Hepatopulmonary Syndrome: Favorable outcomes in the MELD exception era

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Running Title: Survival in Hepatopulmonary Syndrome.

Abbreviations: HPS (Hepatopulmonary syndrome); LT (Liver Transplantation); CTP (Child Turcotte Pugh); MELD (Model for end stage liver disease).
Abstract

Background and Rationale: Hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder occurring as a consequence of advanced liver disease, characterized by hypoxemia due to intrapulmonary vascular dilatations. HPS independently increases mortality, regardless the cause or severity of liver disease. Liver transplantation (LT) improves survival in HPS. We present the largest consecutive series of HPS patients specifically addressing long-term survival relative to the degree of hypoxemia and the era in which LT was conducted. We evaluated 106 HPS patients at the Mayo Clinic from 1986 through 2010. Survival was assessed using Kaplan-Meier methodology. Results: LT was accomplished in 49 HPS patients. Post-LT survival (1, 3, 5 and 10 year) did not differ between groups based on baseline PaO$_2$ obtained at the time of HPS diagnosis. Improvements in overall survival at 1, 3 and 5 years post-LT in those HPS patients transplanted after 1/1/2002 (n=28) (92%, 88% and 88%, respectively) as compared to those transplanted prior to that time (n=21) (71%, 67% and 67%, respectively) did not reach statistical significance (5-year p=0.09). Model for Endstage Liver Disease (MELD) exception to facilitate LT was granted to 21 patients since 1/1/2002 with post-LT survival of 19/21 patients and one wait-list death. Conclusion: Long-term outcome after LT in HPS is favorable with a trend towards improved survival in the MELD exception era since 2002 as compared to earlier HPS transplants. Survival after LT was not associated with PaO$_2$ levels at the time of HPS diagnosis.
Hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder characterized by a clinical triad of hepatic dysfunction (usually with portal hypertension), arterial hypoxemia and intrapulmonary vascular dilatations. HPS is not uncommon and affects between 5-32% of individuals being assessed for liver transplantation (LT) depending upon criteria used to define arterial hypoxemia (1).

LT is the only therapy that has been shown to consistently and significantly improve or resolve HPS. Mortality associated with HPS however can be significant and not necessarily related to the severity of liver disease as measured by MELD (Model for End-Stage Liver Disease) or CTP (Child-Turcotte-Pugh) scores. For those HPS patients with PaO$_2$ < 60 mm Hg, MELD exception has been granted in an attempt to improve survival for those with no other contraindications to LT (2).

In the pre-MELD exception era (up to 2002), we had previously shown that HPS has a poor prognosis with a 5-year survival of 23% without LT as compared to a 76% survival with LT (3).

In this report we present additional and extended 10-year survival data for our cohort of 106 patients with HPS, including 49 patients who underwent LT since the inception of our LT program. We aimed to further define the role of arterial hypoxemia as measured by baseline PaO$_2$ (at the time of HPS diagnosis) in
determining post LT survival, as well as describe outcome by the era in which LT was accomplished. Reasons for not accomplishing LT were also reviewed, along with revisiting the prognostic importance of baseline technetium macroaggregated albumin ($^{99m}$TcMAA) lung-brain perfusion scan used to quantify the severity of HPS.

**Methods:**

The study was carried out at Mayo Clinic in Rochester, Minnesota, approved by the Institutional Review Board (IRB), and only included subjects who had provided research authorization. Institutional and divisional funds were used for the purposes of data collection and statistical analysis. There were no commercial interests involved with the study and the authors do not have any conflicts of interest to disclose with regards to this study. All subjects diagnosed with HPS (defined below) and seen at the Mayo Clinic Liver Transplantation program from 1986 through 2010 are included in this cohort.

**Diagnostic criteria for HPS:**

HPS was diagnosed by using the following criteria: 1) hepatic dysfunction manifesting as chronic liver disease (usually cirrhosis) and/or clinical manifestations of portal hypertension (esophagogastric varices, ascites, splenomegaly); 2) abnormal arterial oxygenation ($\text{PaO}_2 \leq 70$ mm Hg) in the upright position breathing room air; and 3) contrast-enhanced transthoracic echocardiography using agitated saline “positive” for the presence of intrapulmonary shunting. A “positive” echocardiogram was evidenced by the appearance of bubbles in the left atria 4-6 cardiac cycles after their first
appearance in the right atrium. Co-existent pulmonary conditions were
documented, but were not a reason to exclude from this analysis as long as HPS
criteria were met and $^{99m}$TcMAA lung perfusion scanning demonstrated abnormal
uptake over the brain.

