

Six-months immunogenicity of BNT162b2 mRNA vaccine in heart transplanted and ventricle assist device-supported patients

Osnat Itzhaki Ben Zadok^{1,2*}, Aviv A. Shaul^{1,2}, Binyamin Ben-Avraham^{1,2}, Vicky Yaari^{1,2}, Haim Ben Zvi^{2,3}, Noa Eliakim-Raz^{2,4}, Dafna Yahav^{2,4}, Galia Abed¹, Miriam Abuhazira^{2,5}, Yaron D. Barac^{2,5}, Israel Mats^{1,2}, Tzippy Shochat⁶, Dan Aravot^{2,5}, Ran Kornowski^{1,2} and Tuvia Ben-Gal^{1,2}

¹Department of Cardiology, Rabin Medical Center, 39 Jabotinsky St., Petah Tikva, 49100, Israel; ²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel;

³Microbiology laboratory, Rabin Medical Center, Petah Tikva, Israel; ⁴Department of Infectious Diseases, Rabin Medical Center, Petah Tikva, Israel; ⁵Department of Cardio-Thoracic Surgery, Rabin Medical Center, Petah Tikva, Israel; and ⁶Research Unit, Rabin Medical Center, Petah Tikva, Israel

Abstract

Aims To assess the 6 months immunogenicity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine in a population of heart transplanted (HTx) recipients and left ventricular assist device (LVAD)-supported patients.

Methods and results A prospective single-centre cohort study of HTx recipients and LVAD-supported patients who received a two-dose SARSCoV-2 mRNA vaccine (BNT162b2, Pfizer-BioNTech). Whole blood for anti-spike IgG (S-IgG) antibodies were drawn at 6 months after the first vaccine dose. S-IgG data at 6 weeks were available for a subgroup of HTx recipients. S-IgG ≥ 50 AU/mL were interpreted positive. The cohort included 53 HTx recipients and 18 LVAD-supported patients. The median time from HTx or LVAD implantation to the 1st vaccine dose was 90 (IQR 30, 172) months and 22 (IQR 6, 78) months, respectively. The seropositivity rates of S-IgG antibodies and their titre levels in HTx recipients and LVAD-supported patients were 45% and 83% respectively, ($P = 0.006$), and 35 (IQR 7, 306) AU/mL and 311 (IQR 86, 774) AU/mL, respectively, ($P = 0.006$). Reduced SARSCoV-2 vaccine immunogenicity in HTx recipients was associated with older age [odds ratio (OR) 0.917 confidence interval (CI) 0.871, 0.966], $P = 0.011$ and with the use of anti-metabolites-based immunosuppressive regimens [OR 0.224 (CI 0.065, 0.777), $P = 0.018$]. mTOR inhibitors were associated with higher immunogenicity [OR 3.1 (CI 1.01, 9.65), $P = 0.048$]. Out of 13 HTx recipients who were S-IgG seropositive at 6 weeks after the first vaccine dose, 85% remained S-IgG seropositive at 6 month follow-up.

Conclusions At 6 months post-vaccination, S-IgG immunogenicity in HTx recipients is low, particularly in older HTx recipients and in those treated with anti-metabolites drugs.

Keywords SARS-CoV-2; COVID-19; Heart transplantation; Left ventricular assist device; Vaccine

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*Correspondence to: Osnat Itzhaki Ben Zadok, Department of Cardiology, Rabin Medical Center, 39 Jabotinsky St. 49100 Petah Tikva, Israel. Tel: 972-3-9377111; Fax: 972-3-9213221. Email: osnat.irtzhaki@gmail.com

Introduction

Heart transplant (HTx) recipients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carry a poor prognosis with an estimated case fatality rate of 25%.¹ Therefore, the SARSCoV-2 vaccine has been^{2,3} recommended with a high priority to all heart and lung transplant candidates and recipients by recipients by the International Society

for Heart and Lung transplantation (ISHLT).⁴ Nevertheless, the immunocompromised milieu of solid-organ transplant recipients, including the HTx population, has raised concerns regarding the effectiveness and the durability of the immune response elicited by such an intervention.²

We and others have previously reported^{5–7} diminished short-term immunogenicity to the two-dose SARSCoV-2 mRNA vaccine in HTx recipients with S-IgG antibody titers

ranging between 18% and 49% approximately 6 weeks from the first vaccine dose. These findings have led key-opinion leaders to the notion that in order to establish an efficient immune response, an additional, third, dose of vaccine may be required in this unique patient population.⁴ A recent study has shown that a third vaccine dose is capable of eliciting a humoral and cellular responses in the majority of HTx recipients.⁵ Nevertheless, as longer-term immunogenicity induced by the SARSCoV-2 mRNA vaccine in solid-organ transplant recipients is unknown, the actual clinical necessity and patient population volume for such an interventional approach are yet to be determined.

