Outcomes Following Lung Transplant for COVID-19–Related Complications in the US

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IMPORTANCE The COVID-19 pandemic led to the use of lung transplant as a lifesaving therapy for patients with irreversible lung injury. Limited information is currently available regarding the outcomes associated with this treatment modality.

OBJECTIVE To describe the outcomes following lung transplant for COVID-19–related acute respiratory distress syndrome or pulmonary fibrosis.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, lung transplant recipient and donor characteristics and outcomes following lung transplant for COVID-19–related acute respiratory distress syndrome or pulmonary fibrosis were extracted from the US United Network for Organ Sharing database from March 2020 to August 2022 with a median (IQR) follow-up period of 186 (64-359) days in the acute respiratory distress syndrome group and 181 (40-350) days in the pulmonary fibrosis group. Overall survival was calculated using the Kaplan-Meier method. Cox proportional regression models were used to examine the association of certain variables with overall survival.

EXPOSURES Lung transplant following COVID-19–related acute respiratory distress syndrome or pulmonary fibrosis.

MAIN OUTCOMES AND MEASURES Overall survival and graft failure rates.

RESULTS Among 385 included patients undergoing lung transplant, 195 had COVID-19–related acute respiratory distress syndrome (142 male [72.8%]; median [IQR] age, 46 [38-54] years; median [IQR] allocation score, 88.3 [80.5-91.1]) and 190 had COVID-19–related pulmonary fibrosis (150 male [78.9%]; median [IQR] age, 54 [45-62]; median [IQR] allocation score, 78.5 [47.7-88.3]). There were 16 instances of acute rejection (8.7%) in the acute respiratory distress syndrome group and 15 (8.6%) in the pulmonary fibrosis group. The 1-, 6-, and 12-month overall survival rates were 0.99 (95% CI, 0.96-0.99), 0.95 (95% CI, 0.91-0.98), and 0.88 (95% CI, 0.80-0.94) for the acute respiratory distress syndrome cohort and 0.96 (95% CI, 0.92-0.98), 0.92 (95% CI, 0.86-0.96), and 0.84 (95% CI, 0.74-0.90) for the pulmonary fibrosis cohort. Freedom from graft failure rates were 0.98 (95% CI, 0.96-0.99), 0.95 (95% CI, 0.90-0.97), and 0.88 (95% CI, 0.79-0.93) in the 1-, 6-, and 12-month follow-up periods in the acute respiratory distress cohort and 0.96 (95% CI, 0.92-0.98), 0.93 (95% CI, 0.87-0.96), and 0.85 (95% CI, 0.74-0.91) in the pulmonary fibrosis cohort, respectively. Receiving a graft from a donor with a heavy and prolonged history of smoking was associated with worse overall survival in the acute respiratory distress syndrome cohort, whereas the characteristics associated with worse overall survival in the pulmonary fibrosis cohort included female recipient, male donor, and high recipient body mass index.

CONCLUSIONS AND RELEVANCE In this study, outcomes following lung transplant were similar in patients with irreversible respiratory failure due to COVID-19 and those with other pretransplant etiologies.

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SARS-CoV-2 emerged in December 2019 and was declared a pandemic in March 2020 by the World Health Organization (WHO).[1] The clinical manifestations of COVID-19 have a wide spectrum, and most infected individuals experience mild to moderate symptoms.[2] Nevertheless, a large percentage of patients develops severe pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure, with mortality rates as high as 55% in severe COVID-19 cases and 5% in mild to moderate COVID-19 cases.[3,4] Current literature indicates that almost one-third of patients who are hospitalized for COVID-19 develop ARDS and require invasive mechanical ventilation.[2,5] It should be noted that even though the global vaccination effort has demonstrated clear benefit,[6] the incidence of COVID-19 hospitalizations and mortality is still considerable.[7]