**Severity of liver disease**

MELD score and CTP classifications were determined to characterize the
severity of liver disease. For the non-transplanted HPS patients, these data
were determined at the time of HPS diagnosis. For those who underwent
transplantation, data reported were those determined at the time of transplant
listing.

**Technetium Macroaggregated Albumin Lung Perfusion Scan ($^{99m}$ Tc MAA):**

Simultaneous $^{99m}$TcMAA lung and brain perfusion scanning was performed to
quantify the degree of intrapulmonary vascular dilatation via measuring
subsequent brain uptake. The procedure was performed with the use of 2mCi of
$^{99m}$TcMAA injected intravenously in the standing position and quantitative brain
imaging which was subsequently obtained in the supine position. Brain
uptake/shunt fraction was calculated assuming a constant 13% blood flow to the
brain. A fractional brain uptake greater than 5% was considered abnormal. The
formula used for this purpose is as below (2), (GMT = geometric mean counts):

\[
\text{Brain uptake (\%)} = \frac{\text{GMT brain}/0.13}{\text{GMT brain}/0.13 + \text{GMT lung}}
\]

**Pulmonary function studies:**

All pulmonary function tests were performed at Mayo Clinic and complied with
the existing American Thoracic Society standards for acceptability and
reproducibility at the time the study was performed. Expiratory airflow obstruction was defined as $\text{FEV}_1/\text{FVC} < 70\%$ (forced expiratory volume in one second/forced vital capacity). Restrictive physiology was defined as a TLC (total lung capacity) $< 80\%$ predicted. Single breath diffusing capacity for carbon monoxide (DLCO), corrected for hemoglobin as a measure of gas exchange efficiency was abnormal if $< 80\%$ predicted.

**Arterial blood gases (ABGs):**

All subjects underwent ABGs in the upright position, breathing room air ($\text{FiO}_2 21\%$). ABG’s were accomplished via a radial artery single stick in the Mayo Clinic Outpatient Pulmonary Function Laboratory (Radiometer ABL 725, Westlake, Ohio). PaO2 values reported were from the time of initial HPS diagnosis (baseline PaO2).

**Post LT ICU management protocol:**

All patients undergoing LT in this report followed a standardized post LT management protocol for both ICU and post ICU care (Figure 1). All HPS patients undergoing LT arrived in the ICU intubated without any attempt to extubate in the operating room. During the ICU stay, the intensivist and ICU team were primarily in charge of management with input from the transplant team. All patients underwent a liver ultrasound with Doppler assessment within the first 2 hours of arrival in the ICU. Periodic laboratory assessment via protocol included TEG, PT, PTT, Fibrinogen and CBC assessment every few hours post LT for the first 6-12 hours. Patients were extubated once the liver ultrasound was reported normal and vitals were stable. Initially, patients were given a closed face mask.
(non-rebreather) with FiO2 in the 0.5 to 1.0 range. For patients with increased work of breathing or persistent hypoxemia, non-invasive ventilation or high flow nasal oxygen (Optiflow™) was the preferred options. Inhaled NO or alprostadil were also available but only rarely used and only in cases of refractory hypoxemia not responsive to standard measures described above. Re-intubation was avoided as far as possible and only used when all the above measures failed to correct hypoxemia and respiratory distress. Every patient followed bundle strategies to prevent ventilator associated pneumonia. Patients were also encouraged to ambulate early and participate in incentive spirometry to prevent atelectasis.

**Statistical analysis:**

Survival and time to event estimates were obtained using Kaplan-Meier methodology and compared using the log rank test. Univariate Cox proportional hazards models were used to assess associations with the outcomes of liver transplant and mortality. Having a liver transplant was also considered as a time-dependent covariate for the mortality outcome post-HPS diagnosis. Subsequent landmark Kaplan-Meier curves were constructed at 1, 3, 5, and 10 years post-HPS diagnosis, comparing those with and without a transplant at those times. (4) Hazard ratios (HR) with 95% confidence intervals (CI) are provided for all Cox models. Statistical significance was assessed at the 5% level using two-sided tests.

**Results:**
Patient characteristics: Summaries of baseline characteristics and their associations with LT are shown in Table 1. On univariate analysis, higher MELD scores and bilirubin values at time of HPS diagnosis were associated with increased likelihood of LT.

