Hepatopulmonary Syndrome and Post-Liver Transplantation Complications: A Case-Control Study

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ABSTRACT

Background: Although liver transplantation (LT) improves survival in cirrhotic patients with hepatopulmonary syndrome (HPS), few data exist concerning post-operative complications in these patients.

Objective: To compare complications after LT between patients with and without HPS.

Methods: In a case-control study, we retrospectively analyzed all patients who underwent LT in our center from January 2010 to July 2016. We compared cases of identified HPS to controls matched for age, MELD score, comorbidities, red blood cells transfused, and highest dosage of norepinephrine perfused during transplantation.

Results: Among 451 transplanted patients, we identified 71 patients with HPS who could be analyzed. We found a significantly (p<0.001) higher number of post-operative complications in patients with HPS (median 5 *vs* 3), with more occurrence of cardiac, infectious and surgical complications than in the controls: 39.4% *vs* 12.7% (p<0.001), 81.7% *vs* 49.3% (p<0.001), and 59.2% *vs* 40.1% (p<0.029), respectively. There were also more ICU readmissions at 1 month among HPS patients (10 *vs* 1, p=0.01). There was no significant difference concerning ventilation data, lengths of ICU or hospital stay (8.5 [range 3–232] and 32 [14–276] days, respectively on the whole cohort) and death in the ICU (4.2% on the whole cohort). The 1-year survival was higher in HPS patients (94.4% *vs* 81.1%, p=0.034); there was no difference in 5-year survival.

Conclusion: HPS patients seem to have a higher number of complications in the first month following LT.

KEYWORDS: Liver transplantation; Liver cirrhosis; Hepatopulmonary syndrome; Post-operative complications

INTRODUCTION

Hepatopulmonary syndrome (HPS) is defined as a triad of chronic liver disease, arterial hypoxemia and evidence of intrapulmonary vascular dilatations [1]. It occurs in 4%–45% of liver transplantation (LT) candidates, depending on the criteria used to define the arterial hypoxemia [2, 3]. Without LT, patients with HPS have a higher mortality rate than those without HPS [4]. Several studies show that HPS is an independent risk factor for mortality. Although HPS was initially considered a contraindication for LT, when severe hypoxemia was present, the operation appears to be the only effective therapy with mostly complete reversal even in the most severe forms [5]. LT improves HPS survival with a 5-year survival rate of 76% *vs* 23% in HPS patients who do not undergo LT [6].

The impact of HPS on long-term mortality

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following LT remains controversial. Whereas some studies (mainly small non-comparative series [4, 7, 8]) show that HPS patients have a higher morbidity, latest studies report similar mortality following LT in patients with or without HPS even when preoperative p_aO_2 is ≤50 mm Hg [9, 10].

A better knowledge of HPS patient outcomes after LT could influence graft allocation, since there is currently a tendency to attribute better grafts to patients experiencing higher morbidity.

Therefore, the objective of our study was to compare the post-operative outcome in patients with and without HPS following LT, in terms of complications, ventilation parameters, lengths of stay and mortality.

MATERIALS AND METHODS

We conducted a case-control study from January 2010 to July 2016. The study was approved by Comité de Protection des Personnes, Centre de Recherche Clinique du Groupement Hospitalier Nord, Hôpital de La Croix Rousse, Lyon, France. All patients gave their non-opposition. The study was conducted according to good clinical practice standards and the Helsinki declaration. It was registered on clinicaltrials.org (NCT03092401).

Population

We retrospectively analyzed a cohort of all patients who underwent LT from January 1, 2010 to July 31, 2016 at the Hospices Civils de Lyon. We included all patients aged 18 and above who underwent LT for cirrhosis with a graft from donors after brain death. We excluded patients who underwent a double transplantation (liver-kidney, liver-heart) or a re-transplantation and patients with missing data for the matching criteria.

