Received: 26 July 2021 | Revised: 13 September 2021 | Accepted: 17 September 2021

DOI: 10.1111/ctr.14492

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

Excess mortality in solid organ transplant recipients hospitalized with COVID-19: A large-scale comparison of SOT recipients hospitalized with or without COVID-19

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Abstract

Background: Solid-organ transplant (SOT) recipients with coronavirus disease 2019 (COVID-19) have higher risk of adverse outcomes compared to the general population. Whether hospitalized SOT recipients with COVID-19 are at higher risk of mortality than SOT recipients hospitalized for other causes, including non-COVID-19 pneumonia, remains unclear.

Methods: We used logistic regression to compare outcomes of SOT recipients hospitalized with COVID-19 to non-COVID-19 related admissions and with non-COVID-19 pneumonia.

Results: Of 17,012 hospitalized SOT recipients, 1682 had COVID-19. Those with COVID-19 had higher odds of ICU admission (adjusted odds ratio [aOR] 2.12 [95%CI: 1.88–2.39]) and mechanical ventilation (aOR 3.75 [95%CI: 3.24–4.33]). COVID-19 was associated with higher odds of in-hospital death, which was more pronounced earlier in the pandemic (aOR 9.74 [95%CI: 7.08–13.39] for April/May vs. aOR 7.08 [95%CI: 5.62–8.93] for June through November 2020; *P*-interaction = .03). Compared to SOT recipients hospitalized with non-COVID-19 pneumonia, odds of in-hospital death were higher in SOT recipients with COVID-19 (aOR 2.44 [95% CI: 1.90–3.13]), regardless of time of hospitalization (*P*-interaction > .40).

Conclusions: In this large cohort of SOT recipients, hospitalization with COVID-19 was associated with higher odds of complications and in-hospital mortality than non-COVID-19 related admissions, and 2.5-fold higher odds of in-hospital mortality, compared to SOT recipients with non-COVID-19 pneumonia.

KEYWORDS
allograft, coronavirus, COVID-19, heart transplant, kidney transplant, liver transplant, SARS-CoV-2, solid-organ, TRANSPLANT

1 | INTRODUCTION

Since the first reports of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late December 2019, the number of patients developing coronavirus disease 2019 (COVID-19) has risen rapidly, with the World Health Organization declaring a global pandemic on March 11, 2020. To date, over 40 million cases and over 600,000 deaths have been reported in the United States alone.[1]

Several important risk factors for the development of severe COVID-19 have been identified, including obesity, underlying lung disease, diabetes, and chronic kidney disease.[2,3] Solid-organ transplant (SOT) recipients frequently have such co-morbidities and are at higher risk of infection-related complications,[4] in part related to their use of maintenance immunosuppression. Use of maintenance immunosuppression may also blunt the humoral response to vaccination, possibly leaving SOT recipients at higher risk of infection.[5] While prior studies have reported a higher risk of adverse outcomes for SOT recipients with COVID-19 compared with non-SOT recipients, there is limited data comparing outcomes of SOT recipients hospitalized for COVID-19 versus non-COVID-19 related illnesses. Furthermore, there is a paucity of data comparing outcomes of SOT recipients with COVID-19 to non-COVID-19 related pneumonia.

Therefore, in this large multi-center cohort study, we hypothesized that SOT recipients hospitalized with COVID-19 would have a higher risk of mechanical ventilation, intensive care admission, and in-hospital mortality, compared to SOT recipients without COVID-19. We further hypothesized that, among hospitalized SOT recipients, COVID-19 would be associated with a higher risk of adverse outcomes, compared with non-COVID-19 related pneumonia.

2 | METHODS

Solid-organ transplant recipients ≥18 years of age who were discharged from inpatient hospitalization between April 1, 2020 and November 30, 2020 were identified within the Premier Healthcare Database by International Classification of Disease, 10th revision (ICD-10) codes (Table S1). COVID-19 status was defined using the ICD-10 code U07.1 (SARS-CoV-2 virus identified) and hospitalization for non-COVID-19 related pneumonia using respective ICD-10 codes (Table S1). The Premier Healthcare Database is an all-payer, claims-based database encompassing ~20% of US hospitalizations.[6] For SOT recipients without a diagnosis of COVID-19, the first hospitalization within the above timeframe was evaluated, and for SOT recipients with COVID-19, only the first hospitalization related to COVID-19 was considered.