Lung transplant was traditionally not considered as a treatment option for patients with acute lung injury due to infectious causes. However, the substantial volume of patients who required prolonged mechanical ventilation and extracorporeal support during the COVID-19 pandemic led to the use of lung transplant as a lifesaving therapy for patients with irreversible lung injury when all other therapeutic means had failed.[8-10]

Severe COVID-19 can result in 2 distinct types of irreversible lung injury: ARDS and pulmonary fibrosis (PF). COVID-19–related ARDS manifests acutely and requires immediate management, whereas COVID-19–related PF can emerge as a late complication and is currently considered a major cause of morbidity and mortality worldwide.[11,12] COVID-19–associated PF typically presents as a progressive disease in which lung function continuously declines, leading to respiratory failure. However, in some cases, it could also resolve over time.[11,12] The emergence of novel antifibrotic therapeutics including tyrosine kinase inhibitors (eg, nintedanib) and immunomodulators (eg, pirfenidone), has offered promising results by decelerating the rate of lung function decline.[13,14] Nevertheless, lung transplant is still regarded as the only definitive treatment option for severe PF in which medical therapy was ineffective.[15]

The literature regarding lung transplant for COVID-19–related ARDS or PF is evolving but is limited to only a few case series with a limited number of patients,[16-18] prompting this study, which uses the United Network for Organ Sharing (UNOS) registry to identify patients who underwent lung transplant due to COVID-19. This study aims to compare outcomes in patients who underwent lung transplant for COVID-19 vs non–COVID-19 diagnoses.

Key Points

Question What are the outcomes following lung transplant for COVID-19–related complications?

Findings In this cohort study, 385 patients underwent lung transplant due to COVID-19–related acute respiratory distress syndrome or pulmonary fibrosis. The 1-, 6-, and 12- month overall survival and freedom from graft failure were high in both cohorts.

Meaning The findings indicate that lung transplant was associated with good outcomes in patients with irreversible respiratory failure due to COVID-19, with survival comparable to other pretransplant etiologies.

Methods

The institutional review board at the University of North Carolina determined that this study (372183) did not consti-tute human subjects research as defined under federal regu-lations (45 CFR 46.102 [e or l] and 21CFR 56.102€[e][l]), and thus institutional review board approval was waived. Patient consent was not required, given the nature of this study. The data used in the study are derived from a deidentified Organ Procurement and Transplantation Network file.

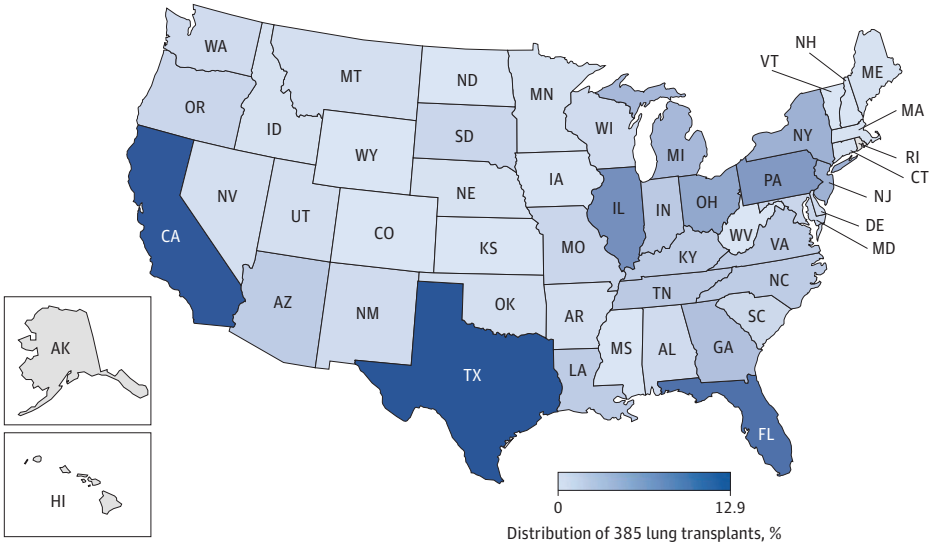
Patient pretransplant, transplant, and follow-up data were obtained from the UNOS Standard Transplant Analysis and Research data file released on August 8, 2022. The UNOS database administers the Organ Procurement and Transplantation Network under contract with the US Department of Health and Human Services. This database contains data on all patients undergoing solid organ transplant in the US since October 1987. We included patients of all ages who were listed and underwent lung transplant due to COVID-19–related ARDS or COVID-19–related PF, as well as their graft donors, between March 2020 and August 2022 in the US. Patients younger than 18 years, those listed for multiple organ transplants, and any individuals with repeat transplants were excluded from our final cohort. Patients were identified using the primary and secondary listing diagnosis codes and transplant diagnosis codes from UNOS for COVID-19–related ARDS (1616) and COVID-19–related PF (1617). Only patients who received single or double lung transplants were included in our study.