Peri-operative Procedure

Surgical technique used portocaval anastomosis in most cases, piggy back technique for caval anastomosis, and for biliary anastomosis choledochocholedochostomy or choledochojejunostomy (in case of pre-operative biliary disease or peri-operative observation of size mismatch). All patients received anesthesia induction with propofol, remifentanil, and cisatracurium. Anesthesia was maintained with desflurane, remifentanil, and cisatracurium. Antibiotic prophylaxis was piperacillin and a personalized prophylaxis adapted to a patient's own ecology in case of history of biliary infections and colonization with multidrug resistant bacteria. Hemostasis was monitored using ROTEM®. Peri-operative hemodynamic monitoring was achieved by transesophageal echocardiography. Immunosuppression was based on corticosteroids, mycophenolate mofetil and tacrolimus. Patients were monitored for the first five post-operative days with daily transthoracic echocardiography, pulmonary ultrasound and hepatic Doppler.

Primary and Secondary Outcomes

HPS was defined as an association of cirrhosis, hypoxemia with a p_aO_2 <80 mm Hg on room air and intrapulmonary vasodilatations diagnosed by contrast transthoracic echocardiography and/or a 100% oxygen method. Contrast echocardiography was performed transthoracically in the 4-chambers window with a semiquantitative grading as described by Vedrinne, *et al* [11]. Hundred percent oxygen technique consisted of a calculation of shunt based on measured p_aO_2 and p_aCO_2 in patients breathing 100% dry oxygen, assuming an arterial-venous oxygen content difference of 5% volume [12]. An extent of shunt above 5% was considered "positive."

We considered early complications (within one month following surgery) and late complications (within one year). Post-operative complications were included *cardiac complications*, defined as cardiogenic shock, myocardial infarction, left ventricular systolic dysfunction, elevation of left ventricular filling pressure, pulmonary hypertension, or other complications; *respiratory complications* that included acute respiratory distress syndrome (ARDS), pulmonary edema, pneumonia, or pleural effusion; *surgical complications* including peritonitis, perforation, hemoperitoneum, ileus, evisceration, hepatic artery stenosis and thrombosis,

portal vein stenosis and thrombosis, splenic vein thrombosis, biliary leak and stricture, bilioma, or cholangitis; *infectious complications* including septic shock, bacteremia, peritonitis, pneumonia, septic liver, cholangitis, wound infection, fungal infection; *neurological complications* including hemorrhage, stroke, seizures, confusion; *nephrological complications* including need for renal replacement therapy; and *acute cellular rejection*.

Data Collection

Data were collected from hospitalization records. We collected demographic and cirrhosis data, comorbidities, pre-operative evaluation (biology, functional lung tests, transthoracic echocardiography, contrast echocardiography and/or 100% oxygen technique) and peri-operative data (ischemic duration, surgical techniques, blood products transfusions, volume of fluid perfused and maximal norepinephrine dosage, *etc*). Data were collected during the early post-operative period (within one month following transplantation) and until one year after transplantation. Data concerned complications, mechanical ventilation, oxygen therapy, biology, lengths of ICU and hospital stay, ICU and hospital readmissions, date of oxygen weaning, complications and death at one-year post-transplantation.

Statistical Analysis

To face the lack of randomization, a propensity score based on a logistic regression model was calculated for each patient. Five variables known for their association with post-operative complications were entered into the model: age, MELD score on transplantation day, number of RBC units transfused during transplantation, norepinephrine maximal dosage during transplantation, and number of comorbidities among cardiovascular (coronary artery disease, cerebrovascular disease), respiratory (COPD, asthma), renal (need for renal replacement therapy before transplantation or chronic renal insufficiency defined as a creatinine clearance <60 mL/min according to renal function tests or calculated with MDRD formula), diabetes and obesity. Once the propensity scores were estimated, HPS patients were matched to controls (1:1 ratio) selecting for each HPS patient a control with the nearest propensity score.

