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Outcomes of Critically Ill Solid Organ Transplant Patients with COVID-19 in the United States

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Abbreviations
ACE2: angiotensin-converting enzyme 2
AIDS: acquired immunodeficiency syndrome
AKI: acute kidney injury
ARDS: acute respiratory distress syndrome
COVID-19: coronavirus disease 2019
CI: confidence interval
ECMO: extracorporeal membrane oxygenation
eGFR: estimated glomerular filtration rate
HIV: human immunodeficiency virus
ICU: intensive care units
IQR: interquartile range
OR: odds ratio
PS: propensity score
RECOVERY: Randomised Evaluation of COVid-19 thERapY
RRT: renal replacement therapy
SOT: solid organ transplant
STOP-COVID: Study of the Treatment and Outcomes in critically ill Patients with COVID-19
US: United States

Abstract

National data on patient characteristics, treatment, and outcomes of critically ill COVID-19 solid organ transplant(SOT) patients are limited.

We analyzed data from a multicenter cohort study of adults with laboratory-confirmed COVID-19 admitted to intensive care units(ICUs) at 68 hospitals across the United States from March 4th to May 8th, 2020. From 4,153 patients, we created a propensity score matched cohort of 386 patients, including 98 SOT patients and 288 non-SOT patients. We used a binomial generalized linear model(log-binomial model) to examine the association of SOT status with death and other clinical outcomes.

Among the 386 patients, the median age was 60 years, 72% were male, and 41% were black. Death within 28 days of ICU admission was similar in SOT and non-SOT patients(40% and 43%, respectively; relative risk[RR] 0.92 [95% Confidence Interval(CI):0.70-1.22]). Other outcomes and requirement for organ support including receipt of mechanical ventilation, development of acute respiratory distress syndrome, and receipt of vasopressors were also similar between groups. There was a trend toward higher risk of acute kidney injury requiring renal replacement therapy in SOT vs. non-SOT patients (37% vs. 27%; RR[95%CI]:1.34 [0.97-1.85]).

Death and organ support requirement were similar between SOT and non-SOT critically ill patients with COVID-19.

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread from Wuhan, China to the rest of the world, leading to more than 20 million confirmed cases of coronavirus disease 2019 (COVID-19) with more than 738,000 deaths as of August 11th, 2020 (1). The spectrum of clinical disease from COVID-19 varies from a mild febrile illness to critical illness, including acute respiratory distress syndrome (ARDS) and multiorgan failure, which are associated with high morbidity and mortality. Identified risk factors for adverse outcomes from COVID-19 include older age, obesity, male sex, and co-morbid conditions, including diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease, chronic lung disease, and malignancy (2-7).

Solid organ transplant (SOT) patients are considered high risk for complications from COVID-19 due to their immunosuppressed status (8, 9). They are more susceptible to infections

with ribonucleic acid respiratory viruses in general, and have a higher risk of complications such as bacterial and fungal superinfection (10). However, since the manifestations of severe COVID-19, including ARDS and organ dysfunction, may be propagated by a pro-inflammatory state due to cytokine release syndrome (11, 12), immunosuppressive therapy could potentially mitigate some of these effects and thereby help prevent severe complications in SOT patients.

Current data on the clinical course of COVID-19 in immunocompromised patients are limited predominantly to case reports and single-center studies. Among hospitalized SOT patients with COVID-19 in New York City, acute mortality rates varied between 13-29% (8, 13-15). A similar case fatality rate of 20-28% was reported in hospitalized SOT recipient cohorts from Italy, Spain, the United Kingdom and the Netherlands (9, 16-18). A cohort study from Switzerland that included 20 hospitalized SOT patients reported a lower mortality rate of 10%, which was similar to the mortality observed in the general population with COVID-19 (19). Small case series from the US have also reported similar mortality rates in SOT patients with COVID-19 that have been observed in the general population (20-23). In addition, there is no data available for outcomes of COVID-19 infected SOT patients admitted in intensive care units. Our paper is aimed to address this knowledge gap.

Previously published studies focusing on SOT patients and COVID-19 lack comparison with a control group to ascertain their risk as compared to the general population (8, 9, 13-18). To address this knowledge gap, we compared outcomes in SOT versus non-SOT patients with COVID-19 who were admitted to intensive care units (ICUs) throughout the US, using data from a multicenter cohort study. We hypothesized that SOT patients would have similar risk of death and organ support requirement compared to non-SOT patients.

Materials and Methods

Study Design and Oversight

We used data from the Study of the Treatment and Outcomes in critically ill Patients with COVID-19 (STOP-COVID). STOP-COVID is a multicenter cohort study that enrolled adults with COVID-19 admitted to participating ICUs at 68 hospitals across the United States. The study was approved by the Institutional Review Board at each participating site with a waiver of informed consent and registered on ClinicalTrials.gov (NCT04343898).

Study Sites and Patient Population

We included consecutive adult patients (≥18 years old) with laboratory-confirmed COVID-19 (detected by nasopharyngeal or oropharyngeal swab) admitted to a participating ICU for illness related to COVID-19 between March 4th and May 8th, 2020. We followed patients until the first of hospital discharge, death, or June 5th, 2020 – the date on which the database for the current analysis was locked. A complete list of participating sites is shown in **Table S1**.

