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Predictors of waitlist mortality in portopulmonary hypertension

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Abstract

Background—The current Organ Procurement Transplantation Network (OPTN) policy grants Model for End Stage Liver Disease (MELD) exception points to patients with portopulmonary hypertension (POPH), but potentially important factors, such as severity of liver disease and pulmonary hypertension, are not included in the exception score, and may affect survival. The purpose of this study was to identify significant predictors of waitlist mortality in patients with POPH.

Methods—We performed a retrospective cohort study of patients in the OPTN database with hemodynamics consistent with POPH [defined as mean pulmonary arterial pressure (mPAP) >25mmHg and pulmonary vascular resistance (PVR) ≥240 dynes•s•cm⁻⁵] who were approved for a POPH MELD exception between 2006 and 2014. Using a Cox proportional hazards model, we identified predictors of waitlist mortality (or removal for clinical deterioration).

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Authorship

All authors contributed to the study design and writing of the manuscript. Drs. DuBrock and Kremers were responsible for data analysis.

Disclosures

The authors declare no conflicts of interest.

Results—One hundred ninety adults were included. Age (HR 1.04, 95% CI 1.00-1.08, $P=0.0499$), initial native MELD score (HR 1.11, 95% CI 1.05-1.17, $P<0.001$), and initial PVR (HR 1.12 per 100 dynes•s•cm⁻⁵, 95% CI 1.02-1.23, $P=0.02$) were the only significant univariate predictors of waitlist mortality and remained significant predictors in a multivariate model, which had a c-statistic of 0.71. PVR and mPAP were not significant predictors of posttransplant mortality.

Conclusions—Both the severity of liver disease and POPH (as assessed by MELD and PVR, respectively) were significantly associated with waitlist, but not posttransplant, mortality in patients with approved MELD exceptions for POPH. Both factors should potentially be included in the POPH MELD exception score to more accurately reflect waitlist mortality risk.

Introduction

Portopulmonary hypertension (POPH), pulmonary arterial hypertension (PAH) that develops in the setting of portal hypertension, affects approximately 5-6% of patients evaluated for liver transplant¹⁻³. Similar to other forms of PAH, POPH is characterized by pulmonary vasoconstriction, obstruction to arterial flow, and vascular remodeling^{4,5}. Diagnostic criteria include an elevated mean pulmonary arterial pressure (mPAP) >25mmHg and an elevated pulmonary vascular resistance (PVR) ≥240 dynes•s•cm⁻⁵ in the absence of an elevated pulmonary artery wedge pressure (PAWP) or alternative etiology of pulmonary hypertension^{5,6}.

POPH is associated with significant morbidity and can lead to right heart failure and death⁷. In the absence of liver transplant or PAH therapy, POPH has been associated with a 5-year survival of 14%⁸. Even in the modern PAH treatment era, POPH was associated with a 5-year survival of only 40% in the multi-center REVEAL study⁷. Case reports and case series have described improved POPH after liver transplant⁹⁻¹¹, but POPH may complicate or preclude liver transplantation because of a high perioperative mortality risk¹².

Since 2006, patients with treated POPH who meet certain hemodynamic criteria have been eligible to receive Model for End Stage Liver Disease (MELD) exception points, or waitlist priority upgrades, in order to expedite liver transplant^{13,14}. According to the current Organ Procurement Transplantation Network (OPTN) policy, patients with POPH who have an adequate hemodynamic response to PAH therapy on follow-up catheterization (defined as mPAP<35mmHg and PVR<400 dynes•s•cm⁻⁵) can be approved for an initial POPH MELD exception score of 22^{13,14,15}. To accrue additional points, patients must undergo repeat right heart catheterizations every 3 months; if catheterization demonstrates a sustained hemodynamic response to PAH therapy, their MELD exception score increases by 10% mortality equivalent points¹⁴.

This system of exception point allocation for POPH has several potential limitations. First, allocation of points and accrual over time does not reflect baseline liver disease severity or pretreatment POPH disease severity, both of which may affect waitlist mortality. It is also controversial whether POPH in the absence of decompensated liver disease should be considered an indication for liver transplant, and there is no minimum liver disease severity required to receive exception points. While case reports and case series have described

improvement or resolution of POPH with liver transplant⁹⁻¹¹, worsening of pulmonary hemodynamics after transplant and perioperative death have also been described^{12,16}.

