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Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019

Farhana Latif, MD; Maryjane A. Farr, MD, MSc; Kevin J. Clerkin, MD, MSc; Marlena V. Habal, MD; Koji Takeda, MD, PhD; Yoshifumi Naka, MD, PhD; Susan Restaino, MD; Gabriel Sayer, MD; Nir Uriel, MD, MSc

IMPORTANCE Recipients of heart transplant (HT) may be at increased risk of adverse outcomes attributable to infection with coronavirus disease 2019 (COVID-19) because of multiple comorbidities and clinically significant immunosuppression.

OBJECTIVE To describe the characteristics, treatment, and outcomes of recipients of HT with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This case series from a single large academic heart transplant program in New York, New York, incorporates data from between March 1, 2020, and April 24, 2020. All recipients of HT followed up by this center who were infected with COVID-19 were included.

INTERVENTIONS Heart transplant and a confirmed diagnosis of COVID-19.

MAIN OUTCOMES AND MEASURES The primary measure was vital status at end of study follow-up. Secondary measures included patient characteristics, laboratory analyses, changes to immunosuppression, and treatment administered for COVID-19.

RESULTS Twenty-eight patients with HT received a confirmed diagnosis of COVID-19. The median age was 64.0 (interquartile range [IQR], 53.5-70.5) years, 22 (79%) were men, and the median time from HT was 8.6 (IQR, 4.2-14.5) years. Comorbid conditions included hypertension in 20 patients (71%), diabetes in 17 patients (61%), and cardiac allograft vasculopathy in 16 patients (57%). Twenty-two participants (79%) were admitted for treatment, and 7 (25%) required mechanical ventilation. Most (13 of 17 [76%]) had evidence of myocardial injury (median high-sensitivity troponin T, 0.055 [IQR, 0.0205-0.1345] ng/mL) and elevated inflammatory biomarkers (median peak high-sensitivity C-reactive protein, 11.83 [IQR, 7.44-19.26] mg/dL; median peak interleukin 6, 105 [IQR, 38-296] pg/mL). Among patients managed at the study institution, mycophenolate mofetil was discontinued in 16 patients (70%), and 6 (26%) had a reduction in the dose of their calcineurin inhibitor. Treatment of COVID-19 included hydroxychloroquine (18 patients [78%]), high-dose corticosteroids (8 patients [47%]), and interleukin 6 receptor antagonists (6 patients [26%]). Overall, 7 patients (25%) died. Among 22 patients (79%) who were admitted, 11 (50%) were discharged home, 4 (18%) remain hospitalized at the end of the study, and 7 (32%) died during hospitalization.

CONCLUSIONS AND RELEVANCE In this single-center case series, COVID-19 infection was associated with a case fatality rate of 25% in recipients of HT. Immunosuppression was reduced in most of this group of patients. Further study is required to evaluate the optimal approach to management of COVID-19 infection in the HT population.

Author Affiliations: Division of Cardiology, Department of Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Latif, Farr, Clerkin, Habal, Restaino, Sayer, Uriel); Division of Cardiac Surgery, Department of Surgery, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Takeda, Naka).

Corresponding Author: Nir Uriel, MD, MSc, Division of Cardiology, Department of Medicine, Columbia University Irving Medical Center, Weill Cornell Medicine, 622 W 168th St, PH 4-129, New York, NY 10032 (nu2126@cumc.columbia.edu).

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Coronavirus disease 2019 (COVID-19) is a pandemic affecting more than 3 million people worldwide and carrying a case fatality rate exceeding 7% as of early May 2020.[1] New York, New York, has emerged as the most recent epicenter of the disease, with more than 150 000 confirmed cases and nearly 11 000 fatalities (as of April 26, 2020).[1] Preexisting cardiovascular diseases, such as hypertension, coronary artery disease, and diabetes, have been associated with an increased risk for COVID-19.[2-4] Disease severity appears to be driven not only by viral invasion and proliferation but also by an intense immune response marked by cytokine storm, myocardial injury, and death.[5,6] Recipients of heart transplant (HT) may be at an increased risk for infection and adverse outcomes with COVID-19 infection because of a number of comorbidities that are common following heart transplant, including hypertension, diabetes, and cardiac allograft vasculopathy. Moreover, while all require maintenance immunosuppression that predisposes recipients to a greater infectious risk, immunosuppression has also been theorized to be protective from cytokine storm. Preliminary case reports[7,8] have not indicated a disproportionate outcome of COVID-19 on the posttransplant population, and a survey[9] from China did not find an increased risk of infection among recipients of HT. In this article, we present a large case series of recipients of HT with COVID-19 and describe their presentation, disease course, outcomes, and immunosuppression management. The aim of this case series is to describe the outcomes of recipients of HT who are chronically immunosuppressed and develop COVID-19 and raise important questions about the role of the immune system in the disease process.