Data Collection

We collected detailed information about demographics, coexisting conditions, home medications (including immunosuppressive medications), symptoms prior to ICU admission, vital signs on ICU admission, and longitudinal data on laboratory values, physiologic parameters, medications, treatments, and organ support in the first 14 days following ICU admission. Definitions of baseline characteristics, comorbidities, treatments, and outcomes are shown in **Table S2**. A detailed description of the data collection and validation process has been previously published (24).

Exposure Variable

The primary exposure was SOT at baseline.

Clinical Outcomes Assessment

The primary outcome was death within 28 days of ICU admission. We also assessed the following secondary outcomes: ICU length of stay, defined as the time between ICU admission until death, discharge from the ICU, or end of follow-up (if still in the ICU at the end of follow-up); receipt and duration of invasive mechanical ventilation; receipt and duration of extracorporeal membrane oxygenation (ECMO, including veno-venous ECMO, veno-arterial ECMO and veno-arterio-venous ECMO); acute kidney injury (AKI) requiring renal replacement therapy (RRT) and the number of days of RRT; acute respiratory distress syndrome (ARDS), ascertained by manual chart review; secondary infection, defined as a suspected or confirmed new infection other than COVID-19 that developed after admission to the ICU based on microbiology cultures or strong clinical suspicion; thromboembolic event, including deep venous

thrombosis, pulmonary embolism, stroke, or other thromboembolic event; receipt of vasopressors and the number of days on vasopressor therapy.

Statistical analysis

We summarized baseline patient characteristics according to SOT status, and presented them as count and percent for categorical variables and median and interquartile range (IQR) for continuous variables.

We used a propensity score to account for differences in clinical and demographic characteristics of SOT and non-SOT patients. We identified variables associated with SOT status using logistic regression and used them to calculate propensity scores. We used STATA's "psmatch2" command suite to generate the propensity score-matched cohort by 1-to-4 nearest neighbor matching with replacement. The following variables were included in the logistic regression model to create the propensity score: age; gender; race; ethnicity; body mass index; comorbidities (diabetes mellitus, hypertension, coronary artery disease [includes any history of angina, myocardial infarction, or coronary artery bypass graft surgery], congestive heart failure [includes both heart failure with preserved and reduced ejection fraction], atrial fibrillation/flutter, chronic obstructive pulmonary disease, asthma, other lung disease, chronic kidney disease [defined as a baseline estimated glomerular filtration rate (eGFR)< 60 ml/min/1.73m^2 on at least two consecutive occasions at least 12 weeks apart prior to hospital admission or per medical history], chronic liver disease (includes cirrhosis, alcohol related liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, hepatitis B or hepatitis C, primary biliary cirrhosis), active malignancy [defined as any malignancy, other than non-melanoma skin cancer, treated in the prior year], human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], smoking status [non-smoker/current/former smoker/unknown]); and medication use prior to hospital admission (renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonist, β-blockers, statins, aspirin, nonsteroidal anti-inflammatory drugs). Differences in patient characteristics between groups were assessed using standardized differences before and after propensity score matching. **Figure S1** shows the distribution of the propensity score in the two groups pre- and post-matching. The associations between SOT status and clinical outcomes were assessed using binomial generalized linear models (log-binomial model) with reporting of relative risks.

Differences in other variables, such as symptoms prior to ICU admission, receipt of immunosuppressive medications, vitals sign, laboratory results, and receipt of invasive mechanical ventilation on ICU admission, as well as treatments and outcomes, were assessed by Student's t-test or Mann-Whitney U test for continuous variables and chi-square-test (or Fisher's exact test) for categorical variables.

We conducted several sensitivity analyses to evaluate the robustness of our main findings. We separately analyzed kidney transplant recipients and their controls in the propensity matched cohort. In addition, we repeated all analyses in the entire cohort. In these analysis, we performed log-binomial unadjusted and multivariable regression, where we adjusted for the same variables included in the calculation of the propensity score. Moreover, we repeated all analyses after creating a different propensity score-matched cohort by 1-to-1 nearest neighbor matching without replacement.

A total of 5% of the data were missing. We did not impute missing values due to the relatively low proportion of missingness. Reported *P* values are two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 13.1 (STATA Corporation, College Station, TX). The study was approved by the Institutional Review Board of the University of Tennessee Health Science Center (20-07289-XP).

Results

Baseline characteristics

A total of 4,512 critically ill patients with COVID-19 were identified as the source population. The flow chart for the cohort is shown in **Figure 1.** We excluded patients who were admitted to ICUs after May 8th, 2020, to allow 28 days follow-up (n=189). We also excluded patients missing data on death (n=15) or SOT status (n=3) and patients with end stage renal disease (n=152), which resulted in a study population of 4,153 patients, including 105 SOT patients. Our propensity score-matched cohort included 386 patients (98 SOT and 288 non-SOT patients). The distribution of the 98 SOT patients included 67 kidney-, 13 liver-, 13 heart-, 4 lung-, and 1 pancreas transplant recipient. Among the 67 kidney transplant patients, there was one combined kidney/liver, four combined kidney/heart, and three combined kidney/pancreas transplant patients.

