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ORIGINAL ARTICLE

Comparative Analysis of Coronavirus disease 2019 Vaccine Efficacy in Heart Transplant Recipients on Standardized Immunotherapy Regimens

Shriya Sharma, MBBS; Jose Ruiz, MD; and Rohan Goswami, MD

Abstract

Objective: To assess the effect of coronavirus disease 2019 (COVID-19) infection on heart transplant recipients requiring immunotherapy. To investigate the effectiveness of vaccination in immunosuppressed heart transplant recipients during the initial years of the COVID-19 pandemic, and to examine the timing of COVID-19 infections in heart transplant recipients' posttransplantation.

Patients and Methods: International data on COVID-19 infection in immunosuppressed populations is limited. Heart transplant recipients requiring immunotherapy are at risk for increased complications with COVID-19 infection. The availability of vaccination and temporal trends in this population has not been well described. We report outcomes in immunosuppressed patients during the initial years of the COVID-19 pandemic from March 1, 2019, to October 31, 2021, at Mayo Clinic in Florida.

Results: A total of 98 patients were reviewed, of which 49 were COVID-19–positive (CP), and 49 were negative (CN). The cohort was well matched, with a median age of 58 years (49–65 years) in both groups. Females consisted of 41% in the CP group and 18.4% in the CN group. Immunosuppression was not significantly different for CP or CN patients. The median time from transplant to CP was 384 days (237–677 days). The CN group's median follow-up after transplant was 947 days (737–1191 days). The CP hospitalization rate was 24% with only 1 death. More CP patients were vaccinated than the CN group (92% vs 78%, P=.025).

Conclusion: Our study sheds light on COVID-19's effect on heart transplant recipients and vaccination in this population. Our findings suggest a potentially heightened infection risk within the first 1.5 years posttransplant, highlighting the need to optimize management strategies and vaccine efficacy in this vulnerable group.

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Infectious diseases pose a considerable challenge after solid organ transplantation, and heart transplant (HT) patients are particularly vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with reported mortality rates reaching up to 25%.[1,2]

Coronavirus disease 2019 (COVID-19) vaccines have proven effective in stimulating targeted immune responses against virus antigens and producing neutralizing antibodies. The emergence of vaccines against COVID-19 has shown promising results in generating specific immune responses and reducing the risk and severity of symptomatic disease. However, vaccine responses have been less satisfactory for the solid organ transplant (SOT) population, including HT recipients, primarily because of limited scientific evidence and the absence of well-defined clinical trials. Vaccines have also reported clinical efficacy in lowering the likelihood and severity of symptomatic COVID-19. In the SOT community, the response to vaccines has been suboptimal, and there is limited scientific evidence and a lack of well-defined clinical trials to support robust recommendations for this specific population.[1]

Heart transplant recipients are at higher risk of experiencing adverse consequences in

From the Division of Heart Failure and Transplant, Mayo Clinic, Jacksonville, FL (S.S., R.G.); and Division of Heart Failure and Transplantation, Tampa General Hospital, Tampa, FL (J.R.).

COVID-19 infection due to the presence of multiple comorbidities and clinically significant immunosuppression.[2] In the context of COVID-19 vaccines, similar to other vaccines for transplant recipients, it is crucial to assess their effectiveness in preventing the disease and their safety, particularly regarding adverse reactions and the potential risk of rejection.[1]

Individuals with preexisting cardiovascular conditions, such as hypertension, coronary artery disease, and diabetes are more susceptible to COVID-19. The severity of the infection is influenced not only by the virus's invasion and growth but also by an aggressive immune response characterized by cytokine storms, myocardial injury, and potential fatalities.[2]

After heart transplantation, immunosuppressive treatments have considerably enhanced graft longevity by decreasing the risk of cellular and antibody-mediated rejection. To mitigate the unintended effects of these therapies and cater to sensitized patients, there has been a transformative shift in the field of immunosuppression. These treatments' timing and specific targets are continuously evolving to complement established therapies with additional adjunctive approaches. Progress in this area will enable a more personalized and tailored approach to immunomodulatory therapies for each patient.[3]