Key Points

Question What are the characteristics and outcomes of patients with heart transplant who are infected with coronavirus disease 2019 (COVID-19)?

Findings In this case series of 28 patients who had received heart transplant in a large academic center, the case fatality rate among patients infected with COVID-19 was 25%. Cardiovascular comorbidities were frequent in this population, and immunosuppressive therapy was reduced in most patients.

Meaning Recipients of heart transplant are at high risk for severe complications from coronavirus disease 2019 infection; management of this population is complex and should take place in a transplant center.

Methods

We retrospectively reviewed all adult recipients of HT (>18 years of age) followed at a large academic center in New York, New York. Those who received a laboratory diagnosis of COVID-19 were included in the study. Laboratory data were collected for patients hospitalized in our health system. Treatment data were collected for those admitted to our hospital or managed by our program as outpatients. Outcomes and follow-up were recorded for all patients through April 24, 2020. All continuous data are presented as medians with interquartile ranges (IQRs). Analyses were performed using SAS version 9.4 (SAS Institute Inc). This study was approved by the Columbia University Irving Medical Center institutional review board. A waiver of consent was granted to protect the safety of the staff, since consent would have required direct exposure while patients were actively infected with COVID-19. All data were deidentified following collection.

Results

In this cohort of recipients of HT (N = 803), we identified 28 who had presented for acute care for COVID-19 disease over a 6-week period. The median age of patients with COVID-19 was 64.0 (IQR, 53.5-70.5) years, 22 (79%) were men, and the median time from transplant was 8.6 (IQR, 4.2-14.5) years (**Table 1**). Twenty patients (71%) had hypertension, 17 of 28 (61%) had diabetes mellitus, 7 of 28 (25%) were obese (body mass index [calculated as weight in kilograms divided by height in meters squared] >30), 10 of 28 (36%) had stage IV or greater chronic kidney disease (with 5 [18%] on hemodialysis), 16 of 28 (57%) had cardiac allograft vasculopathy, and 4 of 28 (14%) had preexisting allograft dysfunction. Disease presentation included fever (19 [83%]), dyspnea or cough (21 [91%]), and gastrointestinal symptoms (11 [48%]).

Twenty-two patients (79%) were admitted, and 6 (21%) were managed as outpatients. Among the inpatients, 7 required admission to the intensive care unit. Seventeen were admitted to the study hospital and thus had complete laboratory data for analysis. Laboratory results are summarized in **Table 2**. The median (IQR) white blood cell count was 4900 (3000-8900) per microliter (to convert to $\times 10^9$/L, multiply by 0.001), with a median (IQR) absolute lymphocyte count of 600 (300-800) per microliter (to convert to $\times 10^9$/L, multiply by 0.001). Evidence of myocardial injury was present in 13 patients (77%), and the median peak high-sensitivity troponin T level was 0.055 (0.0205-0.1345) nanograms per milliliter (to convert to micrograms per liter, multiply by 1.0). Inflammatory parameters were markedly elevated, in that high-sensitivity C-reactive protein was greater than normal in all patients, with a median (IQR) peak of 11.83 (7.44-19.26) milligrams per deciliter (to convert to milligrams per liter, multiply by 10); interleukin 6 was elevated in 15 patients (88%), with a median (IQR) peak of 105 (38-296) picograms per milliliter; and D-dimer was greater than 1 microgram per milliliter in 14 patients (82%). Seven patients had an echocardiogram during hospitalization. When compared with the most recent echocardiogram, left ventricular ejection fraction was unchanged in 5 patients, improved in 1 patient, and decreased in 1 patient. Notably, both patients with changes from baseline had preexisting allograft dysfunction.

Supplemental oxygen was required in 20 of the hospitalized patients (91%), 7 of these patients required intubation (5 at outside hospitals and 2 at our institution), and de novo dialysis was required in 3 patients. Baseline immunosuppressive medications included calcineurin inhibitors in 27 patients (96%), mycophenolate mofetil in 19 (68%), proliferation signal

