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BRIEF COMMUNICATION

# Low mortality in SARS-CoV-2 infected heart transplant recipients at a single center

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## Abstract

Immunosuppressed heart transplant (HT) recipients are thought to be at higher risk of infection and mortality from SARS-CoV-2 infection coronavirus disease 2019 (COVID-19); however, evidence guiding management of HT patients are limited. Retrospective search of electronic health records from February 2020 to February 2021, identified 28 HT recipients out of 400 followed by UC San Diego who tested positive for SARS-CoV-2. Patient demographics, COVID-19 directed therapies, hospital course and outcomes were compared to control HT recipients who tested negative for SARS-CoV-2 during the same period ($n = 80$). Among 28 HT recipients who tested positive for SARS-CoV-2, 15 were admitted to the hospital and 13 were monitored closely as outpatients. Among inpatients, five developed severe illness and two died (7% mortality). Nine patients were treated with remdesivir, and four received dexamethasone and remdesivir. Two outpatients received neutralizing monoclonal antibody therapy and one outpatient received dexamethasone for persistent dyspnea. Immunosuppressed HT recipients, especially Hispanic patients and patients with higher body mass index, were at greater risk of infection and mortality from COVID-19 than the general population. Use of remdesivir and dexamethasone may have improved outcomes in our HT recipients compared to HT recipients at other centers.

KEYWORDS
COVID-19, heart transplant, SARS-CoV-2

## 1 | INTRODUCTION

Solid organ transplant (SOT) recipients who are immunosuppressed may be particularly at risk from coronavirus disease 2019 (COVID-19), the disease caused by infection with novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Early reports from large heart transplant (HT) centers demonstrated 15–33% mortality from COVID-19 (Table 1).[1–5] Given lack of data on appropriate medical therapy early in the pandemic, there was significant variability in the treatment approaches used in these studies, with reported use of the following drugs, often in combination: hydroxychloroquine, corticosteroids, lopinavir/ritonavir, ganciclovir, intravenous immunoglobulins, and monoclonal antibodies against IL-6.[1–3,5–11]

The recent ACTT-1 clinical trial on remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase, demonstrated a shortened median recovery time in the general population versus placebo.[12] The RECOVERY Trial demonstrated that treatment with dexamethasone for up to 10 days significantly improved 28-day mortality in the general population when given to hypoxic patients requiring supplemental oxygen therapy (there was no benefit observed in patients who did not require supplemental oxygen).[13] Mortality has been declining since the early pandemic as clinicians have adapted evidence-based treatment

**TABLE 1** Previously published case series of heart transplant (HT) recipients with COVID-19 infection ($n = 242$) compared with the UCSD case series ($n = 28$)

| Study: Date (2020) Hospital/ CityCountry | Li Feb-Mar Wuhan, China | Kates Feb-Mar UWS eattle, USA | Mathias Feb-Mar Koblenz, Germany | Holz-hauser Mar-Apr Chicago, USA | Fernandez-Ruiz Mar-Apr Spain | Ahluwalia Mar-May BWH Boston, USA | Ballout Jul-Sep U. Kentucky, USA | Bottio Feb-Aug 7 Centers N. Italy | Latif Mar-Apr Columbia NY, USA | Singhvi Mar-May Mt. Sinai, NY, USA | Rivinius Mar-Jun 24 Centers Germany | Genuardi Mar-Oct 11 Centers USA | Duran Feb-Feb UCSD San Diego, USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *n* | 2 | 1 | 1 | 2 | 4 | 5/358 | 4 | 53/2676 | 28/803 | 22/400 | 21 | 99/4841 | 28/400 |
| Prevalence | | | | | | 1.4% | | 2.0% | 3.5% | 5.5% | | 2.0% | 7.0% |
| Age (median) | (43-51) | 74 | 77 | (59-75) | 64 (38-67) | 50 (49-58) | 62 (62-65) | 62 ± 14.5 | 64 (54-71) | 59 (49-71) | 60 ± 12.3 | 60 (46-69) | 57 (46-63) |
| Male | 1 | 1 | 1 | 1 | 4 (100%) | 4 (80%) | 4 | 41 (77%) | 22 (79%) | 14 (64%) | 17 (81%) | 74 (75%) | 21 (75%) |
| Years post HT | (3-16) | 23 | 17 | (8-20) | 13 (9-18) | 21 (6-25) | 2 (.5-4) | 10.5 ± 8.7 | 9 (4-15) | 3 (4-21) | 7.8 ± 6.9 | 6 (2-14) | 3 (.5-6.3) |
| **Maintenance immunosuppression** | | | | | | | | | | | | | |
| Tacrolimus | 2 | 1 | 0 | 1 | 1 | 2 (40%) | 3 (75%) | 25 (47%) | 22 (79%) | 18 (82%) | 10 (48%) | 94 (95%) | 26 (93%) |
| Cyclosporine | 0 | 0 | 0 | 1 | 3 | 2 (40%) | 1 (25%) | 37 (69%) | 5 (18%) | 0 | 5 (24%) | – | 1 (4%) |
| MMF | 2 | 0 | 1 | 2 | 1 | 3 (60%) | 4 (100%) | 30 (57%) | 19 (68%) | 13 (59%) | 18 (86%) | 58 (59%) | 13 (46%) |
| mTORi | 0 | 0 | 1 | 0 | 0 | 2 (40%) | 0 | 15 (28%) | 5 (18%) | 3 (14%) | 9 (43%) | 15 (15%) | 13 (46%) |
| Azathioprine | 0 | 0 | 0 | 0 | 0 | 1 (20%) | 0 | 3 (6%) | 3 (6%) | 0 | 0 | 0 | 2 (7%) |
| Steroids | 0 | 0 | 0 | 0 | 4 | 5 (100%) | 2 (50%) | 22 (42%) | 19 (68%) | 13 (59%) | 15 (71%) | 47 (47%) | 7 (25%) |
| **COVID-19 directed therapies** | | | | | | | | | | | | | |
| Antibiotics | 2 | 0 | 1 | 1 | 0 | 4 | N/A | 40 (75%) | N/A | 9 (41%) | 21 (100%) | 19 (19%) | 7 (25%) |
| Hydroxychloroquine | 0 | 0 | 1 | 2 | 4 | 0 | 0 | 38 (81%) | 18 (64%) | 11 (50%) | 3 (14%) | 0 | 0 |
| Azithromycin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (14%) | 4 (19%) | 0 | 0 |
| Tocilizumab | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 (2%) | 6 (21%) | 1 (5%) | 0 | 6 (6%) | 0 |