Statistical Analysis

Two distinct cohorts, the ARDS cohort and the PF cohort, were generated according to indication for transplant incorporating patients who were listed for lung transplant due to COVID-19–related ARDS and PF, respectively. Patient baseline characteristics, donor baseline characteristics, and clinical outcomes following lung transplant were expressed as frequencies with corresponding percentages for categorical variables and as medians with IQRs for continuous data.

The Kaplan-Meier method was used to estimate and plot overall survival and freedom from graft failure using deidentified time-to-event data. Survival was measured from transplant time to end of follow-up. We used adjusted and unadjusted Cox proportional hazard regression models to examine associations between overall survival and age, sex, body mass index (BMI), and smoking history of both the recipients and the donors, as well as the ABO blood group, race, lung allocation score, history of diabetes, HLA mismatch level, DR mismatch level, A locus mismatch level, B locus mismatch level, and type of life support of the recipients. Finally, we compared early overall survival of patients who received lung transplant due to COVID-19–related lung disease in patients who underwent lung transplant due to other non–COVID-19 etiologies. For this purpose, we used adjusted and unadjusted Cox proportional hazard regression models accounting for all the afore-

Figure 1. Distribution of COVID-19–Related Lung Transplants Across the US



mentioned variables. Data analysis was done using STATA version 17.0 (StataCorp).

Results

A total of 195 patients (142 [72.8%] male; median [IQR] age, 46 [38-54] years) were included in the ARDS group and 190 (150 [78.9%] male; median [IQR] age, 54 [45-62] years) in the PF group. The overall geographical distribution of transplant recipients is presented in **Figure 1**, and the distribution of recipients receiving transplants due to COVID-19–related ARDS and PF are presented in eFigure 1 in Supplement 1.

In the ARDS and PF groups, respectively, the median (IQR) lung allocation score was 88.3 (80.5-91.1) and 78.5 (47.7-88.3), and the median (IQR) BMI (calculated as weight in kilograms divided by height in meters squared) was 27.8 (24.2-31.2) and 26.3 (24.0-29.9). Of the lung transplant recipients from the ARDS and PF cohorts, 2% (number suppressed to protect privacy) and 28 (14.7%) underwent single lung transplant, respectively. The median (IQR) time on the waiting list before transplant was estimated at 11 (5-21) days for the ARDS group and 15 (7-35) days for the PF group. All the recipients' baseline characteristics are presented in **Table 1**.

With regard to the donor cohort, 125 participants in the ARDS group (64.1%) were male, and the median (IQR) age was 32 (23-43) years; in the PF cohort, 113 participants (59.5%) were male, and the median (IQR) age was 34 (24-44) years. The median (IQR) graft ischemia time was 5.9 (5.2-7.1) hours for the ARDS cohort and 5.8 (4.9-7.3) for the PF cohort. Donor characteristics are summarized in **Table 2**.

