

COVID-19 FEATURED PAPER

Challenges in heart transplantation during COVID-19: A single-center experience



Aditi Singhvi, MD,^a Maya Barghash, MD,^a Anuradha Lala-Trindade, MD,^{a,b}
Sumeet S. Mitter, MD,^a Aditya Parikh, MD,^a Estefania Oliveros, MD,^a
Brett M. Rollins, PharmD, MS,^c Danielle L. Brunjes, PhD,^a
Jesus Alvarez-Garcia, MD, PhD,^a Erika Johnston, RN,^a Kieran Ryan, RN,^a
Shinobu Itagaki, MD,^d Noah Moss, MD,^a Sean P. Pinney, MD,^a
Anelechi Anyanwu, MD,^d and Donna Mancini, MD^{a,b}

From the ^aZena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; ^bDepartment of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York; ^cDepartment of Pharmacy, The Mount Sinai Hospital, New York, New York; and the ^dDepartment of Cardiovascular Surgery, Mount Sinai Medical Center, New York, New York.

KEYWORDS:

COVID-19;
heart transplant;
immunosuppression;
inflammatory
biomarkers;
outcomes

BACKGROUND: Orthotopic heart transplantation (OHT) recipients may be particularly vulnerable to coronavirus disease 2019 (COVID-19). OHT during the pandemic presents unique challenges in terms of feasibility and safety.

METHODS: Chart review was performed for consecutive OHT recipients with COVID-19 and waitlisted patients who underwent OHT from March 1, 2020 to May 15, 2020.

RESULTS: Of the approximately 400 OHT recipients followed at our institution, 22 acquired COVID-19. Clinical characteristics included median age 59 (range, 49–71) years, 14 (63.6%) were male, and median time from OHT to infection was 4.6 (2.5–20.6) years. Symptoms included fever (68.2%), gastrointestinal complaints (55%), and cough (46%). COVID-19 was severe or critical in 5 (23%). All patients had elevated inflammatory biomarkers. Immunosuppression was modified in 85% of patients. Most (n = 16, 86.4%) were hospitalized, 18% required intubation, and 14% required vasopressor support. Five patients (23%) expired. None of the patients requiring intubation survived. Five patients underwent OHT during the pandemic. They were all males, ranging from 30 to 59 years of age. Two were transplanted at United Network of Organ Sharing Status 1 or 2, 1 at Status 3, and 2 at Status 4. All were successfully discharged and are alive without allograft dysfunction or rejection. One contracted mild COVID-19 after the index hospitalization.

CONCLUSION: OHT recipients with COVID-19 appear to have outcomes similar to the general population hospitalized with COVID-19. OHT during the pandemic is feasible when appropriate precautions are taken. Further study is needed to guide immunosuppression management in OHT recipients affected by COVID-19.

J Heart Lung Transplant 2020;39:894–903

© 2020 International Society for Heart and Lung Transplantation. All rights reserved.

Reprint requests: Anuradha Lala-Trindade, MD, Department of Population Health Science and Policy, Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, Box 1030, One Gustave L. Levy Place, New York, NY 10129. Telephone: 212-241-7300 Fax: 212-241-5006.

E-mail address: Anu.lala@mountsinai.org

The coronavirus disease 2019 (COVID-19) global pandemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 7 million people and accounts for over 400,000 deaths

worldwide. Although disease manifestations range from mild upper respiratory symptoms to multiorgan failure and death,¹ disease severity among orthotopic heart transplantation (OHT) recipients on chronic immunosuppression is less well studied.^{2–4} The interplay of immunosuppression and SARS-CoV-2 infection may render OHT recipients more susceptible to acquiring COVID-19 and predisposed to more severe disease. Conversely, immunosuppression could be protective by mitigating host immune responses that result in adverse outcomes.⁵

The pandemic has also impacted the delivery of care for patients with advanced heart failure awaiting OHT. Specifically, the risk of contracting COVID-19 and exposure to healthcare workers must be balanced against the high risk of mortality on the waitlist. OHT is life-saving therapy and, as such, judicious use should continue through the pandemic. At the peak of the crisis in New York, logistic factors such as limited intensive care unit (ICU) beds and a shortage of blood products and ventilators resulted in restriction of organ transplantation. Additionally, the pandemic limited donor offers and in some instances precluded transplant donor teams from retrieving organs.

The following report describes the landscape of heart transplant care during the COVID-19 pandemic at our institution in New York, the disease epicenter. Our objectives were to recognize the varied presentations in OHT recipients with COVID-19, report outcomes, and highlight the clinical dilemmas encountered in their management, particularly pertaining to immunosuppression. We also sought to describe our practice and experience with performing 5 heart transplants during the peak of the pandemic and emphasize relevant considerations.

Methods

Data from March 1, 2020 through May 15, 2020 in all adult (age >18 years) OHT recipients with a positive test for SARS-CoV-2 and those who underwent OHT during this time were retrieved via retrospective chart review from the electronic medical record system. Patient demographics, clinical characteristics, laboratory data, management of immunosuppression, and treatment were collected. Outcomes were recorded for all patients. Categorical variables are presented as counts with percentages. Differences in the categorical variables were assessed by the chi-square test or by Fisher's exact test. Continuous variables are presented as medians with interquartile ranges (IQRs) or as means \pm SD as appropriate. Differences in continuous variables were tested by analysis of variance or Student's *t*-test for independent samples. Because of the small sample size, a non-adjusted binary regression logistic analysis was performed to obtain the odds ratio for risk factors for mortality. Two-sided significance levels of 0.05 were used in all analyses. Data were analyzed using Stata SE Version 13.0 (StataCorp LLC, College Station, TX). This study was approved by the Institutional Review Board at Mount Sinai Hospital.