Table 1. Patient Characteristics, Symptoms, Treatment, and Outcomes

Demographics	No. (%)
Total, No.	28
Age, median (IQR), y	64 (53.5-70.5)
Male	22 (79)
Time posttransplant, median (IQR), y	8.6 (4.2-14.5)
BMI, median (IQR)	26.0 (23.5-30.7)
Hypertension	20 (71)
Diabetes	17 (61)
Lung disease	10 (36)
Malignant condition	5 (18)
Chronic kidney disease[a]	10 (36)
Maintenance immunosuppression	
Total, No.	28
Tacrolimus	22 (79)
Cyclosporine	5 (18)
Mycophenolate mofetil	19 (68)
Proliferation signal inhibitor	5 (18)
Prednisone	19 (68)
No. of immunosuppressive medications	
1	3 (11)
2	8 (29)
3	16 (57)
4	1 (3)
Symptoms	
Total, No.	23
Fever	19 (83)
Chest pain	5 (22)
Shortness of breath or cough	21 (91)
Gastrointestinal symptoms	11 (48)
Treatment	
Total inpatients and outpatients, No.	23
Hydroxychloroquine	18 (78)
Tocilizumab	6 (26)
Glucocorticoids	8 (47)
Reduction in immunosuppression medications	19 (83)
Mycophenolate mofetil held	16 (70)
Outcome	
Total, No.	28
Overall mortality	7 (25)
Overall survival	21 (75)
Hospitalized	22 (79)
In-hospital mortality	7 (32)
Discharged	11 (50)
Remain hospitalized	4 (18)
Managed as outpatient	6 (21)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Defined by a glomerular filtration rate less than 30 and presence of hemodialysis.

Table 2. Laboratory Data of 17 Patients of Heart Transplant Admitted at the Study Institution With Coronavirus Disease 2019 Infection

Laboratory data	Median (IQR)
Total, No.	17
Creatinine, mg/dL	
Admission	3.3 (1.5-4.8)
Peak	4.7 (1.5-8.3)
High-sensitivity troponin T, ng/mL	
Peak	0.055 (0.0205-0.1345)
Peak >0.022 ng/mL, No. (%)	13 (77)
D-dimer	
Admission, µg/mL	1.0 (0.7-1.7)
Admission >1.0 µg/mL, No. (%)	10 (59)
Peak, µg/mL	2.0 (1.3-4.8)
Peak >1.0 µg/mL, No. (%)	14 (82)
High-sensitivity C-reactive protein, mg/dL	
Admission	9.9 (4.78-11.74)
Peak	11.83 (7.44-19.26)
Erythrocyte sedimentation rate, mm/h	
Admission	60 (50-75)
Peak	59 (80-101)
Interleukin 6	
Admission, pg/mL	33 (9-84)
Admission >5 pg/mL, No. (%)	13 (76)
Peak	105 (38-296)
Peak >5 pg/mL, No. (%)	15 (88)
Peak procalcitonin, ng/mL	0.6 (0.2-2.7)
Ferritin, ng/mL	
Peak	1079 (622-2719)
Peak >1000 ng/mL, No. (%)	9 (53)
White blood cells on admission, cells/µL	4900 (3000-8900)
Absolute lymphocyte count on admission, cells/µL	600 (300-800)

SI conversion factors: To convert creatinine to µmol/liter, multiply by 88.4; troponin T to µg/L, multiply by 1.0; D-dimer to nmol/L, multiply by 5.476; C-reactive protein to mg/L, multiply by 10; ferritin to µg/L, multiply by 1.0; lymphocytes and white blood cell count to $\times 10^9$/L, multiply by 0.001.

inhibitors in 5 (18%), and corticosteroids in 19 (68%). During infection with COVID-19, mycophenolate mofetil was discontinued in 16 of 23 patients (70%) and the calcineurin inhibitor dosage was reduced in 6 patients (26%). Twenty-three patients (87%) received treatments directed at COVID-19: high-dose corticosteroids (8 of 23 [47%]), hydroxychloroquine (18 of 23 [78%]), or an interleukin 6 receptor antagonist (6 of 23 [26%]) (**Figure**).

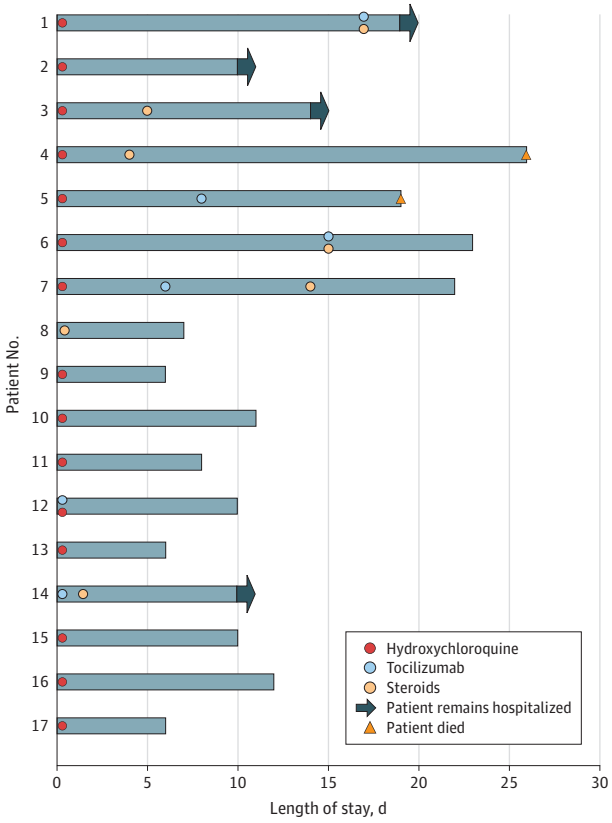
None of the patients in our cohort experienced an episode of clinically overt rejection during this period.

