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**ORIGINAL ARTICLE**

Heart transplant recipients with confirmed 2019 novel coronavirus infection: The Detroit experience

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Abstract

A chronic immunosuppressed state as in solid organ transplant recipients is a reported risk factor for the novel 2019 coronavirus infection. Patients with a history of orthotopic heart transplant (OHT) at a tertiary care transplant center in Detroit, Michigan were retrospectively reviewed from March until May 2020. Clinical parameters and outcomes of 5 OHT recipients and one combined heart–lung recipient with confirmed SARS-CoV-2 were obtained. The cohort was predominately African American males with median age of 59 years (interquartile range, 48.25–73.25). All patients were classified as having mild–moderate disease; none required intubation or ICU admission with no deaths. The most common presenting symptoms were fever and shortness of breath 83% (n = 5), followed by cough and chills 67% (n = 4). All admitted patients (n = 5) received hydroxychloroquine and 3 received high-dose steroids. Antimetabolites were held for 2 patients (33.3%). The calcineurin inhibitor trough goal was decreased in only 1 patient; 3 other patients, without change in goal, required calcineurin inhibitor dosage reduction. Two patients requiring readmission presented 7 and 23 days after initial symptoms onset. In conclusion, our experience with OHT patients infected by the SARS-CoV-2 virus did not have an elevated risk of severe infection. Impact of modifying immunosuppression remains unclear.

KEYWORDS

COVID-19, global pandemic, heart transplant recipients, immunosuppression, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to the novel coronavirus disease 2019 (COVID-19) pandemic was first reported in Wuhan, Hubei Province, China.¹ The first cases emerged in late December 2019 rapidly spreading throughout China and beyond, leading to increasing rates of morbidity and mortality worldwide.² SARS-CoV-2 is the seventh member of the coronaviruses family that is known to infect humans.¹ As of May 24, 2020,

the number of cases exceeds 5 million worldwide accounting for over 337,000 deaths.³

The COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) reported in April 2020 that approximately 92% of hospitalized patients with COVID-19 had at least one co-morbid condition. The most common associated conditions with COVID-19 among hospitalized patients are hypertension, obesity, and underlying cardiovascular disease.⁴ Chronic immunosuppression accounts for approximately 10% of the patients hospitalized. Given the state

of chronic immunosuppression and co-existing medical conditions, the orthotopic heart transplant (OHT) recipient appears to be at particularly high risk of developing severe disease.⁴

There are few published case reports of COVID-19 in heart transplant recipient's population in the United States⁵⁻⁸ with Latif et al reporting the largest case series to date including 28 heart transplant recipients.⁹ The most common presenting symptom among their cohort was cough or dyspnea with 79% of patients requiring hospitalization and an overall mortality rate of 25%. Discontinuing mycophenolate mofetil followed by reducing calcineurin inhibitor were the most frequent modification made to the immunosuppression regimen.⁹

We aim to review clinical parameters and the initial outcomes of OHT recipients and combined heart-other solid organ recipients with laboratory-confirmed SARS-CoV-2 followed by our transplant center in Detroit, Michigan from March 2020 through May 2020.

2 | MATERIALS AND METHODS

We retrospectively reviewed 170 patients with prior history of OHT at Henry Ford Hospital in Detroit, Michigan. Adult OHT recipients ≥ 18 years of age with laboratory-confirmed diagnosis of COVID-19 from March 13, 2020, until May 1, 2020, were included in the study. Patients were followed through May 24, 2020. Subjects were identified in the outpatient setting and during hospital admissions.

Clinical parameters were obtained, including demographics, presenting symptoms, date of laboratory-confirmed COVID-19 test, exposure history, relevant laboratory findings and management of

immunosuppression. Patients were stratified based on severity of disease: mild disease (outpatient care only), moderate disease (hospital admission to general medical ward) and severe disease (requiring ICU admission). Initial outcomes including hospitalizations, intensive care unit admission, readmissions, and death were collected through May 24, 2020. Descriptive data analysis was performed after completion of data collection.