Results are expressed as proportions (percentages), means and standard deviations or medians and range, as appropriate. All continuous variables were tested for normality. Comparisons between groups were performed with *Student's t* test or Wilcoxon test for continuous variables depending on normality and with χ^2 or Fisher exact test for categorical variables. Relationship between post-operative complications and percentage of shunt on 100% oxygen technique were assessed with Pearson's coefficient. We used linear and Cox regression analyses to investigate which variables were independently associated with post-operative complications and one-year mortality, respectively. A p value <0.05 was considered statistically significant. All analyses were performed with IBM® SPSS® Statistics ver 19.0 for Windows® (IBM Corp. Armonk, NY, USA) and *R* (*R* Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From January 2010 to July 2016, 451 patients underwent LT in our center. After applying the inclusion and exclusion criteria, 290 patients left for analysis, 71 of whom were diagnosed with HPS. They were matched to 71 controls from the 219 potential controls (Fig 1). When including patients who were dropped from the waiting list during this period, we came to a prevalence of HPS in our LT waiting population of 10%.

The median age of our population was 58 (range: 53–63); the median MELD score was 19 (range: 14–26). Sixty-nine (48.6%) patients had hepatocellular carcinoma. Pulmonary and cardiovascular comorbidities were present in 39% and 40% of patients, respectively, with no difference between groups. The median duration of transplantation was 408 (range: 339–495 minutes); the median cold ischemia, warm ischemia and anhepatic phase times were 430 (range: 360–513), 41 (35–52), and 90 (65–127) minutes, respectively. The median