The median follow-up time for the 106 HPS patients was 7 years. There were 49 deaths overall, with 15 deaths after transplant. The median follow-up time after transplant was 6.5 years and the median time to transplant after HPS diagnosis was 2.6 years using Kaplan-Meier methodology for all HPS patients. Amongst patients listed prior to 2002, the median time from listing to LT was 9 months whereas it was 6 months for those listed in the MELD exception era. (p=0.27).

Primary causes of liver disease in the LT group were cryptogenic cirrhosis (n=14), alcoholic cirrhosis (n=9), and Hep C (n=6); others included nonalcoholic steatohepatitis - NASH (n=4), autoimmune cirrhosis (n=3), primary biliary cirrhosis - PBC (n=3), biliary atresia (n=2), nodular regenerative hyperplasia - NRH (n=2), Abernethy malformation, ZZ antitrypsin deficiency, sarcoid, hemochromatosis, primary sclerosing cholangitis, and Hep B. Major diagnoses in the non LT group included alcoholic cirrhosis (n=22), Hep C (n=12), cryptogenic cirrhosis (n=7), autoimmune disorders (n=4), NASH (n=3) and PBC (n=3), as well as others including combined variable immune deficiency (n=2), NRH (n=2), and Wilson’s disease (n=1). Hepatocellular carcinoma was present in 3 patients in the LT group and 2 patients in the non-LT group.
Pulmonary angiograms were performed in 27 subjects with the identification of discrete pulmonary arteriovenous communication (via chest CT scanning) in 3 subjects who underwent coil embolization without subsequent improvement in oxygenation. Pulmonary function testing was conducted in 53 patients. The median DLCO was 47% predicted. Spirometry patterns as follows: normal (n=22, 42%); non-specific pattern (n=12, 23%); expiratory airflow obstruction (n=10, 20%) and restrictive lung physiology (n=9, 17%).

**Post-HPS survival:** LT was performed in 49 subjects (23 females) with a median age of 53 years. From the time of HPS diagnosis, survival in the LT cohort tended to be better (without achieving statistical significance) at various time intervals (1, 3, 5 and 10 years) than in those who did not receive LT (HR 0.52, CI 0.26-1.05, p=0.067) ([Figure 2 a-d](#figure2)).

**Association of HPS diagnosis with post-LT survival:** Over the same time period, there were 1,816 LT’s performed (excluding HPS patients) in our center with 1, 3, 5 and 10 year post LT survival of 91%, 85%, 81% and 68% respectively (582 total deaths). Post-LT survivals in those with HPS were 83%, 78%, 78%, and 64% at 1, 3, 5, and 10 years (15 total deaths). No significant survival differences were noted between HPS versus non-HPS transplants (p= 0.37).

**Post-LT survival based on hypoxemia severity, MELD and $^{99m}$TcMAA scanning:**
Survival at 1, 3 and 5 years after LT was not dependent upon baseline PaO$_2$ (obtained at the time of HPS diagnosis) (**Figure 3**). For example, post LT survival at 1, 3 and 5 years for PaO$_2$ > 50 mm/Hg (84%, 80% and 80%) was not significantly different from survival at similar time points for PaO$_2$ ≤ 50 mm/Hg (82%, 76% and 76%) (p= 0.86 and p=0.68 for cutoffs of 50 and 60 mm/Hg, respectively, considering all follow-up time). Using a univariate Cox proportional hazards model, there was no relationship between post LT survival and baseline PaO$_2$ (HR 0.98, CI 0.92-1.03, p=0.39), MELD score (HR 1.05, CI 0.92-1.19, p=0.48), and $^{99}$TcMAA brain uptake quantifications (HR 1.01, 0.98-1.03, p=0.53). Multivariate modeling was performed but not reported due to missing values and low number of events. We also noted that in the MELD exception era, there was no significant difference between PaO$_2$ at the time of HPS diagnosis and PaO$_2$ subsequently obtained weeks prior to LT (data not shown).

**Post-LT Survival in LT subjects in the MELD exception era:**

Survival after LT in the MELD exception era (after 1/1/2002) did seem to improve as compared to the pre MELD era, but this did not reach statistical significance. Patients undergoing LT in the MELD exception era (n=28) had 1, 3 and 5 year survival rates of 92%, 88% and 88% respectively as compared to 71%, 67% and 67% in those transplanted prior to 1/1/2002 (pre MELD era, n=21) (P= 0.06, 0.09, 0.09 respectively for 1, 3 and 5 year survival (**Figure 4**).
There were 21 HPS patients considered LT candidates and given MELD exception (pre-LT $\text{PaO}_2 < 60 \text{ mm Hg}$) beginning in January of 2002 and of these, 20 were successfully transplanted. There were 2 post LT deaths in this group. Cause of death included an Aspergillus pulmonary infection day 144 days post-LT and a presumed massive myocardial infarction 1526 days after LT. There was one HPS patient granted exception that died on the wait list due to peritonitis and sepsis.

