defined according to three different blood gas criteria: a) "classic" criteria (PaO_2 < 70 mmHg and/or A-a PO_2 ≥ 20 mmHg); b) "modern" criteria (A-a PO_2 ≥ 15 mmHg or A-a PO_2 ≥ 20 mmHg PO_2 in patients over 64 years), which corresponds to that proposed by the consensus meeting in 2004 (1); and c) "age-adjusted" criteria, where A-a PO_2 is greater than or equal to that corresponding to the age according to the formula (10 + 0.43 x [age – 20]) (18). These criteria apply to the blood gas analysis results obtained in both the supine and seated position. Diagnosis was completed when the presence of bubbles between the fourth and sixth beat was demonstrated by a transthoracic contrast echocardiography TCE and the presence of liver disease in cirrhotic status. Patients were classified into four degrees of severity according to PaO_2: mild (PaO_2 ≥ 80 mmHg), moderate (PaO_2 < 80 mm Hg and ≥ 60 mm Hg), severe (PaO_2 < 60 mmHg and ≥ 50 mmHg) and very severe (PaO_2 < 50 mmHg) (1).

Lung function tests

The patients underwent spirometric studies following the Spanish Society of Pneumology and Thoracic Surgery SEPAR recommendations and the values of a Mediterranean population were taken as a reference. A pneumotachograph spirometer (Masterlab, Erich Jaeger GmbH, Würzburg, Germany) was used for the studies. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and the FEV1/FVC ratio were recorded. The patient was considered to have obstructive lung disease when the FEV1/FVC ratio was less than 70% or when the FEV1 value was less than 80% of the reference value. Restrictive lung disease was considered when the FVC value was less than 80% of the reference value. Mixed lung disease was considered when both of these criteria were satisfied.

Survival analysis

In order to perform survival analysis of the LT waiting list, the date of LT and the date of death or the last visit before the study concluded was used as the date of last contact. Post-LT survival was calculated using the date of death or the last post-LT visit as the last contact date.

Statistical analysis

The continuous variables are expressed as medians and interquartile ranges (IQRs) and categorical variables as numbers (n) and percentages (%). Comparisons between categorical variables were performed using the Chi-squared test or the Fisher's exact test, and comparisons between continuous variables were performed with the Student's t-test or the Mann-Whitney test. The concordance between the diagnostic criteria was assessed using the kappa coefficient (k). The concordance was considered as moderate if the values were between 0.41 and 0.60, good when the values were between 0.61 and 0.80, and very good when between 0.81 and 1. Survival analyses were performed using the Kaplan-Meier method and Cox regression.

RESULTS

A total of 367 patients were included in the study, of which 316 patients were valid for the HPS study. A total of 194 patients underwent arterial blood gas analysis in the supine and seated position and were finally included in the study. Figure 1 shows the outline of the study.

Characteristics of the study population

The final cohort included 194 patients, 146 (75.3%) were male and 48 (24.7%) were female. The median age was 55 years (IQR: 49-59). The etiology of cirrhosis was alcohol in 93 (47.9%), hepatitis C virus (HCV) in 28 (14.4%), HCV and alcohol in 29 (14.9%), hepatitis B virus (HBV) in 9 (4.6%), HBV and alcohol in 12 (6.2%) and other causes in 23 cases (11.8%). The distribution according to the Child-Pugh classification was: class A, 35 patients (18%); class B, 87 (44.8%); and class C, 72 (37.1%). The median MELD index was 14 (IQR: 11-18).

Prevalence and distribution of HPS severity

The prevalence of HPS according to the blood gas criteria used for diagnosis and the position in which the gases are obtained are shown in table 1. HPS prevalence varied between 19.1% and 34%. The age-adjusted criteria and the blood gas analysis obtained with the patient seated were the least sensitive criteria (19.1%). The most sensitive (34%) was the modern criteria when the blood gas analysis was obtained in the supine position. The severity distribution of patients diagnosed with HPS was different depending on the position in which the blood gas analysis was obtained. When it was performed with the patient seated, the proportion of severe and very severe cases was greater than when performed in the supine position, which was statistically significant. The proportion of severe or very severe cases in the classic criteria with blood gas analysis performed in the supine *versus* seated position was 5/54 (9.2%) *vs* 11/45 (24.4%), p = 0.04; for the modern criterion this was 5/66 (7.6%) *vs* 11/49 (22.4%), p = 0.02; and for the age-adjusted criterion this was 5/43 (11.6%) *vs* 11/37 (29.7%), p = 0.04.

