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RESEARCH ARTICLE

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Prevalence of pulmonary hypertension in patients with COVID-19 related lung disease listed for lung transplantation: A UNOS registry analysis

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Abstract

COVID-19 related lung disease (CRLD) has emerged as an indication for lung transplantation (LT) in highly select patients. The prevalence and prognostic implication of coexisting pulmonary hypertension (PH) in patients with CRLD listed for LT is not known. Adult patients in the United Network for Organ Sharing database listed for LT for COVID-19 related acute respiratory distress syndrome or fibrosis through March 2022 were identified. The prevalence and impact of precapillary PH on pre- and posttransplantation survival was determined. Time-to-event analysis was used to compare outcomes between those with and without precapillary PH. We identified 245 patients listed for LT for CRLD who had right heart catheterization data available at the time of registry listing. Median age of the cohort was 54 years (interquartile range [IQR]: 46, 60), 56 (22.9%) were female, and the median lung allocation score was 81.3 (IQR: 53.3, 89.4). The prevalence of precapillary PH at the time of transplant listing was 27.9%. There was no significant difference in pretransplant mortality in patients with and without precapillary PH (sHR: 0.5; 95% confidence interval [CI]: 0.1–1.7, $p = 0.261$). A total of 187 patients ultimately underwent LT; of those, 60 (31.0%) were identified as having precapillary PH during the waitlist period. Posttransplantation survival was similar between patients with and without pretransplant precapillary PH (hazard ratio: 0.96; 95% CI: 0.2–3.7, $p = 0.953$). We observed a high rate of

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19 acute respiratory distress syndrome; CRLD, COVID-19 related lung disease; ECMO, extracorporeal membrane oxygenation; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; LAS, lung allocation score; LT, lung transplantation; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UNOS, United Network for Organ Sharing; VA, veno-arterial; VV, veno-venous; WU, Wood units.

concomitant precapillary PH in patients listed for LT for CRLD. Though common, coexisting precapillary PH was not associated with a significant difference in either pre- or post-transplantation outcomes.

KEYWORDS
Covid-19, lung transplantation, pulmonary fibrosis, pulmonary hypertension

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in millions of cases of respiratory failure and the acute respiratory distress syndrome (ARDS). Observational studies have suggested that even relatively healthy patients who develop moderate COVID-19 disease (hospitalized, not requiring endotracheal intubation) have high rates of residual lung dysfunction at 12 months after their initial infection.[1] Radiographic signs of pulmonary fibrosis have been described in up to 83% of patients in recovery from moderate, severe and critical illness related to COVID-19 lung disease.[2] While many patients with significant fibrosis after SARS-CoV-2 infection have radiographic improvement at follow up, many others develop persistent pulmonary fibrosis.[3,4] There are no accepted medical treatment options for patients who develop pulmonary fibrosis after SARS-CoV-2 infection. Lung transplantation (LT) is a last-resort treatment option for select patients with severe COVID-19 ARDS or fibrosis (which we refer to collectively as COVID-19 related lung disease [CRLD]), and posttransplant outcomes in these patients appear to be similar to those transplanted for other lung diseases.[5]

Less is known about the prevalence of pulmonary hypertension (PH) in patients with CRLD. SARS-CoV-2 infection causes a variety of injury patterns in the pulmonary vasculature, including endothelial injury, capillary microthrombi formation, and angiogenesis.[6] In a cohort of more than 200 patients with moderate COVID-19 infection, 12% were identified as having a systolic pulmonary artery pressure of more than 35 mmHg. These patients were found to more frequently require intensive care and had a higher in-hospital mortality compared to patients with normal pulmonary artery pressures.[7] PH as a complicating factor was identified in two small cases series of patients who underwent LT for CRLD.[8,9] Histological changes in the pulmonary vasculature have been described in patients with COVID-19 that are similar to lesions in patients with pulmonary arterial hypertension.[10,11]

PH has been identified as a complicating comorbidity in 37%–46% of patients who are listed for LT for other diseases, such as idiopathic pulmonary fibrosis (IPF).[12,13] It is associated with attenuated transplant-free survival in patients with IPF, but has not been shown to affect posttransplant outcomes in IPF.[12,14,15] PH can complicate the course of other fibrotic lung diseases, including idiopathic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis and unclassifiable ILD.[16,17]

To our knowledge, the prevalence of precapillary PH and its effect on pre- and post-transplant outcomes in patients listed for CRLD has not yet been described. Based on the available data from small COVID-19 case series and the high prevalence of PH in other chronic lung diseases, we hypothesized that the prevalence of precapillary PH in patients awaiting LT for CRLD would be high. We examined the United Network for Organ Sharing (UNOS) registry to describe the prevalence of precapillary PH in patients with CRLD awaiting LT and sought to ascertain whether the presence of precapillary PH affected pre- or posttransplant survival.

METHODS

We performed a retrospective review of adult patients in the UNOS database from December 1, 2019 until March 31, 2022. The registry consists of pre- and posttransplantation variables at the time of listing, during the waitlist period, at the time of transplantation, and in the posttransplantation period. Patients were included in our study if they were listed for LT based on transplant codes 1616 and 1617 (COVID-19 ARDS [CARDS] and COVID-19 fibrosis, respectively). Patients listed for transplantation without right heart catheterization (RHC) data were excluded from the primary analysis as were patients listed for dual heart and LT.