**Syndrome resolution post-LT:** Of all the HPS patients undergoing LT, only one did not normalize their $\text{PaO}_2$ post transplant. That patient had concomitant pulmonary fibrosis (pre-LT TLC of $62\%$ predicted with abnormal high resolution chest CT scans), improved the $\text{PaO}_2$ ($54$ to $66 \text{ mm Hg}$) and brain uptake of $^{99m}\text{TcMAA}$ ($24\%$ to $12\%$), but had progressive pulmonary fibrosis necessitating successful double lung transplant 19 months after his liver transplant.

**Reasons for not accomplishing LT:** The reasons for LT refusal/non-accomplishment in the initial cohort of 61 subjects have been described earlier (3). *Table 2* shows the reasons for not accomplishing LT in the subsequent 24 patients evaluated since 2002; 6 HPS patients (5 with MELD exception) were awaiting LT at the time of data analysis. No patients were rejected for LT based solely on severity of HPS or the degree of hypoxemia.
**Peri-transplant morbidity and mortality:** Full perioperative details including OR and ICU management of ventilation, oxygenation, fluid balance, transfusions and length of stay in the ICU and hospital were available for 32 patients undergoing LT and are described in Table 3. The median ICU length of stay for these patients was 2 days (range 1-15 days) with a median hospital stay of 14 days (range 5-65 days) (Table 3). Intubation and mechanical ventilation post LT occurred for a median of 10 hours (range 1-230 hours). Baseline PaO2 < 50 mmHg was noted in 13/28 (46%). Of the 28/49 patients transplanted in the MELD exception era, no patient required a tracheostomy.

Overall, 5/49 patients died within 30 days of LT and none underwent an autopsy. These subjects were transplanted in the years 1989, 1995, 1996, 2000 and 2007. None had received MELD exception. Death causes were as follows: pulmonary infection with CMV and Pneumocystis; massive cerebrovascular bleed; myocardial infarction in the setting of suspected hypertrophic cardiomyopathy and pre-LT pacemaker insertion; portal vein thrombosis with decision to withdraw life support; ventricular fibrillation in the setting of a normal pre-LT dobutamine stress echocardiogram.

Overall, 15/49 transplanted HPS patients had died at the time of this analysis. Causes of death beyond 30 days from LT (n=10) were documented as sudden death (1; etiology unknown), metastatic colon cancer (1), myocardial infarction (2), cerebrovascular accident (2), gastrointestinal sepsis (1), progressive graft
dysfunction (2), and immunocompromised respiratory infection (1). In no circumstance did unresolved HPS appear to be a factor in mortality.

Discussion:

Our data, the largest cohort of HPS patients reported from a single institution over a 25 year period, furthers HPS liver transplant knowledge in three areas; 1) the long-term survival in HPS patients with and without LT; 2) outcome of LT related to the severity of baseline arterial hypoxemia (at the time of HPS diagnosis) and brain uptake after $^{99m}$TcMAA lung perfusion scanning; and 3) HPS wait-list and LT outcome mortality in the era of MELD exception (since 1/1/2002).

Long-term survival

This series describes the longest followup of HPS patients (transplanted or not). At various times from the HPS diagnosis, those who were transplanted had significantly better survival than those not transplanted. The 10-year, 64% post-LT survival of HPS patients provides a unique benchmark.

For comparative purposes, our 30-day mortality post-LT (11%) is comparable to other series (N > 5 cases) reported by other investigators (4-17) (Table 4). Importantly, no intraoperative deaths were noted in this or any other study. Unfortunately, post-transplant hospitalization death did occur, but we believe
those events were not related to the pre-LT severity of HPS. We could not document severe hypoxemia as a direct contributing cause in terms of needing high flow, supplemental oxygen or intubation/mechanical ventilation due to unresolved HPS. These outcomes serve as a reminder that post-LT mortality in HPS patients may not be trivial and the causes are often multifactorial. For those not transplanted our outcome data may appear more favorable than those reported by Schenk et al (13); however patients in that report had more severe liver disease (the majority were Childs C classification). It should be stressed that syndrome resolution post-LT in our cohort (as measured by arterial oxygenation) was almost universal and often preceded the events leading to death.

