IJC Heart & Vasculature 51 (2024) 101379

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

# SARS-CoV2 infections in heart transplant recipients: Vaccines still are our greatest weapon

Heart transplant (HT) patients are at special risk for developing severe forms of coronavirus disease 2019 (COVID-19) [1–3]. Despite prior reports suggest that vaccines administration reduce the rate of Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV2) infection and guarantee better clinical outcomes in immunosuppressed patients [4,5], studies with long-term clinical follow-up are needed to assess the efficacy particularly of booster doses in an epidemiological landscape characterized by rapidly changing viral variants in this frail population [6]. We carried out a retrospective cohort study at Niguarda Hospital, a high-volume HT center in Milan. Over the cohort of patients who received HT from January 2008 to March 2022, we analyzed those who developed SARS-CoV2 infection between March 2020 and January 2023. Patients were considered infected in case of positive results of polymerase chain reaction or antigen tests of nasopharyngeal swab samples. Infected patients were divided in 2 groups: unvaccinated and vaccinated. The achievement of the vaccinated status was defined two weeks after receiving the first dose of mRNA vaccine (BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]), which were the only approved by the Italian Health Ministry for HT patients. The data were collected during hospitalization, ambulatory visits, and phone calls. The primary outcome is represented by death. As secondary outcomes we evaluated the percentage of hospitalization, pneumonia development, requiring supplementary oxygen, mechanical non-invasive ventilation (NIV) and invasive ventilation, need for renal replacement therapy, occurrence of arrhythmias, thromboembolic events, and allograft rejection in the two groups. Cross-sectional comparisons between groups were made using the ANOVA test on continuous variables, the Brown–Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric Mann–Whitney test when necessary. The chi-squared or Fisher exact test was used for discrete variables. Cumulative incidence curves for all causes of death were estimated and compared between groups. A P-value $\leq 0.05$ was considered as a threshold of statistical significance IBM SPSS (Armonk, NY, USA) statistical software version 19 was used for statistical analyses. Of 377 patients who underwent HT from January 2008 to March 2022 and who were alive at the pandemic's beginning, 98 (25.9 %) patients developed COVID-19 during the study period. The mean follow-up was 30 ± 7 months. 24 (27.5 %) patients developed infection before receiving vaccine, whilst 74 (75.5 %) almost after 2 weeks from the first dose. Unvaccinated patients were older. Otherwise, the two groups were well-balanced about all baseline characteristics (Table 1). Regarding the primary outcome, we registered 6 deaths in 24 patients of the unvaccinated group (25.0 %), one death in 7 patients of the group with only one dose (14.2 %), one death in 11 patients of the group with two doses (9.1 %), one death in 50 patients of the group with three doses (2 %) and no deaths in the patient cohort that received four doses (n = 6) (Fig. 1). Comparing the two cohorts, unvaccinated Vs vaccinated with at least one dose, we have a mortality of 25 % Vs 4.1 %, respectively ($p < 0.01$). Every registered death was caused by COVID-19 complications. As concerns the secondary endpoint, we registered a higher rate of events in the unvaccinated group. Particularly we found a higher incidence of pneumonia (58.5 % Vs 28.4 %, $p = 0.01$) and patients requiring oxygen supplementation (50 % Vs 25.7 %, $p = 0.04$), NIV (41.7 % Vs 9.5 %, $p = 0.01$) and invasive ventilation (33.3 % Vs 1.4 %, $p < 0.01$). No difference was found in the rate of allograft rejection during the infection between the two groups (4 % unvaccinated group Vs 2.7 % vaccinated, $p = 1$). We also assessed that vaccinated patients more frequently received antiviral drugs (Remdesivir/Molnupinavir)