Definitions and outcomes

Precapillary PH was defined, in accordance with the criteria delineated by the 6th World Symposium on PH, as a mean pulmonary artery pressure (mPAP) of >20 mmHg, accompanied by a pulmonary vascular resistance (PVR) of ≥3 Wood units (WU) and a pulmonary capillary wedge

pressure (PCWP) ≤15 mmHg during RHC at the time of transplant listing. Isolated postcapillary PH was defined by a mPAP >20 mmHg, PCWP >15 mmHg, and PVR <3 WU. Combined pre- and postcapillary PH was defined by mPAP >20 mmHg, PCWP >15 mmHg, and PVR ≥3 WU. Uncategorized PH was defined as mPAP >20 mmHg with a PVR <3 WU and PCWP ≤15 mmHg.[18] The primary outcome was overall mortality from the date of listing during the waitlist period. Transplantation and removal from the transplant list for other reasons were considered competing risks. A secondary analysis of survival after transplantation was also performed. For the secondary analysis, patients were considered to have precapillary PH if they met hemodynamic criteria at the time of listing or based on subsequent waitlist updates to the Transplant Candidate Registration Form. Finally, as extracorporeal membrane oxygenation (ECMO) may impact the estimation of pulmonary hemodynamics, a sensitivity analysis to estimate the presence and severity of precapillary PH among patients listed for LT was performed with the exclusion of listed patients who received ECMO support.[19]

Statistical analysis

The distribution of all continuous data was examined for normality using visual inspection and the Shapiro–Wilk test. Continuous data is presented as median and interquartile range (IQR) where applicable and compared using the Wilcoxon Rank Sum test. Categorical data are presented as counts with proportions and compared using Fisher's exact test.

For the primary analysis, Fine and Gray competing-risk regression was performed to evaluate overall survival on the waitlist with LT or removal from waitlist as separate, competing risks. Patients removed from the waitlist as they were deemed too ill to undergo transplantation by their listing institution were considered deceased. Adjustments were made for age, sex, and the lung allocation score (LAS). Survival analysis using the Kaplan–Meier method and the log-rank test was used to compare groups in the posttransplant period. The assumption of proportional hazards in these survival models were evaluated through the inclusion of time varying covariates and found to be valid.

Missing data for patients documented to have undergone a RHC at the time of listing for LT required consideration. A total of 30 patients (12.2%) underwent a RHC but had insufficient data recorded to ascertain PH status. To reduce bias introduced by listwise deletion of cases, multiple imputations using chained equations was used. Twenty imputations for all nonredundant variables were performed using logistic regression for binary variables and linear regression for relevant continuous variables.

All relevant statistical tests were two-tailed and a $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA/SE version 17 (StataCorp LP).

RESULTS

A total of 434 patients were identified as listed for LT in the UNOS registry for CRLD from inception until March 31, 2022. Of these, 236 (54.4%) patients were listed for CARDS (listing code 1616), and 198 (45.6%) patients were listed for COVID-19 fibrosis (listing code 1617). A comparison of listings based on the two COVID-19 diagnostic codes by date of listing is included in Figure 1. Of those listed for LT for CRLD, $N = 187$ (43.1%) were excluded from the primary analysis given the absence of RHC data at the time of registry listing, and two other patients were excluded due to being listed for heart-LT, leaving 245 patients for the primary analysis. A consort diagram delineating the patients included in the primary, secondary, and sensitivity analyses is provided in Figure 2. The demographic data of patients excluded from our analysis due to lack of RHC data are provided in Table S1.

The characteristics of the 245 included patients are included in Table 1. The median age of the patients was 54 years (IQR: 46, 60), 56 (22.9%) were female and the median LAS score was 81.3 (IQR: 53.3, 89.4). There were no significant differences in sex, race, body mass index (BMI), or history of diabetes mellitus between the two listing codes. There was a nonsignificant trend toward a greater smoking history in patients with COVID-19 fibrosis (38.2% vs. 26.3%, $p = 0.056$). Patients listed with CARDS were significantly younger, had higher LAS scores, and were more likely to be on a ventilator or supported with ECMO. The distribution of mPAP of the 245 patients is included in Figure S1. Patients listed for COVID-19 ARDS had higher mPAPs than patients listed for COVID-19 fibrosis (27 mmHg vs. 22 mmHg, $p < 0.001$).

Of the 245 patients, 215 patients had complete RHC data, and 140 (65.1%) had a mPAP >20 mmHg (Table 2). Of these, 60 patients (27.9%) had precapillary PH, 17 (7.9%) had postcapillary PH, 9 patients (4.2%) had combined pre- and postcapillary PH, and 54 (25.1%) had uncategorized PH. There was no difference in the rate of precapillary PH (30.8% [28/91] vs. 25.8% [32/124]; $p = 0.445$) based on listing for CARDS and COVID-19 fibrosis, respectively. For our analyses, we split the

