Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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ORIGINAL CONTRIBUTION

Outcomes Associated With COVID-19 Hospitalization in Heart Transplantation Patients

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ABSTRACT

Background. Heart transplantation (HT) recipients infected with COVID-19 may be at an increased risk of severe illness due to chronic immunosuppression.

Materials and Methods. Adult HT patients hospitalized with COVID-19 at the Cleveland Clinic between March 2020 and March 2021 were included in this retrospective cohort analysis. Twenty-four HT cases were matched to 96 non-HT controls, similarly hospitalized with COVID-19, out of 11,481 patients based on different baseline characteristics. Primary outcome was all-cause mortality; secondary outcomes included mechanical ventilation, intensive care unit admission, vasopressor need, dialysis, pneumonia, and 90-day readmission. Subgroup analysis was performed based on the time from transplantation (within 1 year of transplantation and greater than 1 year since transplantation).

Results. Both primary and secondary outcomes were not significant. Subgroup analysis did not show a significant difference in mortality (P = .355) or 30-day readmission (P = .841) between patients who were within 1 year of transplantation and remote transplantation beyond 1 year. Univariable analysis of immunosuppressant continuation, dose-reduction, or discontinuation did not significantly affect HT mortality.

Conclusions. Despite limited sample size, our results suggest that HT patients do not show worse outcomes after acquiring COVID-19, whether in the first year of transplantation or after a remote transplantation procedure. Future studies with multicenter data that incorporate the subsequent COVID-19 variants (eg, Delta and Omicron), the impact of long COVID-19, and assessing full vs reduced immunosuppression regimens would add insights to this patient population.

HEART transplant (HT) recipients infected with coronavirus disease 2019 (COVID-19) may be at increased risk of severe illness due to chronic immunosuppression. The primary objective of this study was to compare the clinical outcomes of HT recipients hospitalized with COVID-19 to a matched cohort of non-heart transplant (NHT) patients.

MATERIALS AND METHODS

This retrospective cohort analysis included adult HT patients hospitalized with COVID-19 at our institution between March 2020 and March 2021. COVID-19 diagnosis was based on a positive confirmatory test for detecting SARS-CoV-2 by reverse-transcriptase polymerase chain reaction. The Cleveland Clinic institutional review board approved the study. The matched cohort, similarly hospitalized with COVID-19, was identified using propensity score matching (PSM) in a 4:1 fashion with baseline characteristics listed in Table 1. In addition, a subgroup

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Table 1. Comparison of Heart Transplant to Matched Non-Heart Transplant Patients Hospitalized for COVID-19

Parameters	HT (n = 24)	NHT (n = 96)	*P* Value	AMD
Characteristics				
Age (y)	62 ± 18	65 ± 18	.552	.13
Female gender (%)	3 (12.5)	13 (13.5)	.893	.02
Body mass index (kg/m^2)	26.3 ± 5.6	27.7 ± 7.2	.374	.17
Admission serum creatinine (mg/dL)	2.47 (1.38-2.99)	1.52 (1.11-4.49)	.322	.14
Comorbidities				
Hypertension (%)	21 (87.5)	87 (90.6)	.648	.02
Diabetes (%)	11 (45.8)	46 (47.9)	.855	.04
Coronary artery disease (%)	11 (45.8)	45 (46.9)	.927	.05
Ever smoker (%)	11 (52.4)	42 (49.4)	.807	.04
Asthma (%)	2 (8.3)	7 (7.3)	.862	.02
Chronic obstructive pulmonary disease (%)	4 (16.7)	15 (15.6)	.900	.05
Cancer history (%)	8 (33.3)	35 (36.5)	.775	.04
Admission symptoms				
Fevers (%)	10 (43.5)	28 (31.1)	.263	-
Fatigue (%)	14 (63.6)	47 (52.2)	.335	-
Dyspnea (%)	11 (47.8)	53 (58.9)	.339	-
Cough (%)	9 (39.1)	45 (49.5)	.376	-
Vomiting (%)	5 (22.7)	23 (25.3)	.804	-
Diarrhea (%)	6 (27.3)	16 (17.8)	.315	-
Loss of appetite (%)	6 (27.3)	20 (22.2)	.615	-
Outcomes				
Need for oxygen (%)	14 (58.3)	64 (66.7)	.444	-
Need for mechanical ventilation (%)	4 (16.7)	10 (10.4)	.394	-
Intensive care unit admission (%)	8 (33.3)	32 (33.3)	1.000	-
Hospital length of stay	6 (4-12)	6 (4-9)	.664	-
All-cause death (%)	3 (12.5)	21 (21.9)	.304	-