Diagnostic and therapeutic approach

All SARS-CoV-2 tests performed used either reverse transcriptase polymerase chain reaction (RT-PCR) via Roche cobas 6800 or the Cepheid GeneXpert Xpress system of nasopharyngeal swab or

bronchoalveolar lavage specimens. Disease severity was categorized as mild (oxygen saturation > 94% and no pneumonia), moderate (oxygen saturation < 94% and pneumonia), severe (high-flow nasal oxygen, no vasopressors, moderate impairment of renal and liver function), and critical and cytokine release syndrome (on vasopressors and intubated) (Supplementary Table S1, available online at www.jhltonline.org). Administration of glucocorticoids and COVID-19-directed therapies as well as consideration for participation in clinical trials was based on the discretion of the treating physicians (details in Supplementary Material online). Institutional protocols were followed for anticoagulation administration (Supplementary Figure S1 online). Modification of immunosuppression occurred on a case-by-case basis.

OHT performed during COVID-19 pandemic

After March 1, 2020, 5 patients underwent OHT at our institution. Follow-up data were collected through May 15, 2020. Priority for transplantation was given to hospitalized patients or outpatients at moderate to high risk of waitlist mortality.

Results

COVID-19 in OHT recipients

Baseline characteristics (Table 1)

Of the approximately 400 OHT recipients followed at our institution, 6% are within the first year of transplant, 25% within 1–5 years, and 69% >5 years from transplant. A total of 22 OHT recipients tested positive for SARS-CoV-2 during the study period. OHT recipients with mild symptoms suggestive of COVID-19 who did not undergo testing (*n* = 4) were not included in this report.

The median age was 58.6 years, 14 (63.6%) were men, and 14 (64%) were African American or Hispanic ethnicity. The median time from OHT was 4.6 years, with only 2 being within 1 year from transplantation. One patient was a heart-kidney transplant recipient. Comorbidities included hypertension in 21 patients (95.5%), diabetes in 12 (54.5%), lung disease in 3 (13.6%), long-term dialysis in 3 (13.6%), and cardiac allograft vasculopathy in 8 patients (36.4%). Two had a recent history of acute allograft rejection, one treated with pulse dose steroids 94 days before COVID-19 diagnosis, and the other received anti-thymocyte globulin and rituximab 20 days before diagnosis.

Maintenance immunosuppression included tacrolimus in 18 (81.8%) patients, mycophenolate mofetil (MMF) in 13 (59.1%), prednisone in 13 (59.1%) (less than 20 mg/day in all), and mammalian target of rapamycin inhibitor (mTORi) in 3 (13.6%). Most were on a 2-drug regimen (59.1%).

Fever was the most common presenting symptom (68%), followed by gastrointestinal symptoms (55%) and cough (46%). All but 1 patient tested positive on initial SARS-CoV-2 RT-PCR performed on nasopharyngeal swab specimens. One patient had 2 negative SARS-CoV-2 RT-PCR tests performed on nasopharyngeal swab specimens but subsequently tested positive on bronchoalveolar lavage. COVID-19 antibody testing was performed in 6 patients. Of these, 4 had positive antibody titers and 2 were negative.

Table 1 Baseline Characteristics

Characteristic	No. (%)
Total, n	22
Demographics	
Age, years, median (IQR)	58.6 (49.1–71.2)
Age ≥ 60 years	10 (45.5)
Male	14 (63.6)
BMI, median (IQR) (kg/m ²)	27.4 (24.8–29.4)
Race	
White	4 (18.2)
Black or African American	8 (36.4)
Hispanic	6 (27.3)
Other	4 (18.2)
Blood group	
A	8 (36.4)
B	2 (9.1)
AB	1 (4.5)
O	10 (45.5)
Time post-transplant, median (IQR) (years)	4.6 (2.5–20.6)
Within 1 year	2 (9.1)
Multiorgan transplant	1 (4.5)
Comorbidities and transplantation related complications	
Hypertension	21 (95.5)
Diabetes	12 (54.5)
Lung disease	3 (13.6)
Chronic kidney disease stage ≥ III	14 (63.6)
End stage renal disease on dialysis	3 (13.6)
Malignancy (excluding non-melanoma skin cancers)	6 (27.3)
HIV	1 (4.5)
Smoking history	
Current	1 (4.5)
Former	7 (31.8)
Recent allograft rejection (within 3 months)	2 (9.1)
Permanent pacemaker	3 (13.6)
Cardiac allograft vasculopathy	8 (36.4)
Charlson comorbidity index ≥ 5	12 (54.5)
Baseline LVEF, median (IQR) (%)	59.5 (55–67)
Maintenance immunosuppression and medications	
Mycophenolate mofetil or mycophenolate sodium	13 (59.1)
Tacrolimus	18 (81.8)
Cyclosporine	4 (18.2)
mTOR inhibitor	3 (13.6)
Prednisone	13 (59.1)
No. Of immunosuppressive medications	
1	1 (4.5)
2	13 (59.1)
3	8 (36.4)
On ACEi or ARB	11 (50)
On statin	20 (90.9)
On chronic anticoagulation	6 (27.3)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; IQR, interquartile ranges; LVEF, left ventricular ejection fraction; mTOR, mammalian target of rapamycin.

Most patients ($n = 19$, 86.4%) required hospitalization. Of these, 16 were hospitalized at the study institution and 3 at outside institutions. Most were characterized as having mild ($n = 7$, 31.8%) or moderate ($n = 10$, 45.4%) disease, with 5 (22.6%) with severe or critical disease. The 3 patients managed outpatient had mild COVID-19.