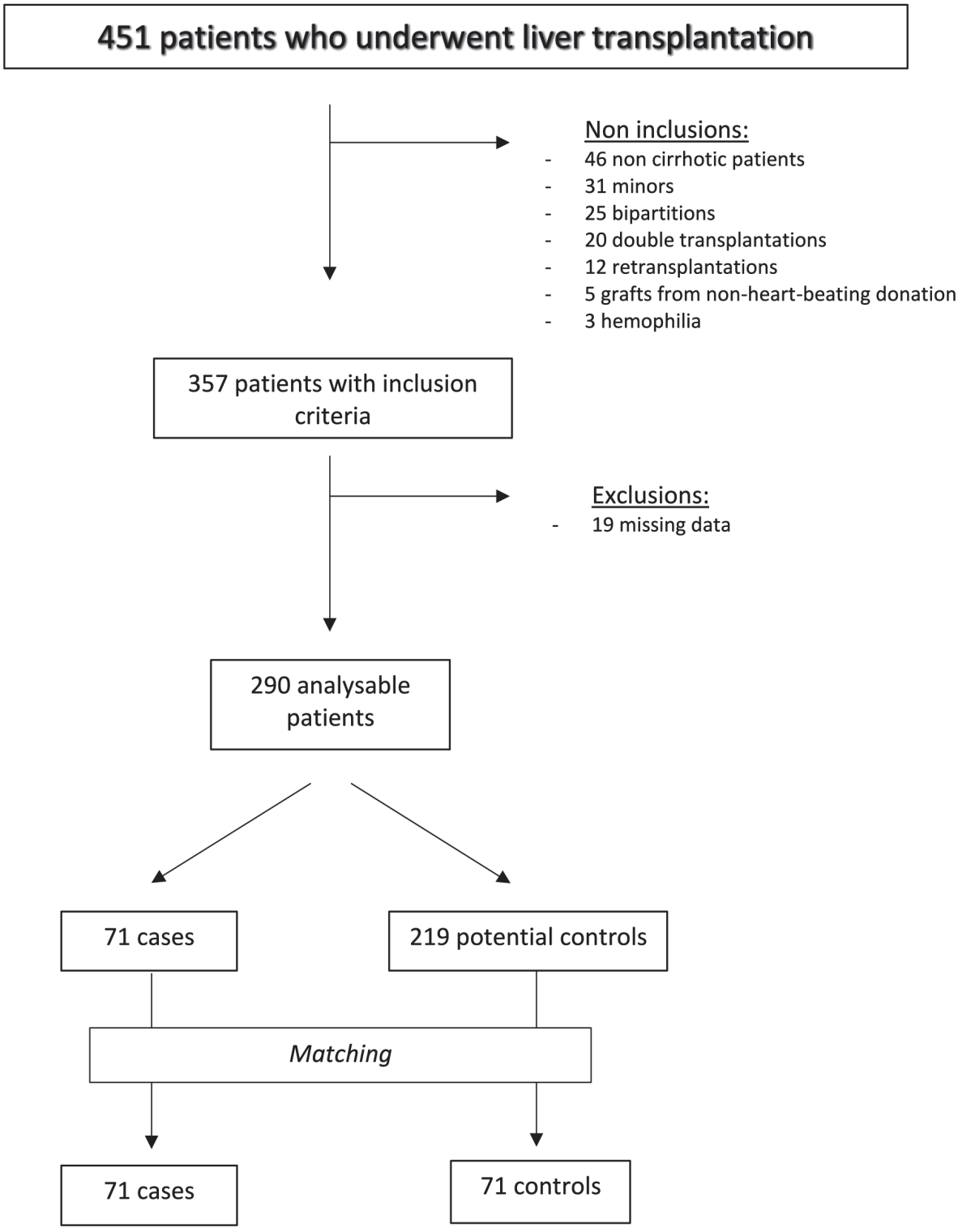

Figure 1: Flow chart

numbers of RBC and FFP packs transfused were 3 (range: 1–6), and 3 (0–6), respectively; there was no difference between groups. The median lengths of ICU and hospital stay were 8.5 (range: 6–17), and 32 (23–49) days, respectively. The median number of post-operative complications at one month (all causes considered) was 4 (range: 2–6). The ICU and one-year mortality were 4.2% and 11.2%, respectively (Table 1).

Table 1: Pre- and intra-operative data of cases and controls expressed as numbers (%) or median [range], unless otherwise specified

Variable	HPS	Controls	p value
Sex (M/F)	52/19	57/14	0.320
Age (yrs)	58 [52–62]	59 [26–63]	0.336
BMI	26 [23–29]	26 [23–29]	0.879
Causes of cirrhosis			
OH	56 (79%)	45 (63%)	0.042
HBV/HCV	14 (20%)	21 (30%)	0.173
NASH	11 (15%)	10 (14%)	0.813
Other	17 (24%)	10 (14%)	0.134
MELD	19 [14–25]	19 [14–26]	0.483
Comorbidities			
COPD/asthma	30 (42%)	25 (35%)	0.389
Diabetes	19 (27%)	21 (30%)	0.709
Cardiovascular	24 (30%)	33 (46%)	0.123
Hypertension	21 (30%)	29 (41%)	0.160
Renal	19 (27%)	20 (28%)	0.851
Obesity	18 (25%)	16 (23%)	0.694
Preoperative evaluation			
Factor V	40 [27–65]	47 [32–74]	0.007
p_aO_2 (mm Hg) (n=131)	71 [62–75]	76 [69–89]	<0.001
SpO_2 (%)	95 [92–96]	97 [96–98]	<0.001
Graft data			
DRI	1.78 [1.45–2.00]	1.84 [1.52–2.10]	0.285
Cytology			
Fibrosis	8 (11%)	14 (20%)	0.190
Steatosis	0 [0–25]	0 [0–5]	0.036
Necrosis	45 (63%)	56 (79%)	<0.001
Anoxia	3 (18%)	17 (24%)	<0.001
Conservation lesions	17 (24%)	23 (32%)	0.400

OH: ethanol; HBV/HCV: hepatitis B and C; NASH: nonalcoholic steatohepatitis; MELD: model for end-stage liver disease; COPD: chronic obstructive pulmonary disease; p_aO_2: partial pressure in arterial blood; SpO_2: arterial oxygen saturation measured by pulse oximetry

