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ORIGINAL ARTICLE

Corticosteroids and Outcomes in Solid Organ Transplant Recipients Infected With Severe Acute Respiratory Syndrome Coronavirus 2

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Abstract

Objective: To examine outcomes in organ transplant and nontransplant patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the initial 22 months of the pandemic.
Patients and Methods: We used Optum electronic health records to compare outcomes between an adult transplant group and a propensity-matched nontransplant group that tested positive for SARS-CoV-2 from February 1, 2020, to December 15, 2021. Baseline characteristics, hospitalization, intensive care unit admission, mechanical ventilation, renal replacement therapy, inpatient, and 90-day mortality were compared between the transplant and nontransplant groups and among specific transplant recipients. Cox proportional analysis was used to examine hospitalization and mortality by organ transplant, medical therapy, sex, and the period of the pandemic.
Results: We identified 876,959 patients with SARS-CoV-2 infection, of whom 3548 were organ transplant recipients. The transplant recipients had a higher risk of hospitalization (30.6% vs 25%, respectively; $P<.001$), greater use of mechanical ventilation (7.8% vs 5.6%, respectively; $P<.001$), and increased inpatient mortality (6.7% vs 4.7%, respectively; $P<.001$) compared with the nontransplant patients. The initiation of mechanical ventilation was significantly more frequent in the transplant group. After adjustment for baseline characteristics and comorbidities, the transplant group had a higher risk of hospitalization (odds ratio, 1.38; 95% confidence interval, 1.19-1.59), without a difference in mortality. In the transplant group, lung transplant recipients had the highest inpatient mortality (11.6%).
Conclusion: Among patients with SARS-CoV-2 infection, the transplant recipients were at a higher risk of hospitalization and inpatient mortality; however, mortality was mainly driven by advanced age and comorbidities rather than by transplant status or immunosuppressive medications. Lung transplant recipients had the greatest inpatient and 90-day mortality.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first described in December 2019, resulted in a worldwide pandemic, recognized as coronavirus disease 2019 (COVID-19). It affected millions of patients, resulting in significant morbidity and mortality.[1,2] The spectrum of symptomatic SARS-CoV-2 infection ranges from mild to severe disease manifestations, with the latter leading to hospitalization and more intensive medical therapies. Moreover, approximately 17%-35% of hospitalized patients with COVID-19 require admission to the intensive care unit (ICU) for the treatment of hypoxemic respiratory failure, acute kidney injury, liver dysfunction, and shock.[3] The risk factors for severe COVID-19 include advanced age, male sex, obesity, type 2 diabetes mellitus, active cancer, and social disparities.[4-6]

Previous studies have described organ transplant recipients as being at a higher risk of complications related to respiratory viral lung infections.[7,8] Notably, during the H1N1 influenza pandemic, patients with chronic

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immunosuppression, including solid organ transplant recipients, were more likely to develop severe disease and had worse outcomes than the general population.[9,10] In addition, among solid organ transplant recipients, lung transplant recipients are particularly vulnerable to lower-respiratory-tract infections and are at an increased risk of complications associated with viral pneumonia.[11]

The purpose of this study was to examine the outcomes of SARS-CoV-2 infection among solid organ transplant recipients during the initial 22 months of the pandemic. We hypothesized that solid organ transplant recipients would have an increase in the likelihood of severe disease, with higher rates of hospitalizations, ICU admissions, and elevated mortality, and that lung transplant recipients would experience worse outcomes than other transplant recipients.

PATIENTS AND METHODS

Study Cohort

We used the Optum database, which consists of more than 90 million patients across the United States. The database contains deidentified inpatient and ambulatory information as well as data on procedures, prescriptions, and medication administration. The University of Texas Medical Branch Institutional Review Board approved this study (IRB # 20-0180). We identified all patients aged older than 18 years with positive SARS-CoV-2 test results between February 1, 2020, and December 15, 2021. Individuals positive for SARS-CoV-2 were identified on the basis of a nasopharyngeal swab that tested positive for SARS-CoV-2 using polymerase chain reaction; rapid antigen detection; or the International Classification for Diseases, 10th Revision, clinical modification (ICD-10) diagnosis code U07.1. Patients were excluded if they did not have at least 1 in-person visit to a clinician in the 12 months before COVID-19 diagnosis. Patients were included on the basis of their first positive test result, and those with reinfection were excluded.