**LT outcome related to severity of hypoxemia and ⁹⁹ᵐTcMAA lung perfusion scanning**

Using a univariate Cox proportional hazards model, we found that long term survival after LT was not related to the degree of arterial hypoxemia before LT, to the brain shunt fraction using ⁹⁹ᵐTcMAA or to the MELD score before LT. A multivariate model was not fitted as discussed earlier. Specifically, we were unable to demonstrate that using a baseline PaO₂ cut-off of either 50 or 60 mmHg, made any difference to post LT survival in HPS patients. In addition, changes in PaO₂ from the time of diagnosis to the time of LT were varied and not statistical significant. Also, those receiving MELD exception had shorter wait times to LT and thus had a lesser likelihood of major changes in PaO₂ compared to patients in the pre-MELD era (3).
The recent experience by Gupta et al (18) demonstrates that transplanting HPS patients with severe hypoxemia (PaO$_2$ < 50 mm Hg; 1/11 deaths) can result in minimal mortality, but perhaps increased morbidity. We would agree with such an aggressive transplant approach with continued clinical efforts to improve long-term outcomes.

The reasons for a lack of association between mortality post-LT and $^{99m}$TcMAA shunt fraction are unclear. One possible explanation may be the poor correlation between PaO$_2$ and $^{99m}$TcMAA shunt fractions which may reflect variability in true cardiac output to the brain (as opposed to an assumed fixed percent that was used in our shunt calculations).

**MELD Exception: LT Outcome and HPS wait-list mortality:**

We found a trend toward improved survival consistent over 5-years in HPS patients in the era since 1/1/2002 (beginning with MELD exception) as compared to those transplanted prior to 2002. Current MELD exception guidelines provide an opportunity to minimize wait-list mortality, but more importantly facilitate post-LT outcomes that minimize morbidity (especially prolonged intubation/mechanical ventilation and hepatic exposure to severe degrees of arterial hypoxemia). One of the 21 HPS patients in our cohort who received MELD exception died on the wait list (peritonitis/sepsis) and the two post-LT deaths were not related to hypoxemia. Indeed, MELD exception has been critically scrutinized with varied
opinions (19). The success of LT in the setting of HPS and the data presented herein lend further credence to the validity of this approach (3). Certainly, continued critical evaluation of outcomes following MELD exception and adherence to rigorous HPS diagnostic criteria would be prudent (20). Not all HPS are appropriate for LT. Since our last report, an additional 24 subjects were denied/pending LT (Table 2), but we wish to emphasize that since the last report (3), no subject was denied LT solely due to the severity of their HPS (degree of hypoxemia). Such decisions not to transplant potentially impact wait list mortality and LT outcomes.

The fact that we could not demonstrate a difference in LT outcomes based upon baseline PaO$_2$ values should be interpreted carefully. Nearly 50% of the HPS patients that were transplanted (23/49) had a baseline PaO$_2$ < 50 mmHg, a level considered to be severe by any standard. Many perioperative factors are to be considered to optimize the LT management as centers transplant such patients (21). Despite such severe abnormal oxygenation, we pay particular attention to intraoperative blood products/fluid administration, intubation with mechanical ventilation using low tidal volumes and low positive end expiratory pressure, early extubation (but relying on combined 100% oxygen via face mask and high flow nasal cannula oxygen), intermittent use of inhaled nitric oxide/alprostadil to favorably impact ventilation-perfusion post operatively and avoiding re-intubation solely due to severe hypoxemia. All of these interventions, as well as
implementing the MELD exception algorithm, may have contributed to the success in managing the most severe HPS patients.

Limitations

Several limitations in this analysis should be noted. First, the data herein represent an uncontrolled, single institution experience that may have reflected selection bias for LT consideration based upon institutional, as opposed to national or multicenter experience. Second, over the years we have used a very stringent arterial hypoxemia criterion to diagnose HPS (PaO₂ ≤ 70 mm Hg in the upright position at rest). This may have lead to a diagnostic bias by excluding the less severely hypoxemic HPS patients with abnormal alveolar oxygen gradients associated with positive contrast-enhanced echocardiograms. The intent of this analysis was not to study a cohort of those with minimal oxygenation abnormalities. Third, although no patients were denied LT solely due to severe hypoxemia, the decision not to transplant was usually due to multiple co-morbidities. Subsequent management in these patients was not controlled in any manner and that may have affected long-term, non-LT outcomes.