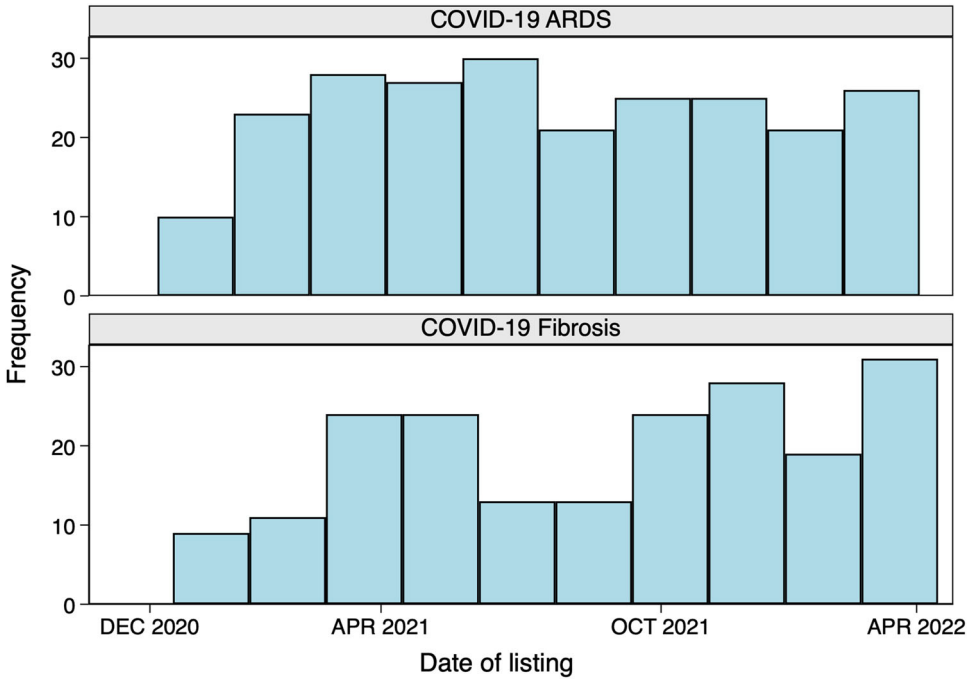

FIGURE 1 Histogram of date of transplant listings by diagnosis code for all patients listed for COVID-19 ARDS ($N = 236$) and COVID-19 fibrosis ($N = 198$). ARDS, acute respiratory distress syndrome.

patients into two groups: those with precapillary PH and those without precapillary PH (which includes patients without any PH, and those patients with post-capillary, combined pre- and postcapillary and uncategorized PH).

Patients with and without precapillary PH had similar age, sex, race, BMI, and LAS scores. Interestingly, there was no significant difference in the rates of mechanical ventilation or support with ECMO between the groups. Patients with precapillary PH were more likely to be supported with inhaled pulmonary vasodilators and had shorter 6-min walk distances than patients without precapillary PH (Table 2). Patients with both precapillary PH and COVID-19 fibrosis ($N = 32$) were able to ambulate further during 6-min walk testing, had lower LAS scores, longer time on the waitlist, and were less likely to require mechanical ventilation or ECMO at the time of listing compared to patients with precapillary PH listed for CARDS ($N = 28$) (Table 3).

As support with ECMO may impact observed cardiac and pulmonary artery pressures, a sensitivity analysis estimating the prevalence and severity of precapillary PH after the exclusion of patients listed for LT while receiving ECMO support was performed. A total of 151 patients were not supported with ECMO at the time of listing for LT. Of these, 45 (29.8%) were found to have precapillary PH. The presence and severity of precapillary PH in the entire cohort compared to the severity observed after the removal of patients supported with ECMO is displayed in Figure 3. Notably, the overall prevalence and severity of precapillary PH was similar between these two analyses.

During the study period, 194 (79.2%) patients with RHC included in their initial Transplant Candidate Registration Form were removed from the waitlist, including 169 (69.0%) who underwent LT. Other reasons for waitlist removal included death, clinical deterioration, and improvement (Table 4). Five patients without precapillary PH and no patients with precapillary PH died while on the waitlist. LAS score was significantly associated with the cumulative incidence of mortality in the pretransplant period (sHR: 1.05; 95% confidence interval [CI]: 1.01–1.08, $p = 0.012$). Figure 4 shows a plot of the cumulative incidence of mortality in the pretransplant period. The presence of precapillary PH at the time of listing was not significantly associated with death (sHR: 0.5; 95% CI: 0.1–1.7, $p = 0.261$) and this relationship persisted after the model was adjusted for age, sex, and the LAS (Table 5).

Posttransplantation outcome

While on the waitlist, an additional 30 patients underwent RHC and precapillary PH status could ultimately be discerned. Of those 30, 11 additional patients (36.6%) were identified as having precapillary PH. Thus, the overall proportion of patients with precapillary PH