Left-ventricular assist device (LVAD)-supported patients, who are often HTx candidates, represent another vulnerable population for severe disease from SARS-CoV-2 infection despite the lack of background immunosuppression therapies.⁸ Possible aetiologies are impaired cellular immunity,⁹ the presence of a permanent artificial device, baseline severe cardiomyopathy and frequent systemic co-morbidities. Published data describing the immunogenicity to the SARSCoV-2 mRNA vaccine in LVAD-supported patients are lacking.

Therefore, in the present study, we aimed to assess the mid-term immunogenicity to a two-dose SARSCoV-2 mRNA vaccine in a population of HTx recipients and LVAD-supported patients.

Methods

We conducted a prospective cohort study of isolated HTx recipients and LVAD-supported patients at the Rabin Medical Center. We included subjects who have received a two-dose SARSCoV-2 mRNA vaccine (BNT162b2, Pfizer-BioNTech, Mainz, Germany, prime-boost regimen on Days 0 and 21, respectively, at a dose of 30 µg each¹⁰) between December 2020 and February 2021. Major exclusion criteria to any subgroup of the study were heart transplantation or LVAD implantation within the previous 30 days, patient's refusal to get a full two-dose vaccine schedule or to participate in the study and a known prior SARSCoV-2 infection (documented by positive PCR nasal swab).

Whole blood for the assessment of anti-spike IgG (S-IgG) antibodies were drawn at 6 months after the first vaccine dose. The HTx recipients group was in continuation with our previous study⁷; thus, S-IgG serologic data at Days 35 to 40 (6 weeks time-point) were available for a subgroup of HTx recipients ($n = 30$). As previously described,⁷ serum was separated by centrifugation, aliquoted and stored at -20°C . SARS-CoV-2 IgG II quantitative testing was performed using the Abbott architect analyser i2000sr platform in accordance with manufacturer's package insert.¹¹ This antibody chemiluminescent microparticle immunoassay was used to quantify

IgG antibodies in human serum and plasma samples. The assay detects antibodies against the receptor binding protein of the S1 subunit of the spike protein of SARSCoV-2. The resulting chemiluminescence following the addition of anti-human IgG-labelled in comparison with the IgG II calibrator/standard indicates the strength of response, which reflects the quantity of IgG present. S-IgG value of 50 AU/mL and greater was interpreted as seropositive.^{11–13}

Clinical and pharmacological data were extracted from patients' electronic records. All HTx recipients were under standard immunosuppressive therapy with oral tacrolimus or cyclosporine, mycophenolate mofetil and/or everolimus and prednisone.

Statistical analysis

The statistical analysis for this paper was generated using SAS Software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented by median and interquartile 25th, 75th range. Categorical variables were presented by (N , %). T test was used to compare the value of baseline continuous variables, which were deemed to have a normal distribution, between study groups and Wilcoxon was used for non-normal variables. Fisher's exact test was used to compare the value of baseline categorical variables between study groups. Logistic regression was used to assess the relationship between study group and baseline values to study outcome (S-IgG immunogenicity at 6 months). Values less than 0.05 were considered statistically significant.

The study protocol was approved by the Institutional Review Board and patients' approval has been obtained (RMC 1069-20).

Results

The study included 53 HTx recipients and 18 LVAD-supported patients who received a two-dose SARSCoV-2 vaccine and provided informed consent to participate in this study (*Figure 1*). Patients' baseline characteristics are reported in *Table 1*. The median time from HTx or LVAD implantation to the 1st vaccine dose was 90 [interquartile (IQR) 30, 172] months and 22 (IQR 6, 78) months, respectively. Sixty-eight per cent ($n = 36$) of HTx recipients were on anti-metabolites-based immunosuppressive regimen, and 78% ($n = 14$) of LVAD-supported patients were implanted with HeartMate 3 LVADs.

