

COVID-19 in hospitalized lung and non-lung solid organ transplant recipients: A comparative analysis from a multicenter study

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Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CLAD, chronic lung allograft dysfunction; ICU, intensive care unit; LTR, lung transplant recipients; mTOR, mammalian target of rapamycin; SOTR, solid organ transplant recipients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Lung transplant recipients (LTR) with coronavirus disease 2019 (COVID-19) may have higher mortality than non-lung solid organ transplant recipients (SOTR), but direct comparisons are limited. Risk factors for mortality specifically in LTR have not been explored. We performed a multicenter cohort study of adult SOTR with COVID-19 to compare mortality by 28 days between hospitalized LTR and non-lung SOTR. Multivariable logistic regression models were used to assess comorbidity-adjusted mortality among LTR vs. non-lung SOTR and to determine risk factors for death in LTR. Of 1,616 SOTR with COVID-19, 1,081 (66%) were hospitalized including 120/159 (75%) LTR and 961/1457 (66%) non-lung SOTR ($p = .02$). Mortality was higher among LTR compared to non-lung SOTR (24% vs. 16%, respectively, $p = .032$), and lung transplant was independently associated with death after adjusting for age and comorbidities (aOR 1.7, 95% CI 1.0–2.6, $p = .04$). Among LTR, chronic lung allograft dysfunction (aOR 3.3, 95% CI 1.0–11.3, $p = .05$) was the only independent risk factor for mortality and age >65 years, heart failure and obesity were not independently associated with death. Among SOTR hospitalized for COVID-19, LTR had higher mortality than non-lung SOTR. In LTR, chronic allograft dysfunction was independently associated with mortality.

KEYWORDS

clinical research/practice, infection and infectious agents - viral, infectious disease, lung (allograft) function/dysfunction, lung disease: infectious, lung transplantation/pulmonology, organ transplantation in general

1 | INTRODUCTION

Solid organ transplant recipients (SOTR) are at risk for poor outcomes from coronavirus disease 2019 (COVID-19) due to the frequent medical comorbidities and the potential impact of immunosuppression.^{1,2} Lung transplant recipients (LTR) with COVID-19 are unique among SOTR because severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) directly infects the allograft. Small observational cohort studies suggest that LTR with COVID-19 may have higher mortality than non-lung SOTR. Mortality as high as 46% has been reported in LTR, compared to ~20% for SOTR as a collective group.^{1,3-6} However, heterogeneity in follow-up duration both within and between these studies precludes meaningful assessment of differences between LTR and non-lung SOTR with COVID-19.

Although advanced age, obesity, chronic lung disease, and heart failure appear to be the key drivers of COVID-19-related mortality among SOTR and the general population,^{1,7,9} risk factors for mortality specifically among LTR have not been assessed in large cohorts.

We previously reported a multicenter registry of SOTR with COVID-19, all of whom were followed for 28 days (or until death if <28 days) using standardized data collection tools.¹ This registry remained open for an additional 7 months to accrue further cases. Here, we report the 28-day morbidity and mortality among SOTR who were hospitalized for COVID-19, directly compare outcomes between LTR and non-lung SOTR, and evaluate risk factors for death specifically in LTR.

2 | MATERIALS AND METHODS

As previously described,¹ the study was approved by the University of Washington Institutional Review Board with waiver of informed consent (STUDY00009698). The Institutional Review Board issued a “not human subjects research” designation for contributors reporting de-identified data accessed during routine clinical care. Study sites underwent review by local institutional review boards if needed to access data or to maintain a key to identify patient records at their discretion.

2.1 | Study design

This multicenter cohort study included recipients of any solid organ transplant who were diagnosed with COVID-19 between February 28, 2020 and December 31, 2020 by SARS-CoV-2 antigen or polymerase chain reaction testing of an upper or lower respiratory sample. Providers were notified of the study through postings on message boards hosted by the American Society of Transplantation, the American Society of Transplant Surgeons, and the International Society for Heart and Lung Transplantation. Contributors at individual study sites entered de-identified patient data into REDCap (Research Electronic Data Capture), a secure, web-based data capture software program, which was hosted at the University of Washington.^{10,11} Clinical information regarding baseline demographics and details of disease presentation were collected in an initial survey, and a second follow-up survey collected clinical data at 28 days after COVID-19 diagnosis (Table S1). The registry remained open to collect follow-up surveys through January 31, 2021. Patients for whom both the initial and follow-up surveys were completed were included in the present study.

2.2 | Statistical analyses

Primary analysis assessed patients who were hospitalized within the 28 days following the first positive SARS-CoV-2 test and who were not already hospitalized for another indication prior to or concurrent with diagnosis (consort diagram, Figure S1). Demographic and

baseline characteristics were assessed as counts and percentages for categorical values and as a mean (standard deviation) for continuous variables. Chi-square and Student's *t* tests were used to compare baseline categorical and continuous variables, respectively. Chi-squared and Fisher's exact tests were used to compare the incidence of death (primary outcome) and seven secondary outcomes between LTR and non-lung SOTR by 28 days after COVID-19 diagnosis. Secondary outcomes included intensive care unit (ICU) admission, mechanical ventilation, acute kidney injury, bacterial pneumonia, fungal pneumonia, bloodstream infection, and acute cellular rejection.

