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ORIGINAL CLINICAL SCIENCE

Coronavirus disease 2019 in heart transplant recipients: Risk factors, immunosuppression, and outcomes



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Abbreviations: CNI, Calcineurin inhibitor; COVID-19, Coronavirus disease 2019; rt-PCR, Reverse transcriptase polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

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BACKGROUND: COVID-19 continues to inflict significant morbidity and mortality, particularly on patients with preexisting health conditions. The clinical course, outcomes, and significance of immunosuppression regimen in heart transplant recipients with COVID-19 remains unclear.

METHODS: We included the first 99 heart transplant recipients at participating centers with COVID-19 and followed patients until resolution. We collected baseline information, symptoms, laboratory studies, vital signs, and outcomes for included patients. The association of immunosuppression regimens at baseline with severe disease were compared using logistic regression, adjusting for age and time since transplant.

RESULTS: The median age was 60 years, 25% were female, and 44% were white. The median time post-transplant to infection was 5.6 years. Overall, 15% died, 64% required hospital admission, and 7% remained asymptomatic. During the course of illness, only 57% of patients had a fever, and gastrointestinal symptoms were common. Tachypnea, oxygen requirement, elevated creatinine and inflammatory markers were predictive of severe course. Age ≥ 60 was associated with higher risk of death and the use of the combination of calcineurin inhibitor, antimetabolite, and prednisone was associated with more severe disease compared to the combination of calcineurin inhibitor and antimetabolite alone (adjusted OR = 7.3, 95% CI 1.8-36.2). Among hospitalized patients, 30% were treated for secondary infection, acute kidney injury was common and 17% required new renal replacement therapy.

CONCLUSIONS: We present the largest study to date of heart transplant patients with COVID-19 showing common atypical presentations and a high case fatality rate of 24% among hospitalized patients and 16% among symptomatic patients.

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Patients with history of solid organ transplantation are potentially at higher risk of severe disease and mortality due to coronavirus disease 2019 (COVID-19) given complex comorbidities and concomitant immunosuppression therapy. To date, only a few case series have been published on heart transplant recipients with COVID-19 infection. A large single center series, published by Latif and colleagues from the early phase of the pandemic in the United States, reported a mortality rate of 25% among 28 heart transplant patients with COVID-19.¹ Another case series described 26 transplant patients in Italy with a 27% overall mortality. Interestingly, glucocorticoid use as part of an immunosuppressive regimen was associated with improved survival, with all 8 of 26 patients using steroids pre-infection surviving.² A second, more recent, series from Italy of 47 patients showed a similar 30% case fatality rate.³

In this current large multi-center series, we explored the clinical course and outcomes of heart transplant recipients with confirmed COVID-19 infection, and the association between immunosuppressive regimen and outcomes.

Material and methods

Advanced heart failure programs and patients

Established in April 2020, the Trans-CoV-VAD registry is a multi-center registry of left ventricular assist device and heart transplant patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Eleven advanced heart failure programs in the United States participated in this registry: The University of Pennsylvania (Philadelphia, PA), Ascension St. Vincent Heart Center (Indianapolis, IN), the Cleveland Clinic (Cleveland, OH), the Medical University of South Carolina (Charleston, SC), MedStar Washington Hospital Center (Washington, DC), Mount Sinai Hospital (New York City, NY), Northwestern University (Chicago, IL), the University of Michigan (Ann Arbor,

MI), Stanford University (Stanford, CA), the University of Pittsburgh (Pittsburgh, PA) and the University of Rochester (Rochester, NY). Each site obtained approval from the local Institutional Review Board. Specific informed consent was waived due to the determination of minimal risk to included patients.

All heart transplant recipients age ≥ 18 years at participating institutions with a confirmed diagnosis of COVID-19 through October 31, 2020 were included in this study. The first case among a heart transplant recipient at a member institution was diagnosed in mid-March 2020. All patients were diagnosed with either a polymerase chain reaction (rt-PCR) test ($n = 95$) or an antibody test specific to SARS-CoV-2 ($n = 4$). Antibody testing was not routine but was used sporadically for clinical suspicion of recovered prior infection. Data were collected via review of the patients' electronic records, and anonymized data were transmitted for collation and storage at a centralized repository maintained by the University of Pennsylvania. Patients were followed until recovery or death, with last patient status updates collected in January 2021.

Clinical variables

Patient demographics, medical history, medications, laboratories, and details of course of COVID-19 were obtained from the electronic record. Hospitalization, whether at a patient's primary transplant institution or an outside hospital, was noted. Severe disease was defined as requiring any of the following: mechanical ventilation, de novo renal replacement therapy, use of vasopressors, or death occurring during the patient's primary hospital admission or episode of care for COVID-19. Proximate cause of death was recorded after review of the chart by the investigators.