Conclusion:

We present a large, single institution cohort of HPS patients diagnosed and managed over a 25 year period. Survival post LT was not dependent on baseline PaO2 values obtained at the time of HPS diagnosis. We observed a trend (without reaching statistical significance) for better 5-year survival in the MELD
exception era (since 1/1/2002) as compared to earlier HPS transplants. Limited experience with HPS-MELD exception suggests a positive impact on survival and our data fully support HPS exception for LT.

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Figure 1:

ICU admission

Protocol labs, hemodynamic assessment & liver ultrasound

Assess for early extubation. Initial Ventilator settings:
Tidal volume 5-7ml/kg
PEEP 5-10 cm/H20
Fi02 0.5 to 1.0

No active bleeding, normal hemodynamics & liver ultrasound

Early extubation with use of closed face mask oxygen with Fi02 0.5 to 1.0

Continued Hypoxemia

Yes

No

BiPAP or Optiflow (high flow nasal oxygen)

Inhaled alprostadil or nitric oxide for refractory hypoxemia

Consider re-intubation for hypoxemia and/or respiratory distress refractory to all measures

Active bleeding or hemodynamic compromise or abnormal ultrasound

Continue close monitoring with frequent reassessment

Early mobilization, Incentive spirometer
Figure 2:

Hazard ratio for death in the LT group vs the non-LT group: 0.52, CI 0.26-1.05, p=0.067
Figure 3:

Survival vs. Years Since Liver Transplant for different PaO2 levels:
- PaO2 > 50
- PaO2 ≤ 50
- PaO2 > 60
- PaO2 ≤ 60

P = 0.67
Figure 4:

Survival

Years Since Liver Transplant

P = 0.09 (5 year)

- - - Tx yr < 2002
- - - Tx yr >= 2002
Figure Legends:

**Figure 1:** Post-LT flow chart of ICU management protocol.

**Figure 2:** Landmark survival analyses for HPS patients (LT vs. No LT group) at 1, 3, 5 and 10 year landmark points (a-d). This figure utilizes the landmark time-to-event analysis to highlight the survival difference between the LT and non-LT cohorts at different time points after initial HPS diagnosis.

**Figure 3:** Post-LT survival based on baseline PaO₂ values. The graphs shown are for PaO₂ ≤ 50 mm/Hg, > 50mm/Hg, ≤ 60 mm/Hg and > 60mm/Hg.

**Figure 4:** Post-LT survival by MELD era. (MELD exception for HPS began during 2002). There were 28 HPS transplanted from 2002 onward.
Table 1: Baseline characteristics at time of HPS diagnosis and associations with liver transplantation

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Overall HPS cohort (n=106)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (median, range)</td>
<td>106</td>
<td>53 (12-70)</td>
<td>0.98 (0.96, 1.00)</td>
<td>0.11</td>
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<tr>
<td>Female sex (%)</td>
<td>106</td>
<td>45 (42%)</td>
<td>1.12 (0.64, 1.96)</td>
<td>0.69</td>
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<tr>
<td>PaO2 mm Hg (median, range)</td>
<td>106</td>
<td>50 (31-70)</td>
<td>1.02 (0.99, 1.05)</td>
<td>0.18</td>
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<tr>
<td>PaO2 ≤ 50 mm (%)</td>
<td>106</td>
<td>58 (55%)</td>
<td>0.64 (0.37, 1.13)</td>
<td>0.12</td>
</tr>
<tr>
<td>PaO2 ≤ 60 mm (%)</td>
<td>106</td>
<td>82 (77%)</td>
<td>0.72 (0.38, 1.33)</td>
<td>0.29</td>
</tr>
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<td>Aa Gradient mm Hg (median, range)</td>
<td>102</td>
<td>58 (25-89)</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.27</td>
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<tr>
<td>DLCO (% predicted) (median, range)</td>
<td>49</td>
<td>46 (15-94)</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.79</td>
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<tr>
<td>99mTc MAA (%) (median, range)</td>
<td>85</td>
<td>18 (1-83)</td>
<td>1.01 (0.99, 1.02)</td>
<td>0.41</td>
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<td>99mTc MAA &gt; 20%</td>
<td>85</td>
<td>36 (42%)</td>
<td>1.09 (0.59, 2.02)</td>
<td>0.79</td>
</tr>
<tr>
<td>99mTc MAA &gt; 30%</td>
<td>85</td>
<td>21 (25%)</td>
<td>1.09 (0.54, 2.22)</td>
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<td>MELD (median, range)</td>
<td>78</td>
<td>14 (6-30)</td>
<td>1.13 (1.05, 1.23)</td>
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<td>INR (median, range)</td>
<td>79</td>
<td>1.3 (0.9-2.7)</td>
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<td>Creatinine (median, range)</td>
<td>79</td>
<td>0.9 (0.4-1.6)</td>
<td>1.78 (0.48, 6.58)</td>
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<td>Bilirubin (median, range)</td>
<td>79</td>
<td>2.8 (0.2-36.5)</td>
<td>1.15 (1.08, 1.24)</td>
<td>&lt;0.001</td>
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Table 2: Reasons for not accomplishing liver transplantation (LT) in HPS patients evaluated since 2002 (n= 24)

