

Heart transplant recipient 1-year outcomes during the COVID-19 pandemic

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Abstract

The COVID-19 pandemic initially brought forth considerable challenges to the field of heart transplantation. To prevent the spread of the virus and protect immunocompromised recipients, our center made the following modifications to post-transplant outpatient management: eliminating early coronary angiograms, video visits for postoperative months 7, 9, and 11, and home blood draws for immunosuppression adjustments. To assess if these changes have impacted patient outcomes, the current study examines 1-year outcomes for patients transplanted during the pandemic. Between March and September 2020, we assessed 50 heart transplant patients transplanted during the pandemic. These patients were compared to patients who were transplanted during the same months between 2011 and 2019 ($n = 482$). Endpoints included subsequent 1-year survival, freedom from cardiac allograft vasculopathy, any-treated rejection, acute cellular rejection, antibody-mediated rejection, nonfatal major adverse cardiac events (NF-MACE), and hospital and ICU length of stay. Patients transplanted during the pandemic had similar 1-year endpoints compared to those of patients transplanted from years prior apart from 1-year freedom from NF-MACE which was significantly higher for patients transplanted during the pandemic. Despite necessary changes being made to outpatient management of heart transplant recipients, heart transplantation continues to be safe and effective with similar 1-year outcomes to years prior.

KEYWORDS

COVID-19, heart transplantation, pandemic, SARS-CoV-2

1 | INTRODUCTION

The COVID-19 pandemic has impacted many aspects of healthcare. The field of solid organ transplantation, and specifically heart transplantation, felt the effects of the pandemic from the onset. Early data showed a 24.1% and 23.8% decrease in donors recovered and completed heart transplants respectively between March and May 2020 in

the United States.¹ Given the highly immunosuppressed patient population, there was considerable concern regarding the continued practice of solid organ transplantation at the onset of the pandemic.² These concerns were reflected in the initial data reflecting a decrease in completed heart transplants at the start of the pandemic. A single center case series reported a case fatality rate of 25% in heart transplant recipients who contracted COVID-19, thus further illustrating

the potential severity of COVID-19 infection in immunocompromised individuals.³

Given potential high waitlist mortality for heart transplant candidates, our center continued the practice of heart transplantation for select recipients. We initially prioritized status 1–3 patients given their high waitlist mortality. Status 4–6 patients were selected on a case-by-case basis.

Several changes were made to post-transplant outpatient management at our center to further prevent the spread of COVID-19 and help protect this immunosuppressed population from acquiring the virus. Firstly, blood draws for immunosuppression adjustments were conducted at home. Early coronary angiograms were eliminated, and video visits were conducted for postoperative months 7, 9, and 11. Despite these changes, there were no modifications to standard immunosuppressant triple drug therapy. This included triple therapy with tacrolimus, mycophenolate mofetil, and a corticosteroid. Routine surveillance for detecting early rejection prior to the pandemic did not change as endomyocardial biopsies were utilized for the first 6 months post-transplant. Increased use of gene expression profiling with AlloMap, was routinely utilized at 7 months post-transplant and onward.

As vaccinations became more readily available, initial data noted that two dose mRNA vaccinations in immunocompromised individuals had a lower efficacy against COVID-19 associated hospitalization when compared to immunocompetent adults (77% vs. 90%, respectively).⁴ Despite this decrease in effectiveness, our center continued recommending vaccinations for our pre- and post-transplant patient populations.

At the onset of the pandemic, initial case series shed light on the feasibility of continuing heart transplantation throughout the pandemic.^{5,6} To prevent the spread of the virus, both centers utilized a mix of in person and telehealth appointments for post-transplant visits. No changes were made immunosuppression regimens and endomyocardial biopsy schedules.

Despite changes being made to post-transplant management, studies have not yet been conducted to analyze the impact these modifications had on patient outcomes. Therefore, we sought to examine 1-year outcomes in patients transplanted at our center during the COVID-19 pandemic.

2 | METHODS

Between the years 2011 and 2020, a total of 532 heart transplant recipients from a single high volume transplant center on the west coast were assessed in a retrospective cohort study fashion. The 532 recipients were subsequently split into two groups: patients transplanted during the beginning of the pandemic between March 6 and September 1, 2020 ($n = 50$) and patients transplanted during these same months between 2011 and 2019 ($n = 482$) who served as the control group. Informed consent was obtained, and our institutional review board approved the study.