The primary outcomes of interest were mechanical ventilation, intensive care utilization, and in-hospital mortality. Intensive care was defined using billing codes for intensive care room and board, or daily ventilator management. Secondary outcomes included venous thromboembolic disease (VTE), need for renal replacement therapy, length of stay, and discharge disposition. Outcomes were identified based on billing and ICD-10 diagnosis and procedure codes (Tables S1 and S2). Discharge disposition and in-hospital death were reported in all patients.

Data were collected and de-identified by Premier Inc, which curates the Premier Healthcare Database, and then analyzed at the Brigham and Women's Hospital, Boston, MA, USA. The Massachusetts General Brigham Institutional Review Board approved the study protocol. The requirement for informed consent was waived since data were de-identified.

2.1 | Statistical analysis

Baseline characteristics and in-hospital resource utilization among hospitalized SOT recipients diagnosed with COVID-19 and SOT recipients without COVID-19 were compared using Student's *t* test, the Wilcoxon Rank Sum test, and Pearson's χ^2 test, as appropriate. Unadjusted and adjusted multivariable logistic regression models were fit to assess the association of COVID-19 status with adverse in-hospital outcomes; length of hospital stay was evaluated using negative binomial regression. Models were adjusted for age, sex, race/ethnicity, geographic region, discharge month, obesity, hypertension, diabetes, heart failure, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, chronic lung disease, cancer, and tobacco use. Analogous approaches were used to compare SOT recipients with COVID-19 to SOT recipients hospitalized with non-COVID-19 related pneumonia. Evidence for effect modification of the association of COVID-19 status with outcomes of interest according to month (April/May vs. June to November) were assessed by the inclusion of cross-product terms. Sensitivity analyses were performed excluding patients admitted on an elective basis. Statistical analyses were conducted using STATA (version 15.0, Stata Corp., College Station, TX, USA). A two-tailed *P*-value $< .05$ was considered statistically significant, without adjustment for multiplicity.

3 | RESULTS

3.1 | Study population

Among the 17,012 SOT recipients hospitalized during the study, mean age was 59 ± 14 years and 9979 (58.7%) were men. The most common allografts were kidney (63.7%), liver (23.1%), and heart (9.3%). COVID-19 was diagnosed in 1682 (9.9%) patients. The most common reasons for hospitalization among SOT recipients without COVID-19 are listed in Table S3.

Solid-organ transplant recipients hospitalized with COVID-19 were similar in age to those hospitalized for other indications (59 ± 13 years vs.59 ± 14 years, $P = .50$). Compared to SOT recipients without COVID-19, SOT recipients with COVID-19 were more frequently male, Black and/or Hispanic, and more frequently had hypertension, diabetes, and obesity ($P < .01$ for all comparisons). Prevalence of heart failure, valvular disease, peripheral vascular disease, cerebrovascular disease,