Clinically, two HTx recipients suffered from SARSCoV-2 infection at 1 week and 1 month after the completion of a two-dose vaccination schedule and were excluded from further antibody titre analysis due to possible cross-reactivity. None of these patients required supplemental oxygen or hospitalization. None of the LVAD-supported patients in our co-

Figure 1 Schematic flowchart of study design presenting the different time-points analysed for S-IgG immunogenicity. Abbreviations: HTx, heart transplantation; LVAD, left-ventricular assist device.

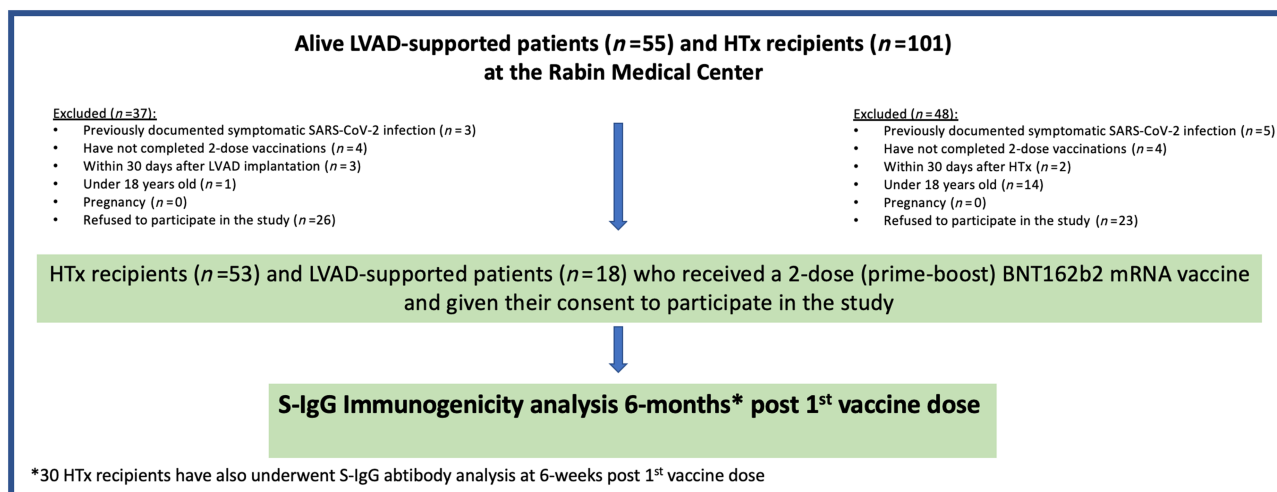


Table 1 Baseline characteristics of study's cohorts: HTx recipients and LVAD-supported patients

	HTx recipients (n = 53)	LVAD-supported patients (n = 18)
Age (years)	62 (45, 69)	66 (56, 73)
Time from HTx or LVAD implantation (months)	90 (30, 172)	22 (6, 78)
Gender (male)	43 (81)	16 (89)
Immunosuppressive regimen (%)		
Calcineurin inhibitors	43 (81)	
mTOR inhibitors	27 (51)	
Oral steroids	36 (68)	
Anti-metabolites ^a	35 (66)	
LVADs (%)		
Heartware		2 (11)
HeartMate2		2 (11)
HeartMate3		14 (78)

Abbreviations: HTx, heart transplantation; LVAD, left-ventricular assist device; mTOR, mammalian target of rapamycin.

Data are presented as median (25th, 75th quartiles) or as percentages, as appropriate.

^aAntimetabolites immunosuppression regimen refer to mycophenolate mofetil, mycophenolic acid.

hort suffered from SARSCoV-2 infection during the study surveillance period.

SARSCoV-2 S-IgG seropositivity rates and their titre levels are presented in *Figure 2*. At 6 months after the completion of a two-dose vaccination schedule, S-IgG seropositivity rates and titre levels in LVAD-supported patients and HTx recipients were 83% and 45%, respectively ($P = 0.006$), and 311 (IQR 86, 774) AU/mL and 35 (IQR 7, 306) AU/mL, respectively ($P = 0.006$). Combined serologic S-IgG data at 6 weeks and 6 months post-vaccination were available for 30 HTx recipients (*Figure 3*). Out of the 13 HTx recipients who were

S-IgG seropositive at 6 weeks [median titre level 662 (IQR 135, 2190) AU/mL], 85% ($n = 11$) had a durable humoral response at 6 months post-vaccination [median titre level 344 (IQR 110, 633) AU/mL].

