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RESEARCH ARTICLE

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Predictors of early mortality after lung transplantation for idiopathic pulmonary arterial hypertension

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Abstract

Lung transplantation remains an important therapeutic option for idiopathic pulmonary arterial hypertension (IPAH), yet short-term survival is the poorest among the major diagnostic categories. We sought to develop a prediction model for 90-day mortality using the United Network for Organ Sharing database for adults with IPAH transplanted between 2005 and 2021. Variables with a p value ≤ 0.1 on univariate testing were included in multivariable analysis to derive the best subset model. The cohort comprised 693 subjects, of whom 71 died (10.2%) within 90 days of transplant. Significant independent predictors of early mortality were: extracorporeal circulatory support and/or mechanical ventilation at transplant (OR: 3; CI: 1.4–5), pulmonary artery diastolic pressure (OR: 1.3 per 10 mmHg; CI: 1.07–1.56), forced expiratory volume in the first second percent predicted (OR: 0.8 per 10%; CI: 0.7–0.94), recipient total bilirubin >2 mg/dL (OR: 3; CI: 1.4–7.2) and ischemic time >6 h (OR: 1.7, CI: 1.01–2.86). The predictive model was able to distinguish 25% of the cohort with a mortality of ≥20% from 49% with a mortality of ≤5%. We conclude that recipient variables associated with increasing severity of pulmonary vascular disease, including pretransplant advanced life support, and prolonged ischemic time are important risk factors for 90-day mortality after lung transplant for IPAH.

KEYWORDS
early mortality, idiopathic pulmonary arterial hypertension, lung transplantation

INTRODUCTION

Considerable progress has been made in the medical therapy of idiopathic pulmonary arterial hypertension (IPAH) in recent decades.[1] Yet mortality remains high in a significant proportion of patients with persistent unfavorable prognostic features despite treatment,[2–5] largely as a result of progressive right heart failure.[6] Lung transplantation represents the only viable alternative to improve long-term survival in high-risk individuals.[7]

Historically, IPAH subjects have had the highest early mortality after lung transplant relative to other diagnostic groups[8,9]; the consequence of a markedly increased risk of primary graft dysfunction (PGD), acute kidney

injury, and other life-threatening postoperative complications.[10,11] However, long-term survival, conditional upon 3-month survival is excellent exceeding a median of 10 years,[8] reflecting the relatively young age and paucity of co-morbidities in this patient population.[12] Hence, strategies to optimize peri-operative management and early outcomes are likely to have a large impact on long-term survival.

We sought to develop a prediction model for 90-day mortality in lung transplant recipients with IPAH using the United Network for Organ Sharing (UNOS) database, to allow identification of high-risk subjects that could be targeted for more intense management. Clinical variables reflecting the severity of pulmonary vascular disease and/or right ventricular (RV) dysfunction were hypothesized to be associated with early mortality.[13]

METHODS

The primary objective was to develop a prediction model for 90-day mortality among lung transplant recipients with IPAH. Standard Transplant Analysis and Research files (STAR) were obtained from UNOS.[14] Recipients aged ≥18 years with a listing diagnosis of primary pulmonary hypertension (PPH, which is the term used in the database for IPAH) who underwent a bilateral lung or combined heart-lung transplant between May 2005 and May 2021 were included. Single-lung and other multiorgan transplant recipients were excluded. Kaplan–Meier 90-day survival curves for IPAH versus other major diagnostic groups were compared with log-rank test. Selected recipient and donor characteristics were assessed for their association with early outcome. Predictor variables were selected for their plausible association with early mortality based on previous literature and clinical reasoning, and their availability in the database. The inclusion start date represents the initiation of the UNOS lung allocation system (LAS). Major changes in the LAS that tended to prioritize PAH candidates were instituted on March 1, 2015. Comparisons between 90-day survivors and deaths were performed with Wilcoxon rank sum or Student's t test for continuous variables and Fisher exact or χ^2 test for categorical variables, as appropriate. Values were taken at the time of transplant if available, otherwise, the most recently obtained timepoint. For selected continuous variables, threshold values based on established prognostic cut-offs were also used. Missing data was imputed with a multiple imputation by chained equations algorithm.[15] Variables were tested with logistic regression analysis for their association with 90-day mortality. Potential risk factors with a p value ≤ 0.1 by univariate analysis were included in multivariable models to derive the best subset model using the Akaike information criterion (AIC).[16] When certain variables were co-linear, the one with the strongest association was selected for the multivariable model. The model with the lowest AIC and where all predictor variables were statistically significant ($p < 0.05$) was selected. The apparent performance of the model was determined by the area under the receiver operator characteristics curve (AUC-ROC). Sensitivity analysis was performed by substituting selected co-linear variables into the model and after excluding heart-lung recipients. The impact of individual predictor continuous variables was graphically displayed by plotting against the probability of 90-day mortality with all other variables in the model fixed.