The study was approved by Henry Ford Health System Institutional Review Board. Formal consent is not required for retrospective electronic data review. Our study meets human subjects and HIPAA privacy requirements.

3 | RESULTS

3.1 | Patient demographics and transplant history

Among the 170 OHT recipients followed at our center, we identified 5 OHT recipients and one combined heart-lung recipient with laboratory-confirmed SARS-CoV-2 infection during our defined study period. Figure 1 shows the time of diagnosis of our cohort relative to the total number of cases across Michigan State.¹⁰ Five of the six patients (83.3%) of the patients with COVID-19 were males median age of 59 years (interquartile range [IQR], 48.25-73.25) and a median body mass index (BMI) of 26.2 kg/m² (IQR, 22.1-30.38). All patients (n = 6) were African Americans with a history of non-ischemic cardiomyopathy prior to transplantation. The median time from transplant was 6.5 years (IQR, 4.25-12.5). One OHT recipient had a history of chronic obstructive airway disease, and the combined heart-lung

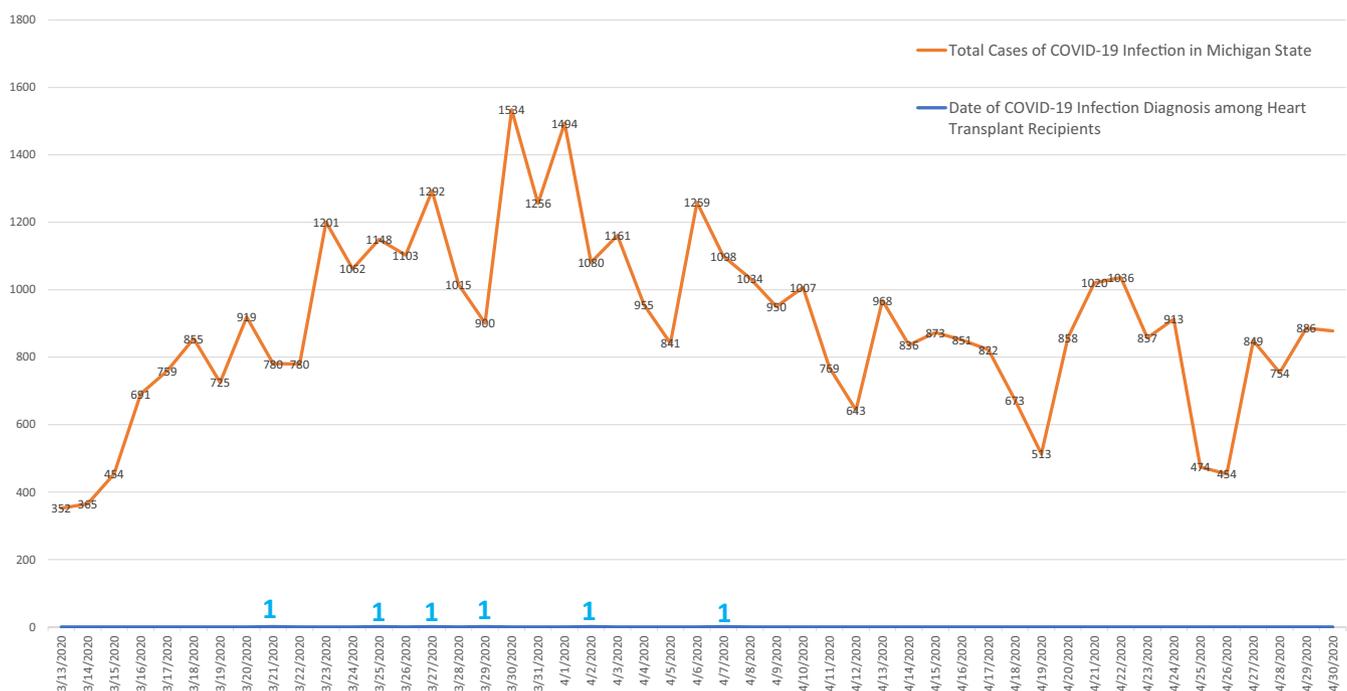


FIGURE 1 Date of diagnosis for heart transplant recipients with COVID-19 infection Relative to Total COVID-19 Cases across the State of Michigan