Statistical analysis

Demographics, patient characteristics, symptoms, and details of presentation were compared for patients with severe and non-severe disease, excluding patients who were asymptomatic

Table 1 Demographics of Heart Transplant Recipients with Symptomatic COVID-19 by Disease Severity

	Not severe <i>n</i> = 68	Severe <i>n</i> = 24	<i>p</i> value
Age, years*	58 (45-67)	66 (49-74)	0.07
Female	19 (25%)	6 (25%)	1.0
Body mass index, kg/m, ²	28.5 (6.1)	30.2 (5.6)	0.24
Race			0.70
Asian	4 (6%)	0 (0%)	
Black	30 (44%)	10 (42%)	
White	29 (43%)	12 (50%)	
Other or missing	5 (7%)	2 (8%)	
Hispanic/Latino	8 (12%)	3 (13%)	1.0
Ischemic cardiomyopathy	9 (13%)	7 (29%)	0.11
Hypertension	54 (79%)	24 (100%)	0.02
Diabetes	33 (49%)	18 (75%)	0.03
Obstructive sleep apnea	11 (16%)	10 (42%)	0.02
Chronic obstructive pulmonary disease	6 (9%)	7 (29%)	0.04
On dialysis prior to infection	5 (7%)	3 (12%)	0.43
Home O2 use	2 (3%)	2 (8%)	0.28
Time since transplant, years*	4.9 (2.0-13.5)	10.9 (4.0-16.2)	0.20
Coronary allograft vasculopathy	15 (22%)	9 (38%)	0.18
History of acute cellular rejection	17 (25%)	5 (21%)	0.79
Time since acute cellular rejection, months**	15 (1-238)	15 (1-181)	0.82
History of antibody mediated rejection	6 (9%)	2 (8%)	1.0
Time since antibody mediated rejection, months**	17 (0-75)	45 (18-72)	0.64

COVID-19, coronavirus disease 2019.

Values are mean (SD) or *n* (%) unless otherwise specified.

*Values shown are median (IQR); *p* value is the result of a Wilcoxon test. Values shown are median (range).

***p* value is the result of a Wilcoxon test.

throughout their course. Comparisons were made with student's *t*-test, χ^2 , or Fisher's test as appropriate. Categorized age and time since transplant were examined as predictors of severe disease using logistic regression. We then created two additional models to examine the association of specific immunosuppression agents (the first model) and regimens (second model) with severe disease using logistic regression adjusting for patient age and time since transplant, both considered as continuous variables. For immunosuppression regimens, we selected the most common combinations in the cohort: calcineurin inhibitor (CNI) + antimetabolite (reference), CNI + prednisone, CNI + antimetabolite + prednisone, and CNI + proliferation signal inhibitor (PSI). The latter regimen could be with or without prednisone (combined due to low numbers). As a supplemental analysis, all models were repeated using death as the outcome, rather than severe disease.

All analyses were performed using R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) with a two-sided $\alpha = 0.05$.

Results

Patients

A total of 99 patients with a history of heart transplantation were diagnosed with COVID-19 during the study period and were included in this series (Table S1). The median age was 60 years (IQR, 46-69), 25 (25%) were female and 44 (44%) were white. The median time post-transplant to infection was 5.6 (IQR, 2.0-13.7) years.

Of the 99 patients included, 35% remained in the ambulatory setting and were never hospitalized, including 7 patients who remained asymptomatic during their illness.

In total, 11 patients were tested while asymptomatic, 3 for definite viral exposures, 7 as part of routine clinical care per individual hospital protocols, and 1 for unknown reasons. Four later developed symptoms (including 2 who were ultimately hospitalized, 1 of whom died). Severe illness developed in 24 patients, with criteria met by: need for mechanical ventilation (20 patients), new renal replacement therapy (11), and use of vasopressors (13). Fifteen patients died of COVID-19.

Compared to patients who had more mild disease, patients with severe COVID-19 were more likely to have chronic comorbidities such as hypertension, diabetes, and chronic obstructive pulmonary disease (Table 1). Specifically, while hypertension was common overall (84/99, 85%), all patients with severe COVID-19 had hypertension. While both the median age at diagnosis and time from transplant to diagnosis were greater in patients with severe disease compared to patients with less severe disease, neither difference was statistically significant (66 vs 58, *p* = 0.07, and 10.9 vs 4.9 years, *p* = 0.20, respectively). Included transplant centers reported a total of 4,841 living heart transplant recipients under management in 2020, for a COVID-19 incidence rate of 20.5 cases per 1,000 persons through October 31.