Given the lack of prospective data on the role of liver transplant in POPH, the current MELD exception policy was developed on the basis of predominantly retrospective observational studies^{12,14}. There have also been no new prospective studies to assist with evidence-based revision of this policy. Goldberg et al recently reported that waitlist candidates with POPH MELD exceptions had a higher risk of death compared to nonexception waitlist candidates¹⁷. No study to date, however, has characterized significant predictors of waitlist or posttransplant mortality in patients with POPH. Our overall goal was to identify predictors of waitlist death in patients with POPH in order to enable evidence-based modification of the current MELD exception policy and to prioritize organ allocation to patients with high waitlist mortality and low posttransplant mortality.

We hypothesized that the severity of both liver disease and POPH would be associated with increased waitlist mortality. To address this hypothesis, we performed a retrospective analysis of the OPTN database to identify significant predictors of waitlist mortality at the time of listing. As secondary aims, we sought to describe the initial and posttreatment pulmonary hemodynamics in patients with POPH and predictors of posttransplant mortality.

Materials and Methods

Study Design

We performed a retrospective cohort study.

Subjects

We evaluated all patients ≥ 18 years old in the OPTN databaseⁱ who applied for an initial or extension POPH MELD exception between January 1, 2006 and December 31, 2014. Only waitlist candidates with hemodynamics consistent with POPH (defined as a documented initial mPAP>25mmHg and an initial PVR ≥ 240 dynes•s•cm⁻⁵) and at least one approved POPH MELD exception were included in the analysis. Exception narratives were reviewed to also identify patients with POPH who were approved for a MELD exception with an alternative OPTN exception code, such as “other”. Duplicate listings of candidates at multiple centers were excluded. Regions were categorized by the median MELD at liver transplant into low (regions 3, 6, 10 and 11), mid (regions 2, 4, 7, 8) and high (regions 1, 5, and 9) MELD regions as previously described¹⁸.

Hemodynamic and laboratory variables

If adequate data were available to calculate missing hemodynamic parameters, calculation was performed using the following equation: mPAP-PAWP [Transpulmonary gradient

ⁱThis study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States (U.S.), submitted by the members of the OPTN, and has been described elsewhere. The HRSA and U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor. The data reported here have been supplied by the UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation by the OPTN or the U.S. Government

(TPG)] = Cardiac output (CO)*PVR. Initial posttreatment hemodynamic variables refer to the initial right heart catheterization performed after initiation of PAH targeted therapy according to review of the initial MELD exception narrative. Initial treatment response (PVR, mPAP and CO) was defined as: (Initial posttreatment value) – (Initial pretreatment value). All references to “MELD” in our analysis refer to native MELD laboratory score at the time of listing.

Outcomes

Our primary outcome was waitlist mortality, and our primary aim was to identify significant predictors of waitlist mortality in patients with hemodynamics consistent with POPH. We defined waitlist mortality as waitlist removal for death or clinical deterioration. This included OPTN codes: “died” and “too sick for transplant” since prior studies have demonstrated that removal from the waitlist for clinical deterioration is equivalent to death^{19,20}. Candidates who were removed from the waitlist due to death during transplant were also included in our primary outcome since they did not survive to completion of liver transplantation. Waitlist candidates who were removed for transplantation or other reasons were censored at the time of removal. Candidates who were still active on the transplant list were censored at the time of last follow-up.

Statistical Methods

Descriptive data were expressed as median (interquartile range)(IQR) for continuous variables and n(%) for categorical variables. Excluded patients were compared to the final cohort of included patients using a Mann-Whitney-U test, chi-square test, or Fisher's exact test as appropriate in the supplemental materials. To address our primary outcome, we used a Cox proportional hazards model. Significant variables with a $P < 0.05$ on univariate analysis were included in our multivariate model if they remained significant after adjustment. We also included confounders if their inclusion in the multivariate model affected the coefficients of other variables by more than 20%. We evaluated the nonlinearity by fitting smooth splines, and the proportional hazards assumption by inspecting the scaled Schoenfeld residuals. We limited our model to 4 predictors to avoid overfitting. Harrell's c-statistics were determined for the final multivariate model and for each variable within the model to assess their predictive accuracy. Kaplan-Meier survival curves were generated and the log-rank test was used to compare groups within the cohort stratified by median values of significant predictors. As a sensitivity analysis, we evaluated the robustness of our model in all patients approved for a POPH MELD exception regardless of whether they met hemodynamic criteria for POPH. Cox regression was also used to identify univariate predictors of posttransplant mortality. Significance was defined as $P < 0.05$. The degree of missingness was reported in tables when the proportion exceeded 5% as the total number of patients (n) included in the analysis. Statistical analysis was performed in SAS version 9.4 (SAS Institute, Cary, NC) and the survival package of R (The R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the institutional review board, OPTN and the Health Resources and Services Administration (HRSA).