Univariable logistic regression was used to assess risk factors for mortality among three hospitalized cohorts: (1) LTR only, (2) non-lung SOTR only, and (3) LTR and non-lung SOTR combined, and multivariable logistic regression was used to determine risk factors for mortality among the entire SOTR cohort. Variables that were selected a priori for consideration of inclusion in our multivariable model (based on our hypothesis and/or prior studies showing significance) included receipt of lung transplant (vs. non-lung transplant), age, and comorbidities (hypertension, diabetes mellitus, heart failure, obesity, chronic kidney disease, coronary artery disease, and chronic lung disease). We evaluated other covariates with at least a prevalence of 5% and a $p < .2$ in the univariable analysis of the entire SOTR cohort for inclusion; based on this, use of mammalian target of rapamycin (mTOR) inhibitor was included as well. Age was assessed as a dichotomous variable (age ≤ 65 years vs. >65 years) based on clinical relevance and in accordance with prior studies.^{12,13} Interactions between lung transplant history and other covariates were considered in the final model. A separate multivariable logistic regression model was used to identify risk factors for mortality specifically in the LTR cohort. For consistency, this model contained the same covariates as the multivariable model used to assess risk factors for mortality in the full SOTR cohort, with the exception that type of lung transplant (single lung vs. bilateral lung) was assessed in place of lung transplant vs. no lung transplant and chronic lung allograft dysfunction (CLAD) was assessed in place of chronic lung disease. Complete data were available for the majority of variables; multiple imputation by chained equations was used to handle the missing data for multivariable models.¹⁴ All results were considered statistically significant at a two-sided p value $\leq .05$. All analyses were performed using Stata version 16.1 (Stata Corporation, College Station, TX) and R version 4.0.2.

3 | RESULTS

3.1 | Study population

There were 1,701 cases of COVID-19 in SOTR entered into the registry during the study period. Cases were excluded from analysis if there was no laboratory-confirmed COVID-19 diagnosis ($n = 8$), $>10\%$ of requested data were missing on initial or follow-up surveys ($n = 5$), data were duplicated in another entry ($n = 9$), the

contributor reported that the case was diagnosed after December 31, 2020 ($n = 1$), or follow-up reports for a living patient were submitted earlier than 28 days after COVID-19 diagnosis ($n = 62$). Of the 1616 SOTR who met inclusion criteria, 1081 (66%) were hospitalized within 28 days of COVID-19 diagnosis, including 120/159 (75%) LTR and 961/1457 (66%) non-lung SOTR ($p = .02$, Table S2). These 1081 patients were included in the primary analysis (consort diagram, Figure S1).

3.2 | Baseline characteristics of hospitalized LTR and non-lung SOTR

Baseline demographics, clinical characteristics, and therapeutic interventions in hospitalized lung and non-lung SOTR are summarized in Table 1. Thirty-four LTR (29%) received a single lung transplant and 16 (14%) LTR had CLAD at baseline. Most LTR were receiving a calcineurin inhibitor (114, 97%) and corticosteroids (117, 98%) at the time of presentation, and 84 (70%) were receiving a regimen that included a calcineurin inhibitor, corticosteroid, and anti-metabolite. Reduction in immunosuppression after COVID-19 diagnosis was less common in LTR vs. non-lung SOTR (64/120 [57%] vs. 686/961 [74%]), and LTR were more likely to receive treatment with corticosteroids, remdesivir, and/or convalescent plasma (Table 1).

3.3 | Crude incidence of outcomes by 28 days in hospitalized lung and non-lung SOTR

We compared the crude incidence of death (primary outcome) and seven secondary outcomes, assessed by 28 days, in hospitalized lung and non-lung SOTR (Table 2). LTR and non-lung SOTR had similar rates of admission to the ICU (52/1120 [44%] vs. 346/925 [37%], $p = .18$), need for mechanical ventilation (33/120 [28%] vs. 250/961 [27%], $p = .74$) and bacterial pneumonia (12/120 [10%] vs. 72/961 [8%], $p = .33$). Fungal pneumonia occurred more commonly among LTR vs. non-lung SOTR (3/120 [3%] vs. 1/961 [0.4%], $p = .01$). Crude 28-day mortality was significantly higher among LTR compared to non-lung SOTR (29/120 [24%] vs. 157/961 [16%], $p = .032$). Unadjusted survival curves demonstrate time to death during the first 28 days after COVID-19 diagnosis in hospitalized lung and non-lung SOTR (Figure 1A) and in all hospitalized SOTR, stratified by organ (Figure 1B).