Internal validation of the final model was performed using the bootstrap approach.[17] The prediction method was repeated in 2000 bootstrap samples equal in size to the data set with replacement from the original sample. The apparent performance (AUC of ROC) was determined in each sample (bootstrap performance) and in the entire sample (test performance). Optimism was calculated as the difference between the bootstrap and test performance. The average estimate of optimism from the bootstrap samples was subtracted from the original apparent performance to obtain an optimism-corrected estimate of performance.

In a post-hoc analysis to detect other potential risk factors, the multivariable model with the lowest AIC but not restricted to where all predictor variables had a p-value < 0.05 was generated. Statistical analysis was performed with R Version 4.1.3. Guidelines developed by the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD)[18] were applied.

RESULTS

Cohort characteristics

During the observation period, 693 subjects with a listing diagnosis of PPH were identified and included in the analysis. Table 1 summarizes key recipient and donor variables of the patient cohort. Ninety-three percent ($N = 642$) underwent bilateral lung transplantation, while the remainder received a combined heart-lung transplant. They were predominantly young to middle-aged females, consistent with a diagnosis of IPAH. Advanced severity of disease was indicated by a median pulmonary vascular resistance (PVR) of nearly 10 Woods units (WU), impaired 6-min walk distance (6MWD), and hospitalized status in 30%. Ten percent required

TABLE 1 Cohort characteristics.

Variable[a]	Overall (n = 693)	90-day posttransplant outcome			Missing values (N)
		Survival (n = 622)	Death (n = 71)	p Value	0
Age, year	48 (36, 58)	48 (36, 58)	48 (35, 58)	0.73	0
Gender: Female, n (%)	480 (69)	435 (70)	45 (63)	0.35	0
Ethnicity, n (%)					
White	473 (68)	417 (67)	56 (79)	0.13	0
Black	91 (13)	85 (14)	6 (9)		
Other	129 (19)	120 (19)	9 (13)		
Combined heart-lung transplant, n (%)	51 (7.4)	47 (8)	4 (6)	0.73	0
Days on waitlist	61 (18,160)	57 (17,158)	78 (16, 161)	0.57	0
Medical condition, n (%)					
In ICU	145 (21)	120 (19)	25 (35)	0.008	0
Hospitalized, non-ICU	79 (11)	72 (12)	7 (10)		
Nonhospitalized	469 (68)	430 (69)	39 (55)		
ECMO and/or ventilator, n (%)	70 (10.1)	52 (8.4)	18 (25)	<0.001	0
Recent Era (≥03/01/2015) n (%)	402 (58)	365 (59)	37 (52)	0.35	0
Pulmonary hemodynamics					
Mean PAP, mmHg	54 (45, 64)	54 (44, 63)	58 (48, 68)	0.021	24
Systolic PAP, mmHg	84 (70, 99)	84 (69, 98)	89 (75, 105)	0.015	15
Diastolic PAP, mmHg	36 (29, 45)	35 (29, 44)	41 (30, 50)	0.009	15
Cardiac Index (L/min/m^2)	2.5 (2.0, 3.1)	2.5 (2.0, 3.1)	2.4 (1.9, 2.9)	0.123	42
Cardiac Index <1.8, n (%)	91 (13)	81 (13)	10 (14)	0.75	
PAWP, mmHg	12 (9, 15)	11 (8, 15)	12 (10, 17)	0.072	58
PVR (Wood Units)	9.6 (6.4, 13.6)	9.5 (6.5, 13.2)	11.8 (6.3, 16.4)	0.031	82
CVP, mmHg	11.6 (9, 15)	11.3 (9, 14)	12.2 (10, 15)	0.022	334
CVP > 15, n (%)	152 (22)	134 (22)	18 (25)	0.56	
Exercise capacity and pulmonary function					
6-min walk distance, m	240 (138, 332)	244 (147, 335)	202 (91, 269)	0.003	8
FVC % predicted	70 (57, 84)	72 (58, 84)	64 (55, 74)	0.011	22
FEV_1 % predicted	62 (48, 75)	63 (49, 76)	55 (43, 66)	0.003	24
FEV_1% predicted/FVC% predicted	0.9 (0.79, 0.98)	0.9 (0.8, 0.99)	0.87 (0.8, 0.95)	0.098	24
Any O_2 use, n (%)	636 (92)	575 (92)	61 (86)	0.095	0
O_2 use, L/min	4 (2, 7)	4 (2, 6)	6 (3, 9)	0.015	57
PCO_2, mmHg	36 (31, 43)	36 (31, 43)	34 (32, 43)	0.7	62
End-organ dysfunction and co-morbidity					
eGFR mL/min/1.7 m^2	73 (56, 92)	73 (55, 92)	74 (60, 92)	0.43	0
eGFR <60, n (%)	208 (30)	190 (31)	18 (25)	0.305	
Total bilirubin, mg/dL	0.6 (0.4, 1)	0.6 (0.4, 1)	0.8 (0.5, 1.4)	0.002	1

(Continues)

TABLE 1 (Continued)