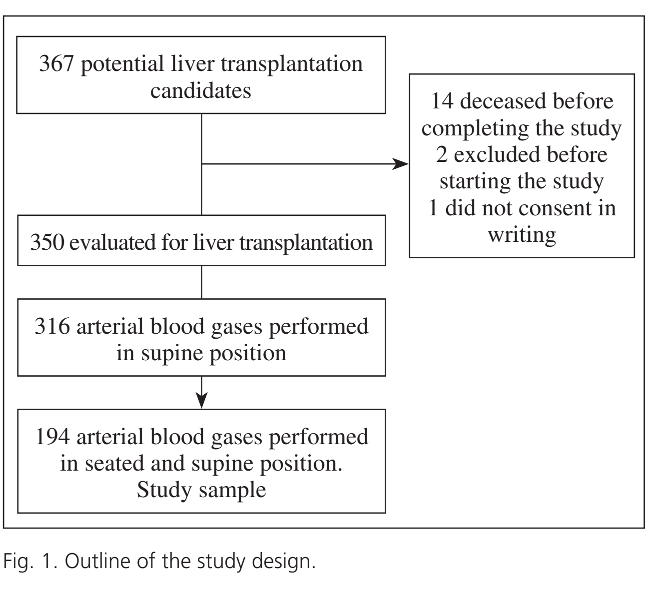

Fig. 1. Outline of the study design.

Concordance between the diagnostic criteria

There was a moderate level of concordance between the different criteria for the diagnosis of HPS (K > 0.6). The concordance was higher when the blood gas analysis criteria that were compared were obtained when the patient was in the same position than when obtained in a different position (Table 2).

Analysis of modern criterion according to its position

The prevalence of HPS using the modern criterion with the patient seated was 25.3% and 34% when in the supine position. The concordance between both criteria was moderate (K = 0.69). When the blood gas analysis was performed with the patient seated, four cases were diagnosed which were not diagnosed in the supine position. Three (75%) of these cases had orthodeoxia, three (75%) were mild and one (25%) was moderate; two (50%) patients died on the LT waiting list. Twenty-one cases were diagnosed with gas analysis performed in the supine position that were not diagnosed in an upright position. None of these cases had orthodeoxia, 17 (80.9%) cases were mild and four (19.1%) cases were moderate. Six (28.6%) of these died, three of them during the pre-LT period and three post-LT. The characteristics of patients with a different HPS diagnosis according to the position in which the gases were obtained are shown in table 3.

Pre- and post-LT survival

No decrease in survival among HPS patients was observed, neither in the pre-LT period or the post-LT period, regardless of the blood gas criteria used and the position in which arterial blood gases were obtained. Figure 2 shows the Kaplan-Meier survival curves for the pre- and post-LT periods using the modern criterion with the patient seated and the classic criteria in a supine position.

DISCUSSION

This is the first study to analyze the influence of the physical position of the patient when obtaining arterial

Table 1. Prevalence and distribution of the severity of HPS according to different blood gas criteria

Patient position	*Criteria*	*(HPS n, %)*	*Mild*	*Moderate*	*Severe*	*Very severe*
Supine	Classic	(n = 54, 27.8%)	27 (50%)	22 (40.7%)	4 (7.4%)	1 (1.9%)
	Modern	(n = 66, 34%)	39 (59.1%)	22 (33.3%)	4 (6.1%)	1 (1.5%)
	According to age	(n = 43, 22.2%)	16 (37.2%)	22 (51.2%)	4 (9.3%)	1 (2.3%)
Seated	Classic	(n = 45, 23.2%)	13 (28.9%)	21 (46.7%)	8 (17.8%)	3 (6.7%)
	Modern	(n = 49, 25.3%)	17(37.7%)	21 (42.9%)	8 (16.3%)	3 (6.1%)
	According to age	(n = 37, 19.1%)	7 (19.9%)	19 (51.4%)	8 (21.6%)	3 (8.1%)

Table 2. Concordance between the different blood gas criteria according to patient position

		Classic supine	*Modern seated*
Supine	Classic	K = 1	K = 0.69
	Modern	K = 0.85	K = 0.69
	According to age	K = 0.82	K = 0.65
Seated	Classic	K = 0.71	K = 0.94
	Modern	K = 0.69	K = 1
	According to age	K = 0.67	K = 0.82

blood gas analysis in the diagnosis and prognosis of HPS in a large cohort of cirrhotic patients evaluated as candidates for LT. It also provides information on HPS survival in patients diagnosed with different blood gas criteria.