Heart and other SOT societies strongly support and prioritize administering the SARS-CoV-2 vaccine to all transplant candidates and recipients, including those within the first 3 months after transplantation, and their household members who have a healthy immune system. However, there are specific concerns unique to this sub-population of solid organ recipients, mainly regarding the potential decrease in vaccine effectiveness in immunocompromised individuals and uncertainties surrounding the longevity of the immune response.[4]

Our study aimed to present the results and findings concerning the health outcomes of immunosuppressed individuals during the early stages of the COVID-19 pandemic.

METHODS

Study Population

We retrospectively reviewed all individuals who received a HT from March 1, 2019, to October 31, 2021, at Mayo Clinic in Florida. Patients were divided into 2 groups: those who were diagnosed with COVID-19 (COVID-19-positive [CP] based on a positive diagnosis of SARS-CoV-2 using the reverse transcriptase-polymerase chain reaction technique) and those who were not diagnosed with COVID-19 (COVID-19-negative [CN] based on a negative virology test for SARS-CoV-2). After institutional review board approval, the transplant team reviewed the electronic patient charts and records to abstract demographic characteristics and clinical data.

Inclusion and Exclusion Criteria

All HT recipients aged 18 and above with positive nasopharyngeal reverse transcriptase-polymerase chain reaction tests for SARS-CoV-2 were included in the CP group. A well-matched cohort of CN patients was included in the study.

Data Sources

We obtained medical records and data for hospitalized patients and outpatients with laboratory-proven COVID-19 infection from electronic medical records after institutional review board approval as exempt for retrospective data collection with the approval number 21-003115. The HT team followed all COVID-19-infected HT recipients who required hospitalization at our institution. Also, patients in home isolation were followed remotely by the transplant staff.

Study Outcomes

The primary outcome was vaccine efficacy in patients after HT. In this study, the variables compared between 2 groups of transplant recipients were their clinical characteristics, including diabetic status, hypertension, body mass index (BMI), glomerular filtration rate (GFR), ejection fraction, immunosuppression, median trough tacrolimus level, the median time from transplant to CP, median follow-up after transplant for the CN group, CP hospitalization rate, number of deaths in the CP group, markers of inflammation for hospitalized patients (IL6, D-dimer, and C-reactive protein [CRP]), and the vaccination rate in the CP group and the CN group.

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Statistical Analyses

All continuous data are presented as medians with interquartile ranges (IQRs). Statistical analysis was performed using SPSS v27 utilizing the χ^2 test to determine the significance between the groups with a *P* value of $<.05$.

RESULTS

This study followed 98 HT patients from March 2019 to October 2021, of which 49 were CP and 49 were CN. Table 1 outlines baseline and clinical characteristics further. In both groups, the median age at infection was 58 years (49— 65 years), with 41% females in CP and 20.4% in CN. A total of 59% Caucasian and 39% African American were in the CP group, whereas there were 71% Caucasian, and 24% African American were in the CN group. The average height was 1.736 m (1.93-1.57 m), weight of 87.81 kg (156-48.9 kg), BMI of 29.05 kg/m^2(50.36-19.83 kg/m^2), left ventricular ejection fraction of 62.16% (72%-52%), HbA1c of 5.9 (9.0-4.7), and GFR of 52.5 mL/min/(41.75-64.75 mL/min) in the CP group, whereas in the CN group, the average height was 1.75 meters (1.70-1.81 meters), weight of 90 kg (76.6-103 kg), BMI of 28.72 kg/m^2(25.06-32.60 kg/m^2), left ventricular ejection fraction of 62% (59%-65%), HbA1c of 5.9 (5.5-6.5), and GFR of 55 mL/min (46.25-65 mL/min). About 35 (71%) were hypertensive in both groups, and 16 (32%) and 27 (55%) were diabetic in the CP and CN groups. There were 20 (40%) obese in the CP group and 19 (39%) in the CN group.