Variable[a]	Overall ($n = 693$)	90-day posttransplant outcome			Missing values (N)
		Survival ($n = 622$)	Death ($n = 71$)	p Value	0
Total bilirubin >2 mg/dL, n (%)	40 (5.8)	30 (4.8)	10 (14)	0.005	
Body mass index (kg/m^2)	24.6 (21, 29)	24.7 (21, 29)	24 (22, 28)	0.62	1
Body mass index >30, n (%)	118 (17)	108 (17)	10 (14)	0.63	
Pretransplant diabetes, n (%)	73 (11)	66 (11)	7 (10)	1	0
Donor and procedural characteristics					
Donor age, year	34 (23, 45)	33 (23, 45)	37 (23, 45)	0.41	0
Donor age >50, n (%)	103 (15)	92 (15)	11 (16)	1	
Donor smoking >20 pack/year, n (%)	68 (10)	59 (10)	9 (13)	0.52	0
Donor/Recipient predicted TLC ratio	1.05 (0.96, 1.2)	1.04 (0.96, 1.2)	1.11 (0.96, 1.2)	0.25	0
Ischemic time, hour	5.5 (4.6, 6.6)	5.3 (4.5, 6.3)	5.7 (4.3, 7.2)	0.065	10
Ischemic time >6 h, n (%)	226 (33)	193 (31)	33 (47)	0.013	
Transplant center PPH volume during study period, n (%)					
Tertile 1: 1–4	63 (9)	54 (9)	9 (13)	0.31	0
Tertile 2: 5–10	124 (18)	115 (19)	9 (13)		
Tertile 3: 11–43	506 (72.4)	453 (73)	53 (75)		

Abbreviations: CVP, central venous pressure; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; TLC, total lung capacity.

[a]Values presented as median (IQR) unless otherwise indicated.

extracorporeal membrane oxygenator (ECMO) and/or ventilator use at the time of transplant. Among the 70 subjects in this category, 65 were on ECMO and 29 were on mechanical ventilation at transplant.

Postoperative mortality and morbidity

Seventy-one deaths occurred for a 90-day mortality of 10.2%. In comparison, mortality for all other diagnostic groups during the observation period was significantly lower (Figure 1). Causes of death were pulmonary/graft failure in 20 (28%), multiorgan failure in 12 (17%), infection in 10 (14%), cerebrovascular in 9 (13%), cardiovascular in 8 (11%), hemorrhage in 6 (8%), and other in 6 (9%). Early posttransplant morbidity was high as suggested by continued intubation at 72 h in 38%, ECMO use at 72 h in 14%, and dialysis before discharge in 19%. ECMO use at 72 h was recorded in 35% of 90-day nonsurvivors versus 11% of survivors ($p < 0.001$). Dialysis was applied in 55% of 90-day decedents compared with 15% of survivors ($p < 0.001$). The median length of stay in survivors was 28 days (IQR: 16, 56).

Risk factors for early mortality

Variables listed in Table 1 were assessed for their relationship with 90-day mortality. Results of the univariate logistic regression analysis are presented in Table 2. Significant or marginal associations (p value ≤ 0.1) were observed for ECMO and/or ventilator use pretransplant, in intensive care unit (ICU) at transplant, 6MWD, FEV_1 (forced expiratory volume in 1 s) % predicted, FVC (forced vital capacity) % predicted, O_2 use, central venous pressure (CVP), pulmonary artery mean (mPAP), systolic (sPAP) and diastolic pressure (dPAP), PVR, ischemic time and recipient total bilirubin. As expected, mPAP, sPAP, and dPAP were highly correlated with each other and moderately correlated