In the overall cohort of 4,153 patients (prior to applying the propensity matching), the median age was 62 years (IQR, 52-71 years), 64% were male, and 30% were black (**Table S3**). The SOT patients were younger are were more likely to be male, black, and to have diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, chronic kidney disease, and chronic liver disease. SOT patients were also more likely to be receiving a beta-blocker, statin, or aspirin prior to hospital admission as compared to non-SOT patients **(Table S3)**.
In the propensity score matched cohort, SOT and non-SOT patients had similar baseline characteristics (**Table 1**). The median age was 60 years, 72% were male, and 41% were black **(Table 1)**. The SOT and non-SOT groups were well-balanced, as evidenced by the small standardized differences between groups (**Table 1**). Immunosuppressive medications were present almost exclusively in SOT patients prior to admission **(Table 2)**.

Symptoms prior to admission and clinical characteristics on the day of ICU admission

Table 2 shows symptoms, vital signs, laboratory values, and data on receipt of invasive mechanical ventilation on ICU admission. SOT patients experienced nasal congestion and diarrhea more frequently as symptoms of COVID-19 infection, and had longer time elapsed between the start of symptoms and ICU admission, than non-SOT patients; other symptoms were similar between the groups. SOT patients had lower temperature, higher systolic blood pressure, lower white blood cell count, lower absolute lymphocyte count and higher serum ferritin compared to non-SOT patients in the propensity score matched cohort. Interestingly, the C-reactive protein were similar between the two groups (**Table 2**).

Medications in the 14 days following ICU admission

Table 3 describes the treatments received in the 14 days after ICU admission. A higher proportion of SOT patients received corticosteroids (SOT: 65% vs. non-SOT: 38%, $p<0.001$) and a lower proportion received non-steroidal anti-inflammatory drugs (SOT: 0% vs non-SOT: 5%, $p=0.03$) in the propensity score matched cohort. The use of other medications, including hydroxychloroquine, azithromycin, remdesivir, tocilizumab, and anticoagulants was similar between groups (**Table 3**).

Clinical outcomes and organ support

Tables 4-5 and Figure S2 show the clinical outcomes and organ support requirements in SOT and non-SOT patients. Death within 28 days of ICU admission was similar in SOT and non-SOT patients (40% and 43%, respectively; relative risk [RR] 0.92 [95% Confidence Interval (CI): 0.70-1.22]). Other outcomes and requirement for organ support were also similar between groups, including receipt of mechanical ventilation, development of acute respiratory distress syndrome, receipt of extracorporeal membrane oxygenation (ECMO) and receipt of vasopressors **(Tables 4-5 and Figure S2)**. There was a trend toward higher risk of AKI requiring RRT in SOT vs. non-SOT patients (37% vs. 27%; RR [95%CI]: 1.34 [0.97-1.85]). **Figure S3** shows the clinical outcomes and organ support requirements in SOT and non-SOT patients using the 1:1 PS matched cohort as a sensitivity analysis. Death within 28 days of ICU admission and requirement for organ support were also similar between groups (**Figure S3**). In addition, clinical outcomes and organ support requirements were similar between kidney transplant patients versus non-transplant propensity score (PS) matched controls **(Tables S4 and Figures S4)**.

Clinical outcomes and organ support requirements in the entire cohort

Table S5 and Figure S5 shows the clinical outcomes and organ support requirement in SOT and non-SOT patients in the entire cohort (n=4,153). Similar to the propensity score matched cohort, death within 28 days, mechanical ventilation, ECMO requirement, development of ARDS, secondary infection, thromboembolic events, and requirement for vasopressors were all similar between groups. The risk of AKI requiring RRT was higher in SOT patients compared to non-SOT patients (36% in SOT vs. 19% in non-SOT, $RR_{\text{unadjusted model}}$ [95%CI]: 1.89 [1.46-2.46], $RR_{\text{adjusted model}}$ [95%CI]: 1.43 [1.09-1.87]) **(Table S5 and Figure S5)**.

Discussion

We used data from a large, nationally-representative, multicenter cohort study of critically ill adults with COVID-19 to compare outcomes of SOT patients with non-SOT patients. We present three major findings. First, 28-day mortality in SOT patients was similar to non-SOT patients. Second, there was no difference between groups in the duration of ICU length of stay, risk of ARDS, secondary infection, thromboembolic events, vasopressor use, or receipt or duration of invasive mechanical ventilation. Finally, SOT patients had a trend toward higher rates of AKI requiring RRT. To the best of our knowledge, this is the first study assessing

outcomes of COVID-19 infection in SOT patients using a control group of non-transplant patients as comparator in ICU patients.