Among the SARS-CoV-2-positive individuals, we identified 3548 patients with a history of solid organ transplants using the following ICD-10 codes: Z94.0, Z94.1, Z94.2, Z94.3, and Z94.4. Subsequently, we generated a propensity score on the basis of birth year, sex, race, comorbidities, and the time period (wave) of COVID-19 diagnosis and then used a greedy nearest neighbor algorithm with a 0.2 caliper of the logit of the propensity score to match each transplant patient to 2 nontransplant patients, matching 92.9% (3296) of the transplant patients.

Data regarding patient demographics as well as clinical and prescribed medication history were collected. Comorbidities were identified using ICD-10 diagnosis codes in the 12 months prior to SARS-CoV-2 infection. For body mass index (calculated as the weight in kilograms divided by the height in meters squared), we utilized the reported value at the time of positive SARS-CoV-2 test results (or, if unavailable, the most recent value within the previous year); obesity was defined as a body mass index of 30 kg/m^2 or more. Immunosuppressive medications that were prescribed in the 12 months before SARS-CoV-2 infection, including steroids, calcineurin inhibitors, antimetabolites, and mammalian target of rapamycin inhibitors, and medications administered during hospitalization (remdesivir, corticosteroids, monoclonal antibodies, and tocilizumab) were identified using procedure codes or national drug codes, with the product and therapeutic class names from the 2019 Red-Book Select database (RED BOOK Select Extracts, Truven Health Analytics; 2019).

The primary outcome was the frequency of hospitalization associated with SARS-CoV-2 infection, defined as admission from 4 days prior to 14 days after the positive SARS-CoV-2 test result. This interval was chosen because test results were commonly delayed during the early phases of the pandemic. Alternatively, patients could develop symptoms within 14 days of test positivity. The secondary outcomes included ICU admission, initiation of mechanical ventilation or renal replacement therapy, length of hospital stay, 30-day readmission, inpatient mortality, and 90-day mortality. The clinical outcomes were compared between the transplant and nontransplant groups. For the transplant patients, we conducted a subset analysis by the type of organ transplant.

Statistical Analyses

Demographics and clinical characteristics were summarized as frequencies and percentages or

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TABLE 1. Comparison of Baseline Demographics of Solid Organ Transplant Recipients and Matched Nontransplant Subjects Who Tested Positive for Severe Acute Respiratory Syndrome Coronavirus 2 in the Period From February 2020 to December2021[a]

Characteristics	Total, n (%) N=9888	Transplant history, n (%) N=3296	No transplant, n (%) N=6592	*P*
Age (y)				
18-64	6468 (65.4)	2156 (65.4)	4312 (65.4)	1.00
≥65	3420 (34.6)	1140 (34.6)	2280 (34.6)	
Sex				
Male	6090 (61.6)	2030 (61.6)	4060 (61.6)	1.00
Female	3795 (38.4)	1265 (38.4)	2530 (38.4)	
Race or ethnicity				
African American	1905 (19.3)	635 (19.3)	1270 (19.3)	1.00
Asian	228 (2.3)	76 (2.3)	152 (2.3)	
Caucasian	5397 (54.6)	1799 (54.6)	3598 (54.6)	
Hispanic	1077 (10.9)	359 (10.9)	718 (10.9)	
Other or unknown	1281 (13)	427 (13)	854 (13)	
Comorbidities				
Obesity[b]	3807 (38.5)	1244 (37.7)	2563 (38.9)	.55
DM	3584 (36.2)	1155 (35)	2429 (36.8)	.08
HTN	8049 (81.4)	2606 (79.1)	5443 (82.6)	<.001
Asthma	846 (8.6)	265 (8.0)	581 (8.8)	.20
COPD	1403 (14.2)	442 (13.4)	961 (14.6)	.12
CKD	3074 (31.1)	1026 (31.1)	2048 (31.1)	.95
CHF	2537 (25.7)	830 (25.2)	1707 (25.9)	.44
CAD	2408 (24.4)	800 (24.3)	1608 (24.4)	.90
Liver disease	1439 (14.6)	442 (13.4)	997 (15.1)	.02
Immunosuppressive medications[c]				
Any	3273 (33.1)	2137 (64.8)	1136 (17.2)	<.001
Corticosteroids	2653 (26.8)	1536 (46.6)	1117 (16.9)	
Calcineurin inhibitors	1771(17.9)	1740 (52.8)	31(0.5)	
Antimetabolites	1430 (14.5)	1399 (42.4)	31 (0.5)	
mTOR inhibitors	167 (1.7)	163 (4.9)	4 (0.1)	
Organ transplant type				
Kidney		2043 (62)		
Liver		495 (15)		
Heart		294 (8.9)		
Lung		294 (8.9)		
Multiple		170 (5.2)		