<table>
<thead>
<tr>
<th>Reason</th>
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<th>Comments</th>
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<td>Pending LT</td>
<td>6</td>
<td>5/6 given HPS MELD exception 1/6 HCC MELD exception</td>
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<tr>
<td>Denied LT due to:</td>
<td>12</td>
<td>CVID (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial lung disease (1)</td>
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<td></td>
<td>Advanced emphysema (1)</td>
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<tr>
<td></td>
<td></td>
<td>HPS → POPH (4)*</td>
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<td></td>
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<td>Continued ETOH use (2)</td>
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<td>Aortic stenosis/age&gt;70 (1)</td>
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<td>Metastatic HCC (1)</td>
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<td>Died on waitlist from:</td>
<td>3</td>
<td>Renal abscess/sepsis (1)</td>
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<td>Peritonitis/sepsis (1)</td>
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<td>Pneumonia/ ARDS (1)</td>
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<tr>
<td>Lost to follow-up</td>
<td>3</td>
<td>Never completed transplant evaluation</td>
</tr>
</tbody>
</table>

*These patients evolved into portopulmonary hypertension (POPH) and were denied LT until pulmonary hemodynamics could be improved.
CVID = Common variable immune deficiency
ETOH= alcohol use
HCC= Hepatocellular carcinoma
ARDS= adult respiratory distress syndrome
### Table 3: Perioperative details including oxygenation, ventilation, fluid balance and length of stay for LT subjects.