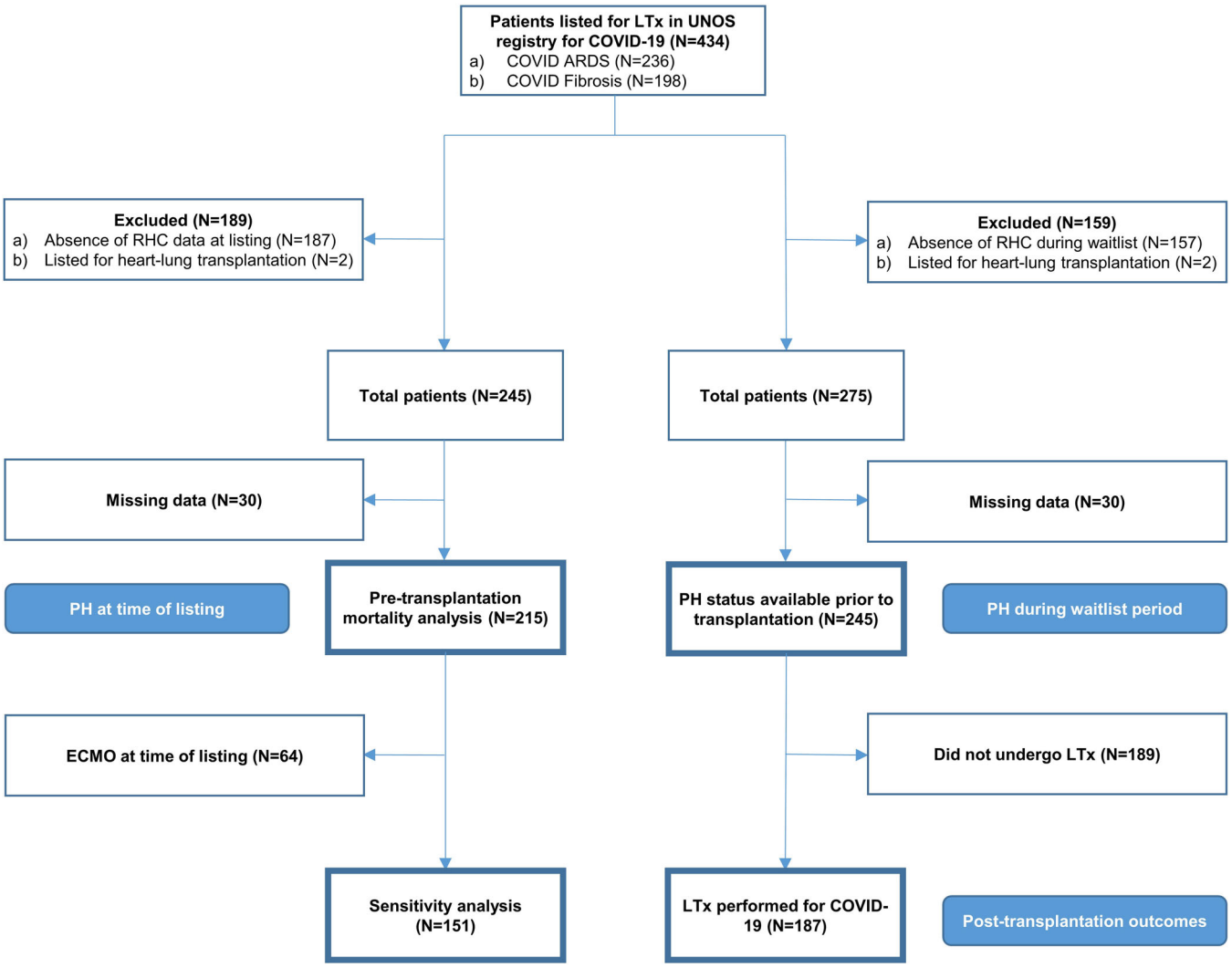

FIGURE 2 Consort diagram.

within the cohort was 29.0% (71/245). Of the 187 of these patients who underwent transplantation, the prevalence of precapillary PH was 31.0%. After transplantation, median follow-up time was 171 days (IQR: 26, 195). A total of 10 patients died after transplantation (7 without precapillary PH [7/129], 3 with precapillary PH [3/58]). At 120 days after transplantation, the estimated survival for all patients was 95.0% (95% CI: 89.7%–97.6%). Estimated survival for patients without precapillary PH at 120 days was 96.4% (95% CI: 89.0%–98.8%) compared to 95.7% (95% CI: 84.0%–98.9%) in patients with precapillary PH. There was no significant difference in early posttransplant survival in patients with and without precapillary PH (hazard ratio: 0.96; 95% CI: 0.2–3.7, $p = 0.953$). A Kaplan–Meier survival curve comparing early posttransplant survival in patients with and without precapillary PH diagnosed during the waitlist period is shown in Figure 5.

DISCUSSION

In this review of the UNOS Registry, we identified 245 patients with complete RHC data who were listed for LT for CRLD from the beginning of the pandemic until March 31, 2022. We found the prevalence of precapillary PH in patients at the time of registry listing to be 27.9% while the prevalence of precapillary PH in those who ultimately underwent LT was 31.0%. No statistical difference in pre- or posttransplantation survival was noted based on the presence of precapillary PH in this cohort. Notably, the rate of survival 4 months after transplantation in patients with CRLD was excellent and comparable to survival among patients who underwent LT for other diseases.[20]

Previous studies have estimated the prevalence of PH by noninvasive echocardiography in patients hospitalized with COVID-19 to be approximately 15% and found that the presence of PH was associated with increased disease

TABLE 1 Baseline demographic data in patients with right heart catheterization at time of listing by diagnosis code.

	All ($N = 245$)	CARDS ($N = 114$)	COVID fibrosis ($N = 131$)	p value
Age (years) ($N = 245$)	54 (46, 60)	51 (44, 56)	56 (49, 62)	<0.001
Sex, female	56/245 (22.9)	28/114 (24.6)	28/131 (21.4)	0.648
Ethnicity (Hispanic)	85/245 (34.7)	41/114 (36.0)	44/131 (33.6)	0.788
Race (white)	122/245 (49.8)	51/114 (44.7)	71/131 (54.2)	0.159
BMI ($N = 244$)	27.5 (24.1, 30.7)	27.2 (23.2, 30.7)	27.6 (24.7, 30.8)	0.443
Diabetes mellitus	72/243 (29.6)	35/114 (30.7)	37/129 (28.7)	0.779
Hx of smoking	80/245 (32.7)	30/114 (26.3)	50/131 (38.2)	0.056
Creatinine (at listing) ($N = 245$)	0.60 (0.46, 0.79)	0.53 (0.40, 0.75)	0.65 (0.52, 0.80)	<0.001
FEV1, % ($N = 106$)	34 (25, 47)	28 (18, 45)	35 (27, 50)	0.082
FVC, % ($N = 108$)	33 (23, 44)	27 (18, 39)	33 (25, 44)	0.001
6MWT distance (m)[a] ($N = 121$)	280 (100, 590)	187 (83, 437)	336 (115, 693)	0.040
LAS (at listing) ($N = 245$)	81.3 (53.3, 89.4)	87.4 (72.8, 91.7)	71.3 (44.1, 86.3)	<0.001
Lung preference				
Single	58/245 (23.7)	19/114 (16.7)	39/131 (29.8)	0.017
Double	238/245 (97.1)	113/114 (99.1)	125/131 (95.4)	0.126
Days on waitlist ($N = 245$)	16 (7, 35)	15 (6, 31)	17 (7, 42)	0.057
Functional status requires hospitalization (at listing)	153/245 (62.5)	77/114 (67.5)	76/131 (58.0)	0.146
Ventilator	67/245 (27.4)	42/114 (36.8)	25/131 (19.1)	0.002
On ECMO (at listing)	86/245 (35.1)	61/114 (53.5)	25/131 (19.1)	<0.001
Inhaled prostacyclin	3/245 (1.2)	2/114 (1.8)	1/131 (0.8)	0.599
Inhaled nitric oxide	9/245 (3.7)	6/114 (5.3)	3/131 (2.3)	0.310
Inhaled vasodilator (prostacyclin or iNO)	12/245 (4.9)	8/114 (7.0)	4/131 (3.1)	0.235
Pan-resistant bacterial lung infection	7/234 (3.0)	5/112 (4.5)	2/122 (1.6)	0.264
mPAP (mmHg) ($N = 245$)	25 (20, 32)	27 (22, 35)	22 (18, 29)	<0.001
PCWP (mmHg) ($N = 234$)	8 (5, 12)	9 (5, 12)	8 (5, 11)	0.075
CO (L/min) ($N = 212$)	6.1 (5.1, 7.2)	6.5 (5.3, 8.1)	5.7 (4.9, 6.9)	0.003
CI (L/min/m^2) ($N = 211$)	3.1 (2.6, 4.0)	3.5 (2.7, 4.5)	3.0 (2.5, 3.7)	0.001
PVR (Wood units) ($N = 205$)	2.4 (1.6, 3.5)	2.5 (1.7, 3.9)	2.2 (1.6, 3.3)	0.193
Pre-capillary PH	60/215 (27.9)	28/91 (30.8)	32/124 (25.8)	0.445

