Published in final edited form as:
Gastroenterology. 2008 October ; 135(4): 1168–1175. doi:10.1053/j.gastro.2008.06.038.

Impact of Hepatopulmonary Syndrome on Quality of Life and Survival in Liver Transplant Candidates

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Abstract

Background & Aims—Hepatopulmonary syndrome (HPS) affects 10%–30% of patients with cirrhosis and portal hypertension, but the impact on functional status, quality of life, and survival is poorly defined. We assessed the impact of HPS in patients evaluated for liver transplantation.

Methods—We performed a prospective multicenter cohort study of patients being evaluated for liver transplantation in 7 academic centers in the United States. Patients with HPS (defined as an increased alveolar-arterial oxygen gradient with intrapulmonary vasodilation) were compared with those without HPS in terms of demographics and clinical variables. New York Heart Association functional class, quality of life, and survival were assessed.

Results—Seventy-two patients with HPS and 146 patients without HPS were compared. There were no differences in age, sex, or etiology or severity of liver disease between the groups; however, patients with HPS were less likely to have a history of smoking (P = .03). Patients with HPS had worse New York Heart Association functional class (P = .005) and had significantly worse quality of life in certain domains compared with patients without HPS. In addition, patients with HPS also

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The authors have no conflicts of interest to report.

The Pulmonary Vascular Complications of Liver Disease Study Group also includes the following: Columbia University: Jenna Reinen, BA, Jeffrey Okun, BA, Sonja Olsen, MD, Debbie Rybak, BA, Daniel Rabinowitz, PhD, Lori Rosenthal, NP, Evelyn M. Horn, MD; Mayo Clinic: Linda Stadheim, RN, Russell Wiesner, MD; University of Alabama: Dottie Faulk, J. Stevenson Bynon, MD, Devin Eckhoff, MD, Harpreet Singh, Rajasekhar Tanakella, Raymond Benza, MD; University of Colorado: David Badesch, MD, Ted Perry; University of North Carolina: Carrie Nielsen, RN, Roshan Shrestha, MD; University of Pennsylvania: Vivek Ahya, MD, Harold Palevsky, MD, Rajender Reddy, MD, Michael Harhay, Sandra Kaplan, RN, Darren Taichman, MD, PhD; University of Southern California, James Knowles, MD, PhD.

had a significantly increased risk of death compared with patients without HPS despite adjustment for age, sex, race/ethnicity, Model for End-Stage Liver Disease score, and liver transplantation (adjusted hazard ratio = 2.41; 95% confidence interval, 1.31–4.41; $P = .005$).

Conclusions—HPS was associated with a significant increase in risk of death as well as worse functional status and quality of life in patients evaluated for liver transplantation.

The hepatopulmonary syndrome (HPS) occurs when intrapulmonary vascular dilation leads to abnormal systemic oxygenation in the setting of liver disease or portal hypertension.[1] This syndrome has been found in 10%–32% of patients with cirrhosis being evaluated for liver transplantation and may also be seen in noncirrhotic portal hypertension and acute hepatitis.[2–5] Currently, the only established treatment for HPS is liver transplantation.

The mechanism for HPS is currently unknown. Despite this, 2 small single-center studies have suggested that the presence of HPS may be associated with increased mortality in cirrhotic patients being evaluated for liver transplantation.[6,7] Similarly, survival after liver transplantation may be lower in patients with HPS relative to those without HPS.[5] However, the association between HPS and the risk of death remains controversial. It is also unclear whether it is the presence of the syndrome itself or the severity of gas exchange abnormalities in those with HPS that affects long-term outcome. In addition, whether HPS influences functional status and quality of life has never been studied.

Therefore, we sought to prospectively evaluate clinical characteristics, functional status, and survival of patients with HPS compared to those without HPS in a cohort of patients with advanced liver disease and portal hypertension being evaluated for liver transplantation.

Patients and Methods

Study Design and Study Sample

The Pulmonary Vascular Complications of Liver Disease study enrolled a cohort of 536 patients evaluated for liver transplantation at 7 centers in the United States between 2003 and 2006. The only inclusion criterion was the presence of portal hypertension with or without intrinsic liver disease. We excluded patients with active infection, with recent (<2 weeks) gastrointestinal bleeding, or who had undergone prior liver or lung transplantation. The study was approved by the institutional review board of each center, and patients provided informed consent.