AMD, absolute mean difference; HT, heart transplant; NHT, non-heart transplant.

analysis of HT patients was performed based on the time from transplant to COVID-19 diagnosis (before and after 1 year).

The primary outcome was all-cause mortality. Secondary outcomes included mechanical ventilation, intensive care unit admission, vasopressor need, dialysis, pneumonia, and 90-day readmission. PSM was performed to the nearest match, with a caliper of 0.1. Absolute mean differences of <0.1 were used to indicate minimal match imbalances. A 2-sided *P* value of <.05 indicated statistical significance.

The student *t* test was used for continuous normally distributed variables, reported as mean ± standard deviation, and the Mann-Whitney *U* test for non-normally distributed variables, reported as median (25-75th percentile). χ^2 test was used for categorical variables, reported as numbers (percentages). Kaplan-Meier analysis was used to determine the time to event with group comparison using the Log-Rank test. Cox proportional hazard models were used for covariate correction in time to event analysis. All statistical analyses were performed using SPSS (Version 25) and R via Jamovi (Version 2.2.5).

RESULTS

A total of 24 HT cases were matched to 96 NHT controls out of 11,481 patients. Five HT patients were within the first year of transplantation. Original reasons for HT, in descending order, were ischemic cardiomyopathy (41.7%), nonischemic cardiomyopathy (20.8%), familial cardiomyopathy (12.5%), significant valvulopathy (8.3%), myocarditis (8.3%), and amyloidosis (8.3%). A total of 20 (83.3%) HT patients were on tacrolimus, 23 (95.3%) on mycophenolate mofetil (MMF), 12 (50.0%) on prednisone, 3 (12.5%) on cyclosporine, and 1 (4.0%) on everolimus. Within the first 24 hours of admission, tacrolimus was held in 5 (23.8%) patients (dose-reduced in 5 and continued in 11), and MMF was held in 9 (42.9%) patients (dose-reduced in 4 and continued in 8). Only 2 transplant patients had their first COVID-19 vaccination in the study period. Baseline characteristics and admission symptoms can be seen in Table 1.

During a median follow-up of 72 days (26-107), 3 deaths (12.5%) occurred in the HT group and 21 (21.9%) in the NHT group; there was no statistically significant difference between the groups for the primary outcome of mortality on Log-Rank testing (*P* = .255) or univariable Cox regression analysis (hazard ratio (HR) 0.50, 95% confidence interval [CI] 0.15-1.69, *P* = .265). Furthermore, no difference was seen between groups for the secondary outcomes based on unadjusted odds ratios obtained via χ^2 testing. Univariable Cox regression analysis for mortality in the total sample (HT and NHT) showed age (HR 1.06, 95% CI 1.03-1.10, *P* < .001), cancer history (HR 3.19, 95% CI 1.40-7.24, *P* 006), high-flow nasal cannula use (HR 2.91, 95%CI 1.27-6.70, p== .012), and mechanical ventilation (HR 3.99, 95% CI 1.64-9.72, *P* = .002) to be significant; on a multivariable analysis model including these variables, only age (HR 1.08, 95%CI 1.04-1.13, *P* < .001) and mechanical ventilation (HR 4.76, 95% CI 1.61-14.11, *P* = .005) remained significant. On a subgroup analysis of HT patients alone, none of these variables were significant on univariable or multivariable Cox regression, including univariable analysis of immunosuppressant continuation, dose-reduction, or discontinuation. Further subgroup analysis using Log-rank testing to compare those with remote HT to HT within the prior 1

Table 2. Review of Previous Studies With Heart Transplant Recipients Who Acquired COVID-19