Results

Subjects

One hundred and ninety patients with hemodynamics consistent with POPH and at least one approved POPH MELD exception were included in the final analysis. The flow diagram of patients included and excluded is shown in Figure 1. Fifty-three candidates (19.1%) were excluded due to insufficient hemodynamic data and 29 (10.5%) were excluded because they did not meet hemodynamic criteria for POPH. All patients excluded for not meeting hemodynamic criteria had an initial pretreatment PVR $< 240 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$. Characteristics of the excluded patients are detailed in Supplemental Table 1 with *P*-values for comparison to the final cohort. Excluded and included patients were similar with respect to demographics and liver disease severity. Excluded patients were more likely to be listed before 2010 and had a lower initial mPAP, TPG, and PVR and a higher cardiac output.

Patients with hemodynamics consistent with POPH had a median age of 54 years (IQR 48-58) with a median initial native MELD score of 12 (IQR 9-15) and a median initial pretreatment PVR of $450 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$. Fifty-four percent ($n=103$) of patients underwent liver transplant. Four (2.1%) of patients were missing initial native MELD scores (including one patient who died) and were not included in models that included MELD score. Patient characteristics, complications of liver disease and other reasons for waitlist removal are detailed in Table 1.

Waitlist Mortality

Overall composite waitlist mortality or removal for clinical deterioration was 23.2% ($n=44$) with a median time on the waitlist of 344 days. Seven percent ($n=13$) of patients died on the waitlist, 14.2% ($n=27$) of patients were removed for clinical deterioration and 2.1% ($n=4$) were removed due to intraoperative death at the time of transplant. Unadjusted 1-year waitlist mortality or removal for clinical deterioration was 11.1% ($n=21$).

Age, initial MELD score, and initial PVR were the only significant univariate predictors of overall waitlist mortality (Table 2). Age (c-statistic 0.61), initial MELD (c-statistic 0.66) and initial PVR (c-statistic 0.61) had meaningful but limited predictive accuracy. All three variables remained significant in a multivariate model. Spline fits did not show any deviation from linearity for the three model terms (all $P > 0.34$). Tests for deviation from the proportional hazards assumption were not significant for each of the three model terms (all $P > 0.85$). The model using both age and MELD had a c-statistic of 0.66, while the model using age, MELD and PVR had a c-statistic of 0.71. The interaction (product) term between PVR (per 100 $\text{dynes} \cdot \text{s} \cdot \text{cm}^{-5}$) and MELD, when added to the model, was positive at 0.0143 ($SE=0.0104$), suggesting a stronger effect of PVR at higher MELD scores, but was not significant ($P=0.17$), so we did not include it in the final model.

Other hemodynamic parameters (initial mPAP, TPG and CO and posttreatment mPAP, PVR and CO), initial treatment response (mPAP, PVR and CO), and demographic and clinical variables, including gender, race, diagnosis category), and the presence of ascites or encephalopathy at the time of listing, were not significant predictors of waitlist mortality (Table 2).

For illustrative purposes, we used the median values for initial PVR (450 dynes•s•cm⁻⁵) and MELD (12) to stratify the cohort into 4 groups [low MELD and low PVR (n=41), low MELD and high PVR (n=59), high MELD and low PVR (n=51), and high MELD and high PVR (n=35)]. We plotted waitlist survival for each group to illustrate the effect of these variables on waitlist mortality or removal for clinical deterioration (Figure 2). Of the 41 patients with low initial MELD and PVR, only one was removed for clinical deterioration within the first year and no patients died within one year of listing. Two patients in the low MELD/Low PVR group were removed due to waitlist death, both after >5 years of waitlist time, and 3 patients were removed for clinical deterioration. This figure lacks the granularity of the numerical values of MELD, PVR and age used in the Cox regression model, so is solely intended for illustrative purposes.