At the time of transplant, 39 patients in the ARDS cohort (20.0%) were receiving extracorporeal membrane oxygenation (ECMO), 6.7% (number suppressed to protect privacy) were mechanically ventilated, and 105 (53.8%) required both ECMO and mechanical ventilation; 38 (19.5%) did not require mechanical life support. In the PF cohort, 27 patients (13.7%) were receiving ECMO, 6.3% (number suppressed to protect privacy) were mechanically ventilated, 43 (22.6%) required both ECMO and mechanically ventilation; 109 (57.4%) required no life support. Moreover, 34 patients (18.26%) and 48 (27.1%) in the PF group were receiving corticosteroids before transplant, while 66 (36.1%) in the ARDS group and 51 (28.7%) in the PF group received intravenous antibiotics 2 weeks before transplant. More details regarding the laboratory findings and the HLA, DR locus, A, locus and B locus mismatch levels are summarized in eTable 1 in Supplement 1.

In terms of early outcomes in the ARDS and PF groups, 28 (15.3%) and 10.3% of patients (number suppressed to protect privacy) required postoperative dialysis, respectively. The median (IQR) partial pressure of oxygen (Pao_2)/fraction of inspired oxygen (Fio_2) ratio was 297 (202-393) in the ARDS group and 279 (191-361) in the PF group. A total of 55 patients in the ARDS group (30.1%) and 35 in the PF group (20.0%) required ECMO support on postoperative day 3. The median (IQR) length of hospital stay was 30 (21-51) days in the ARDS cohort and 22 (16-38) days in the PF cohort. The median (IQR) follow-up time was 186 (64-359) days in the ARDS cohort and 181 (40-350) days in the PF cohort. During follow-up, 8.7% of patients in the ARDS group and 8.6% in the PF group (numbers suppressed to protect privacy) experienced an acute rejection episode. During the 1-, 6-, and 12-month follow-up periods, freedom from graft failure was 0.98 (95% CI, 0.96-0.99), 0.95 (95% CI, 0.90-0.97), and 0.88 (95% CI, 0.79-0.93) in the ARDS cohort and 0.96 (95% CI, 0.92-0.98), 0.93 (95% CI, 0.87-0.96), and 0.85 (95% CI, 0.74-0.91) in the PF cohort, respectively (eFigure 2 in Supplement 1). Moreover, primary graft dysfunction was assessed by calculating postoperative Pao_2 at 72 hours divided by the Fio_2 at 72 hours. A ratio of less than 300 is indicative of primary posttransplant graft dysfunction .[19,20] All posttransplant outcomes are summarized in **Table 3**.

Table 1. Patient Demographic and General Characteristics When Listed for Lung Transplant

Characteristic	No. (%) Patients with ARDS (n = 195)	Patients with PF (n = 190)
Age, median (IQR), y	46 (38-54)	54 (45-62)
Sex		
Female	53 (27.2)	40 (21.1)
Male	142 (72.8)	150 (78.9)
Race[a]		
African American	16 (8.2)	<11[b]
Asian	<11[b]	<11[b]
Hispanic	55 (28.2)	57 (30.0)
White	107 (54.9)	107 (56.3)
Other[c]	<11[b]	16 (8.4)
Smoking history	38 (19.6)	53 (28.2)
BMI, median (IQR)	27.8 (24.2-31.2)	26.3 (24.0-29.9)
Diabetes	51 (26.3)	46 (24.6)
Lung Allocation Score, median (IQR)	88.3 (80.5-91.1)	78.5 (47.7-88.3)
ABO blood group		
A	67 (34.4)	63 (33.1)
AB	<11[b]	<11[b]
B	20 (10.3)	23 (12.0)
O	99 (50.8)	101 (53.2)
Functional status at listing		
Moribund	32 (16.5)	<11[b]
Very sick	113 (58.3)	89 (47.3)
Severely disabled	16 (8.3)	28 (14.9)
Disabled	<11[b]	18 (10.1)
Requires considerable care	<11[b]	11 (5.9)
Requires occasional care	<11[b]	19 (10.1)
Cares for self	<11[b]	<11[b]
Normal	<11[b]	<11[b]
NA	15 (7.7)	<11[b]
Highest education		
Grade school	<11[b]	10 (5.3)
High school	61 (31.4)	69 (36.7)
College	50 (25.8)	44 (23.4)
Bachelor's degree	42 (21.7)	30 (16.0)
Postcollege degree	24 (12.4)	17 (9.0)
NA	<11[b]	18 (9.6)
Insurance type		
Private	148 (76.3)	129 (67.5)
Medicaid	30 (15.5)	25 (13.1)
Medicare	<11[b]	12 (6.3)
Other public insurance	<11[b]	21 (11.0)
Type of transplant		
Single	<11[b]	28 (14.7)
Double	192 (98.5)	162 (85.3)
Total days on waiting list, median (IQR)	11 (5-21)	15 (7-35)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PF, pulmonary fibrosis; NA, not available.