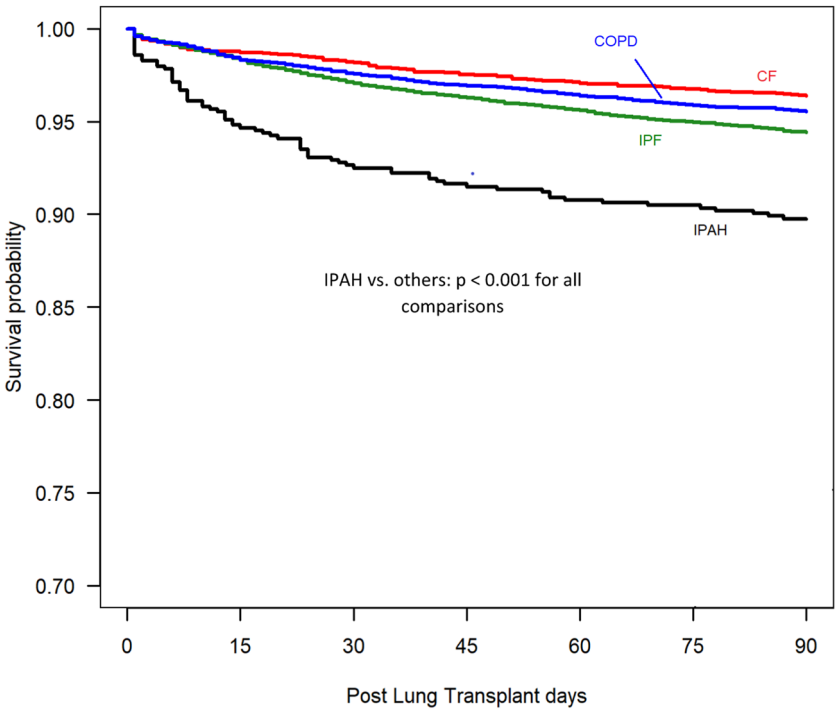

FIGURE 1 Kaplan–Meier curves of 90-day survival after lung transplant among the four major diagnostic group categories: IPAH (idiopathic pulmonary arterial hypertension, $N = 693$; mortality 10.2%), CF (cystic fibrosis, $N = 2977$; mortality 3.65%), IPF (idiopathic pulmonary fibrosis, $N = 10{,}778$; mortality 5.67%), COPD (chronic obstructive pulmonary disease, $N = 6983$; mortality 4.39%). Comparisons between groups with log-rank test.

with PVR (Supporting Information: Table S1). Only dPAP and PVR were included in the best multivariable subset model. Similarly, FEV_1% and FVC % were colinear and only the former was supplied in the multivariable model. Ischemic time >6 h and bilirubin >2 mg/dL were included as dichotomous rather than continuous variables in the model. No significant difference in mortality was noted in the more recent era.

Predictors of 90-day mortality selected in the best subset model, yielding the lowest AIC (429.51) and where all predictor variables had a p value < 0.05, are listed in Table 3. ECMO and/or ventilator use at transplant, lower FEV_1% predicted, higher dPAP, recipient bilirubin >2 mg/dL and ischemic time >6 h were independently associated with early mortality after lung transplant. The resultant linear prediction equation and receiver operator characteristics (ROC) curve are displayed in Figure 2. The area under the ROC curve (AUC) of 0.693 indicates overall modest discrimination for 90-day mortality. The average of the estimates of optimism with the bootstrap internal validation method was 0.02, yielding an optimism-corrected estimate of performance (ROC-AUC) of 0.673.

At either end of the predictor equation range, L had clinical utility (Figure 2). When the value of L was −1.942 (corresponding to a specificity for 90-day mortality of 79%) or higher, which included 172 subjects (25% of cohort), the positive predictive value for mortality was ≥0.2. With L of −2.496 or lower (corresponding to sensitivity of 75%), which comprised 336 subjects (49% of cohort), the negative predictive value was ≥0.95. Among the five predictor variables, ECMO and/or ventilator use at transplant had the greatest relative importance (Supporting Information: Figure S1). Figure 3 displays the greater probability of death with decreasing FEV_1 and the additive effect of ECMO/ventilator use.

A sensitivity analysis was performed by substituting sPAP for dPAP and FVC% predicted for FEV_1 in the final model. Results are presented in Supporting Information: Table S2. In both cases, the predictive value for 90-day mortality was similar. The post-hoc multivariable analysis, where the best subset model with the lowest AIC (428.24) and not restricted to all predictor variables with a p value of <0.05, is presented in Table 4. In this model, 6MWD and ischemic time >6 h demonstrated trends for 90-day mortality, whereas pretransplant ECMO/ventilator use, dPAP, FEV_1% predicted and bilirubin >2 mg/dL remained significant independent predictors. Excluding heart-lung recipients did not appreciably change the predictor variables (Supporting Information: Table S3).

DISCUSSION

Refinements in peri-operative management have reduced early mortality after lung transplantation. The 90-day graft failure rate in the most recent UNOS report was below 5% for all recipients.[19] Short-term outcomes have consistently been the poorest among those with IPAH/PPH. In the ISHLT (International Society for Heart and

TABLE 2 Univariate logistic regression model for 90-day mortality.

