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A proposed strategy for management of immunosuppression in heart transplant patients with COVID-19

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Abstract

There is limited experience in management of orthotopic heart transplant (OHT) patients with COVID-19. In this study, we present our initial experience using a standardized management algorithm. Data collection was performed on OHT patients with COVID-19 after March 10, 2020 (declaration of state of emergency in Massachusetts). Among the 358 OHT patients currently followed at our program, 5 patients (1.4%) tested positive for COVID-19 (median age 50 years [IQR, 49-58], duration post-OHT 21 years [IQR, 6-25], and 4 of 5 [80%] were men). Among the 5 OHT patients, 2 of 5 (20%) had mild disease and had no change in baseline immunosuppression therapy. Two of 5 (20%) had moderate disease and received remdesivir as part of a clinical trial and reduced immunosuppression therapy. One patient (20%) died prior to presenting to the hospital, consistent with 20% case fatality rate. Four patients (80%) are doing well 4 weeks post-discharge. In this small cohort of OHT patients with COVID-19, we report a 1.4% COVID-19 infection rate and 20% case fatality rate. All OHT patients managed under our clinical management algorithm had good short-term outcomes. Further study to estimate the true risk profile of OHT patients and validate the proposed management strategy is warranted.

KEYWORDS
COVID-19, heart transplantation, immunosuppression

1 | INTRODUCTION

As the coronavirus disease 2019 (COVID-19) pandemic ensues, it has posed a greater challenge in heart transplant recipients, a particularly vulnerable patient cohort. Transplant recipients are likely susceptible given the immunosuppressed state, presence of co-morbidities including hypertension, diabetes mellitus, and chronic kidney disease, and frequent contact with the healthcare system, leading to an overall increase in mortality. The attributable risk, however, is largely unknown. Preliminary reports suggest that the clinical course of COVID-19 may be similar in orthotopic heart transplant (OHT) and non-transplant patients.[1]

Calcineurin inhibitors (CNIs) are the cornerstone treatment that block T-cell activation, effectively suppressing alloimmunity. In vitro studies have demonstrated that CNIs may inhibit viral replication of coronaviruses and hepatitis C,[2] whereas there have not been consistent data to support the same with the use of mycophenolate mofetil (MMF).[3,4] mTOR inhibitors may also suppress viral replication, and thus, clinical investigation is ongoing.[5] Although there may be inhibitory effects of these medications, lowering the dosage or withholding select immunosuppressive drugs in the early disease course may attenuate clinical expression of the disease depending on severity albeit with increased risk for rejection. The impact of change of immunosuppressive therapy needs to be further evaluated.

Early in the course of the COVID-19 crisis, we developed a prospective standardized management algorithm for our heart transplant patients with COVID-19 (Figure 1). In addition, heart transplant recipients are strongly advised to practice prevention measures,[6] including minimizing routine clinical visits, use of video or telephone visits, and to post-postpone any non-essential routine surveillance testing (echocardiography, right heart catheterization, and endomyocardial biopsy).

In this report, we summarize our initial experience and challenges in managing heart transplant patients at Brigham and Women's Hospital (BWH) from the time of declaration of state of emergency by the Governor of Massachusetts on March 10, 2020, and to describe short-term outcomes of COVID-19 patients after implementing the prospective clinical management algorithm.

2 | METHODS

Data were collected by the electronic medical record on all heart transplant patients with either a confirmed diagnosis of COVID-19 or those persons under investigation (PUI) admitted to BWH or cared for as an outpatient from March 10, 2020, to May 15, 2020. Information including demographics, transplant history and complications, co-morbidities, clinical presentation and course, medications, and laboratory values was reviewed. COVID-19 positive patients were confirmed by positive nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2. Outpatients who tested positive were also included. All testing was performed based on self-reporting of symptoms. Management of immunosuppression therapy is outlined in Figure 1. Continuous data are reported as medians with interquartile ranges (IQRs). This project was undertaken as a quality improvement initiative, and as such was exempt from ethics committee review per institutional policy.

