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Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study

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(See the Editorial Commentary by Haidar on pages e4100–2.)

Background. The coronavirus disease 2019 (COVID-19) pandemic has led to significant reductions in transplantation, motivated in part by concerns of disproportionately more severe disease among solid organ transplant (SOT) recipients. However, clinical features, outcomes, and predictors of mortality in SOT recipients are not well described.

Methods. We performed a multicenter cohort study of SOT recipients with laboratory-confirmed COVID-19. Data were collected using standardized intake and 28-day follow-up electronic case report forms. Multivariable logistic regression was used to identify risk factors for the primary endpoint, 28-day mortality, among hospitalized patients.

Results. Four hundred eighty-two SOT recipients from >50 transplant centers were included: 318 (66%) kidney or kidney/pancreas, 73 (15.1%) liver, 57 (11.8%) heart, and 30 (6.2%) lung. Median age was 58 (interquartile range [IQR] 46–57), median time post-transplant was 5 years (IQR 2–10), 61% were male, and 92% had ≥1 underlying comorbidity. Among those hospitalized (376 [78%]), 117 (31%) required mechanical ventilation, and 77 (20.5%) died by 28 days after diagnosis. Specific underlying comorbidities (age >65 [adjusted odds ratio [aOR] 3.0, 95% confidence interval [CI] 1.7–5.5, $P < .001$], congestive heart failure [aOR 3.2, 95% CI 1.4–7.0, $P = .004$], chronic lung disease [aOR 2.5, 95% CI 1.2–5.2, $P = .018$], obesity [aOR 1.9, 95% CI 1.0–3.4, $P = .039$]) and presenting findings (lymphopenia [aOR 1.9, 95% CI 1.1–3.5, $P = .033$], abnormal chest imaging [aOR 2.9, 95% CI 1.1–7.5, $P = .027$]) were independently associated with mortality. Multiple measures of immunosuppression intensity were not associated with mortality.

Conclusions. Mortality among SOT recipients hospitalized for COVID-19 was 20.5%. Age and underlying comorbidities rather than immunosuppression intensity-related measures were major drivers of mortality.

Keywords. COVID-19; SARS-CoV-2; coronavirus; transplantation; solid organ transplantation.

The coronavirus disease 2019 (COVID-19) pandemic has affected over 10 million people, with over 500 000 deaths worldwide. Estimated mortality rates among those hospitalized with COVID-19 vary widely and have been associated with advanced age and comorbidities in the general population; however, less is known about outcomes of COVID-19 in solid organ transplant (SOT) recipients [1–3]. Based on experience with other respiratory viruses in immunocompromised populations, there has been concern about a disproportionately severe impact of COVID-19 in SOT recipients related to immunosuppression [4, 5]. However, because of the unique contribution of a dysregulated and exaggerated immune response in COVID-19 morbidity and mortality, there has also been discussion of a possible favorable effect of immunosuppression in SOT recipients who develop COVID-19 [6]. Concerns about unfavorable

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outcomes, along with other issues such as infection control and resource availability, have led to changes in immunosuppression management and a substantial decrease or even temporary discontinuation of transplants at many centers around the world. As of 11 April 2020, the overall rate of deceased donor organ transplantation had fallen by 51% in the United States, by 87% in Spain, and by 91% in France [7].

The clinical aspects and impact of COVID-19 in SOT recipients remain uncertain. Early results have varied, with mortality rates ranging from 7.1% to as high as 53% in one small series [8, 9]. These studies had important limitations including small size, single-center or limited geographic locale, or limited follow-up [8–21]. More precise estimates of morbidity and mortality of COVID-19 in SOT, identification of risk factors for mortality, and comparison to general populations are critical for 2 main purposes: (1) to better understand the impact of transplant-related immunosuppression on outcomes of COVID-19, and (2) to inform transplant program practices in the COVID-19 era and in the event of resurgence of the epidemic.

We report the results of a large, prospective, multicenter study of SOT recipients with COVID-19, all of whom were followed for 28 days, using standardized data collection tools, to assess patient characteristics, clinical presentation, outcomes, and risk factors for mortality.

METHODS

Study Oversight

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

Study Design

This multisite prospective cohort study included recipients of any SOT with laboratory-confirmed COVID-19 by polymerase chain reaction of an upper or lower respiratory sample. Study data were collected using the secure, web-based data capture software program REDCap (Research Electronic Data Capture), hosted at the University of Washington [22, 23]. The standardized electronic case report form included only de-identified patient data. The initial component collected patient demographics, baseline comorbidities, transplant-related history, presenting symptoms, focused laboratory values, and imaging. The follow-up component included hospital and intensive care unit (ICU) admission, mechanical ventilation, death and time to death, complications, and management strategies. Table S1 describes all variables collected. Potential contributors were notified of the study through message boards hosted by the American Society of Transplantation (AST), the American Society of Transplant Surgeons, and the International Society for Heart and Lung Transplantation. The study period included reports received 7 March to 13 May for cases diagnosed from 1 March 2020 to 15 April 2020 to ensure 28-day follow-up for all patients.