To confirm the generalizability of our model, we refit the model separately for patients with low and high MELD scores and for waitlist times of less than one year and greater than one year. In these analyses, the parameter estimates for PVR varied by less than 10% and so continued to support the association between increased PVR and mortality in patients with both low and high initial MELD scores and in both early and late time frames. In a sensitivity analysis of all patients 18 years old approved for a POPH MELD exception (n=216 with adequate data), age (HR 1.04, 95% CI 1.00-1.08, $P=0.03$), MELD score (HR 1.13, 95% CI 1.07-1.19, $P<0.001$) and initial PVR (HR 1.20 per 100 dynes•s•cm⁻⁵, 95% CI 1.09-1.32, $P<0.001$) remained significant predictors of waitlist mortality in a multivariate model with similar effect estimates. Additionally, when the 4 intraoperative deaths were censored at the time of death rather than coded as waitlist deaths, the results were also similar (Age: HR 1.05, 95% CI 1.00-1.09, $P=0.03$; MELD: HR 1.13, 95% CI 1.07-1.12, $P<0.001$, initial PVR: HR 1.22 per 100 dynes•s•cm⁻⁵, 95% CI 1.10-1.35, $P<0.001$).

Posttransplant mortality

One hundred and three patients underwent liver transplantation. Seventy-five percent (n=77) of patients were still alive at last follow-up, 17.5% (n=18) had died, 4% (n=4) were re-transplanted and 4% (n=4) had unknown status at follow-up. Of the 18 patients who died posttransplant, 14 died within 1 year of transplant. Neither initial MELD (HR 0.99, 95% CI 0.89-1.11, $P=0.88$) nor initial PVR (HR 1.10 per 100 dynes•s•cm⁻⁵, 95% CI 0.95-1.27, $P=0.20$) were significant predictors of posttransplant mortality. Other demographic and clinical variables were also not significant predictors of posttransplant mortality (Table 3).

Discussion

In our analysis of liver transplant waitlist candidates with POPH, we found that both liver disease severity and POPH severity, as assessed by initial native MELD score and initial PVR, were important predictors of waitlist mortality. We also developed a multivariate model for prediction of waitlist mortality. In waitlist candidates with POPH, prior studies have described increased risk of death in multistate survival models¹⁷ and increased risk of death or graft failure posttransplant compared to nonexception candidates²¹. In contrast to these studies, we chose to identify predictors of waitlist mortality and develop a model for prediction of waitlist mortality since this information could potentially be used to modify the

MELD exception policy to prioritize organ allocation to patients with a higher risk of waitlist death. To the best of our knowledge, this is the first study in the largest cohort of waitlist candidates with POPH that has identified significant predictors of waitlist mortality.

Important features of the patients included in our analysis include relatively mild liver disease and POPH. Similar to prior studies in POPH^{17,21,22}, patients in our cohort had mild liver disease with a median initial native MELD of 12. Additionally, although we restricted our analysis to patients with an initial PVR ≥ 240 dynes•s•cm⁻⁵, half of all candidates had an initial pretreatment PVR ≤ 450 dynes•s•cm⁻⁵. We also found that patients with a low initial MELD and PVR had low waitlist mortality. This study raises the question of whether patients with low initial MELD scores and PVR are appropriate candidates for organ allocation given their low waitlist mortality and the unclear role of liver transplant in the management of POPH. It is also important to recognize that liver transplant may potentially be harmful due to the perioperative risk of transplant and the need for posttransplant immunosuppression.

Our finding of liver disease severity as an important predictor of mortality in POPH is consistent with a prior retrospective study by Le Pavéc et al of 154 patients with POPH evaluated in a French PAH referral center between 1984 and 2004²³. In this cohort, both the presence and severity of cirrhosis (as determined by Child-Pugh class) and cardiac index were the most important prognostic indicators. Although cardiac output was not a significant predictor of waitlist mortality in our analysis, our power to detect this was limited by missing data for most of the cohort. Our study, which included patients in the more modern PAH treatment era, identified predictors of waitlist mortality, while the Le Pavéc study included both pre and posttransplant follow-up in patients who underwent liver transplantation. Since transplantation status can affect mortality, particularly in the era of 1984-2004 before hemodynamic contraindications to liver transplantation were well established¹², our study is more applicable to the current real-world practice of evaluating waitlist mortality risk in patients with POPH.