The study sample included new patients evaluated with contrast echocardiography, spirometry, and arterial blood gas sampling (tests routinely performed for all patients evaluated for liver transplantation). We excluded patients with a significant obstructive ventilatory defect, defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.70 with FEV_1 percent predicted <80%, or a significant restrictive ventilatory defect, defined as FVC percent predicted and (if performed) total lung capacity percent predicted <70%. We also excluded patients with intracardiac shunting (defined in the following text).

Data Collection and Variables

Patients underwent a physical examination and laboratory assessment. The Model for End-Stage Liver Disease (MELD) score was calculated.[8] The etiology of underlying liver disease, past medical history, current medications, social history, and New York Heart Association (NYHA) functional class were recorded. Chest radiography was interpreted locally at each center. Pulmonary function test results are expressed using sex- and race-specific prediction equations, where appropriate.[9–11] Arterial blood gas sampling was performed while the subject breathed room air in the seated position.

Contrast transthoracic echocardiography was interpreted at each center. Agitated saline was injected via a peripheral vein during imaging. Appearance of micro-bubbles in the left heart ≥3 cardiac cycles after saline injection was considered "late," consistent with intrapulmonary shunting. Appearance of microbubbles in the left heart <3 cardiac cycles after venous injection was considered "early," consistent with intracardiac shunting. We administered the Liver Disease Quality of Life 1.0 questionnaire (LDQOL).[12] This questionnaire includes the Medical Outcomes Study Short Form-36 (SF-36) (version 2.0).[13]

Survival and liver transplantation status and dates were obtained from the medical record, the subjects' physicians, the subjects themselves, and the Social Security Death Index as of December 31, 2006. Patients who were alive were censored at this date.

Criteria for HPS

HPS was defined by (1) contrast echocardiography with late appearance of microbubbles after venous injection of agitated saline and (2) an alveolar-arterial oxygen gradient ≥15 mm Hg (or ≥20 mm Hg if age older than 64 years), as previously recommended.[1] Patients who did not meet both criteria were considered to be in the non-HPS group. Patients with either "early" or indeterminate timing of the appearance of microbubbles in the left heart after agitated saline injection were excluded. Sensitivity analyses were performed after inclusion of patients with missing data in the non-HPS group and in which HPS was defined by an alveolar-arterial gradient greater than the upper limit of normal from the Crapo[14] and Harris[15] regression equations.

Statistical Analyses

Continuous data were summarized using mean ± SD or median (interquartile range), as appropriate. Categorical variables were summarized with n (%). We compared patients with and without HPS using unpaired Student *t* tests, Wilcoxon rank sum tests, χ^2 tests, and Fisher exact tests, as appropriate. We used bivariate and multivariate linear regression to analyze the association between HPS status and the LDQOL and SF-36 scales after adjustment for age, sex, and MELD score.

Survival was assessed using the Kaplan–Meier estimator and Cox proportional hazards models, and the results are expressed with a hazard ratios (HRs) in bivariate and multivariate analyses. To determine whether certain characteristics might explain differences in survival between the 2 groups, we included in the models factors believed to be potential confounders and a term for liver transplantation as a time-varying covariate. We forced age, sex, race, and liver transplantation into the model and retained other variables that resulted in a change of the HPS term coefficient by >20%. The proportional hazards assumption was assessed with log-log plots.

Results

A total of 536 patients were enrolled in the Pulmonary Vascular Complications of Liver Disease cohort (Figure 1). A total of 473 of these patients (88%) were new evaluations. Of these, 335 (71%) had pulmonary function testing and arterial blood gases, of which 281 (84%) had interpretable contrast transthoracic echocardiography. We excluded 15 patients (5%) with intracardiac shunting, leaving 266 patients. Thirty (11%) of these patients had an obstructive ventilatory defect on spirometry, and 18 (7%) demonstrated a restrictive ventilatory defect, leaving 218 (82%, or 41% of the total new patient cohort) in the final study sample. We compared the final study sample with those new patients who were excluded (n = 255). There were no apparent differences in terms of age, sex, race, ethnicity, body mass index, etiology of liver disease, MELD score, or smoking history between the groups (data not shown). In

addition, the median time from the initial diagnosis of liver disease to entry into the study cohort was 3 years in both groups.