(Continues)

**TABLE 1** (Continued)

| Study: Date (2020) Hospital/ CityCountry | Li Feb-Mar Wuhan, China | Kates Feb-Mar UWS eattle, USA | Mathias Feb-Mar Koblenz, Germany | Holz-hauser Mar-Apr Chicago, USA | Fernandez-Ruiz Mar-Apr Spain | Ahluwalia Mar-May BWH Boston, USA | Ballout Jul-Sep U. Kentucky, USA | Bottio Feb-Aug 7 Centers N. Italy | Latif Mar-Apr Columbia NY, USA | Singhvi Mar-May Mt. Sinai, NY, USA | Rivinius Mar-Jun 24 Centers Germany | Genuardi Mar-Oct 11 Centers USA | Duran Feb-Feb UCSD San Diego, USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glucocorticoids | 1 | 0 | 0 | 0 | 0 | 0 | 4 (100%) | 10 (21%) | 8 (29%) | 5 (23%) | 8 (38%) | 19 (19%) | 5 (18%) |
| Lopinavir/Ritonavir | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 21 (45%) | 0 | 0 | 0 | 0 | 0 |
| Ganciclovir | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Remdesivir | 0 | 0 | 0 | 0 | 0 | 2 (40%) | 2 (50%) | 0 | 0 | 1 (5%) | 0 | 11 (11%) | 9 (32%) |
| Convalescent plasma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5%) | 0 | 11 (11%) | 1 (4%) |
| REGN-CoV-2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (7%) |
| Anticoagulation | 0 | 0 | 0 | 0 | 0 | 0 | | 4 (9%) | N/A | 11 (50%) | 8 (38%) | 2 (2%) | 0 |
| Reduced IST | N/A | 0 | 0 | 2 | 0 | 2 (40%) | 4 (100%) | 19 (36%) | 19 (68%) | 13 (59%) | 11 (52%) | 52 (53%) | 10 (36%) |
| **Hospital course** | | | | | | | | | | | | | |
| Outpatient | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 14 (26%) | 6 (21%) | 3/22 (14%) | 2 (10%) | 36 (36%) | 13 (46%) |
| Hospitalized | 2 | 0 | 1 | 2 | 4 | 3 | 4 (100%) | 39 (74%) | 22 (79%) | 19 (86%) | 19 (90%) | 63 (64%) | 15 (54%) |
| ICU | 1 | 0 | 1 | 2 | 1 | 0 | 1/4 (25%) | 4 (9%) | 7 (25%) | 5/22 (23%) | 15/21 (71%) | 24 (24%) | 5 (18%) |
| Intubation | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 2 (4%) | 7 (25%) | 5/22 (23%) | 8/21 (38%) | 20 (20%) | 3 (11%) |
| New RRT | 0 | 0 | 0 | N/A | 0 | 0 | 0 | 0 | 3 (11%) | 3/22 (14%) | 5/21 (24%) | 11 (11%) | 0 |
| ECMO | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3/21 (14%) | 0 | 0 |
| Remains hospitalized | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1/38 (2%) | 4/22 (18%) | 0 | 4/21 (19%) | 0 | 0 |
| Discharged | 2 | 0 | 1 | 1 | 3/4 | 3/3 | 4 | 24/39 (62%) | 11/22 (50%) | 14/19 (74%) | 10/19 (53%) | 49/63 (78%) | 13/15 (87%) |
| In-hospital mortality | 0 | 0 | 0 | 1/2 | 1/4 | 0 | 0 | 14/39 (36%) | 7/22 (32%) | 5/19 (26%) | 7/19 (37%) | 14/63 (22%) | 2/15 (13%) |
| **Overall Mortality** | **0** | **0** | **0** | **1** | **1/4** | **1/5 (20%)** | **0** | **14/53 (26%)** | **7/28 (25%)** | **5/22 (23%)** | **7/21 (33%)** | **15 (15%)** | **2/28 (7%)** |