Clinical presentation

Figure 1 shows the cumulative incidence of select symptoms for severe and non-severe disease. Despite fever being

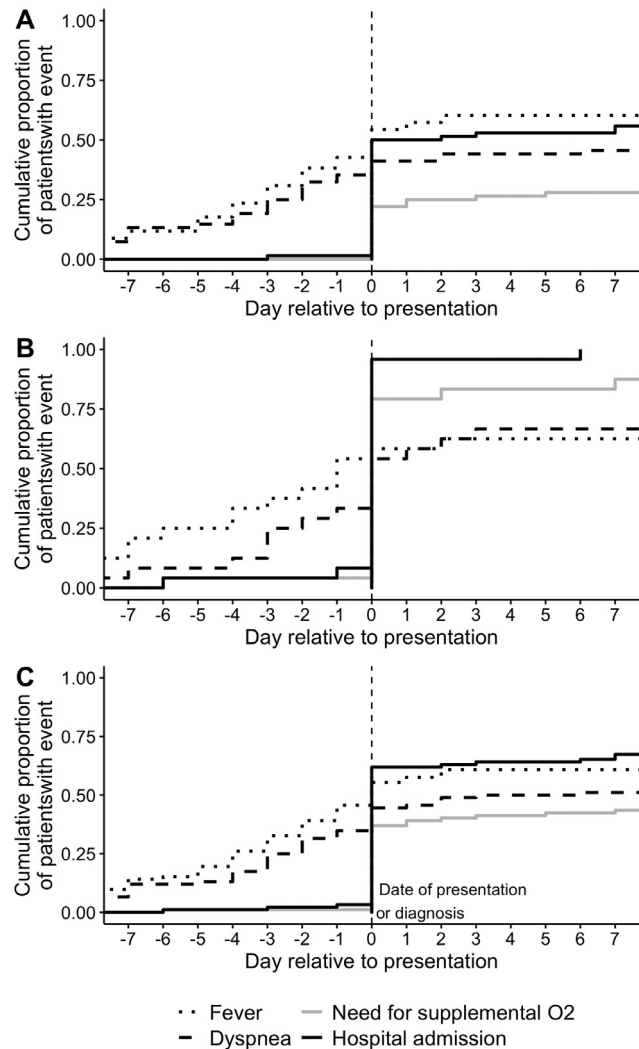


Figure 1 Course of COVID-19 in heart transplant recipients. Cumulative incidence of select symptoms, need for supplemental oxygen, and hospital admission relative to date of diagnosis or first medical attention for COVID-19, shown for (A) Patients with non-severe disease, (B) patients with severe disease, and (C) all patients.

the most common symptom of SARS-CoV-2 infection, with 51% having a measured or reported fever at or before initial presentation, 43/99 patients (43%) remained without either a subjective or objective fever throughout their illness. Other common symptoms included cough (present in 49% upon presentation and 55% by the end of illness) and dyspnea (41% upon presentation and 50% by the end of illness). Gastrointestinal complaints (abdominal pain, nausea, vomiting, or diarrhea) were also common, present in 46% of patients during illness; in particular, diarrhea was present in 36%. Among hospitalized patients, the median symptom onset was 5 days prior to admission; 95% of patients ultimately requiring admission were admitted within 8 days of first symptom onset.

Vital signs at time of presentation were available for 88% of patients with severe disease and 66% of patients with symptomatic non-severe disease. Of patients with available vital signs, there were no significant differences

Table 2 Vital signs at Diagnosis Among Heart Transplant Recipients with Symptomatic COVID-19 by Disease Severity

	Not severe <i>n</i> = 68	Severe <i>n</i> = 24	<i>p</i> value
Heart rate, bpm			0.29
<60	0 (0%)	1 (5%)	
60-99	21 (47%)	10 (50%)	
≥100	24 (53%)	9 (45%)	
Systolic blood pressure, mmHg			0.62
<90	2 (5%)	0 (0%)	
90-139	29 (66%)	14 (70%)	
≥140	13 (30%)	6 (30%)	
Respiratory rate, min ⁻¹			0.009
<20	22 (54%)	3 (15%)	
≥20	19 (46%)	17 (85%)	
Temperature, °F			0.50
<100.4	33 (77%)	13 (65%)	
≥100.4	10 (23%)	7 (35%)	
SaO ₂ , %			0.48
<92%	6 (13%)	5 (24%)	
≥92%	39 (87%)	16 (76%)	
Hypoxia <92% or supplemental O ₂	10 (22%)	14 (67%)	0.001

COVID-19, coronavirus disease 2019.

Values are *n* (%). Data were not available in all cases; *p* values and percentages consider patients with non-missing values only.

between patients who ultimately had severe and non-severe disease, with the exception of respiratory rate, which was more likely to be $\geq 20 \text{ min}^{-1}$ in patients with severe disease (85% vs 46%, $p = 0.009$). In particular, hypotension at presentation was not predictive of disease severity, however requiring supplemental oxygen was strongly associated with severe outcomes (Table 2).