TABLE 1 Baseline demographics of the COVID-19 heart transplant recipient

	All (n = 6)
Age in years, median (IQR ^a)	59 (48.25-73.25)
Male sex n (%)	5 (83.3)
African American n (%)	6 (100)
Median years from heart transplant to diagnosis (IQR)	6.5 (4.25-12.5)
Co-morbidities n (%)	
Hypertension	6 (100)
Diabetes mellitus	5 (83.3)
Body mass index ≥ 30 kg/m ²	2 (33.3)
Chronic obstructive pulmonary disease	1 (16.7)
Chronic kidney disease stage IV or greater	1 (16.7)
History of induction with heart transplant	6 (100)
Maintenance immunosuppression n (%)	
Calcineurin inhibitor (tacrolimus or cyclosporine)	6 (100)
Mycophenolate mofetil	4 (66.7)
Sirolimus	1 (16.7)
Steroids	1 (16.7)

^aIQR, Interquartile range.

transplant recipient had history of long-standing systemic sarcoidosis and severe pulmonary hypertension prior to transplantation. One OHT recipient had a history of cardiac allograft vasculopathy. For maintenance immunosuppression, 1 (16.7%) patient was on steroids, 4 (66.7%) on mycophenolate mofetil, 5 (83%) on tacrolimus, 1(16.7%) on sirolimus, and 1(16.7%) of the patients was on cyclosporine. Specifically, four of the six infected OHT patients were on dual immunosuppression with mycophenolate mofetil and tacrolimus. One patient, transplanted over a decade ago, was on cyclosporine monotherapy, and the final patient was on triple therapy with prednisone, tacrolimus, and mycophenolate mofetil. Immunosuppression regimens are listed in Table 1.

3.2 | Clinical presentation

The most common presenting symptoms included fever and shortness of breath 83% (n = 5), cough and chills 67% (n = 4), followed by gastrointestinal symptoms 60% (n = 3) (Table 2). Three patients reported their significant other as being COVID-19 positive; another patient reported a possible exposure to a sick family member. Two patients had laboratory-confirmed SARS-CoV-2 as outpatients; one of the two patients required hospitalization. The remaining 4 patients were tested as inpatients (3 in the emergency department prior to general medical floor admission), and one patient was diagnosed after being directly admitted to the hospital in response to a telemedicine video visit. Average length of symptoms prior to hospitalization and test result was 5.8 days with a range of 1 day

TABLE 2 Symptoms and laboratory values on presentation among hospitalized transplant patients with COVID-19 infection

	All hospitalized (n = 5)
Symptoms on presentation n (%)	
Fever	5 (100)
Dyspnea	5 (100)
Cough	4 (80)
Diarrhea	3 (60)
Fatigue	2 (40)
Myalgia	2 (40)
Loss of appetite	2 (40)
Sore throat	2 (40)
Nausea	1 (20)
Ageusia	1 (20)
Blood count median (IQR ^a)	
White blood cell K/microliter	4.1 (3.45-5.5)
Absolute lymphocytic count K/microliter	0.8 (0.55-1.0)
Chemistry panel median (IQR)	
Serum creatinine mg/dL	2.65 (2.26-5.53)
AST ^b units/L	23 (17.5-28)
Albumin g/dL	3.7 (3.3-4.5)
Additional laboratory findings median (IQR) on presentation	
Procalcitonin ng/mL	0.25 (0.1-0.39)
C-reactive protein mg/L	1.7 (0.75-10.05)
D-dimer mg/mL	0.34 (0.3-1.93)
Ferritin ng/mL	302 (136-410)

^aIQR, Interquartile range.