There were 72 patients with HPS and 146 without HPS in the study sample (Table 1). Patients with HPS had similar age, sex, and etiologies and severity of liver disease compared with those without HPS. Patients with HPS were more likely to be non-Hispanic white than non-HPS patients ($P = .03$). Most patients in both groups had liver disease attributable to alcohol use and/or hepatitis C infection, and the mean MELD score was 13 in both groups ($P = .76$). The median time from diagnosis of liver disease to evaluation for transplantation (and entry into the study) was 3 years (range, 1–11 years) for patients with HPS compared with 4 years (range, 1–9 years) for non-HPS patients ($P = .60$). There were no differences between the groups in reported complications of portal hypertension, prior transjugular intrahepatic portosystemic shunt placement, or medical comorbidities. Patients with HPS were less likely than non-HPS patients to be current or past smokers and tended to have a higher prevalence of chronic alcohol use. We found no differences in the use of diuretics, beta-blockers, prophylaxis for encephalopathy or spontaneous bacterial peritonitis or nitrates between the groups (data not shown).

While common in both groups, dyspnea and orthopnea were significantly more frequent in those with HPS compared with those without (Table 2). Cyanosis was rare but also significantly more frequent in patients with HPS. There was also significantly more clubbing and asterixis noted in those with HPS than in those without. There were no differences in laboratory results between the groups.

Table 3 shows the results from cardiopulmonary testing. Chest radiography showed more interstitial markings in patients with HPS than in those without. FVC percent predicted and FEV_1 percent predicted were slightly lower in HPS versus non-HPS patients, and arterial blood gas results showed characteristic differences. Transthoracic echocardiography with contrast showed that patients with HPS had more frequent right atrial and ventricular dilatation and right ventricular hypertrophy than patients without HPS. Valvular and left-sided cardiac morphology were similar between the groups.

Patients with HPS had worse NYHA functional class compared with patients without HPS (Wilcoxon rank sum test, $P = .005$) (Table 4). A total of 134 patients (62%) returned the LDQOL questionnaire. Patients who returned the questionnaire were similar to those who did not in terms of age (53 ± 10 vs 51 ± 9 years), sex (37% vs 40% female), MELD score (13 ± 5 vs 14 ± 5), and prevalence of HPS (31% vs 36%). Table 4 shows the adjusted least square means (standard errors) for the SF-36 scales; unadjusted results were similar. Patients with HPS had significantly lower scores (indicating worse quality of life) than non-HPS patients on the General Health, Role Emotional, Mental Health, and Mental Component Score scales. Notably, patients with HPS had lower scores on virtually every other SF-36 scale; however, these and the liver disease–specific scale scores from the LDQOL (data not shown) were not significantly different from those of the non-HPS patients.

A total of 125 patients (57%) from the study sample were listed for liver transplantation, 69 (32%) underwent transplantation, and 47 (21%) died. There were 361 person-years of follow-up, and the median follow-up time was 1.7 years. There were no patients lost to follow-up. The 1- and 2-year survival rates were 88% (95% confidence interval [CI], 83%–92%) and 78% (95% CI, 71%–84%), respectively.

There were no differences between the patients with HPS and the non-HPS patients in terms of the probability of listing (51% vs 60%, respectively; $P = .21$) or liver transplantation (29% vs 33%, respectively; $P = .58$). Despite these similarities, patients with HPS had a doubling in the risk of death compared with patients without HPS (HR = 2.03; 95% CI, 1.15–3.60; $P =$.

015) (Figure 2 and Table 5). This result was unchanged after adjustment for age, sex, and race/ethnicity (non-Hispanic white vs other). Further adjustment for MELD score increased the HR for HPS versus non-HPS (HR = 2.41; 95% CI, 1.31–4.42; P = .005), whereas adjustment for the performance of liver transplantation did not significantly change this result.

We performed additional analyses after adjusting for other variables, including demographics, anthropomorphics, liver disease and complications, medical comorbidities, spirometry, echocardiographic measures, and laboratory measures. None of these variables were significant confounders. We examined the risk of death associated with the partial pressure of oxygen while breathing room air and the alveolar-arterial oxygen gradient after adjustment for HPS status; there were no associations between the partial pressure of oxygen or alveolar-arterial oxygen gradient in patients with HPS and the risk of death (data not shown).