[a]CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; mTOR, mammalian target of rapamycin.
[b]Obesity defined as a body mass index of 30 kg/m^2 or more.
[c]Medications prescribed in the 365 days before a positive test result for severe acute respiratory syndrome coronavirus 2.

mean ± standard deviation. Continuous variables were compared using t tests, whereas categorical variables were assessed using chi-square tests. A multivariable logistic regression model with random effects for hospital network was used to determine the risk of hospital admission on the basis of transplant status or specific solid organ transplant. Multivariable Cox proportional hazards models with random effects for hospital network were used to estimate the odds ratios (ORs) for hospitalization and inpatient mortality, accounting for clinical characteristics. The patients were censored at the time of death, hospital discharge, or the end of the study period (December 15, 2021). We also tested an a priori hypothesis regarding differential response to corticosteroids by sex by

TABLE 2. Comparison of Inhospital Treatment and Outcomes Between Patients With a History of Organ Transplant and Nontransplant Patients Who Tested Positive for Severe Acute Respiratory Syndrome Coronavirus 2 in the Period From February 2020 to December 2021

Characteristic	Total, n (%) N=9888	Transplant history, n (%) N=3296	No transplant, n (%) N=6592	*P*
Hospitalization	2661 (26.9)	1010 (30.6)	1651 (25)	<.001
ICU admission	637 (6.4)	258 (7.8)	379 (5.7)	<.001
Medications prescribed				
Corticosteroids	1756 (17.8)	937 (14.2)	819 (24.8)	<.001
Remdesivir	711 (7.2)	292 (8.9)	419 (6.4)	<.001
Tocilizumab	146 (1.5)	72 (2.2)	74 (1.1)	<.001
Monoclonal antibodies	699 (7.1)	371 (11.3)	328 (5)	<.001
Mechanical ventilation	622 (6.3)	256 (7.8)	366 (5.6)	<.001
CRRT	741 (7.5)	200 (6.1)	541 (8.2)	<.001
LOS (d), mean ± SD		11.8±14.6	9.9±10.8	<.001
Inpatient mortality	529 (5.3)	222 (6.7)	307 (4.7)	<.001
30-d readmission	389 (3.9)	137 (4.2)	252 (3.8)	.42
90-d mortality	1240 (12.5)	443 (13.4)	797 (12.1)	.06

CRRT, continuous renal replacement therapy; ICU, intensive care unit; LOS, length of stay.

examining the interaction of sex and the use of corticosteroids with inpatient mortality.[12] All analyses were performed using SAS 9.4 (SAS, Inc). The statistical significance level was set at $P < .05$.