Clinical characteristics (Table 2)

Median temperature on presentation was 37.5°C. Only 2 patients had a systolic blood pressure <100 mm Hg (Supplementary Table S2 online).

All patients ($n = 17$) had lymphopenia, with a median absolute lymphocyte count of 0.6 (IQR, 0.5–0.7) K/ μ l. Nine patients developed acute kidney injury during the hospitalization, and 3 (17.6%) patients had elevation of transaminases to greater than 3 times the upper limit of normal. Inflammatory biomarkers were significantly elevated (Figure 1). Two patients had creatinine kinase elevation >1,000 U/liter and rhabdomyolysis. Most (82.4%) had abnormal chest radiographs, with multifocal opacities being the most common finding ($n = 6$, 35.3%).

Myocardial injury with elevated troponin I level was present in 3 (17.6%) patients, 1 of whom also had ST-T wave changes. All patients with elevated troponin I level had an echocardiogram which showed hyperdynamic left ventricular function in 2 patients and unchanged moderately reduced allograft function in 1. Notably, of the 8 patients with cardiac allograft vasculopathy, only 1 had an elevated troponin I level. Two others had ST-T wave changes without troponin elevation.

Management (Table 3)

Of the 16 patients hospitalized at the study institution, on presentation 8 required supplemental oxygen and 1 needed intubation. Another patient who did not require supplemental oxygen ultimately required intubation. All 3 patients admitted to outside institutions required intubation and ultimately expired. Three patients required renal replacement therapy, of whom 1 had renal recovery. No patients were placed on extracorporeal membrane oxygenation. A timeline of disease progression in our cohort is depicted in Figure 2.

Most patients received COVID-19-directed therapy including hydroxychloroquine,⁶ hydroxychloroquine and azithromycin,³ remdesivir,¹ convalescent plasma,¹ and tocilizumab.¹ One patient who received hydroxychloroquine and azithromycin developed significant corrected QT interval prolongation, and hydroxychloroquine dose was reduced and azithromycin withdrawn. The patient who received remdesivir developed significant elevation in transaminases, necessitating termination. High dose glucocorticoids were used in 5 (25%) patients and anticoagulation in 11 (55%) patients. Concomitant antibiotics were administered in 9 patients, although only 1 had documented bacteremia and pneumonia with *Staphylococcus aureus*.

In terms of the background immunosuppression, the trough range targeted for calcineurin inhibitors (CNIs) was

Table 2 Diagnostic Studies in Hospitalized Patients

Laboratory studies	Admission Median (IQR)	Peak Median (IQR)
WBC count (K/ μ l)	5.3 (4.1–6.3)	—
Absolute lymphocyte count (K/ μ l)	0.6 (0.5–0.7)	—
Platelet count (K/ μ l)	207 (180–267)	—
Creatinine (mg/dl)	2 (1.25–2.61)	2.19 (1.53–3.57)
AST (U/liter)	31 (24–48.5)	54.5 (26.3–66.5)
ALT (U/liter)	25 (17–30)	27 (17.75–72.5)
LDH (U/liter)	334.5 (249.3–452.3)	355 (299.5–452.5)
BNP (pg/ml)	107.7 (57.7–193.5)	—
CK (CPK) (U/liter)	164 (71.5–195)	85 (53.5–381)
Troponin I (ng/ml)	0.02 (0.01–0.02)	0.02 (0.01–0.03)
D-dimer (μ g/ml)	1.01 (0.45–1.6)	1.26 (0.89–3.35)
>1, n (%)	11 (64.7)	—
Ferritin (ng/ml)	601.5 (294.3–1,061)	933 (463–1,592)
>1,000, n (%)	8 (4.7)	—
C-reactive protein (mg/liter)	54.3 (26.9–119.7)	119.15 (92.7–159.03)
Procalcitonin (ng/ml)	0.15 (0.085–1.255)	—
IL-6 (pg/ml)	62.9 (42.95–76.45)	—
COVID antibodies positive, n (%)	4/6 (66.7)	—
Duration from onset of symptoms to date of COVID antibody test (days)	24 (9–40)	—
Tacrolimus trough level on admission (ng/ml)	10.75 (7.7–11.8)	—
Cyclosporine trough level on admission (ng/ml)	208 (141.9–219)	—
Sirolimus trough level on admission (ng/ml)	26	—
Everolimus trough level on admission (ng/ml)	2.3	—
Electrocardiogram		
New ST-T changes, n (%)	3 (17.6)	—
Chest radiograph findings		
Normal, n (%)	3 (17.6)	—
Interstitial pattern, n (%)	1 (5.9)	—
Unilateral consolidation, n (%)	5 (29.4)	—
Bilateral consolidation, n (%)	2 (11.8)	—
Multifocal opacities, n (%)	6 (35.3)	—

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; COVID, coronavirus disease; CPK, creatine phosphokinase; IL, interleukin; IQR, interquartile range; LDH, lactate dehydrogenase; WBC, white blood cell;

Data available in 17 patients (details were not available for 2 of the patients hospitalized at outside institutions).

not modified. Four (22.2%) patients presented with supra-therapeutic tacrolimus levels. All 3 patients on mTORi either had their drug held or dose reduced.

One of 2 patients on sirolimus had an elevated level of 26 ng/ml on admission. Anti-metabolite doses were reduced in 3 (23.1%) patients and held in 7 (53.8%). For those managed as outpatients, one had his MMF held during the acute infection.

