Risk Factors Associated With COVID-19 Mortality in Heart Transplant Recipients: A United Network for Organ Sharing Database Analysis

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The coronavirus disease-2019 (COVID-19) pandemic has had wide-ranging impacts on American healthcare delivery, with myriad resources being diverted to prevention in vulnerable populations.[1] The immunocompromised, notably solid organ transplant recipients (SOTRs), remains susceptible to severe COVID-19 disease and death.[2] Accordingly, SOTRs have been prioritized for COVID-19 vaccination and, more recently, booster immunization. Indeed, chronic immunosuppression may blunt vaccine efficacy due to its deleterious effect on humoral immunity, which is necessary for production of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) neutralizing antibodies.[3] With the constant threat of emerging variants containing mutations that render vaccine-elicited antibodies ineffective, those with low titers to begin with remain especially vulnerable. Despite an abundance of clinical data on COVID-19 in the general population and among those with comorbid conditions, granular data on COVID-19 in heart transplant (HTx) recipients remain limited. Herein, we report the risk factors associated with COVID-19 mortality in HTx recipients.

The United Network for Organ Sharing (UNOS) database was queried for all HTx recipients greater than or equal to 18 years of age who expired between January 31, 2020, and January 6, 2022. January 31, 2020 represents the date of the Public Health Emergency declaration.[4] Recipients with COVID-19 listed as a primary, secondary, or tertiary cause of death were considered to have COVID-19–related death; those without were considered controls.

Demographics of cases and controls were compared using Wilcoxon rank-sum and χ^2 tests for continuous and categorical variables, respectively. Univariate odds ratios with 95% confidence intervals were calculated for 37 recipient characteristics to assess the relationship between potential risk factors and COVID-19–related death. Variables with significant univariate odds ratios or those of biological interest were included in a multivariable logistic regression model. Analyses were performed in Stata version 17 (College Station, TX). A two-tailed p-value ≤0.05 was considered statistically significant. Given the UNOS database is publicly available and deidentified, this study was deemed exempt from Institutional Review Board approval.

During the study period, 3,002 deceased HTx recipients were identified, of which 439 were cases. Cases and controls were similar regarding sex, blood type, and ventilator dependence. Cases were significantly older ($p = 0.005$), had a higher body mass index (BMI) ($p = 0.005$) more likely to be Black or Hispanic ($p < 0.001$), and were more likely to have a history of cigarette use ($p = 0.01$), diabetes ($p < 0.001$), and ischemic heart failure ($p = 0.003$) (Table 1). Seven characteristics including age, BMI, ethnicity, region, ischemic heart failure, diabetes, cigarette use, and bridging with left ventricular assist device were significantly associated with COVID-19–related death on univariate analysis and included in the final model. Compared with the Northeast region, the West region was significantly associated with decreased likelihood of COVID-19–related death on univariate analysis; therefore, region was included in the final multivariable model as well. Chronic steroid exposure at HTx was also included due to biological interest. In multivariable logistic regression, increasing age, identifying as Black and Hispanic, presence of diabetes, history of smoking, and chronic steroid use at HTx were independently associated with COVID-19–related death (Figure 1).

In this study, we identify increasing age, minority racial status, history of diabetes, cigarette use, and chronic steroids before HTx as risk factors for COVID-19–related death in HTx recipients. While several studies have also associated age, diabetes, tobacco use, and immunosuppression with increased risk of COVID-19 mortality in the general population,[5,6] our results extend these risk factors to the heart transplant community specifically. Increasing age up to 59 years appears to be associated with a linear increase in odds of COVID-19–related death, after which odds plateau. This attenuation is likely related to selection bias, as recipients transplanted greater than or equal to 60 years of age tend to be less critically ill than their younger counterparts, as evidenced by lower rates of intensive care requirement.[7] Notably, recipients greater than or equal to 70 years display lower rates of chronic obstructive pulmonary disease compared with those aged 18–59 years.[7] Although COVID-19 vaccination rates are highest among older adults nationwide, the applicability of these results to HTx recipients remains unclear given COVID-19 vaccine prioritization of SOTRs.