The number of patients in the study (*n*) reflects the number of HT recipients who tested positive for SARS-CoV-2 out of the total number of HT recipients followed at each transplant program (if this data was reported). Age and years post HT are reported as median with interquartile ranges for all studies except Bottio and Rivinius which reported mean ± standard error of the mean (SEM).
Genuardi reported use of immunosuppression under drug class rather than individual drug names ("calcineurin inhibitors" are listed under tacrolimus, "proliferation signal inhibitors" are listed under mTORi).
*Abbreviations*: UW, University of Washington; BWH, Brigham and Women's Hospital; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitors; REGN-CoV-2 (casirivimab/imdevimab); IST, immunosuppressive therapy; ICU, intensive care unit; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

approaches from these trials. The 1-month mortality rates reported in the ACTT-1 and RECOVERY trials were 11–26%, and as of May 7 2021, the global case fatality rate reported by the WHO is now down to 2.09%.[14]

In this study, we describe the clinical course, treatment, and outcomes of 28 HT recipients who tested positive for SARS-CoV-2 during the first year of the global pandemic at University of California San Diego (UCSD). The goal of our study was to assess disease severity and clinical outcomes in HT recipients with COVID-19.

## 2 | METHODS

We carried out a single center retrospective study of HT recipients followed at UCSD who tested positive for SARS-CoV-2 between February 1, 2020 and February 28, 2021. This study was approved and overseen by the UCSD Institutional Review Board (IRB# 200575) and was granted a waiver of informed consent. De-identified patient health information was acquired by retrospective search of Epic Systems (Madison, WI, USA) electronic medical records and was aggregated in a central REDCap database for analysis. We included any HT recipient with a positive test result for SARS-CoV-2 performed on nasal or nasopharyngeal swabs and/or bronchoalveolar lavage fluid via a rapid test or polymerase chain reaction (PCR) that was performed at UCSD laboratories using one of the following platforms: Roche (Basel, Switzerland), Hologic (Marlborough, MA, USA), and Abbot (Chicago, IL, USA). Patients were tested if they had any symptoms of COVID-19 or as a screening precaution prior to any planned invasive cardiac procedure (i.e., surveillance endomyocardial biopsy or right heart catheterization). A population of 80 HT recipients with negative SARS-CoV-2 PCR tests during the same time period was included as a control. At UCSD, our COVID-19 treatment protocol was data driven. No patients were treated with hydroxychloroquine, lopinavir/ritonavir, ivermectin etc. We only used dexamethasone, remdesivir, and monoclonal antibodies as dictated by patient clinical status. Univariate analysis using Man Whitney U Test, Chi squared test, or Fisher's exact tests as appropriate was performed using GraphPad Prism9, with $P$-values $< .05$ considered statistically significant.

## 3 | RESULTS

### 3.1 | COVID-19 presentation and patient demographics

Out of the 400 HT recipients followed by our practice, 28 (7%) tested positive for SARS-CoV-2 during the first year of the pandemic (Table 1). Among these, 21 were symptomatic and seven were asymptomatic, the majority (21, 75%) were male and the median age was 57 years old (Tables 1 and 2). Most (24, 86%) had HT only, while four patients were dual-organ transplant recipients. Most patients (93%) were taking a calcineurin inhibitor in combination with at least one other immunosuppressant when they tested positive for SARS-CoV-2 (Table S1). The majority (21, 75%) of HT recipients who tested positive for SARS-CoV-2 were Hispanic (Table 2). When compared to control patients transplanted at UCSD in the past year who were not infected with SARS-CoV-2 ($n = 80$), patients who tested positive had significantly higher body mass index (BMI) and there were significantly more Hispanic patients and significantly fewer white patients than controls (Table 2).