HPS status met the assumption of proportional hazards in all analyses. There were no particularly influential subjects in the cohort. We conducted sensitivity analyses to explore the potential effects on our results due to excluding patients (n = 255) from the study sample. Under the conservative assumption that excluded patients did not have HPS, the prevalence of HPS would have been 15% (95% CI, 12%–19%). Patients with HPS still had significantly lower quality of life than non-HPS patients (including patients with missing data) in terms of the Mental Component Score, General Health, and Mental Health scales and worse NYHA functional class (all P < .05). However, the Role Emotional scale scores were no longer significantly different (P = .09). In addition, patients with HPS continued to have a significantly increased risk of death compared with the non-HPS patients (including those with missing data) (HR = 1.72; 95% CI, 1.07–2.76; P = .021). Analysis of data available from the excluded patients showed that 27 were found to have both an alveolar-arterial oxygen gradient >15 mm Hg and intrapulmonary shunting, fulfilling 2 major criteria for HPS. Sensitivity analyses with definitions of HPS using the age-corrected upper limits of normal for alveolar-arterial oxygen gradient from the Crapo and Harris equations showed similar results (data not shown).

Discussion

We have shown that HPS is a common complication in patients with liver disease who are referred for evaluation for liver transplantation. Non-Hispanic white patients were more likely to experience this complication than patients of other races and ethnicities, as were never-smokers. Notably, type or severity of liver disease and history of complications related to portal hypertension were not associated with the occurrence of HPS. Patients with HPS had a more than doubling in the risk of death compared with patients without HPS, which was not accounted for by differences between the groups in demographics, medical comorbidities, type or severity of liver disease, cardiopulmonary function, or the use of liver transplantation. In addition, patients with HPS had significantly worse functional status and poorer quality of life on a number of scales from the SF-36.

We found that 33% of our patients had HPS based on established diagnostic criteria, in line with prior studies using similar criteria.[1,2,16] We also confirmed prior observations that intrapulmonary shunting by echocardiography is present in approximately 50% of those without HPS.[2,6] Together these findings support that alterations in the pulmonary microvasculature are common in cirrhosis. As our findings and prior work have shown that severity of liver disease and its complications do not affect the risk of HPS,[2,7,17] other factors must account for the susceptibility to HPS. We did show racial and ethnic differences in the occurrence of HPS, suggesting the possible influence of genetic or environmental factors. Smoking was actually less common in patients with HPS. Radiographic pulmonary interstitial changes and echocardiographic changes were more frequently seen in patients with HPS than in controls, as has been shown in previous studies.[18–21]

The most important finding in this study is that HPS was associated with a significantly increased risk of death. This result persisted even after accounting for age, sex, MELD score, liver transplantation, and other potential confounders. Prior studies have had important limitations and have shown conflicting results regarding the association of HPS with mortality. Two studies have suggested that the presence of HPS increased mortality in patients being evaluated for liver transplantation,[6,7] while a more recent analysis of the United Network of Organ Sharing database did not.[22] The first study showing an increased risk was a small single-center study of an ethnically homogeneous population with a minority of patients with viral hepatitis, not representative of the liver transplant population in the United States. The second was a retrospective single-center study that did not adjust for potential confounders. Finally, the study of the United Network of Organ Sharing database lacked an operational definition of HPS. In contrast, ours was a large, multicenter, carefully phenotyped prospective cohort with an ethnic makeup similar to that of the United Network of Organ Sharing liver transplant wait list,[23] which clearly showed a statistically and clinically significant increase in mortality irrespective of liver transplantation with complete follow-up on all patients.

The mechanism of the association between HPS and adverse outcomes remains unexplained. While it has been presumed that hypoxemia is a likely contributor to mortality, we have found that it is the syndrome itself, rather than the severity of hypoxemia, that impacted on survival. This novel result suggests that factors such as vasoactive or inflammatory substances may mediate the effect of HPS on survival in cirrhosis. The only therapy considered effective for HPS is liver transplantation.[1] That the increased risk of death associated with HPS persisted after adjustment for liver transplantation showed that this association was not attributable to differential use of liver transplantation. Of course, the efficacy of liver transplantation in treating HPS cannot be determined in an unbiased way in an observational study such as this. The significant impact of HPS on survival underscores the need to develop effective medical therapies and define the utility of liver transplantation for this disease.

HPS also had a negative impact on NYHA functional class. Interestingly, despite the physician assessment of more dyspnea with less activity in the patients with HPS, these patients did not believe that the physical components of quality of life, such as self-care, energy level, and disability, were as affected by HPS as the mental components, including nervousness and depression, difficulties with work, and self-evaluation of general health. The association of HPS with both functional status and emotional aspects of quality of life magnifies the impact of this syndrome on patients with already-reduced quality of life associated with chronic liver disease. It is not known how the presence of HPS influences perceptions of mental and emotional well-being, but this finding makes establishment of effective therapy for HPS a high priority.