[a] Race and ethnicity data were collected via patient self-report and reported because understanding associations of race and ethnicity with organ transplant outcomes is essential for addressing health disparities and promoting equitable health care practices.

[b] Cells <11 were suppressed to uphold patient confidentiality and comply with United Network for Organ Sharing data protection regulations.

[c] Other included American Indian, Native Hawaiian, and multiracial non-Hispanic. These groups were combined to protect the privacy and confidentiality of individuals within these groups.

Table 2. Donor Characteristics

Characteristic	No. (%) Donors for ARDS cohort (n = 195)	Donors for PF cohort (n = 190)
Age, median (IQR), y	32 (23-43)	34 (24-44)
Sex		
Female	70 (35.9)	77 (40.5)
Male	125 (64.1)	113 (59.5)
Race[a]		
African American	30 (15.4)	44 (23.2)
Asian	<11[c]	<11[c]
Hispanic	49 (25.1)	39 (20.5)
White	107 (54.9)	101 (53.2)
Other[b]	<11[c]	<11[c]
BMI, median (IQR)	24.8 (22.3-29.3)	25.6 (22.2-29.4)
ABO blood group		
A	68 (34.4)	59 (31.0)
AB	<11[c]	<11[c]
B	17 (8.7)	22 (11.6)
O	106 (54.4)	108 (56.8)
Circumstance of death		
Motor vehicle crash	28 (14.4)	32 (16.8)
Suicide	41 (21.0)	24 (12.6)
Homicide	15 (7.7)	16 (8.4)
Other unintentional circumstances	40 (20.6)	36 (18.9)
Natural causes	55 (28.2)	67 (35.3)
NA	16 (8.2)	15 (7.9)
Pulmonary infection	130 (66.7)	140 (73.7)
Urinary infection	29 (14.9)	25 (13.2)
Graft ischemia time, median (IQR), h	5.9 (5.2-7.1)	5.8 (4.9-7.3)
Medications		
Corticosteroids	138 (71.9)	146 (78.9)
Diuretics	146 (76.0)	129 (69.7)
Antihypertensives	72 (37.5)	71 (38.4)
History of diabetes	14 (7.2)	18 (9.5)
History of hypertension	50 (25.6)	49 (25.8)
History of cocaine abuse	28 (14.6)	39 (21.1)
Blood urea nitrogen, median (IQR)	19 (13-30)	20 (14-37)
Creatinine, median (IQR)	0.9 (0.7-1.2)	1 (0.7-1.5)
Bilirubin, median (IQR)	0.7 (0.5-1.2)	0.7 (0.5-1.2)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PF, pulmonary fibrosis; NA, not available.

[a] Race and ethnicity data were collected via patient self-report and reported because understanding associations of race and ethnicity with organ transplant outcomes is essential for addressing health disparities and promoting equitable health care practices.

[b] Other included American Indian, Native Hawaiian, and multiracial non-Hispanic. These groups were combined to protect the privacy and confidentiality of individuals within these groups.