^bAST, Aspartate transaminase.

to 13 days. Among the hospitalized patients (83%; n = 5), 1 patient (20%) required supplemental oxygen briefly on the index hospitalization and during a readmission due to hypoxia. Another patient also required oxygen supplementation during a readmission. Vital signs for the admitted patients are presented in Table 3.

3.3 | Laboratory and imaging findings

Four (80%) of the hospitalized patients had elevated ferritin with a median peak ferritin level of 315 ng/mL (IQR, 195-828), and two patients had elevated D-Dimer on presentation with median peak D-Dimer of 0.38 mg/mL (IQR, 0.295-1.93). Two patients had a slightly elevated high sensitive troponin I on admission that peaked at 33 ng/dL and 191 ng/dL. All patients that required hospitalization (n = 5) had elevated C-reactive protein with a median peak level

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Respiratory rate (breaths per minute)	20	18	20	16	18
Pulse oximetry (%) on room air	98	93	99	96	99
Systolic blood pressure (mmHg)	113	141	142	93	130
Diastolic blood pressure (mmHg)	52	89	97	60	85
Heart rate (beats per minute)	72	78	105	99	93
Temperature (celsius)	38.3	38.3	38.4	36.3	37.2

TABLE 3 Admission vital signs in the index hospitalization

of 2.9 mg/dL (IQR, 1.2-10.95). Four of the hospitalized patients had lymphopenia on admission, and however, all (n = 5) eventually developed lymphopenia during their hospital stay with a median nadir of absolute lymphocyte at 0.5 K/ μ L (IQR, 0.2-0.75). Procalcitonin levels were elevated in 2 patients (40%). One patient was tested for interleukin-6 with a level <5 pg/mL. Serum creatinine level was elevated in all hospitalized patients with a median increase of 0.87 mg/dL (IQR, 0.415-2.69) on presentation when compared to baseline serum creatinine levels. Changes in inflammatory markers after initiation of high-dose steroids are included in Table 4. Furthermore, secondary infections were not confirmed in this population. Specifically, CMV was not routinely checked, and however, all patients received simultaneous nasopharyngeal swabs for influenza infection of which none returned positive. In terms of chest x-ray findings of the admitted patients on presentation, one demonstrated mild vascular congestion, 2 showed new lung consolidation (1 patient in the right infrahilar and the other patient with bilateral infiltrates), and 2 did not have acute cardiopulmonary process.

3.4 | Treatment

All hospitalized patients (n = 5) received hydroxychloroquine with discontinuation of the medication in one patient due to prolongation of QTc interval. Three of the five patients received high-dose steroids (intravenous solumedrol 40 mg every 12 hours for 3 days

duration) on initial presentation. One of them received steroids due exertional dyspnea with borderline oxygen saturation requiring supplemental oxygen to maintain oxygen saturation of at least 96%. Two patients were given high-dose steroids due to significantly elevated inflammatory markers with continued symptoms (n = 2). One additional patient received high-dose steroids upon readmission. None of the patients received interleukin-6 inhibitors or remdesivir. Two patients received antibiotics for concern of bacterial superinfection during hospital stay. Modifications to the maintenance immunosuppression regimens were made in 4 of the 5 patients hospitalized OHT recipients, and no changes in immunosuppression were made to the outpatient OHT recipient. Mycophenolate mofetil was held in 2 patients (33.3%) during the hospitalization and at discharge. The calcineurin inhibitor (CNI) trough goal was decreased in only 1 (16.7%) patient; cyclosporine trough goal was decreased from 50-75 ng/mL to 25-50 ng/mL in that patient. However, 3 (50%) other patients, without change in goal, required tacrolimus dosage reduction. A reduction in the dose of rapamycin was made in the heart-lung recipient. There was one hospitalized patient that had no modifications to immunosuppression regimen.