RESULTS

Baseline Characteristics

Between February 1, 2020, and December 15, 2021, we identified 876,959 patients who tested positive for SARS-CoV-2, including 3548 solid organ transplant recipients. To compare the outcomes between the solid organ transplant and nontransplant groups, a 2:1 propensity matching was performed on the basis of age, sex, race, and comorbidities, which resulted in 6592 patients in the nontransplant group and 3296 patients in the transplant group. The characteristics of the entire cohort revealed a predominance of men (61.6%), and the majority were younger than 65 years (65.4%) (Table 1). Hypertension (81.4%) was the most common comorbidity, followed by obesity (38.5%), diabetes mellitus (36.2%), and chronic kidney disease (31.1%). In the solid organ transplant group, the frequency of organ transplant in decreasing order was kidney (62%), liver (15%), heart (8.9%), lung (8.9 %), and multiorgans (5.2%). A prescription for immunosuppressive medications 12 months earlier was noted in 3273 patients (33.1%), with corticosteroids, calcineurin inhibitors, and antimetabolites prescribed more frequently to the transplant recipient group than to the nontransplant group (Table 1).

Treatment

From the entire cohort of 9888 SARS-CoV-2-positive patients, 2661 (26.9%) were hospitalized for SARS-CoV-2 infection and 637 (6.4%) were admitted to the ICU. Invasive mechanical ventilation was initiated in 622 patients (6.3%), and 741 patients (7.5%) received renal replacement therapy. In the 2661 hospitalized patients who received medical therapies directed at the treatment of SARS-CoV-2 infection, the frequency of prescriptions in decreasing order was corticosteroids (66%), remdesivir (26.7%), monoclonal antibodies (26.3%), and tocilizumab (5.5%) (Table 2). A comparison of the groups revealed that corticosteroids were most frequently prescribed for the treatment of SARS-CoV-2 infection and that remdesivir and monoclonal antibodies were more often administered to the organ transplant group. Variation of treatment on the basis of individual organ transplant groups revealed that corticosteroids and tocilizumab were more often prescribed to lung transplant recipients than to nonlung transplant recipients (Table 3).

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TABLE 3. Comparison of Inhospital Treatment and Outcomes by Transplant Types Among Solid Organ Transplant Recipients Who Tested Positive for Severe Acute Respiratory Syndrome Coronavirus 2 From February 2020 to December 2021[a]

Outcomes/Treatment	Kidney, n (%) N=2043	Liver, n (%) N=495	Lung, n (%) N=294	Heart, n (%) N=294	Multiple, n (%) N=170	*P*
Hospitalization	664 (32.5)	133 (26.9)	84 (28.6)	80 (27.2)	49 (28.8)	.06
ICU admission	155 (7.6)	40 (8.1)	25 (8.5)	24 (8.2)	14 (8.2)	.98
Medications prescribed						
Dexamethasone or steroids	545 (26.7)	97 (19.6)	81 (27.6)	56 (19.1)	40 (23.5)	.002
Remdesivir	177 (8.7)	44 (8.9)	34 (11.6)	24 (8.2)	13 (7.7)	.52
Tocilizumab	46 (2.3)	2 (0.4)	16 (5.4)	3 (1.0)	5 (2.9)	<.0001
Monoclonal antibodies	226 (11.1)	56 (11.3)	33 (11.2)	35 (11.9)	21 (12.4)	.98
Mechanical ventilation	177 (8.7)	33 (6.7)	20 (6.8)	13 (4.4)	13 (7.8)	.09
CRRT	155 (7.6)	19 (3.8)	8 (2.7)	8 (2.7)	10 (5.9)	<.0001
LOS, mean (SD)	11.8 (15.1)	9.8 (8.6)	12.5 (14.6)	12.6 (18.2)	14.3 (13.1)	.38
Inpatient mortality	138 (6.8)	31 (6.3)	34 (11.6)	5 (1.7)	14 (8.2)	<.0001
30-d readmission	86 (4.2)	16 (3.2)	12 (4.1)	15 (5.1)	8 (4.7)	.76
90-d mortality	274 (13.4)	55 (11.1)	57 (19.4)	33 (11.2)	24 (11.1)	.01

[a]CRRT, continuous renal replacement therapy; ICU, intensive care unit; LOS, length of stay.

