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Heart transplantation for COVID-19 myopathy in the United States

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Title: Heart transplantation for COVID-19 myopathy in the United States

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Non-standard abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; UNOS, United Network for Organ Sharing; OPTN, Organ Procurement and Transplant Network

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Abstract

Evidence on characteristics and outcomes of patients undergoing heart transplantation for coronavirus disease 2019 (COVID-19) associated cardiomyopathy is limited to case reports. Of all 6332 patients aged ≥18 years undergoing heart transplant from July 2020 through May 2022 in the United Network for Organ Sharing database, 12 (0.2%) patients had COVID-19 myocarditis and 98 (1.6%) patients with the same level of care had non-COVID-19 myocarditis. Their median age was 49 (range 19-74) years. All patients were hospitalized in the intensive care unit and 92.7% (n=102) were on life support prior to transplantation. No patients with COVID-19 myocarditis required ventilation whilst waitlisted. Survival free from graft failure was 100% among COVID-19 patients and 88.5% among non-COVID-19 patients at a median of 257 (range 0-427) days post-transplant. These findings indicate that transplantation is rarely performed for COVID-19 related cardiomyopathy in the United States, yet early outcomes appear favorable in select patients.

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Introduction:

Myocardial injury occurs in approximately 20% of patients hospitalized with coronavirus disease 2019 (COVID-19) and is associated with a four-fold adjusted risk of death.[1,2] Optimal management for these patients remains unclear. National registry data indicates that mortality among COVID-19 patients requiring extracorporeal membrane oxygenation (ECMO), of which approximately 20% do not have acute respiratory distress syndrome, approaches 40%.[3] Evidence on characteristics and outcomes of patients undergoing heart transplantation for COVID-19 associated cardiomyopathy refractory to circulatory support is limited to case reports.[4]

Methods:

The United Network for Organ Sharing (UNOS) database, which includes information on all Organ Procurement and Transplant Network (OPTN) transplant recipients, was queried for patients aged ≥18 years with undergoing heart transplantation from July 2020 through May 2022 (n=6332). Patients with a waitlist or transplant diagnosis of COVID-19 cardiomyopathy (n=12, 0.2%) were compared to those with a diagnosis of non-COVID-19 myocarditis with the same level of care (n=98, 1.6%) (hospitalized in the intensive care unit). Variables were defined according to UNOS standard definitions. This study was approved by the Institutional Review Board at Cedars-Sinai Medical Center, with a waiver of informed consent.

Results:

Recipient characteristics stratified by COVID-19 status are outlined in Table 1. The overall median recipient age was 49 (range 19-74) years and 36 (32.7%) were female (one with COVID-19). Non-white race was observed in 9 (75.0%) recipients with COVID-19 and 44 (44.9%) with non-COVID-19 myocarditis. Patients with and without COVID-19 were

predominantly allocated the highest (n=5, 41.7% and n=28, 28.6% respectively) or second highest (n=7, 68.3% and n=59, 60.2% respectively) OPTN priority status out of a possible six. All patients were hospitalized in the intensive care unit and 102 (92.7%) were on life support prior to transplantation: 6 (50.0%) COVID-19 and 21 (21.4%) non-COVID-19 patients received ECMO; 5 (41.7%) COVID-19 and 38 (38.8%) non-COVID-19 patients had an intra-aortic balloon pump; and 5 (41.7%) COVID-19 and 55 (56.1%) non-COVID-19 patients received inotropic support. No patients with COVID-19 cardiomyopathy required mechanical ventilation at waitlist registration or transplantation. The median waitlist time was 17 (range 2-125) days for COVID-19 and 10 (range 1-2163) days for non-COVID-19 patients. Donor characteristics are outlined in Table 2. The overall median donor age was 29.5 (range 13-56) years and 25 (22.7%) were female (one for recipients with COVID-19). Of the 104 donors with an available COVID-19 nucleic acid test, 3 (2.9%) donors had a positive result, these were donors for non-COVID-19 myocarditis candidates. The overall median ischemic time was 3.4 (range 1.3-6.5) hours.