Our study suggests that SOT status is not associated with a higher risk of mortality in critically ill patients with COVID-19. Our observed mortality rate of 40% in SOT patients and 43% in the non-SOT group is lower than the 62% mortality rate reported among critically ill patients with COVID-19 in Wuhan (3) and the 50% mortality rate reported in the Seattle region (5). It was, however, higher than other cohorts from Italy (26%) (7) and New York City (15-21%) (4, 6). These comparisons are limited by different risk profile of patients, ICU admission criteria, and follow-up. Similarly, the case fatality rate of COVID-19 in hospitalized SOT patients reportedly varies between 10-33% (8, 9, 13-16), but among critically ill SOT patients it may be as high as 50% (8). Previous experience with respiratory viruses suggests a higher mortality in SOT patients compared to non-SOT patients, yet we report no difference in the 28-day mortality risk in our cohort. One potential explanation is that there was a higher use of corticosteroid treatment in SOT patients compared to non-SOT patients. The recent "Randomised Evaluation of COVid-19 thERapY (RECOVERY)" study indicated that dexamethasone therapy reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 (25). We hypothesize that immunosuppressive medications may have mitigated pro-inflammatory cytokine activation in SOT patients, which might result in lower risk of developing cytokine release syndrome. Since the earliest reports of COVID-19 infection, cytokine release syndrome has been identified as a primary contributor to the pathophysiology of severe COVID-19 infection, including ARDS and organ dysfunction (26, 27). Coronavirus infection results in the activation of monocyte, macrophage, and dendritic cells, which in turn release IL-6 and other cytokines, contributing to the clinical manifestations of severe infection. Ensuing endothelial injury can lead to multi-organ involvement. However, in our dataset C-reactive protein levels and interleukin-6 levels were similar between the two groups despite the immunosuppression, which does not support our hypothesis. In addition, serum ferritin level was higher in SOT patients. Further studies are needed to clarify the potential role of cytokine release syndrome in this population.

SOT patients had a non-significant trend toward a more than 30% higher risk of AKI requiring RRT compared to their non-SOT counterparts similar to what was reported in a recent single center study (23). Initial reports of AKI in hospitalized patients with COVID-19 varied

from 15% to 50% (9, 13, 18, 19), and has been reported to be as high as 90% among mechanically ventilated patients (28). A multicenter cohort study of more than 5,000 hospitalized patients from New York City reported a 36% incidence of AKI, with 14% of those with AKI (5% of all patients) requiring RRT (28). In another large study of 3,235 hospitalized patients from New York City with 815 ICU patients, the need for RRT was present in 34% of ICU patients (29), which is similar to our reported results. Similarly, the reported incidence of AKI in SOT patients varies according to the type of organ transplant and severity of disease (30). In the first report of US kidney transplant patients, 40% (6/15) of the patients had AKI and 2 patients required RRT (15). The mechanisms of AKI in transplant patients are multifactorial. Virus particles can directly infect the renal tubular epithelium and podocytes through an angiotensin-converting enzyme 2 (ACE2)-dependent pathway and cause mitochondrial dysfunction and acute tubular necrosis. Endothelial dysfunction due to endothelial injury increases the risk of microthrombi and contributes to AKI (11). In addition to AKI associated with ARDS and critical illness, use of calcineurin inhibitors as the predominant immunosuppression could increase the risk of endothelial injury in these patients; especially in the setting of higher rate of diarrhea.

There was a significant difference in symptoms at presentation between SOT and non-SOT patients. Fever and cough were the most common symptoms in both groups, consistent with previous description of COVID-19 symptoms. Interestingly, SOT patients presented with more nasal congestion and diarrhea compared to non-SOT patients. Although other case reports and cohorts of SOT patients presenting with gastrointestinal symptoms exist (20, 31), this has not been consistently shown in other studies, where the presenting symptoms in SOT patients were similar to the general population (18, 22, 32). Our findings are important, as diarrhea in SOT patients is common and can be multifactorial, related to medications or other viral infections. Given the myriad of clinical manifestations that have been described in patients with COVID-19, the index of suspicion for COVID-19 should be high in SOT patients who present with gastrointestinal symptoms.

Our study has several strengths. First, we included patients from geographically-diverse sites from across the United States, thereby maximizing generalizability. Second, we used propensity score matching to create comparable groups to assess the risk of SOT status with several clinically relevant outcomes. Third, all data were captured by manual chart review, which allowed us to include detailed and reliable data on both clinical characteristics and outcomes.

Fourth, to the best of our knowledge our study included the highest number of SOT ICU patients from the USA. Finally, all patients had follow-up until the first of hospital discharge, death, or at least 28 hospital days.

Our study also has its limitations. First, the transplant vintage of SOT patients was not available in this dataset and hence, the effect of duration of immunosuppression and time since transplantation on outcomes cannot be determined. Second, although we captured data on the use of immunosuppressive medications prior to hospital admission, we did not capture data on their use following ICU admission. Thus, our study does not address the important question of whether, and how, immunosuppression should be decreased in critically ill patients with COVID-19. Third, our study collected data in the first 14 days of ICU stay, so our study does not address the potential association with data after first two weeks of ICU stay. Finally, these observations are restricted to ICU patients and may not be applicable for non-ICU or ambulatory SOT patients.