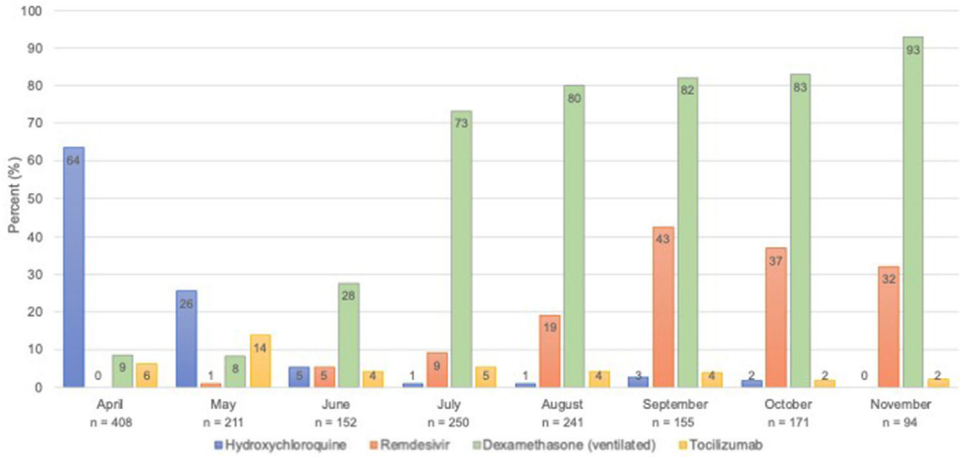

FIGURE 1 Temporal trends in in-hospital medication use for COVID-19. The bar graph shows the proportion of SOT recipients with COVID-19 treated with each respective therapeutic agent by month of hospitalization. Since treatment with dexamethasone is only indicated in hypoxic patients requiring supplemental oxygen, use of dexamethasone was evaluated in mechanically ventilated patients only. *N* refers to the number of SOT recipients with COVID-19 hospitalized and discharged during each respective month

and cancer was lower among SOT recipients with COVID-19, as compared to those without COVID-19 ($P < .05$ for all comparisons) (Table 1).

3.2 | In-hospital medication use

Calcineurin inhibitor use during the hospitalization was more common among SOT recipients with versus without COVID-19 (86.9% vs. 84.4%, $P = .01$); antimetabolites and prednisone were prescribed less frequently in SOT recipients with COVID-19 (50.8% vs. 61.3%, $P < .001$; and 55.5% vs. 58.9%, $P = .01$, respectively). Among SOT recipients with COVID-19, 35.9% were treated with dexamethasone (46.1% of the 347 patients who required mechanical ventilation), 14.1% with remdesivir, 5.6% with tocilizumab, and 19.7% with hydroxychloroquine (Table 1). Temporal trends in medication use with respect to the treatment of COVID-19 are illustrated in Figure 1. Use of hydroxychloroquine sharply declined over time while use of dexamethasone (in mechanically ventilated patients) and remdesivir increased over the duration of the study.

3.3 | Mechanical ventilation and intensive care utilization

The frequency of mechanical ventilation and ICU admission was significantly higher among SOT recipients with COVID-19, as compared to those without COVID-19 (mechanical ventilation: 20.6% vs. 6.9%, adjusted odds ratio [aOR] 3.75 [95% CI: 3.24–4.33]; ICU admission: 30.9% vs. 18.0%, aOR 2.12 [95% CI: 1.88–2.39]). Renal replacement therapy was also instituted more frequently in SOT recipients with COVID-19 than those without COVID-19 (21.6% vs. 15.1%; aOR 1.24 [95% CI: 1.07–1.44]). The association of COVID-19 with these outcomes was not modified by time (Table 2).

Similar patterns of association were noted in sensitivity analyses that excluded patients admitted electively (Table S4).

3.4 | In-hospital mortality

When compared to SOT recipients without COVID-19, SOT recipients with COVID-19 experienced higher in-hospital mortality (17.2% vs. 2.6%). After adjustment for demographic and clinical covariates, hospitalization with COVID-19 was strongly associated with greater odds of in-hospital mortality when compared with hospitalization for other indications. There was heterogeneity in this association by time of hospitalization, with greater odds of in-hospital mortality in SOT recipients discharged in April/May 2020 (aOR 9.74; 95% CI: 7.08–13.39) as compared with those discharged in subsequent months (aOR 7.08; 95% CI: 5.62–8.93; *P*-interaction = .03). Temporal trends in in-hospital mortality over the course of the study are shown in Figure 2.

Cardiac arrest occurred with higher frequency among SOT recipients with COVID-19 (3.5% vs. .9%; aOR 4.05 [95% CI: 2.88–5.69]), regardless of time of hospitalization. Among SOT recipients who experienced cardiac arrest, resuscitation was unsuccessful in 91.5% of patients with COVID-19 and 72.2% of patients without COVID-19 ($P = .003$) (Table 2).

Similar patterns of association were noted in sensitivity analyses that excluded patients admitted electively (Table S4).

3.5 | Venous thromboembolic disease

During hospitalization, the frequency of VTE was similar among SOT recipients with and without COVID-19 (4.2% vs. 3.5%, aOR 1.13 [95% CI: .86–1.47]). However, the use of anticoagulation was higher in SOT recipients with COVID-19 than in SOT recipients without COVID-19 (91.0% vs. 68.2%, $P < .001$).