Table 3 shows select laboratory studies available upon presentation. Most patients presented with normal white blood cell counts or leukopenia; most (74%) had lymphopenia. Mild elevations in aspartate aminotransferase and alanine aminotransferase were present in 50% and 38% of patients, respectively. Elevated inflammatory markers such as C-reactive protein and ferritin were common as well. Compared to patients with non-severe disease, patients with severe disease were more likely to present with elevated serum creatinine, blood urea nitrogen, aspartate aminotransferase, and neutrophil count. They were also more likely to have high ferritin on admission; none of the patients with severe disease had a normal ferritin on admission (range, 308-5981 ng/mL). Elevation in troponin was present in about one-third of patients, more commonly among patients who would later go on to have more severe disease courses.

Transplant recipients often have baseline laboratory abnormalities and are prone to chronic renal disease. Among the 46 included patients not on dialysis and with available serum creatinine values on days 1 and 3 of hospitalization, 23 had acute kidney injury, defined as rise in creatinine of $\geq 0.3 \text{ mg/dL}$ or 50%. Six (26%) of these patients died and 6 (26%) otherwise met criteria for severe illness.

Table 3 Laboratory Values in Heart Transplant Recipients with Symptomatic COVID-19 Upon Presentation

	Not severe n = 68	Severe n = 24	p value
White blood cell count, 10 ⁹ /L			0.31
<4.0	7 (16%)	4 (19%)	
4.0-10.0	33 (77%)	13 (62%)	
≥10.0	3 (7%)	4 (19%)	
Neutrophil count, 10 ⁹ /L			0.03
<2.0	1 (2%)	2 (11%)	
2.0-7.9	40 (93%)	12 (67%)	
≥8.0	2 (5%)	4 (22%)	
Lymphocyte count, 10 ⁹ /L			0.44
<1	30 (70%)	15 (83%)	
1-3.9	13 (30%)	3 (17%)	
Hemoglobin g/dL			0.79
<12.0	15 (36%)	8 (40%)	
12.0-15.9	26 (62%)	11 (55%)	
≥16.0	1 (2%)	1 (5%)	
Platelets, 1000/μL			0.60
<150	11 (27%)	6 (30%)	
150-399	28 (68%)	14 (70%)	
≥400	2 (5%)	0 (0%)	
Creatinine, mg/dL			0.006
<1.4	16 (37%)	1 (5%)	
1.4-2.4	17 (40%)	8 (38%)	
≥2.5	10 (23%)	12 (57%)	
Blood urea nitrogen, mg/dL			0.01
<20	17 (40%)	1 (5%)	
20-59	21 (49%)	14 (67%)	
≥60	5 (12%)	6 (29%)	
Aspartate aminotransferase, U/L			0.03
<30	22 (56%)	6 (35%)	
30-89	16 (41%)	7 (41%)	
≥90	1 (3%)	4 (24%)	
Alanine aminotransferase, U/L			0.09
<30	28 (70%)	8 (44%)	
30-89	12 (30%)	9 (50%)	
≥90	0 (0%)	1 (6%)	
Total bilirubin, mg/dL			0.39
<1.2	35 (90%)	18 (100%)	
≥1.2	4 (10%)	0 (0%)	
Lactate dehydrogenase, U/L			0.26
<150	1 (4%)	1 (8%)	
150-299	10 (42%)	2 (15%)	
≥300	13 (54%)	10 (77%)	
C-reactive peptide, mg/L			0.03
<5	5 (20%)	0 (0%)	
5-10	1 (4%)	5 (33%)	
≥10	19 (76%)	10 (67%)	
Ferritin, ng/mL			0.03
<300	8 (32%)	0 (0%)	
300-899	9 (36%)	5 (33%)	
≥900	8 (32%)	10 (67%)	
	18 (58%)	10 (83%)	0.23

(continued on next page)

Table 3 (Continued)

	Not severe n = 68	Severe n = 24	p value
BNP > 100 pg/mL, or nt-proBNP > 300 pg/mL			0.003
Troponin			
Within normal	26 (79%)	4 (29%)	
1-3x ULN	2 (6%)	5 (36%)	
>3x ULN	5 (15%)	5 (36%)	

BNP, B-type natriuretic peptide; COVID-19, coronavirus disease 2019; ULN, upper limit of normal.

Values are n (%). Data were not available in all cases; p values and percentages consider patients with non-missing values only.

This compares to only 1 death and no other critically ill patients among the 13 patients with baseline normal renal function who did not have acute kidney injury.