Five patients (18%) had a prior history of either cellular mediated rejection (CMR), antibody mediated rejection (AMR) or both that required escalation of immunosuppression (Table 2). For 4/5 patients with history of rejection, the episode of rejection and treatment with burst and taper of immunosuppression occurred more than 1 year prior to COVID-19 diagnosis. The fifth patient had AMR2 without graft dysfunction and had completed treatment with steroid burst/taper 8 months prior to his COVID-19 diagnosis. Seven patients in the study (25%) had history of coronary allograft vasculopathy (CAV) detected on routine surveillance angiography after transplant (Table 2). While there was an observed trend toward higher rates of CMR and CAV in the COVID-19 infected HT recipients, the proportion of patients with COVID-19 and rejection were not significantly different compared to the control group (Table 2). Although we noted evidence of elevated inflammatory markers in HT recipients admitted with COVID-19 infection, including C-reactive protein (CRP), high sensitivity-CRP (hsCRP), and D-dimer (Table 4), all patients who experienced prior episodes of rejection had completed their burst and taper of immunosuppression at least 8 months prior to COVID-19 diagnosis and, thus, their rejection was not clearly temporally associated with their infection.

### 3.2 | COVID-19 presentation and disease course

Among 28 cases of COVID-19, 15 (54%) were admitted to the hospital for closer monitoring (Table 3, Figure 1). The most common presenting symptoms were cough (36%), fevers (25%), gastrointestinal symptoms (25%), shortness of breath (21%), loss of taste/smell (21%), and myalgias (7%), which is similar to the presenting symptoms reported in other studies on HT recipients[1–3,7–11,15–17] and in the general population.[12,13] Atypical symptoms were also quite common (reported in 46% of patients) and included chills, generalized pain and weakness, dizziness, sore throat, altered mental status, chest pain, headache, diffuse tingling, and rhinorrhea.

Among 15 inpatients, the median length of stay was 6 days (IQR 2–14 days), 7/15 (47%) were symptomatic without requiring oxygen and 3/15 (20%) required oxygen by nasal cannula. Five patients became critically ill and were upgraded to the ICU (Figure 1), among which three required intubation, mechanical ventilation, paralytics, proning, and pressor support (Table 3). None of the patients required inotropes, renal replacement therapy (RRT), or extracorporeal membrane oxygenation (ECMO). Two of the three mechanically ventilated patients ultimately died in the ICU despite the above measures. Both patients who expired had initially presented to outside hospitals and were subsequently transferred after respiratory failure and intubation, but only Patient #1 had significant delay from onset of symptoms to receipt of COVID-19 directed therapies (he was given remdesivir + dexametha-

**TABLE 2** Demographics of HT recipients with or without COVID-19 infection

| | +COVID-19*n* = 28 | -COVID-19*n* = 80 | *P*-value |
|---|---|---|---|
| Median age, years (IQR) | 57 (46–63) | 57 (49–65) | .5510 |
| BMI, kg/m$^2$ (IQR) | 28.1 (25.1–31.4) | 25.4 (22.8–29.3) | .0174 |
| Gender | | | |
| Male | 21 (75%) | 60 (75%) | >.9999 |
| Ethnicity | | | |
| White | 3 (10%) | 35 (44%) | .0013 |
| Hispanic | 21 (75%) | 14 (18%) | <.0001 |
| African American | 2 (7%) | 13 (16%) | .3448 |
| AAPI | 2 (7%) | 10 (13%) | .7276 |
| Middle Eastern | 0 | 4 (5%) | .5707 |
| Native American | 0 | 3 (4%) | .5666 |
| Brazilian | 0 | 1 (1%) | >.9999 |
| Comorbidities | | | |
| Hypertension | 20 (71%) | 49 (61%) | .3701 |
| Hyperlipidemia | 10 (34%) | 18 (23%) | .2114 |
| Diabetes | 7 (25%) | 38 (48%) | .0461 |
| CKD | 5 (18%) | 15 (19%) | >.9999 |
| ESRD on IHD | 0 | 3 (4%) | .5666 |
| Lung disease | 1 (4%) | 1 (1%) | .4531 |
| Hx malignancy | 2 (7%) | 2 (3%) | .2756 |
| Hx VAD | 9 (32%) | 14 (18%) | .1148 |
| History of rejection | | | |
| CMR | 4 (14%) | 3 (4%) | .0726 |
| AMR | 3 (10%) | 9 (11%) | >.9999 |
| CAV | 7 (25%) | 9 (11%) | .1186 |

Demographics of patients who tested positive for SARS-CoV-2 ($n = 28$) were compared to HT recipients who tested negative during the same time period ($n = 80$). Median age and body mass index (BMI) with interquartile range at time of COVID-19 test are reported. Gender and ethnicity were self-reported by the patients.