TABLE 1 Baseline characteristics of SOT recipients according to COVID-19 status

	Without COVID-19 $n = 15330$	With COVID-19 $n = 1682$	*P*-value
Allografts			
Kidney transplant	9602 (62.6%)	1235 (73.4%)	<.001
Liver transplant	3658 (23.9%)	276 (16.4%)	<.001
Heart transplant	1425 (9.3%)	153 (9.1%)	.79
Lung transplant	794 (5.2%)	46 (2.7%)	<.001
Pancreas transplant	779 (5.1%)	68 (4.0%)	.06
Intestinal transplant	65 (.4%)	1 (.1%)	.02
Demographics			
Age	59.1 ± 14.1	58.9 ± 13.2	.50
Male sex	8935 (58.3%)	1044 (62.1%)	.003
Race/ethnicity			<.001
Hispanic	2871 (19.2%)	482 (29.5%)	
Black, Non-Hispanic	1908 (12.8%)	350 (21.4%)	
Other	1375 (9.2%)	221 (13.5%)	
White, Non-Hispanic	8780 (58.8%)	580 (35.5%)	
Black and/or Hispanic	4779 (31.2%)	832 (49.5%)	<.001
Discharge month			<.001
April	2244 (14.6%)	408 (24.3%)	
May	2364 (15.4%)	211 (12.5%)	
June	2382 (15.5%)	152 (9.0%)	
July	2254 (14.7%)	250 (14.9%)	
August	2155 (14.1%)	241 (14.3%)	
September	1914 (12.5%)	155 (9.2%)	
October	1599 (10.4%)	171 (10.2%)	
November	418 (2.7%)	94 (5.6%)	
Region			<.001
Midwest	3285 (21.5%)	343 (20.4%)	
Northeast	2897 (19.0%)	455 (27.1%)	
South	6962 (45.6%)	681 (40.6%)	
West	2108 (13.8%)	199 (11.9%)	
Urban hospital	13779 (90.3%)	1545 (92.1%)	.02
Teaching hospital	10147 (66.5%)	1150 (68.5%)	.10
Comorbid conditions			
Hypertension	12704 (82.9%)	1485 (88.3%)	<.001
Diabetes	8175 (53.3%)	994 (59.1%)	<.001
Heart failure	4041 (26.4%)	403 (24.0%)	.03
Valvular disease	1483 (9.7%)	100 (5.9%)	<.001
Arrhythmia	3979 (26.0%)	448 (26.6%)	.55
Cerebrovascular disease	1049 (6.8%)	82 (4.9%)	.002
Peripheral vascular disease	856 (5.6%)	55 (3.3%)	<.001
Chronic kidney disease	11626 (75.8%)	1304 (77.5%)	.12
Hemodialysis	705 (4.6%)	60 (3.6%)	.05
Chronic lung disease	2389 (15.6%)	244 (14.5%)	.25

(Continues)

TABLE 1 (Continued)

	Without COVID-19 $n = 15330$	With COVID-19 $n = 1682$	*P*-value
Tobacco use	959 (6.3%)	53 (3.2%)	<.001
Cancer	821 (5.4%)	31 (1.8%)	<.001
Obesity	2781 (18.1%)	369 (21.9%)	<.001
Morbid obesity	1009 (6.6%)	141 (8.4%)	.01
In-hospital medication use			
Calcineurin inhibitor	12945 (84.4%)	1462 (86.9%)	.01
Mycophenolate mofetil	8794 (57.4%)	815 (48.5%)	<.001
Azathioprine	643 (4.2%)	39 (2.3%)	<.001
mTOR inhibitor	951 (6.2%)	88 (5.2%)	.11
Belatacept	53 (.3%)	2 (.1%)	.12
Steroids	10365 (67.6%)	1405 (83.5%)	<.001
Prednisone	9023 (58.9%)	934 (55.5%)	.01
Dexamethasone	1541 (10.1%)	604 (35.9%)	<.001
Remdesivir	0 (.0%)	238 (14.1%)	<.001
Tocilizumab	2 (.0%)	94 (5.6%)	<.001
Hydroxychloroquine	166 (1.1%)	332 (19.7%)	<.001
Azithromycin	1321 (8.6%)	642 (38.2%)	<.001
Intravenous immunoglobulin	327 (2.1%)	29 (1.7%)	.27
Anticoagulation	10452 (68.2%)	1530 (91.0%)	<.001
Discharge disposition			<.001
Home	12389 (80.8%)	1090 (64.8%)	
Post-acute care	1447 (9.4%)	167 (9.9%)	
Death/hospice	624 (4.1%)	313 (18.6%)	
Other	870 (5.7%)	112 (6.7%)	

Abbreviations: COVID-19, coronavirus disease 2019; mTOR, mammalian target of rapamycin.