3.4 | Risk factors for 28-day mortality: Lung vs. non-lung SOTR

In LTR, there was no association between death by 28 days and hypertension, diabetes, coronary artery disease, heart failure, or chronic kidney disease in either univariable (Table 3) or multivariable (Table 4) analysis. After adjusting for comorbidities, CLAD (aOR

3.3, 95% CI 1.0–11.3, $p = .05$) was independently associated with increased mortality. Adjusted mortality trended higher in LTR over age 65 (aOR 1.5, 95% CI 0.6–4.2, $p = .4$) and those with obesity (aOR 2.7, 95% CI 0.9–7.6 $p = .07$). Surrogates of immunosuppression intensity (receipt of induction therapy in the 3 months prior to diagnosis or receipt of triple therapy with a calcineurin inhibitor, anti-metabolite, and steroids) were not associated with mortality.

Among non-lung SOTR, the strongest predictors of death in univariable analysis included age >65 years (OR 2.3, 95% CI 1.6–3.8 $p < .001$) and comorbidities: heart failure (OR 3.8, 95% CI 2.2–6.6, $p < .001$), obesity (OR 1.6, 95% CI 1.1–2.2, $p = .02$), and chronic lung disease (OR 4.1, 95% CI 2.4–7.3, $p < .001$). Hypertension, diabetes mellitus, coronary artery disease, and chronic kidney disease were also associated with increased mortality; mTOR inhibitor use was associated with lower 28-day mortality (Table 3). There was no association between death and the receipt of any specific organ type (heart, liver, or kidney), induction immunosuppressive therapy in the three months preceding COVID-19 diagnosis, or three-drug maintenance immunosuppression with a CNI, corticosteroid, and anti-metabolite.

3.5 | Lung transplantation as an independent risk factor for mortality in hospitalized patients: multivariable analysis of all hospitalized SOTR

Lung, but not other organ transplant type, was associated with increased 28-day mortality in univariable analysis of all hospitalized SOTR (Table 3). Lung transplantation remained independently associated with death after adjusting for age and comorbidities (aOR 1.7, 95% CI 1.0–2.8, $p = .04$, Table 4), but several other factors were more strongly associated with mortality: age >65 years (aOR 2.1, 95% CI 1.5–3.0), heart failure (aOR 2.3, 95% CI 1.3–3.9, $p = .007$), obesity (aOR 1.7, 95% CI 1.2–2.4, $p = .005$), and chronic lung disease (aOR 2.7, 95% CI 1.5–4.6, $p < .001$). Diabetes mellitus, coronary artery disease, and chronic kidney disease were not associated with mortality in the multivariable model (Table 4). Baseline mTOR inhibitor use at the time of COVID-19 diagnosis was associated with decreased mortality (aOR 0.3, 95% CI 0.1–0.8, $p = .03$) but the number of SOTR receiving these agents was small (61 SOTR: nine lung and 52 non-lung).

4 | DISCUSSION

In this large multicenter cohort study of SOTR hospitalized for COVID-19, receipt of a lung (compared to non-lung organ) transplant was independently associated with increased mortality after controlling for comorbidities. Among LTR, single lung transplant and CLAD were independently associated with death. Age >65 years, obesity, and extra-pulmonary comorbidities which were important risk factors for mortality in non-lung SOTR were not independently associated with mortality among LTR.

In the present study, 24% of hospitalized LTR died within 28 days of COVID-19 diagnosis. Smaller observational studies in hospitalized

TABLE 1 Baseline characteristics of hospitalized SOTR with COVID-19

Features of hospitalized SOTR	Lung (n = 120)	Non-lung (n = 961)	p value
Mean age in years (SD)	60.6 (13.0)	961 (57.0)	.005
Age >65 years, n (%)	48 (40.0)	289 (30.0)	.03
Mean day of hospitalization relative to first positive SARS-CoV-2 test (SD)	2.3 (4.8)	2.3 (4.8)	
Male, n (%)	62 (51.7)	610 (63.5)	.01
Race, n (%)			.05
Indigenous peoples	0 (0.0)	18 (1.9)	
Asian	3 (2.5)	44 (4.6)	
Black or African Descent	29 (24.2)	328 (34.1)	
White or Caucasian	75 (62.5)	498 (51.8)	
Pacific Islander	0 (0.0)	4 (0.4)	
Other or unknown	13 (10.8)	69 (7.2)	
Geographic location, n (%)			<.001
Northeastern United States	28 (23.3)	298 (23.3)	
Midwestern United States	12 (10.0)	91 (9.5)	
Southern United States	33 (27.5)	319 (33.2)	
Western United States	42 (35.0)	181 (18.8)	
International	5 (4.2)	28 (2.9)	
Organ n (%) ^a			
Heart	–	131 (13.6)	
Liver	–	154 (16.0)	
Kidney	–	72 (7.0)	
Other	–	3 (0.3)	
Single lung transplant	34 (28.6)	–	
Comorbidities, n (%)			
Hypertension	60 (50.0)	776 (80.8)	<.001
Diabetes mellitus	56 (46.7)	489 (50.9)	.38
Heart failure	8 (6.7)	58 (6.0)	.79
Obesity (BMI ≥ 30 kg/m ²) ^b	29 (24.8)	347 (37.2)	.01
Chronic kidney disease	62 (51.7)	336 (35.0)	<.001
Coronary artery disease	23 (19.2)	171 (17.8)	.71
Chronic lung disease	–	55 (5)	
Chronic lung allograft dysfunction	16 (13.3)	–	
Immunosuppression, n (%) ^{c,d,e,f}			
Recent induction therapy, n (%)	1 (0.8)	62 (6.5)	.01
CNI, anti-metabolite, steroids	84 (70.0)	485 (50.5)	<.001
Any CNI containing regimen	117 (97.5)	878 (91.4)	.02
Any anti-metabolite containing regimen	86 (71.7)	727 (75.7)	.34
Any steroid containing regimen	117 (97.5)	674 (70.2)	<.001
Any mTOR inhibitor containing regimen	9 (7.5)	52 (5.4)	<.001
Covid-19 treatments and interventions			
Reduction in immunosuppression ^g	64 (56.6)	686 (74.1)	<.001
Corticosteroids (≥ 6 -mg dexamethasone equivalents/day)	67 (55.8)	304 (31.6)	<.001