Disease course and outcomes

Including one patient who died in the emergency department, 63 patients (64%) were hospitalized. Indications for admission included (not mutually exclusive): abnormal chest imaging (51 patients), hypoxia within 24 hours of initial assessment (38), troponin elevation > 3x upper limit of normal (10), and systolic blood pressure < 90 mmHg (2). The most common chest imaging finding was diffuse or focal pneumonia, consolidation, or groundglass opacity—present in all but 4 of the 51 patients with abnormal imaging. The remaining 4 patients had effusion or edema alone without clear pneumonia, consolidation, or groundglass opacities. Fifteen patients died, 14 of whom had proximate causes of death which could be fully adjudicated by the investigators: hypoxic respiratory failure (6 patients), multi-organ system failure (3), septic shock (2), undifferentiated shock (1), uncontrolled gastrointestinal hemorrhage (1), and catastrophic intracranial bleed (1). Deaths occurred a median of 19 days after diagnosis (range 0-155). One additional death occurred unexpectedly after a collapse at home over 100 days post recovery from an ambulatory case of COVID-19; autopsy revealed an acute right coronary artery thrombosis; we did not attribute this death to COVID-19 in our analysis. Two of the 15 deaths occurred within 3 years of transplant; one occurred in the first year.

Several major complications were noteworthy: 19 patients were treated for confirmed or suspected secondary infection, 11 had de novo renal replacement therapy started, and 2 patients suffered new venous thromboembolism, although data on the latter was only available on 77 patients due to this question's later addition into the collection forms; thus, our estimated prevalence was 3% (2/77). Despite the high frequency of elevations in troponin and B-type natriuretic peptide (Table 3), only 1 patient had new heart failure during their disease course. Selected SARS-CoV-2 treatment and other hospital outcomes are shown in Table 4. Over half of symptomatic patients had immunosuppression regimens reduced at diagnosis.

Table 4 Selected Illness Course Details and Outcomes

	Ambulatory patients <i>n</i> = 29	Hospitalized patients <i>n</i> = 63	All symptomatic patients <i>n</i> = 92
Severe disease criteria met	–	24 (38%)	24 (26%)
Mechanical ventilation	–	20 (32%)	20 (22%)
New renal replacement therapy	–	11 (17%)	11 (12%)
Use of vasopressors	–	13 (21%)	13 (14%)
Died	–	15 (24%)	15 (16%)
Immunosuppression reduced	4 (14%)	48 (76%)	52 (57%)
Selected treatments			
Remdesivir	0 (0%)	11 (17%)	11 (12%)
Convalescent plasma	0 (0%)	11 (17%)	11 (12%)
Tocilizumab	0 (0%)	6 (10%)	6 (7%)
Dexamethasone or other pulsed steroid	0 (0%)	19 (30%)	19 (21%)

Values are *n* (%).

Immunosuppression

The most common immunosuppression regimen was the combination of a CNI with an antimetabolite, used by 37% of patients. An additional 21% used a CNI, an antimetabolite, and prednisone at baseline; 16% used a CNI with prednisone, and 13% used a CNI with a PSI (7 with prednisone and 6 without). Other regimens accounted for the other 13%, including 5 patients (5%) not using a CNI at baseline. In total, 47 patients were taking prednisone at the time of diagnosis; 33/47 (70%) were taking 5 mg/day or less, 43/47 (91%) were taking 10 mg/day or less, and the remaining 4/47 (9%) were taking > 10 mg/day. Among these patients on prednisone, 33 (70%) were admitted and 13 had severe disease. Among the 52 patients who were not on prednisone, 29 (56%) were admitted and 11 had a severe disease. Prednisone use was not associated with a significant increase in either admission ($p = 0.20$) or severe disease ($p = 0.60$). Dichotomizing on high dose (> 10 mg/day) did not meaningfully change our findings. Use of tacrolimus was less common among patients with severe disease (88% vs 67%, $p = 0.03$).

While both age ≥ 60 years and time since transplant were not statistically associated with more severe disease, confidence intervals were wide and did not exclude large positive associations between both risk factors and poor outcomes (Figure 2). Age ≥ 60 , adjusted for time since transplant, was associated with an over 7-fold increase in odds of death, (odds ratio [OR] 7.6, 95% confidence interval [CI] 1.9-51) (Figure S1). Adjusted for age and time since transplant, use of a PSI ($n = 15$ patients) was significantly associated with a more severe COVID-19 course (OR 6.8, 95% CI 1.3-41). Compared to the most common drug regimen of CNI and antimetabolite, a “triple therapy” regimen of CNI with antimetabolite and prednisone was associated with increased odds of severe COVID-19 (OR 7.3, 95% CI 1.8-36) and death (OR 17.8, 95% CI 2.1-245) after adjustment for age and time since transplant.