Notably, mPAP, which is currently used to stratify perioperative risk in patients with POPH¹², was not a significant predictor of waitlist mortality. This may be due to the relationship between mPAP and both PVR and CO by the following equation: $mPAP = CO \times PVR + PAWP$. Accordingly, mPAP can be elevated due to an increase in PVR associated with pulmonary vasoconstriction and vascular remodeling, but can also be elevated in patients with a high CO and hyperdynamic circulation²⁴. The use of PVR to stratify severity of POPH and determine waitlist mortality risk may therefore be more appropriate than mPAP. Additionally, our findings suggest that baseline pretreatment PVR may be more important as a predictor of waitlist mortality than treatment response or posttreatment PVR, since these variables were not significant predictors of mortality.

The unadjusted 1-year posttransplant mortality rate of 14% observed in our cohort was similar to that previously reported by Salgia et al for patients with POPH MELD exceptions transplanted between 2002 and 2010 (1-year unadjusted survival rate of 85%)²¹. While it is important that neither initial nor posttreatment PVR or mPAP were significant predictors of posttransplant mortality in this cohort of patients, we would caution interpretation of these

findings given the risk of Type II error in the smaller sample size of patients who underwent transplantation. Further prospective studies to identify predictors of posttransplant mortality and pulmonary hemodynamic response to liver transplant are still needed.

We acknowledge several limitations to our study. These include the relatively small sample size, missing data in the OPTN database, the retrospective nature of the study and exclusion of a significant number of patients who did not meet hemodynamic criteria for POPH. We also did not compare mortality rates in patients with POPH to nonexception waitlist candidates as this analysis has already been published by Goldberg et al. Compared to the cohort analyzed by Goldberg et al from 2006-2012¹⁷, however, our cohort had a smaller percentage of patients with missing or inadequate hemodynamic data. Potential reasons for this include calculation of hemodynamic parameters and an improvement in submission of complete hemodynamic data after 2010 when the MELD exception for POPH was standardized¹⁴. Additionally, our results may not be generalizable to all patients with POPH, particularly patients who do not respond adequately to PAH therapy or who are never listed for transplant due to comorbid illnesses. Despite these limitations, this analysis represents the largest and most comprehensive national study of waitlist candidates with POPH to date.

Our findings have potential implications for the current MELD exception policy for POPH. Similar to the native MELD score in nonexception waitlist candidates^{25,26}, an ideal MELD exception policy would assign points based on predicted waitlist mortality, thus allocating organs to patients most likely to die from their liver disease (or complications of their liver disease) and minimizing organ allocation to patients with a low risk of waitlist death. Based on our analysis, the initial MELD exception allocation score for POPH should be a function of both native MELD score and initial PVR to more accurately reflect waitlist mortality risk. Additionally, patients with mild liver disease and mild pulmonary hypertension (initial MELD ≤ 12 and initial PVR ≤ 450 dynes $\cdot$ s $\cdot$ cm⁵) had overall low waitlist mortality and may not be appropriate candidates for prioritized organ allocation.

Suggested future analyses would include data simulation to model the effect of modifying the MELD exception criteria for POPH and to translate the predicted hazard ratio of death or waitlist removal (based on a patient's initial MELD and PVR) to an appropriate initial exception score that is reflective of waitlist mortality in a patient's listing region. Additional studies accounting for longitudinal measurements in both MELD and PVR over time may also be helpful in predicting waitlist mortality at different intervals. Lastly, although this study has described significant predictors of waitlist mortality and quantified the risks associated with these factors, prospective studies to identify the short-term and long-term effects of liver transplant and PAH targeted therapy on hemodynamics and outcomes of POPH are warranted. These studies would further help to optimize the MELD exception for POPH and to identify patients most likely to benefit from liver transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	Confidence interval
CO	Cardiac output
HR	Hazard ratio
HRSA	Health Resources and Services Administration
IQR	Interquartile range
MELD	Model for end stage liver disease
mPAP	Mean pulmonary arterial pressure
NASH	Nonalcoholic steatohepatitis
NOS	Not otherwise specified
OPTN	Organ Procurement and Transplantation Network
PAWP	Pulmonary artery wedge pressure
PAH	Pulmonary arterial hypertension
POPH	Portopulmonary hypertension
PVR	Pulmonary vascular resistance
TPG	Transpulmonary gradient

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Figure 1.
Flow diagram of patients included and excluded in the final analysis

Figure 2.

