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Patients After Orthotopic Heart Transplantation With COVID-19: Are We Fast Enough With Vaccinations?

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ABSTRACT

Background. Patients after orthotopic heart transplantation (HTx) are especially susceptible to infections owing to permanent need for immunosuppression. Vaccinations against COVID-19 have been available since January 2021 and are recommended in organ recipients.

Aim. The aim of this study was to analyze COVID-19 susceptibility and mortality in HTx and number of patients with COVID-19 previously vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Patients and Methods. We analyzed a whole cohort of 552 patients after HTx who were SARS-CoV-2 positive and remained under surveillance of the transplantation center during March 2020 to September 2021.

Results. Among 552 patients after HTx, 10 were COVID-19 survivors prior to transplantation and 103 had SARS CoV-2 infection after transplantation.

Mean age of patients with COVID-19 was 55.6 (±14) years, and mean time from transplantation to SARS-CoV-2 infection was 2856 (±2596) days (range, 16-9569 days; interquartile range, 397-4763 days). Among the patients who were COVID-19 positive, 15 were asymptomatic, 10 died, and 51 infections occurred in the era of vaccinations.

In the group of patients who were positive for COVID-19 in 2021, 6 received only a single dose of the mRNA vaccine and 3 were vaccinated twice. Among the vaccinated patients with COVID-19, 2 died of severe COVID-19: 1 after a single dose and 1 after 2 standard doses of the vaccine.

Conclusion. We observed high susceptibility to SARS-CoV-2 infection in the group of patients after HTx. The majority of patients infected in 2021 did not received the vaccine. Vaccination does not fully protect against severe COVID-19 in patients after HTx.

ACCORDING to current International Society for Heart and Lung Transplantation guidelines [1] all patients after solid organ transplantation should receive vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The optimal timing for the vaccination is at least 1 month after transplantation, 3 to 6 months after induction or lymphodepletion therapy, or at least 1 month after rejection treatment with high doses of steroids.

In Poland we have wide access to SARS-CoV-2 vaccines: 2 recombinant nonreplicating viral vector vaccines (Ad26.COV2-S, ChAdOx1-S) and 2 mRNA vaccines are available. The vaccinations in our country have been accessible since January 2021. Observations performed in the general population showed that the vaccines reduce occurrence of the infection and severity of the disease [2−4]. Furthermore, many studies confirmed the safety and efficacy of the vaccination in subpopulations of transplant recipients [5,6].

There are no cutoff values for vaccination efficacy. However, it seems that antibody titers needed to prevent severe infection in solid organ recipients is lower than the titers necessary to

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fully prevent the infection [6,7]. There is also the possibility that after vaccination patients develop parallel cellular immunity, which can also be present in the absence of vaccination-induced antibodies [8].

AIM OF THE STUDY

The aim of this study was to assess vaccination efforts in patients after heart transplantations in a single heart transplant center and evaluate morbidity and mortality due to SARS-CoV-2 infection in this group of patients.

MATERIALS AND METHODS

This study was a single-center prospective observational study in adult patients after heart transplantation (HTx). The whole group consisted of 552 patients (127 women) after HTx. Data according to current and previous COVID-19 infection and vaccination were collected between March and September 2021. Additionally, patients with SARS-CoV-2 infection who died before this period were included.

The data were collected during hospitalization, home medical visits, and phone calls and from the open database of the National Health Fund. During medical visits and phone calls, we encouraged patients to receive vaccinations according to the current vaccination guidelines.

Patients were considered positive for COVID-19 based on positive results of reverse transcriptase polymerase chain reaction tests of nasopharyngeal swab samples or a history of typical signs and symptoms of COVID-19 with the presence of anti-SARS-CoV-2 antibodies.

The study was performed in accordance with the Declaration of Helsinki. The Bioethics Committee of the Medical University of Silesia gave permission to proceed the study (Decision No. PCN/CMN/0022/KB1/30/21.

Statistical Analysis

Categorical variables are presented as counts and percentages. Continuous variables are presented as means and standard deviations or medians with lower and upper quartiles.

RESULTS

Among the whole analyzed population (552 patients, 127 women), the percentage of unvaccinated patients was 20.3% (112 patients). The majority of vaccinations were started between the second half of March and April 2021 (Fig 1). None of the vaccinated patients developed severe adverse effects of vaccination or acute graft rejection following immunization.

Among the 552 analyzed patients, 10 patients had SARS-CoV-2 infection prior to HTx (1.18%) and 103 patients were infected after transplantation (18.7%). Mean age of patients infected after Htx was 55.6 (±14) years. In the group of 103 infected patients, 83 patients received tacrolimus (mean trough blood level [C_0] prior to the infection = 9.3 ± 3.6 μg/L), 14 patients received cyclosporine (C_0 = 103.9 ± 26.8 μg/L), 67 patients received mycophenolate mofetil (C_0 concentration 1.6 ± 0.91 mg/L), 9 patients received everolimus (C_0 = 4.59 ± 2.19 μg/L), and 4 patients received sirolimus (C_0 = 14.41 ± 2.2

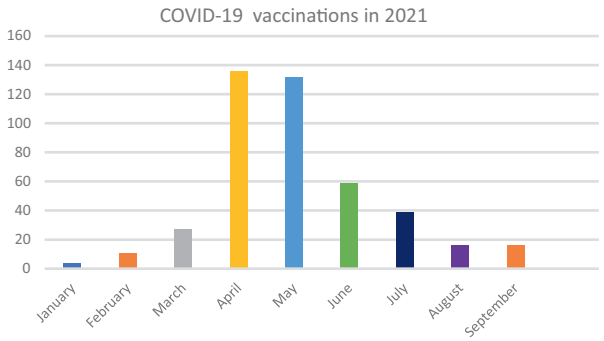

Fig 1. Timing of severe acute respiratory syndrome coronavirus 2 vaccinations in heart transplant recipients in 2021.