Statistical Analyses

Results are presented descriptively in prespecified subpopulations, including in patients stratified by death by 28 days, hospitalized patients only, and by organ(s) transplanted. The primary outcome was 28-day mortality in the subset of patients hospitalized after COVID diagnosis. We summarized published studies of COVID-19 in hospitalized SOT and general populations as of 19 June 2020 and calculated pooled weighted estimates of mortality and baseline comorbidities. Studies of SOT recipients that included ≥10 patients and outcomes of patients hospitalized with COVID-19 were considered for inclusion. The association between baseline covariates and death was assessed in univariate and multivariable analyses using logistic regression for both the subset hospitalized after COVID diagnosis and among the full cohort. We assessed all collected variables, and those that either had a $P < .1$ in univariate analysis or that were considered important based on results of previous studies, and for which there were adequate events to allow for meaningful analysis, were considered for the multivariable model. Stepwise regression was used to inform the final model and potential interactions among covariates were assessed. Complete data were available for the majority of variables; missing data were handled via multiple imputation using the multivariate by chained equations method [24]. The final multivariable logistic regression model included age; sex; mechanistic target of rapamycin (mTOR)-containing maintenance immunosuppression regimen, baseline comorbidities (congestive heart failure [CHF], chronic lung disease, diabetes mellitus, obesity) individually or in combination; initial absolute lymphocyte count; and evidence of pneumonia on initial chest imaging. Both age and absolute lymphocyte count were assessed as dichotomous variables (age <=65 vs >65 years, lymphocytes <0.5 vs >=0.5 × 10^9/L), based on clinical relevance and previously published studies, and after analyzing the effects as continuous variables and as multiple discrete strata. Although there are no defined well-validated measures of immunosuppression intensity, we assessed the following as potential surrogates, in accordance with prior studies: earlier time post-transplant, thoracic (lung or heart) compared to nonthoracic organ transplant, receipt of augmented immunosuppression within 3 months of COVID-19 diagnosis, or a higher number of baseline maintenance immunosuppressive agents [10, 11, 16, 25]. Number of maintenance immunosuppressive agents was assessed by comparing those on 2 immunosuppressants and those on 3 or more immunosuppressants to those receiving 0 or 1 immunosuppressants at baseline as a reference, considering all immunosuppressants and separately

considering only the most commonly used immunosuppressants (calcineurin inhibitors, antimetabolites, and steroids). All analyses were performed using Stata version 13.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Study Population

A total of 538 cases were submitted between 7 March and 14 May 2020; 56 were excluded, leaving 482 in the final study population. Reasons for exclusion were: No confirmed COVID-19 diagnosis (n = 6), duplicate reports (n = 6), reports missing >10% of requested data (n = 4), reports submitted with <28 days of follow-up (n = 18), and cases previously published as of the date of data extraction (n = 21). One report was withdrawn by the contributor. (Consort diagram; Supplemental Figure 1)

Baseline Characteristics of the Study Population

Baseline characteristics of the complete study population and stratified by vital status on day 28 are shown in Table 1. The overall study population included patients with mostly community-acquired infection (83%), from a range of geographic locales, and included a small proportion of lung transplant recipients (~6%) and recent transplant recipients (~6%). Most were receiving calcineurin inhibitor-based maintenance immunosuppression (91%). A high proportion had at least one of the underlying comorbidities listed in Table 1 (445 [92.3%] overall, and 97% of kidney, 78% of liver, 87% of heart, and 86.7% of lung recipients).

Summary of Clinical Outcomes.

Seventy-eight percent of the cohort was hospitalized for COVID-19. A small number were already hospitalized for another indication at the time of diagnosis (6.4%), and the remainder (16%) were managed on an outpatient basis. Of patients hospitalized due to COVID-19, 147 (39%) required ICU care, and 117 (31%) required mechanical ventilation. The mortality rate by day 28 after COVID-19 diagnosis among the overall cohort was 90 of 482 (18.7%) and 77 of 376 (20.5%) among those hospitalized. A summary of clinical outcomes is shown in Table 2 for the entire cohort and for the subset hospitalized due to COVID-19. Table S2 shows the baseline characteristics and outcomes stratified by organ type transplanted.

Unadjusted Kaplan-Meier analyses of mortality by day 28 after diagnosis, separately for all patients and the hospitalized subset, by specific organ transplant type, and by thoracic (heart or lung) versus nonthoracic organ transplant, are shown in Figure 1. For the majority of subsets assessed, mortality appeared to stabilize by the end of the 28-day follow-up.