Discussion

This multi-center registry represents the largest descriptive series of heart transplant recipients with COVID-19. We describe the clinical characteristics and outcomes of this patient population, finding a high mortality among heart transplant recipients with COVID-19 of 15%. Contrary to a previous report which suggested that baseline prednisone use was associated with more mild disease,² we did not find evidence of a protective effect of prednisone therapy in our cohort. We found that older age is strongly associated with death from COVID-19, and that both PSI-based immunosuppression regimens and “triple therapy” regimens with CNI, antimetabolite, and prednisone were both associated with more severe COVID-19 courses compared with standard immunosuppression with CNI and antimetabolite alone. Finally, some clinical and laboratory factors on presentation, such as tachypnea, elevated ferritin, troponin, and aspartate aminotransferase were associated with increased odds of severe clinical course.

Death or severe illness, defined as vasopressor therapy, new renal replacement therapy, or mechanical ventilation, were observed in 24% of patients and well over half (64%) of patients required hospitalization. This hospitalization rate was far higher than the 14.0% hospitalization rate observed among U.S. adults (median case age 48 years) during a time period mostly contemporaneous with our study. Our overall case fatality rate of 15% was also considerably higher than the 5.4% quoted in that study. However, our asymptomatic case rate was almost double (7% vs 4%), suggesting that this difference was not due to underdiagnosis of mild cases in our population.⁴ Data published later in the course of the pandemic suggests a true infection fatality rate in the general population significantly lower, under 1%, depending on case age mix, providing a more dramatic contrast with our data.⁵ However, because disease incidence rates, testing and other resource availability varied considerably across the county during the early phases of COVID-19 in 2020, direct comparisons to other reports should be considered in context. For example, estimates of