Transplant and Nontransplant Outcomes

A comparison of the outcomes demonstrated that the organ transplant group had a greater rate of hospitalization than the nontransplant group (30.6% vs 25%, respectively; $P<.001$) (Table 2). In addition, the transplant recipients were significantly more likely to require ICU admission (7.8%) than the nontransplant patients (5.7%) ($P<.001$). Consequently, the mean length of hospital stay was significantly longer in the organ transplant group than in the nontransplant group (11.8±14.6 vs 9.9±10.8 days, respectively; $P<.001$). The initiation of mechanical ventilation was significantly more frequent in the organ transplant group, whereas the use of renal replacement therapy was more frequent in the nontransplant group. The inpatient mortality was significantly greater in the organ transplant recipients than in the nontransplant patients (6.7% vs 4.7%, respectively; $P<.001$). Yet, there was no difference in the 90-day mortality rate between the groups (Table 2). After adjustment for demographics, comorbidities, and immunosuppressive medications, the organ transplant recipients had a higher risk of hospitalization than the nontransplant patients (OR, 1.38; 95% confidence interval [CI], 1.19-1.59) (Table 4). However, the inpatient mortality did not differ between the groups (OR, 1.02; 95% CI, 0.78-1.35) after adjustment for covariates (Table 5). Further analysis revealed that the risk of hospitalization and inpatient mortality were increased in both the groups for patients aged 65 years or older ([OR, 1.50; 95% CI, 1.34-1.67] vs [OR, 1.79; 95% CI, 1.46-2.20], respectively). The comorbidities associated with an elevated risk of hospitalization included diabetes, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, and congestive heart failure. Notably, immunosuppressive medications were not associated with an elevated risk of hospitalization or mortality (Tables 4 and 5).

A multivariate model analysis of the effect of various infectious waves on the risk of hospitalization demonstrated that the greatest risk occurred in the early months of the pandemic (February 2020-May 2020) compared with that in the later months (Table 4). In contrast, the impact of various infectious waves on inpatient mortality was similar throughout the different waves (Table 5). Corticosteroid prescription for the treatment of SARS-CoV-2 infection was associated with lower mortality in men (OR, 0.37; 95% CI, 0.20-0.68); however, there was no difference in mortality in

TABLE 4. Multivariate Model for the Risk of Hospitalization Among Patients Infected With Severe Acute Respiratory Syndrome Coronavirus 2 in the Period From February 2020 to December 2021[a]

Variable	Odds ratio (95% CI)
History of organ transplant[b]	1.38 (1.19-1.59)
Age≥65 y	1.50 (1.34-1.67)
Sex	
Male[c]	1.17 (1.05-1.30)
Race or ethnicity[d]	
African American	1.56 (1.36-1.78)
Asian	2.09 (1.49-2.93)
Hispanic	1.57 (1.32-1.85)
Other or unknown	1.42 (1.17-1.72)
Comorbidities	
Obesity (BMI≥30 kg/m^2)	1.02 (0.92-1.13)
DM	1.18 (1.06-1.31)
HTN	1.28 (1.09-1.50)
Asthma	1.07 (0.90-1.28)
COPD	1.43 (1.23-1.65)
CKD	1.49 (1.33-1.67)
CHF	1.42 (1.25-1.61)
CAD	1.12 (0.99-1.27)
Liver disease	0.85 (0.75-0.97)
Immunosuppressive medications	0.96 (0.84-1.10)
Any	0.97 (0.78-1.21)
Calcineurin inhibitors	1.28 (1.03-1.60)
Antimetabolites	0.85 (0.75-0.97)
Corticosteroids mTOR inhibitors	0.88 (0.60-1.27)
Period of diagnosis[e]	
February 2020-May 2020	9.67 (8.03-11.66)
June 2020-September 2020	5.43 (4.47-6.58)
October 2020-February 2021	5.00 (4.30-5.81)
March 2021-June 2021	5.28 (4.38-6.37)

[a]BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; mTOR, mammalian target of rapamycin.
[b]Compared with the nontransplant group.
[c]Compared with women.
[d]Compared with White or Caucasian race.
[e]Compared with July 2021-Dec 2021.

women (OR, 0.95; 95% CI, 0.31-2.88) (Table 5, Figure).