Risk Factors for Mortality

Risk factors for mortality were analyzed among the subset of patients hospitalized with COVID-19, since mortality occurred primarily in this group and because comparator studies in general populations focus on this subset (Table 3). Age >65, CHF, chronic lung disease, and obesity, rather than all comorbidities assessed, were the baseline factors independently associated with mortality by 28 days. These comorbidities were common: the proportions with 1 or ≥2 were 200 (42.3%) and 84 (17.8%), respectively. Rates of these baseline comorbidities were similar among the different organ transplant groups except for lung recipients, in whom 9 (32%) had ≥2 of these comorbidities. When these specific comorbidities were assessed in combination in multivariable analysis (omitting the individual components), the strength of the association with mortality was higher with a greater number of comorbidities: 1 vs 0, adjusted odds ratio (aOR) 3.0 (95% confidence interval [CI]: 1.4–6.3), ≥2 vs. 0, aOR 11.0 (95% CI: 5.0–24.0), suggesting a cumulative effect of baseline comorbidities on mortality. Race, ethnicity, and male sex were not associated with mortality. Presence of pneumonia at baseline (assessed by abnormal chest imaging) and lymphopenia (<0.5 thousand/mL) were independently associated with mortality. Qualitatively and quantitatively similar results were seen in the overall cohort for all of these analyses (data not shown).

We explored multiple potential surrogates of immunosuppression intensity (earlier time post-transplant, thoracic [lung, heart] compared to nonthoracic organ transplant, or receipt of augmented immunosuppression within 3 months), and did not find an association of any of these factors with mortality. Results of the analysis between thoracic vs nonthoracic organs and mortality were similar when thoracic organ was restricted to lung transplant only. We also assessed the association between a higher number of maintenance immunosuppressive agents (0–1 vs 2 and 0–1 vs 3 or more immunosuppressants at baseline) and death in univariate analysis and similarly found no association either when considering all types of maintenance immunosuppression or when restricting analysis to calcineurin inhibitors, antimetabolites, and steroids only. (Table 3).

Interventions and Treatments

The most commonly used intervention was immunosuppression modification in 337 (70%) patients. (Figure 2) In 56% the antimetabolite (mycophenolate or azathioprine) was discontinued, 10% had the antimetabolite reduced, and <1% had all immunosuppression discontinued. The most commonly used treatment was chloroquine or hydroxychloroquine, in 296 (61%) patients. QTc prolongation was reported in 13/296 (4.4%). One patient experienced ventricular fibrillation with Torsade de pointes, and 1 patient developed a junctional arrhythmia. Fourteen (2.9%) patients were treated with remdesivir, 49 (10%) received corticosteroids, and 63 (13%) received an anti-interleukin 6 (IL-6)-receptor monoclonal antibody, either tocilizumab (57) or sarilumab (5).

Table 1. Baseline Characteristics and Clinical Data, All Patients and Patients by Clinical Group

	All Patients (n = 482)	Patients Alive at 28 days (n = 392)	Patients Deceased by 28 days (n = 90)
Baseline characteristics			
Age in years, median (IQR)	57.5 (46–67)	55 (43–65)	66.5 (59–73)
Age >65 (%)	141 (29.3)	94 (24)	47 (52.2)
Male sex (%)	295 (61.2)	234 (59.7)	61 (67.8)
Race (%)			
Asian or Pacific Islander	25 (5.1)	23 (5.9)	2 (2.2)
Black	198 (41.1)	163 (41.6)	35 (38.9)
White	229 (47.5)	184 (46.9)	45 (50)
Other or unknown	30 (6.2)	22 (5.6)	8 (8.9)
Hispanic ethnicity (%)	100 (20.8)	79 (20.2)	21 (23.3)
Geographic location (%)			
Northeast	225 (46.7)	185 (47.2)	40 (44.4)
Midwest	101 (21)	82 (20.9)	19 (21.1)
South	75 (15.6)	63 (16.1)	12 (13.3)
West	62 (12.9)	47 (12)	15 (16.7)
International	19 (3.9)	15 (3.8)	4 (4.4)
Organ transplant[a] (%)			
Kidney or kidney/pancreas	318 (66)	261 (66.6)	57 (63.3)
Liver or liver/kidney	73 (15.2)	58 (14.8)	15 (16.7)
Heart or heart/kidney	57 (11.8)	49 (12.5)	8 (8.9)
Any lung transplant	30 (6.2)	20 (5.1)	10 (11.1)
Bilateral lung	19 (63.3)	13 (65)	6 (60)
Other transplants	4 (1)	4 (1)	0 (0)
Time from transplant in years, median (IQR)	5 (2–10)	5 (2–10)	5 (2–11)
Recent transplant* (%)	28 (5.9)	23 (6)	5 (5.6)
Baseline comorbidities (%)[b]			
Hypertension	373 (77.4)	299 (76.3)	74 (82.2)
Coronary artery disease	105 (21.8)	78 (19.9)	27 (30)
Congestive heart failure	40 (8.3)	19 (4.9)	21 (23.3)
Diabetes	246 (51)	186 (47.5)	60 (66.7)
Chronic kidney disease	180 (37.3)	144 (36.7)	36 (40)
Chronic lung disease	50 (10.4)	28 (7.1)	22 (24.4)
Obesity (BMI >30 kg/m^2)	166 (35.1)	125 (32.3)	41 (47.7)
Number of high-risk factors[c]			
0	189 (40.0)	177 (45.7)	12 (14.0)
1	200 (42.3)	166 (42.9)	34 (39.5)
2 or more	84 (17.8)	44 (11.4)	40 (46.5)
Maintenance immunosuppression[d,e] (%)			
CNI, antimetabolite, and steroids	239 (49.6)	192 (49.0)	47 (49.6)
CNI and steroids	72 (14.9)	52 (13.3)	20 (22.2)
CNI and antimetabolite	71 (14.7)	59 (15.1)	12 (13.3)
mTOR inhibitor regimen	32 (6.6)	31 (7.9)	1 (1.1)
Other	107 (22.2)	90 (23)	17 (18.9)
Recent augmented immunosuppression[f] (%)	41 (8.5)	33 (8.4)	8 (8.9)
Blood type[g] (%)			
A	149 (35.6)	121 (35.6)	28 (35.9)
B	74 (17.7)	63 (18.5)	11 (14.1)
AB	22 (5.3)	15 (4.4)	7 (9.0)
O	173 (41.4)	141 (41.5)	32 (41.0)
Clinical data			
Source of infection (%)			
Community acquired	385 (82.8)	324 (86.2)	61 (68.5)
Healthcare associated	70 (15.1)	43 (11.4)	27 (30.3)
Presenting symptoms (%)			
Fever	263 (54.6)	215 (54.9)	48 (53.3)
Cough	353 (73.2)	286 (73)	67 (74.4)
Dyspnea	282 (58.5)	209 (53.3)	73 (81.1)