(Continues)

TABLE 1 (Continued)

Features of hospitalized SOTR	Lung (n = 120)	Non-lung (n = 961)	p value
Remdesivir	65 (54.2)	253 (26.3)	<.001
Convalescent plasma	34 (28.3)	158 (16.4)	.001

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin; SOTR, solid organ transplant recipients; SD, standard deviation.

^aLung includes 1 lung/liver, 2 heart/lung recipients and 1 lung/kidney/islet cell. Heart includes 14 heart/kidney and 1 heart/kidney/small bowel recipients. Liver includes 34 liver/kidney and 2 liver/pancreas/small bowel. Kidney includes 18 kidney/pancreas recipients. Other includes 1 vascular composite allograft and 2 small bowel recipients.

^bType of lung transplant (single vs. double) was available for 119 lung recipients.

^cBMI was available for 117 lung and 932 non-lung recipients.

^dInduction of immunosuppression includes receipt of any of the following agents in the three months prior to Covid-19 diagnosis: antithymocyte globulin (35 non-lung, 0 lung), alemtuzumab (2 non-lung, 0 lung), basiliximab (15 non-lung, 1 lung), ≥ 500 mg methylprednisolone/day $\times 3$ or more days (21 non-lung, 0 lung), rituximab (4 lung, 0 non-lung), plasmapheresis (1 lung, 0 non-lung), or bortezomib (1 lung, 0 non-lung). Some patients received more than one induction agent.

^eCNI in lung recipients: tacrolimus (n = 113), cyclosporine (n = 4). CNI in non-lung recipients: tacrolimus (n = 821), cyclosporine (n = 58).

^fAntimetabolite in lung recipients: mycophenolate (n = 73), azathioprine (n = 13). Antimetabolite in non-lung recipients: mycophenolate (n = 690), azathioprine (n = 34), leflunomide (n = 4).

^gMaintenance corticosteroid dose equivalents in lung recipients: ≤ 20 mg prednisone/day (n = 111), >20 mg prednisone/day (n = 6). Maintenance steroid dose equivalents in non-lung recipients: ≤ 20 mg prednisone/day (n = 664), >20 mg prednisone/day (n = 30).

^hReduction in immunosuppression in lung recipients: hold anti-metabolite (n = 54), decrease anti-metabolite (n = 4), change calcineurin inhibitor goal (n = 13), hold and decrease mTOR inhibitor (n = 2) hold all immunosuppression (n = 2). Reduction in immunosuppression in nonlung recipients: hold anti-metabolite (n = 521), decrease anti-metabolite (n = 86), change calcineurin inhibitor goal (n = 222), hold or decrease mTOR inhibitor (n = 11), delay or withhold belatacept (n = 4), decrease prednisone (n = 1), hold all immunosuppression (n = 18). Some patients experienced more than one change.

TABLE 2 Outcomes among hospitalized solid organ transplant recipients with COVID-19 (lung vs. non-lung)

	Lung (n = 120)	Non-lung (n = 961)	p value
Death by 28 days	29 (24.2)		.032*
ICU admission	52 (43.7)		
Mechanical ventilation	33 (27.5)		
Extracorporeal membrane oxygenation			
Acute kidney injury ^b	40 (33.3)	394 (41.0)	
Bacterial pneumonia ^c	12 (10.0)	72 (7.5)	
Fungal pneumonia ^d	3 (2.5)	4 (0.4)	.01*
Bloodstream infection ^e	2 (1.7)	52 (5.4)	.08
Acute cellular rejection	2 (1.7)	9 (1.0)	.45

^aICU admission status was available for 119 lung and 925 non-lung recipients.