Outcomes (Table 3)

Overall mortality was 22.7%, with a mortality of 26.3% in hospitalized patients. None of the patients admitted at outside institutions survived. Four patients (21% of all hospitalized) required ICU admission, all of whom expired, 2 from progressive respiratory failure and acute respiratory distress syndrome, 1 from intracranial hemorrhage, and 1 from refractory shock. Another patient who died from respiratory failure elected to pursue comfort care.

At the study institution, 2 (12.5%) patients required ICU admission and 14 (87.5%) patients recovered and were discharged. Mortality among those hospitalized at the study institution was 12.5%. Mortality including those managed in the outpatient setting by the study institution was 10.5%. There were no episodes of rejection or diagnosed thrombo-embolic events.

Risk factors for mortality (Supplementary Table S3 online)

None of the demographic variables, including age, sex, body mass index, time since transplant, or comorbidities, had a statistically significant association with mortality. Baseline immunosuppression, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, or statin use were not associated with mortality either. Lymphocyte count was lower, and peak creatinine, peak troponin I level, peak D-dimer, and peak ferritin were higher in

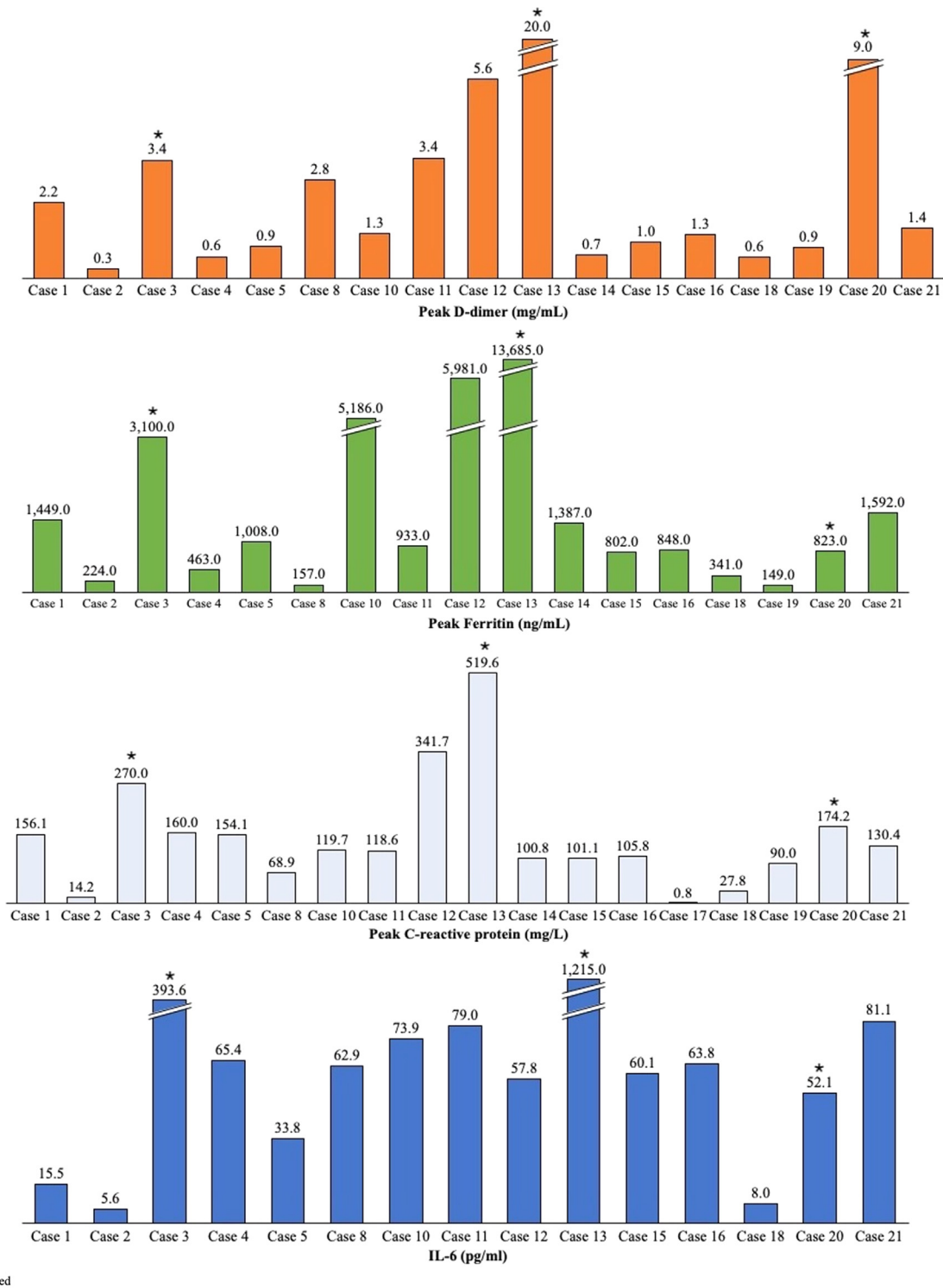


Figure 1 Range of Inflammatory Biomarkers.

the patients that did not survive; however, the result was not statistically significant.