The baseline cardiac medications in the CP group included Aspirin in 43 (88%), statin in 47 (96%), angiotensin converting enzymes inhibitor, angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitor in 22 (45%), mineralocorticoid antagonist in 2 (4%), and β-blocker in 26 (53%). In the CN group, the medications were as follows: Aspirin in 37 (76%), statin in 44 (90%), angiotensin converting enzymes inhibitor, angiotensin receptor blockers or angiotensin receptor-neprilysin inhibitor in 27(55%), mineralocorticoid antagonist in 2(4%), and β-blocker in 29(59%).

The etiology of cardiomyopathy was classified as ischemic, nonischemic, and infiltrative (amyloid/sarcoid) in both groups. About 14(29%) and 33(67%) were ischemic and non-ischemic, respectively in CP patients compared with 35 (71%) who were ischemic and 12 (24%) who were nonischemic in the CN group. About 2 (4%) had infiltrative (amyloid/sarcoid) etiology in both groups.

Baseline immunosuppressive medications in the CP group included calcineurin inhibitors in 41 patients (83%), mycophenolate mofetil in 42 (86%), proliferation signal inhibitors in 15 (31%), azathioprine in 5 (10%), and corticosteroids in 9 (18%) of patients. In the CN group, 48 (98%) patients were on

TABLE 1. Baseline and Clinical Characteristics of Patients in COVID Positive and Negative Groups

Characteristic	CP (n=49)	CN (n=49)
Age (y), (median, IQR)	58 (49-65)	58 (49-65)
Female (%)	20 (41%)	9 (18.4%)
Race		
African American	19 (39%)	12 (24%)
Others	1 (2%)	2 (4%)
Caucasian	29 (59%)	35 (71%)
Clinical characteristics		
Height (m)	1.74 (1.93-1.57)	1.75 (1.70-1.81)
Weight (kg)	87.81 (156-48.9)	90 (76.6-103)
BMI (kg/m^2)	29.05 (50.36-19.83)	28.72 (25.06-32.60)
LV ejection fraction (%)	62.16 (72-52)	62 (59-65)
Hemoglobin A1c	5.9 (9.0-4.7)	5.9 (5.5-6.5)
GFR (mL/min)	52.5 (41.75-64.75)	55 (46.25-65)
Comorbidities		
Hypertension	35 (71%)	35 (71%)
Diabetes	16 (32%)	27 (55%)
Obesity	20 (40%)	19 (39%)
Baseline cardiac medications		
Aspirin	43 (88%)	37 (76%)
Statin	47 (96%)	44 (90%)
ACE inhibitor, ARB or ARNI	22 (45%)	27 (55%)
Mineralocorticoid antagonist	2 (4%)	2 (4%)
β-Blocker	26 (53%)	29 (59%)
Etiology of cardiomyopath		
Ischemic	14 (29%)	35 (71%)
Nonischemic	33 (67%)	12 (24%)
Infiltrative (amyloid/sarcoid)	2 (4%)	2 (4%)

ACE, angiotensin converting enzymes; ARB, angiotensin receptor blockers ARNI, angiotensin receptor-neprilysin inhibitor; GFR, glomerular filtration rate.

calcineurin inhibitors and 2% were on sirolimus. (Table 2)

Figure 1 illustrates the time of COVID-19 infection after transplant and the corresponding percentage of individuals affected within various time frames. Most cases (53.1%) occurred over 365 days posttransplant, followed by 28.6% between 180 and 365 days, 8.2% between 90 and 180 days, 4.1% between 30 and 90 days, and 6.1% in less than 30 days after transplant. Among all patients with COVID-19, 45 (92%) were vaccinated. Of those vaccinated, 27 (60%) patients received Pfizer initial and booster doses, whereas 18 (40%) received Moderna initial and booster doses. Twelve patients (24%) were hospitalized within 90 days of infection, with only 2 requiring intensive care unit level of care. The median time from transplant to infection was 384 days (237-677 days).