Kaplan-Meier survival curves for the composite outcome of waitlist mortality or removal from the waitlist due to clinical deterioration in four groups of patients stratified by the median MELD and PVR for the cohort [$\text{MELD} \leq 12$ and $\text{PVR} \leq 450 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ ($n=41$), $\text{MELD} \leq 12$ and $\text{PVR} > 450 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ ($n=59$), $\text{MELD} > 12$ and $\text{PVR} \leq 450 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ ($n=51$), and $\text{MELD} > 12$ and $\text{PVR} > 450 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ ($n=35$)]. The groups had significantly different waitlist mortality rates (log-rank $P=0.006$).

Table 1

Patient Characteristics

Patient Characteristic (n=190)	
Age at listing, years	54 (48-58)
Male gender	103 (54.2)
Race	
White	146 (76.8)
Black	7 (3.7)
Hispanic	23 (12.1)
Other	14 (7.4)
Diagnosis	
Hepatitis C virus	73 (38.4)
Alcohol	34 (17.9)
Alcohol and Hepatitis C virus	17 (9.0)
Autoimmune liver disease	15 (7.9)
Primary biliary cirrhosis	10 (5.3)
Nonalcoholic steatohepatitis	7 (3.7)
Other	34 (17.9)
Region	
Low MELD at transplant (Regions 3, 6, 10 and 11)	55 (29.0)
Mid MELD at transplant (Regions 2, 4, 7, and 8)	93 (49.0)
High MELD at transplant (Regions 1, 5, and 9)	42 (22.1)
Listing Year	
Before 2010	62 (32.6)
2010-2014	128 (67.4)
MELD Score	
Initial native MELD	12 (9-15)
Native MELD at waitlist removal	14 (10-20)
Complications of liver disease (n=186)	
Ascites	131 (70.4)
Encephalopathy	103 (55.4)
Initial pulmonary hemodynamics	
mPAP, mmHg	46 (40-54)
TPG, mmHg (n=55)	34 (27-41)
PVR, dynes•s•cm ⁻⁵	450 (360-608)
CO, L/min (n=55)	6.1 (5.2-7.4)
Initial post-treatment pulmonary hemodynamics	
mPAP, mmHg	31 (26-33)

Patient Characteristic (n=190)	
PVR, dynes•s•cm ⁻⁵	200 (147-266)
CO, L/min (n=151)	7.2 (5.8-8.9)
Initial treatment response	
mPAP, mmHg	-16 (-23- -10)
PVR, dynes•s•cm ⁻⁵	-246 (-362- -148)
CO, L/min (n=40)	1.1 (-0.1- 3.1)
Waitlist Time	
Days on waitlist	344 (153-725)
Time from listing to exception approval, days	18 (5-419)
Time from approval to waitlist removal, days	185 (88-367)
Reasons for Waitlist Removal	
Died	17 (9.0)
Too sick	27 (14.2)
Liver transplant	103 (54.2)
Other	8 (4.2)
Still on waitlist	35 (18.4)

Data reported as median (interquartile range) or n(%)

CO: Cardiac output, IH: Inhaled, IV: Intravenous, MELD: Model for End Stage Liver Disease, mPAP: Mean pulmonary arterial pressure, NOS: Not otherwise specified, PDE5: Phosphodiesterase 5, PVR: Pulmonary vascular resistance, SC: Subcutaneous, TPG: Transpulmonary gradient

Table 2

Univariate and multivariate predictors of waitlist mortality or removal for clinical deterioration