Specific Outcomes of Organ Transplant

A multivariable logistic regression model determined that the rate of hospitalization did not differ according to the type of transplant (Table 3). Although the frequency of the initiation of mechanical ventilation was similar for all transplant groups, continuous renal replacement therapy was employed more often in the kidney transplant group. Although the length of stay was significantly greater in the transplant group than in the nontransplant group (11.8±14.6 and 9.9±10.8, respectively; $P<.001$), the length of stay was similar among the various transplant recipients. Notably, the inpatient and 90-day mortality rate were significantly greater among lung transplant recipients (Table 3).

DISCUSSION

In this retrospective study, spanning 22 months of the pandemic, the patients infected with SARS-CoV-2 and with a history of organ transplant had the following: a) an increased risk of hospitalization and initiation of mechanical ventilation compared with the nontransplant patients; b) after adjustment for baseline characteristics and comorbidities, no difference in mortality was observed between the groups; c) age of 65 years or older and medical comorbidities were independently associated with an increased risk of hospitalization, regardless of transplant status; and lung transplant recipients had the highest inpatient and 90-day mortality compared with other transplant recipients.

In the current study, the SARS-CoV-2 infection-related hospitalization, ICU admission, and mortality for the transplant recipients were comparable with those from a previous large, multicenter analysis.[13] In contrast, Kates et al[14] reported outcomes from a multicenter study that included 482 transplant recipients, of whom 78% were hospitalized for SARS-CoV-2 infection and mechanical ventilation initiated in 31%, with a 28-day mortality rate of 20.5%. However, in another multicenter study of 98 solid organ transplant recipients with SARS-CoV-2 infection, the initiation of mechanical ventilation occurred in 56% of the patients, and the 28-day mortality rate was 40%.[15] In the present report, the findings of the lower rates of hospitalization and less frequent initiation of mechanical ventilation in the transplant group may be because the earlier studies were conducted during the first few months of the pandemic, when treatment options were limited and protocols more varied. This is supported by an analysis that examined hospitalization according to the period of diagnosis

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during the pandemic, in which the risk of hospitalization was 1.7 times greater during the first wave compared with those in subsequent waves. In addition, the observed differences in mortality among the studies may be related to advances in SARS-CoV-2 diagnostics and the use of therapeutic agents that have led to improved outcomes.[14-20]

Respiratory viral infections, including influenza, respiratory syncytial virus, parainfluenza virus, rhinovirus, human metapneumovirus, and coronavirus, are associated with severe disease and increased mortality among organ transplant recipients.[8,21] Our results suggest an increased risk of severe disease among organ transplant recipients with SARS-CoV-2 infection, as demonstrated by the higher hospitalization rate, increased risk of ICU admission, longer length of hospital stay, greater need for mechanical ventilation, and elevated mortality compared with that in the nontransplant group. However, in concordance with other studies, the increased mortality appears to be driven mainly by advanced age and comorbid conditions in the organ transplant group.[13-15] Most transplant recipients in our cohort were kidney transplant recipients who also carried a large burden of comorbidities, including congestive heart failure, diabetes mellitus, and advanced age, which may explain the trend toward worse outcomes, with increased hospitalization and mortality, among kidney transplant recipients.[22,23]

Another finding concerns the increased rate of mortality among lung transplant recipients, similar to that with other respiratory viruses, and is recognized to be a significant cause of complications and mortality in this group.[24,25] A previous prospective study described a 23.6% incidence of respiratory infections in 98 lung transplant recipients and reported an attributable mortality rate of 5.1%.[11] Recent single-center studies have described outcomes in lung transplant recipients with SARS-CoV-2, with the reported mortality ranging from 6.5% to 34%.[26-29] However, multicenter reports comparing mortality among organ transplant recipients have found that the receipt of a lung transplant compared with that of a nonlung transplant was not associated with increased mortality due to SARS-CoV-2 infection.[13,14] The findings of the current study revealed significantly increased inpatient and 90-day mortality among lung transplant recipients compared with those in other solid organ transplant groups. This may be explained by direct contact of the lung graft with the ambient environment, leading to greater vulnerability to infection, greater net state of immunosuppression in lung transplant recipients compared with that in nonlung transplant recipients, an increased risk of complications associated with lung graft failure,[11] and larger sample size.