Concerning the 71 HPS patients, the diagnosis was established with the contrast echocardiography for 27 patients and the 100% oxygen method for the remaining 44. The mean pre-operative p_aO_2 was 68.7 mm Hg; the mean shunt was measured at 9.7% with the 100% oxygen method and grade 3 with contrast echocardiography. Ten patients needed home oxygen therapy before LT with a median oxygen flow of 4 (range: 2–4) L/min. The recovery rate after LT was 90% with a median delay for oxygen weaning of 169 (range: 7–400) days.

We identified a higher number of early post-operative complications in patients with HPS (median of 5.9 *vs* 3.7, p<0.001) (Table 2). Patients with HPS had more frequent cardiac, infectious and surgical complications than the controls (39.4% *vs* 12.7%, p<0.001; 81.7% *vs* 49.3%, p<0.001; and 59.2% *vs* 40.1%, p=0.029, respectively). Patients with HPS had a higher

Table 2: Primary and secondary outcomes in cases and controls. Results are expressed as number of patients presenting with the complication unless otherwise specified.

Variable	HPS	Controls	p value
Total complications at 1 month	5 [3-9]	3 [1-5]	<0.001
Cardiac complications	28 (39%)	9 (13%)	<0.001
MI	1 (1%)	0 (0%)	1
LV function alteration	10 (14%)	2 (3%)	<0.001
Cardiogenic shock	9 (13%)	3 (4%)	<0.001
Pulmonary hypertension	7 (10%)	3 (4%)	0.001
Acute pulmonary edema	19 (27%)	4 (6%)	<0.001
Pulmonary complications	56 (79%)	50 (70%)	0.335
Surgical complications	42 (59%)	29 (41%)	0.029
Digestive complications	20 (28%)	12 (17%)	0.108
Biliary complications	25 (35%)	11 (15%)	0.007
Vascular complications	24 (34%)	14 (20%)	0.058
Acute cellular rejection	12 (17%)	7 (10%)	0.324
Infectious complications	58 (82%)	35 (49%)	<0.001
Pneumonia	21 (30%)	13 (18%)	0.168
Peritonitis	13 (18%)	4 (6%)	<0.001
Septic liver	7 (10%)	7 (10%)	1
Acute cholangitis	24 (34%)	7 (10%)	<0.001
Wound infection	3 (4%)	2 (3%)	0.104
Septicemia	23 (32%)	15 (21%)	0.255
Septic shock	13 (18%)	6 (8%)	0.006
Fungal infection	16 (23%)	3 (4%)	<0.001
Other infections	37 (52%)	19 (27%)	0.314
Neurological complications	27 (38%)	28 (39%)	1
Nephrological complications	23 (32%)	22 (31%)	1
Ventilation data			
Extubation delay	12 [6-27]	12 [6-24]	0.822
Reintubation	13 (18%)	10 (14%)	0.649
Duration of mechanical ventilation (days)	0.6 [0.25-2]	0.5 [0.25-1.9]	0.643
Mechanical ventilation at day 7	8 (11%)	8 (11%)	1
Duration of CPAP + NIV (days)	5 [3-10]	5 [3-8]	0.285
Oxygen therapy at 1 year	1 (1%)	0 (0%)	0.338
Hospitalization data			
ICU length of stay (days)	8.5 [5-16.5]	8.5 [6-16]	0.718
ICU readmission at 1 month	10 (14%)	1 (1%)	0.008
Hospital length of stay (days)	35 [25-53]	31 [23-42]	0.156
Late complications			
Retransplantation	2 (3%)	4 (6%)	0.318
Total complications at 1 year	1 [0-3]	1 [0-2.5]	0.621
ICU death	1 (1%)	5 (7%)	0.095
Death at 5 years	9 (6%)	18 (13%)	0.063