Prevalence of HPS

The prevalence of HPS reported in different studies varies widely. The prevalence depends on the group of patients studied and whether systematic screening is carried out or only symptomatic patients are studied, blood gas criteria and the method used for the demonstration of IPVD. In an attempt to unify criteria and therefore standardize the study of HPS, in 2004 the ESR Task Force proposed the following criteria for the diagnosis of HPS: the presence of liver disease, A-a $PO_2 \geq 15$ mmHg or A-a$PO_2 \geq 20$ mmHg in patients over 64 years, an arterial blood gas analysis obtained with the patient seated and the demonstration of IPVD by transthoracic contrast echocardiography (1). The suitability of these criteria had not been previously assessed, with the exception of a study by Schenk et al. (13).

This study showed that the blood gas criteria proposed by the ESR Task Force (modern criterion) had the highest prevalence of HPS (34%), greater than the classic criteria (27.8%) and the age-adjusted criteria (22.2%) when the blood gas analysis was performed in the supine position. In the seated position, the results were 25.3%, 23.2% and 19.1%, respectively. These findings are in accordance with those of Schenk et al., although less prevalent as the criteria are not the same. The prevalence of HPS was 32% when the cutoff for A-a PO_2 was ≥ 15 mmHg, 31% when A-a PO_2 > 20 mmHg and 28% when A-a PO_2 was calculated according to age in the prospective study of 98 patients with the blood gas analysis performed with the patient seated. The prevalence was also lower in this study when PaO_2 was used instead of A-a PO_2 for the diagnosis of HPS. These data show that when reducing the cutoff value of A-a PO_2, the sensitivity increases and thus changes in blood oxygenation are detected and, together with a positive echocardiography, HPS is diagnosed, which results in an increase in prevalence.

This study showed that when the blood gas analysis is performed in the supine position, HPS prevalence is higher than when performed with the patient seated, regardless of the criterion used. This finding had not been previously reported and may seem paradoxical. When HPS was first defined, orthodeoxia was found to be a characteristic phenomenon of HPS (19). This may be the reason why performing blood gas analysis with the patient seated as a standard method for the diagnosis of HPS was proposed. However, subsequent studies have reported a prevalence of orthodeoxia of around 25-30% in HPS patients (17,20). Moreover, the same prevalence among patients with and without HPS was observed. Thus suggesting that the presence of orthodeoxia is not characteristic of this syndrome as was previously thought, at least in mild to moderate cases, which represents the majority of HPS patients (17). Thus, in order to obtain the most sensitive criteria for HPS diagnosis, gas analysis should be performed in the supine position.

Distribution of HPS severity

In this study, the distribution of severity was modified according to the position in which the gases were obtained. The proportion of severe and very severe cases increased when arterial blood gas analysis was obtained when the patient was seated. This observation is useful because it allows us to adequately compare studies. Using the same criteria and the same blood gas position (seated modern criterion), we observed that the severity distribution in our cohort was similar to that of Deberaldini et al., with a clear predominance of mild and moderate cases as opposed to severe and very severe ones (21).

Table 3. Patient characteristics that differ in HPS diagnosis according to the modern criteria