Utilizing an independent t-test, the two groups were compared for baseline characteristics as well as the following endpoints: subsequent 1-year survival, 1-year freedom from cardiac allograft vasculopathy (CAV: stenosis $\geq 30\%$), 1-year freedom from any-treated rejection, 1-year freedom from acute cellular rejection, 1-year freedom from antibody-mediated rejection, hospital and ICU length of stay, and 1-year freedom from nonfatal major adverse cardiac events (NF-MACE: myocardial infarction (MI), new onset congestive heart failure (CHF), percutaneous coronary intervention (PCI), implantation of implantable cardioverter defibrillator/pacemaker, or stroke).

3 | RESULTS

Table 1 depicts raw demographic data and t-test analysis comparing the two groups. Mean donor age for patients transplanted during the pandemic was significantly lower than the control group's mean donor age (32.6 ± 11.8 vs. 36.3 ± 12.6 years, $p = .046$). The percentage of urgent status patients transplanted during the pandemic was significantly lower than the control group's percentage of urgent status patients (64.0% vs. 85.3% , $p < .001$). Of the patients transplanted during the pandemic, one patient was status 1, 23 patients were status 2, eight patients were status 3, 15 patients were status 4, 0 recipients were status 5, and three patients were status 6.

Patients transplanted during the pandemic had a significantly higher percentage of treated hypertension compared to the control group (69.4% vs. 51.7% , $p = .018$). There was no significant difference in mean recipient age for patients transplanted during the pandemic compared to the control group (52.7 ± 13.9 vs. 54.2 ± 13.0 years, $p = .420$). There was no significant difference in mean ischemic time for patients transplanted during the pandemic compared to the control group (190.2 ± 42.2 vs. 175.1 ± 48.9 min, $p = .522$). Percentage of insertion of mechanical circulatory support device was also similar between patients transplanted during the pandemic and the control group (16.3% vs. 23.6% , $p = .247$). The remaining baseline characteristic comparisons including mean body mass index (BMI), female gender, females with prior pregnancy, cytomegalovirus (CMV) mismatch, diabetes mellitus, prior blood transfusions, and mean creatinine immediately prior to transplant were similar between both groups.

Table 2 depicts the raw endpoint data and t-test analysis comparing the two groups. 1-year freedom from NF-MACE was significantly higher in patients transplanted during the pandemic compared to the control group (98.0% vs. 86.9% , $p = .024$). 1-year survival was similar between patients transplanted during the pandemic and the control group (94.0% vs. 90.5% , $p = .438$). Of the three deaths from the group of patients transplanted during the pandemic, one patient had a left ventricular assist device (LVAD). Of the 46 patients transplanted prior to the pandemic who died within one year post transplant, 12 had pre transplant mechanical circulatory support devices (5 LVADs, two biventricular assist devices, five total artificial hearts). There was no significant difference in 1-year freedom from CAV between patients transplanted during the pandemic and the control group (100.0% vs.

TABLE 1 Raw demographics and t-test analysis for patients transplanted during the COVID-19 pandemic versus patients transplanted prior to the COVID-19 pandemic

	Patients transplanted during COVID-19 pandemic (n = 50)	Patients transplanted prior to COVID-19 pandemic (n = 482)	p-value
Recipient Age, mean years \pm SD	52.7 \pm 13.9	54.2 \pm 13.0	.420
Donor Age, mean years \pm SD	32.6 \pm 11.8	36.3 \pm 12.6	.046
Body Mass Index, mean kg/m ² \pm SD	26.0 \pm 4.4	25.1 \pm 4.7	.205
Female (%)	32.0%	29.9%	.755
Previous pregnancy in females (%)	62.5%	74.3%	.314
Ischemic Time, mean mins \pm SD	190.2 \pm 42.2	175.1 \pm 48.9	.522
Urgent Status at Transplant (%)	64.0%	85.3%	<.001
Cytomegalovirus mismatch (%)	22.0%	24.1%	.744
Diabetes mellitus (%)	40.8%	30.9%	.158
Treated hypertension (%)	69.4%	51.7%	.018
Insertion of mechanical circulatory support device (%)	16.3%	23.6%	.247
Prior blood transfusion (%)	34.7%	40.1%	.463
Pre-transplant creatinine, mean mg/dl \pm SD	1.6 \pm 1.6	1.5 \pm 1.1	.563

TABLE 2 Raw endpoints and t-test analysis for patients transplanted during the COVID-19 pandemic versus patients transplanted prior to the pandemic

