Prospective Evaluation of Outcomes and Predictors of Mortality in Patients With Hepatopulmonary Syndrome Undergoing Liver Transplantation

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The hepatopulmonary syndrome (HPS) occurs in a subgroup of patients with cirrhosis and results from intrapulmonary vasodilatation, which may cause significant hypoxemia. Liver transplantation has emerged as a therapeutic option for patients with HPS based on retrospective case series and reports. However, morbidity and mortality appear to be increased after transplantation for HPS, and no prospective studies evaluating clinical features that may predict poor surgical outcome are available. Therefore, we prospectively evaluated the utility of the degree of hypoxemia, the arterial oxygen response to 100% oxygen administration, and the macroaggregated albumin (MAA) scan quantification of intrapulmonary shunting as predictors for outcome after liver transplantation. Our cohort consisted of 24 patients with cirrhosis and HPS who underwent liver transplantation over a 5-year period at 2 transplant centers who were followed at least 1 year after transplantation. All patients underwent preoperative evaluation for HPS with standardized methods. Seven patients (29%) died postoperatively, 5 of cardiorespiratory complications. All deaths occurred within 10 weeks after transplantation. A preoperative arterial oxygen tension (PaO_2) of ≤ 50 mm Hg alone or in combination with a MAA shunt fraction ≥ 20% were the strongest predictors of postoperative mortality. In conclusion, we found that mortality is increased after liver transplantation for HPS, particularly in patients with more severe hypoxemia and significant intrapulmonary shunting. Preoperative testing for the severity of HPS can be used to stratify patients according to the risk for postoperative mortality. (HEPATOLOGY 2003;37:192-197.)

The hepatopulmonary syndrome (HPS) occurs when intrapulmonary vasodilatation results in hypoxemia.[1] This syndrome occurs most commonly in the setting of cirrhosis and is found in 8% to 17% of such patients.[2,3] No clearly effective medical therapies have been found. The natural history of HPS is incompletely defined, but the syndrome frequently is progressive and associated with significant morbidity and mortality.

Over the last 10 to 15 years, hypoxemia related to HPS in otherwise suitable candidates for liver transplantation has evolved from a contraindication to liver transplantation to a relative indication; however, increasing experience with liver transplantation for HPS has led to concern that postoperative mortality may be increased relative to cirrhotic patients without HPS.[4] Reviews of small case series and individual cases reports have found 1-year survival after liver transplantation in HPS to be between 68% and 80%.[5] In addition, only a relatively small number of adult patients undergoing liver transplantation for HPS have been reported.

Retrospective review of these cases has suggested that the degree of hypoxemia on room air and on 100% oxygen and the severity of intrapulmonary shunting may correlate with poor surgical outcome.[6] However, reported methods for assessing these variables vary between publications, and no prospective evaluation using uniform techniques has been undertaken to define whether they can predict outcome after liver transplantation. The aim of the present study is to evaluate prospectively the utility of the degree of hypoxemia, the arterial oxygen response

Abbreviations: HPS, hepatopulmonary syndrome; MAA, macroaggregated albumin; OLT, orthotopic liver transplantation; ABG, arterial blood gases; GMT, geometric mean of technetium; PFTs, pulmonary function tests; PaO_2, arterial oxygen tension.

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to 100% oxygen administration, and the macroaggregated albumin (MAA) scan quantification of intrapulmonary shunting, with standardized methods, as predictors for outcome after liver transplantation in patients with HPS.