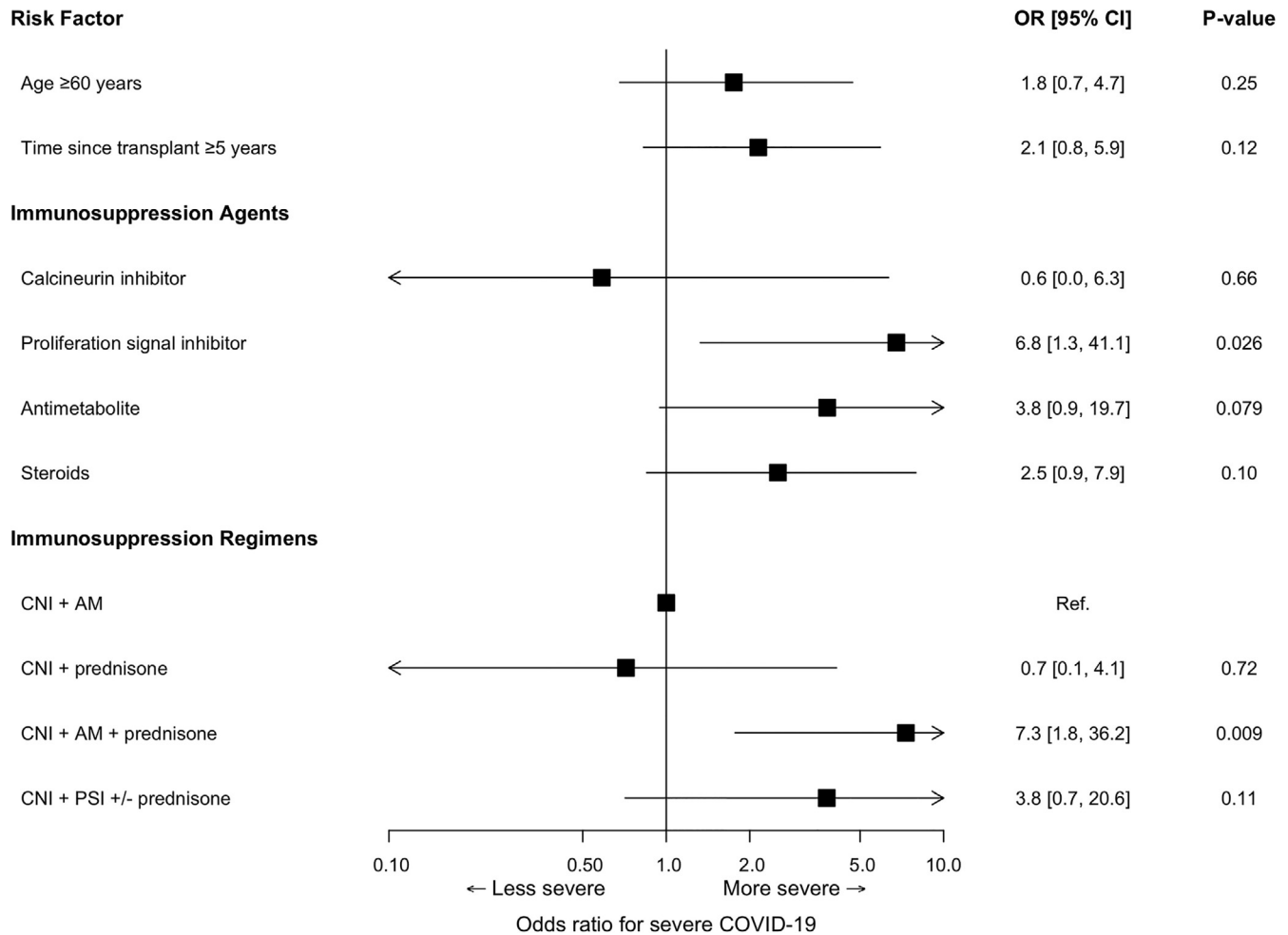


Figure 2 Association of immunosuppressive regimen with odds of severe COVID-19. Odds ratios (OR) for severe disease (vs non-severe disease) among heart transplant recipients diagnosed with COVID-19. Figure shows the result of three different models, one for risk factors of age and time since transplant, a second for individual immunosuppression agents (adjusted for age and time since transplant), and a final for combination regimens (again adjusted for age and time since transplant). CNI = calcineurin inhibitor; AM = antimetabolite; PSI = proliferation signal inhibitor. Patients on the combination of CNI and PSI were grouped together whether or not they also took prednisone due to low numbers.

mortality among hospitalized patients ranges considerably, and is dependent on hospital resources and threshold for admission. In a meta-analysis, mortality among hospitalized COVID-19 cases in North America was 21%, slightly lower than our estimate of 24%.⁶

Deaths were usually due to complications of COVID-19 infection, including secondary infection, hypoxic respiratory failure, shock and multi-organ failure. One patient died unexpectedly of acute coronary thrombosis over 3 months after a symptomatic infection with SARS-CoV-2 which did not require hospitalization. Despite a pro-thrombotic milieu which is known to be one of the consequences of COVID-19,⁷ we could not confidently attribute this death to the virus, and did not include this death in our mortality figures or other analyses.

Epidemiology

Included transplant centers reported a total of 4,841 living heart transplant recipients under management in 2020, for a

COVID-19 incidence rate of 20.5 cases per 1,000 persons through October 31. This is below the U.S. national cumulative incidence of 27.9 cases per 1,000 persons during the same period.⁸ However, care should be taken in interpreting this figure as although participating sites were distributed across the U.S., the sex, age, and specific geographic breakdown of the transplant recipient population at risk would not be expected to reflect that of the entire country.

We noted a high proportion of COVID-19 cases among persons self-identified as Black race (42% of cases). Conversely, data from the Organ Procurement and Transplantation Network showed that at the 11 participating centers from 2013 to 2019, transplant recipients were 74% white, 15% Black, 4% Asian, and 7% other, markedly different from the racial composition of infected persons of 44% white, 42% Black, 4% Asian, and 9% other (*p* < 0.0001). To account for geographic variation in intensity of the pandemic during the study period, we re-ran the comparison with weighting for case incidence at each center and found the result unchanged. Such a finding mirrors that of the

pandemic in the U.S. at large, where Blacks face a disproportionate share of disease burden, a reflection of underlying economic and societal inequities.^{9,10} We note that severe outcomes or death in our cohort were not associated with race.

The current literature published on COVID-19 in heart transplant recipients consists of single center or relatively smaller series, with mortality ranging from 10% to 35%, and mortality among the hospitalized ranging from 32% to 41%.^{1,2,11,12} Rivinius et al. published a multicenter survey of all heart transplant patients with COVID-19 infection in Germany, reporting 38% rate of severe disease and 33% mortality.¹² Iacovoni et al. described the Italian experience of 26 heart transplant patients, with mortality rate as high as 27%.² A second Italian case series of 47 patients reported a 30% mortality.³ Latif and colleagues described the experience of an academic center in New York, with total of 28 patients with mortality rate of 25%.¹ We note that our cohort, comprised of less than 50% self-identified white race, is considerably more diverse than that described in the Asian and European reports. Compared to the previous largest report (Bottio, et al., 47 Italian patients), our cohort is slightly younger (57 vs 62 years) and has a slightly shorter mean time since transplant (8.6 vs 10.5 years).

The variability in the mortality rate is likely to be multifactorial, and may reflect the timing of the COVID-19 disease and evolution in management strategies and therapies. Although our registry's current mortality rate is at the lower end of previous publications of heart transplant patients, it is clearly higher than the mortality rate of the general population. This may be secondary to the rate of comorbidities in this patient population, but may also reflect the immunocompromised physiology of these patients. Another consideration is that 70% of the hospitalized patients in our cohort were treated entirely at the primary transplant institution, a number which increases if patients transferred in from outside hospitals are included. Along with the number of asymptomatic patients included here, this likely reflects that our study was conducted during the early and mid-phases of the epidemic in the U.S., where resources such as tertiary care beds and testing supplies were not as constrained as during the hyperacute surge captured in the Northern Italian cohorts, for example.