Heart transplantation performed during COVID-19 pandemic (Table 4)

Patients who were transplanted were all men, age range from 30 to 59 years. Patient 1 had recurrent ventricular

tachycardia (VT) complicated by cardiogenic shock requiring intra-aortic balloon pump placement. Patient 2 had post –left ventricular assist device (LVAD) implant right ventricular failure requiring a temporary right ventricular assist device. Patient 3 had VT storm refractory to multiple anti-arrhythmic drugs. Patient 4 had been supported on a durable LVAD for 23 months, and patient 5 was supported with a durable LVAD with a driveline infection, device malfunction, and a chest wall deformity, complicating donor size

Table 3 Management and Outcomes

Management	No. (%)
Total hospitalized, n	19
Supplemental oxygen	12 (63.2)
Maximum amount of respiratory support required	
Nasal cannula	5 (26.3)
High-flow nasal cannula or non-rebreather mask	3 (15.8)
Mechanical ventilation	4 (21.1)
Vasopressor support	3 (15.8)
Renal replacement therapy (not including long-term dialysis)	3 (15.8) ^a
Total, n	20^b
Hydroxychloroquine	11 (55)
Azithromycin	4 (20)
Remdesivir	1 (5)
Tocilizumab	1 (5)
Convalescent plasma	1 (5)
High dose glucocorticoids	5 (25)
Treatment dose anticoagulation	11 (55)
Antibiotics	9 (45)
Anti-metabolite dose reduction	3/13 (23.1)
Anti-metabolite held	8/13 (61.5)
mTOR inhibitor dose reduction	1/3 (33.3)
mTOR inhibitor held	2/3 (66.7)
ACEi or ARB held	8/11 (72.7)
Outcomes	
Total, n	22
Outpatient management	3 (13.6)
Overall hospitalized	19 (86.4)
Hospitalized at outside institutions	3 (13.6)
Overall ICU admission in hospitalized patients	4 (21.1)
Overall discharged	14 (73.7)
Overall survival	17 (77.3)
Survival in hospitalized patients	14 (73.7)
Survival in patients requiring ICU admission	0
Outcomes at study institution, total n	16
ICU admission	2 (12.5)
Palliative care/ Do not resuscitate	2 (12.5)
Discharged	14 (87.5)
Length of stay, days, median (IQR)	7 (4-9)
Survival in hospitalized patients	14 (87.5)
Survival in patients requiring ICU admission	0

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; IQR, interquartile range; mTOR, mammalian target of rapamycin.

^aOf these 3, 1 had renal recovery.

^bExcluding 2 of the patients hospitalized at outside institutions for whom details were not available.

requiring hospitalization. No changes were made in his immunosuppression. None of the patients developed acute rejection or allograft dysfunction. Weekly endomyocardial biopsies (EMBs) were performed during the first month and biweekly during the second month, as is our standard biopsy schedule. SARS-CoV-2 RT-PCR was performed within 48 hours before EMB, and all cardiac catheterization lab personnel wore full personal protective equipment. After Month 2, patients were transitioned to non-invasive rejection surveillance that included both gene expression profiling and donor-derived cell-free DNA.

Discussion

We report 22 cases of COVID-19 in OHT recipients, with a wide spectrum of presentations and with a 23% overall mortality. We also demonstrate the feasibility of performing transplantation with favorable short-term outcomes during the pandemic.

Presentation and disease severity of COVID-19 among OHT recipients

OHT recipients may be more susceptible to severe disease than the general population by virtue of chronic immunosuppression. In our population, however, 22.7% had severe or critical disease and 18.2% were intubated. This distribution is similar to that reported in the general population by the Chinese Center for Disease Control.¹ It is also similar to a recent report by Latif et al.⁴ exclusively on patients with OHT. Despite the potential for atypical presentation because of chronic immunosuppression, patients in our cohort presented with symptoms similar to the general population.⁷ The highly prevalent lymphopenia seen in our patients may have resulted from the use of anti-metabolites rather than COVID-19. Anti-metabolites may also be associated with lower maximum temperatures.

Mortality from COVID-19

The overall mortality rate for our cohort was 22.7%; ICU admission rate was 21%, with 80% mortality in those with severe to critical disease. This is higher than the case fatality rates reported by the Chinese and U.S. Centers for Disease Control and Prevention.^{1,8} However, the comparison for overall mortality should be interpreted with caution because the data in OHT recipients represents primarily hospitalized patients. Notably, the outcomes in OHT recipients appear to be similar to that of non-transplant hospitalized patients with similar demographics and medical complexity.^{9,10} A large health system across New York City reported an ICU admission rate of 14.2% and 21% mortality in 2,634 patients hospitalized with COVID-19.⁹ Our institution has also reported a mortality of 18.5% in 2,736 hospitalized COVID-19 patients.¹⁰

Patients with comorbid conditions have a higher risk of mortality in COVID-19.¹¹ In our cohort, 77.3% of patients

matching. All of the patients survived and were discharged with normal allograft function (Figure 3a). Post-transplant complications included pulmonary embolism, gastrointestinal bleed, and VT. None developed COVID-19 during the index admission, but 1 subsequently developed mild disease