Variable	Odds ratio (95% CI)	*p* Value
Age, year	0.99 (0.98–1.01)	0.57
Gender: Male	1.34 (0.8–2.2)	0.26
Ethnicity: Black versus White	0.53 (0.22–1.26)	0.15
Days on waitlist	1 (0.99–1.001)	0.95
Combined heart-lung transplant	0.73 (0.26–2.1)	0.56
In ICU versus not in ICU	2.3 (1.2–3.6)	0.009[a]
ECMO and/or ventilator at transplant	3.7 (2–6.8)	<0.001[a]
Recent Era (≥03/01/2015)	0.77 (0.5–1.3)	0.29
mPAP, per 10 mmHg	1.2 (1.03–1.42)	0.023
PA systolic pressure, per 10 mmHg	1.15 (1.03–1.28)	0.016
PA diastolic pressure, per 10 mmHg	1.31 (1.09–1.57)	0.004[a]
PVR (WU)	1.05 (1.0–1.09)	0.021[a]
Cardiac Index (L/min/m^2)	0.83 (0.6–1.1)	0.26
Cardiac Index <1.8	1.22 (0.6–2.4)	0.56
PAWP, mmHg	1.02 (0.99–1.05)	0.20
CVP, mmHg	1.06 (1.0–1.12)	0.036[a]
CVP > 15	1.24 (0.7–2.2)	0.46
6 MWD, per 10 m	0.97 (0.95–0.99)	0.003[a]
FVC, per 10% predicted	0.85 (0.74–0.96)	0.012
FEV_1, per 10% predicted	0.82 (0.72–0.94)	0.003[a]
O_2 use, L/min	1.05 (1.00–1.09)	0.021[a]
PCO_2, mmHg	1.00 (0.97–1.03)	0.97
eGFR mL/min/1.7 m^2	1.01 (0.99–1.01)	0.21
eGFR <60	0.77 (0.4–1.4)	0.37
Total bilirubin, mg/dL	1.11 (0.94–1.23)	0.09
Total bilirubin >2 mg/dL	3.2 (1.5–6.9)	0.003[a]
Body mass index (kg/m^2)	0.99 (0.94–1.05)	0.84
BMI > 30	0.79 (0.4–1.6)	0.52
Pretransplant diabetes	0.92 (0.4–2.1)	0.85
Donor age, year	1.0 (0.99–1.03)	0.34
Donor age >50	1.06 (0.5–2.1)	0.88
Donor smoking >20 pack/year	1.39 (0.7–2.9)	0.39
Donor/Recipient predicted TLC ratio	1.59 (0.52–4.9)	0.42
Ischemic time, hour	1.19 (1.03–1.36)	0.015
Ischemic time >6 h	1.93 (1.2–3.2)	0.009[a]
Center volume: tertile 3 versus 1	0.7 (0.3–1.5)	0.3

Note: Abbreviations as in Table 1.

[a]Indicates variables supplied for the multivariable best subset model.

TABLE 3 Multivariable model of 90-day mortality.

Predictor	Estimate	Odds ratio (95% CI)	*p* Value
Intercept	−2.405	–	–
ECMO or ventilator use at transplant	0.97	3 (1.4–5)	0.003
FEV_1, per 10% predicted	−0.206	0.8 (0.7–0.94)	0.004
Recipient bilirubin >2 mg/dL	1.17	3 (1.4–7.2)	0.005
PA diastolic pressure, per 10 mmHg	0.254	1.3 (1.07–1.56)	0.009
Ischemic time >6 h	0.532	1.7 (1.01–2.86)	0.045

Lung Transplant) registry from 1990 to 2013, 3-month survival was 78% in this group, compared with 91% for chronic obstructive pulmonary disease (COPD).[20] Our findings in this analysis of US data from 2005 to 2021 confirm a high 90-day mortality of 10.2% relative to other diagnoses. We identified ECMO and/or ventilator use at transplant, higher pulmonary artery pressure, reduced FEV_1 percent predicted, prolonged ischemic time, and total recipient serum bilirubin over 2 mg/dL as significant independent risk factors for early death. Lower 6MWD demonstrated a strong trend for greater 90-day mortality. Our linear regression model was able to distinguish 25% of the cohort with a predicted 90-day mortality of ≥20% from 49% of the cohort with a mortality of ≤5%, thereby identifying high-risk versus low-risk recipients.

The higher early mortality in these patients stems from an increased incidence of serious postoperative complications.[10,11] Both a diagnosis of PAH and increasing pulmonary artery pressure are established risk factors for severe PGD, the most common cause of early deaths after lung transplant.[13,21] The odds ratio for severe PGD among PAH recipients was 3.5 relative to COPD in the

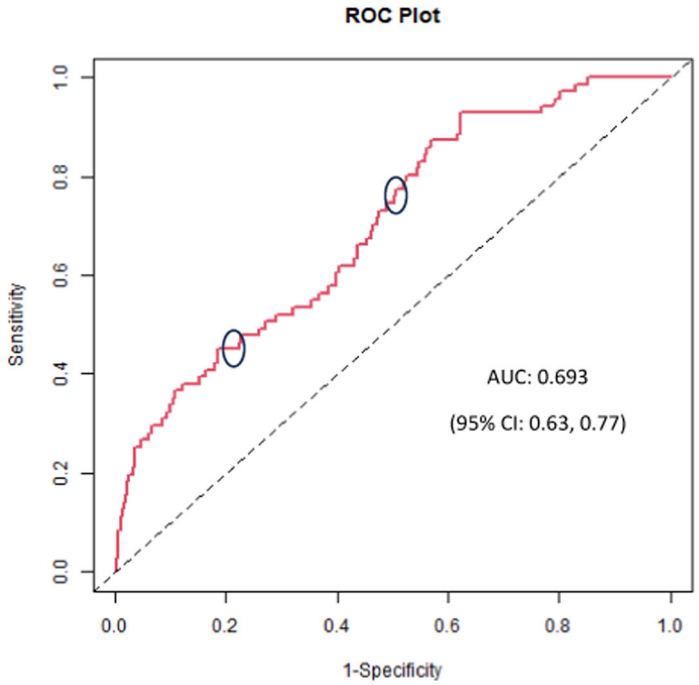

FIGURE 2 Receiver operator characteristics (ROC) curve of the linear predictor equation (L) for 90-day mortality. The predictor has clinical utility in identifying high-risk (≥20%) versus low-risk (≤5%) subjects when L is higher (to the left of lower circle) or lower (to the right of upper circle), respectively. See text. FEV_1 per 10% predicted; dPAP per 10 mmHg.