TABLE 2 In-hospital outcomes and resource utilization of SOT recipients according to COVID-19 status

	Without COVID-19 $n = 15330$	With COVID-19 $n = 1682$	Unadjusted effect estimate (95% CI)	*P*-value	Adjusted[a] effect estimate (95% CI)	*P*-value	*P*- interaction
Venous thromboembolism	540 (3.5%)	71 (4.2%)	1.21 (.94–1.55)	.14	1.13 (.86–1.47)	.38	.10
Intensive care	2763 (18.0%)	519 (30.9%)	2.03 (1.82–2.27)	<.001	2.12 (1.88–2.39)	<.001	.51
Mechanical ventilation	1057 (6.9%)	347 (20.6%)	3.51 (3.07–4.01)	<.001	3.75 (3.24–4.33)	<.001	.29
Renal replacement therapy	1400 (15.1%)	217 (21.6%)	1.33 (1.15–1.53)	<.001	1.24 (1.07–1.44)	.01	.40
Cardiac arrest	133 (.9%)	59 (3.5%)	4.15 (3.04–5.67)	<.001	4.05 (2.88–5.69)	<.001	.28
In-hospital death	405 (2.6%)	289 (17.2%)					.03
April–May 2020	140 (3.0%)	140 (22.6%)	9.33 (7.25–12.01)	<.001	9.74 (7.08–13.39)	<.001	
June–Nov 2020	265 (2.5%)	149 (14.0%)	6.43 (5.21–7.95)	<.001	7.08 (5.62–8.93)	<.001	
Length of stay	4 [2, 7]	6 [3, 12]	1.62 (1.54–1.69)	<.001	1.61 (1.54–1.69)	<.001	.12

Effect estimates are presented as odds ratios (derived from logistic regression models for venous thromboembolism, intensive care, mechanical ventilation, renal replacement therapy, cardiac arrest, in-hospital death) or ratios (derived from negative binomial regression models for length of stay). Reference is SOT recipients without COVID-19. P-interaction refers to test for effect modification of the association of COVID-19 status with outcomes of interest according to month (April/May vs. June to November).

[a]Adjusted for age, sex, race, geographic region, discharge month, obesity, hypertension, diabetes, heart failure, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, chronic lung disease, cancer, and tobacco use.

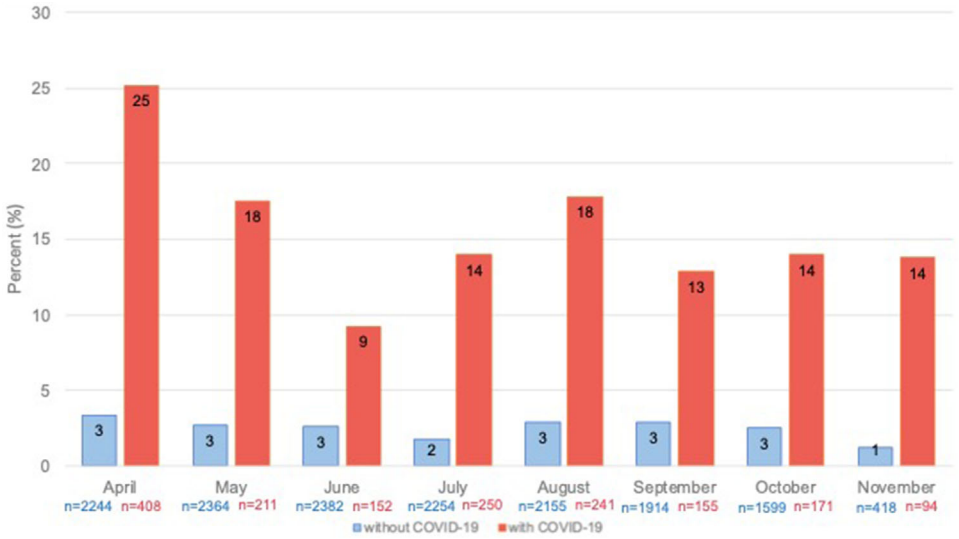

FIGURE 2 Temporal trends in in-hospital mortality in SOT recipients hospitalized with and without COVID-19. The bar graph shows in-hospital mortality in SOT recipients hospitalized with (red) and without (blue) COVID-19 by month of hospitalization. *N* refers to the total number of SOT recipients with and without COVID-19, respectively, who were hospitalized and discharged during each respective month