3 | RESULTS

Among the 358 OHT patients currently followed at our program, 19 patients (5.3%) were evaluated during the COVID-19 pandemic after March 10, 2020 (declaration of state of emergency in Massachusetts). Clinical diagnoses among OHT patients during the COVID-19 pandemic are outlined in Figure 2. A total of 5 OHT patients (1.4% of total OHT cohort currently followed at our program) were confirmed positive for COVID-19 (Table 1). Among the 5 OHT patients, 3 (60%) were admitted, 1 (20%) was managed as an outpatient, and 1 (20%) had a pulseless electrical activity (PEA) cardiac arrest prior to presentation to the hospital, consistent with 20% case fatality rate. All remaining hospitalized patients were ruled out for COVID-19 with two serial negative tests. Median age was 50 years [IQR, 49-58], body mass index 30.6 kg/m^2 [IQR, 22.5-31.1], duration post-OHT 21 years [IQR, 6-25], median left ventricular ejection fraction was 65% [IQR, 45-65], 4 of 5 patients (80%) were men, and 4 of 5 patients (80%) were either Black or Hispanic ethnicity. All (100%) had transplant-related co-morbidities including hypertension, diabetes, and chronic kidney disease. Cardiac allograft vasculopathy was present in 2 of 5 patients (40%), and none had underlying parenchymal lung disease. Maintenance immunosuppression included tacrolimus in 2 (40%), cyclosporine in 2 (40%), mycophenolate mofetil in 3

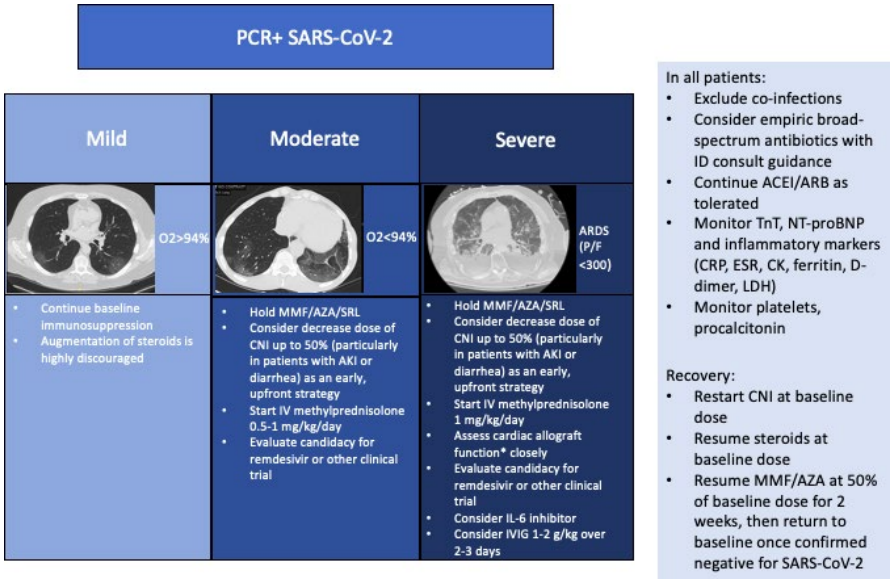

FIGURE 1 Management principles for heart transplant patients with COVID-19. * Evaluate for increased LV wall thickness or decline in allograft function, decrease in QRS amplitude, clinical evidence of increased filling pressures, significantly elevated NT-proBNP and/or troponin levels from baseline.ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; AZA, azathioprine; CK, creatinine kinase; CNI, calcineurin inhibitor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ID, infectious diseases; IL-6, interleukin-6; IV, intravenous; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; NT-proBNP, N-terminal pro B-type natriuretic peptide; SRL, sirolimus; TTE, transthoracic echocardiogram

(60%), azathioprine in 1 (20%), sirolimus in 2 (40%), and prednisone in 5 (100%). Two of 5 patients had mild disease defined as oxygen saturation >94% and normal to mildly abnormal chest imaging findings and had no change in baseline immunosuppression therapy. Two of 5 patients (20%) had moderate disease classified as oxygen saturation <94% with abnormal chest imaging findings and received remdesivir as part of a clinical trial and reduced immunosuppression therapy. All hospitalized patients received standard deep venous thrombosis prophylaxis.