Immunosuppression induction in COVID-19 patients comprised basilixumab and corticosteroids (n=5, 41.7%); anti-thymocyte globulin and corticosteroids (n=2, 16.7%); an undisclosed immunosuppressant and corticosteroids (n=1, 8.3%); corticosteroids alone (n=3, 25.0%) or none documented (n=1, 8.3%). A heart-liver transplant was performed in 1 (8.3%) COVID-19 patient (for cirrhosis), a heart-kidney transplant was performed in 1 (8.3%) COVID-19 and 5 (5.1%) non-COVID-19 patients.

Postoperatively, 2 (16.7%) COVID-19 patient and 15 (15.3%) non-COVID-19 patients had an acute rejection episode, 9 (9.2%) non-COVID-19 patients and 0 (0%) COVID-19 patients required treatment with an additional anti-rejection agent. New dialysis was required in 1 (8.3%) COVID-19 and 8 (8.6%) non-COVID-19 patients. No other in-hospital adverse events were

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captured in COVID-19 patients, but 3 (3.1%) non-COVID-19 patients had a stroke and 1 (1.0%) required a pacemaker. The median post-operative length of stay was 21 (range 9-50) days among COVID-19 and 16 (range 7-375) days among non-COVID-19 patients. Survival free from graft failure was 100% (n=12) among COVID-19 and 93.9% (n=92) among non-COVID-19 patients at a median follow-up of 276 (range 0-370) and 257 (range 0-427) days respectively. Graft failure-free survival among non-COVID-19 patients at 30 days, 90 days and 6 months was 96.8% (95% confidence interval (CI) 93.3-100.0), 96.8% (95% CI 93.3-100.0), and 92.8% (95% CI 87.2-98.4) respectively. Immunosuppression maintenance regimen in COVID-19 patients comprised tacrolimus, mycophenolate mofetil and corticosteroids (n=7, 58.3%); tacrolimus and mycophenolate mofetil (n=4, 33.3%); or tacrolimus and corticosteroids (n=1, 8.3%).

Discussion

This national registry analysis confirms that heart transplantation for COVID-19 cardiomyopathy is rarely performed, accounting for 0.2% of contemporary transplant practice in the United States. Despite a high risk pre-operative profile, patients undergoing transplant for COVID-19 cardiomyopathy infrequently experienced in-hospital complications and all were alive without graft failure at an average follow-up of 9 months post-transplant.

A recent multi-center study of COVID-19 associated myocarditis reported that over half of patients did not have COVID-19 associated pneumonia.[5] The COVID-19 patients undergoing transplantation in this study similarly did not require mechanical ventilation when waitlisted. We therefore suspect that the ECMO was required for cardiac rather than respiratory support. These findings indicate that this population may represent a unique entity of COVID-19 infection, with predominant cardiomyopathy rather than respiratory features. Patients with concomitant pneumonia in the aforementioned study were more likely to require mechanical circulatory

support or experience in-hospital mortality than those with isolated myocarditis.[5] The absence of heart-lung transplants in this study suggests that these patients may not be considered transplant candidates. Transplant centers may encounter patients with COVID-19 cardiomyopathy, who should be evaluated as other non-COVID-19 candidates, we should proceed cautiously and evaluate transplant protocols as we learn more about the disease.

This study is limited by its retrospective nature, small sample size and limited follow-up period. Information is lacking on the COVID-19 testing assay used, mechanism of diagnosis of COVID-19 myopathy and patients' vaccine status. The use of a registry precluded granular information on COVID-19 symptomology and management, including time from diagnosis to listing, COVID-19 status at transplant, COVID-19 treatment pre-transplant and COVID-19 monitoring post-transplant. A minority of COVID-19 patients in this series were classified as having active myocarditis. Heart transplantation is generally not performed in active myocarditis, we suspect the COVID-19 patients developed cardiomyopathy from residual myocardial damage secondary to myocarditis.[6] Genomic sequencing results were not available, but the predominant COVID-19 variants during the study period were Alpha, Delta, Omicron BA.1 and Omicron BA.2.[7] The clinical implications of these findings may be of limited relevance to newly emerging variants of concern.

Heart transplantation is rarely performed for COVID-19 related cardiomyopathy in the United States, yet early outcomes appear favorable in select patients. This cohort may represent a unique entity of COVID-19 infection without prominent lung pathology.