Abbreviations: BMI, body mass index; CARDS, COVID-19 acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAS, lung allocation score; mPAP, mean pulmonary artery pressure; 6MWT, 6-min walk test; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

[a]In patients able to walk >0 m.

severity and worse in-hospital outcomes.[7,21] Not surprisingly, the prevalence of precapillary PH in patients with CRLD listed for LT is higher than in patients with more moderate disease, and in fact is quite similar to the rate of PH in patients waitlisted with chronic ILDs such as IPF, NSIP, and COPD. Although it is impossible to ascertain the timing of COVID-19 infection in these patients, it is interesting to note that PH likely developed over the course of weeks to months, whereas in other fibrotic lung disorders, PH is apt to develop over a much longer period.

The prognostic significance of PH in the setting of chronic ILD has been investigated in other contexts. In patients with IPF and idiopathic fibrotic NSIP, co-existing PH has been found to be associated with significantly worse overall and transplant-free

TABLE 2 Baseline demographic data based on the presence or absence of PH at the time of listing in complete cases.

	All ($N = 215$)	No isolated precapillary PH ($N = 155$)	Precapillary PH ($N = 60$)	p value
Age (years) ($N = 215$)	55 (46, 61)	54 (46, 61)	56 (46, 61)	0.511
Sex, female	48/215 (22.3)	32/155 (20.7)	16/60 (26.7)	0.364
Ethnicity (Hispanic)	78/215 (36.3)	62/155 (40.0)	16/60 (26.7)	0.082
Race (white)	106/215 (49.3)	72/155 (46.5)	34/60 (56.7)	0.224
BMI ($N = 213$)	27.3 (24.0, 30.5)	27.8 (24.7, 30.7)	26.0 (23.0, 29.6)	0.065
Diabetes mellitus	61/213 (28.6)	46/153 (30.1)	15/60 (25.0)	0.504
Hx of smoking	70/215 (32.6)	54/155 (34.8)	16/60 (26.7)	0.330
Creatinine (at listing) ($N = 215$)	0.60 (0.47, 0.80)	0.60 (0.47, 0.79)	0.62 (0.49, 0.80)	0.429
FEV1, % ($N = 101$)	35 (25, 47)	34 (26, 48)	37 (24, 46)	0.851
FVC, % ($N = 108$)	31 (22, 44)	31 (23, 44)	31 (20, 42)	0.763
6MWT distance (m)[a] ($N = 113$)	280 (100, 590)	323 (117, 693)	218 (75, 495)	0.091
LAS (at listing) ($N = 215$)	80.6 (49.4, 89.1)	81.0 (49.4, 89.0)	78.7 (48.8, 89.6)	0.922
Lung preference				
Single	51/215 (23.7)	38/155 (24.5)	13/60 (21.7)	0.723
Double	208/215 (96.7)	148/155 (95.5)	60/60 (100)	0.194
Days on waitlist ($N = 215$)	16 (7, 36)	16 (6, 36)	16.5 (9, 40)	0.345
Functional status requires hospitalization (at listing)	128/215 (59.5)	91/155 (58.7)	37/60 (61.7)	0.758
Ventilator	54/215 (25.1)	36/155 (23.2)	18/60 (30.0)	0.300
On ECMO (at listing)	64/215 (29.8)	49/155 (31.6)	15/60 (25.0)	0.407
Inhaled prostacyclin	2/215 (0.9)	1/155 (0.7)	1/60 (1.7)	0.481
Inhaled nitric oxide	7/215 (3.3)	2/155 (1.3)	5/60 (8.3)	0.019
Inhaled vasodilator (prostacyclin or iNO)	9/215 (4.2)	3/155 (1.9)	6/60 (10.0)	0.016
Pan-resistant bacterial lung infection	3/205 (1.5)	3/147 (2.0)	0/58 (0)	0.560
mPAP (mmHg) ($N = 215$)	23 (19, 31)	21 (17, 27)	30 (27, 36)	<0.001
PCWP (mmHg) ($N = 211$)	8 (5, 12)	9 (5, 12)	8 (6, 10)	0.070
CO (L/min) ($N = 208$)	6.1 (5.1, 7.2)	6.5 (5.2, 7.9)	5.3 (4.7, 6.3)	<0.001
CI (L/min/m^2) ($N = 207$)	3.1 (2.6, 4.0)	3.3 (2.7, 4.2)	2.8 (2.5, 3.3)	<0.001
PVR (Wood units) ($N = 205$)	2.4 (1.6, 3.5)	1.9 (1.4, 2.5)	4.0 (3.4, 5.1)	<0.001

Abbreviations: BMI, body mass index; CARDS, COVID-19 acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAS, lung allocation score; mPAP, mean pulmonary artery pressure; 6MWT, 6-min walk test; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

[a]In patients able to walk >0 m.

survival.[14,17,22] Relatedly, others have investigated the impact of pretransplantation PH on posttransplantation outcomes in patients with chronic lung disease and reached conflicting conclusions.[12,23,24] In our analysis, the presence of precapillary PH in patients with CRLD before lung transplant did not significantly affect waitlist mortality or posttransplant survival. Indeed, observed waitlist and early posttransplant deaths were very low. Notably, the median time on the LT waitlist was 16 days (IQR: 7, 35) due to the high LAS of these patients and their propensity to be transplanted soon after listing. This short waitlist duration limits the ability to assess significant differences in pretransplantation survival between groups.