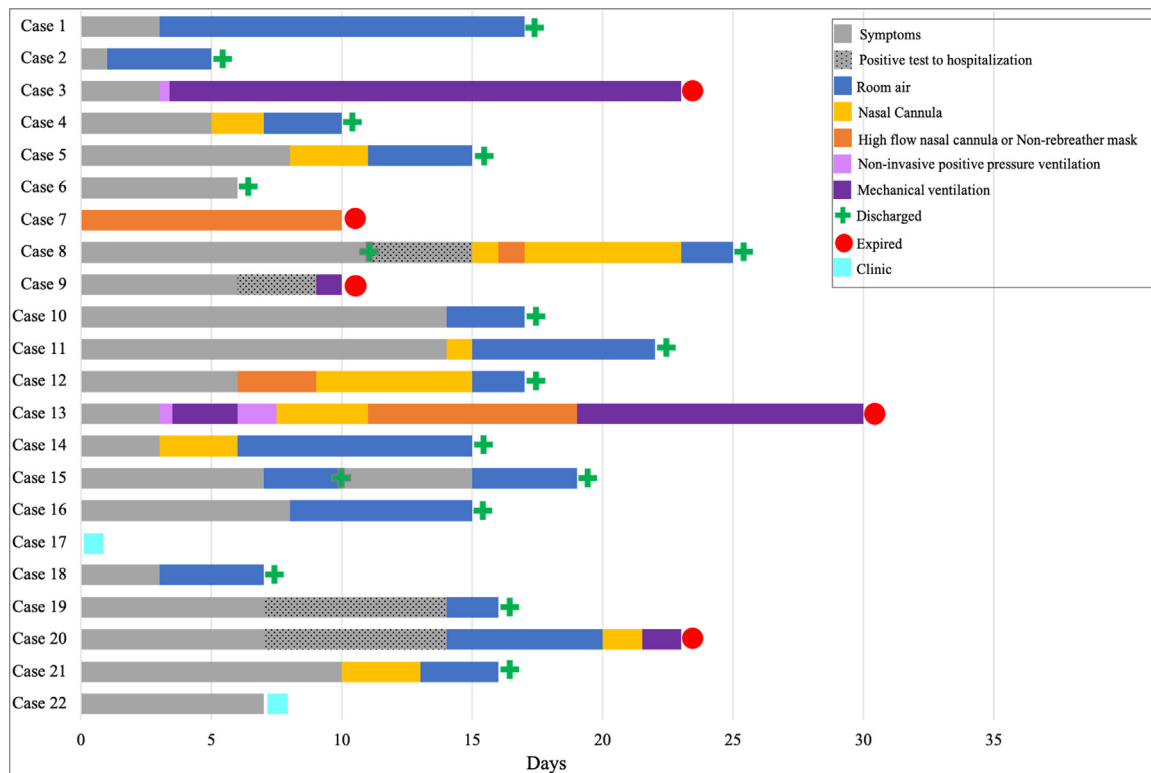


Figure 2 Disease Progression and Outcomes.

had 2 or more comorbid conditions with a median Charlson comorbidity index of 5 (IQR, 1–7). In our cohort, 64.7% of the hospitalized patients also had a D-dimer >1 mg/ml, which is associated with an approximately 20-fold risk of mortality.¹¹ Myocardial injury is also a poor prognostic marker.^{6,10} All 3 patients with elevated troponin I level in our cohort expired.

In regards to mortality in transplant recipients, Latif et al.⁴ and Pereira et al.¹² reported a mortality of 25% and 24% in hospitalized OHT and solid organ transplant recipients, respectively. Data reported by the New York State Thoracic Transplant consortium shows that, as of June 10, 2020, 127 OHT recipients were diagnosed with COVID-19 in New York State, 22 of the 83 patients hospitalized required ICU care (27%), and 17 expired (20.5%), although many remained hospitalized at the time of reporting.

One surprising finding was a lower mortality rate in those patients treated at the transplant center. Similar to our cohort, Latif et al.⁴ reported a mortality rate of 12.5% for those patients treated at the transplant center. It is unclear whether this reflects that those patients treated at outside institutions were too ill to be transferred or the need for a higher level of expertise in caring for these patients that cannot be provided locally.

Our analysis is limited given the small sample size. Although none of the variables had a statistically significant association with mortality, patients who died were older, had a higher body mass index, increased incidence of lung disease, and chronic prednisone use. Patients who died also had a lower lymphocyte count on presentation and higher peak creatinine, peak troponin I level, and peak D-dimer.

None of the therapies used seemed to have an association with mortality.

Immunosuppression: predisposing or protective against severe COVID-19?

Immunosuppression could render patients more susceptible to contracting COVID-19. Specifically, MMF prevents lymphocyte proliferation and antibody production. It decreases immune response to influenza vaccine and is associated with a higher frequency of viral infections.^{13,14}

Conversely, immunosuppression may make patients less susceptible to contracting the disease and/or ameliorate its severity. Immunosuppressants activate the renin-angiotensin-aldosterone system, which could modulate the expression of pulmonary ACE2 receptors, which are the binding site for the SARS-CoV-2 viral particles.¹⁵ CNIs actually inhibit the replication of SARS-CoV-2 in vitro.¹⁶ Additionally, in the latter stage of the disease, the clinical phenotype is a consequence of the host immune response, which is attenuated by steroid use. Of the 22 recipients in our cohort, 13 were on steroids as maintenance therapy but still had elevated interleukin (IL)-6 levels, and 4 (30.8%) of those developed severe or critical disease.

Management of immunosuppression and potential interactions with COVID-19 therapies

COVID-19 is characterized by significant lymphopenia, which prompted a decrease or suspension of MMF in 11 of