MI: myocardial infarction; LV: left ventricle; CPAP: continuous positive airway pressure; NIV: non-invasive ventilation; ICU: intensive care unit

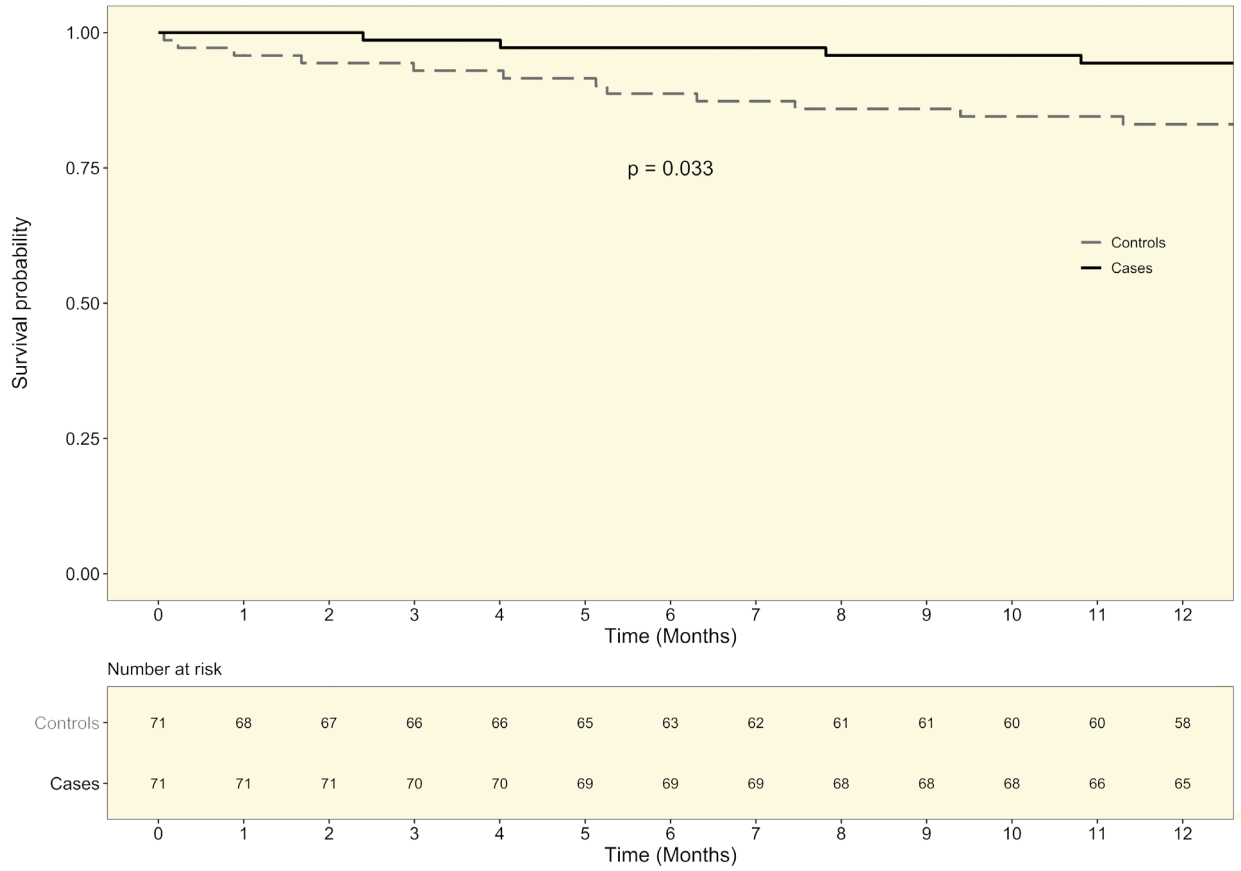

Figure 2: Kaplan Meier survival curve at 1 year

mean±SD oxygen flow rate on day 7 than the controls (1.7±3.3 *vs* 0.5±0.9 L/min, p=0.019). Patients with HPS were also more frequently readmitted to the ICU than controls (10 *vs* 1 patient at one month, p=0.008). We did not find any significant differences between cases and controls concerning ventilation data, other oxygen therapy variables, and lengths of stay. One-year survival was higher in the HPS group (94.4% *vs* 81.1%, p=0.033) (Fig 2).