TABLE 3 Baseline demographic data in patients with precapillary PH at time of listing by diagnosis code.

	All ($N = 60$)	CARDS ($N = 28$)	COVID fibrosis ($N = 32$)	p value
Age (years) ($N = 60$)	56 (46, 61)	52 (45, 59)	58 (53, 62)	0.106
Sex, female	16/60 (26.7)	9/28 (32.1)	7/32 (21.9)	0.397
Ethnicity (Hispanic)	16/60 (26.7)	9/28 (32.1)	7/32 (21.9)	0.397
Race (white)	34/60 (56.7)	14/28 (50.0)	20/32 (62.5)	0.435
BMI ($N = 60$)	26.0 (23.0, 29.6)	25.1 (21.9, 27.4)	27.6 (23.9, 30.5)	0.086
Diabetes mellitus	15/60 (25.0)	8/28 (28.6)	7/32 (21.9)	0.567
Hx of smoking	16/60 (26.7)	7/28 (25.0)	9/32 (28.1)	0.999
Creatinine (at listing) ($N = 60$)	0.62 (0.49, 0.80)	0.60 (0.43, 0.80)	0.65 (0.53, 0.82)	0.323
FEV1, % ($N = 24$)	37 (24, 46)	37 (7, 45)	36 (24, 55)	0.594
FVC, % ($N = 24$)	33 (22, 45)	30 (7, 40)	33 (23, 50)	0.256
6MWT distance (m) ($N = 37$)[a]	218 (75, 495)	100 (56, 266)	265 (140, 591)	0.029
LAS (at listing) ($N = 60$)	78.7 (48.8, 89.6)	86.7 (75.6, 92.6)	62.2 (41.6, 83.8)	<0.001
Lung preference				
Single	13/60 (21.7)	2/28 (7.1)	11/32 (34.4)	0.013
Double	60/60 (100)	28/28 (100)	32/32 (100)	–
Days on waitlist	17 (9, 40)	15 (7, 29)	24 (11, 66)	0.094
Functional status requires hospitalization (at listing)	37/60 (61.7)	20/28 (71.4)	17/32 (53.1)	0.187
Ventilator	18/60 (30.0)	14/28 (50.0)	4/32 (12.5)	0.002
On ECMO (at listing)	15/60 (25.0)	11/28 (39.3)	4/32 (12.5)	0.034
Inhaled prostacyclin	1/60 (1.7)	1/28 (3.6)	0/32 (0)	0.467
Inhaled nitric oxide	5/60 (8.3)	4/28 (14.3)	1/32 (3.1)	0.175
Inhaled vasodilator (prostacyclin or iNO)	6/60 (10.0)	5/28 (17.9)	1/31 (3.1)	0.088
Pan-resistant bacterial lung infection	0/58 (0)	0/28 (0)	0/30 (0)	–
mPAP (mmHg) ($N = 60$)	30 (27, 36)	32 (28, 38)	30 (24, 34)	0.112
PCWP (mmHg) ($N = 60$)	8 (6, 10)	8 (6, 11)	8 (6, 10)	0.541
CO (L/min) ($N = 60$)	5.3 (4.7, 6.3)	5.7 (5.2, 6.2)	5.0 (4.4, 6.3)	0.110
CI (L/min/m^2) ($N = 59$)	2.8 (2.5, 3.3)	3.0 (2.7, 3.5)	2.7 (2.4, 3.0)	0.013
PVR ($N = 60$)	4.0 (3.4, 5.1)	4.1 (3.5, 5.6)	4.0 (3.4, 4.7)	0.722

Abbreviations: BMI, body mass index; CARDS, COVID-19 acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAS, lung allocation score; mPAP, mean pulmonary artery pressure; 6MWT, 6-min walk test; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

[a]In patients able to walk >0 m.

It is notable that there was no difference in the lung function between the precapillary PH and no precapillary PH groups, but a significant difference in their functional ability as evidenced by the lower 6-min walk distance in the precapillary PH group. This is similar to what has been described in other forms of PH-ILD.[14] The recent approval of inhaled treprostinil for PH due to ILD raises the important question of whether these patients might be candidates for PH therapy. Interestingly, only 12 of the 245 patients (4.9%) were identified as receiving