^bAcute kidney injury defined as $>50\%$ increase in creatinine from baseline.

^cIncludes cases in which a pathogen was isolated on respiratory culture; excludes empirically treated cases. Respiratory bacterial pathogens in lung recipients included *Pseudomonas* spp. (n = 10), *Klebsiella* spp. (n = 1), *Escherichia coli* (n = 1), *Stenotrophomonas maltophilia* (n = 1). Pathogens in non-lung recipients included *Pseudomonas* (n = 24), *Klebsiella* spp. (n = 11), *E. coli* (n = 7), *Stenotrophomonas maltophilia* (n = 4), *Burkholderia* spp. (n = 5), *Citrobacter* spp. (n = 3), *Enterobacter* spp. (n = 3), *Acinetobacter* spp. (n = 2), *Proteus* spp. (n = 1), *Achromobacter* spp. (n = 1), *Hafnia* spp. (n = 1), *Capnocytophaga* spp. (n = 1), *Staphylococcus aureus* (n = 25), and *Streptococcus* spp. (n = 5). Some patients had more than one pathogen isolated.

^dIncludes cases in which a pathogen was identified; excludes diagnoses based on galactomannan or imaging findings alone. *Aspergillus* was isolated in 2 lung recipients and 3 non-lung recipients. One non-lung recipient had *Rhizopus* and one non-lung recipient had *Cryptococcus*.

^eBloodstream pathogens in lung recipients included *Stenotrophomonas maltophilia* (n = 1) and *Enterococcus* spp. (n = 1). Bloodstream pathogens in non-lung recipients included *Pseudomonas* spp. (n = 8), *E. coli* (n = 10), *Enterobacter* spp. (n = 2), *Stenotrophomonas maltophilia* (n = 1), *Proteus* spp. (n = 1), *Staphylococcus aureus* (n = 22), *Streptococcus* spp. (n = 1), *Enterococcus* spp. (n = 8), and *Candida* spp. (n = 6). Excludes possible contaminants: coagulase-negative staphylococcus (0 lung, 18 non-lung recipients) *Bacillus* spp (1 non-lung recipient), and *Corynebacterium* spp (1 non-lung recipient).

*Statistically significant at $p \leq .05$.