Patients with CP stayed for a median duration of 25 days (9.75-37 days) in the intensive care unit and 38 days (18-56 days) for the CN group. Patients were transferred to a general medical floor where they stayed for a median of 8 days (6-11.25 days) for CP and 11 days (5.75-12 days) for CN.

In patients with CP, 27 (55%) presented with respiratory symptoms such as shortness of breath and cough. Among these individuals, 2 of them required mechanical ventilation. 6% exhibited gastrointestinal symptoms, such as diarrhea, nausea, and vomiting. And 16% experienced a combination of respiratory and gastrointestinal symptoms. 22% of patients with CP were asymptomatic.

TABLE 2. Comparison of Immunosuppressive Therapy in COVID Positive and Negative Groups

Immunotherapy	CP (n=49)	CN (n=49)
Steroids	9 (18%)	1 (2%)
Tacrolimus	36 (73%)	47 (96%)
Trough Tacrolimus	7.68 (<1-24.2)	8.7 (<1-59.6)
Cyclosporine	5 (10%)	1 (2%)
Trough Cyclosporine	141.8 (55-328)	111
Sirolimus	15 (31%)	1 (2%)
Trough Sirolimus	7.28 (2.7-14.7)	4.1
Mycophenolate	42 (86%)	49 (100%)
Azathioprine	5 (10%)	0 (0%)

The median duration of hospitalization was 5 days (4-9 days). Of the hospitalized patients, 11 (92%) were discharged, and 1 (8%) died in the hospital. Three of the 4 unvaccinated patients were hospitalized, and 1 died while hospitalized. Treatment for hospitalized patients was a combination of remdesivir, monoclonal antibody, supplemental oxygen, steroids, antibiotics (ceftriaxone or azithromycin), and convalescent plasma. Eighteen patients (37%) were treated with monoclonal antibodies (casirivimab/indevimab/sotorovimab/bebtelovimab), 8(16%) with evusheld (tixagevimab/cilgavimab), and 13 (26%) with remdesivir. (Table 3).

The laboratory test results for the hospitalized patients showed elevated levels of CRP at 53.7 mg/L (19.77-89.9 mg/L), ferritin at 377 ng/mL (255.5-545.05 ng/mL), and D-dimer at 1408.5 ng/mL (763-2226.5 mg/mL). The procalcitonin level is slightly raised at 0.14 ng/mL (0.07-0.495 ng/mL). Interleukin-6 is elevated at 19.22 pg/mL (12-0.495 pg/mL), suggesting potential systemic inflammation (Table 4) The CP group was more vaccinated than the CN group (92% vs 78%; P=.025). The remaining 37 patients were managed as outpatients. In the CN group, 38(78%) were vaccinated.

DISCUSSION

Based on our vaccination records, a considerable number of individuals, both CP and CN, have received COVID-19 vaccines. Our results found that the CP group has a higher vaccination rate, with the most receiving both Pfizer initial doses and booster shots. Interestingly, the Moderna vaccine was more commonly administered for initial and booster doses in the CN group. Despite vaccination, our data brings to light the potentially limited understanding of the vaccine efficacy in the early years of COVID-19, when Pfizer was the prominent vaccine being used across the globe. Furthermore, it is important to understand the role of organ-specific medical therapy and the role of baseline nonimmunosuppressive medications and their role in the virulence of COVID-19 infection. The assessment of vaccine effectiveness involves comparing the occurrence of health outcomes between individuals who have been vaccinated and those who have not.

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Within our study group, the difference in rates of COVID-19 infection provides valuable insight into the potential difference based on vaccine type and when it was administered.