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Author Contributions:

Study design: George Gill, Amy Roach, Dominic Emerson, Joanna Chikwe

Data analysis: George Gill, Amy Roach, Georgina Rowe

Data interpretation: All authors

Writing of manuscript: George Gill, Amy Roach, Georgina Rowe, Joanna Chikwe

Critical analysis of manuscript: All authors

Final approval of the manuscript: All authors

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Table 1: Recipient characteristics of patients undergoing heart transplantation for COVID-19 cardiomyopathy or non-COVID-19 myocarditis.

Recipient Characteristics	**COVID-19 cardiomyopathy N=12**	**Non-COVID-19 cardiomyopathy N=98**
Median age, years (range)	46 (24-55)	50 (19-74)
Male gender (%)	11 (100.0)	63 (64.3)
Median weight, kg (range)	84.2 (41.1-103.4)	76.4 (47.9-152.1)
Ethnicity (%)		
Black	4 (33.3)	23 (23.5)
White	3 (25.0)	54 (55.1)
Hispanic	2 (16.7)	16 (16.3)
Other	3 (25.0)	5 (5.1)
Diagnosis (%)		
COVID-19: history of myocarditis	9 (75.0)	
COVID-19: active myocarditis	3 (25.0)	
Non-viral myocarditis		44 (53.0)
Non-COVID-19 viral myocarditis		39 (47.0)
Viral serology status		
Cytomegalovirus positive (%)	8 (66.7)	51 (52.0)
HBV core antibody positive (%)	0 (0)	5/96 (5.2)
HBV surface antigen positive (%)	0 (0)	0/97 (0)
HCV seropositive (%)	0 (0)	2 (2.0)
Diabetes mellitus (%)	3 (25.0)	16 (16.3)
Median Karnofsky performance status*, % (range)	20 (10-20)	20 (10-60)
OPTN priority status (%)		
Status 1	5 (41.7)	28 (28.6)
Status 2	7 (58.3)	59 (60.2)
Status 3	0 (0)	11 (11.2)
Any Life support Measures (%)	11 (91.7)	91 (92.9)
Extra corporeal membrane oxygenation (%)	6 (50.0)	21 (21.4)
Intra-aortic balloon pump (%)	5 (41.7)	38 (38.8)
Inotropes (%)	5 (41.7)	56 (56.1)
Ventricular assist device in situ (%)	2 (16.7)	30 (30.0)
Mechanical Ventilation (%)	0 (0)	11 (11.2)
Dialysis whilst on waitlist (%)	1 (8.3)	7 (7.1)
Transfusion pre-transplant (%)	4 (33.3)	21 (21.4)

*Functional status missing in 4 patients with non-COVID-19 myopathy

COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; OPTN, Organ Procurement and Transplant Network

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Table 2: Donor characteristics for patients undergoing heart transplantation for COVID-19 cardiomyopathy or non-COVID-19 myocarditis.

Donor Characteristics	**COVID-19 cardiomyopathy N=12**	**Non-COVID-19 cardiomyopathy N=98**
Median age, years (range)	35 (20-48)	29 (13-56)
Male gender (%)	11 (91.7)	74 (75.5)
Median weight, kg (range)	81.7 (72.6-103.8)	78.4 (52.2-179.8)
ABO match level (%)		
Identical	10 (83.3)	71 (72.4)
Compatible	2 (16.7)	27 (27.6)
Diabetes mellitus (%)	1/12 (8.3)	6/98 (6.3.1)
Hypertension (%)	2/12 (16.7)	12/98 (12.5)
Median LVEF, % (range)	60.0 (55.0-79.0)	60.0 (38.0-78.0)
COVID-19 nucleic acid test result (%)	11	93
Positive	0 (0.0)	3 (3.2)
Pending	0 (0.0)	1 (1.1)
Negative	11 (100.0)	89 (95.7)
Cause of death (%)		
Anoxia	8 (66.7)	46 (46.0)
Head trauma	3 (25.0)	43 (43.0)
Stroke	1 (8.3)	9 (9.0)
Other	0 (0)	2 (2.0)
Median ischemic time, hours (range)	3.3 (2.1-4.7)	3.4 (1.3-6.5)

COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction

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