Conclusion

In conclusion, SOT patients with critical illness due to COVID-19 infection have a similar risk of death, ARDS, and requirement for organ support as non-SOT patients. Further studies are needed to assess the effect of specific immunosuppression and other therapeutic regimens on clinical outcomes.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table 1: Baseline characteristics of solid organ transplant and non-transplant patients after propensity score matching

Post-Match				
Characteristics	**Cohort (n=386)**	**Non-SOT Patients (n=288)**	**SOT Patients (n=98)**	**St Diff**
Demographics				
Age (years) median (IQR)	60 (51-70)	61 (51-70)	58 (52-69)	**-0.004**
Sex (male) – no. (%)	277 (72)	205 (71)	72 (73)	**-0.051**
Race – no. (%)				**0.078**
White	128 (33)	99 (34)	29 (30)	
Black	159 (41)	116 (40)	43 (44)	
Asian/Other	99 (26)	73 (25)	26 (27)	
Ethnicity – no. (%)				**0.036**
Hispanic	68 (18)	48 (17)	20 (20)	
Non-Hispanic	287 (74)	221 (77)	66 (67)	
Unknown	31 (8)	19 (7)	12 (12)	
Body mass index (kg/m^2) Median[a] (IQR)	29 (25-33)	29 (26-34)	29 (25-33)	**-0.103**
Coexisting conditions – no. (%)				
Diabetes mellitus	253 (66)	189 (66)	64 (65)	**-0.007**
Hypertension	317 (82)	235 (82)	82 (84)	**0.055**
Coronary artery disease	104 (27)	78 (27)	26 (27)	**-0.012**
Congestive heart failure	71 (18)	51 (18)	20 (20)	**0.069**
Atrial fibrillation or atrial flutter	48 (12)	35 (12)	13 (13)	**0.033**
Chronic obstructive pulmonary disease	21 (5)	15 (5)	6 (6)	**0.039**
Asthma	23 (6)	17 (6)	6 (6)	**0.009**
Other pulmonary disease	50 (13)	37 (13)	13 (13)	**0.012**
Smoking Status[b]				**-0.029**
Non-Smoker	240 (62)	180 (63)	60 (61)	
Former Smoker	109 (28)	78 (27)	31 (32)	
Current Smoker	8 (2)	8 (3)	0 (0)	
Unknown	29 (8)	22 (8)	7 (7)	
Chronic kidney disease	198 (51)	143 (50)	55 (56)	**0.129**
Chronic Liver Disease	35 (9)	23 (8)	12 (12)	**0.141**
HIV/AIDS	10 (3)	7 (2)	3 (3)	**0.038**
Active malignancy	25 (6)	18 (6)	7 (7)	**0.036**
Home medications – no. (%)				
ACE-I	75 (19)	59 (20)	16 (16)	**-0.107**
ARB	80 (21)	59 (20)	21 (21)	**0.023**
Mineralocorticoid receptor antagonist	9 (2)	7 (2)	2 (2)	**-0.026**
Beta blocker	223 (58)	162 (56)	61 (62)	**0.122**
Statin	229 (59)	171 (59)	58 (59)	**-0.004**
NSAID	2 (1)	1 (0)	1 (1)	**0.081**

Aspirin	186 (48)	138 (48)	48 (49)	**0.021**

Abbreviations: ACE-I, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; HIV/AIDS, Human immunodeficiency virus infection/acquired immune deficiency syndrome; NSAID, nonsteroidal anti-inflammatory drug; SOT, solid organ transplant; St Diff: Standardized differences

Table 2: Clinical characteristics on the day of ICU admission in solid organ transplant patients and non-transplant patients in the propensity score matched cohort

Clinical Characteristics:	**Cohort (N=386)**	**Non-SOT (N =288)**	**SOT (N=98)**	**P value**
Symptoms prior to ICU admission – no. (%):				
Cough	269 (70)	196 (68)	73 (74)	0.23
Sputum production	46 (12)	32 (11)	14 (14)	0.40
Hemoptysis	7 (2)	6 (2)	1 (1)	0.50
Sore throat	35 (9)	27 (9)	8 (8)	0.72
Nasal congestion	31 (8)	18 (6)	13 (13)	**0.03**
Headache	33 (9)	24 (8)	9 (9)	0.80
Fever	236 (61)	177 (61)	59 (60)	0.83
Chills	83 (22)	60 (21)	23 (23)	0.58
Dyspnea	272 (70)	198 (69)	74 (76)	0.21
Nausea or vomiting	76 (20)	59 (20)	17 (17)	0.50
Diarrhea	92 (24)	58 (20)	34 (35)	**<0.01**
Myalgia or arthralgia	97 (25)	70 (24)	27 (28)	0.52
Confusion or altered mental status	46 (12)	35 (12)	11 (11)	0.81
Fatigue or malaise	143 (37)	111 (39)	32 (33)	0.30
Days from symptom onset to ICU admission median (IQR)[a]	7 (4-10)	7 (4-10)	7 (6-11)	**<0.01**
Days from symptom onset to hospital admission median (IQR)[b]	5 (3-8)	5 (3-7)	6 (3-8)	**0.04**
Immunosuppressive medications 30 days prior to ICU admission – no. (%):				
Corticosteroids*	29 (8)	14 (5)	15 (15)	**<0.01**
Calcineurin inhibitor	82 (21)	1 (0)	81 (83)	**<0.01**
Mycophenolate mofetil	69 (18)	2 (1)	67 (68)	**<0.01**
Azathioprine	3 (1)	3 (1)	0 (0)	0.31
Rituximab	0 (0)	0 (0)	0 (0)	N/A
Other major ISU therapy	20 (5)	7 (2)	13 (13)	**<0.01**
Vital signs on the day of ICU admission – median (IQR):				
Temperature – ^{o}C[c]	37.8 (37.1-38.6)	37.9 (37.2-38.8)	37.4 (36.9-38.2)	**<0.01**
Lowest systolic blood pressure – mmHg	99 (88-114)	98 (86-112)	105 (92-117)	**0.03**
Highest heart rate – beats per min	103 (90-118)	103 (91-118)	101 (88-116)	0.32
Laboratory findings on the day of ICU admission – median (IQR)				
White blood cell count – per mm^3[d]	7.5 (5.5-10.5)	7.9 (5.6-11.2)	6.6 (4.9-8.5)	**<0.01**
Lymphocyte percentage – per mm[e]	0.70 (0.45-1.05)	0.79 (0.52-1.15)	0.50 (0.30-0.81)	**<0.01**