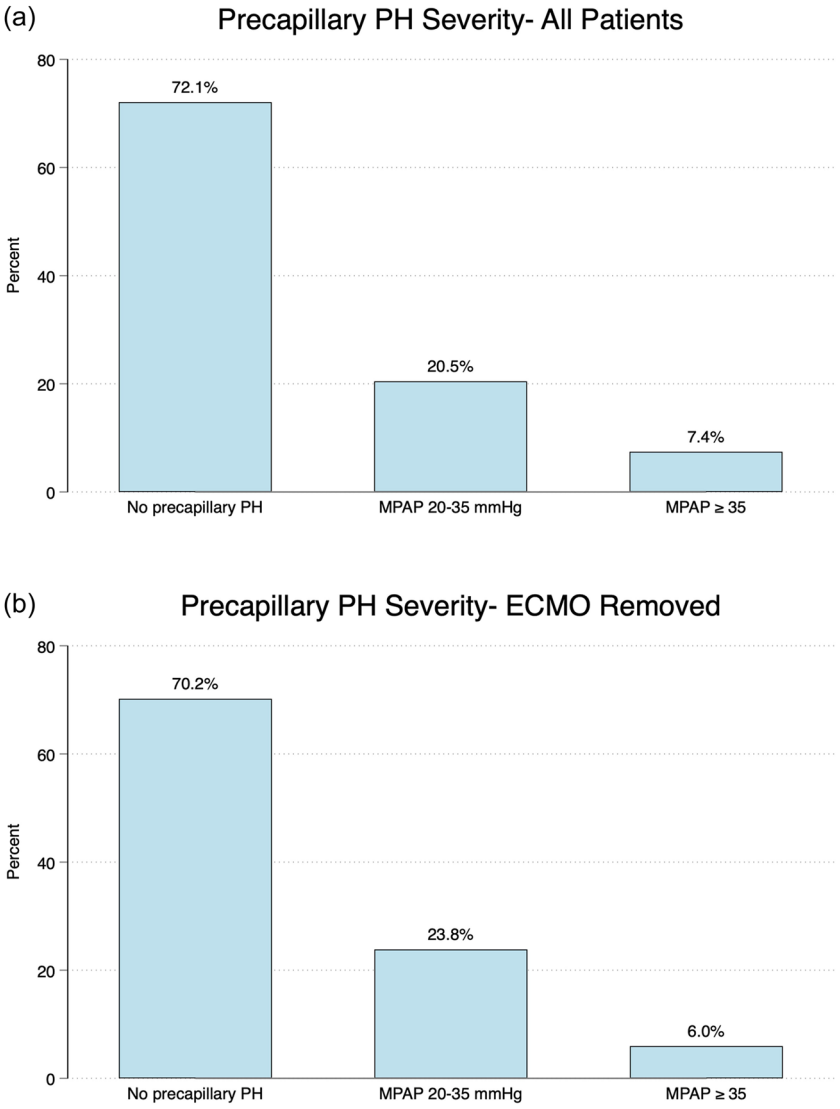

FIGURE 3 Presence and severity of precapillary PH in all patients (A) and among patients not receiving extracorporeal life support at the time of listing (B). PH, pulmonary hypertension.

TABLE 4 Patients removed from the waitlist (only patients with initial right heart catheterization data).

Waitlist removal reason ($N = 194$)	No precapillary PH ($N = 139$)	Precapillary PH ($N = 55$)
Transplanted	120	49
Condition deteriorated	10	3
Improved	4	2
Died	5	0
Removed in error	0	1

Abbreviation: PH, pulmonary hypertension.

pulmonary vasodilators at the time of listing. While we cannot recommend this due to lack of data in this population, it is notable that all subgroups with fibrotic lung disease in the INCREASE study appeared to derive benefit.[25,26] Future clinical trials for PH due to ILD should consider CRLD as one of the indications for inclusion.

A few limitations to these analyses are important to acknowledge. First, this was a retrospective analysis of existing UNOS registry data. Given the small number of total registered patients that have undergone LT for CRLD to date, statistical power to detect differences in outcomes between the studied groups is limited by the available data. Relatedly, though prior evidence suggests worse pretransplantation outcomes among patients with precapillary PH and the highest pulmonary artery pressures (mPAP >35 mmHg), given the small number of deaths in this cohort both before and after transplantation, we were unable to assess if severity of precapillary PH was related to pre- or posttransplantation survival.

Second, this data might not be applicable to all patients with CRLD, as only highly select patients are eligible for LT. Before the creation of COVID-19 specific listing codes, there was heterogeneity in the codes used

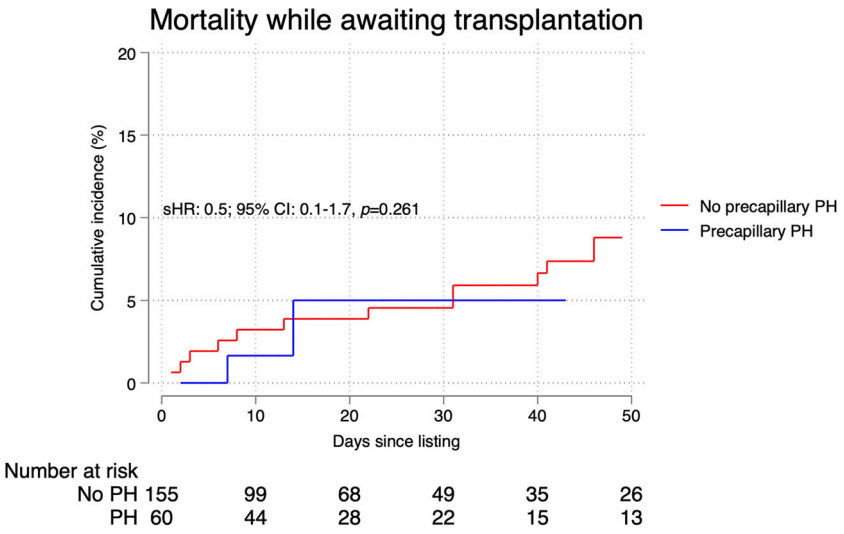

FIGURE 4 Cumulative incidence curve for mortality during the waitlist period based on the presence or absence of pulmonary hypertension in complete cases.

	Unadjusted sHR (95% CI)	*p* value	Adjusted sHR (95% CI)[a]	*p* value	Adjusted sHR (95% CI)[b]	*p* value
Pulmonary hypertension	0.5 (0.1–1.7)	0.261	0.5 (0.2–1.7)	0.247	0.5 (0.1–1.8)	0.274

TABLE 5 Association of precapillary PH with death during the waitlist period.

Abbreviations: CI, confidence interval; HR, hazard ratio; LAS, lung allocation score; PH, pulmonary hypertension.

[a]Adjusted for age and sex.

[b]Adjusted for LAS score.