Comorbid conditions documented on admission or discharge summary from index hospital admission or on the last clinic visit progress note.

Any prior history of rejection requiring treatment was also compared.

Statistical significance was determined using Mann Whitney U Test for Age and BMI. For gender, ethnicity, comorbidities and rejection chi-squared test or Fisher's exact test when more than one variable was compared

*Abbreviations*: AAPI, Asian American and Pacific Islander; CKD, chronic kidney disease; ESRD, end-stage renal disease; IHD, intermittent hemodialysis; VAD, ventricular assist device; CMR, cell-mediated rejection; AMR, antibody mediated rejection; CAV, chronic allograft vasculopathy.

sone 5 days after intubation on arrival to UCSD). The second transfer, Patient #2, did receive a dose of steroids, remdesivir and convalescent plasma at the outside hospital. None of the other patients died during the study or follow up period (Figure 1).

## 3.3 | Laboratory assessment and echocardiography

All 15 inpatients underwent serum laboratory assessment of inflammatory and cardiac biomarkers (Table 4). Patients did not have significant elevation of cardiac biomarkers but we noted elevated C-reactive protein (CRP), high sensitivity CRP (hsCRP), and D-dimer. Most inpatients (9/15) had evidence of acute kidney injury, with a significant increase in their median peak serum creatinine compared to their baseline outpatient creatinine from prior to admission (1.4 (1.1–2.1) vs. 1.1 (1.0–1.5) mg/dl; $P = .0009$). There were no differences in total white blood cell counts, absolute lymphocytes, absolute neutrophils, or neutrophil/lymphocyte ratio (Table 5) between patients infected with COVID-19 ($n = 28$) or control HT recipients without COVID-19 ($n = 80$). All patients in our study had recent documentation of normal cardiac function within 1 year of COVID-19 diagnosis. Seven inpatients (47%) had repeat echocardiogram during index hospital admission due to hemodynamic instability and/or concern for graft dysfunction. None demonstrated any change in left ventricle (LV) size or function; and no patient developed new RV dysfunction or pulmonary hypertension.