Hemoglobin – g/dl[f]	11.8 (10.0-13.8)	11.7 (9.9-13.6)	11.9 (10.6-13.6)	0.47
Serum creatinine – mg/dl[g]	1.6 (1.0-2.8)	1.5 (1.0-2.9)	1.7 (1.0-2.7)	0.42
C-reactive protein – mg/L[i]	156 (88-223)	159 (91-224)	143 (84-208)	0.49
Serum albumin – g/dl[j]	3.3 (2.8-3.6)	3.3 (2.8-3.6)	3.2 (2.9-3.6)	0.55
D-Dimer - ng/ml[k]	1,254 (620-2,975)	1,332 (610-3,402)	1,140 (640-2,390)	0.60
Interleukin-6 - pg/ml[l]	51 (15-184)	68 (13-195)	37 (15-84)	0.61
Serum ferritin – ng/ml[m]	1,132 (541-2,112)	998 (450-1,983)	1,429 (657-2,957)	**0.03**
Type of Ventilation - no. (%):				
Invasive mechanical ventilation	226 (59)	171 (59)	55 (56)	0.34
BIPAP or CPAP	7 (2)	6 (2)	1 (1)	
High-flow nasal cannula or non-rebreather mask	88 (23)	68 (24)	20 (20)	
None of the above	65 (17)	43 (15)	22 (22)	

Abbreviations: eGFR, Estimated glomerular filtration rate; CPAP, Continuous Positive Airway Pressure Ventilation; BiPAP, Bilevel Positive Airway Pressure Ventilation, ISU: Immunosuppressive N/A: Not applicable.

*Corticosteroids: >10mg prednisone/day (or equivalent)

[a]Data regarding days from symptom onset to ICU admission were missing for total 4 patients (1%), 1 SOT patient and 3 non-SOT patients.

[b]Data regarding days from symptom onset to hospital admission were missing for total 14 patients (3.6%), 3 SOT patient and 11 non-SOT patients.

[c]Data regarding temperature were missing for total 2 patients (0.5%), 1 SOT patient and 1 non-SOT patients.

[d]Data regarding white-cell count were missing for total 16 patients (4%), 3 SOT patient and 13 non-SOT patients.

[e]Data regarding lymphocyte percentage were missing for total 76 patients (19.6%), 18 SOT patient and 58 non-SOT patients.

[f]Data regarding hemoglobin were missing for total 16 patients (4%), 3 SOT patient and 13 non-SOT patients.

[g]Data regarding serum creatinine were missing for total 13 patients (3.4%), 3 SOT patient and 10 non-SOT patients.

[h]Data regarding eGFR were missing for total 13 patients (3.4%), 3 SOT patient and 10 non-SOT patients.

[i]Data regarding C-reactive protein were missing for total 150 patients (38.8%), 40 SOT patient and 110 non-SOT patients.

[j]Data regarding serum albumin were missing for total 63 patients (16.3%), 14 SOT patient and 49 non-SOT patients.

[k]Data regarding D-Dimer were missing for total 194 patients (50%), 40 SOT patient and 154 non-SOT patients.

[l] Data regarding interleukin-6 were missing for total 304 patients (79%), 75 SOT patient and 229 non-SOT patients.

[m]Data regarding serum ferritin were missing for total 163 patients (42%), 34 SOT patient and 129 non-SOT patients.

All other variables had no missing data.

Table 3: Treatments in the first 14 days after intensive care unit admission of non-transplant patients and solid organ transplant patients in the propensity score matched cohort