The characteristics of HTx recipients who succeeded versus failed to demonstrate S-IgG immunogenicity at 6 months post-vaccination are presented at *Table 2*. Reduced SARSCoV-2 vaccine immunogenicity was associated with older age [odds ratio (OR) 0.917 confidence interval (CI) 0.871, 0.966], $P = 0.011$] and with the use of anti-metabolites-based protocols [OR 0.224 (CI 0.065, 0.777), $P = 0.018$]. Notably, patients treated with mTOR inhibitors were more likely to demonstrate S-IgG antibodies [OR 3.1 (CI 1.01, 9.65), $P = 0.048$].

Discussion

In this study, we report the mid-term S-IgG immunogenicity of HTx recipients and LVAD-supported patients following a two-dose SARSCoV-2 mRNA vaccine. We found that only 45% of HTx recipients were S-IgG seropositive at 6 months post-vaccination, similar to the short-term immunogenicity previously observed in this population, and a significantly lower seropositivity rate as compared with LVAD-supported patients. Older age and the use of anti-metabolites-based regimens were associated with failure to demonstrate S-IgG seropositivity at 6 month follow-up. Eighty-five per cent of HTx recipients who elicited humoral S-IgG immune response at 6 weeks post-vaccination demonstrated S-IgG seropositivity at 6 months, albeit with lower titre levels.

Over the months following the Food and Drug Administration (FDA) approval and global distribution of SARSCoV-2

Figure 2 S-IgG seropositive rates and titre levels in HTx recipients and LVAD-supported patients. (A) S-IgG antibody rates and (B) titre levels. Abbreviations: HTx, heart transplanted; LVAD, left-ventricular assist device.

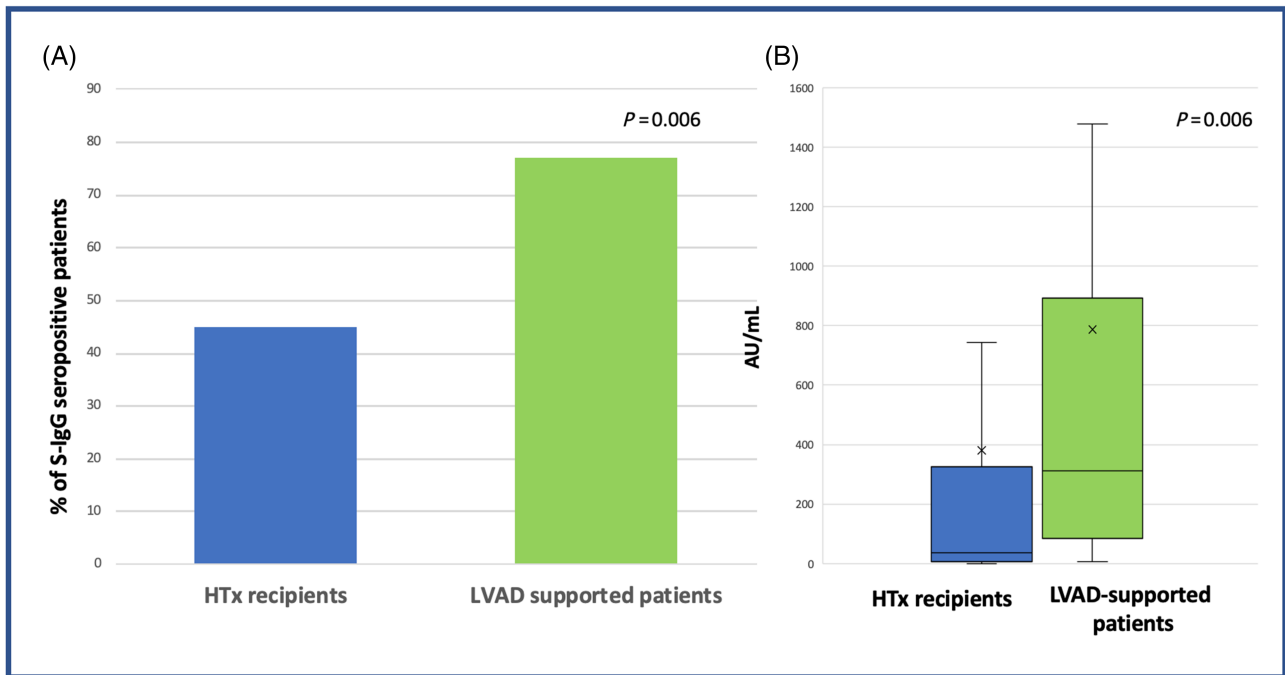
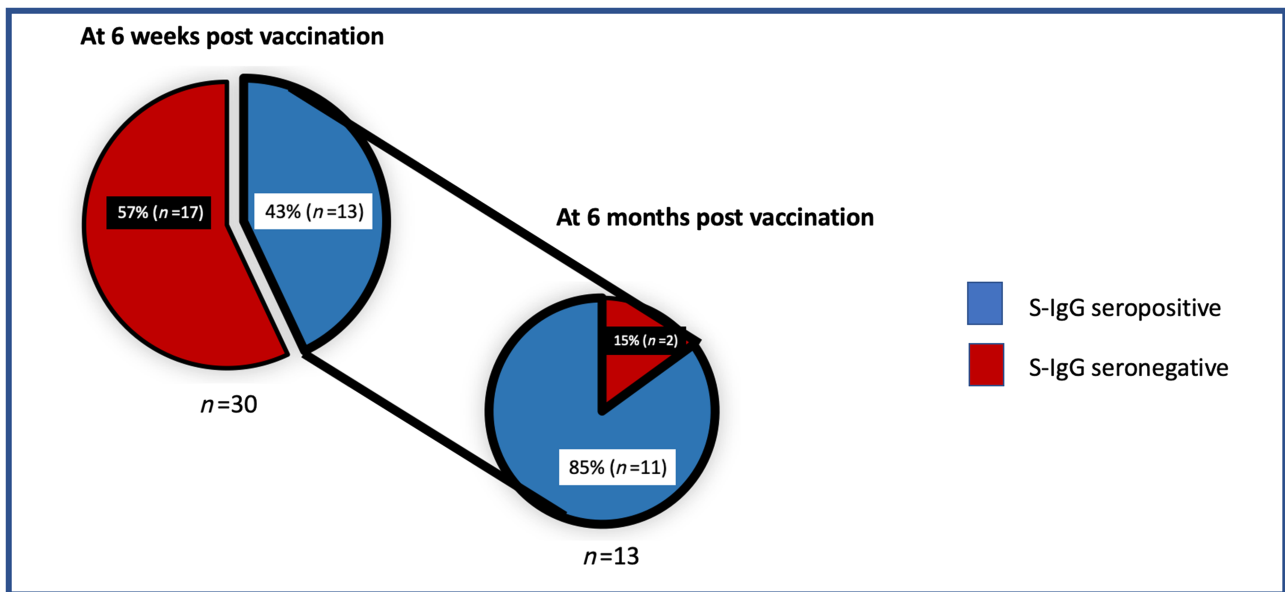