<table>
<thead>
<tr>
<th>Number</th>
<th>Last status</th>
<th>Age/sex</th>
<th>Pre-LT PaO2/FiO2 (mmHg)</th>
<th>ICU LOS (days)</th>
<th>Respir LOS (days)</th>
<th>Initial OR FiO2</th>
<th>Highest OR FiO2 &amp; vent settings</th>
<th>Highest ICU FiO2 &amp; vent settings</th>
<th>Highest post extubation O2 settings</th>
<th>Highest ICU PEEP (cmH2O)</th>
<th>ICU ventilation (post LT) (hours)</th>
<th>ROM (max or min)</th>
<th>Fluid balance (first 24 hrs) (liters)</th>
<th>Final post balances (liters)</th>
</tr>
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<tbody>
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<td>1</td>
<td>Alive</td>
<td>41/F</td>
<td>47/19</td>
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<td>100%</td>
<td>60% SIMV</td>
<td>70% CMF</td>
<td>5</td>
<td>5</td>
<td>1500</td>
<td>13.4</td>
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</tr>
<tr>
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<td>58/F</td>
<td>67/-</td>
<td>2</td>
<td>6</td>
<td>66%</td>
<td>95%</td>
<td>60% SIMV</td>
<td>40% CMF</td>
<td>5</td>
<td>9</td>
<td>1100</td>
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</tr>
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<td>3</td>
<td>Alive</td>
<td>44/F</td>
<td>48/28</td>
<td>6</td>
<td>14</td>
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<td>91%</td>
<td>80% SIMV</td>
<td>100% Optiflow</td>
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<td>0</td>
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</tr>
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<td>46/24</td>
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<td>80% SIMV</td>
<td>40% CMF</td>
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<td>70% CMF</td>
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<td>46/9</td>
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<td>90%</td>
<td>50% CPAP + PS</td>
<td>40% CMF</td>
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<td>100%</td>
<td>60% SIMV</td>
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<td>55%</td>
<td>60% SIMV</td>
<td>50% CMF</td>
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<td>100%</td>
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<td>35% CMF</td>
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<td>52/25</td>
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<td>90%</td>
<td>70% CPAP + PS</td>
<td>70% CMF</td>
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<td>60% CPAP + PS</td>
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<td>0</td>
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<td>58/F</td>
<td>58/7</td>
<td>20</td>
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<td>4550</td>
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<td>10</td>
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<td>60% SIMV</td>
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<td>52/M</td>
<td>45/17</td>
<td>3</td>
<td>14</td>
<td>55</td>
<td>95</td>
<td>60% CPAP + PS</td>
<td>100% CMF</td>
<td>5</td>
<td>16</td>
<td>0</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Comments: Patient # 1 received 40ppm of Nitric oxide (NO) for 1 day. Patients # 2 received alprostadil at a dose of 40 mcg/hr for 2 days and patient # 6 received the same dose for 4 hrs. Patient # 4 underwent bilateral lung transplantation for lung fibrosis 19 months after LT. Patient # 30 underwent retransplantation after 6 days for primary graft dysfunction.
Table 4: Mortality following liver transplant in HPS (series with n > 5 cases)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Early Mortality**</th>
<th>Late Mortality***</th>
<th>Pre-LT PaO$_2$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott (5)</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>59</td>
</tr>
<tr>
<td>Hobieka (6)</td>
<td>9</td>
<td>44%</td>
<td>0%</td>
<td>59</td>
</tr>
<tr>
<td>Fewtrell (7)</td>
<td>8</td>
<td>13%</td>
<td>0%</td>
<td>83 (Hgb sat)</td>
</tr>
<tr>
<td>Barbe (8)</td>
<td>11</td>
<td>36%</td>
<td>0%; 48 months f/u</td>
<td>57</td>
</tr>
<tr>
<td>Egawa (9)</td>
<td>21</td>
<td>10%</td>
<td>28%; 12 months f/u</td>
<td>57</td>
</tr>
<tr>
<td>Collisson (10)</td>
<td>6</td>
<td>0%</td>
<td>50%; 28 months f/u</td>
<td>52</td>
</tr>
<tr>
<td>Taille (11)</td>
<td>23</td>
<td>9%</td>
<td>22%; 72 months f/u</td>
<td>52 (median)</td>
</tr>
<tr>
<td>Arguedas (12)</td>
<td>25</td>
<td>29%</td>
<td>0%; 12 months f/u</td>
<td>54</td>
</tr>
<tr>
<td>Schenk (13)</td>
<td>7</td>
<td>0%</td>
<td>43%; 24 months f/u</td>
<td>75 (median)</td>
</tr>
<tr>
<td>Kim (14)</td>
<td>13</td>
<td>8%</td>
<td>0%; 90 days f/u</td>
<td>NR</td>
</tr>
<tr>
<td>Krowka (15)</td>
<td>32</td>
<td>17%</td>
<td>no f/u beyond Tx hosp</td>
<td>51</td>
</tr>
<tr>
<td>Schiffer (16)</td>
<td>9</td>
<td>32%</td>
<td>0%; 6 months f/u</td>
<td>60</td>
</tr>
<tr>
<td>Deberaldini (17)</td>
<td>25</td>
<td>32%</td>
<td>8%; 48 months f/u</td>
<td>75</td>
</tr>
<tr>
<td>Gupta (18)</td>
<td>21</td>
<td>0%</td>
<td>5%; 70 months f/u</td>
<td>51</td>
</tr>
<tr>
<td>Current Cohort</td>
<td>49</td>
<td>10%</td>
<td>20%; 120 months f/u</td>
<td>58 (median)</td>
</tr>
</tbody>
</table>

* mean PaO$_2$ mm Hg at time of diagnosis unless otherwise stated

** 30-day or during transplant hospitalization mortality.

*** variable followup time periods from the time of transplant up to the month listed
References:


**Figure 1**

A

BS pool (μmol/100g)

WT

Hm

***

B

Fecal BS output (mmol/day/100g)

WT

Hm

*

C

Relative expression

WT

Hm

D

μmol/100g liver

Cholesterol

Cholesterol

CAM

Bile acid

Bile acid
Figure 2

A

B

C

D

E

F

192x261mm (300 x 300 DPI)
**Figure 3**

**A**
Total biliary BS output after 3 weeks of feeding
- Control
- 0.1% CA
- 0.1% GDCA

**B**
ALT
- Control
- 0.1% CA
- 0.1% GDCA