Regardless of the HPS diagnostic means used, similar results were obtained. We also found more total complications at one month in HPS patients whose diagnosis was made with contrast echocardiography (n=27) than the controls (median: 5 [range: 3.5–8] *vs* 2 [1.3–4.5], p=0.004), with more cardiac and infectious complications (57.7% *vs* 15.4%, p=0.003; and 88.5% *vs* 42.3%, p=0.001, respectively). They also required more oxygen at day 7 (median: 2 [range: 0–4.5] *vs* 0 [0–0.5] L/min, p<0.001). Subgroup analysis in HPS patients with p_aO_2<60 mm Hg was not possible because of small numbers (11 patients).

We found a significant, yet small, correlation between total complications at one month and percentage of shunt at the pre-operative 100% oxygen technique (r=0.251, p=0.03). However, we did not find any significant correlation between p_aO_2 and post-operative complications in HPS patients (r=-0.166, p=0.174).

We looked for other factors associated with total complications at one month. Using a univariate analysis, we found that HPS, MELD score at transplantation, pre-operative bilirubinemia, creatininemia, hemoglobinemia, factor V, intra-operative number of RBC and FFP packs transfused, intra-operative maximal norepinephrine dosage, and the duration of surgery, were risk factors for post-operative complications (Table 3). Using a multivariate analysis, HPS was the only independent risk factor left (β=0.26, 95% CI: 0.90–3.28,

Table 3: Factors associated with post-operative complications at one month in univariate logistic regression

Variable	β Coefficient (95% CI)	p vale
HPS	2.18 (0.93–3.44)	0.001
MELD	0.13 (0.06–0.20)	<0.001
Bilirubinemia	0.008 (0.003–0.012)	0.002
Creatininemia	0.01 (0.00–0.02)	0.044
Hemoglobinemia	-0.04 (-0.06–0.01)	0.009
Factor V	-0.03 (-0.05 to -0.01)	0.001
Duration of surgery	0.007 (0.001–0.013)	0.027
Max norepinephrine dosage	0.79 (0.20–1.38)	0.009
Number of FFP packs	0.48 (0.31–0.65)	<0.001
Number of RBC packs	0.45 (0.29–0.61)	<0.001

MELD: model for end-stage liver disease; FFP: fresh frozen plasma; RBC: red blood cells

p=0.001).

Finally, we looked for factors associated with one-year mortality. In univariate analysis, the factors associated with mortality were HPS (protective factor), the number of comorbidities, pre-operative creatininemia and p_aO_2 (Table 4). In multivariate analysis, the only factor associated with mortality was p_aO_2 (adj HR: 1.06, 95% CI 1.01–1.12, p=0.03).

DISCUSSION

In our study, the complication rate (particularly cardiac, infectious and surgical complications) among the 71 patients with HPS in the month following LT was higher than patients without HPS. Although patients with pre-operative HPS were more often readmitted to the ICU, no difference was observed between study groups in terms of long-term complications, and lengths of ICU and hospital stay.

To our knowledge, this is the first case-control study to evaluate the outcome difference with such a large number of patients. Two other retrospective case-control studies with smaller sample sizes compared post-operative complications after LT in patients with and without HPS, and did not find any difference [14, 15].