Figure 3 S-IgG seropositive rates in HTx recipients at 6 weeks and at 6 months post-vaccination. Serologic S-IgG data at both 6 weeks and 6 months timepoints were available for 30 HTx recipients. Abbreviations: HTx, heart transplantation.



mRNA vaccines, data regarding the short-term humoral response to the vaccines in the general population and in solid organ recipients have accumulated. Studies in heart, kidney, and lung transplant recipients approximately 6 weeks after

the first vaccine dose have shown poor short-term S-IgG immunogenicity ranging between 18% and 49%,^{5,7} 29% and 54%,^{14,15} and 18%¹⁶ seropositivity rates, respectively. These findings are not surprising, since a weaker immunogenicity

Table 2 Baseline characteristics of study HTx patients stratified by their S-IgG immunogenicity to a two-dose (prime-boost) BNT162b2 mRNA vaccine at 6 months

	S-IgG seronegative (n = 29)	S-IgG seropositive (n = 24)	P value
Age (years)	67 (62, 70)	45 (36, 61)	0.001
Time from HTx or LVAD implantation (months)	75 (15, 164)	107 (38, 178)	0.685
Gender (male)	26 (90)	17 (71)	0.115
Immunosuppressive drugs			
Calcineurin inhibitors	23 (79)	20 (83)	0.940
mTOR inhibitors	11 (38)	16 (67)	0.048
Oral steroids	21 (72)	15 (63)	0.459
Anti-metabolites ^a	23 (79)	12 (50)	0.002
Immunosuppressive drug protocol			
CNI-reduced ^b	5 (17)	12 (50)	0.018
Anti-metabolites based protocols ^c	24 (83)	12 (50)	

Abbreviations: CNI, calcineurin inhibitors; HTx, heart transplantation; mTOR, mammalian target of rapamycin.

Data are presented as median (25th, 75th quartiles) or as percentages, as appropriate.