Similar patterns of association were noted in sensitivity analyses that excluded patients admitted electively (Table S4).

3.6 | Disposition

Among SOT recipients hospitalized with COVID-19, 64.8% were discharged home, 9.9% were transferred to post-acute care facilities, and 18.6% died or were transferred to hospice (Table 1). Hospital length of stay was 61% (95% CI: 54–69%) longer in SOT recipients with COVID-19, as compared to those without COVID-19 after adjustment for demographic and clinical covariates (Table 2).

Similar patterns of association were noted in sensitivity analyses that excluded patients admitted electively (Table S4).

3.7 | COVID-19 versus non-COVID-19 pneumonia in hospitalized SOT recipients

Since medical management (e.g., changes in immunosuppression, institution of antimicrobial therapy, and escalation of care) of SOT recipients hospitalized with non-COVID-19 pneumonia may be similar to that of SOT recipients hospitalized with COVID-19, clinical characteristics and in-hospital outcomes were compared among these groups.

Compared to SOT recipients hospitalized with non-COVID-19 pneumonia (n = 1547), SOT recipients with COVID-19 (n = 1682) were younger, more frequently identified as Black and/or Hispanic, and had a lower prevalence of comorbid conditions, with the exception of hypertension (Table S5). After adjusting for potential confounders, odds of intensive care utilization and mechanical ventilation were not significantly different among SOT recipients with COVID-19 and SOT recipients hospitalized with non-COVID-19 pneumonia (intensive care: 30.9% vs. 36.8%, aOR .88 [95%CI: .74–1.04]; mechanical ventilation: 20.6% vs. 21.8%; aOR 1.00 [95%CI: .83–1.21]). Nevertheless, the odds of in-hospital death were significantly higher in SOT recipients with COVID-19, as compared with SOT recipients with non-COVID-19 pneumonia (17.2% vs. 9.4%; aOR 2.44 [95% CI: 1.90–3.13]), regardless of time of hospitalization (P-interaction = .68). (Table 3)

4 | DISCUSSION

In this large multicenter cohort study, SOT recipients hospitalized with COVID-19 experienced a higher risk of mechanical ventilation and intensive care use, in-hospital cardiac arrest, and in-hospital mortality, compared with SOT recipients without COVID-19 hospitalized during the same period. SOT recipients with COVID-19 were more likely to die in hospital, compared to those with non-COVID-19 related pneumonia, despite being younger and having a lower burden of comorbid conditions.

Patients with SOTs tend to have a high burden of comorbid diseases, including respiratory disorders, cardiovascular disease, and obesity, which are known risk factors for the development of severe COVID-19 and mortality in the general population.[2,3] Similar risk factors have subsequently been reported in observational studies of SOT recipients in the United States[7] and from studies of kidney transplant recipients.[8–10] Concordant with prior studies, in this analysis SOT recipients hospitalized with COVID-19 more frequently identified as Black and/or Hispanic, a finding which may be in part reflective of underlying social, socioeconomic and structural inequities within the healthcare system.[11] Of note, while SOT recipients require the use of chronic immunosuppression, which places them at a higher risk for infection-related adverse events,[4] the study by Kates et al. did not find an association of multiple measures of immunosuppression intensity

TABLE 3 In-hospital outcomes and resource utilization in SOT recipients hospitalized with non-COVID-19 pneumonia and SOT recipients hospitalized with COVID-19