In concordance with studies in the general population, we recognize minority race as a significant risk factor for mortality in HTx recipients. While the disproportionate impact of COVID-19 among minorities in the United States is likely

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Table 1. Demographic Characteristics Among Adult HTx Recipients and Donors Included in the Study

Recipient	Cases (n = 439)	Controls (n = 2,563)	*p*
Age, years	56.7 ± 9.4	54.3 ± 12.1	**0.005**
Female sex	98 (22.3)	606 (23.6)	0.55
BMI, kg/m^2	28.1 ± 4.6	27.4 ± 5.0	**0.005**
Blood type O	165 (37.6)	1,023 (39.9)	0.36
Ethnicity			
White	265 (60.4)	1,727 (67.4)	**<0.001**
Black	105 (23.9)	556 (21.7)	
Hispanic	54 (12.3)	172 (6.7)	
Other	15 (3.4)	108 (4.2)	
Region			
Northeast	110 (25.1)	545 (21.3)	0.24
Southeast	159 (36.2)	944 (36.8)	
Midwest	105 (23.9)	623 (24.3)	
West	65 (14.8)	451 (17.6)	
Ischemic HF etiology	194 (44.2)	917 (35.8)	**0.003**
Diabetes mellitus	181 (41.2)	763 (29.8)	**<0.001**
Cerebrovascular accident	29 (6.6)	146 (5.7)	0.50
Cigarette use	202 (46.0)	984 (38.4)	**0.010**
Chronic steroid use	47 (10.7)	200 (7.8)	0.066
LVAD at HTx	151 (34.4)	748 (29.2)	**0.028**
IABP at HTx	37 (8.4)	252 (9.8)	0.36
Independent (functional status)	40 (9.1)	239 (9.3)	0.89
Ventilator dependent	10 (2.3)	55 (2.2)	0.86
Inotrope dependent	185 (42.1)	1,011 (39.5)	0.29
Retransplant	15 (3.4)	73 (2.9)	0.51
Multiorgan transplant	28 (6.4)	142 (5.5)	0.48
Kidney	26 (5.9)	125 (4.9)	
Liver	2 (0.5)	17 (0.7)	
Years from transplant to death	9.5 ± 7.4	9.7 ± 8.1	0.60
COVID as cause of death (cases only)			
Primary	402 (91.6)	-	
Secondary	26 (5.9)	-	
Tertiary	11 (2.5)	-	
Donor			
Age, years	32.3 ± 11.5	32.2 ± 11.7	0.75
Female sex	126 (28.7)	734 (28.6)	0.98
Sex mismatch	98 (22.3)	620 (24.2)	0.40
BMI, kg/m^2	27.7 ± 6.3	27.3 ± 5.9	0.24
Blood type O	207 (47.2)	1,319 (51.5)	0.10
Ethnicity			
White	304 (69.3)	1,683 (65.7)	0.49
Black	64 (14.6)	411 (16.0)	
Hispanic	60 (13.7)	385 (15.0)	
Other	11 (2.5)	84 (3.3)	
Diabetes mellitus	13 (3.0)	81 (3.3)	0.82
Cocaine abuse	72 (16.4)	425 (16.6)	0.77
Alcohol abuse	61 (17.3)	326 (16.3)	0.46
Smoking	74 (17.2)	415 (16.7)	0.33
Hypertension	55 (12.8)	369 (14.8)	0.50
Baseline LVEF	61.7 ± 6.9	61.6 ± 7.2	0.91
Ischemic time ≥4 hours	69 (15.7)	499 (19.5)	0.11

BMI, body mass index; HF, heart failure; HTx, heart transplant; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.

Bold indicates significance of $p<0.05$.

mediated by higher rates of risk factors such as diabetes, cardiovascular disease, and pulmonary disease, the effect is compounded by lower vaccination rates and decreased access to care among disadvantaged populations.[8]

We also report chronic corticosteroid use before HTx as a significant risk factor for COVID-19–related death. While corticosteroids have proven effective in mitigating COVID-19 severity,[9] they may compromise COVID-19 vaccine efficacy by blunting humoral immunity.[10] Further study is required to understand the interplay between immunosuppression, vaccine efficacy, and severe disease prevention.