^aAntimetabolites immunosuppression regimen refer to mycophenolate mofetil, mycophenolic acid.

^bCNI-reduced protocols include CNIs and mTOR inhibitors.

^cAnti-metabolites based protocols refer to CNI-based immunosuppression regimens (CNIs and anti-metabolites) and CNI-free immunosuppression regimens (mTOR inhibitors and anti-metabolites).

in solid organ recipients has been reported in response to other formulations as well (i.e. influenza vaccine).¹⁷ In contrary, in the general immunocompetent population, the short-term S-IgG immunogenicity following SARSCoV-2 vaccines has been markedly higher with reported seropositivity rates ranging between 91% and 99%.^{18,19} This discrepancy is attributed to the lack of a competent host immunity in the immune-suppressed patient, which is needed in order to generate a fully protective immune response following vaccination.

Studies investigating longer-term immunogenicity after natural SARS-CoV-2 infection in the general population demonstrated relatively stable seropositivity rates at a follow-up of 3 months^{18,20} and a modest decline (90% seropositivity rate) at a longer follow-up of 8 months.²¹ Although evidence regarding the durability of the humoral response following the administration of mRNA SARS-CoV-2 vaccines are yet scarce, current data are suggestive of an antibody decay similar to that of natural infection.^{22–24} Recently, Pegu et al. demonstrated the persistence, albeit at lower levels, of both binding and functional antibodies against SARSCoV-2 variants in the majority of subjects 6 months after vaccination.²² In a study investigating 122 individuals who received a two-dose SARSCoV-2 mRNA vaccine, S-RBD IgG levels were decreased to 23% on average of their peak level (mean level decreased from 26 928 AU/mL to 5702 AU/mL at 12 weeks), but remained significantly higher compared with patients recovered from SARS-CoV-2.²³ These observations are compatible

with our findings regarding the durability of the humoral immune response in LVAD-supported patients, suggesting that this population should be regarded as 'non at risk' with respect to SARS-CoV-2 immunogenicity. Other factors such as the presence of a permanent artificial device, systemic co-morbidities and frequent clinic visits and hospitalizations may increase their vulnerability for SARS-CoV-2 acquisition and disease severity. Importantly, considering the high S-IgG seropositivity among LVAD-supported patients and the low S-IgG seropositivity among HTx recipients, it is imperative to encourage LVAD-supported patients who are in candidacy to heart transplantation to get vaccinated, as currently recommended by the ISHLT.⁴

Data describing longer-term immunogenicity after SARS-CoV-2 vaccines in solid-organ recipients are limited. This study demonstrates low S-IgG seropositivity in HTx recipients at 6 months post-vaccination (particularly in older subjects and those who use anti-metabolites drugs), results which contrast the immunogenicity observed in LVAD-supported patients and the general immunocompetent population at post-vaccination mid-term follow-up. Although initial reports are encouraging,⁵ whether an added third vaccine dose will increase the S-IgG seropositivity rate of HTx recipients or rather this will not affect those who remained S-IgG seronegative after a two-vaccine dose regimen deserves further study in larger cohorts.

Another important observation of this study was the higher S-IgG immunogenicity found with the use of mTOR inhibitors, possibly suggesting to prefer the latter in the population of HTx recipients during this ongoing SARSCoV-2 era. Nevertheless, as such a step involves other immune-related considerations, this strategy should be more thoroughly investigated before high-level recommendations could be provided.

Moreover, we found that the majority of HTx recipients, who elicited humoral S-IgG immune response at 6 weeks post-vaccination, demonstrated S-IgG seropositivity at 6 months. We believe that these findings, although observed in a small group of patients, may offer some reassurance to HTx recipients and their caregivers regarding longer-term S-IgG immunogenicity.

This study has several limitations. First, this study is limited by its small sample size and single-centre design. Nevertheless, our advanced heart failure unit is a referral centre which integrates the management of approximately 50% of HTx recipients in Israel. Second, the overall low incidence of SARSCoV-2 symptomatic cases in our cohort prevents us from evaluating the clinical implication of low S-IgG immunogenicity in HTx recipients. This low SARSCoV-2 infection rate is probably attributed to the low overall infection rate in Israel at the time of the study. Third, this study lacks a neutralization assay testing. However, strong correlation has been previously reported between S-IgG titers and neutralization antibody levels.^{21,25}

In conclusion, at 6 months post-vaccination S-IgG immunogenicity in HTx recipients is low, and thus, their protection from the SARS-CoV-2 achieved by its targeted vaccine is impaired. These findings suggest the need for other immunization strategies, such as an added booster vaccine dose in HTx recipients or the avoidance of anti-metabolites immunosuppressive regimens— all of which deserve focused study. The high S-IgG immunogenicity observed in LVAD-supported patients supports their vaccination during candidacy and before undergoing heart transplantation.