Table 4 Characteristics of Heart Transplants Performed During COVID-19 Pandemic

Characteristic	No. (%)
Total, n	5
Demographics	
Age, years, median (range)	47 (30–59)
Male	5 (100)
Race	
White	2 (2)
Black or African American	1 (1)
Hispanic	0 (0)
Other	2 (40)
Blood group	
A	0 (0)
B	1 (20)
AB	3 (60)
O	1 (20)
Medical/transplant characteristics	
UNOS status at transplantation	
1	1 (20)
2	1 (20)
3	1 (20)
4	2 (40)
Mechanical support	
Biventricular support	1 (20)
Temporary univentricular support	1 (20)
Durable univentricular support	2 (20)
Ischemic time, minutes, median (range)	183 (122–236)
Retrospective crossmatch negative	5 (100)
Induction immunosuppression	0 (0)
Post-transplant LOS, days, median (range)	16 (14–48)
Etiology of heart failure	
Ischemic	2 (40)
Non-ischemic	2 (40)
Mixed	1 (20)
Medical history/comorbidities	
Hypertension	2 (40)
Diabetes mellitus	4 (80)
Chronic kidney disease Stage \geq III	3 (60)
Peripheral arterial disease	1 (20)
Malignancy	1 (20)
Connective tissue disease	1 (20)
Diverticulosis	1 (20)
Endocarditis	1 (20)
Post-transplant complications	
Acute allograft rejection	0 (0)
COVID-19	1 (20)
GI bleed	1 (20)
Chyle leak	1 (20)
Ventricular tachycardia	1 (20)
Venous thromboembolism	1 (20)
Bacterial sepsis	1 (20)

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal; LOS, length of stay; UNOS, United Network of Organ Sharing.

13 patients. Three were on mTORi and pneumonitis was considered in their evaluation.¹⁷ We maintained CNIs at therapeutic levels given the potentially beneficial immunomodulatory effects and to offset the known risk of rejection from CNI withdrawal.

Drug interactions with medications used in OHT recipients are important to consider and are described in [Supplementary Table S4](#) online. The metabolism of mTORi and CNIs may be altered by anti-retroviral agents, hydroxychloroquine, and IL-6 inhibitors, necessitating dose reductions and drug level monitoring.^{18,19} Lastly, drug metabolism will also be altered in COVID-19 patients with elevated IL-6 levels as IL-6 inhibits CYP P450 metabolism. We did note elevated tacrolimus and sirolimus levels in some patients who had been on stable doses previously.

Transplantation during the pandemic

Weighing the life-saving benefit of transplantation in the sickest patients against the risk of COVID-19 exposure posed unique challenges to waitlisted patients. Whereas some centers restricted OHT to those listed as United Network of Organ Sharing Status 1–3, we opted to evaluate recipients on a case-by-case basis. Patient 5, for example, was Status 4 but had recurrent low flow alarms because of outflow obstruction, progressive driveline infection, and donor size constraints, thereby facing a high risk of adverse events.

Appropriate precautions were undertaken to minimize the risk of exposure to the patients and the healthcare team. Logistic challenges, including shortage of ICU beds, staffing, medical supplies, and equipment, were navigated without compromising the quality of care. Post-operative care aimed to mitigate the risk of nosocomial COVID-19 spread among recent OHT recipients. Standard immunosuppression was instituted without modifications. For transitional care planning, effective patient and caregiver education was delivered via telephone. Patients were advised to self-quarantine with universal mask wearing; family members were screened for symptoms; and outpatient transplant care was modified to incorporate mobile phlebotomy, telehealth video visits, more frequent telephone follow-up, SARS-CoV-2 testing before EMB, and earlier transition to non-invasive rejection surveillance ([Figure 3b](#)).

The short-term outcomes following the 5 OHT recipients do not seem to have been compromised during the COVID-19 pandemic. Only 1 patient contracted mild COVID-19. Although their outcomes in the absence of transplantation cannot be known, mortality risk for deferring transplant was high for all those transplanted. Given the possibility of COVID-19 resurgence, it is necessary to develop strategies whereby life-saving heart transplantation can be carried out through such outbreaks. Our experiences provide a useful framework, demonstrating modifications to standard care protocols can be undertaken without obvious detrimental effect on the delivery of care. Broader application could be considered in the non-COVID-19 setting (such as utilization of telemedicine and screening of caregivers). As more information and understanding of COVID-19 emerges, concrete evidence-based guidelines can be established.