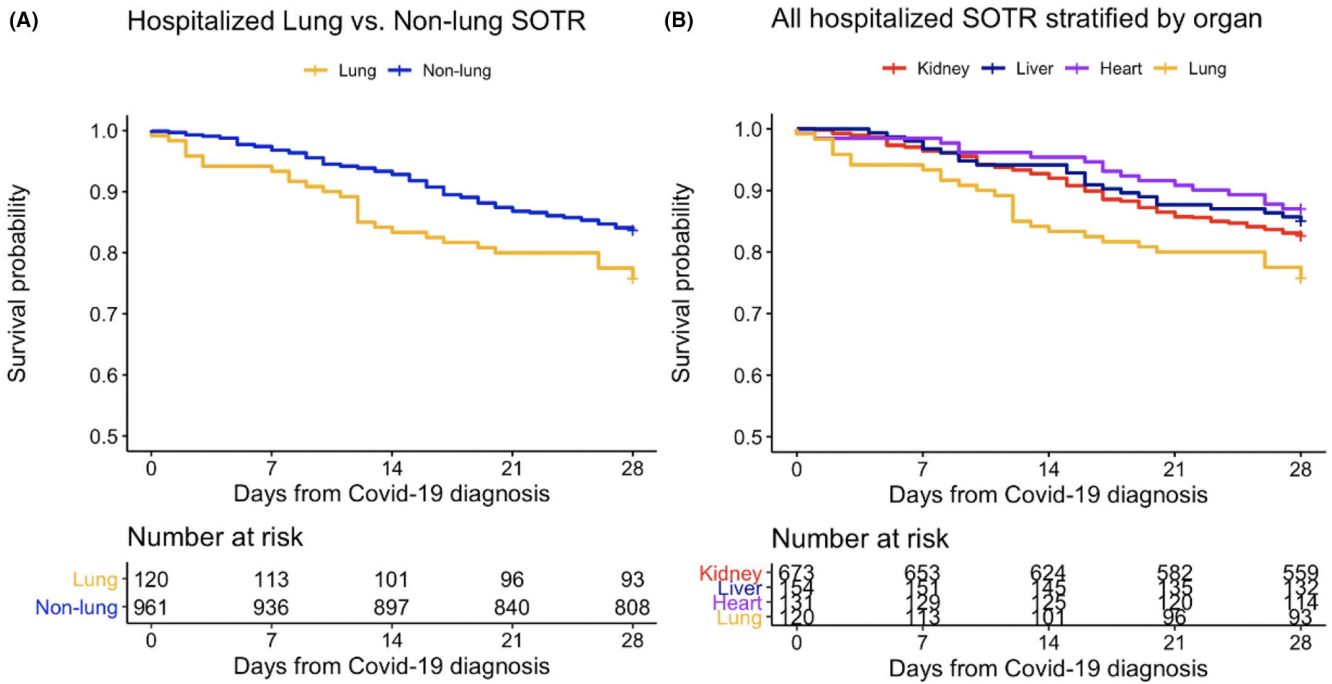


FIGURE 1 Unadjusted Kaplan–Meier curves for all-cause mortality within 28-days after COVID-19 diagnosis for hospitalized solid organ transplant recipients. Abbreviation: solid organ transplant recipients (SOTR). Note: Lung includes 1 lung/liver and 2 heart/lung recipients. Heart includes 14 heart/kidney and 1 heart/kidney/small bowel recipients. Liver includes 33 liver/kidney, 2 liver/pancreas/small bowel. Kidney includes 17 kidney/pancreas recipients. Recipients of other organs (1 vascular composite allograft and 2 small bowel recipients) not included [Color figure can be viewed at wileyonlinelibrary.com]

LTR conducted early in the COVID-19 pandemic reported mortality rates ranging from 13% to 46%, though these studies were heterogeneous, and duration of follow-up varied within and between studies.^{3,6,15-17} Most investigations of LTR with COVID-19 were conducted either outside the United States or were limited to a single center. This study focused on LTR from a broad range of locations primarily in the United States and provides a more precise estimate of mortality in a larger and more geographically diverse population than previously reported cohorts. Combining data from the present study with those from previous studies with ≥ 10 LTR, we calculated a pooled weighted average mortality of 31% among LTR hospitalized with COVID-19 (Table S3). Thus, we have identified hospitalized lung transplant recipients as a specific subpopulation of SOTR in whom new therapies or novel interventions are urgently needed to improve outcomes.

We observed a 50% increase in the odds of death in LTR compared to non-lung SOTR hospitalized for COVID-19. Lung transplant was more strongly associated with death than several comorbidities, including coronary artery disease, chronic kidney disease, and diabetes mellitus, conditions which have been associated with both COVID-19 and all-cause mortality in the general population.¹⁸ However, the magnitude of risk conferred by lung transplant was lower than that of other high-risk conditions, including age >65 years, obesity, chronic lung disease, and heart failure, all of which independently conferred at least a two-fold increase in the odds of mortality. The strong association between these high-risk conditions and mortality is consistent with multiple investigations in

both SOTR and the general population.^{13,19} Notably, hospitalization occurred in a higher proportion of lung recipients (75%) than non-lung SOTR (66%). While this could indicate predisposition to severe COVID-19 after SARS-CoV-2 infection in LTR, this study was not designed to determine differences in the incidence of hospitalization between organ groups.

There are multiple potential mechanisms that may contribute to increased mortality in hospitalized LTR with COVID-19. Compared to non-lung SOTR, LTR typically receive more intensive maintenance immunosuppression,²⁰ leading to a theoretic increased risk for severe complications of COVID-19 and other infections. For example, 70% of LTR in this study were receiving a three-drug regimen containing a calcineurin inhibitor, anti-metabolite, and corticosteroids, compared to 50% of non-lung SOTR. However, neither this combination regimen nor any of its components were associated with death in either lung or non-lung SOTR. Likewise, induction immunosuppressive therapy in the 3 months preceding COVID-19 diagnosis was not associated with mortality, although the numbers of those who received induction immunosuppression in the preceding three months were small. While there is no standardized measure of immunosuppression intensity, these data imply that features of baseline immunosuppression are not prominent predictors of mortality in SOTR with COVID-19. It is worth noting that maintenance immunosuppression with mTOR inhibitors was associated with reduced mortality, particularly in non-lung SOTR. In vitro investigations have shown that mTOR inhibitors may enhance autophagy of cells infected with SARS-CoV-2 and inhibit translation of SARS-CoV-2

TABLE 3 Risk factors for 28-day mortality in hospitalized lung and non-lung solid-organ transplant recipients with COVID-19, univariable logistic regression models