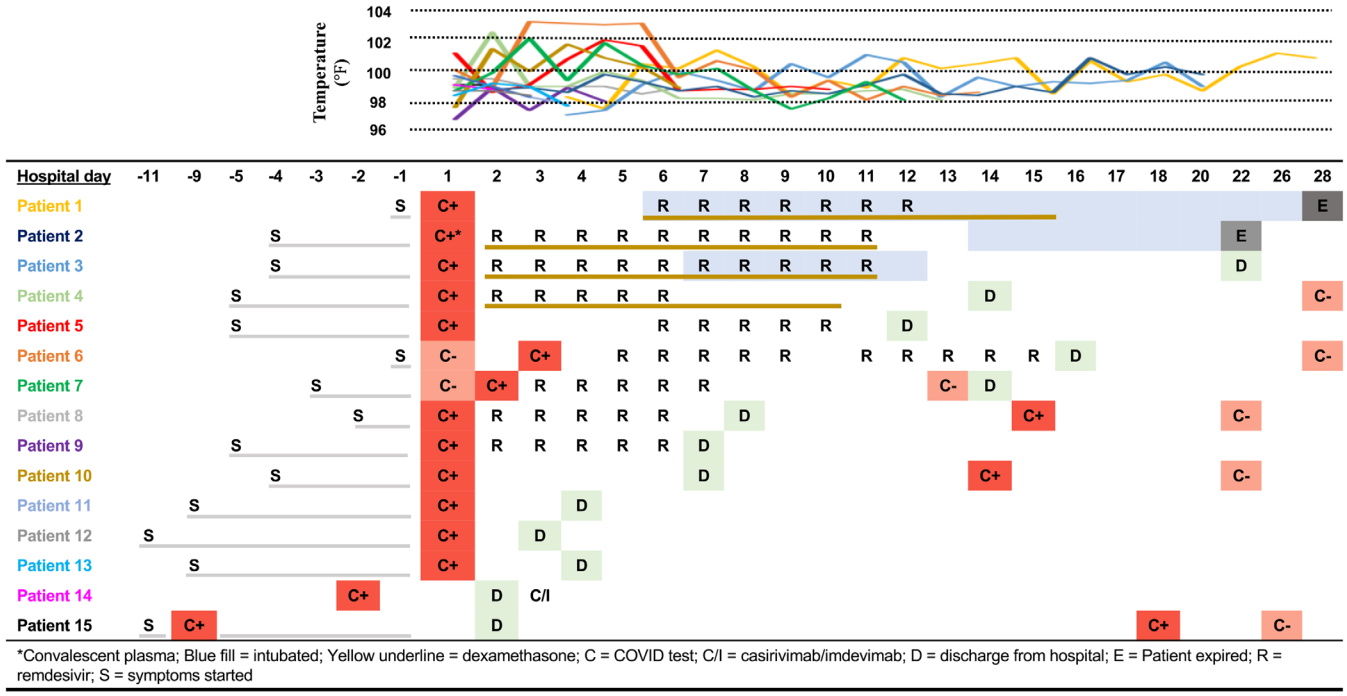


**FIGURE 1** Hospital course and COVID-19 directed therapeutics of HT recipients admitted for COVID-19 ($n = 15$). Patients were admitted on hospital day 0, two patients with the longest hospital stay expired while in house (mortality = 7%). Fever curves are plotted in upper panel

### 3.4 | COVID-19 directed therapeutics and management of immunosuppression

Among the 15 inpatients, those who had oxygen saturation < 94% or abnormalities on chest imaging concerning for pneumonia received remdesivir ($n = 9$). In all cases, patients received a 200 mg intravenous (IV) loading dose followed by 100 mg IV once daily × four more doses (total of five doses) per the ACTT-1 clinical trial protocol (Table 1). Three patients had continued symptoms despite this treatment with ongoing hypoxia, or worsening of pneumonia following five doses of remdesivir, and an additional 5 days of 100 mg IV daily were given to these patients (for a total of 10 doses). Because many of these patients were admitted and treated prior to publication of the results of the RECOVERY Trial, only four out of nine patients who received remdesivir also received therapy with dexamethasone. Of note, both patients in the study who expired received 10 days of remdesivir and dexamethasone and were intubated, paralyzed and proned. The first patient had only 1 day of symptoms prior to arrival at the outside hospital (Figure 1; Patient #1). The second patient (Figure 1; Patient #2) had 4 days of symptoms prior to arrival at the outside hospital where he was given a dose of convalescent plasma, remdesivir, and dexamethasone prior to transfer to UCSD.

Ten admitted patients had the antimetabolite either held or reduced (typically the mycophenolate mofetil (MMF) or sirolimus was held) and the calcineurin inhibitor was continued with doses adjusted using daily serum trough levels. Seven patients were treated with antibiotics during the course of their hospitalization. Five patients received empiric antibiotics that were discontinued after cultures resulted negative, and two patients had positive cultures and received full course of antibiotics (both critically ill patients who later expired developed ventilator associated bacterial pneumonia and urinary tract infection). No patient at our center received hydroxychloroquine, azithromycin, tocilizumab, or antiviral therapy other than remdesivir (Table 1). All patients received prophylactic anticoagulation per hospital protocol to prevent venous thrombosis, but no patient received empiric therapeutic anticoagulation to prevent COVID-19 related blood clots as has been reported in other studies (Table 1).[1,3,11] Two outpatients with mild disease received casirivimab and imdevimab (REGN-CoV-2) neutralizing antibody treatment within first 5 days of symptom onset without complications. Of note: this therapy received emergency use authorization in November 2020, which is why only two patients in our study received this drug. A third outpatient, who was not admitted due to local pandemic surge conditions and lack of hospital beds, had ongoing dyspnea 2 weeks into illness which resolved with an outpatient course of dexamethasone. These three patients did not require admission during the follow up period.

### 3.5 | Survival and post-discharge outcomes

Two of the severely ill patients died in the ICU (7% overall mortality, 13% in-hospital mortality). Six patients out of 28 HT recipients in this study had a total of 10 admissions after their initial COVID-19 diagnoses (Table S2); however, none of these readmissions were clearly related to COVID-19. Four patients were readmitted only once (and one of these admissions was for a planned ablation for a supraventricular tachycardia that was present prior to COVID-19 diagnosis). Two patients were readmitted twice and one patient was readmitted

**TABLE 3** Clinical course of COVID-19 infection after index diagnosis

| | |
|---|---|
| Admitted | 15 (54%) |
| Outpatient Obs | 13 (46%) |
| Prodromal Sx (d) | 3 (0–5) |
| Cough | 10 (36%) |
| SOB | 6 (21%) |
| Fever | 7 (25%) |
| Myalgia | 2 (7%) |
| GI symptoms | 7 (25%) |
| Loss of taste | 6 (21%) |
| Loss of smell | 6 (21%) |
| Other* | 13 (46%) |
| Median length of Stay in days (IQR) | 6 (2–14) |
| Oxygen/ICU | |
| None | 7 (25%) |
| O2 NC | 3 (11%) |
| Salter | 1 (4%) |
| HFNC | 1 (4%) |
| NIPPV | 0 |
| Intubation | 3 (11%) |
| Paralyzed/Proned | 3 (11%) |
| Vasopressors | 3 (11%) |
| Inotropes | 0 |
| ECMO | 0 |
| New RRTICU admission | 05 (18%) |