3.5 | Outcomes

The average length of stay for the five hospitalized patients was 5.6 days with a range of 2 to 12 days. Five of the 6 patients were

TABLE 4 Changes in inflammatory markers in response to steroids administration

Marker (Units)	Patient 1—baseline	Patient 1—72 hours post-steroids	Patient 2	Patient 2—72 hours post-steroids	Patient 3	Patient 3—72 hours post-steroids
HS-cTn (ng/dL)	22	20	20	191	<18	<18
LDH (IU/L)	287	297	294	344	274	332
CPK (IU/L)	98	128	106	109	86	47
D-dimer (mg/mL)	0.74	0.53	0.53	0.92	0.34	0.36
CRP (mg/dL)	9.7	4.8	9.1	2.6	10.4	0.9
Ferritin (ng/mL)	353	393	201	348	185	265

CPK, creatine phosphokinase; CRP, C-reactive protein; HS-cTn, high-sensitivity cardiac troponin; LDH, lactate dehydrogenase.

categorized as moderate disease (requiring hospitalization) and the patient who did not require hospitalization was categorized as mild disease. No patient in our cohort required an ICU admission or intubation. There were no deaths in the studied cohort. One patient with history of chronic kidney disease stage 4 required initiating renal replacement therapy due to acute or chronic renal injury and was discharged after tunneled catheter placement. On 30-day follow up, patient continues to require intermittent hemodialysis. Treatments used and outcomes were summarized in Table 5.

Two patients required readmissions due to progression of symptoms. One of our two patients requiring readmission was a dual organ recipient who had been hospitalized for 5 days for primarily cough and low-grade fever symptoms. This patient subsequently required rehospitalization the day after index discharge with recurrent fever and hypoxia requiring supplemental oxygen for an additional 7 days. No new infection was identified. This second presentation occurred 7 days after the onset of symptoms. This patient also unfortunately was hospitalized a third time with complaints with acute renal injury and uremic symptoms. During this hospitalization, patient has tested negative for COVID-19 PCR. Ultimately, the symptoms were attributed to AKI and uremia as well as underlying known slow gastric emptying, managed conservatively without further complications. The second patient requiring readmission had been hospitalized for 3 days for primarily dyspnea and gastrointestinal symptoms at the index hospitalization. He had a relatively delayed readmission; patient presented after 7 days from discharge and 23 days after the initial symptoms' onset. On the readmission, patient presented with worsening dyspnea, hypoxia with SaO₂ of 80% requiring 6 liters oxygen by nasal cannula with worsening chest x-ray finding showing bilateral infiltrates. The patient subsequently improved after a 3-day course of intravenous high-dose steroid with a gradual wean of oxygen.

TABLE 5 Summary of treatments used and outcomes among heart transplant recipients with COVID-19 infection

	All (n = 6)
Changes in immunosuppression n (%)	
Decrease or hold of calcineurin inhibitor	4 (66.7)
Decrease or hold of antimetabolites	2 (33.3)
Decrease or hold of MTOR inhibitor	1 (16.7)
Antiviral treatment n (%)	
Hydroxychloroquine	5 (83.3)
Azithromycin	0
Remdesivir	0
Immunomodulating therapy n (%)	
Bolus steroids	3 (50)
Tocilizumab	0
Intensive care admission	0
Death	0
Discharge	6 (100)
Readmission	2 (33.3)

None of the six solid organ transplant recipients in our cohort required recent treatment for rejection. There were also no concerns for active rejection or major thromboembolic processes in our studied cohort.