Treatments	All Patients (N=386)	Non-SOT (N=288)	SOT (N=98)	P value
Antibiotics/antivirals – no. (%)				
Chloroquine	3 (1)	1 (0)	2 (2)	0.10
Hydroxychloroquine	258 (67)	196 (68)	62 (63)	0.38
Azithromycin	199 (52)	150 (52)	49 (50)	0.72
Hydroxychloroquine and Azithromycin	307 (80)	233 (81)	74 (76)	0.25
Remdesivir	26 (7)	20 (7)	6 (6)	0.78
Ribavirin	1 (0)	1 (0)	0 (0)	0.56
Lopinavir/ritonavir (Kaletra)	14 (4)	11 (4)	3 (3)	0.73
Therapeutic Anticoagulation – no. (%)[a]				
Any	176 (46)	130 (45)	46 (47)	0.78
Heparin drip	132 (34)	96 (33)	36 (37)	0.54
Enoxaparin	41 (11)	35 (12)	6 (6)	0.09
Bivalirudin	4 (1)	1 (0)	3 (3)	**0.02**
Argatroban	1 (0)	1 (0)	0 (0)	0.56
Anti-inflammatory medications – no. (%)				
Corticosteroids	173 (45)	109 (38)	64 (65)	**<0.01**
NSAIDs	13 (3)	13 (5)	0 (0)	**0.03**
Aspirin	128 (33)	94 (33)	34 (35)	0.71
Statin	132 (34)	92 (32)	40 (41)	0.11
Tocilizumab	70 (18)	47 (16)	23 (23)	0.11
Other interleukin-6 inhibitor or interleukin-6 receptor inhibitor	2 (1)	1 (0)	1 (1)	0.42
Vitamin C	32 (8)	28 (10)	4 (4)	0.08
Other medications – no. (%)				
Convalescent Plasma	12 (3)	7 (2)	5 (5)	0.19
ACE-I	12 (3)	10 (3)	2 (2)	0.48
ARB	14 (4)	11 (4)	3 (3)	0.73
Tissue Plasminogen Activator	5 (1)	4 (1)	1 (1)	0.78
Specific interventions for hypoxemia – no. (%)				
Neuromuscular blockade	142 (37)	105 (36)	37 (38)	0.82
Inhaled epoprostenol	18 (5)	13 (5)	5 (5)	0.81
Inhaled nitric oxide (iNO)	22 (6)	14 (5)	8 (8)	0.22
Proned position	126 (33)	92 (32)	34 (35)	0.62
Enrolled in a clinical trial – no. (%)[b]	75 (19)	55 (19)	20 (20)	0.79

Each of the above interventions was assessed during the 14 days following ICU admission.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAIDs, non-steroidal anti-inflammatory drugs; N/A: not applicable.

[a]Data on therapeutic anticoagulation were missing for total 1 patients (0.3%) in the non-SOT patients.

[b]Data on enrollment in a clinical trial were missing for total 1 patients (0.3%) in the non-SOT patients.

All other variables had no missing data.

Table 4: Clinical outcomes and organ support requirement in non-transplant patients and solid organ transplant patients in the propensity score matched cohort

Primary Outcomes	Non-SOT (*n*=288)	SOT (*n*=98)	*P* value*
Death within 28 days, *n* (%)	124 (43)	39 (40)	0.57
Cause of death, *n* (%)**			0.50
ARDS/respiratory failure	39 (29)	13 (30)	
Heart failure	5 (4)	1 (2)	
Septic shock	16 (12)	10 (23)	
Kidney failure	42 (32)	13 (30)	
Liver failure	10 (8)	2 (5)	
Other	21 (16)	4 (9)	
Days of ICU stay, median (IQR)	11 (5-21)	11 (7-19)	0.42
Mechanical ventilation (days 1-14)			
Received mechanical ventilation, *n* (%)	223 (77)	78 (80)	0.66
Days of mechanical ventilation, median (IQR)	11 (6-14)	9 (6-13)	0.18
ECMO (days 1-14)			
Received ECMO, *n* (%)	9 (3)	1 (1)	0.26
Days of ECMO, median (IQR)	8 (5-9)	14 (14-14)	0.16
Acute RRT (days 1-14)			
Received acute RRT, n (%)	79 (27)	36 (37)	0.08
Days of acute RRT, median (IQR)	7 (3-10)	6 (3-9)	0.76
ARDS (days 1-14), *n* (%)	205 (71)	73 (74)	0.56
New infection (days 1-14), *n* (%)	99 (34)	24 (24)	0.07
New thromboembolic event (days 1-14), *n* (%)	23 (8)	9 (9)	0.71
Vasopressor (days 1-14)			
Received vasopressor, *n* (%)	201 (70)	62 (63)	0.23
Days on vasopressor, median (IQR)	5 (3-9)	5 (3-9)	0.52

Abbreviations: SOT: Solid organ transplantation; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; IQR: Interquartile range; ECMO: Extracorporeal membrane oxygenation; RRT: Renal replacement therapy.

**P* values for continuous variables with median (IQR) are result of Mann-Whitney test and categorical variables are chi-square test.

**: patients could have had more than one cause of death

Table 5: Relative risk of clinical outcomes and organ support in non-transplant patients and solid organ transplant patients in the propensity score matched cohort using binomial generalized linear model (log-binomial model) (SOT versus non-SOT (reference) patients)

Primary Outcomes	Relative Risk	95% Confidence Interval of Relative Risk	*P* value
Death within 28 days, *n* (%)	0.92	0.70-1.22	0.58
Mechanical ventilation (days 1-14)	1.03	0.91-1.16	0.65
ECMO (days 1-14)	0.33	0.04-2.54	0.29
Acute RRT (days 1-14)	1.34	0.97-1.85	0.07
ARDS (days 1-14), *n* (%)	1.04	0.91-1.20	0.55
New infection (days 1-14), *n* (%)	0.71	0.48-1.04	0.08
New thromboembolic event (days 1-14), *n* (%)	1.15	0.55-2.40	0.71
Vasopressor (days 1-14)	0.91	0.77-1.07	0.26