**Table 1**
Demographics, immunosuppressive therapy and therapeutic management of SARS-CoV2 infection.

| | NV (N = 24) | V (N = 74) | p VALUE |
|---|---|---|---|
| *Demographics* | | | |
| Age | 57.5 (43.2–63.2) | 53.5 (44.7–60.0) | 0.349 |
| Male | 7 (29.2) | 23 (31.1) | 0.86 |
| CKD | 18 (75.0) | 47 (63.5) | 0.091 |
| Hypertension | 5 (20.8) | 30 (40.5) | 0.08 |
| Diabetes | 2 (8.3) | 13 (17.6) | 0.275 |
| CAV | 6 (25.0) | 11 (14.9) | 0.255 |
| Prior Allographt Rejection | 15 (62.5) | 37 (50.0) | 0.286 |
| *Immunosuppressive therapy* | | | |
| Ciclosporine | 12 (5) | 23 (31.1) | 0.93 |
| Tacrolimus | 11 (45.8) | 47 (63.5) | 0.126 |
| Mycophenolate Mofetil | 16 (66.6) | 38 (51.3) | 0.19 |
| Mycophenolic Acid | 3 (12.5) | 20 (27.0) | 0.145 |
| Everolimus | 2 (8.3) | 9 (12.2) | 0.606 |
| Azathioprine | 1 (4.2) | 1 (1.4) | 0.397 |
| Metyliprednisone | 14 (58,0.3) | 37(50.0) | 0.478 |
| *Covid treatment* | | | |
| Monoclonal antibodies | 0 (0) | 13 (17.6) | 0.027 |
| Antiviral drugs | 0 (0) | 24 (32.4) | 0.006 |
| Remdesivir | 0 (0) | 19 (25.7) | 0.006 |
| Molnupinavir | 0 (0) | 5 (6.8) | 0.19 |
| Steroid uptitration | 3 (12.5) | 20 (27.0) | 0.145 |
| Mycophenolate interruption | 2 (8.3) | 9 (12.2) | 0.606 |
| *Covid Vaccine* | | | |
| 1 Dose | 0 | 7 (9.4) | |
| 2 Dose | 0 | 11 (14.9) | |
| 3 Dose | 0 | 50 (67.5) | |
| 4 Dose | 0 | 6 (8.1) | |

CAV: coronary allograft vasculopathy; CKD: chronic kidney disease; NV: non-vaccinated; V: vaccinated.
Values are expressed as medians and first to third quartile, or counts and percentages, as appropriate.

https://doi.org/10.1016/j.ijcha.2024.101379
Received 27 December 2023; Received in revised form 9 February 2024; Accepted 27 February 2024
Available online 4 March 2024