TABLE 5. Multivariate Model for the Risk of Mortality Among Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 in the Period From February 2020 to December 2021[a]

Variable	Odds ratio (95% CI)
History of organ transplant[b]	1.02 (0.78-1.35)
Age≥65 y	1.79 (1.46-2.20)
Sex	
Male[c]	0.91 (0.74-1.11)
Comorbidities	
Obesity (BMI≥30 kg/m^2)	0.87 (0.70-1.07)
DM	0.83 (0.67-1.02)
HTN	1.14 (0.77-1.70)
COPD	0.97 (0.76-1.25)
CKD	0.94 (0.76-1.16)
CHF	1.18 (0.94-1.47)
Immunosuppressive medications	0.89 (0.66-1.19)
Any	0.84 (0.57-1.25)
Calcineurin inhibitors	1.21(0.82-1.77)
Antimetabolites	0.89 (0.69-1.15)
Corticosteroids mTOR inhibitors	0.53 (0.24-1.17)
COVID-19 therapeutics	
Remdesivir	0.56 (0.43-0.73)
Steroids	0.93 (0.71-1.22)
Women[d]	0.95 (0.31-2.88)
Men[d]	0.37 (0.20-0.68)
Period of diagnosis[e]	
February 2020-May 2020	1.24 (0.75-2.04)
June 2020-September 2020	1.51 (0.88-2.58)
October 2020-February 2021	1.65 (1.02-2.68)
March 2021-June 2021	1.70 (1.01-2.87)

[a]BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HTN, hypertension; mTOR, mammalian target of rapamycin.
[b]Compared with the nontransplant group.
[c]Compared with women.
[d]Compared with patients who did not receive steroids.
[e]Compared with July 2021-Dec 2021.

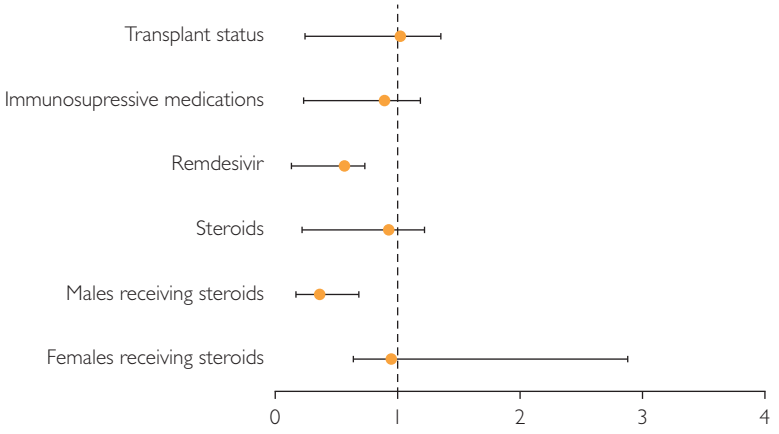

FIGURE. Multivariate model, odds ratios with 95% confidence intervals, for factors associated with mortality among patients infected with severe acute respiratory syndrome coronavirus 2 in the period from February 2020 to June 2021. Immunosuppressive medications were those received before the diagnosis of coronavirus disease 2019, including calcineurin inhibitors, steroids, antimetabolites, and mammalian target of rapamycin inhibitors.