[c] Cells <11 were suppressed to uphold patient confidentiality and comply with United Network for Organ Sharing data protection regulations.

With regard to survival, the 1-, 6-, and 12- month overall survival was 0.99 (95% CI, 0.96-0.99), 0.95 (95% CI, 0.91-0.98), and 0.88 (95% CI, 0.80-0.94) for the ARDS cohort and

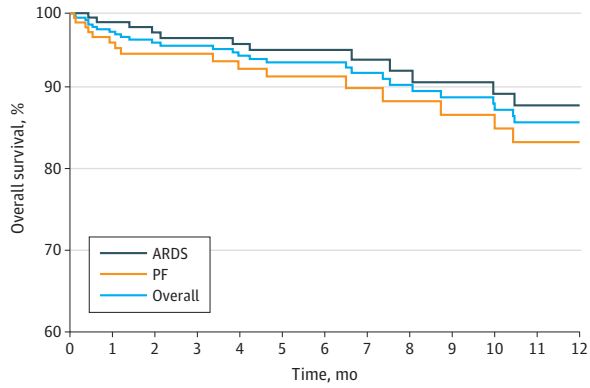
Table 3. Posttransplant Outcomes Summary

Outcome	No. (%)	
	Patients with ARDS (n = 204)	Patients with PF (n = 190)
Acute rejection	16 (8.7)	15 (8.6)
Stroke	<11[a]	<11[a]
Postoperative dialysis	28 (15.3)	18 (10.3)
Fio_2 (%) at 72 h, median (IQR)	40 (30-40)	40 (35-50)
Pao_2 at 72 h, median (IQR)	114 (84-144)	114 (90-146)
Pao_2/Fio_2 ratio, median (IQR)	297 (202-393)	279 (191-361)
Pao_2/Fio_2 ratio ≥300	121 (62.1)	116 (60.1)
Pao_2/Fio_2 ratio 300-200	19 (20.0)	41 (21.6)
Pao_2/Fio_2 ratio ≤200	38 (17.9)	33 (17.4)
NO at 72 h	28 (15.3)	31 (177)
Intubated at 72 h	111 (60.7)	96 (54.9)
ECMO at 72 h	55 (30.1)	35 (20.0)
LOS, median (IQR), d	30 (21-51)	22 (16-38)
Follow-up, median (IQR), d	186 (64-359)	181 (40-350)

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; NO, nitric oxide; Pao_2, partial pressure of oxygen; PF, pulmonary fibrosis; LOS, length of hospital stay.

[a] Cells <11 were suppressed to uphold patient confidentiality and comply with United Network for Organ Sharing data protection regulations.

Figure 2. Survival Following COVID-19–Related Lung Transplant in the US



No. at risk

ARDS	183	169	141	130	129	127	119	72	66	63	62	61	44
Overall	356	308	251	232	227	223	210	129	120	114	113	110	84
PF	173	139	110	102	98	96	91	57	54	51	51	49	40

ARDS indicates acute respiratory distress syndrome; PF, pulmonary fibrosis.

0.96 (95% CI, 0.92-0.98), 0.92 (95% CI, 0.86-0.96), and 0.84 (95% CI, 0.74-0.90) for the PF cohort, respectively (**Figure 2**). Receipt of a graft from a donor with a heavy and prolonged history of smoking was associated with worse overall survival in the ARDS cohort in both unadjusted and adjusted analyses. Regarding the PF group, female sex and high BMI in recipients were associated with worse overall survival, whereas receipt of a graft from a female donor was associated with favorable overall survival in adjusted analyses. Moreover, comparison of overall survival between patients who received lung transplant due to COVID-19–related lung diseases and patients who received lung transplant for non–COVID-19 etiologies demonstrated no significant difference (unadjusted hazard ratio, 0.73; 95% CI, 0.51-1.06; $P = .10$ and adjusted hazard ratio, 0.79; 95% CI, 0.54-1.16; $P = .23$, respectively) (eFigure 3 in Supplement 1). All the findings of the adjusted and unadjusted Cox proportional hazard regression model analyses are summarized in eTable 2 in Supplement 1.