There are several limitations to this study. First, we only included patients being considered for liver transplantation, so we do not know whether our findings are generalizable to all patients with HPS. Second, there were missing data that excluded some patients and could result in selection bias. However, the study sample appeared similar to the excluded patients with respect to multiple measured variables. In addition, sensitivity analyses showed that effects on survival and quality of life remained after a conservative approach which included all patients in the analysis. Nevertheless, the precise magnitude of the adverse effects of HPS on quality of life and survival is not fully defined. Third, it is possible that unmeasured or imprecisely measured variables could have accounted for the association between HPS and outcome. However, we collected extensive demographic and clinical data that were included in multivariate analyses that did not change our conclusions. Finally, our cohort was relatively small, albeit the largest (and only) prospective multicenter study of patients with HPS.

In summary, HPS is common in patients being evaluated for liver transplantation and is associated with significant adverse effects on functional status, quality of life, and survival. Therefore, HPS is an important and potentially modifiable risk factor for morbidity and mortality in cirrhosis. Understanding the mechanisms of the adverse effects of HPS and developing effective medical therapies merit high priority to improve the outcomes of patients with advanced liver disease.

Acknowledgments

Supported by National Institutes of Health grants DK064103, DK065958, RR00645, RR00585, RR00046, RR00032, and HL67771.

Abbreviations used in this paper

CI	confidence interval
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HPS	hepatopulmonary syndrome
HR	hazard ratio
LDQOL	Liver Disease Quality of Life
MELD	Model for End-Stage Liver Disease
NYHA	New York Heart Association
SF-36	Short Form-36

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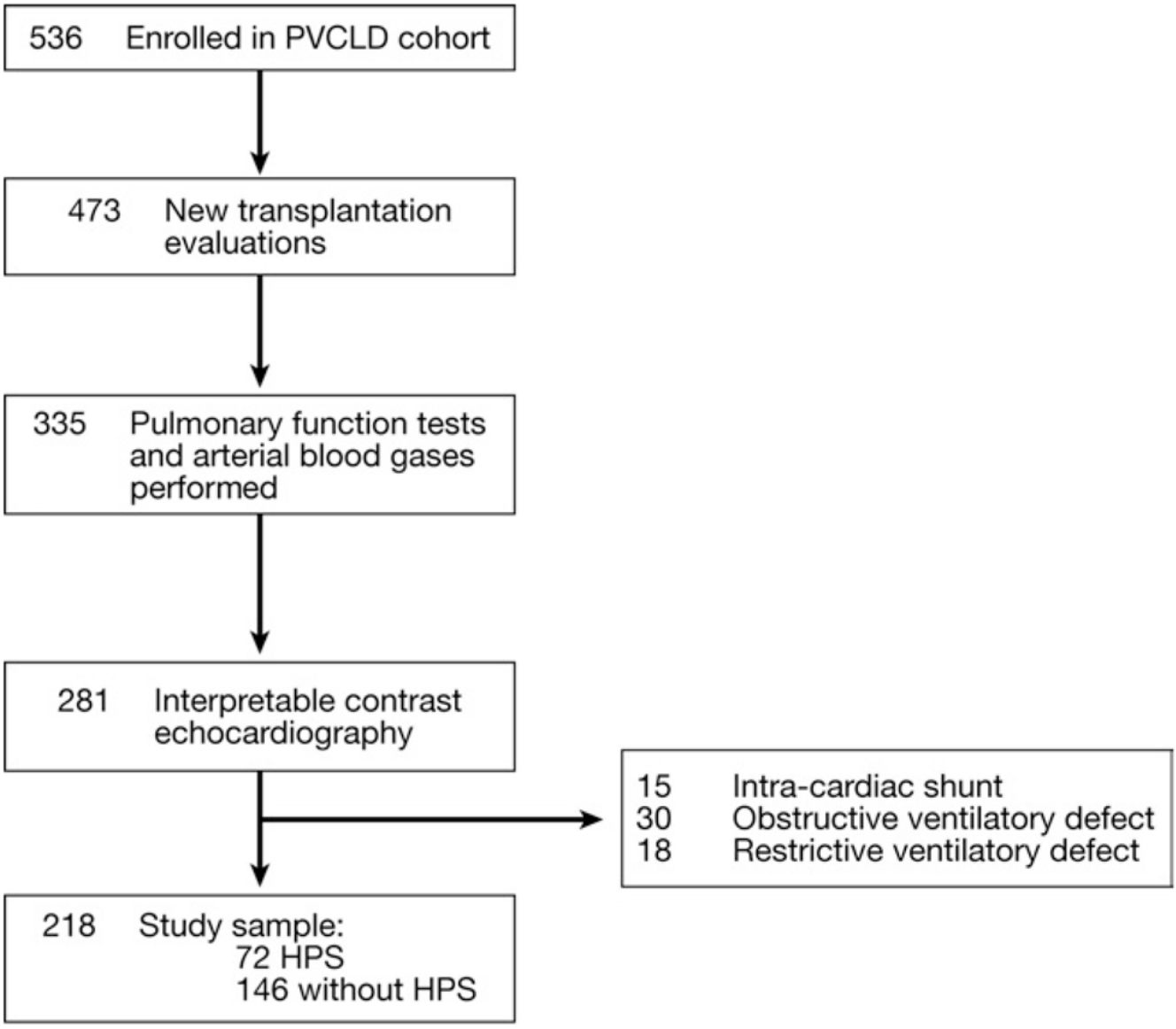