	Non-COVID-19 pneumonia *n* = 1547	COVID-19 *n* = 1682	Unadjusted effect estimate (95% CI)	P-value	Adjusted[a] effect estimate (95% CI)	P-value	P-interaction
Venous thromboembolism	87 (5.6%)	71 (4.2%)	.74 (.54–1.02)	.07	.67 (.47–.95)	.03	.02
Intensive care	570 (36.8%)	519 (30.9%)	.76 (.66–.89)	<.001	.88 (.74–1.04)	.13	.46
Mechanical ventilation	338 (21.8%)	347 (20.6%)	.93 (.79–1.10)	.40	1.00 (.83–1.21)	.99	.33
Renal replacement therapy	242 (24.9%)	217 (21.6%)	.75 (.63–.90)	.002	.79 (.64–.97)	.03	.76
Cardiac arrest	55 (3.6%)	59 (3.5%)	.99 (.68–1.43)	.94	.98 (.64–1.50)	.94	.28
In-hospital death	146 (9.4%)	289 (17.2%)	1.99 (1.61–2.46)	<.001	2.44 (1.90–3.13)	<.001	.68
Length of stay	6.0 [3.0, 11.0]	6.0 [3.0, 12.0]	.84 (.78–.90)	<.001	.91 (.84–.98)	.01	.42

Effect estimates are presented as odds ratios (derived from logistic regression models for venous thromboembolism, intensive care, mechanical ventilation, cardiac arrest, in-hospital death) or ratios (derived from negative binomial regression models for length of stay). Reference is SOT recipients with non-COVID-19 pneumonia. P-interaction refers to test for effect modification of the association of COVID-19 status with outcomes of interest according to month (April/May vs. June to November).

[a]Adjusted for age, sex, race, geographic region, discharge month, obesity, hypertension, diabetes, heart failure, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, chronic lung disease, cancer, and tobacco use.

with mortality.[7] Conversely, the cytokine storm that accompanies the development of severe COVID-19 has led some to postulate that the use of immunosuppression may mitigate against the development of severe disease.[12,13] However, most reports to date suggest that reduction of immunosuppression is a common approach in SOT recipients with COVID-19 infection,[8,14–16] with billing codes for inpatient use of anti-metabolites in our analyses also showing significantly lower use of prednisone, mycophenolate mofetil, and azathioprine in SOT recipients with COVID-19, compared to SOT recipients without COVID-19. Of note, the optimal management of immunosuppression remains unclear and has not been formally tested in randomized controlled clinical trials.

COVID-19 infection appears to be associated with a pro-thrombotic tendency,[17–22] often manifested by development of VTE.[23] In our analyses, the average VTE frequency was 4.3%, which is similar to that reported by Kates et al.,[7] but lower than the 9% reported in a study of critically ill SOT recipients.[24] The difference in the latter may be simply attributable to an overall higher risk of such events in critically ill patients. Although we did not find a significant difference in the frequency of VTE between SOT recipients with and without COVID-19, it should be noted that the frequency of anticoagulation use was substantially higher in the group with COVID-19.

Multiple prior studies have reported worse outcomes of SOT recipients with COVID-19 as compared with non-SOT recipients.[7,9,10] Our analyses address a different and a unique question: comparing outcomes of hospitalized SOT recipients with COVID-19 to SOT recipients with non-COVID-19 related admissions. This allows us to further interrogate the risks associated with COVID-19 in this immunosuppressed population. Furthermore, although vaccines against SARS-CoV2 are increasingly widely available, early data suggests that humoral responses to vaccination are markedly lower in SOT recipients than the general population, suggesting that this disease may present an ongoing risk to SOT recipients despite vaccination.[25,26]

In our study, 21% of SOT recipients with COVID-19 required mechanical ventilation, as opposed to 7% in comparators without COVID-19. Other studies have reported frequency of ventilation of 29–35% for SOT recipients with COVID-19.[7–10,27–29] The risk for ICU admission was 31% in our study, which compares with 34–39% reported in similar studies.[7,8,27–29] Differences across studies may reflect geographical and temporal variation in treatment, immunosuppressive management, and access to care.