Variable	Univariate Model		Multivariate Model	
	HR (95%CI)	P	HR (95%CI)	P
Age at listing	1.04 (1.00-1.08)	0.0499	1.05(1.00-1.09)	0.03
Female gender (male reference)	1.37 (0.76-2.48)	0.30		
Race Category		0.08		
White	Reference			
Black	3.21 (0.75-13.71)	0.12		
Hispanic	0.33 (0.10-1.07)	0.06		
Other	0.56 (0.13-2.34)	0.43		
Diagnosis Category		0.40		
Hepatitis C	Reference			
Alcohol	0.68 (0.30-1.56)	0.36		
Alcohol and Hepatitis C	0.17 (0.02-1.28)	0.08		
Autoimmune	1.63 (0.60-4.46)	0.34		
Primary Biliary Cirrhosis	0.41 (0.09-1.89)	0.25		
NASH	0.00 (0.00-0.00)	0.99		
Other	0.95 (0.43-2.12)	0.90		
Initial native MELD	1.11 (1.05-1.17)	<0.001	1.13(1.08-1.20)	<0.001
Complications of Liver Disease				
Ascites	1.74 (0.83-3.64)	0.14		
Encephalopathy	1.00 (0.54-1.86)	0.99		
Initial Hemodynamics				
mPAP, mmHg	1.02 (0.98-1.05)	0.40		
TPG, mmHg (n=55)	1.04 (0.98-1.11)	0.21		
PVR, per 100 dynes•s•cm ⁻⁵	1.12 (1.02-1.23)	0.02	1.21(1.09-1.33)	<0.001
CO, L/min (n=55)	0.67 (0.42-1.08)	0.10		
Posttreatment Hemodynamics				
mPAP, mmHg	0.99 (0.94-1.04)	0.72		
TPG, mmHg (n=55)				
PVR, per 100 dynes•s•cm ⁻⁵	1.14 (0.89-1.47)	0.30		
CO, L/min (n=151)	0.99 (0.85-1.17)	0.95		
Treatment Response				
mPAP, mmHg	1.02 (0.99-1.05)	0.33		
PVR, per 100 dynes•s•cm ⁻⁵	1.09 (0.98-1.22)	0.13		
CO, L/min (n=40)	0.95 (0.64-1.41)	0.79		

CO: Cardiac output, HR: Hazard ratio, MELD: Model for End Stage Liver Disease, mPAP: Mean pulmonary arterial pressure, NASH: Nonalcoholic steatohepatitis PVR: Pulmonary vascular resistance, TPG: Transpulmonary gradient

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Table 3

Univariate predictors of posttransplant mortality (n=99)

Variable	HR (95%CI)	P
Age at listing	1.00 (0.94-1.06)	0.97
Female gender (male reference)	0.61 (0.23-1.64)	0.33
Race Category		0.99
White	Reference	
Black	0.98 (0.13-7.49)	0.98
Hispanic	0 (0-0)	0.99
Other	1.28 (0.29-5.63)	0.74
Diagnosis Category		0.51
Hepatitis C	Reference	
Alcohol and Hepatitis C	1.23 (0.38-3.93)	0.73
Alcohol	0 (0-0)	0.99
Autoimmune	1.65 (0.35-7.65)	0.52
Other	0.31 (0.07-1.44)	0.14
Initial MELD	0.99 (0.89-1.11)	0.88
Complications of Liver Disease		
Ascites	1.64 (0.53-4.97)	0.39
Encephalopathy	1.21 (0.45-3.27)	0.71
Initial Hemodynamics		
mPAP, mmHg	1.01 (0.95-1.06)	0.81
TPG, mmHg (n=38)	1.06 (0.95-1.18)	0.33
PVR, per 100 dynes•s•cm ⁻⁵	1.10 (0.95-1.27)	0.20
CO, L/min (n=38)	1.03 (0.66-1.63)	0.89
Post treatment Hemodynamics		
mPAP, mmHg	0.96 (0.89-1.04)	0.31
PVR, per 100 dynes•s•cm ⁻⁵ (n=93)	1.13 (0.75-1.70)	0.56
CO, L/min (n=75)	0.83 (0.62-1.11)	0.20
Treatment Response		
mPAP, mmHg	0.98 (0.93-1.03)	0.39
PVR, per 100 dynes•s•cm ⁻⁵ (n= 93)	0.90 (0.77-1.05)	0.16
CO, L/min (n=27)	0.74 (0.49-1.11)	0.15

CO: Cardiac output, HR: Hazard ratio, MELD: Model for End Stage Liver Disease, mPAP: Mean pulmonary arterial pressure, PVR: Pulmonary vascular resistance, TPG: Transpulmonary gradient