L = -2.41 -0.21(FEV_1 per 10%) + 0.97(ECMO or VENT) + 0.25(dPAP per 10 mmHg) + 1.17(Total Bili > 2) + 0.53(Isch time > 6 hr)

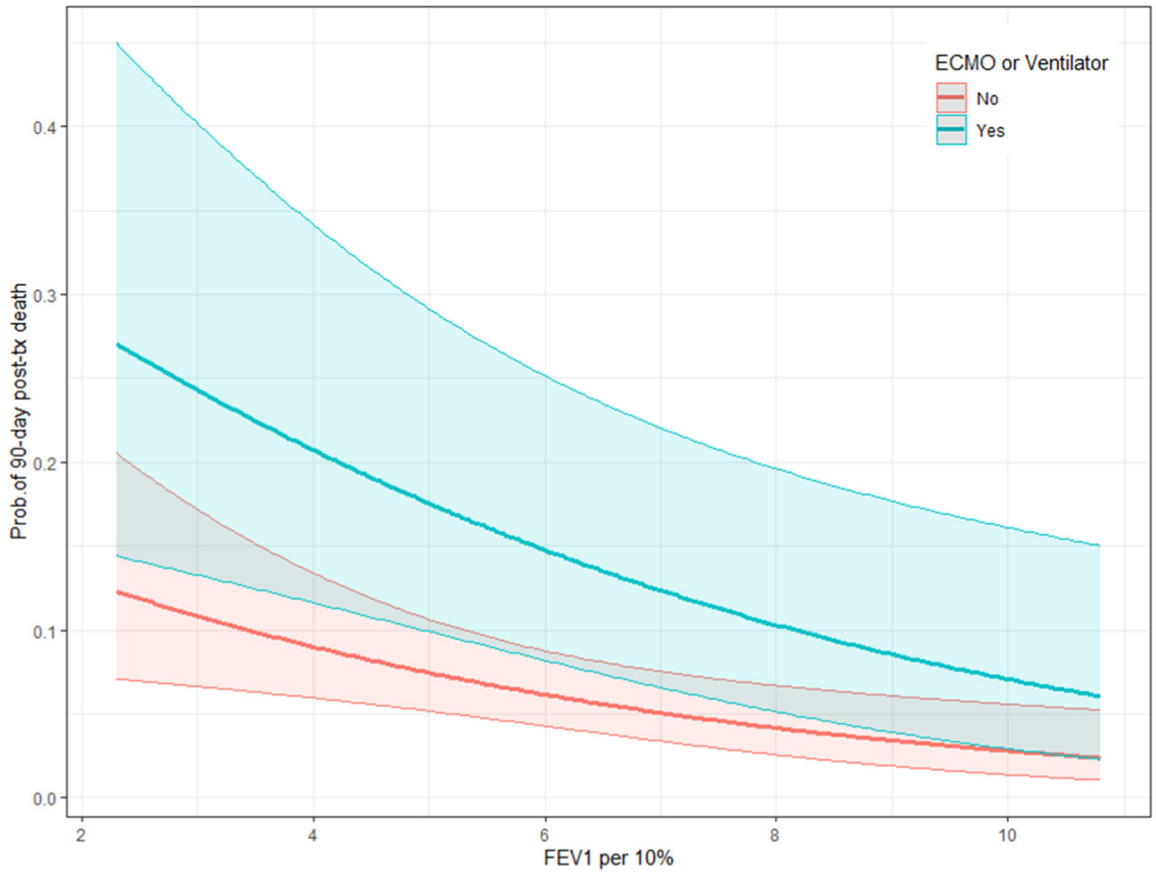

FIGURE 3 Graph demonstrating greater probability of 90-day mortality with decreasing FEV_1% predicted. At any given level of FEV_1, the risk of death more than doubles with ECMO and/or ventilator use at transplant. Results adjusted for PA diastolic pressure of 36 mmHg, recipient bilirubin <2 mg/dL and ischemic time <6 h. Shaded areas represent 95% confidence intervals.

TABLE 4 Alternate post-hoc multivariable model of 90-day mortality.