Numerous case series of hospitalized SOT recipients with COVID-19 have reported mortality rates of 17–30%.[10,15,29,30] The mortality rate of 17% for SOT recipients with COVID-19 in our analyses most closely approximates the larger of these studies.[7,9] However, we further report significantly higher adjusted odds of in-hospital mortality when compared to SOT recipients without COVID-19 (more than 7-fold higher) and to SOT recipients with non-COVID-19 pneumonia (more than 2-fold higher). The attenuation in observed risk with non-COVID-19 pneumonia comparators may partly reflect the availability of effective anti-microbial therapy in the latter group, as compared with the paucity of direct anti-viral therapy against SARS-CoV-2. When compared to those without COVID-19, SOT recipients with COVID-19 experienced significantly higher rates of in-hospital cardiac arrest in our study (3.5% vs. .9%), coupled with higher rates of unsuccessful resuscitation (91.5% vs. 72.2%). While we were unable to more granularly define the type of arrest, this observation highlights an important potential contributor to morbidity and mortality in these high-risk patients.

The major strengths of this study include the large sample size and ability to make comparisons with SOT recipients without COVID-19. Limitations included the use of ICD-10 codes and billing codes, which may be subject to misclassification. There may also be an inherent bias in the type of patient hospitalized during this timeframe. On one hand, at this earlier phase of the pandemic there may have been a relatively low threshold to admit SOT recipients with COVID-19 out of an

abundance of caution, potentially leading to a less "sick" cohort. On the other hand, there may have been a higher threshold to admit SOT recipients for non-COVID-19 related issues, potentially leading to a "sicker" comparator group. However, in both cases, we would expect this bias to result in more conservative effect estimates. Similarly, indications for hospitalization varied greatly among SOT recipients without COVID-19 and may have included elective admissions, which inherently carry a lower risk of adverse in-hospital outcomes. Since using such a heterogeneous comparator group may bias the association of COVID-19 with adverse in-hospital outcomes, we conducted additional sensitivity analyses excluding elective admissions, and found similar overall patterns of association. To further address this potential bias, we also compared SOT recipients hospitalized with COVID-19 to those with non-COVID-19 pneumonia, where management and risk of adverse outcomes may be more comparable. Additional limitations include an inability to ascertain the time since transplant, baseline and changes in immunosuppression, detailed laboratory data including markers of disease severity or microbiologic data in SOT recipients hospitalized with non-COVID-19 pneumonia, and to determine the proportion of patients that acquired COVID-19 during hospitalization, as opposed to being admitted for COVID-19. Furthermore, we caution generalizability of our findings to patients in different healthcare systems and to non-hospitalized patients.

In conclusion, compared with hospitalized SOT recipients without COVID-19, SOT recipients with COVID-19 have markedly higher risks of morbidity and mortality. These findings emphasize that SOT recipients are highly vulnerable to adverse outcomes following COVID-19 when compared to other illnesses that required acute hospitalization, and highlight the need for early risk stratification and intervention in caring for SOT recipients with COVID-19.

ACKNOWLEDGMENTS

Mc Causland is supported by NIDDK grants U01DK096189 and R03DK122240 and a research grant to his institution from Advanced Instruments. Jering is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant T32HL007604. Claggett reported personal fees from Amgen, Boehringer Ingelheim, Corvia, MyoKardia, and Novartis outside the submitted work. Solomon reported grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, Neurotronik, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Respicardia, Sanofi Pasteur, Theracos and personal fees from Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Sanofi-Pasteur, Tenaya, Dinaqor, Tremeau, CellProThera, and Moderna outside the submitted work.

CONFLICT OF INTEREST

The other authors report no conflicts.

AUTHOR CONTRIBUTIONS

Research idea and study design: Karola S. Jering, Martina M. McGrath, Finnian R. Mc Causland, Brian Claggett, Scott D. Solomon; data acquisition: Karola S. Jering, Brian Claggett, Jonathan W. Cunningham, Scott D. Solomon; data analysis/interpretation: Karola S. Jering, Martina M. McGrath, Finnian R. Mc Causland, Brian Claggett, Jonathan W. Cunningham, Scott D. Solomon; supervision or mentorship: Scott D. Solomon. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Data can be requested from Premier Healthcare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Jering KS, McGrath MM, Mc Causland FR, Claggett B, Cunningham JW, Solomon SD. Excess Mortality in Solid Organ Transplant Recipients Hospitalized with COVID-19: a Large-Scale Comparison of SOT Recipients Hospitalized With or Without COVID-19. *Clin Transplant*. 2022;36:e14492. https://doi.org/10.1111/ctr.14492