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Conflict of interest

None.

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References

- Latif F, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y, Restaino S, Sayer G, Uriel N. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. *JAMA Cardiol* 2020; **5**: 1165–1169.
- Aslam S, Goldstein DR, Vos R, Gelman AE, Kittleson MM, Wolfe C, Danziger-Isakov L. COVID-19 vaccination in our transplant recipients: the time is now. *J Heart Lung Transplant* 2021; **40**: 169–171.
- SARS-CoV-2 vaccination in heart and lung transplantation Recommendations from the ISHLT COVID-19 Task Force. March 15th 2021.
- Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic July 2021. 2021
- Peled Y, Ram E, Lavee J, Sternik L, Segev A, Wieder-Finesod A, Mandelboim M, Indenbaum V, Levy I, Raanani E, Lustig Y, Rahav G. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. *J Heart Lung Transplant* 2021; **40**: 759–762.
- Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med* 2021; **385**: 661–662.
- Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, Pertzov B, Eliakim-Raz N, Abed G, Abuhazira M, Barac YD, Mats I, Kramer MR, Aravot D, Kornowski R, Ben-Gal T. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients—a prospective cohort study. *Eur J Heart Fail* 2021; **23**: 1555–1559.
- Ben Gal T, Ben Avraham B, Abu-Hazira M, Frigerio M, Crespo-Leiro MG, Oppelaar AM, Kato NP, Stromberg A, Jaarsma T. The consequences of the COVID-19 pandemic for self-care in patients supported with a left ventricular assist device. *Eur J Heart Fail* 2020; **22**: 933–936.
- Kimball PM, Flattery M, McDougan F, Kasirajan V. Cellular immunity impaired among patients on left ventricular assist device for 6 months. *Ann Thorac Surg* 2008; **85**: 1656–1661.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**: 2603–2615.
- Abbott Core Laboratory: SARS-CoV-2 immunoassays: advancing diagnostics of COVID-19. <https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2>. Accessed April 7, 2021.
- Narasimhan M, Mahimainathan L, Araj E, Clark AE, Markantonis J, Green A, Xu J, SoRelle JA, Alexis C, Fankhauser K, Parikh H, Wilkinson K, Reczek A, Kopplin N, Yekkaluri S, Balani J, Thomas A, Singal A, Sarode R, Muthukumar A. Clinical evaluation of the Abbott Alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays in infected, recovered, and vaccinated groups. medRxiv. 2021:2021.2002.2017.21251940.
- Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, Rechavi Y, Schwartz IF, Schwartz D, Lellouch Y, Shashar M. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. *Clin J Am Soc Nephrol* 2021; CJN.03500321.
- Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, Tau N, Mashraki T, Neshet E, Rahamimov R. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect* 2021; **27**: 1173.e1–1173.e4.
- Cucchiari D, Egri N, Bodro M, Herrera S, Del Risco-Zevallos J, Casals-Urquiza J, Cofan F, Moreno A, Rovira J, Banon-Maneus E, Ramirez-Bajo MJ, Ventura-Aguilar P, Pérez-Olmos A, Garcia-Pascual M, Pascal M, Vilella A, Trilla A, Ríos J, Palou E, Juan M, Bayés B, Diekmann F. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant* 2021; **21**: 3971–3979.
- Shostak Y, Shafran N, Heching M, Rosengarten D, Shtraichman O, Shitenberg D, Amor SM, Yahav D, Ben Zvi H, Pertzov B, Kramer MR. Early humoral response among lung transplant recipients vaccinated with BNT162b2 vaccine. *Lancet Respir Med* 2021; **9**: e52–e53.
- Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, Rotstein C, Lilly L, Schiff J, Singer L, Humar A, Kumar D. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine in adult solid-organ transplant recipients. *Clin Infect Dis* 2018; **66**: 1698–1704.
- Wajnsberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, McMahon M, Meade P, Mendu DR, Muellers K, Stadlbauer D, Stone K, Strohmeier S, Simon V, Aberg J, Reich DL, Krammer F, Cordon-Cardo C. Robust neutralizing