	Patients transplanted during COVID-19 pandemic (n = 50)	Patients transplanted prior to COVID-19 pandemic (n = 482)	p-value
1-Year survival	94.0%	90.5%	.438
1-Year freedom from CAV	100.0%	96.5%	.192
1-Year freedom from NF-MACE	98.0%	86.9%	.024
1-Year freedom from Any Treated Rejection	90.0%	84.2%	.262
1-Year freedom from Acute Cellular Rejection	90.0%	92.1%	.658
1-Year freedom from Antibody-Mediated Rejection	94.0%	94.8%	.845
Average Length of Hospital Stay (Days)	23.0 \pm 37.2	17.2 \pm 19.7	.079
Average Length of ICU Stay (Days)	11.1 \pm 20.6	8.3 \pm 8.2	.069

96.5%, $p = .192$). There was no significant difference in 1-year freedom from any treated rejection between patients transplanted during the pandemic and the control group (90.0% vs. 84.2%, $p = .262$). Both groups had similar 1-year freedom from acute cellular rejection for patients transplanted during the pandemic and control groups respectively (90.0% vs. 92.1%, $p = .658$). There was no significant difference in 1-year freedom from antibody-mediated rejection between the patients transplanted during the pandemic and the control group (94.0% vs. 94.8%, $p = .845$). Both groups had similar average hospital length of stays for patients transplanted during the pandemic and the control group respectively (23.0 \pm 37.2 vs. 17.2 \pm 19.7 days, $p = .079$). Lastly, there was no significant difference in average length of stay between patients transplanted during the pandemic and the control group (11.1 \pm 20.1 vs. 8.3 \pm 8.2 days, $p = .069$).

4 | DISCUSSION

As changes to post heart transplant management have been implemented to prevent the spread of the COVID-19 virus, the current study sought to evaluate if these modifications impacted 1-year outcomes in patients transplanted during the pandemic. Overall, patients transplanted during the pandemic had similar 1-year endpoints compared to those of patients transplanted from years prior with the exception of 1 year freedom from NF-MACE. Patients transplanted during the pandemic had a significantly higher freedom from NF-MACE.

Such a difference in NF-MACE may be attributed to the difference in sample sizes between the two groups. It also may be possible that in a pandemic time where many individuals have been working from home or have had more time away from work, adherence to post-transplant

diet, routine exercise, and medication regimens have increased. Such adherence to diet and exercise specifically could explain the increase in 1-year freedom from NF-MACE in patients transplanted during the pandemic as prior research has shown that cardiac rehabilitation and exercise can lead to decreased rates of major adverse cardiac events.⁷ Further studies are warranted to help further decipher the underlying reason for the difference in NF-MACE events between the two groups.

Many factors may have played a role in the similar 1-year outcomes found between the two groups in the current study. Although telehealth visits were utilized for postoperative months 7, 9, and 11, in person visits were still conducted within the first 6 months. As such, in person care was established in the early post-transplant period in which risk of acute rejection is at the highest.⁸ The results of the current study suggest that telemedicine is a feasible option for post-transplant outpatient management. With the pandemic continuing to affect the field of medicine and threaten immunosuppressed patients, telemedicine is a beneficial tool that can be utilized without affecting patient outcomes. Moreover, even when COVID-19 reaches endemic levels, this telemedicine model will still serve the post heart transplant patient population well given their immunocompromised state and increased susceptibility to complications from the virus and various other sources of infections.³

As endomyocardial biopsies continue to be the gold standard in detection of acute cellular rejection, we continued routine surveillance during the first 6 months post-transplant.⁹ This adherence to a biopsy schedule even during the pandemic helps explain the similarity in 1-year freedom from any treated rejection between the two groups in the current study. Early signs of cellular rejection would have been picked up on biopsies and immunosuppression regimens would be adjusted accordingly prior to patients developing symptomatic signs of rejection needing subsequent treatment.

Triple immunosuppressive therapy continues to be a staple of post-transplant management to help prevent rejection in the short and long term periods.^{10,11} Thus, no changes were made to the triple therapy immunosuppression maintenance regimens at our center. This triple therapy regimen was also utilized by centers in prior case series that showed favorable outcomes in the early postoperative period for patients transplanted at the start of the pandemic.^{5,6} Therefore, we expected to have similar 1-year freedom from any treated rejection, acute antibody mediated rejection, and acute cellular rejection between the two groups which was seen in the current study. And although patients were transitioned to video visits after postoperative month 6, at home blood draws were conducted to adjust immunosuppression dosages accordingly and further help prevent rejection.