Figure 1.
Selection of study sample.

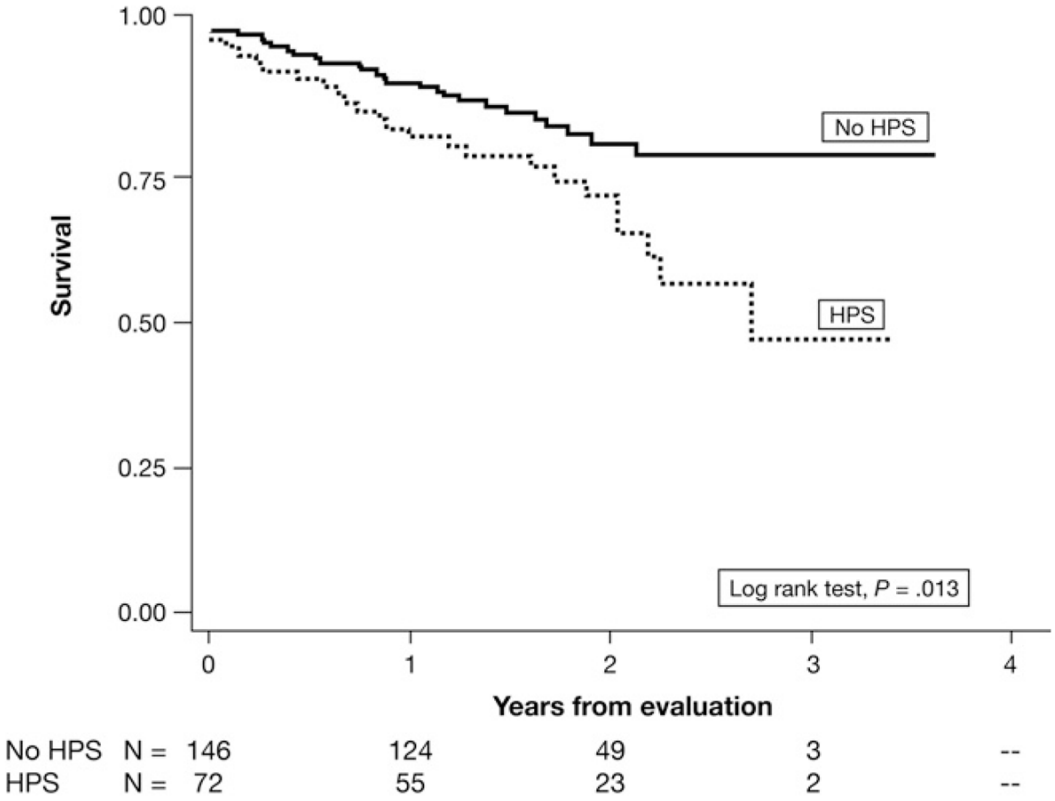

Figure 2.
Kaplan–Meier survival estimates of patients with HPS and patients without HPS (No HPS) (n = 218).