Shown are the type of assay used for detection of SARS-CoV-2 infection. The patient's presenting symptoms along with the duration of prodromal illness and length of hospital stay during index admission presented as median with interquartile range. The patient's requirement of oxygen ($O_2$) or respiratory support, need for ICU, renal replacement therapy, use of pressor/inotropic support or extracorporeal membrane oxygenation (ECMO) are also reported.

*Abbreviations*: SOB, Shortness of breath; GI, gastrointestinal; $O_2$, oxygen; HFNC, high flow nasal cannula; NIPPV, noninvasive positive pressure ventilation; renal replacement therapy (RRT).

**TABLE 4** Laboratory assessment on index admission for patients with HT admitted for COVID-19 infection

| Laboratory test | $n = 15$ | Median (IQR) |
|---|---|---|
| CPK (0–175 U/L) | 8 | 71 (10–206) |
| CK-MB (-0-4.8 ng/ml) | 5 | 2 (0–3) |
| CK Index (%) | 4 | 3.2 (0–5.1) |
| TnT Gen V (< 22 ng/L) | 10 | 13 (6–76) |
| NT-pro-BNP (0–899 pg/ml) | 12 | 493 (126–15833) |
| Lactate (.5–2.0 mmol/L) | 10 | 1.7 (.7–4.1) |
| CRP (< .5 mg/dl) | 7 | 5.0 (.9–21) |
| hsCRP (0–4.9) | 6 | 104 (39–268) |
| Ferritin (30–400 ng/ml) | 4 | 211 (60–2524) |
| Procalcitonin (0–.08 ng/ml) | 13 | .11 (.05–.58) |
| LDH (25-275 U/L) | 9 | 237 (157–816) |
| D-dimer (< 241 ng/ml) | 10 | 408 (158–1189) |
| Baseline Cr (.67–1.17 mg/dl) | 15 | 1.1 (.5–2.4) |
| Peak Cr (.67–1.17 mg/dl) | 15 | 1.44 (.6–3.2) |

The peak values of each of the following laboratory tests are reported with associated reference range used by the UCSD Clinical Laboratories. Median and interquartile range for each test result are reported along with the number of tests resulted from the COVID-19 index admission.

*Abbreviations*: CPK, Creatinine phosphokinase; CK-MB, creatinine kinase-muscle-brain; CK Index, creatinine kinase index; TnT Gen V, high sensitivity/fifth generation troponin T; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; hsCRP, high sensitivity CRP; LDG, lactate dehydrogenase; Cr, creatinine.

three times (Table S2). One patient had readmission for acute cholecystitis, returning to the hospital with abdominal pain 118 days after his COVID-19 diagnosis. He was treated with antibiotics and scheduled for interval cholecystectomy 176 days after his COVID-19 diagnosis (this patient's second readmission). No deaths were reported in any of these readmissions and all six patients remained alive for the duration of the follow up period.

## 4 | DISCUSSION

We note a mortality of 7% in our HT recipients infected with SARS-CoV-2 (Table 1). Compared to reports from other large transplant centers with estimated mortality rates of 15–33%,[1–3,11] the mortality seen in our patients seems lower. This may be related to the overall decrease in mortality seen since the start of the pandemic, with improvement in disease management as more evidence-based therapeutics became available including remdesivir, dexamethasone and monoclonal antibodies. As noted in Table 1, few patients in the five studies from large transplant centers with higher COVID-19 related mortality received either remdesivir or dexamethasone.[1–3,11] In the largest multicenter study of 99 patients from across the United States, steroids were used in 19% of patients, remdesivir in 11%, and convalescent plasma in 11% of patients.[5] In the other four studies from large transplant centers ($n = 124$ patients), 21–38% of patients received high dose glucocorticoids for COVID-19 but none received a course of remdesivir. Two more recent small case series[16,17] did use remdesivir either alone or in combination with dexamethasone, with 100% survival of all patients receiving these therapeutics (Table 1). Several neutralizing antibodies have been developed that limit disease severity when given early in the disease course to high-risk ambulatory patients, though no benefit is noted when given after hospital admission. These included bamlanivimab, bamlanivimab/etesevimab, and casirivimab/mdevimab.[18–21] The two outpatients in our study who received casirivimab/imdevimab both recovered without complication or need for inpatient admission.[22,23]