Discussion

Traditionally lung transplant has not been regarded as a therapeutic option for patients with acute lung injury due to an infectious etiology. Nevertheless, during the COVID-19 pandemic, thousands of infected patients experienced irreversible lung injury requiring extended periods of mechanical life support with ECMO, mechanical ventilation, or both.[21] In these critically ill patients who did not show sufficient response to medical therapy and did not recover despite prolonged hospitalization and optimized care, lung transplant became a life-saving option. In this context, investigators reporting on the first consecutive lung transplants for COVID-19–associated ARDS in the US, Italy, Austria, and India tried to establish some preliminary guidelines and indications for lung transplant in the setting of COVID-19.[22] While many single-center retrospective studies describing lung transplant in patients with COVID-19 have been published since,[16,18,22-25] most describe limited patient numbers and short follow-up periods. This creates limitations in establishing data-driven guidelines for lung transplant in patients with end-stage lung disease due to COVID-19.

In our report, we aimed to summarize the early outcomes of lung transplant for COVID-19–related ARDS and PF in the US. To our knowledge, this study represents the largest series to date of patients receiving lung transplants for both COVID-19–related ARDS and COVID-19–related PF. As shown in Figure 1, most transplants were performed in California, Texas, and Florida, a finding that is consistent with data indicating that both the number of cases and COVID-19–related mortalities were comparatively higher in these states.[26]

Our findings suggest that lung transplant was associated with similar survival outcomes for patients who underwent COVID-19–associated ARDS and PF as for patients who received lung transplants for non–COVID-19 causes the US, which is in congruence with a contemporary report by Freischlag et al[27] in which patients with COVID-19 were matched with patients receiving lung transplants for other etiologies based on their baseline characteristics. The rates of acute graft failure were low in both the ARDS and PF cohort and the baseline characteristics of the patients receiving transplants were in line with current recommendations regarding patient selection: patients were younger than 65 years, were listed only for lung transplant and not for multiple organ transplant, had limited comorbidities, and had a BMI between 24 and 30.[22]

One notable finding is that patients with COVID-19–related ARDS who received a graft from a donor with heavy

and prolonged smoking history were associated with significantly worse survival outcomes. The current literature examining the impact of donor grafts with a heavy and prolonged smoking history remains controversial; however, most reports maintain that recipients of lungs individuals with a history of smoking 20 cigarette packs per year or more have less favorable overall survival.[28-30] A potential explanation of this finding might lie in the hypothesis that patients who received grafts from such donors were critically ill and urgently scheduled for transplant despite the less than ideal quality grafts as a salvage therapy for their disease. Our analyses also revealed that patients with COVID-19–related PF who received a graft from a female donor had better overall survival, while female sex and high BMI in recipients were associated with worse survival outcomes. While recipient BMI is a well-established predictor of mortality in patients undergoing lung transplant,[31] our findings regarding the sex of the donor and the recipient are not in congruence with current literature that suggests that female donor grafts are associated with worse overall survival and female recipients generally have more favorable prognoses than male recipients.[32] Even though our models were adjusted for multiple variables, the inherent limitation of not having access to patient-level data prevents us from delving deeper into the explanation of these findings.