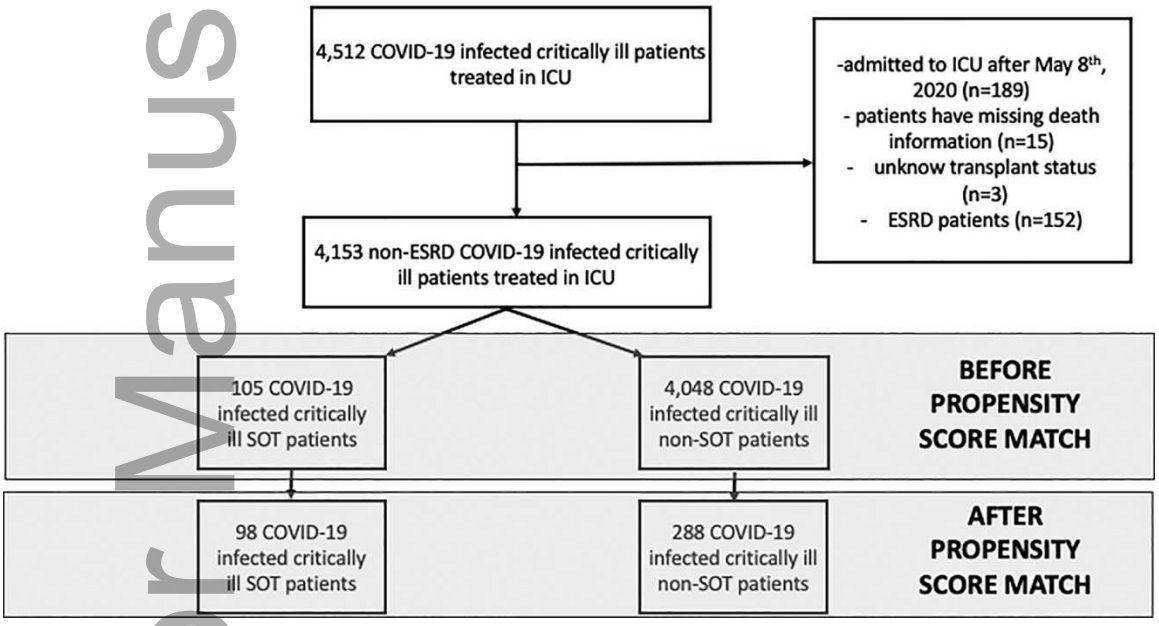
Abbreviations: ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; RRT: Renal replacement therapy.

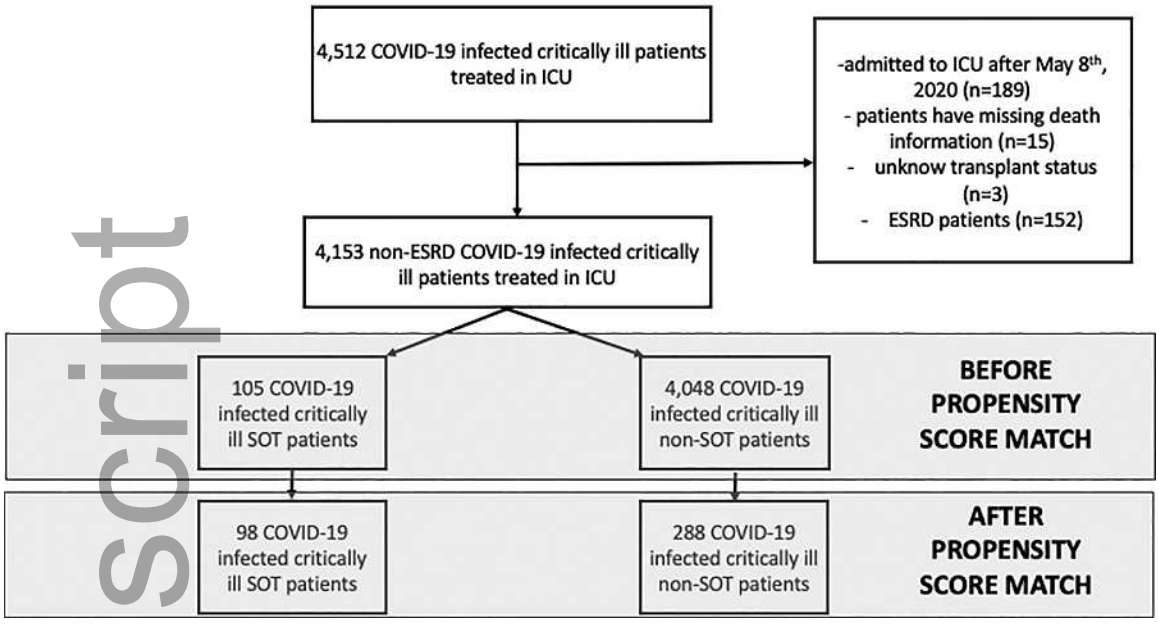
Legend of Figures:

Figure 1: Flow chart of patient selection

Abbreviations: SOT: Solid organ transplantation; ICU: Intensive care unit; ESRD: End stage renal disease.

Figure 1:





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