Table 1. Continued

	All Patients (n = 482)	Patients Alive at 28 days (n = 392)	Patients Deceased by 28 days (n = 90)
Upper respiratory symptoms	141 (29.3)	123 (31.4)	18 (20)
Gastrointestinal symptoms	231 (47.9)	183 (46.7)	48 (53.3)
Absolute lymphocyte count x10^9/L	0.7 (0.47–1)	0.74 (0.5–1.1)	0.53 (0.4–0.9)
Abnormal chest imaging	249 (81.9)	227 (79.4)	67 (91.8)
	n = 359	n = 286	n = 73

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; IQR, interquartile range; mTOR, mechanistic target of rapamycin.

[a]Kidney: includes 13 kidney/pancreas transplants. Liver: includes 16 liver/kidney transplants. Heart: includes 5 heart/kidney transplants, 1 recipient of heart, kidney, and small bowel transplants. Lung: includes 2 heart/lung transplants, 1 lung/liver transplant, and 1 recipient of lung, kidney, and islet cell transplants. Other transplants include 2 small bowel transplants and 2 vascular composite allograft transplants.

[b]Recent transplants refers to transplants performed after 1 January 2020.

[c]Number of most significant comorbidities: age >65, congestive heart failure, chronic lung disease, and obesity. Nine patients with unknown BMI are excluded (n = 473). When considering only congestive heart failure, chronic lung disease, and obesity, but not age >65, 267 patients (56.5%) had none of the 3, 162 patients (34.3%) had 1, and 44 patients (9.3%) had 2+. When considering all of the assessed baseline comorbidities without age: 0:37 (8%), 1:77 (16%); 2+:368 (76%).

[d]Tacrolimus in 410 patients, cyclosporine in 29 patients.

[e]Antimetabolite: mycophenolate in 319 patients; azathioprine in 19 patients

[f]Recent augmented immunosuppression refers to medications administered for induction of immunosuppression or for other indications including treatment of rejection within the past 3 months. Includes polyclonal anti-thymocyte antibodies (n = 15), basiliximab (n = 11), alemtuzumab (n = 1), and others (n = 14).
[g]Blood type is reported for n = 418 patients.

DISCUSSION

In this multicenter cohort study of SOT recipients with COVID-19, the 28-day mortality rate among hospitalized patients was 20.5%. Older age, CHF, chronic lung disease, obesity, lymphopenia, and radiographic abnormalities at presentation were associated with mortality, but transplant-related measures of immunosuppression intensity were not.

The mortality rate of hospitalized patients in the cohort was similar to pooled weighted estimates derived from prior studies (Table S3a) [8–21] although these studies were small

Table 2. Clinical Outcomes

	All Patients (n = 482)	Patients Hospitalized Due to COVID-19[a] (n = 376)
Outcomes (%)		
28-day all-cause mortality	90 (18.7)	77 (20.5)
Required hospital admission[a]	376 (78)	
Required intensive care	163 (33.8)	147 (39.1)
Required mechanical ventilation	130 (27)	117 (31.1)
Required vasopressors	109 (22.6)	96 (25.5)
Acute kidney injury (Cr increase by 0.3 or >50% of baseline)	182 (37.8)	167 (44.4)
Newly required renal replacement therapy	60 (12.4)	55 (14.6)
Acute liver injury (LFTs >3× ULN)	32 (6.6)	28 (7.5)
Acute MI	10 (2.1)	9 (2.4)
Thromboembolic complications[b]	13 (2.7)	11 (2.9)
Infections during the follow-up period		
Bacterial pneumonia[c]	35 (7.3)	30 (8.0)
Invasive fungal infection[d]	3 (0.6)	3 (0.8)
Bloodstream infection[e]	23 (4.8)	23 (6.1)
Transplant-related events during the follow-up period[f]		
Acute cellular rejection	6 (1.3)	4 (1.1)
Antibody-mediated rejection	1 (0.21)	0 (0)