Patients and Methods

Subjects and Data Collection. We prospectively analyzed a cohort of 24 patients with cirrhosis and HPS who underwent orthotopic liver transplantation (OLT) between February, 1996 and March, 2001 at 2 transplant centers (University of Alabama at Birmingham and The Mayo Clinic). Patients were identified from those who initially presented to our Hepatology Clinic or to Liver Transplantation Evaluation Clinic. Patients with dyspnea, cyanosis, clubbing, or arterial blood gas (ABG) abnormalities underwent formal evaluation for HPS. HPS was defined by (1) a positive contrast echocardiogram consistent with intrapulmonary shunting, (2) an arterial oxygen tension (PaO_2) < 70 mm Hg or an age corrected alveolar-arterial oxygen gradient ($P[A\text{-}a]O_2$) > 20 mm Hg, and (3) an elevated MAA lung perfusion scan shunt fraction (>6%) if intrinsic cardiopulmonary disease was present. Selection criteria for candidacy for liver transplantation in patients with HPS in our centers was the same as for non-HPS patients and included commonly accepted UNOS (United Network for Organ Sharing) criteria for listing. These criteria did not change over the study period. Demographic and clinical data were recorded and incorporated into a database. Patients were followed until 1 year after OLT.

HPS Assessment. All identified HPS patients underwent identical pre-OLT studies at both centers, which included (1) ABG measurements on room air (fraction of inspired oxygen [FiO_2] = 21%), (2) ABG measurements at an $FiO_2 = 100\%$, and (3) MAA lung perfusion scan. Standardized protocols for these assessments were used at each center. Specifically, ABGs on room air were obtained in the standing position after a 5-minute equilibration period. One hundred percent ABG measurements were obtained while the patient was breathing 100% oxygen through a mouthpiece and wearing a nose clip in the sitting position after a 15- to 20- minute equilibration period.[7] MAA lung perfusion scans were performed as reported previously.[2] The extrapulmonary shunt fraction, assuming that 13% of the cardiac output is delivered to the brain,[8] was calculated with the geometric mean of technetium (GMT) counts around the brain and lung as depicted in the following formula:

$$(\text{GMT brain})/(\text{GMT brain} + \text{GMT lung})$$

A shunt fraction was considered elevated if the value was >6%.[7]

Data Analysis. Descriptive data are expressed as proportions, and quantitative data are summarized as mean and standard deviation (SD) or median and interquartile range, as appropriate. Comparisons between groups for normally distributed quantitative data were performed with a Student's *t* test or analysis of variance. For non–normally distributed data, comparisons were made with Kruskal-Wallis test or Wilcoxon rank sum test. Relationships between variables were assessed by Spearman's coefficient. The value of the results of ABG measurements and the MAA scan as predictors of mortality were explored by calculating likelihood ratios.

Results

Baseline Characteristics. A total of 26 patients with HPS were evaluated during the study. One patient was not listed for transplantation because of a history of coronary artery disease and ischemic cardiomyopathy. This patient had severe HPS with a room air PaO_2 of 28 and an MAA shunt of 61%. The 100% PaO_2 corrected to 86 mm Hg. One patient died of biliary sepsis while waiting for transplant. This patient had a room air PaO_2 of 39 and an MAA shunt of 28%. The 100% PaO_2 corrected to 351 mm Hg. Twenty-four patients with HPS underwent liver transplantation and are the focus of this study. Demographic data are outlined in Table 1. The mean age of the cohort was 50 ± 14 years, and 14 were men (58%). The most common etiologies of liver disease included cryptogenic liver disease (29%), alcoholic liver disease alone (25%), or hepatitis C (17%). Most patients had advanced liver disease, with 88% having Child-Pugh class B or C disease.

Pulmonary and HPS Evaluation. The results of pulmonary and HPS testing for each patient are outlined in Table 1. Two patients (patients 9 and 20) had moderate obstructive lung disease based on American Thoracic Society criteria.[9] Each of these patients had elevated MAA shunt fractions, indicating that HPS contributed significantly to hypoxemia. Three patients had mild (patient 1) or moderate restrictive (patients 3 and 5) abnormalities attributed to the presence of ascites. Ten patients did not undergo complete pulmonary function tests (PFTs). Three of these patients (patients 7, 12, and 21) presented with acute illness and were unable to undergo PFTs and underwent transplantation at the time of initial evaluation. Each of these patients had an elevated MAA shunt fraction. Two patients had normal spirometry and chest radiographs, and lung volume measurements were not performed. An additional 5 patients at one center had normal chest radiographs and no clinical findings to support intrinsic lung disease, and PFTs were not performed. Of these 5 patients, 4 had elevated MAA shunt fractions.