	SHP supine	*SHP seated*	*Sex*	*Age*	*Etiology*	*Child Pugh*	*MELD*	*PaO_2 supine*	*PaO_2 seated*	*A-a PO_2 supine*	*A-a PO_2 seated*	*Orthodeoxia*	*Respiratory pathology*	*Death*
1	No	Yes	F	59	Alcohol	11	21	113	86	0	18	Yes	No	No
2	No	Yes	F	61	Alcohol	8	12	95	92	9	16	No	No	Yes
3	No	Yes	M	57	HBV	10	18	87	77	13	24	Yes	Yes	No
4	No	Yes	M	65	Alcohol	10	14	96	87	14	20	Yes	No	Yes
5	Yes	No	F	54	Other	10	19	85	91	16	12	No	No	Yes
6	Yes	No	M	52	Alcohol	10	22	90	95	16	12	No	No	No
7	Yes	No	F	57	HCV	10	19	93	100	16	10	No	No	No
8	Yes	No	M	63	Alcohol	11	20	90	104	24	10	No	No	No
9	Yes	No	M	44	HBV	6	10	85	93	16	9	No	No	No
10	Yes	No	M	52	Alcohol	12	25	80	92	17	8	No	No	Yes
11	Yes	No	M	56	Alcohol	12	17	88	104	19	7	No	No	Yes
12	Yes	No	M	54	Alcohol	9	16	89	106	21	6	No	No	Yes
13	Yes	No	M	59	Alcohol	10	20	83	104	22	4	No	No	Yes
14	Yes	No	M	46	ALC/HCV	11	23	96	115	16	0	No	No	No
15	Yes	No	F	46	Other	8	14	87	119	21	0	No	Yes	Yes
16	Yes	No	M	63	Alcohol	10	17	89	118	23	0	No	No	No
17	Yes	No	M	46	Alcohol	10	17	86	109	33	15	No	No	No
18	Yes	No	M	49	ALC/HCV	9	16	93	102	21	12	No	No	No
19	Yes	No	F	62	Alcohol	10	21	81	98	28	12	No	No	No
20	Yes	No	M	54	Alcohol	6	13	76	99	49	11	No	No	No
21	Yes	No	M	62	ALC/HCV	5	8	70	97	31	9	No	Yes	No
22	Yes	No	M	44	Alcohol	8	7	87	103	22	6	No	No	No
23	Yes	No	M	40	ALC/HCV	8	13	86	100	17	5	No	No	No
24	Yes	No	F	61	Other	7	12	75	104	29	3	No	No	No
25	Yes	No	F	36	Other	10	19	77	111	34	0	No	No	No

F: Female; HPS: Hepatopulmonary syndrome; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALC: Alcohol; M: Male; MELD: Model for End-Stage Liver Disease; PaO_2: Partial pressure of arterial oxygen; A-a PO_2: Alveolar-arterial oxygen gradient.