Table 1

Demographics, Liver Disease Characteristics, and Past Medical History

Variable	n	HPS (n = 72)	No HPS (n = 146)	*P* value
Age (*y*), mean ± SD	218	52 ± 9	53 ± 10	.86
Female sex, n (%)	218	30 (42)	53 (36)	.44
Race/ethnicity, n (%)	218			.03
Non-Hispanic white		65 (90)	110 (75)	
Hispanic white		3 (4)	18 (12)	
Non-Hispanic black		1 (1)	12 (8)	
Other		3 (4)	6 (4)	
Etiology of liver disease, n (%)				
Alcohol	218	28 (39)	60 (41)	.76
Hepatitis C infection	218	33 (46)	67 (46)	.99
Autoimmune hepatitis	218	4 (6)	5 (3)	.48
Nonalcoholic fatty liver disease	218	8 (11)	16 (11)	.97
Hepatitis B infection	218	1 (1)	9 (6)	.17
Primary sclerosing cholangitis	218	2 (3)	11 (8)	.23
Primary biliary cirrhosis	218	4 (6)	7 (5)	.81
Cryptogenic cirrhosis	218	7 (10)	12 (8)	.71
MELD score, mean ± SD	218	13 ± 4	13 ± 5	.76
Past medical history, n (%)				
Ascites	218	40 (56)	78 (53)	.77
Variceal bleeding	218	18 (25)	33 (23)	.69
Encephalopathy	217	33 (46)	66 (46)	.97
Spontaneous bacterial peritonitis	218	6 (8)	6 (4)	.22
Hepatocellular carcinoma	218	5 (7)	14 (10)	.52
Hepatic hydrothorax	218	4 (6)	4 (3)	.30
Transjugular intrahepatic portosystemic shunt	218	4 (6)	13 (9)	.39
Chronic obstructive pulmonary disease	217	5 (7)	4 (3)	.15
Venous thromboembolism	217	5 (7)	8 (6)	.68
Diabetes mellitus	217	26 (36)	44 (30)	.39
Hypertension	217	24 (33)	42 (29)	.51
Hypercholesterolemia	217	3 (4)	7 (5)	1.0
Coronary artery disease	217	1 (1)	4 (3)	1.0
Hypothyroidism	217	6 (8)	8 (6)	.43
Depression	217	19 (26)	32 (22)	.48
Smoking	218	35 (49)	93 (64)	.03
Chronic alcohol use	215	43 (61)	104 (72)	.08
Intravenous drug use	213	10 (14)	30 (21)	.22
Blood transfusion	191	22 (36)	46 (35)	.93

Table 2

Symptoms, Physical Findings, and Laboratory Evaluation

Variable	n	HPS	No HPS	*P* value
Symptoms, n (%)				
Dyspnea	218	34 (48)	42 (29)	.007
Orthopnea	208	17 (25)	18 (13)	.03
Chest pain	212	6 (9)	13 (9)	.89
Palpitations	211	13 (18)	18 (13)	.29
Syncope	212	8 (11)	7 (5)	.09
Weight loss	215	12 (17)	32 (22)	.36
Signs, n (%)				
Cyanosis	215	7 (10)	2 (1)	.007
Jaundice	216	27 (38)	52 (36)	.76
Ascites	217	35 (49)	69 (48)	.89
Lower extremity edema	217	44 (61)	72 (50)	.11
Physical examination				
Body mass index (kg/m^2), mean ± SD	218	30 ± 6	29 ± 6	.06
Pulse (*beats/min*), mean ± SD	218	81 ± 14	75 ± 13	.002
Systolic blood pressure (*mm Hg*), mean ± SD	218	123 ± 17	119 ± 19	.13
Diastolic blood pressure (*mm Hg*), mean ± SD	218	70 ± 10	70 ± 12	.87
Room air oxygen saturation (%), mean ± SD	135	96 ± 3	97 ± 2	.005
Ascites, n (%)	215	29 (40)	58 (41)	.97
Spider angiomata, n (%)	209	26 (37)	56 (39)	.78
Lower extremity edema, n (%)	215	45 (63)	73 (51)	.08
Clubbing, n (%)	214	12 (17)	10 (7)	.03
Asterixis, n (%)	215	9 (13)	5 (4)	.02
Laboratory results, median (interquartile range)				
Blood urea nitrogen (*mg/dL*)	214	12 (10–17)	13 (10–18)	.15
Creatinine (*mg/dL*)	218	0.9 (0.8–1.1)	0.9 (0.8–1.2)	.75
Hemoglobin (*g/dL*)	218	12.8 (11.6–14.2)	12.8 (11–13.8)	.17
Platelet count ($10^9/L$)	215	94 (62–137)	90 (67–144)	.80
International normalized ratio	218	1.3 (1.2–1.5)	1.3 (1.1–1.5)	.66
Alanine aminotransferase (*U/L*)	218	39 (26–65)	45 (31–68)	.15
Aspartate aminotransferase (*U/L*)	218	59 (46–95)	68 (43–96)	.67
Total bilirubin (*mg/dL*)	218	2.2 (1.2–3.2)	2 (1.3–3.4)	.48
Alkaline phosphatase (*U/L*)	217	133 (105–202)	132 (92–200)	.63
Total protein (*g/dL*)	211	7.0 (6.3–7.5)	7.1 (6.5–7.6)	.17
Albumin (*g/dL*)	212	3.0 (2.6–3.4)	3.1 (2.7–3.6)	.16