Table 1. Demographic and Clinical Characteristics of Patients With HPS

Patient No.	Age	Gender	Etiology	Child-Pugh Class	PaO_2 (mm Hg) RA	$P(A\text{-}a)O_2$ (mm Hg) RA	PaO_2 (mm Hg) 100%	MAA (%)	CXR	FEV_1/FVC (%)	TLC (%)
1	52	F	Cryptogenic	C	47	74	547	38	NL	76	71
2	63	F	ETOH	B	36	74	301	68	NL	76	88
3	63	F	Cryptogenic	B	49	59	265	20	NL	80	67
4	67	M	ETOH	B	45	75	375	18	NL	74	105
5	54	M	Cryptogenic	B	51	75	375	45	NL	87	66
6	54	M	Cryptogenic	C	59	55	552	13	NL	86	95
7	50	M	α1AT def	C	53	45	360	10	NL	N/A	N/A
8	62	M	ETOH	C	67	42	488	3	NL	73	N/A
9	55	M	ETOH	C	69	37	522	2	NL	63	135
10	37	F	HCV/ETOH	B	69	52	355	14	NL	75	101
11	12	M	Biliary atresia	A	51	52	191	63	NL	N/A	N/A
12	35	M	HHC	B	42	67	160	60	NL	N/A	N/A
13	37	M	HCV	A	38	80	449	67	NL	N/A	N/A
14	23	F	NASH	C	45	59	352	30	NL	N/A	N/A
15	47	M	PSC	C	61	44	458	14	NL	67	112
16	63	M	HCV	C	51	66	495	42	NL	76	N/A
17	61	M	Idiopathic ductopenia	B	66	33	499	1	NL	N/A	N/A
18	44	M	HCV	B	64	39	408	12	NL	81	85
19	44	F	ETOH	C	46	73	302	28	NL	89	108
20	61	F	Cryptogenic	B	52	68	314	13	FN	69	145
21	67	M	Cryptogenic	C	35	76	82	21	I	N/A	N/A
22	58	F	PBC	B	64	39	436	3	NL	77	81
23	46	M	ETOH	B	77	33	523	3	NL	73	101
24	55	F	Cryptogenic	C	70	32	612	7	NL	N/A	N/A

Abbreviations: ETOH, alcoholic cirrhosis; α1AT def, alpha-1 antitrypsin deficiency; HCV, hepatitis C; HHC, hereditary hemochromatosis; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; RA, room air; NL, normal; FN, fibronodular infiltrate; I, interstitial infiltrate; N/A, not available; FEV_1/FVC, forced expiratory volume (1-second)/forced vital capacity; TLC, total lung capacity.

No patient had elevated estimated pulmonary artery systolic pressures or systolic dysfunction on echocardiographic testing (data not shown). The mean PaO_2 on room air was 54 ± 12 mm Hg, showing moderate to severe hypoxemia in the majority of patients. Most patients had significant correction on 100% oxygen with a mean value of 393 ± 133 mm Hg. The MAA shunt fraction also was significantly elevated in the majority of patients, with a mean shunt fraction of 25 ± 22%.

Correlation of MAA Shunt Fraction With Gas Exchange. Prior studies have shown that the MAA shunt fraction correlates with the severity of gas exchange abnormalities in HPS.[7,10] Our findings here confirm this result and reveal a strong inverse correlation between the MAA shunt fraction and the PaO_2 on room air ($r = -0.74$; Fig. 1) and a strong positive correlation between the MAA and $P(A\text{-}a)O_2$ ($r = 0.71$; Fig. 2). In contrast, the MAA shunt fraction correlated weakly with PaO_2 on 100% oxygen ($r = -0.43$; Fig. 3).