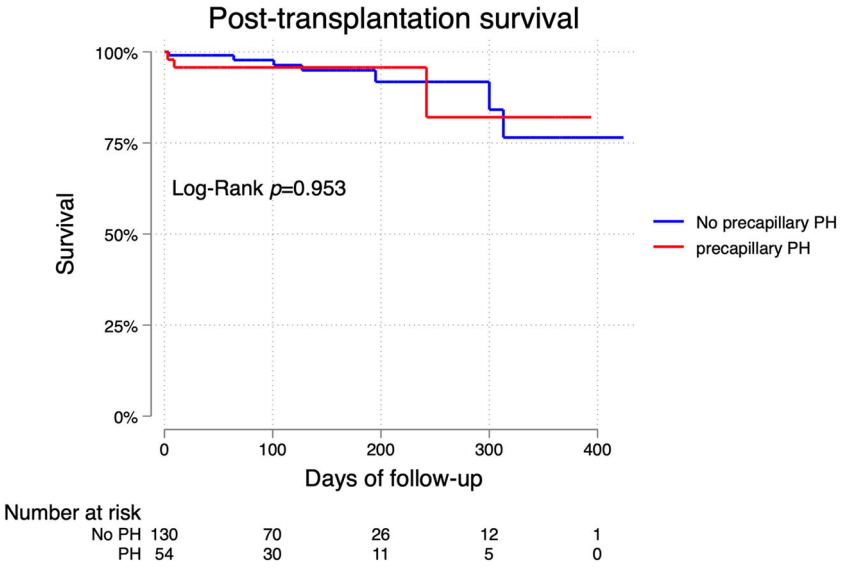

FIGURE 5 Kaplan–Meier survival curve comparing posttransplant survival in patients with and without pulmonary hypertension diagnosed during the waitlist period.

for these patients. Thus, the earliest patients with COVID-19 who received a lung transplant may be missing from this analysis. The decision to list post-COVID-19 patients as COVID-19 fibrosis versus CARDS might be somewhat arbitrary; specifically, this designation is likely center dependent with additional subjectivity imposed by the significant overlap and evolution from ARDS to a more chronic fibrotic ILD picture. One could assume that those listed with ARDS may be in their index hospitalization from COVID-19 infection with acute, refractory hypoxemic respiratory failure and thus, may constitute a different phenotype than those with subacute or chronic hypoxemic respiratory failure from COVID-19 fibrosis. Data on time from COVID-19

infection would be helpful to delineate these two groups more clearly; however, they are not available in the UNOS registry. Any differences between these two groups should therefore be viewed with caution.

Additionally, more than 40% of patients listed for LT did not have RHC data entered in their Transplant Candidate Registration Form, presumably because it was not performed, either due to clinical instability or the need for prohibitively high-level respiratory support. This missing data may have introduced bias related to our estimate of not only the prevalence of precapillary PH in this population, but the sequelae as well. Furthermore, a significant number of patients who had RHC data were also on ECMO, which can confound RHC measurements. The UNOS database does not distinguish between veno-arterial and veno-venous ECMO, which affect RHC measurements in different ways. We are unable to distinguish these populations based on available information, which is another limitation of our study.

The demographic data of patients excluded from our analysis due to lack of RHC data demonstrates they were much more likely to be on ECMO at the time of listing (68.2%) than patients who were included in the study (35.1%). This suggests that these excluded patients were more severely ill than those who were included in our analysis. It is also possible that the exclusion of a large proportion of patients without RHC data (who were more likely to be on ECMO) may have resulted in the exclusion of many sick patients with precapillary PH who went on to have worse pre- and posttransplant outcomes. This may in turn explain the lack of differences in pre- and posttransplant outcomes between the included patients with and without precapillary PH.

Last, the ability to distinguish between precapillary, postcapillary, combined pre- and postcapillary, and uncategorized PH is limited given missing data and inherent limitations in accuracy of interpretation of RHC data, particularly because waveforms can be influenced by many factors, including positive pressure ventilation. We chose to compare patients with precapillary PH to all other patients (those without PH and those with postcapillary, combined pre- and postcapillary and uncategorized PH), but a significant number of patients in the latter group had some form of nonisolated precapillary PH. This should be kept in mind when interpreting nuances between these subgroups of patients with PH.

CONCLUSIONS

As the COVID-19 pandemic continues to evolve, more patients infected with SARS-CoV-2 are likely to develop CRLD for which the only treatment option might be LT. Though we observed a high rate of concomitant precapillary PH in patients with CRLD listed for LT, these findings were not associated with discernable differences in either pre- or posttransplantation outcomes. Lung transplant is an effective therapy for patients with severe CRLD, and early posttransplant outcomes appear to be quite good. The presence of precapillary PH in this group of patients does not appear to be associated with greater rate of death on the waitlist or with posttransplantation complications. More research is needed in this population to define which patients with CRLD might be candidates for PH therapy and who are most likely to benefit from LT.

AUTHOR CONTRIBUTIONS

Christopher Thomas, Abhimanyu Chandel, and Steven D. Nathan: study design, data analysis, and writing of manuscript. **Christopher S. King, Shambhu Aryal, A. Whitney Brown, Vikramjit Khangoora, Alan Nyquist, Anju Singhal, Onix Cantres Fonseca, and Oksana Shlobin**: writing of manuscript.

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CONFLICT OF INTEREST STATEMENT

Steven D. Nathan is a consultant for United Therapeutics, Roche, Bellerophon, and Merck. He is on the speaker bureau for United Therapeutics and Boehringer-Ingelheim. Oksana Shlobin is a consultant for United Therapeutics, Janssen and Altavant, and serves on the speaker bureau of United Therapeutics, Bayer and Janssen. Christopher S. King is a consultant for United Therapeutics, Actelion, Altavant, Merck and Boehringer-Ingelheim. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Our study was done in strict compliance with the International Society for Heart and Lung Transplantation statement on transplant ethics.

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