In addition to graft failure and infection, CAV continues to be among the leading causes of death in heart transplant recipients.¹² Coronary angiography detects CAV in 8% and 30% of patients in post-transplant years 1 and 5 respectively. By post-transplant year 10, CAV is detected in 50% of patients.¹² However, coronary angiography is not as sensitive at detecting CAV compared to intravascular ultrasonography which detects CAV in 75% of patients 3 years post-transplant.^{13,14} Given the lower sensitivity of coronary angiography and relatively low rates of CAV found in patients in the early post-transplant period, our center

was more inclined to defer the early coronary angiogram for our recipients. Despite this decision, 1-year freedom from CAV was still comparable between the two groups. Such a result was also most likely due to the fact that immunosuppression regimens were not altered for these recipients, as prior research has shown mycophenolate mofetil to delay the progression of CAV and even partially reverse it.¹⁵

The current study saw a significant difference in mean donor age between patients transplanted during the pandemic and the control group. Mean donor age was significantly lower for patients transplanted during the pandemic. Initial US data showed a 23.8% decrease in donors recovered between March and May 2020.¹ Given the early uncertainty surrounding continuing organ procurement and transplantation at the onset of the pandemic, it may be possible that organ procurement organizations (OPOs) shifted to prioritizing offering younger donors. It may also be possible that the demographics of the donor pool during the pandemic changed as well leading to the differences in mean donor ages between the two groups. Of note, preliminary data examining demographics of organ donors found an increasing trend in the number of donors with mechanism of death listed as drug intoxication.¹⁶ Between March and May 2020, there was a 35% increase in the number of donors whose mechanism of death was drug intoxication when compared to the previous year.¹⁶ Opioid overdose is the leading cause of drug related death in the United States.¹⁷ Furthermore, opioid related deaths are most prevalent in the 25–34 year age group.¹⁸ Therefore, it would be reasonable to postulate that the increased prevalence of donors whose mechanism of death was due to drug intoxication, thus having a lower age of death, may have accounted for the decreased mean donor age seen in the group of patients transplanted during the pandemic.

In addition, there was a significantly high percentage of recipients transplanted as urgent status in the control group. Considering that during the start of the pandemic, our center prioritized status 1–3 patients for transplantation, we expected to have similar if not higher percentages of urgent status at transplant for patients transplanted during the pandemic. This discrepancy was due to the high number of status 4 patients (15) in the cohort transplanted during COVID-19. Status 4 patients include those with dischargeable LVADs without discretionary 30 days.¹⁹ Patients with LVADs are susceptible to various complications including pump thrombosis, infection, device failure, and bleeding.²⁰ As such, although we did prioritize status 1–3 patients during the pandemic, we did not hesitate in transplanting status 4 patients if suitable donor hearts became available given the potential for LVAD complications. Despite the initial decrease in overall numbers of donors available in the United States, it is possible that suitable donors for status 4 patients were more readily available in our region (region 5: Arizona, California, Nevada, New Mexico, and Utah) as smaller transplant programs may have suspended transplanting potential recipients at the start of the pandemic. With less transplant centers available to accept donor hearts, the overall donor heart availability suitable for nonurgent status patients may have increased in our region, thus explaining the difference in percentage urgent status between the two groups. Further analysis of the donor pool is needed to understand the impact of the pandemic on donor heart allocation.

5 | STUDY LIMITATIONS

The current study's limitations included a relatively small sample size for patients transplanted during the pandemic when compared to the control group. Moreover, the current study only examines 1-year outcomes of heart transplant recipients as opposed to solid organ transplantation as a whole. Further studies examining 1-year outcomes of other types of solid organ transplantation during the pandemic are warranted.

6 | CONCLUSIONS

Despite changes being made to the outpatient management of heart transplant recipients at our center during the COVID-19 pandemic, patients transplanted during the pandemic have acceptable outcomes with comparable 1-year endpoints to years prior. As the pandemic approaches its 2 year anniversary, these changes in outpatient management, specifically telemedicine, may be continued to prevent the spread of the COVID-19 virus and protect and immunocompromised transplant recipient population.

CONFLICT OF INTEREST

All authors have no relevant disclosures or conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Gabriel Esmailian: concept/design and drafting article, Nikhil Patel: data analysis/interpretation and data collection, Jignesh Patel: concept/design, Lawrence Czer: data analysis/interpretation, Matthew Rafiei: critical revision and approval of article, Dominick Megna: data analysis/interpretation, Dominic Emerson: data analysis/interpretation, Danny Ramzy: data analysis/interpretation, Alfredo Trento: data analysis/interpretation, Joanna Chikwe: data analysis/interpretation, Fardad Esmailian: Concept/design and approval of the article, Jon Kobashigawa: critical revision and approval of article

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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