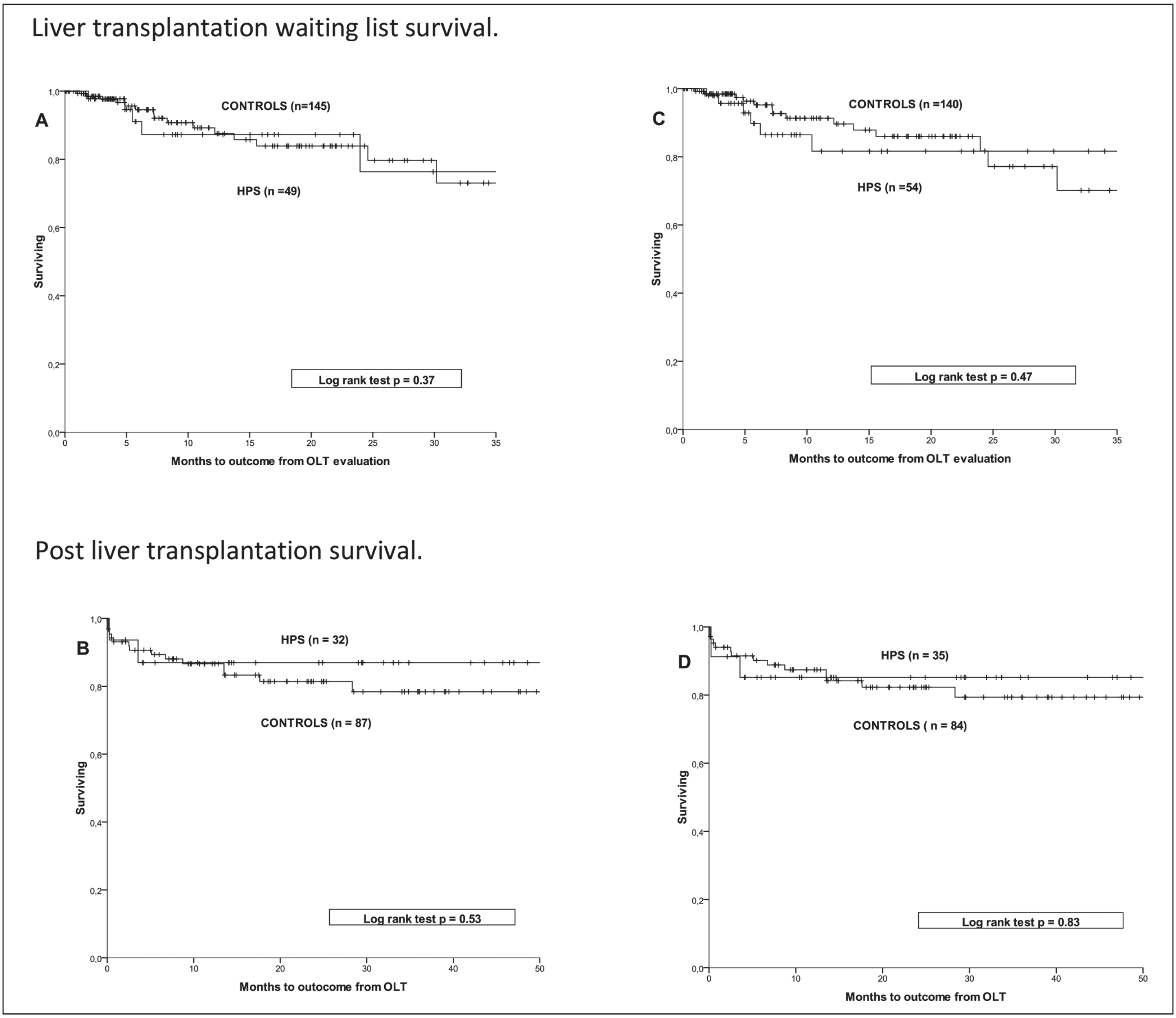

Fig. 2. Survival curves in patients with hepatopulmonary syndrome and without hepatopulmonary syndrome (controls) according to modern criteria in the upright position (A-B) and classic criteria in the supine position (C-D).

This supports the implementation of arterial blood gases analysis with the patient seated, as more severe and very severe cases are detected in this way. It has been reported that patients with HPS with a $PaO_2 < 50$ mmHg and a cerebral uptake in a macro-aggregated albumin lung scan greater than 20% have a higher post-LT mortality (16,22,23), although other studies have not confirmed this. This finding has recently been corroborated by the analysis of HPS patients of the UNOS database (United Network for Organ Sharing). In this study, a higher post-LT mortality was observed in patients with a $PaO_2 < 50$ mmHg as well as in the multivariate analysis with a $PaO_2 \leq 44$ mmHg (14). If patients with very severe HPS also have a higher mortality and are more frequently diagnosed when performing blood gas analysis with the patient seated, this should be the position of choice for the diagnosis of HPS as it is has the greatest clinical impact for the patient.

Pre- and post-LT survival

In this study we did not observe a lower survival rate in HPS patients either on the active liver transplant waiting list (pre-LT) or post-LT, regardless of the criteria used and without adding exceptional MELD points in HPS patients. We have previously reported the same findings but using a different diagnostic criteria for HPS (classic criterion in supine) to that currently recommended (modern standard seated) (17). In this study of a smaller cohort of HPS patients, no differences in mortality were found when using the modern criterion.

This is the first study to examine the influence of the physical position of the patient when the blood gas analysis is obtained for diagnosis and the distribution of HPS severity. It is also the first prospective study to compare survival during the pre- and post-LT period in HPS patients with different diagnostic blood gas criteria. These findings have implications in terms of the diagnosis and prognosis of HPS. However, this study has several limitations. First, the number of patients in the cohort is low, although it is one of the largest in the current literature. Second, the study was conducted in a single center, which therefore limits its application to other populations with other ethnic or geographic characteristics. However, this has enabled the implementation of a strict protocol and unified diagnosis of HPS in a large population of candidates evaluated for LT. In this study we have found arguments in favor of performing blood gas analysis in both positions, although definitive conclusions cannot be drawn. A greater number of severe or very severe cases which may have a greater clinical relevance are detected in the seated position. Multicentre and well recorded studies would be required to determine when to start HPS screening, how to do it and the diagnosis criteria to apply, as well as the impact on these patients.

In conclusion, we found that the position at which arterial blood gas analysis and blood gas criteria are used for the diagnosis of HPS influences the prevalence and distribution of the severity. The prevalence is lower when the gases were obtained with the patient seated but the proportion of severe and very severe patients increased. The blood gas criteria currently proposed as a standard is the most sensitive. Regardless of the criteria used, the presence of HPS is not associated with increased mortality neither for patients on the waiting list for liver transplantation or post-LT. Further studies are required to determine what criteria should be used for the diagnosis of HPS.

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