Interval Between HPS Testing and OLT. The interval between the time HPS testing was performed and OLT was undertaken could influence the performance of these tests as predictors of outcome after OLT, because the results may change during the waiting period. The ABG and MAA results used for our analysis were the latest available before OLT. For room air ABGs, the closest measurement to OLT was performed at a median of 10.7 weeks (2.9 to 22.7) before transplant, and for 100% oxygen PaO_2 values the closest measurement was 22.7 weeks (10.7 to 38.3) before transplant. For MAA scans, the clos-

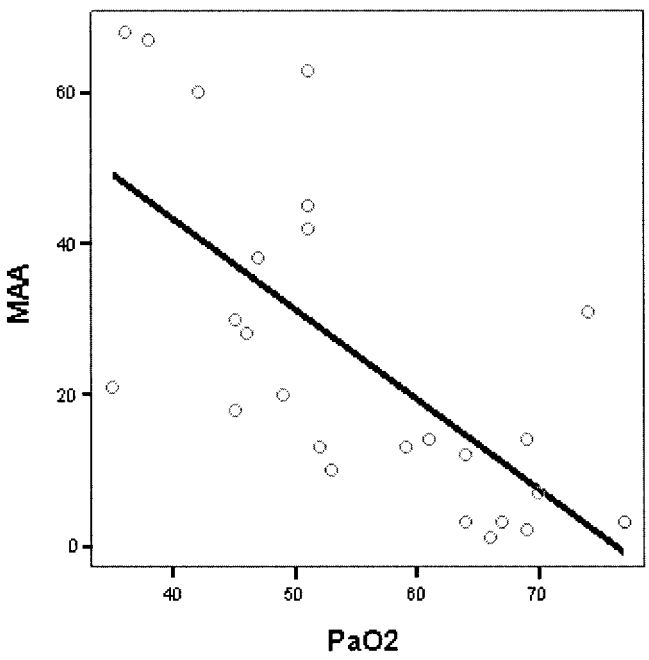

Fig. 1. Correlation between MAA lung perfusion scan and PaO_2 on room air.

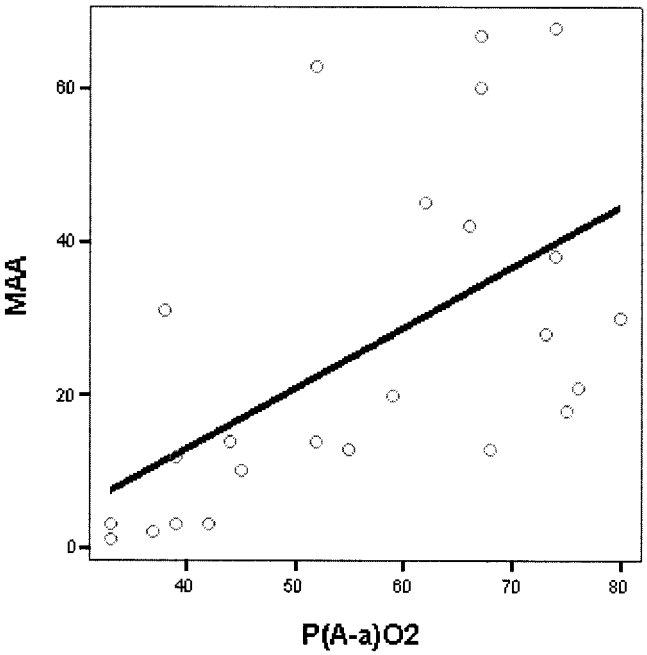

Fig. 2. Correlation between MAA lung perfusion scan and $P(A\text{-}a)O_2$ on room air oxygen.

est measurement to OLT was performed at a median of 22.4 weeks (10.7 to 35.3) before transplant. In a subset of 4 patients, serial MAA shunt measurements were available over time during the waiting period for OLT. In this group, the MAA shunt fraction did not significantly change over a median of 11.5 months.