Vaccination

Vaccines developed to combat symptomatic COVID-19 have shown remarkable efficacy in clinical trials among immunocompetent individuals, substantially reducing severe disease, hospitalization, and fatalities. These vaccines employ different technologies, such as micro-ribonucleic acid, replication-deficient adenovirus vectors, inactivated SARS-CoV-2 virus, or protein subunits of SARS-CoV-2. Most vaccines target the viral spike protein and receptor-binding domain (RBD), crucial for viral entry, aiming to stimulate both cellular (T-regulatory and T-helper cells) and humoral (Immunoglobulin G anti-spike or anti-RBD antibody) immune responses.[5]

Although vaccines have reported high effectiveness in both trials and observational studies, there remains a residual risk of severe COVID-19 outcomes, such as hospital admission or death, even after allowing sufficient time for immunity to develop. This risk in vaccinated groups encompasses factors, such as exposure risk, breakthrough infections if exposed, and the possibility of a breakthrough infection progressing to a severe outcome.

The specific risk factors contributing to severe outcomes in vaccinated individuals are currently unknown, primarily because of the limited representation of certain populations in clinical trials. These populations include elderly individuals, those with complex comorbidities (such as recipients of SOTs or individuals receiving immunosuppressive treatment for autoimmune disorders), and patients undergoing cancer treatment with chemotherapy or radiotherapy.[6]

The ongoing waves of the COVID-19 pandemic have highlighted the importance of enhancing vaccine responses in vulnerable immunocompromised groups, such as SOT recipients. Many vaccines require repeated doses to achieve effective and durable protection against infection. These additional immunogenic stimulations not only strengthen and prolong adaptive immunity but also affect its overall quality. Early findings in SOT patients show promising results concerning the immunogenicity and antibody response after receiving a third (booster) vaccine dose.[7]

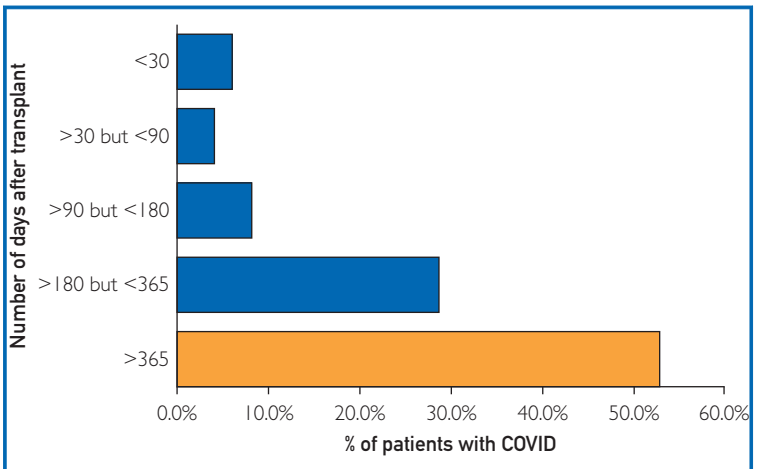

FIGURE 1. Timing of COVID-19 infection posttransplant and percentage of affected individuals across time intervals.

Because of the higher risk of adverse outcomes from COVID-19 in immunosuppressed SOT recipients, various organizations, including the International Society of Heart and Lung Transplantation, have advocated for COVID-19 vaccination in this group, although there is uncertainty surrounding vaccine responses and clinical effectiveness.[5]

Peled et al[7] performed a study to assess the safety and immunogenicity of a third dose (booster) of the Pfizer BNT162b2 vaccine in HT patients. The results showed that 18 days after receiving the third dose, the proportion of patients with a positive antibody response significantly increased from 23%-67%, accompanied by a rise in neutralizing capacity. Moreover, the third dose generated SARS-CoV-2 neutralization titers more than 9 times higher and Immunoglobulin G anti-RBD antibody levels more than 3 times higher than those achieved after the initial 2 primary doses.[7]