Authors	Year	Number of Heart Transplant Cases	Data	Conclusions
Case-Control Matched				
Chaudhry et al	2020	5 (among other solid organ transplants included)	−47 SOT COVID cases −100 NontransplantCOVID controls −Presenting symptoms −SOT: 55% −Diarrhea Case Fatality Rate: −23% SOT −25% Control	Transplant status by itself does not confer an increased risk for mortality.
Sharma et al	2021	9 (among other solid organ transplants included)	−41 SOT COVID cases −121 Non-Transplant COVID controls Presenting symptoms SOT: −43% Dyspnea −32% Cough −32% Fever Case fatality rates: −17% SOT −13% Control	The case fatality rate was similar between SOT recipients and their matched non-SOT controls with COVID-19.
Nonmatched Observational				
Latif et al	2020	28 (6 outpatients, 22 hospitalized)	Presenting symptoms: −83% Fever −91% Dyspnea or Cough −48% Gastrointestinal Case fatality rate: −25% HT	HT recipients displayed a higher case fatality rate than other reported populations.
Bottio et al	2021	47 (9 outpatients, 38 hospitalized)	Presenting symptoms: −81% Fever and hypoxemic respiratory failure Case fatality rate: −29.7% HT −15.4% Quoted general population	HT recipients are vulnerable to COVID-19 infection and display 2-fold higher mortality than the general population.
Case-Series				
Li et al	2020	2	Presenting symptoms: −Case 1: Fever, chills, fatigue, poor appetite, diarrhea −Case 2: Fever, fatigue, poor appetite −Both cases survived hospitalization	COVID-19 presentations in heart transplant recipients appear similar to those observed in nontransplant recipients.

HT, heart transplant; SOT, solid organ transplant.

year did not show a significant difference in mortality ($P = .355$) or 90-day readmission ($P = .841$).

DISCUSSION

Our PSM analysis suggests that HT patients hospitalized for COVID-19 do not show worse outcomes than their matched NHT cohorts. This is the largest study comparing COVID-19 positive HT patients to a matched NHT cohort. Other studies have integrated matching solid organ transplant groups to nontransplant groups acquiring COVID-19, of which a subset of the sample consisted of HT recipients [1,2]. Others have provided detailed reports on the characteristics and outcomes of HT without comparison to matched controls [3−5]. Table 2 provides a tabular representation of the studies.

Our results confirm that those of the aforementioned analyses, which displayed similar mortality rates and mechanical ventilation requirements in the organ transplant recipients compared with nontransplant controls despite decreases in immunosuppression [1−3,6,7]. This suggests that transplant status does not necessarily confer an increased mortality risk. However, results from previous meta-analyses and multicenter case series targeting the HT population have demonstrated higher case fatality rates (25.6% and 29.7%) than those of the general population, seemingly attributed to initial disease severity and more severe comorbidities [4,5,8]. These studies, however, were not matched in the same manner, and variability could be explained by demographic differences and limited health resources at the height of the pandemic surge.

Limitations

Our study has its limitations in that it is a retrospective single-center study with a small sample size that confines our ability to make a definitive statement about the impact of COVID-19 on the HT population and the ability to evaluate the effectiveness of reducing immunosuppression on admission. In addition, we had limited follow-up time and mostly accounted for patients with

more severe COVID-19 infections. Also, the advent of the vaccine occurred toward the end of our study period and was not accounted for. Future studies with multicenter data that incorporate the subsequent COVID-19 variants (eg, Delta and Omicron) and the impact of long COVID-19 would be intriguing to examine on this patient population. However, our PSM analysis demonstrating a similar mortality profile remains a strength of our study. Further studies are required to compare COVID-19 outcomes in HT patients at full vs reduced doses of immunosuppression while also taking into account vaccination status.

CONCLUSIONS

Contrary to what may be expected, mortality was not increased within the first year of transplantation, which is in line with a recent study that matched kidney transplantation recipients to nontransplant cohorts [2]. While this may be an artifact of the small numbers studied, it could also signify that poor outcomes could be more related to the burden of chronic disease rather than the degree of chronic immunosuppression. This is not to say that transplantation patients should be treated with lesser precaution; however, it lends credence to the idea that HT should not be delayed to reduce morbidity and mortality of patients on waiting lists.

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