4 | DISCUSSION

Our center performs approximately 25 heart transplants annually with more than 40% of our transplant recipients being African Americans. Historically, access to care, wait-list survival and post-transplant outcomes have been a challenge for minority communities. The addition of a pandemic which has a predilection for the elderly and those with co-morbid conditions can add to that burden.^{11,12} A recent CDC morbidity and mortality weekly report showed a disproportionate rate of hospitalization among blacks⁴ with high death rates reported in New York City among black race (92.3 deaths per 100,000 population) compared to white, Hispanic and Asian races.¹³ Our cohort of OHT recipients were all African Americans falling within mild-to-moderate disease category with 83.3% (n = 5) hospitalized. Fortunately, there were no cases of severe disease in our cohort. Like the COVID-NET report⁴ and the study by Latif et al,⁹ we had a higher rate of COVID-19 infection among male patients compared to females. Interestingly, the one female patient in our cohort did not require hospitalization. All of our patients had significant co-morbid conditions including hypertension, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. Noteworthy, we had 2 patients with readmissions, 7 and 23 days after initial symptoms onset, a relatively delayed presentation of symptoms progression that could warrant patient education of this observation and a potential need for longer isolation and monitoring. Comparing to the New York Report,⁹ we had similar rates of hospitalizations among COVID-19 infected heart transplant recipients. We had no deaths in our studied cohort, and however, there was a higher fatality rate among the hospitalized patients in New York (32%).⁹ From another New York series among solid organ transplant recipients infected with SARS-CoV-2, almost a quarter of the patients died.⁸ None of the patients in our cohort met the criteria for severe disease requiring ICU admission or intubation. This could be related to a small sample size. Additionally, further precautions and social distancing could have been performed by this vulnerable population due to inherent knowledge of their immunosuppressive status. Although, the exact mechanism of cardiac involvement by SARS-CoV-2 is not yet known, with suggestions of direct or indirect cardiac involvement,¹² this virus can lead to marked inflammatory response that is likely related to severe disease states and cytokine storm.¹⁴ It has been suggested that immunosuppression and immunomodulators could prevent the cytokine storm¹⁵⁻¹⁷; hence, they could lead to less severe cases as in our cohort. It is interesting to note that our cohort did well despite no clear guidance on immunosuppression regimen in this pandemic and no proven treatments for COVID-19 that could reduce mortality.²

4.1 | Limitations

Despite that COVID-19 infection is a new disease with limited data on heart transplant patients, we must acknowledge limitations of this study. Keeping in mind that our transplant center is one of the 3 transplant centers in Michigan, United States, this is a single-center retrospective study which makes generalizability of the data not possible. Additionally, this case series presents a small number of subjects that limits the ability to perform inferential analysis. Enrollment of subjects was based on notifications and admissions to our institution which cannot exclude presentation of our transplant patients to other health facilities with limited access to their electronic medical records.

5 | CONCLUSION

We are presenting our experience of OHT and heart-lung transplant recipients who acquired SARS-CoV-2 virus at a tertiary care transplant center in Detroit, Michigan. This cohort reflected predominately moderate disease severity and was managed with symptomatic COVID-19 treatment along with modifying the long-term immunosuppression regimens. Our cohort is unique in consisting entirely of individuals of black race. The impact of modifying immunosuppression remains unclear; and thus, individualized approaches in changing immunosuppression regimens is imperative.

CONFLICT OF INTEREST

The authors of this manuscript have conflicts of interest to disclose. Dr Williams is a consultant for Novartis and Astra-Zeneca. Dr Lanfear has received research grants from NHLBI, Amgen, Bayer, and Janssen; he has acted as consultant for Amgen, Janssen, Ortho Diagnostics and Novartis. Dr Cowger has no pertinent disclosures to this article, is a consultant and speaker for Abbott/Medtronic. Drs. Al-Darzi, Aurora, Grafton, Hannawi, Michaels, Nemeh, Selektor, and Tita have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Drs. Al-Darzi, Aurora, Michaels, and Williams have contributed to research design, data collection and analysis, data interpretation, drafting the paper, and approval of the submitted and final versions. Drs. Cowger, Grafton, Selektor, Tita, Hannawi, Lanfear, and Nemeh have contributed by data interpretation, critical revision of the article, and approval of the submitted and final versions.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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