Table 3

Cardiopulmonary Testing and Abdominal Imaging

Variable	n	HPS	No HPS	*P* value
Chest radiography, n (%)				
Cardiomegaly	207	9 (13)	12 (9)	.30
Interstitial lung disease	207	5 (7)	1 (1)	.02
Hyperinflation	207	1 (2)	2 (1)	1.0
Pleural effusion	207	8 (12)	15 (11)	.83
Pulmonary function testing, mean ± SD				
FVC (*% predicted*)	218	86 ± 14	91 ± 15	.045
FEV_1 (*% predicted*)	218	85 ± 14	91 ± 15	.02
FEV_1/FVC	218	0.77 ± 0.05	0.78 ± 0.06	.41
Total lung capacity (*% predicted*)	136	89 ± 17	94 ± 15	.08
$DLCO_{corr}$, (*% predicted*)	211	54 ± 16	63 ± 15	.0001
Arterial blood gas				
pH, mean ± SD	218	7.45 ± 0.03	7.43 ± 0.04	.006
pCO_2 (*mm Hg*), mean ± SD	218	33 ± 5	35 ± 5	.04
pO_2 (*mm Hg*), mean ± SD	218	74 ± 14	90 ± 13	<.0001
Alveolar-arterial oxygen gradient (*mm Hg*), median (interquartile range)	218	27 (20–40)	10 (4–15)	<.001
Echocardiography				
Right atrial dilation, n (%)	205	17 (26)	18 (13)	.02
Right ventricular dilation, n (%)	211	28 (41)	38 (27)	.03
Right ventricular hypertrophy, n (%)	211	22 (32)	24 (17)	.01
Right ventricular dysfunction, n (%)	212	5 (7)	3 (2)	.12
Right ventricular systolic pressure (*mm Hg*), mean ± SD	141	39 ± 16	36 ± 10	.30
Left atrial size (*cm*), mean ± SD	195	4.2 ± 0.7	4.0 ± 0.7	.09
Left ventricular hypertrophy, n (%)	214	26 (38)	48 (33)	.37
Pericardial effusion, n (%)	209	5 (7)	18 (13)	.24
Intrapulmonary shunt, n (%)	218	72 (100)	67 (46)	<.001
Abdominal imaging, n (%)				
Splenomegaly	207	51 (80)	113 (79)	.91
Ascites	214	26 (38)	64 (42)	.62

$DLCO_{corr}$, diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (% predicted).

Table 4

Functional Status and SF-36 Results

Variable	N	HPS	No HPS	*P* value
NYHA, n (%)	217			.005
I		12 (17)	48 (33)	
II		35 (49)	62 (43)	
III		19 (26)	33 (23)	
IV		6 (8)	2 (1)	
SF-36[a]		n = 42	n = 92	
Physical Component Score		30 (2)	32 (1)	.32
Mental Component Score		37 (2)	43 (2)	.02
General Health		23 (4)	34 (3)	.006
Physical Functioning		34 (5)	40 (4)	.20
Role Physical		27 (6)	36 (5)	.08
Role Emotional		50 (6)	64 (5)	.03
Bodily Pain		44 (5)	48 (4)	.51
Mental Health		53 (4)	63 (3)	.01
Vitality		30 (4)	33 (4)	.45
Social Functioning		43 (6)	50 (5)	.28
Health Transition		3.8 (0.2)	3.5 (0.2)	.24

[a] Least square mean (SE) adjusted for age (53 years), female sex, and MELD score (13).

Table 5

Cox Proportional Hazards Models for the Risk of Death (N = 218)

	HR of HPS vs no HPS	95% CI	*P* value
Unadjusted	2.03	1.15–3.60	.015
Adjusted for age, sex, and race	1.95	1.09–3.50	.025
Adjusted for age, sex, race, and MELD score	2.41	1.31–4.42	.005
Adjusted for age, sex, race, MELD score, and liver transplantation	2.41	1.31–4.41	.005