The patient who died was a 61-year-old Hispanic woman who was 6 years post-OHT complicated by acute cellular and antibody-mediated rejection with persistent elevation in donor-specific antibodies that had been managed previously with plasmapheresis, intravenous immunoglobulin, and rituximab. She had a viral prodrome and sustained a PEA arrest at home; subsequent testing was positive for COVID-19. All surviving patients had early rejection during their transplant course, but no recent rejection.

In the patients who survived, laboratory data revealed elevated inflammatory markers (median high-sensitivity C-reactive protein 44 mg/L [IQR, 34.4-44.5], erythrocyte sedimentation rate 48 mm/h [IQR, 28.5-50], and ferritin 670 mcg/L [IQR, 593-763]) and normal to mildly elevated cardiac biomarkers (high-sensitivity Troponin-T 14 ng/mL [IQR, 11.5-20] and N-terminal pro B-type natriuretic peptide 165 pg/mL [IQR, 150.5-1134.5]). No co-infections were detected; however, all admitted patients received empiric antibiotics for community-acquired pneumonia. In patients who had an oxygen requirement, the oxygen saturation normalized within 24 hours of presentation. The duration of hospitalization ranged from 4 to 8 days. Criteria for discharge included clinical improvement in symptoms, hemodynamic stability, adequate oral intake, and off oxygen therapy for at least 24 hours prior to discharge. Four of 5 patients (80%) are currently doing well with self-isolation precautions at home with marked improvement in clinical symptoms up to 4 weeks post-discharge. Following discharge, patients who had a change in their immunosuppression regimen resumed home dose calcineurin inhibitor and steroid therapy. Half-dose adjunctive therapy (MMF, azathioprine, or sirolimus) was also initiated two weeks after discharge, and full dose was resumed once repeat testing for SARS-CoV-2 was negative. All hospitalized patients tested negative within 4 weeks of the initial positive test.

All patients were closely monitored by our transplant nursing team using telehealth and video calls after discharge. They received ongoing reinforcement to follow CDC guidelines for social distancing, hand hygiene practices, and use of facemask.

4 | DISCUSSION

In this report, we describe 5 OHT patients with COVID-19, which represents a COVID-19 infection rate of 1.4% in our population. In this small cohort, there was one death (20% case fatality rate) in an older patient with multiple co-morbidities including a history of acute cellular and antibody-mediated rejection who had a PEA cardiac arrest at home. This highlights the need to maintain a low threshold to admit and closely monitor these patients. Among the remaining patients, none required mechanical ventilation. All patients who survived had good short-term outcomes up to 4 weeks post-discharge under our current protocol for adjusting immunosuppressive therapy with COVID-19 coupled with very close clinical follow-up.