Abbreviations:COVID-19, coronavirus disease 2019; LFT, liver function test; MI, myocardial infarction; ULN, upper limit of normal.

[a]Required hospital admission/hospitalized patients does not include 31 patients who were hospitalized for another indication at the time of diagnosis. These previously hospitalized patients are included in measures such as intensive care admission and mechanical ventilation for all patients.

[b]Thromboembolic complications include 4 cerebrovascular accidents, 2 pulmonary embolisms, 5 deep vein thrombosis, 1 arterial thrombosis, and 2 unspecified events. One patient experienced 2 events.

[c]Bacterial pneumonia pathogens isolated: *Pseudomonas aeruginosa* (n = 16), nonlactose-fermenting gram negatives (n = 5), other gram negative organisms (n = 9), *Staphylococcus aureus* (n = 7), other gram positive organisms (n = 5). Some patients had multiple pathogens isolated.

[d]Invasive fungal infection includes 2 patients with *Aspergillus* species pneumonia and 1 patient with unspecified mold infection. In addition, 1 patient was diagnosed with pneumonia due to *Cryptococcus* species and 1 patient was diagnosed with *Pneumocystis pneumonia*.

[e]Bloodstream infection pathogens isolated: *Candida* spp. (n = 3), *Escheria coli* (n = 7), *Enterococcus spp* (n = 3), *Pseudomonas aeruginosa* (n = 5), *Staphylococcus aureus* (n = 4), other gram negative organisms (n = 6). Some patients had multiple pathogens isolated. Excludes coagulase negative staphylococci (n = 7).

[f]Acute cellular rejection and antibody-mediated rejection were diagnosed at or near the time of COVID-19 testing.

and heterogeneous. A small proportion of patients (33 [8.7%]) in this cohort remained hospitalized by day 28, so it is possible that the eventual mortality rate may have been slightly higher. Among the underlying comorbidities assessed, CHF, chronic lung disease, and obesity were independently associated with increased mortality. The prevalence of these baseline comorbidities was high, and the magnitude of the association of these comorbidities with mortality was greater with increasing numbers of comorbidities, suggesting cumulative impact. Several previously described comorbidities associated with mortality in the general population (diabetes, chronic kidney disease, hypertension) [2, 3, 26] were not independently associated with mortality in this SOT cohort. Reason(s) for this difference remain uncertain but might be related to definitions utilized or other differences in populations. Pneumonia at the time of diagnosis, as defined by chest imaging abnormalities, was also associated with mortality among hospitalized patients, as similarly reported in general population studies [27, 28]. Collectively, these findings are compatible with underlying comorbidities and illness severity at presentation as the major determinants of mortality in SOT recipients. Although there have been concerns about geographic variability in outcomes,