Among all patients with HT diagnosed with COVID-19, 22 (79%) were hospitalized and 7 (25%) died (Table 1). Of the hospitalized patients, 11 (50%) were discharged, 4 (18%) remain hospitalized at the end of the study, and 7 (50%) died in the hospital. Six patients (21%) were treated as outpatients. The mortality rate of the patients admitted to the study center with COVID-19 was 11.2% (2 of 17 patients), while all 5 patients admitted to outside institutions died.

Discussion

In this case series of recipients with HT who had confirmed COVID-19 infection, we report a high case fatality rate of 25%, which was much higher than currently reported in other patient populations. Of note, we did not routinely test patients who were asymptomatic, and there were limitations on testing patients with mild symptoms at the earliest phases of the

Figure. Inpatient Course for 17 Patients With Heart Transplant Admitted to the Study Institution With Coronavirus Disease 2019 Infection



The length of hospitalization is indicated by the length of each line. Timing of medication administration is indicated along each line.

pandemic. Therefore, we may have underestimated the prevalence of COVID-19 infection in this transplant population. Furthermore, we were unable to address whether cardiovascular risk factors, immunosuppression, or HT status itself increased the risk of mortality among this population. The effect of immunosuppression on the course of this disease remains unclear. While in vitro evidence suggests that immunosuppressive medications may inhibit viral replication,[10-14] long-term immunosuppression nonetheless increases susceptibility to infection, dampening the ability to mount an effective response. Most patients in this case series had their immunosuppression medications reduced following diagnosis, although the population size is too small to evaluate the effectiveness of this strategy. Whether immunosuppression can temper the immune dysregulation seen in cases of severe disease remains unknown. The high case fatality rate in this cohort does not suggest a protective benefit from immunosuppression; however, randomized studies to assess each individual immunosuppressive agent would be needed to provide a definitive answer.

Managing recipients of HT with COVID-19 has increased complexity because they have more intense immunosuppression than many other solid organ transplant recipients, combined with the potential for the virus to cause both primary and secondary myocardial injury.[15] Although our cohort is small, we recommend that patients who have received HT are treated at a transplant center while infected with COVID-19. Furthermore, these patients will require ongoing monitoring in the recovery phase as an immunosuppression regimen is reintroduced and the consequences to the allograft itself become apparent. The high case fatality rate in this cohort calls for close monitoring of recipients of HT and a low threshold for hospitalization during acute infection with COVID-19.

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Acquisition, analysis, or interpretation of data: Latif, Farr, Clerkin, Habal, Takeda, Restaino, Uriel.
Drafting of the manuscript: Farr, Clerkin, Naka, Restaino, Sayer, Uriel.
Critical revision of the manuscript for important intellectual content: Latif, Farr, Clerkin, Habal, Takeda, Naka, Sayer, Uriel.
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REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1

2. Richardson S, Hirsch JS, Narasimhan M, et al; and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. Published online April 17, 2020. doi:10.1001/jama.2020.6775

3. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med*. Published online April 22, 2020. doi:10.1056/NEJMc2010419

4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA*. 2020;323:1239-1242. doi:10.1001/jama.2020.2648

5. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629. doi:10.1172/JCI137244

6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

7. Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. *J Heart Lung Transplant*. 2020;39(5):496-497. doi:10.1016/j.healun.2020.03.006

8. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients. *Am J Transplant*. Published online April 16, 2020. doi:10.1111/ajt.15929

9. Zong-Li Ren RH, Wang Z-W, Zhang M, et al. Epidemiological and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China. *J Heart Lung Transplant*. Published online March 25, 2020. doi:10.1016/j.healun.2020.03.008

10. Shen L, Niu J, Wang C, et al. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. *J Virol*. 2019;93(12):93. doi:10.1128/JVI.00023-19

11. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. *Viruses*. 2013;5(5):1250-1260. doi:10.3390/v5051250

12. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. *Virus Res*. 2012;165(1):112-117. doi:10.1016/j.virusres.2012.02.002

13. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-coronavirus-host interactome. *PLoS Pathog*. 2011;7(10):e1002331. doi:10.1371/journal.ppat.1002331

14. Li HS, Kuok DIT, Cheung MC, et al. Effect of interferon alpha and cyclosporine treatment separately and in combination on Middle East respiratory syndrome coronavirus (MERS-CoV) replication in a human in-vitro and ex-vivo culture model. *Antiviral Res*. 2018;155:89-96. doi:10.1016/j.antiviral.2018.05.007

15. Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation*. Published online March 21, 2020. doi:10.1161/CIRCULATIONAHA.120.046941