- antibodies to SARS-CoV-2 infection persist for months. *Science (New York, NY)* 2020; **370**: 1227–1230.
19. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, Arnthorsson AO, Helgason D, Bjarnadottir K, Ingvarsson RF, Thorsteinsdottir B, Kristjansdottir S, Birgisdottir K, Kristinsdottir AM, Sigurdsson MI, Arnadottir GA, Ivarsdottir EV, Andresdottir M, Jonsson F, Agustsdottir AB, Berglund J, Eiriksdottir B, Fridriksdottir R, Gardarsdottir EE, Gottfredsson M, Gretarsdottir OS, Gudmundsdottir S, Gudmundsson KR, Gunnarsdottir TR, Gylfason A, Helgason A, Jensson BO, Jonasdottir A, Jonsson H, Kristjansson T, Kristinsson KG, Magnusdottir DN, Magnusson OT, Olafsdottir LB, Rognvaldsson S, le Roux L, Sigmundsdottir G, Sigurdsson A, Sveinbjornsson G, Sveinsdottir KE, Sveinsdottir M, Thorarensen EA, Thorbjornsson B, Thordardottir M, Saemundsdottir J, Kristjansson SH, Josefsdottir KS, Masson G, Georgsson G, Kristjansson M, Moller A, Palsson R, Gudnason T, Thorsteinsdottir U, Jonsdottir I, Sulem P, Stefansson K. Humoral immune response to SARS-CoV-2 in Iceland. *N Engl J Med* 2020; **383**: 1724–1734.
 20. Isho B, Abe KT, Zuo M, Jamal AJ, Rathod B, Wang JH, Li Z, Chao G, Rojas OL, Bang YM, Pu A, Christie-Holmes N, Gervais C, Ceccarelli D, Samavarchi-Tehrani P, Guvenc F, Budyłowski P, Li A, Paterson A, Yue FY, Marin LM, Caldwell L, Wrana JL, Colwill K, Sicheri F, Mubareka S, Gray-Owen SD, Drews SJ, Siqueira WL, Barrios-Rodiles M, Ostrowski M, Rini JM, Durocher Y, McGeer AJ, Gommerman JL, Gingras AC. Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. *Sci Immunol* 2020; **5**: eabe5511.
 21. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A, Nakao C, Rayaprolu V, Rawlings SA, Peters B, Krammer F, Simon V, Saphire EO, Smith DM, Weiskopf D, Sette A, Crotty S. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science (New York, NY)* 2021; **371**.
 22. Pegu A, O'Connell S, Schmidt SD, O'Dell S, Talana CA, Lai L, Albert J, Anderson E, Bennett H, Corbett KS, Flach B, Jackson L, Leav B, Ledgerwood JE, Luke CJ, Makowski M, Nason MC, Roberts PC, Roederer M, Rebolledo PA, Rostad CA, Roupheal NG, Shi W, Wang L, Widge AT, Yang ES, Group Tm-S, Beigel JH, Graham BS, Mascola JR, Suthar MS, McDermott AB, Doria-Rose NA. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. *Science (New York, NY)* 2021: eabj4176.
 23. Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, Haljasmägi L, Rumm P, Maruste R, Käerner J, Gerhold JM, Planken A, Ustav M, Kisand K, Peterson P. Declined antibody responses to COVID-19 mRNA vaccine within first three months. medRxiv 2021:2021.2004.2019.21255714.
 24. Eliakim-Raz N, Massarweh A, Stemmer A, Stemmer SM. Durability of response to SARS-CoV-2 BNT162b2 vaccination in patients on active anticancer treatment. *JAMA Oncol* 2021; **7**: 1716–1718.
 25. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, Cho A, Jankovic M, Schaefer-Babajew D, Oliveira TY, Cipolla M, Viant C, Barnes CO, Bram Y, Breton G, Hägglöf T, Mendoza P, Hurley A, Turroja M, Gordon K, Millard KG, Ramos V, Schmidt F, Weisblum Y, Jha D, Tankelevich M, Martinez-Delgado G, Yee J, Patel R, Dizon J, Unson-O'Brien C, Shimeliovich I, Robbiani DF, Zhao Z, Gazumyan A, Schwartz RE, Hatzioannou T, Bjorkman PJ, Mehandru S, Bieniasz PD, Caskey M, Nussenzweig MC. Evolution of antibody immunity to SARS-CoV-2. *Nature* 2021; **591**: 639–644.