Table 4: Factors associated with 1-year mortality in univariate Cox model

Variable	HR (95% CI)	p value
HPS	0.31 (0.1–0.97)	0.043
Comorbidities	0.19 (0.04–0.90)	0.041
Creatininemia	1.00 (1.00–1.01)	0.049
p_aO_2	1.06 (1.02–1.10)	0.002

The higher number of cardiac complications cannot be due to pre-operative differences, because patients were matched on cardiovascular comorbidities, and no difference between groups was found concerning pre-operative echocardiographic assessment. The increase in surgical complications with 35% of biliary complications and 34% of vascular complications in cases was in accordance with high incidences reported in different case series. Although these series were small (less than 23 patients) they found rates of biliary complications ranging from 26% to 38% and of vascular complications from 29% to 30%. The proportion of septic complications seems higher than what has been reported in the literature [8, 16]. Various uncontrolled case series reported rates ranging from 52% to 57% [8, 17]; it was 82% in our HPS population.

Hypoxemia is believed to be the main hypothesis for higher rate of complications in patients with HPS. Hypoxemia is indeed a known risk factor for cardiovascular complications, and its adverse effects on depressed immune function, decreased resistance to bacterial infection, wound healing, or anastomotic leaks and strictures are well-known too [18-22].

However, we were not able to demonstrate a convincing association between the level of hypoxemia and the development of complications. It might be because of a lack of power since we found a correlation, yet small, on the whole population which would mean that hypoxemia itself, whatever its origin, leads to a higher post-operative morbidity.

The lack of difference in long-term outcome or hospital stay could be explained by early HPS resolution with a mean delay of 169 days, so hypoxemia would not affect the long-term outcome. Unexpectedly, there was a better one-year survival in cases. We hypothesized that it could be attributed to differences in graft quality between cases and controls. Indeed, although DRI was comparable, there was a trend towards a longer anoxia time in controls as well as more necrosis and anoxia-induced lesions.

Our study has several limitations. Concerning the diagnosis of vasodilatations, we used both contrast echocardiography and 100% oxygen technique. Most of the patients were diagnosed according to the 100% oxygen method, which does not appear in the classical definitions of HPS [1, 24, 25]. In fact, contrast echocardiography does not have a 100% sensitivity; therefore, 100% oxygen method might help diagnose patients that were underdiagnosed by contract echocardiography [12]. However, Ferreira, *et al*, found a good correlation between 100% oxygen method and contrast echocardiography or with scintigraphy among 51 cirrhotic patients with 28 having intrapulmonary vasodilatations and 16 having HPS [26]. False-positive shunts can be observed with the 100% oxygen technique; it is due to a slow azote flushing by oxygen and can be seen in obstructive lung disease. In our HPS patients, 12 had obstructive disorders and were identified among the 44 patients diagnosed with the 100% oxygen method. Also, when comparing our patients with a positive contrast echocardiography and those with a shunt identified by the 100% oxygen technique, we found no outcome difference.

We designed a case-control study with a ratio of one control per case since we had only 219 potential controls, but we calculated a β risk of 78% with a 1/1 ratio which is good enough. Even if it remained a relatively small cohort, we had more patients than most of the studies previously published. However, we identified few severe HPS since only 10 patients needed oxygen therapy before LT, so we could not analyze this subgroup while these patients should be at even higher risk of complication and poor outcome. Although the study period was quite long (over almost six years), surgical techniques and critical care have not changed. Besides, there was no difference in the period of transplantation between groups. Because it was a retrospective study, we had to exclude one patient with HPS for missing data. A larger prospective study would be needed to confirm these results and extrapolate these results to other centers.

HPS is an underdiagnosed syndrome that seems to be associated with an increased incidence of post-operative complications following LT. Cirrhotic patients need to be actively and more systematically screened for HPS to refer them as soon as possible to LT centers. These patients need an extra vigilance to maximize oxygen delivery and to investigate complications in the early post-operative period. However, the results of the present study need to be confirmed by further larger prospective studies. Confirming that HPS patients experience higher post-LT morbidity could lead LT teams to consider allocating better grafts to these patients in order to improve their post-operative outcome.

CONFLICTS OF INTEREST: None declared.

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