Covariate	Lung (n = 120)		Non-lung (n = 961)		All SOTR (n = 1081)	
	Unadjusted OR (95% CI)	p-value	Unadjusted OR ratio (95% CI)	p-value	Unadjusted OR ratio (95% CI)	p-value
Age >65 years	1.3 (0.6–3.0)	.6	2.3 (1.6–3.3)	<.001	2.1 (1.6–3.0)	<.001
Male sex	0.6 (0.3–1.3)	.2	1.2 (0.8–1.7)	.44		
Black race ^a	0.5 (0.2–1.6)	.3	1.1 (0.7–1.5)	.74	1.0 (0.7–1.4)	.84
Latinx or Hispanic ethnicity	1.0 (0.3–2.7)	>.9	0.9 (0.6–1.4)	.7	0.9 (0.6–1.3)	.6
Region (vs. Midwest)						
Northeast	1.7 (0.3–9.5)	.6	0.9 (0.5–1.6)	.7	0.9 (0.5–1.6)	.79
South	1.6 (0.3–8.9)	.5	0.8 (0.5–1.4)	.4	0.8 (0.5–1.5)	.54
West	1.8 (0.3–9.4)	.5	0.8 (0.4–1.6)	.6	1.0 (0.5–1.8)	.91
Organ ^a						
Lung					2.6 (1.0–2.6)	.04
Single lung transplant	2.2 (0.9–5.3)	.08				
Heart	–		0.7 (0.5–1.3)	.3	0.7 (0.4–1.2)	.15
Liver	–		0.9 (0.5–1.4)	.6	0.8 (0.5–1.3)	.40
Kidney	–		1.1 (0.8–1.7)	.5	0.9 (0.7–1.3)	
Comorbidities						
Hypertension	0.6 (0.3–1.5)	.3	2.2 (1.3–3.7)	.004	1.4 (0.9–2.1)	.12
Diabetes mellitus	0.8 (0.3–1.8)	.5	1.9 (1.3–2.7)	.001	1.6 (1.2–2.2)	.003
Heart failure	1.05 (0.2–5.5)	>.9	3.8 (2.2–6.6)	<.001	3.2 (1.9–5.5)	<.001
Obesity (BMI ≥30 kg/m ²)	2.0 (0.8–5.2)	.2	1.6 (1.1–2.2)	.02	1.5 (1.1–2.1)	.008
Chronic kidney disease	1.2 (0.5–2.8)	.7	1.3 (0.9–1.8)	.2	1.29 (0.9–1.8)	.11
Coronary artery disease	0.6 (0.2–2.0)	.4	1.6 (1.1–2.4)	.03	1.4 (1.0–2.1)	.07
Chronic lung disease	2.9 (1.0–8.7)	.06	4.1 (2.4–7.3)	<.001	4.0 (2.4–6.6)	<.001
CLAD	2.9 (1.0–8.7)	.06				
Immunosuppression						
Recent induction therapy	–	>.99	0.5 (0.2–1.3)	.2	0.5 (0.2–1.2)	.1
CNI, anti-metabolite, and steroids use	1.9 (0.7–5.1)	.2	0.9 (0.6–1.2)	.5	1.0 (0.7–1.4)	>.9
Any CNI containing regimen	–	>.99	1.2 (0.7–2.2)	.5	1.3 (0.7–2.5)	.4
Any anti-metabolite containing regimen	1.7 (0.6–4.6)	.3	0.9 (0.6–1.3)	.5	0.9 (0.7–1.3)	.8
Any steroid containing regimen	0.6 (0.1–7.2)	.7	1.1 (0.7–1.6)	.7	1.1 (0.8–1.6)	.5
Any mTOR containing regimen	0.4 (0.0–3.1)	.4	0.2 (0.1–0.8)	.03	0.3 (0.1–0.8)	.02

Abbreviations: BMI, body mass index; CI, confidence interval; CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin; OR, odds ratio.

^aRefers to patients who received a transplant of the specified organ, with or without transplant other organs: lung (n = 120), heart (n = 133), liver (n = 155), kidney (n = 723). Reference is no transplant of the listed organ.

structural proteins.²² Thus, it is biologically plausible that mTOR inhibitors may offer protection against severe COVID-19, but the efficacy of mTOR inhibitors has not been assessed in prospective randomized trials and the clinical benefits of mTOR inhibitors requires further exploration.

Anti-metabolites and/or calcineurin inhibitors were held or reduced after COVID-19 diagnosis in 57% of LTR and 74% of non-lung

SOTR. However, because underlying disease severity likely influenced management decisions, we were unable to accurately evaluate the relationship between immunosuppression reduction and mortality due to substantial confounding by indication. LTR were more likely to receive treatment with corticosteroids, remdesivir, or convalescent plasma and more frequent use of these agents may reflect more severe disease in LTR, but assessment of the relationships

TABLE 4 Risk factors for 28-day mortality: multivariable logistic regression

Covariate	Lung (n = 120)		All SOTR (n = 1081)	
	aOR ratio (95% CI)	p value	aOR ratio (95% CI)	p value
Age >65 years	1.5 (0.6–4.2)	.4	2.0 (1.4–2.8)	<.001*
Lung transplant	—	—	1.7 (1.0–2.8)	.04
Single lung transplant	2.6 (1.0–7.2)	.06	—	—
Comorbidities				
Hypertension	0.6 (0.3–1.7)	.3	1.3 (0.8–2.0)	.3
Diabetes mellitus	0.6 (0.2–1.7)	.3	1.3 (0.9–1.7)	.3
Heart failure	0.9 (0.2–7.0)	>.9	2.3 (1.2–3.9)	.007
Obesity (BMI ≥30 kg/m ²)	2.7 (0.9–7.6)	.07	1.7 (1.2–2.4)	.005
Chronic kidney disease	1.0 (0.4–2.6)	>.9	1.1 (0.8–1.5)	.6
Coronary artery disease	0.5 (0.2–1.9)	.3	1.1 (0.7–1.7)	.7
Chronic lung disease	—	—	2.7 (1.5–4.6)	<.001
CLAD	3.3 (1.0–11.3)	.05*	—	—
Immunosuppression				
mTOR containing regimen	0.3 (0.03–3.5)	.4	0.3 (1.0–0.8)	.05

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CLAD, chronic lung allograft dysfunction; mTOR, mammalian target of rapamycin; SOTR, solid organ transplant recipients.