Predictor	Estimate	Odds ratio (95% CI)	*p* Value
Intercept	−2.17	–	–
ECMO or ventilator use at transplant	0.792	2 (1.1–4.3)	0.02
FEV_1, per 10% predicted	−0.183	0.8 (0.7–0.96)	0.013
PA diastolic pressure, per 10 mmHg	0.269	1.3 (1.08–1.59)	0.006
Recipient bilirubin >2 mg/dL	1.23	3 (1.5–7.72)	0.003
Ischemic time >6 h	0.52	1.7 (0.998–2.83)	0.051
6-min walk distance, per 10 m	−0.019	0.98 (0.96–0.002)	0.072

large multicenter prospective Lung Transplant Outcomes (LTOG) study.[22] The basis for this observation is felt to be due, in part, to the effects of longstanding RV dysfunction with consequent underfilling, atrophy and transient dysfunction of the left ventricle (LV). The subsequent elevation in left heart filling pressure promotes alveolar edema formation in the setting of increased pulmonary capillary permeability resulting from ischemia-reperfusion injury. We do not have data on PGD in this cohort. However, the frequency of intubation and ECMO use at 72 h posttransplant suggests a high incidence of severe PGD and the largest proportion of deaths were related to respiratory/graft failure.

Pulmonary arterial hypertension is also associated with markedly higher rates of acute kidney injury (AKI) following lung transplantation compared with other diagnoses.[23–25] In a UNOS analysis of early dialysis following lung transplant between 1994 and 2014, PPH was independently associated with a nearly two-fold increased risk. Dialysis before hospital discharge was required in 12% of PPH recipients, compared with 5.7% in the entire population.[23] Our observed rate of 19% suggests a rising incidence of severe AKI over time and the use of dialysis in 55% of nonsurvivors indicates that AKI was an important contributor to early deaths. Any degree of postoperative AKI has been linked to greater short and long-term mortality after lung transplant and the need for dialysis imparts a 10-fold increased risk of 1-year mortality.[26]

The need for advanced life-support, in the form of ECMO and/or mechanical ventilation at the time of transplant was the strongest risk factor for 90-day mortality in this cohort with an odds ratio of 2 to 3 after adjustment for other variables. The overwhelming majority of patients in this category were on ECMO with or without mechanical ventilation with only 5 on the latter alone. There has been increasing application of ECMO as a bridge to transplant in recent years for all indications.[27] While outcomes can be satisfactory relative to the dire hemodynamic derangement, early posttransplant mortality is considerably higher compared with nonsupported recipients.[28] These patients are prone to numerous complications, including PGD,[21] AKI,[23] and bleeding.[29] Moreover, failure of bridging to transplant is as high as 40%.[27,30] Awake ECMO and ambulatory status impart a favorable impact compared with mechanical ventilation.[31]

The demonstration of a relationship between higher pulmonary artery pressures and 90-day mortality on multivariate analysis suggests increasing risk with more severe pulmonary vascular disease. While dPAP had a stronger relationship with 90-day survival than mPAP or sPAP, the 3 are highly correlated[32] and sPAP was also a predictor of mortality when substituted for dPAP in our sensitivity analysis. Our finding of higher PAP rather than lower cardiac index (CI) or elevated right atrial pressure (RAP or CVP) as a predictor of early post-transplant mortality is novel. The latter are hemodynamic indices of RV dysfunction and are strongly linked to survival in IPAH whereas PAP is not a clear prognostic variable.[1] We observed that RAP, but not CI, was associated with early mortality by univariate analysis. RAP failed to achieve significance in the multivariate model; although this variable was missing in many subjects as its collection was mandated only in more recent years. RAP was an additive predictor of severe PGD in subjects with PH in the LTOG cohort.[13]

A single-center study identified pretransplant left ventricular diastolic dysfunction (LVDD) as a predictor of increased postoperative morbidity and early mortality in lung transplant recipients with PAH. Those subjects with LVDD had higher PAP and RAP, but similar CI to those without LVDD.[33] Further, in a subset of subjects in the LTOG study with available echocardiograms, LVDD was found to be an independent predictor of severe PGD and 1-year mortality,[34] supporting the concept that postoperative LV rather than RV dysfunction contributes to early complications in severe PH.[35] Higher PAP may thus serve as a surrogate marker for the effects of pulmonary vascular disease on LV filling with consequent alterations in LV structure and function [36–38] that would be anticipated to adversely impact the early postoperative course.

Spirometric indices are frequently abnormal in IPAH and correlate with the severity of pulmonary hypertension.[39,40] Mild airflow limitation is common and

may reflect limited space in the bronchovascular bundle due to vascular remodeling and/or concomitant structural small airways disease.[41] While mild restriction (reduced total lung capacity; TLC) has been described in a minority of IPAH patients, percent predicted FVC is typically lower than percent predicted TLC and can often be attributed to small airways disease based on an elevated residual volume/total lung capacity (RV/TLC) ratio.[41] One large series of IPAH subjects demonstrated a significant correlation between RV/TLC ratio and mPAP.[40] Our cohort on average had a reduced FEV_1% predicted relative to FVC% suggesting an obstructive ventilatory defect. When we substituted FVC% for FEV_1% in the best subset model, it remained a significant, but weaker, predictor of 90-day survival. The link between lower FEV_1% and early posttransplant mortality has not been previously reported and may represent the effects of more severe pulmonary vascular remodeling on small airways.