Proper patient selection remains paramount for lung transplant related to COVID-19, as for other lung transplant indications. The current literature suggests that a time frame of approximately 4 weeks should elapse between the beginning of the respiratory failure and the evaluation for lung transplant, as patients have been noted to fully recover during this time frame.[17,22,23,33] Nevertheless, this time frame is to some extent arbitrary. Kurihara et al[16] reported that 36 patients in their study died while being evaluated for transplant or awaiting transfer after completion of lung transplant evaluation. Ultimately, patients listed for lung transplant due to COVID-19 generally have had prolonged hospitalizations with treatment-resistant respiratory failure and neuromuscular deconditioning, putting them at high risk of poor posttransplant outcomes.[18] According to our findings, 57 patients in the ARDS cohort (37.9%) and 74 (40.0%) in the PF cohort had a Pao_2/o_2 ratio less than 300, suggesting high rates of potential primary graft dysfunction in patients undergoing transplant due to COVID-19.[20] Of note, the current literature suggests an incidence of primary graft dysfunction ranging from 10% to approximately 30% in patients who received lung transplant due to non-COVID-19 indications.[20,34] We reason that the high prevalence of critical illness in our recipient cohorts and high rates of primary graft dysfunction explain why more than half of patients undergoing transplant remained intubated more than 3 days postoperatively, and that one-fourth of the patients remained on ECMO for similar periods. This likely also explains the prolonged hospitalization noted in our study. Although primary graft dysfunction is historically associated with high rates of posttransplant morbidity and mortality, advancements in critical care management approaches, including the routine use of ECMO, have considerably improved the outcomes following primary graft dysfunction, which is also reflected in our results.[20,35-37]

Single-center experiences have also described the degree of difficulty associated with the conduct of transplant in this patient population.[9,10,16,17] Patients listed for lung transplant due to COVID-19 typically require ECMO and mechanical ventilation for extensive periods of time and thus are vulnerable to secondary bacterial pneumonia with pleural space complications that may contribute to more demanding and difficult operations.[22] In addition, both prolonged ECMO and COVID-19 infection are association with dysregulation of coagulation pathways, which may impose greater risks for both intraoperative and postoperative hemorrhages or thrombosis.[38,39] Immunosuppression is also challenging in this group of transplant recipients, since a balance must be struck between risks of allograft rejection and infection, including COVID-19 recurrence.

Limitations

The findings of this study should be interpreted with caution as there are several inherent limitations due to the study's design and the lack of access to individual patient data. First, we could not scrutinize the interval from onset of respiratory failure until the day of the transplant to further elucidate appropriate time intervals required prior to listing. Moreover, due to the fact that Organ Procurement and Transplantation Network does not capture intraoperative data, we were unable to assess the association of intraoperative variables with outcomes. It should be noted that the UNOS database acquires patient data, including the distinction between pretransplant diagnoses of ARDS and PF, from individual transplant centers based on center-level discretion and clinical judgment. Preoperative biopsy, explanted lung pathology, and radiologic findings are not provided. In addition, we had no access to data regarding the modalities used to diagnose COVID-19 or data regarding the diagnostic tests used to identify COVID-19 recurrence in the allograft. Additionally, UNOS does not capture data regarding the immunosuppressive agents used, and thus we could not assess the impact of immunosuppression on outcomes.

Nevertheless, given the small numbers of lung transplant for COVID-19 in individual centers, the strength of our study is the large patient sample that we were able to identify using the Organ Procurement and Transplantation Network, which provides information about real-world patient outcomes from all over the US. Therefore, this study not only helps fill an important gap in the current literature but also raises awareness around lung transplant following COVID-19 and identifies areas for future research.

Conclusions

The findings of this study suggest that lung transplant offers encouraging early results in patients with COVID-19–related ARDS and PF. Comparable survival outcomes were noted between patients who underwent lung transplant for COVID-19 and non-COVID-19 etiologies. High rates of potential primary graft dysfunction following lung transplant were observed in both the ARDS and PF cohorts, whereas more than half of patients undergoing transplant remained

intubated, and one-fourth continued receiving ECMO for more than 3 days postoperatively. Organizing a multidisciplinary care team is of paramount importance to overcome the challenges that emerge due to the complexity of this treatment modality. Further evidence is warranted from high-quality studies in order to elucidate the role of lung transplant for irreversibly COVID-19–related lung injury, clarify its indications and contraindications, and lead to a paradigm shift in the management of patients with and following COVID-19.

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