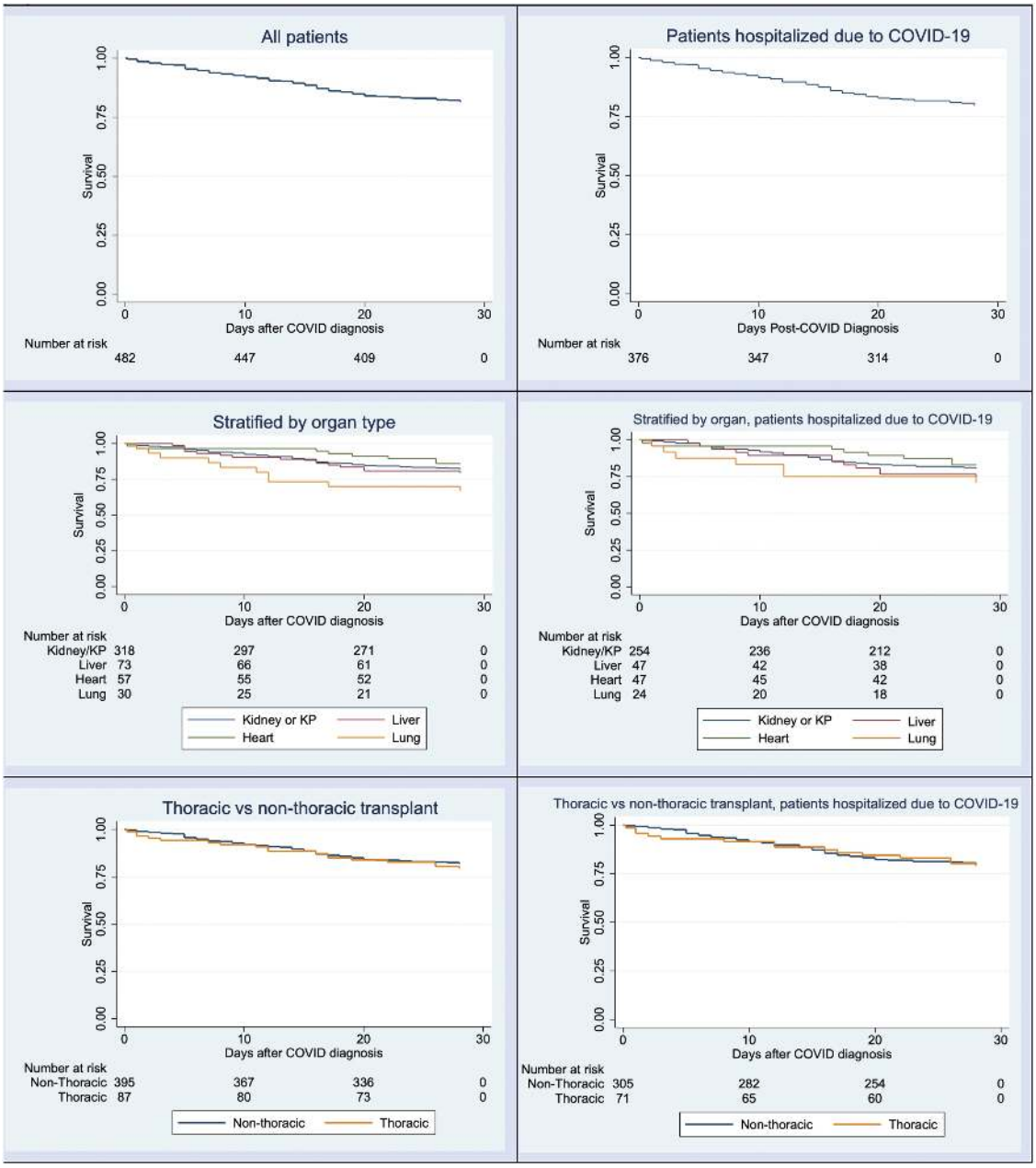

Figure 1. Unadjusted Kaplan-Meier all-cause mortality within 28-days after COVID-19 diagnosis for selected populations. Abbreviation: COVID-19, coronavirus disease 2019.

Table 3. Death by 28 Days Among Hospitalized Patients, n = 376 (77 Deceased), Logistic Regression Models

Variable	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Demographic				
Age in years				
>65 years	3.1 (1.8–5.1)	<.001	3.0 (1.7–5.5)	<.001
Male	1.2 (.73–2.1)	.42	1.3 (.70–2.3)	.43
Race/Ethnicity				
Black race	0.87 (.52–1.5)	.60		
Hispanic ethnicity	1.3 (.72–2.3)	.40		
Transplant-related				
Years from transplant	1.0 (.97–1.0)	.74		
Recent transplant[a]	0.56 (.13–2.7)	.49		
Maintenance IS				
mTOR regimen	0.16 (.021–1.2)	.073	0.18 (.02–1.4)	.10
Number of immunosuppressants[b]				
2	1.4 (.53–3.7)	.49		
3+	1.1 (.44–2.88)	.81		
Organ transplanted[c]				
Liver and liver/kidney	1.4 (.68–2.9)	.36		
Heart and heart/kidney	0.84 (.37–1.9)	.67		
Lung	1.7 (.66–4.3)	.28		
Baseline comorbidities				
Hypertension	1.4 (.72–2.7)	.99		
Coronary artery disease	1.3 (.72–2.3)	.41		
Congestive heart failure	4.8 (2.3–9.7)	<.001	3.2 (1.4–7.0)	.004
Chronic lung disease	4.7 (2.4–9.2)	<.001	2.5 (1.2–5.2)	.018
Chronic kidney disease	1.0 (.62–1.7)	.92		
Diabetes	2.1 (1.2–3.6)	.006	1.5 (.82–2.7)	.19
Obesity (BMI>=30)	1.8 (1.1–3.0)	.028	1.9 (1.0–3.4)	.039
Number of high-risk comorbidities[d]				
1	2.0 (1.1–3.6)	.023		
2+	9.0 (4.2–19.1)	<.001		
Presenting variables9				
Lymphocyte count, $\times 10^9$/L[e]				
<0.5	2.0 (1.1–3.3)	.021	1.9 (1.1–3.5)	.033
Abnormal chest imaging	2.8 (1.2–6.9)	.021	2.9 (1.1–7.5)	.027

Abbreviations: BMI, body mass index; CI, confidence interval; mTOR, mechanistic target of rapamycin; OR, odds ratio.

[a]Recent transplants refers to transplants performed after 1 January 2020.