Outcome After Liver Transplantation. The cohort was followed for a total of 1 year after OLT. During the follow-up interval, 7 patients (29%) died at a mean of 45 days (3 to 71) after OLT. All deaths occurred within the first 10 weeks after surgery. Each of these patients remained in the intensive care unit at the time of death. Of the 7, 6 had persistent hypoxemia requiring ventilatory support, and 1 died of a myocardial infarct on postoperative day 3. Table 2 summarizes the time of death after OLT and the cause for each patient. Of the 7 patients, 5 (patients 1, 2, 3, 13, and 14) died of complications previously associated with transplantation for HPS (sepsis/respiratory failure, sepsis/pulmonary hypertension, hypoxemia/intracranial hemorrhage, and adult respiratory distress syndrome). Each of these patients had prolonged hypoxemia after OLT. One of the remaining 2 patients (patient 21) had persistent hypoxemia after OLT and died at week 8 with atrial fibrillation and a cerebrovascular accident.

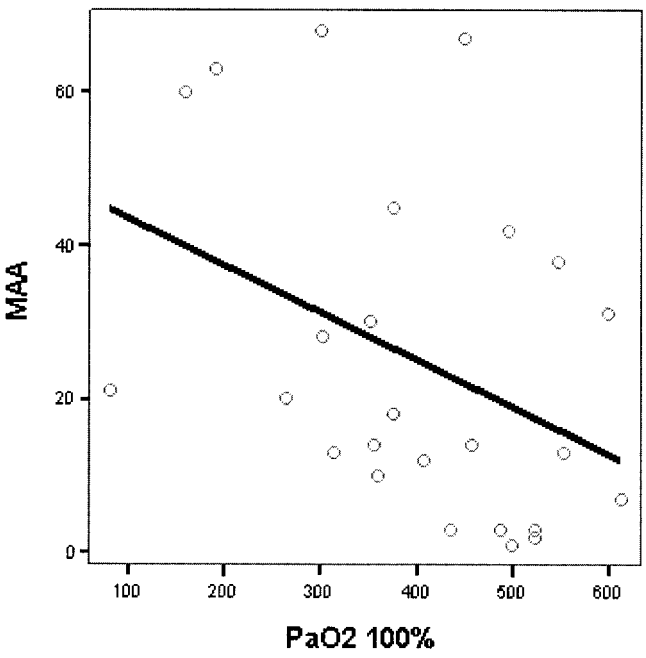

Fig. 3. Correlation between MAA lung perfusion scan and PaO_2 on 100% oxygen supplementation.

Table 2. Number of Days From OLT and Death and Cause of Death in Patients With HPS

Patient No.	Time of Death (Days After OLT)	Cause of Death
1	71	Sepsis, pulmonary hypertension
2	28	Respiratory failure, intracranial hemorrhage
3	24	Respiratory failure
13	60	Pneumonia, respiratory failure
14	71	Sepsis, respiratory failure
16	3	Myocardial infarction
21	60	Atrial fibrillation, cerebrovascular accident

Among the 17 survivors, 14 remained in the intensive care unit for less than 7 days, 2 (patients 5 and 23) for between 7 and 14 days, and 1 (patient 11) for 70 days. Of 17 survivors, 12 had a room air PaO_2 of > 75 mm Hg within 6 months after transplant. By 1 year after transplant, all survivors had a room air $PaO_2 > 75$ mm Hg.

Table 3 compares demographic and HPS test results in patients who survived and those who died after OLT. There were no statistically significant differences in demographic characteristics or in the PaO_2 on 100% oxygen between survivors and nonsurvivors. In contrast, the room air PaO_2 was significantly lower ($P = .001$), the $P(A\text{-}a)O_2$ was significantly higher ($P = .002$), and the MAA shunt fraction significantly higher ($P = .018$) in patients who died compared with those who survived.