Consistent with national data, our study demonstrates that Hispanic patients had significantly higher rates of infection and white patients had significantly lower rates of infection compared to a control pop-

**TABLE 5** White blood cell (WBC) count data from HT recipients who tested positive for SARS-CoV-2 ($n = 28$) compared to HT recipients who tested negative for SARS-CoV-2 ($n = 80$)

| Laboratory test | +COVID-19 ($n = 28$) | −COVID-19 ($n = 80$) |
|---|---|---|
| WBC (1000 cells/mm$^3$) | 6.30 (4.95–7.68) | 5.90 (4.60–7.95) |
| Lymphocytes (1000 cells/mm$^3$) | 1.03 (.75–1.40) | 1.10 (.71–1.54) |
| Neutrophils (1000 cells/mm$^3$) | 4.18 (3.13–5.50) | 3.74 (2.67–5.27) |
| N/L ratio | 3.18 (2.64–5.00) | 3.28 (2.18–5.30) |

Total WBC count is shown along with absolute counts of lymphocytes and neutrophils, and the ratio of neutrophils to lymphocytes (N/L Ratio). Median and interquartile ranges are reported for each laboratory test result; no statistical significance was detected between the two groups using the Mann Whitney U Test

ulation of HT without COVID-19. Data from the Centers for Disease Control note Hispanic patients in the general population have 1.3-fold higher rates of infection, 3.1-fold higher rates of hospitalization, and 2.3-fold higher rates of mortality than white/non-Hispanic patients as of March 2021.[24] Similar results were noted in recent HT publications as well; Mt. Sinai Hospital in New York City,[1] reported 64% of their HT recipients diagnosed with COVID-19 were African American or Hispanic.[2] Genuardi et al. reported that out of 99 HT recipients diagnosed with COVID-19 at their centers, 12% were Hispanic, 42% were African American, and 44% were white.[5]

Unlike other studies that have hypothesized that recent rejection and escalation of immunosuppression may increase risk of COVID-19 and severity, our results are not consistent with this hypothesis. Most patients in our study with history of rejection had remote treatment with increased immunosuppression > 1 year prior to their COVID-19 diagnosis, and no other patients treated for rejection during the pandemic with burst immunosuppression contracted COVID-19. None of the patients with COVID-19 developed rejection following the infection episode. The only patient who was treated within 1 year prior to his COVID-19 diagnosis (and the patient with the most severe history of rejection: two episodes of AMR with graft dysfunction) had only mild illness with COVID-19 and was never admitted to the hospital. Similarly, patients with history of CAV had mixed outcomes. Four patients had only mild symptoms and were never admitted, three developed severe symptoms and were admitted for treatment (all three were treated with remdesivir, two were also treated with dexamethasone), and all recovered without any mortality. Some have also suggested that patients with fresh transplant on triple agent immunosuppression may be at the highest risk for infection. Out of 72 HTs performed at UCSD during 2020, there were three cases of COVID-19 infection within 6 months after transplant, but all had mild course of illness and recovered with no mortality. Like most other studies, ours reported that hypertension was the most common comorbidity in COVID-19 infected HT recipients, although this was not significantly more common than in the control population. Interestingly, our study showed a significantly lower rate of diabetes in the COVID-19 infected group compared to control HT recipients; this could potentially play a role in the low mortality of our cohort though we are unable to test this hypothesis.

Our COVID-19 protocol evolved over time as new evidence and data became available. However, it is important to note that at the beginning of the pandemic, we never used hydroxycholoroquine, lopinovir/ritonavir, ivermectin, azithromycin, or other therapeutic trends that received outsized attention as there was lack of strong evidence for their use, and the use of these drugs was not logical. Of course, remdesivir, steroids and neutralizing antibody cocktails were later added to our protocol as evidence became available. Lack of drug toxicity and lack of drug-drug interactions could potentially have played a role in our improved outcomes as well. With the benefit of the recently published ACTT-1 and RECOVERY trials, we believe the improved mortality observed in this study reflects our center's current treatment algorithm that we have adapted over the course of the pandemic to incorporate new evidence-based therapeutics to utilize close outpatient observation, neutralizing monoclonal antibody therapy for outpatients early in the disease course, and prompt admission with reduction in immunosuppression and evidence-based treatment with remdesivir and dexamethasone for moderate/severe illness with hypoxia.

## 5 | CONCLUSION

We describe 28 HT recipients who developed SARS-CoV-2 infection during the first year of the pandemic. We demonstrate reduced mortality of 7% in this single center cohort based on a multi-pronged evidence-based treatment strategy.

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### CONFLICT OF INTEREST

None.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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