[b]Comparison is 0 or 1 immunosuppressants. All maintenance immunosuppressant types were considered. When restricted to the most commonly-used immunosuppressant types (calcineurin inhibitors, antimetabolites, steroids), results were unchanged. (2: OR 1.5, $P = .44$; 3+: OR 1.2, $P = .69$).

[c]Comparison is kidney or kidney-pancreas transplant.

[d]Combination of most significant co-morbidities: congestive heart failure, lung disease, and obesity, reference is 0 of these 3. In multivariable analysis, omitting the three individual comorbidities and replacing it with the composite, the results were: aOR 2.3(1.2–4.2) for 1 vs none and aOR 8.9 (4.0–19.7) for 2 or more vs none.

[e]Categorical: <0.5 vs >=0.5 $\times$ 10^9/L.

an independent association of mortality with geographic location was not identified in this study. Although black and Hispanic patients comprised a higher proportion of this cohort relative to Organ Procurement and Transplantation Network data as of 4 June 2020, we did not observe an association of these factors with mortality. The observational study design precluded assessment of the relationship between various treatments utilized and mortality.

An unexpected finding was the lack of association of correlates of immunosuppression intensity at baseline with increased mortality. Neither earlier time post-transplant, receipt of a thoracic compared to nonthoracic organ transplant, receipt of recent augmented immunosuppression, nor type of maintenance immunosuppression regimen or number of agents was associated with mortality [25]. The finding of an apparent lack of association of immunosuppression-related factors on mortality should be interpreted cautiously given the lack of well-defined surrogates for immunosuppression intensity, limited power based on the sample size, and the possibility of confounding. However, this important issue should be explored in future studies, given the importance for predicting risk and/or management of SOT patients with COVID-19.

The potential negative impact of SOT-related immunosuppression on clinical outcomes of COVID-19 has been debated,