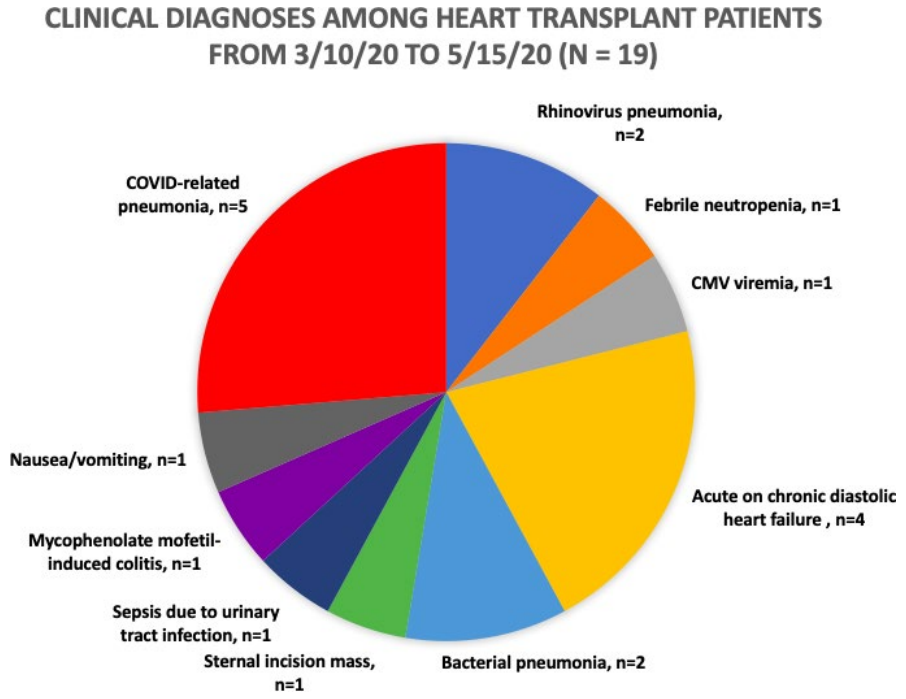

FIGURE 2 Clinical diagnoses among heart transplant patients (n = 19)

TABLE 1 Clinical characteristics of heart transplant patients with COVID-19

Age (years)	Ethnicity	BMI (kg/m^2)	Time from OHT (years)	Rejection history	CAV	LVEF (%)	Baseline immuno-suppression	Presenting symptoms	Initial →Discharge Pulse O2 (%)	P/F ratio	Severity	Laboratories WBC (10^9/L) ALC (cells/mm^3) CRP (mg/L) ESR (mm/h) Ferritin (mcg/L) TnT (ng/mL) NT-pro BNP (pg/mL) Procalcitonin (ng/mL)	Change in immunosuppression	Additional therapy	Hospital Duration (days)
50	Black	31.1	3.5	Early 2R	Yes	65	TAC, MMF, prednisone	Fatigue, cough, anosmia, dysguesia, N/V	93→96	442	Moderate	WBC 4.5, ALC 820 CRP 45 ESR 52 Ferritin 515→807 LDH 289→289 TnT 9→ <6 NT-proBNP 165 Procalcitonin 0.1	MMF held, CNI reduced 50%, methylpred 0.5 mg/kg	Remdesivir × 3 d	4
58	White	30.6	21	Early 2R	No	65	Cyclo, AZA, prednisone	Fever, fatigue, N/V	86→95	351	Moderate	WBC 6.82, ALC 580 CRP 25→7.4 ESR 9 Ferritin 670→829 LDH 363→458 TnT 26→12 NT-proBNP 136→404 Procalcitonin 0.24	AZA held, CNI reduced 33%, methylpred 0.5 mg/kg	Remdesivir × 4 d	5
49	Black	17	25	Early 2R	Yes	45	Cyclo, SRL, prednisone	Fever, SOB	97→100	462	Mild-moderate	WBC 3.13, ALC 580 CRP 44 ESR 48 Ferritin 855→845 LDH 380 Tn T 14→8 NT-proBNP 2104→2089 Procalcitonin 0.11	Continued baseline regimen	Supportive only	8
26	Hispanic	22.5	25	Early rejection	Yes	38	SRL, MMF, prednisone	Fever, myalgias, sore throat, diarrhea	N/A	N/A	Mild	Not done	Continued baseline regimen	Supportive only	N/A

(Continues)

TABLE 1 (Continued)

Age (years)	Ethnicity	BMI (kg/m^2)	Time from OHT (years)	Rejection history	CAV	LVEF (%)	Baseline immuno-suppression	Presenting symptoms	Initial →Discharge Pulse O2 (%)	P/F ratio	Severity	Laboratories WBC (10^9/L) ALC (cells/mm^3) CRP (mg/L) ESR (mm/h) Ferritin (mcg/L) TnT (ng/mL) NT-pro BNP (pg/mL) Procalcitonin (ng/mL)	Change in immunosuppression	Additional therapy	Hospital Duration (days)
61	Hispanic	36.9	6	Recurrent grade 1 rejection, pAMR 2 and persistent DSA s/p plasmapheresis IVIG, rituximab	No	65	MMF, Tac, prednisone	Cardiac arrest							N/A

Abbreviations: ALC, absolute lymphocyte count; AZA, azathioprine; BMI, body mass index; CNI, calcineurin inhibitor, CRP; c-reactive protein; Cyclo, cyclosporine; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase test; MMF, mycophenolate mofetil; NT-proBNP, N-terminal pro b-type natriuretic peptide; N/V, nausea/vomiting, O2, oxygen; Procal, procalcitonin; SRL, sirolimus; Tac, tacrolimus; TnT, high-sensitivity Troponin-T; WBC, white blood cell count.