Recipient bilirubin is a known risk factor for 1-year survival among all lung transplant recipients with increasing mortality noted as levels rise above 0.6 mg/dL.[8] We did not find a continuous relationship, however, total bilirubin >2 mg/dL, reflecting hepatic congestion due to right heart failure, predicted early death consistent with previous reports.[42]

Increasing severity of PAH and its impact on cardiac function is anticipated to adversely impact posttransplant outcomes. A recent report from the French National PH Referral Center found reduced survival postlisting and after transplant in PAH subjects with high-risk clinical features.[43] An important component of risk stratification models is a reduced 6MWD and our observation of a trend for lower 6MWD as a predictor of 90-day mortality is consistent with these findings. Preoperative 6MWD has been shown to adversely impact 90-day, as well as overall survival after lung transplant, in a large UNOS database analysis of all recipient diagnoses.[44]

In a previous UNOS analysis of 448 IPAH/PPH recipients between 1998 and 2011, ECMO and/or ventilator support at transplant, recipient male sex, older donor age, and donor-recipient sex mismatch predicted overall mortality after transplant.[45] No effect of heart-lung transplant, which comprised a quarter of that cohort, versus bilateral was observed. In contrast to our results, that study did not find a relationship between PAP or spirometric values and posttransplant survival, although overall survival was assessed, not 90-day. 6MWD was only dichotomized between less than or greater than 150 feet and not found to predict post-transplant survival. Consistent with our results, CI was not associated with posttransplant survival but did predict waitlist mortality. The protective effects of donor-recipient sex matching may have been attributable to better size matching rather gender effects per se.[46] We did not find an impact of donor-to-recipient size matching based on the ratio of donor/recipient predicted total lung capacity, as was demonstrated in a UNOS analysis of IPAH recipients between 1989 and 2010.[47]

Uncertainty exists regarding the impact of ischemic time on outcomes after lung transplantation.[48] Among all recipient diagnoses, ischemic time beyond 6 h was independently associated with 30-day mortality in a UNOS analysis between 1989 and 2014.[49] We found greater 90-day mortality with ischemic time over 6 h. While the donor age in this cohort was relatively young (median 34 years), it was slightly older than in the previous UNOS study of IPAH transplants (median 28 years).[45] There appears to an interaction between donor age with ischemic time where older donors combined with prolonged ischemic time significantly impact 1-year survival.[50]

As with any analysis of UNOS registry data, ours is limited by the retrospective nature and reliability of the database.[14] Certain variables, such as hemodynamics and pulmonary function were obtained at varying timepoints before actual transplantation. We attempted to account for missing data with multiple imputation. Cardiac output measurements, which could have been obtained with either thermodilution or assumed Fick estimate are prone to errors,[51] especially when the latter technique is utilized with supplemental oxygen.[52] Key clinical predictors of outcome in PAH, such as brain natriuretic peptide and echocardiographic variables were not recorded.[2] The use of prophylactic, pre-emptive VA-ECMO post-operatively after bilateral lung transplant, which is suggested to improve early outcomes for IPAH,[53] could not be captured. We included heart-lung recipients, which may have different risk factors, however, results were similar after excluding this small number of subjects. While this study represents the largest such analysis to date, the sample size is relatively small compared with other reports using this data set due to the small proportion lung transplants performed for IPAH. The potential for overfitting of the multivariate model was reduced by application of the bootstrapping internal validation method. Further validation of the model would require an external data set.

Pulmonary vascular disease was the indication for the first successful application of lung transplantation as a combined heart-lung procedure.[54] As lung transplant volumes for other conditions grew, the proportion for IPAH/PPH fell from 12% in 1990 to 2.7% in 2015.[20] Yet the actual number of lung transplants for PPH/IPAH has climbed in the United States this past decade from a nadir of 24 lung plus 10 heart-lung in 2008 to an all-time

annual high of 97 lung plus 17 heart-lung procedures in 2022 surpassing cystic fibrosis.[55] Thus, the need for LTX in IPAH remains despite medical therapy. A better understanding and appropriate management of candidates at high risk for early complications and mortality will translate into improved long-term outcomes. In this contemporary analysis, a multivariable model incorporating factors associated with advanced pulmonary vascular disease, namely ECMO and/or ventilator support at transplant, higher pulmonary artery pressure, lower FEV_1 percent predicted, and total bilirubin >2 mg/dL, as well as long ischemic time was able to categorize 74% of candidates into those at low versus high risk for 90-day mortality. Identification of high-risk candidates may allow the application of more intensive strategies to mitigate complications that ultimately result in early mortality. Early referral and timely listing are critical to reduce the need to transplant patients with advanced disease. Our findings may also be relevant for strategies to optimize the allocation of donor organs for IPAH.

AUTHOR CONTRIBUTIONS

Reda E. Girgis and Renzo Loyaga-Rendon conceived the study. Nabin K. Manandhar-Shrestha obtained the data and performed statistical analyses. Reda E. Girgis wrote the manuscript draft. All authors reviewed, edited, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This research was conducted and reported in accordance with the international standards for responsible research publication developed by the 2nd World Conference on Research Inegrity.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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