We found that older patients were more likely to die from COVID-19, and that patients who were over five years post-transplant, independent of age, had a trend toward increased disease severity, although the latter was not statistically significant. This suggests that in a post-transplant population, similar to the non-transplant patients, accumulated comorbidities and complications, frailty, or other unmeasured factors may predispose to morbidity and mortality from COVID-19. We observed higher prevalence of comorbidities among patients with severe illness, congruent with previous reports,⁶ however relativity small numbers may have limited overall statistical power.

Clinical presentation

The clinical presentation of heart transplant recipients may be challenging, with only 51% of the patients presenting

with a history of subjective or objective fever. Tachypnea and oxygen requirement at presentation were associated with severe clinical course, however hypotension at presentation was not predictive of disease severity. Importantly, 88% of patients with respiratory rate < 20 on presentation had mild disease, which may play a role in the risk stratification of this patient population. Like in the general patient population, lymphopenia was very common, although it was not associated with severe clinical course. Elevated creatinine, troponin and ferritin levels at presentation were associated with severe clinical course. This finding supports the theory that like in the general population, severe clinical course in heart transplant recipients may reflect an inflammatory state, or cytokine storm, despite chronic immunosuppression therapy.

Contrary to a prior report, we show that systemic steroids (i.e. chronic therapy with prednisone) was not protective from severe COVID-19 disease. This may be secondary to the fact that most of the patients were on chronic low dose prednisone dose, which may not suffice to suppress the immune system and to prevent cytokine storm. However, as a sensitivity analysis, we stratified prednisone dose (none, 1-5 mg/day, and ≥ 6 mg/day) and found similar results. We did find, however, that patients taking "triple therapy" with a CNI, antimetabolite and prednisone were significantly more likely to have a severe disease course, even after adjustment for age and time since transplant. It is possible that this more intensive immunosuppression regimen may predispose to increased risk of secondary infection, although we do not have adequate power to detect this. As an alternate theory, in the modern immunosuppression era, 80% of patients are maintained on CNI and antimetabolite (without prednisone),¹³ making the use of triple therapy a possible marker for unmeasured confounding patient factors. A similar explanation is likely to account for our finding of an association between PSI-based regimens and severe disease. However, care should be taken not to over-generalize associations between baseline immunosuppression and outcomes as practice patterns are heterogeneous and there were limited numbers of patients taking certain regimens in our cohort.

As expected, most of the transplant recipients (64%) were admitted at presentation. Given that 7% of the patients were asymptomatic, the vast majority of the symptomatic heart transplant patients with COVID-19 were admitted. This reflects the appropriate concerns of physicians regarding the unfavorable outcomes of this patient population, as is reflected by the high mortality rate of our registry.

Limitations and conclusions

Our study has limitations that align with its retrospective characteristics as well as to the different clinical practice of different programs in the registry. Moreover, 4 patients in our cohort were diagnosed retrospectively via antibody testing, and 11 other patients had a positive rt-PCR test for screening purposes; both of these considerations make it difficult to determine the true incidence of disease among all transplant recipients under the care of participating

centers. Practice patterns of testing and screening were similar across participating centers: all sites in our registry used pre-procedure (surgery, endoscopy, or catheterization) rt-PCR screening in all or most patients. Nine of 11 routinely tested all patients on hospital or emergency department admission and none used routine in-office testing for asymptomatic patients. No centers used antibody testing in transplant patients except in cases with high clinical suspicion. Our work is not intended to determine the true incidence of disease among transplant recipients. However, our experience of COVID-19 among heart transplant recipients at 11 high-volume centers in the U.S. would likely generalize widely.

In conclusion, we present the largest case series of heart transplant recipients with COVID-19 infection and describe the main clinical, laboratory findings, and associations of immunosuppression regimen with outcome. Our findings suggest that heart transplant recipients are at high risk of morbidity and mortality from COVID-19 compared to the general population. Understanding the unique clinical course of COVID-19 among heart transplant recipients is essential in an effort to improve their outcomes and may help motivate continued vigilance to mitigation measures and spur vaccination efforts for this vulnerable patient population.

Author contributions

All co-authors contributed to either the study design (M.V.G., N.M., S.S.N., B.A.H., S.S., E.V., P.A., T.S., E.H., K.M.A., S-P.C., A.K., H.V., E.A.B., R.J.T., and E.Y.B.), data analysis (M.V.G., N.M., R.J.T., and E.Y.B.), data collection and integrity (M.V.G., N.M., S.S.N., B.A.H., S.S., E.V., M.M., S.C., T.S., E.H., K.M.A., S-P.C., R.G-C., E.M., M.R., A.K., H.V., K.D., J.A-G., R.J.T., and E.Y.B.), or writing and/or critical review of manuscript (all co-authors).

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Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.healun.2021.05.006>.

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