As a retrospective analysis of UNOS data, it is important to note the limitations of this study. There are several variables potentially relevant to this analysis, which are not available in the UNOS database. Given that vaccination is shown to improve mortality rates in the general population, knowledge of vaccination status likely adds insight to this analysis. Notably, COVID-19 vaccination status is unavailable in the UNOS database. While these data are not concretely available, several transplant organizations strongly recommend that SOTRs be vaccinated. Second, granular data regarding immunosuppressive regimen, or the decision of treatment used during COVID-19 infection, were not available for analysis. Both variables may have a significant effect on a patient's outcome, especially, earlier in the pandemic when the effects of treatment regimens were more uncertain. As such, our analysis is limited by these unknown variables.

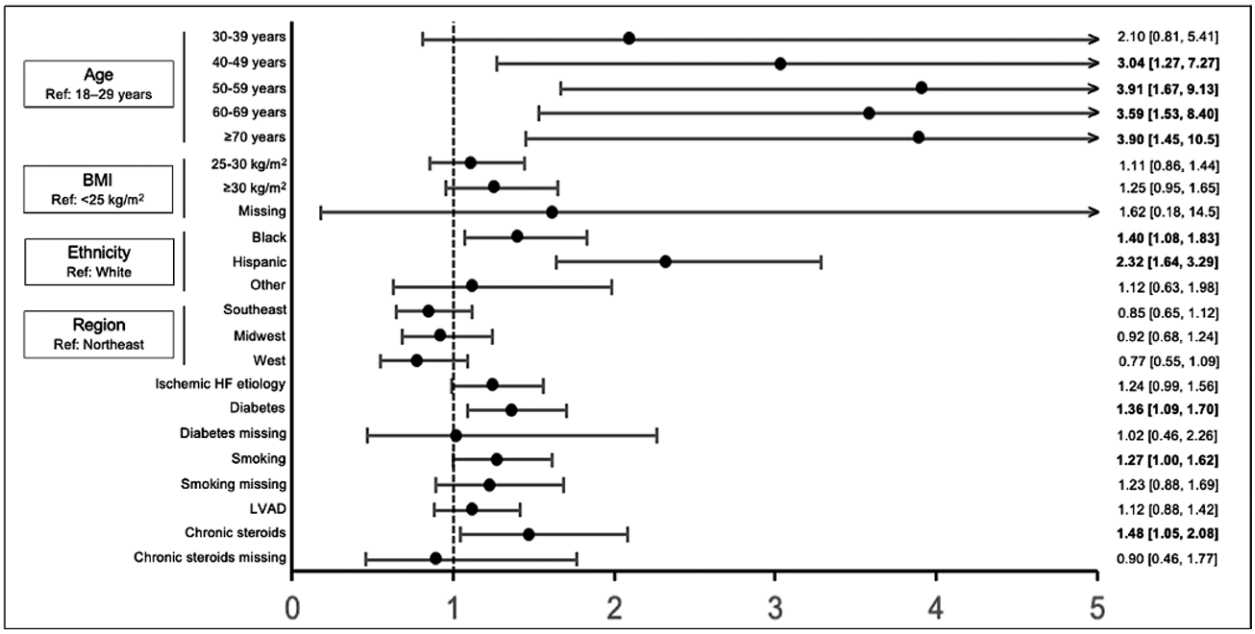

Figure 1. Multivariable predictors of COVID-19–related death among adult HTx recipients. Point estimates are displayed with associated 95% confidence intervals. Regions are comprised of the following UNOS regions: Northeast: 1,2,9; Southeast: 3, 4, 11; Midwest: 7, 8, 10; West: 5, 6. BMI, body mass index; COVID-19, Coronavirus Disease-2019; HF, heart failure; HTx, heart transplant; LVAD, left ventricular assist device; UNOS, United Network for Organ Sharing.

Identifying risk factors for COVID-19 mortality in HTx recipients may prove critical as social distancing and masking regulations are lifted. Specifically, transplant centers may seek to leverage this data to ensure pre-op vaccination in individuals with noted risk factors. Furthermore, assessing the risk of mortality from COVID-19 may inform the intensity of follow-up and careful consideration of patient management postoperatively. While the threat of emerging SARS-CoV-2 variants persists, HTx recipients with increased COVID-19 mortality risk should also be duly informed.

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