Immunosuppression

Baseline immunosuppressive medical therapy may affect patients' underlying immune response after solid organ transplantation. Given this potential confounder, our data highlights similar rates of immunotherapy (based on trough levels above) that were not found to interact with the rate of COVID-19

TABLE 3. Summary of Vaccination, Symptoms, COVID-19 Therapies, Posttransplant Length of Stay, and Outcomes in Posttransplant Patients

Vaccination data	CP (n=49)	CN (n=49)
Total vaccinated	45 (92%)	38 (78%)
Moderna initial	18 (40%)	24 (63%)
Moderna booster	18 (40%)	23 (61%)
Pfizer initial	27 (60%)	14 (37%)
Pfizer booster	27 (60%)	15 (39%)
	Symptoms	
Respiratory	27 (55%) with 2 hospitalizations requiring MV	
Gastrointestinal	3 (6%)	
Respiratory and gastrointestinal	8 (16%)	
Asymptomatic	11 (22%)	
	COVID-19 therapies	
Monoclonal antibody		18 (37%)
Remdesivir		13 (26%)
Evusheld		8 (16%)
Posttransplant length of stay	CP	CN
Intensive care unit	25 (9.75-37)	38 (18-56)
General medical floor	8 (6-11.25)	11 (5.75-12)
Hospitalized after COVID-19	12 (24%)	-
General medical floor	10 (83%)	-
Intensive care unit	2 (17%)	-
Died after COVID-19	2 (4%)	-
Recovered after COVID-19	47 (96%)	-

CP, COVID-19-positive; CN, COVID-19-negative; MV, mechanical ventilation.

TABLE 4. Inflammatory Markers in Hospitalized Patients With COVID-19-Positive

Inflammatory Markers	COVID-19-Positive Hospitalized
CRP	53.7 (19.77-89.9)
Ferritin	377 (255.5-545.05)
D-dimer	1,408.5 (763-2226.5)
Procalcitonin	0.14 (0.07-0.495)
Interleukin-6	19.22 (12-0.495)

Abbreviations: CRP, C-reactive protein.

infection. Furthermore, patients within the CN group were also on similar baseline immunotherapy.

We follow a standardized institutional protocol for initiating immunotherapy during transplantation, considering patient risk factors for allosensitization and donor-specific antibody development. This protocol is applied universally to all transplant recipients. In our diverse patient population, those identified as high risk (eg, African American, multiparous, presensitized >50% calculated panel-reactive antibodiy, or dual organ recipients) receive up to 6 mg/kg of rabbit-derived antithymocyte globulin for induction. Low-risk patients undergo basiliximab induction therapy. If patients started on antithymocyte globulin experience complications such as a drop in platelet count or bleeding diatheses requiring transfusion, they are switched to basiliximab (20 mg) on postoperative day 1 followed by a second dose on postoperative day 4. Because of the incorporation of induction immunotherapy, our monitoring focuses on postinduction T and B cell counts (CD4/CD8) and the early initiation of calcineurin inhibitor therapy (within 72 hours of transplantation). Considering this standardization, we believe that there is no substantial need to evaluate the effect of induction on patients with or without COVID-19 following heart transplantation.

Immunotherapy primarily focuses on T-cell function and comprises induction and maintenance immunosuppression. Maintenance immunosuppression commonly involves a multimodal regimen to suppress T-cell function, including a calcineurin inhibitor with or without glucocorticoids and an antimetabolite cell cycle inhibitor. In cases of rejection, additional treatments, such as high-dose glucocorticoids, anti-T-cell or anti-B-cell therapies or complement inhibition may be administered.[8] They are believed to have an increased risk of severe COVID-19 infection due to their ongoing immunosuppressed condition. Nevertheless, emerging evidence suggests that severe COVID-19 may stem from a systemic hyperinflammatory state, and immunosuppressive therapy could offer benefits in certain cases by dampening this systemic inflammation. Recipients of various organs may experience distinct clinical courses and outcomes compared with HT and heart-kidney transplant recipients, primarily because of differences in survival rates and immunosuppression approaches.[9]

Vaccination timing, dosing, manufacturer, patient gender, and time to infection were found to be more significant than underlying

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immunotherapy—our discussion of inflammatory makers below further expands upon this.