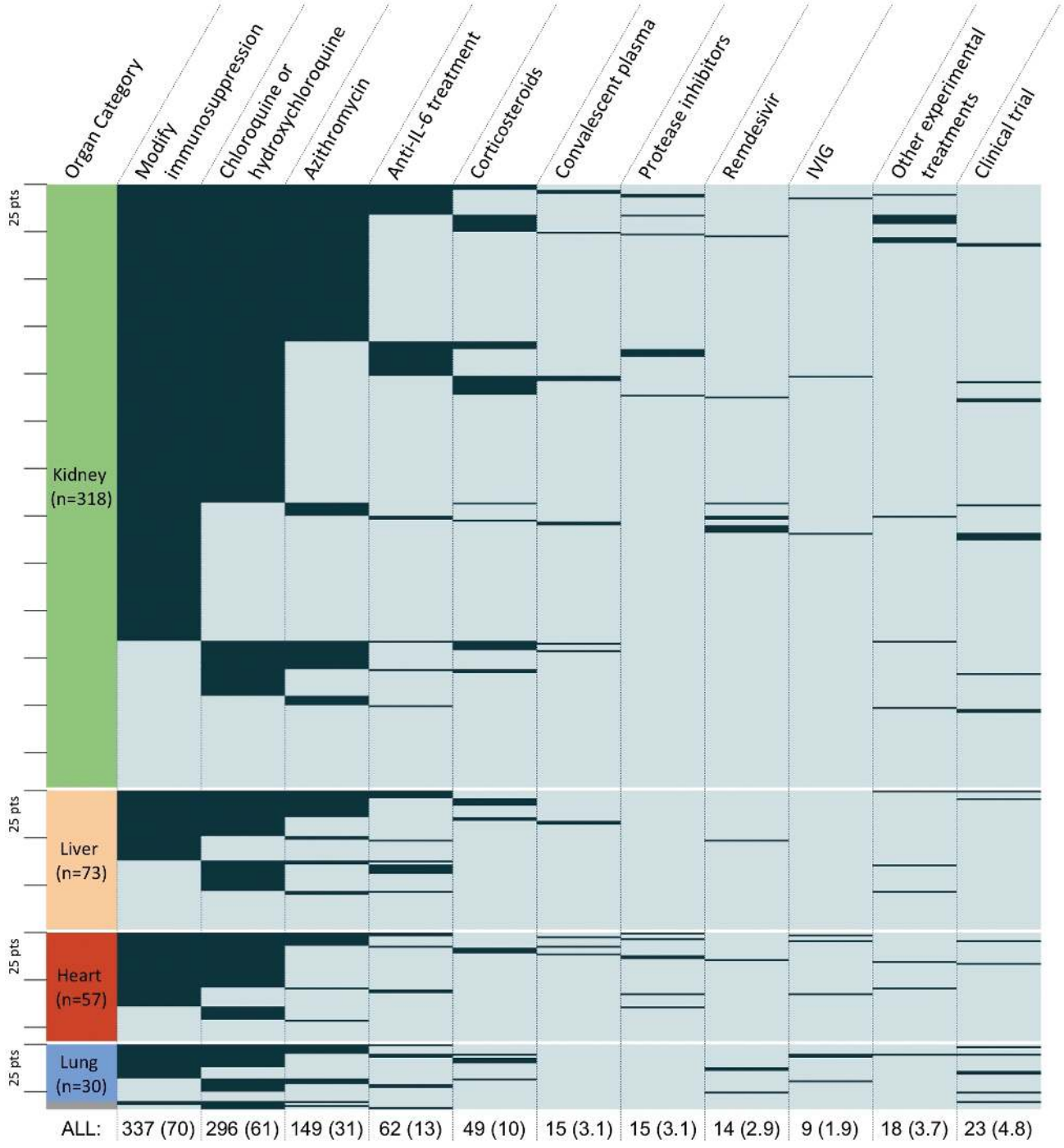

Figure 2. Medical management of COVID-19 in solid organ transplant recipients in the University of Washington Registry. Pattern frequencies graph representing management strategies used in 482 solid organ transplant recipients with COVID-19, diagnosed between 1 March 2020 and 15 April 2020. Columns show the proportion of patients who received each treatment and are labeled in the format n (%). Treatments used in combination are shown together horizontally. Abbreviation: COVID-19, coronavirus disease 2019; IL-6, interleukin 6; IVIG, intravenous immunoglobulin.

and few studies have directly compared outcomes in SOT and general populations. The few studies that included multivariable analyses of risk factors for mortality among hospitalized general populations with COVID-19 had variable durations of follow-up (reviewed in Table S3b) [2, 27–31]. Mortality estimates ranged from 8 to 33% in these studies (pooled weighted average, 19.3% [933 of 4831]) and were generally comparable to the mortality among the SOT cohort in the current study. Among general population cohort studies, the prevalence of baseline comorbidities and median age were also similar to those in the

current SOT cohort. Additionally, there was a consistent association of age and underlying comorbidities with increased mortality across general population studies, similar to that found in the present SOT cohort, highlighting the impact of these factors on mortality across different populations. Similarly, in a large population of patients with cancer, age and comorbidities were associated with mortality but not stage of malignancy or recent treatments including chemotherapy or immunotherapy [32]. However, future comparisons between general and immunocompromised populations should include careful adjustment for comorbidities and the use of well-validated mortality risk scores in this setting.

There are several implications of our findings. First, we identified specific factors (age >65 years, CHF, chronic lung disease, obesity) for COVID-19 mortality in hospitalized SOT recipients that should facilitate targeting of future studies of prevention or treatment to high-risk SOT populations. SOT is a life-saving and quality of life-improving intervention, and immunosuppression-related factors in this setting did not appear to independently impact mortality. These findings support current Center for Medicare and Medicaid Services recommendations that SOT be considered a grade 3b procedure (ie, do not delay), even in the setting of widespread COVID-19 activity [33], as long as other necessary resources to safely perform transplantation and associated care are available. Although similar to the general population, mortality among SOT recipients hospitalized with COVID-19 is very high, and prevention of new infections using evidence-based individual and institutional strategies such as those put forth by the AST will be essential to mitigate the negative effects of this pandemic [34].

The strengths of the study include the flexible design, broad multi-center participation, standardized data collection, and standardized 28-day duration of follow-up. We demonstrate the feasibility and importance of a broadly collaborative, multidisciplinary approach to rapidly develop a dataset to inform on an emerging infectious challenge. We also acknowledge potential limitations. We relied on clinician-reported cases, which may be subject to reporting bias; however, contributors attested that cases were reported consecutively and not selectively. As for all reported prior studies, diagnosis of COVID-19 and subsequent inclusion may be subject to testing bias. We focused on hospitalized patients, and thus these conclusions may not be broadly generalizable to all patients diagnosed and managed in the outpatient setting, particularly as testing practices evolve. The pragmatic study design precluded the collection of extensive laboratory parameters as well as complex clinical risk scores. Future studies should consider the predictive value of clinical risk scores such as the Sequential Organ Failure Assessment (SOFA) in COVID-19 outcomes. Independent verification of all submitted data also was not feasible. Despite follow-up of all patients for 28 days, 33 (8.7%) were still hospitalized, so the total mortality rate might eventually be slightly higher than that reported, and longer-term outcomes were not assessed. The numbers of patients with nonkidney organ transplants and those who were early in the post-transplant period was small, and even though these factors were not associated with mortality in multivariable analysis, this may have been limited by power. Thus, additional studies are needed in non-kidney organ transplant recipients and those who are recently transplanted. The sample size, although substantially larger than previously reported, might not have been large enough to identify less frequent covariates or those with lesser association with mortality.

In summary, among hospitalized SOT recipients with COVID-19 with high rates of underlying medical comorbidities, mortality was similar to that described in the general population and was driven largely by underlying medical comorbidities and certain clinical features at presentation, rather than surrogate measures of immunosuppression intensity. Future studies to better define the attributable effect of immunosuppression on outcomes in SOT recipients are warranted.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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