*Denotes statistically significant at $\alpha \leq 0.05$.

between various treatments and mortality is again limited by confounding.

Direct infection of the transplanted organ in LTR may also account for differences in mortality between LTR and non-lung SOTR. Chronic lung disease and other medical conditions that decrease pulmonary reserve such as heart failure and obesity were the strongest predictors of death in all SOTR with COVID-19, indicating the importance of underlying pulmonary status on COVID-19 prognosis. Like heart failure and obesity, lung transplantation, even if uncomplicated, may have an unfavorable effect on lung disease in COVID-19. Disruption of thoracic lymphatic drainage during lung transplant surgery predisposes LTR to pulmonary edema, and denervation of the transplanted lung during procurement results in impairment of the cough reflex and mucociliary clearance.²¹ Thus, altered physiology following lung transplantation, like other underlying conditions that impact native lung function, may contribute to the excess mortality in LTR.

The risk factors for mortality among hospitalized LTR with COVID-19 differed from those of non-lung SOTR. Among LTR, lung-associated parameters, including single lung transplant and the presence of CLAD had the greatest association with mortality. Obesity, heart failure and age >65 years, which were strong predictors of death in the non-lung cohort, were not significantly associated with mortality in LTR. However, there was still a trend toward increased mortality among LTR with obesity and advanced age, and the study may not have been powered to detect the effect of these conditions. At the same time, these observations suggest that conditions traditionally considered to be high risk may be less important when lung function is already compromised, as in LTR. The effect of age and other comorbidities on outcomes of COVID-19 in LTR requires additional investigation.

Strengths of our study include the relatively large sample size, geographic and institutional diversity, rigorous and comprehensive statistical analyses, and standardized data collection with 28-day follow-up. We acknowledge potential limitations. Mild or asymptomatic SARS-CoV-2 infections may not have come to the attention of transplant providers, and therefore, the registry may be biased toward more severe cases. Thus, the incidence of hospitalization in this cohort (75% of lung recipients and 66% of non-lung recipients) may overestimate the true incidence of hospitalization. To account for this potential bias, we limited our analysis to only patients who were hospitalized after the diagnosis of COVID-19 to include a more homogenous study population and focus on the most vulnerable patients. In order to perform a study of such magnitude in a timely fashion during a global pandemic, an accessible and concise data collection tool was necessary. This pragmatic study design precluded collection of potentially relevant but identifiable health information, such as date of organ transplant, and the need for efficiency prevented acquisition of detailed clinical information, including measurements required to calculate standardized metrics of disease severity (i.e., the sequential organ failure assessment [SOFA]).

In summary, LTR hospitalized with COVID-19 had higher 28-day mortality compared to non-lung SOTR. While lung transplantation remained an independent risk factor for death after adjusting for age and comorbidities, several traditional comorbidities were stronger predictors of mortality in the entire SOTR cohort. Mortality in LTR with COVID-19 was closely linked to features of the allograft—single lung transplant and CLAD—rather than age or extra-pulmonary comorbidities. These findings should be corroborated in other cohorts, and future investigations should

assess the long term outcomes of COVID-19 in LTR who survive the acute illness.

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DISCLOSURE

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AUTHOR CONTRIBUTIONS

M.R.H. provided clinical data, performed data extraction and statistical analyses, created figures, and wrote the initial manuscript. O.S.K designed the initial study and provided clinical data. R.M.R. provided critical feedback on study design. E.D.L provided clinical data, assisted with study design, and provided critical feedback on data interpretation. C.E.F. and A.P.L. provided study oversight and critical feedback on study design and data interpretation. C.E.F. assisted with statistical analyses. K.S., C.N.K., S.G., J.M.S., B.D.A., M.H-M., E.A.B., M.M.C., A.M. (Ashrit Multani), A.V.P., O.E.B., B.H., R.M.L., L.M., Y.C., S.F., C.G.M., J.G., E.I.D., D.D. (Daniela Diaz), R.V., G.G., M.L., M.M., M.M.A., V.H., M.E.M., Z.S.C., P.S., K.H., A.V., J.M.Y., J.A.M., S.A.M., S.D.T., M.G.I., R.T., A.C.D., D.V.D. (David van Duin), A.M. (Adrienne Maximin), C.G., J.D.G., S.S.D.W., R.G., and J.N. contributed a significant amount of clinical data and editorial review.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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