Table 3. Comparison of Demographic and Clinical Variables Between Survivors and Nonsurvivors After OLT

	Alive	Expired	*P*
Age	50 ± 13	53 ± 17	NS
Child-Pugh Score	9 ± 2	9 ± 1	NS
PaO_2 (FiO_2 = 21%)	59 ± 10	43 ± 7	.001
PaO_2 (FiO_2 = 100%)	408 ± 123	356 ± 159	NS
$P(A\text{-}a)O_2$	49 ± 14	70 ± 8	.002
MAA (%)	18 ± 20	41 ± 20	.018

Table 4. Test Performance Characteristics in Predicting Mortality After Liver Transplantation

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR +
PaO_2 (Room Air)					
≤50 mm Hg	86	82	67	93	4.85
≤60 mm Hg	100	53	47	100	2.13
≤70 mm Hg	100	12	32	100	1.13
MAA					
≥10%	100	35	39	100	1.55
≥20%	100	76	64	100	4.25
≥30%	71	82	63	88	4.05
PaO_2 ≤50 mm Hg (Room Air) + MAA ≥20%	86	88	75	94	7.29
PaO_2 ≤60 mm Hg (Room Air) + MAA ≥20%	100	76	63	100	4.25

Predictive Value of Diagnostic Tests. We evaluated the ability of room air and 100% oxygen PaO_2 measurements and MAA shunt fraction values to predict post-OLT mortality in our cohort. Table 4 summarizes the results of using different thresholds of room air PaO_2 and MAA shunt fraction for predicting postoperative mortality.

For room air PaO_2, a threshold value of ≤ 50 mm Hg had the best predictive value for postoperative mortality, with a sensitivity of 86%, specificity of 82%, positive predictive value of 67%, and negative predictive value of 93%. For MAA shunt fraction, a threshold value of ≥ 20% had the best predictive value for postoperative mortality, with a sensitivity of 100%, specificity of 76%, positive predictive value of 64%, and a negative predictive value of 100%. A combination of a room air PaO_2 level of ≤ 50 mm Hg and an MAA shunt fraction ≥ 20% further increased predictive value with a sensitivity of 86%, specificity of 88%, positive predictive value of 75%, and a negative predictive value of 94%. The weakest predictor of mortality was the PaO_2 on 100% oxygen, which was associated with a sensitivity of 29%, specificity of 88%, and positive and negative predictive values of 50% and 75%, respectively.

Discussion

HPS is an increasingly recognized complication of chronic liver disease that may contribute to increased morbidity and mortality. No effective medical therapies have been found, and OLT is the only currently available treatment for HPS. However, increasing experience with OLT for HPS has resulted in the recognition of unique postoperative complications and has suggested that significant mortality may occur. No prospective studies have evaluated mortality after OLT or the utility of preoperative HPS testing in predicting outcome in patients undergoing OLT. In the present study, we have prospectively tested and followed a cohort of 24 patients who have undergone OLT. One-year mortality was 29%. All deaths occurred within the first 10 weeks, predominantly in patients with delayed resolution or worsened hypoxemia after transplantation. A combination of a $PaO_2 < 50$ mm Hg and an MAA shunt fraction >20% was a strong predictor of adverse outcome after OLT. These findings reveal that mortality after OLT is increased in HPS and that preoperative testing can help define patients at risk for increased mortality.

Retrospective data suggest that mortality is increased after liver transplantation in patients with HPS relative to patients transplanted without HPS. One-year survival rates in patients transplanted for HPS have been reported to be between 68% and 80%.[5] In addition, unique postoperative complications, including pulmonary hypertension,[11,12] embolic cerebral hemorrhage,[13] and postoperative deterioration in oxygenation have been described. Our prospective analysis confirms that mortality is increased after OLT in patients with HPS. We found a 1-year survival rate of 71% in HPS patients, a rate lower than the reported national average and less than the overall 1-year survival of between 90% and 92% at our centers.[14] However, the overall survival after OLT in our cohort with HPS is not significantly different than that found in several other clinical situations in which OLT is routinely performed.[15,16] Of our nonsurvivors, 5 of 7 had delayed resolution or worsening of hypoxemia or other unique complications associated with HPS, or both, and all deaths occurred within the first 12 weeks after OLT. All patients who survived had significant improvement or resolution of HPS. These findings suggest that delayed resolution of hypoxemia and early complications may increase mortality after OLT in HPS.