Inflammatory Markers

In our study, HT patients requiring hospitalization showed notable increases in inflammatory markers, like CRP, ferritin, D-dimer, interleukin-6 (IL-6), and procalcitonin, even though they were undergoing immunosuppression to maintain allograft function. Each laboratory parameter holds the potential to play a significant role in categorizing risk and predicting the outcomes of COVID-19. Similar to the general population, these laboratory findings indicate a higher level of illness severity in HT patients with COVID-19 and could be used for risk stratification purposes.

Extensive evidence supports the pivotal role of inflammatory mechanisms in COVID-19-related organ dysfunction and mortality. Patients with COVID-19 typically exhibit higher levels of inflammatory cytokines, such as IL-6 and tumor necrosis factor-α than healthy individuals. Moreover, serologic indicators of inflammation, such as CRP and erythrocyte sedimentation rate, are elevated in patients with COVID-19. This hyperinflammatory response plays a relevant role in viral pathogenesis. However, this proinflammatory reaction can also be used to identify patients with COVID-19 at a high risk of developing severe disease and respiratory complications through risk stratification.[10]

Future Outlook

Amid the extensive research efforts to understand all aspects of SARS-CoV-2, there is a need for further investigation into the vaccine-induced immune response. As the pandemic continues, there are concerns that the emergence of SARS-CoV-2 variants may compromise the efficacy of both natural and vaccine-induced immunity. It is crucial to prioritize the development of optimized vaccination strategies, especially for the immunocompromised population, and our study provides a potential pathway to address this need, offering optimism for enhanced protection against infection.

CONCLUSION

Our study aimed to assess the effect of COVID-19 infection on HT recipients requiring immunotherapy, evaluate the effectiveness of vaccination in this population, compare outcomes between patients with CP and CN, examine the timing of COVID-19 infections posttransplantation, and highlight the need for larger studies to evaluate vaccine efficacy. Despite a small sample size, our findings contribute to understanding the potential protection against SARS-CoV-2 infection achieved by targeted vaccines in HT recipients. The observed infection patterns suggest a potentially heightened risk within the first 1.5 years posttransplant, possibly because of a weakened immune system or the absence of bivalent boosters before 2022. These results highlight the importance of further research to optimize the management and vaccination strategies for immunosuppressed populations, particularly HT recipients, in resolving the effect of COVID-19 and improving overall outcomes.

Limitations

This study has some limitations that should be considered. First, it was performed at a single center, and variations in COVID-19 transmission rates, strains, and incidence over time and across different locations may affect the generalizability of the results. The retrospective nature of the analysis has provided valuable insights for generating hypotheses, but prospective studies are needed to confirm these findings. In addition, the small sample size limits the ability to draw definitive conclusions and extend the results to a broader population but can be used for further hypothesis generation. Despite measures taken to ensure data accuracy and reliability, further research and larger studies are necessary to validate and explore the potential risk factors for severe outcomes in this vulnerable patient group.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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Abbreviations and Acronyms: **BMI,** body mass index; **CP,** COVID-19-positive; **CN,** COVID-19-negative; **CRP,** C-reactive protein; **GFR,** glomerular filtration rate; **HT,** heart transplant; **IL6,** interleukin 6; **RT-PCR,** reverse transcriptase-polymerase chain reaction; **SOT,** solid organ transplant; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2

Correspondence: Address to Rohan M. Goswami, MD, Division of Heart Failure and Transplant, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224 (goswami.rohan@mayo.edu; Twitter: @doc_swami).

ORCID

Shriya Sharma: https://orcid.org/0000-0003-4273-9228; Rohan Goswami: https://orcid.org/0000-0002-0921-1416

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