TABLE 2 Ongoing challenges and solutions in management of heart transplant patients with COVID-19

Current challenges	Potential solutions
Addressing patients' fears regarding the COVID-19 pandemic	Ongoing reinforcement of CDC guidelines including stay-at-home orders, social distancing, hand-hygiene and use of face masks
Reducing exposure of patients to hospital-related infections	Increase use of virtual health (telemedicine, video visits)
Outpatient testing for COVID-19	Dedicated outpatient respiratory clinics established
Delay in turnover time for COVID-19 testing results	Testing capacity has increased and use of serological testing now available
Delay in surveillance endomyocardial biopsies	Endomyocardial biopsies were performed on schedule in (a) all patients less than 6-12 mo from OHT; (b) patients with recent adjustment in immunosuppression regimen; and (c) clinical suspicion for or recent episode of rejection Surveillance endomyocardial biopsies in other cases were re-scheduled to June 2020 or beyond AlloMap testing is considered in lower risk patients
Performing laboratory testing in COVID positive patients	COVID-specific lab draw stations are available through Partners Health Appointment-only testing available
Establishing routine home lab draws	Coordination with home agencies
Delays in lab processing of CMV-PCR levels	Continue CMV prophylactic regimen until CMV PCR levels can be routinely obtained to allow for discontinuation of drug
Determining changes immunosuppression therapy in COVID-19 patients	BWH protocol has been established to provide guidance on adjustment of immunosuppression therapy

Abbreviations: CDC, Centers for Disease Control and Prevention; CMV, Cytomegalovirus; OHT, orthotopic heart transplant.

Similar results were observed in a larger cohort of 28 patients in which cardiovascular co-morbidities were highly prevalent and immunosuppression therapy was reduced, although no patients received remdesivir.[3,5,7] The authors reported a case fatality rate of 25%, one of the highest reported in the literature.[8] These experiences differ from an initial report describing 2 OHT patients (one with mild disease 2.5 years post-OHT and the second with more severe disease 15 years post-OHT) from China who both achieved clinical recovery.[1]

Since the emergence of the novel coronavirus, there are no current recommendations for management of heart transplant patients with COVID-19 due to limited experience. In the disease process,

there is an initial viral response phase, followed by escalating phases of disease progression dictated by the host inflammatory response.[7]

In transplant recipients, it is possible that much of the damage in the late phase of disease is a result of an overactive immune system driven by T-cell activation, the primary target of immunosuppressive therapy. Immunosuppressed patients may have a protective mechanism due to impaired T-cell response that can alter the disease severity and clinical course[9]; however, this remains largely speculative and is not supported by our current study. Subsequent case series describe a range of severity of clinical course of COVID-19 in solid organ transplants, although management of immunosuppression regimen and anti-viral strategies varied among institutions.[10-13] Table 2 summarizes ongoing challenges and potential solutions in the management of transplant patients with COVID-19.[14]

Among the patients who survived (80%) with good short-term outcomes, we cannot exclude the fact that remdesivir or augmentation of steroids may have played a role in clinical improvement.[15,16] Recently, the RECOVERY trial demonstrated that low dose dexamethasone (6 mg/d for up to 10 days) was associated with an improvement in survival in hospitalized patients receiving invasive mechanical ventilation or oxygen therapy.[16] Overall, very close monitoring, particularly in those on reduced-dose immunosuppression, is imperative in this high-risk patient population. Future investigation is needed to help identify the true risk profile of transplant patients with COVID-19, understand mechanisms of disease progression, and help validate the proposed management strategy in a larger cohort of patients.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Monica Ahluwalia: Collected all the clinical data; All authors (Monica Ahluwalia, Michael M. Givertz, Mandeep R. Mehra): Participated in the conception, design, analysis, and interpretation of data, drafted the manuscript and revised it critically for important intellectual content and finalized the approval of the manuscript submitted.

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