We evaluated the use of preoperative HPS testing in predicting outcome after OLT in our cohort. Retrospective studies have suggested that the degree of room air hypoxemia and the increase in the MAA shunt fraction may correlate with operative risk.[6] However, methods for performing ABGs and MAA scans are not standardized between published reports, complicating the task of defining absolute values that might be useful in assessing outcome. In the present study, we performed preoperative HPS testing in a standard fashion between 2 centers and prospectively assessed outcome after OLT in HPS. We found that both the room air PaO_2 and the MAA shunt fraction had good sensitivity and specificity for predicting mortality. In contrast, the PaO_2 on 100% oxygen was of lesser value. More severe hypoxemia on room air and higher shunting correlated with increased postoperative mortality. The combination of a low PaO_2 and a high MAA fraction had the highest likelihood ratio for mortal-

ity. Specifically, a room air PaO_2 <50 mm Hg and a MAA shunt fraction ≥20% were 7.5 times as likely to be seen in HPS patients who die after OLT relative to those who survive after OLT. This data supports the belief that preoperative HPS testing reflects the severity of underlying HPS and appears to identify the group at increased risk for delayed resolution, unique complications, and increased mortality after OLT.

There are several limitations in the present study. First, the number of patients is relatively small, and the results limited to 2 transplantation centers with experience with HPS; therefore, generalization of our results regarding preoperative HPS testing and outcome of OLT to all centers should be made with caution. In addition, the results of HPS testing performed at other centers can only be compared with our findings if similar techniques are used. Nonetheless, our data reflect the first prospective evaluation of OLT for HPS and includes the largest cohort of adults studied. Second, HPS testing was not performed immediately before OLT. Therefore, we cannot be completely sure that the values used to predict outcome in this analysis reflect the actual values at the time of OLT. However, room air ABGs were measured a median of 10.7 weeks before OLT and, based on data regarding the natural history of HPS,[17] we would not anticipate major changes in ABG values over this time interval. In contrast, MAA scans were performed a median of 22 weeks before OLT. Although no published data have evaluated MAA shunt fractions over time in HPS, we found no significant change over a median of 46 weeks in a subset of 4 patients followed with serial scans in our cohort. Finally, from a clinical standpoint, the diagnosis and assessment of severity of HPS are generally made at the time of consideration for OLT, and serial ABG measurements are used to assess progression. In our study, we used this type of approach, and it reflects a clinically applicable strategy.

Our results show that mortality is increased after OLT for HPS, particularly in patients with more severe hypoxemia and significant intrapulmonary shunting as determined by the MAA shunt fraction. These findings support that HPS testing is useful in defining the risk of death associated with OLT. The major clinical implication of our study is that detection and assessment of severity of HPS in otherwise suitable OLT candidates can stratify risk and may minimize adverse transplant outcomes related to the presence of HPS. The importance of detecting and assessing severity of HPS is highlighted by the recently implemented MELD scoring system for OLT where a decline in the room air PaO_2 to below 60 mm Hg significantly increases priority for transplantation.[14] Our results suggest that using a PaO_2 value of between 50 and 60 mm Hg will identify all patients at risk of death after transplantation. We found that OLT mortality was high in patients with severe hypoxemia and an MAA shunt fraction >20%, not all patients with these findings died, our numbers are small and no other therapeutic options are available in this group. Therefore, decisions regarding transplant candidacy in patients with severe HPS must be made on an individual basis until more data are available. A major priority for future investigation is to understand the epidemiology, natural history, and pathogenesis of HPS so that effective medical therapies can be developed and OLT can be targeted to the group of HPS patients most likely to benefit.

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