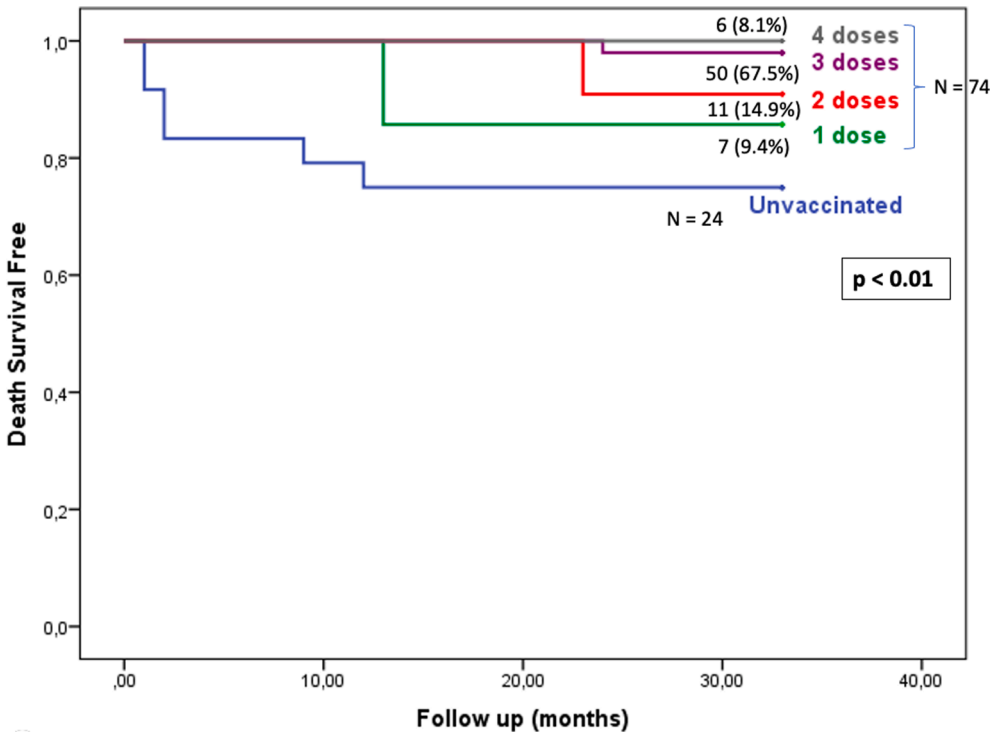


**Fig. 1.** Mortality of heart transplant recipient during SARS-CoV2 infection according to vaccination status and number of vaccine doses received.

and/or monoclonal antibodies, whose use hasn't been established yet during the first phase of the pandemic (Table 1). Our findings strongly support the effectiveness of mRNA vaccines in reducing the rate of death and severe disease in HT patients who develop SARS-CoV2 infection. By comparing the incidence of primary outcome according to the number of doses received from each patient, we assess an additional protective effect against mortality offered from booster vaccine doses (Fig. 1). Since COVID-19 vaccines were available, our HT unit firmly recommends each patient's immunization. To overcome the mistrust of patients, we offered an informative interview allowing them to make informed decisions. This brought us to reach a high percentage of vaccinated patients, as evidenced by only 2 patients who developed infection before receiving the vaccine when they were already available. The lower number of infections in unvaccinated patients could be justified by two reasons. At first, Italy was severely impacted by the pandemic bringing the adoption of stringent measures that were progressively loosened with the increasing percentage of the vaccinated population and reduction in circulating virus. Secondly, the easing of those measures occurred contemporary to the spreading of the Omicron variant of coronavirus, which presents higher transmissibility [7]. Despite the majority of infections taking place when HT patients were fully vaccinated, the rate of adverse outcomes was significantly lower compared to the previous period when vaccines were not still available, strongly supporting vaccine importance. However, since a lower fatality rate with the Omicron variant was reported [7], better outcomes cannot certainly attribute solely to vaccination. When commenting our results, it must be considered how therapeutic approach to COVID-19 has progressively evolved bringing the frequent administration of antiviral drugs and monoclonal antibodies. However, data regarding the effectiveness of those strategies in HT recipients remains mainly based on observational studies, and results are conflicting [4,8]. Our study presents several limitations. This is a single-center retrospective study with a limited sample size. Furthermore, the circulating virus variants have progressively changed their characteristics making it complex to clarify how the differences in patients' outcomes depend on vaccine status rather than changing viral variants. Finally, the small number of patients who faced infection having already received the second booster dose doesn't allow us to assess how much this administration could contribute to a further reduction in the occurrence of severe complications. In conclusion, despite the World Health Organization ended the global emergency status for COVID-19, we believe that periodic booster vaccination remains paramount in HT recipients, particularly in an era of variants with a persistently high rate of infections.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Andrea Tedeschi*
*Cardiology Department, Guglielmo da Saliceto Hospital, Piacenza, Italy*
*"De Gasperis" Cardio Center, Niguarda Hospital, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*

Piero Gentile, Matteo Palazzini, Gabriella Masciocco, Filippo Leidi, Massimiliano Monticelli, Enrico Ammirati, Andrea Garascia
*"De Gasperis" Cardio Center, Niguarda Hospital, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*

* Corresponding author at: Cardiology Department, Guglielmo da Saliceto Hospital, Piacenza, Italy.
*E-mail address:* andrea.tedeschimd@gmail.com (A. Tedeschi).