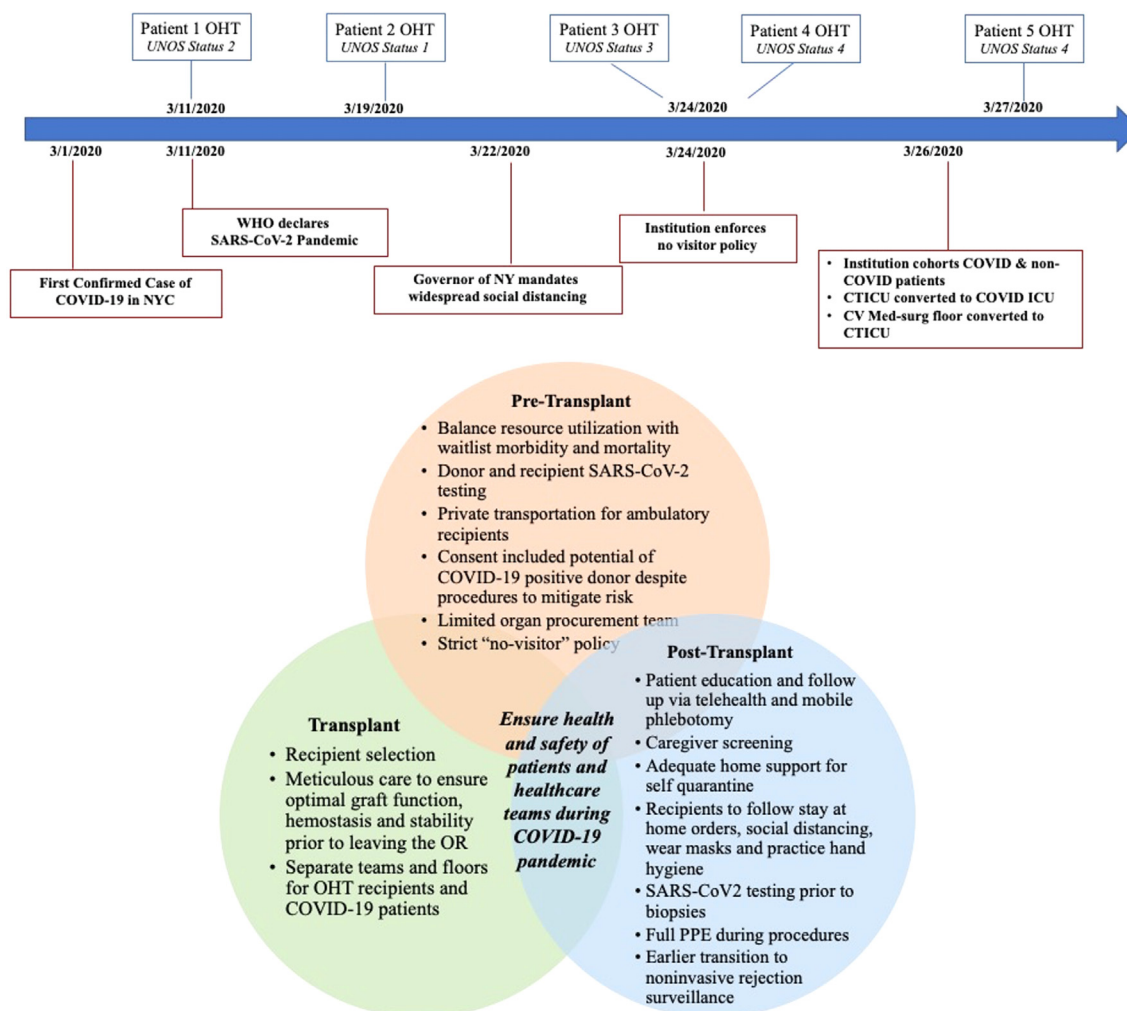


Figure 3 (a) Heart transplants performed during the COVID-19 pandemic (top panel). (b) Care of the transplant recipients and the healthcare team (bottom panel). COVID-19, coronavirus disease 2019; CTICU, cardiothoracic intensive care unit; NY, New York; NYC, New York City; OHT, orthotropic heart transplant; OR, operating room; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UNOS, United Network of Organ Sharing, WHO, World Health Organization.

Conclusion

The COVID-19 pandemic has posed unique challenges for the management of OHT recipients and those awaiting transplantation. In this limited case series across a single institution at the epicenter of the pandemic, we observed intubation and in-hospital mortality rates similar to other hospitalized patients. Further, we found highly judicious pursuance of transplantation feasible and life-saving for select candidates. Further work is needed to understand how practices should evolve to optimize patient outcomes amidst COVID-19.

Disclosure statement

S.P. has received personal fees from Care Dx, Medtronic, Procyron, and Abbott Inc. S.S.M. has received speaking fees from Abbott Laboratories and an honoraria from Cowen & Co. J.A.G. has received grant support from

Daniel Bravo Andreu Private Foundation. The other authors have no additional disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.healun.2020.06.015>.

References

- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [e-pub ahead of print]. JAMA. doi: 10.1001/jama.2020.2648, accessed June 15, 2020.
- Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. J Heart Lung Transplant 2020;39:496-7.
- Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930-6.

4. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019 [e-pub ahead of print]. *JAMA Cardiol.* doi: 10.1001/jamacardio.2020.2159, accessed June 15, 2020.
5. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363-74.
6. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China [e-pub ahead of print]. *JAMA Cardiol.* doi: 10.1001/jamacardio.2020.0950, accessed June 15, 2020.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [e-pub ahead of print]. *JAMA.* doi: 10.1001/jama.2020.1585, accessed June 15, 2020.
8. Centers for Disease Control and Prevention. Cases in the U.S. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>.
9. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area [e-pub ahead of print]. *JAMA.* doi: 10.1001/jama.2020.6775, accessed June 15, 2020.
10. Lala A, Johnson KW, Russak AJ, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection [e-pub ahead of print]. *J Am Coll Cardiol.* doi: <https://doi.org/10.1016/j.jacc.2020.06.007>, accessed June 15, 2020.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.
12. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the U.S. epicenter [e-pub ahead of print]. *Am J Transplant.* doi: 10.1111/ajt.15941, accessed June 15, 2020.
13. Kobashigawa J, Miller L, Renlund D, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. *Transplantation* 1998;66:507-15.
14. Ong JP, Barnes DS, Younossi ZM, et al. Outcome of de novo hepatitis C virus infection in heart transplant recipients. *Hepatology* 1999;30:1293-8.
15. Letizia C, d'Ambrosio C, De Ciocchis A, Scavo D, Pozzilli P. Serum angiotensin-converting enzyme levels in patients with recent-onset insulin-dependent diabetes after one year of low-dose cyclosporin therapy. IMDIAB Study Group. *Int J Clin Pharmacol Res* 1995;15:209-13.
16. 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;165:112-7.
17. Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000;343:225-6.
18. van Maarseveen EM, Crommelin HA, Mudrikova T, van den Broek MP, van Zuilen AD. Pretransplantation pharmacokinetic curves of tacrolimus in HIV-infected patients on ritonavir-containing cART: a pilot study. *Transplantation* 2013;95:397-402.
19. Tanaka E, Taniguchi A, Urano W, Yamanaka H, Kamatani N. Pharmacogenetics of disease-modifying anti-rheumatic drugs. *Best Pract Res Clin Rheumatol* 2004;18:233-47.