We found that the receipt of immunosuppressive medications, including corticosteroids, calcineurin inhibitors, antimetabolites, and mammalian target of rapamycin inhibitors, prior to SARS-CoV-2 infection was not associated with increased rate of hospitalization or mortality. However, our findings that solid organ transplant recipients aged 65 years or older and with comorbidities were associated with poor outcomes was similarly reported in patients with cancer and COVID-19, which suggested that advanced age and comorbidities were associated with increased mortality rather than the stage of malignancy or the use of chemotherapy or immunotherapy.[30] A previous report indicated that cytokine release syndrome was associated with poor outcomes and mortality among patients with SARS-CoV-2 infection.[31] However, the use of immunosuppressive medications to reduce activation of proinflammatory cytokines may result in a blunted host response to infection, with delay in viral clearance. Consequently, further studies are needed to guide the optimal management of antirejection medications in organ transplant recipients with COVID-19 and other viral respiratory tract infections.

Since the beginning of the pandemic, effective medical therapies for the treatment of severe COVID-19 have increased to include monoclonal antibodies, remdesivir, corticosteroids, and interleukin-6 inhibitors.[17-20,32] Although immunomodulatory therapies are associated with better outcomes in nontransplant patients with severe COVID-19, their role in the transplant population is less defined. In the current study, systemic steroids were administered to 24.8% of the organ transplant patients and were associated with significant reduction in mortality. Interestingly, the mortality benefit was observed mainly in men. Although the exact underlying molecular mechanisms for our observation are unclear, the increased risk of severe disease in men because of delayed viral RNA clearance and a higher prevalence of cardiovascular comorbidities may explain the observed differential response to systemic steroids.[33-35] Furthermore, sex differences in susceptibility and immune response to viral infections, including SARS-CoV-2, have been previously reported.[36,37]

We reported the outcomes of COVID-19 among solid organ transplant recipients from a large nationwide database, for which we used propensity-score matching to assess the risk of organ transplant status and immunosuppression on several clinical outcomes, including hospitalization, ICU admission, need for mechanical ventilation, renal replacement therapy, and mortality. Our data

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spanned 22 months of the COVID-19 pandemic and included a large sample of hospitalized individuals. We acknowledge several limitations of our study, including its retrospective design. Additionally, data regarding the time from initial transplant were not available, and, therefore, we could not determine the association between the outcomes and the duration of immunosuppression or graft function. Another limitation concerns the identification of prescribed immunosuppressants in only 64.8% of the patients in the transplant group in the 12 months prior to COVID-19 diagnosis. Data were obtained from all hospital networks included in the Optum database, and it is likely that our dataset did not capture medications prescribed from other hospital networks or those prescribed more than 1 year before COVID-19 diagnosis. However, the multivariate analysis did not suggest an increased risk of hospitalization or mortality with the use of immunosuppressive medications. Another limitation concerns the lack of information on the management of immunosuppressive medications after hospital admission, and this study does not address whether immunosuppressants should be maintained, reduced, or discontinued in organ transplant recipients hospitalized with SARS-CoV-2 infection. An additional limitation concerns the limited number of patients (7%) who were prescribed one of the various monoclonal antibody therapies that did not allow for the assessment of the effect of these agents on the outcomes. This did not allow a part of the analysis. Lastly, we observed a decrease in the risk of hospitalization in the late study period (June 2021-December 2021) compared with that in the earlier months of the pandemic (February 2020-June 2021). Interestingly, the time of diagnosis did not impact the inpatient mortality rates. Decreased rates of hospitalization for SARS-CoV-2 have been widely observed, and whether this is related to vaccination or adaptive mutations in the viral genome resulting in more contagious and less virulent subvariants remains unclear.[38]

CONCLUSION

Solid organ transplant recipients infected with SARS-CoV-2 were more likely to develop severe disease, requiring hospitalization, with increased mortality compared with the non-transplant population. The increased mortality appears to be driven by advanced age and comorbidities rather than immunosuppressive medications or the type of organ transplant. In the organ transplant group, lung transplant recipients had the highest mortality.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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Abbreviations and Acronyms: **CI,** confidence interval; **COVID-19,** coronavirus disease 2019; **ICD-10,** International Classification for Diseases, tenth revision; **ICU,** intensive care unit; **OR,** odds ratio; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2

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