μg/L). Prednisone was administered in 17 patients with a mean daily dose of 5.125 ± 2.43 mg.

Mean time from HTx to infection was 2856 (±2596) days (range, 16-9569 days; interquartile range, 397-4763 days). In 19 patients the infection occurred during the first year after transplantation. Detailed clinical characteristics of the investigated group are presented in Table 1. Among the group infected after HTx, 15 patients were asymptomatic and 10 died. Symptoms of the affected patients are presented in Table 2.

From January 2021 to September 2021 (the era of vaccination), we noted 51 infections (Fig 2).

In the patients infected in 2021, only 3 were fully vaccinated (2 doses of mRNA vaccine; 5.9%). Among the infected patients, 6 patients were partially vaccinated (a single dose of mRNA vaccine; 11.8%). In the group of previously vaccinated patients, 2 died of SARS-CoV-2 infection: 1 patient after 2 doses of mRNA vaccine (fully vaccinated) and 1 patient after a single dose of mRNA vaccine (partially vaccinated).

Among the remaining 94 SARS-CoV-2-infected and unvaccinated patients, 8 died during the course of the disease.

DISCUSSION

Patients after solid organ transplantation have decreased immune response against infections and are frequently multimorbid. The prognosis in case of SARS-CoV-2 infection is less favorable than that in the general population: a survey of all heart transplant centers in Germany performed between March and June 2020 showed 33.3% mortality due to COVID-19 [9]; in the Italian heart transplant population, mortality was almost 30% [10].

Efforts have been made to prevent Polish population from the SARS-CoV-2 pandemic and their consequences. One of the best large-scale preventive measures in case of highly contagious infective diseases is vaccination. Immunocompromised patients are advised to receive immunization, as well as their caregivers and people from their home environment. Unfortunately, less than 50% [11] of the general Polish population, despite wide accessibility and known efficacy in reducing the incidence and severity of the disease, have received the vaccine. A low percentage of vaccinated people in the general population is

Table 1. Clinical Characteristics of the Investigated Group

		Infected Post HTx, 103 Patients	Infected Prior to HTx, 10 Patients	Controls (Uninfected), 439 Patients	Total (Whole Group of Patients), 552 Patients
Age, mean ± SD		55.6 ± 14	45 ± 9.5	54.3 ± 15.1	54.4 ± 15
Sex, female, *n* (%)		19 (18.4)	2 (20)	106 (24.1)	127 (23)_
BMI (kg/m^2), ±SD		26.8 ± 4.1	29 ± 5.1	26.8 ± 5.2	26.8 ± 5
Diabetes, *n* (%)		52 (50.5)	5 (50)	217 (49.4)	274 (49.6)
Mean time posttransplant to onset ±SD; range (IQR), d		2856 ± 2596; 16-9569 (397-4763)			
Original cardiovascular disease/cardiomyopathy, *n* (%)	Ischemic	40 (38.8)	2 (20)	148 (33.7)	190 (34.4)
	Dilated	46 (44.7)	7 (70)	216 (49.2)	269 (48.7)
	Hypertrophic	2 (1.9)	1(10)	21(4.8)	24 (4.3)
	Valvular	2 (1.9)	0 (0)	6 (1.4)	8 (1.4)
	Arrhythmic	2 (1.9)	0 (0)	5 (1.1)	7 (1.3)
	Restrictive	4 (3.9)	0 (0)	15 (3.4)	19 (3.4)
	Congenital heart disease	3 (2.9)	0 (0)	12 (2.7)	15 (2.7)
	Other	4 (3.9)	0 (0)	16 (3.6)	20 (3.6)

HTx, heart transplantation; IQR, interquartile range.

disadvantageous for this group of patients. However, positive results have been found. After advising patients regarding vaccinations, we achieved a much higher percentage of vaccinated persons in our transplant group (79.7%) compared to the general population. These results are comparable with U.S. transplant centers, with a vaccination rate of about 70% [5].

Our data show lower incidences of SARS-CoV -2 infection in vaccinated patients when compared to unvaccinated patients. Infected patients were mainly unvaccinated (94% of HTx recipients with COVID-19 in 2021), which is in line with results obtained from a large cohort of solid organ transplant (renal, heart, lung, liver) recipients in the United States. They showed an almost 80% calculated reduction in COVID-19 susceptibility when compared to the nonimmunized group [5]. In our population, we cannot reliably perform such calculation and estimate how many patients benefited from immunization. The third wave of the COVID-19 pandemic in Poland started in parallel with vaccination among the investigated population. Hence, this situation could be interpreted in 2 ways: the vaccination protected patients from infection or the chance of exposure to the virus was lower. We will likely be able to perform this calculation after the fourth wave of the pandemic.

As suggested by other authors, vaccination itself does not prevent severe COVID-19, and we observed severe course of the disease after a full course of the vaccination. Adequate humoral and/or cellular response to the vaccination is necessary [12]. Diabetes, older age, high maintenance immunosuppression, and lowered estimated glomerular filtration rate are predictors of weakened response to the vaccination [13,14]. These factors are also markers of poorer outcomes in the general population in case of COVID-19 infection. In the group of HTx recipients, 2 vaccine doses followed by a booster is not enough. Immunity against the infection is connected with the level of circulating neutralizing antibodies. Schemes of follow-ups after the vaccination with assessment of humoral (more accessible) or cellular response are urgently needed; however, the protective levels are still being assessed [15]. Temporary modification

Table 2. Clinical Symptoms in the Affected (Symptomatic) Patients

Symptoms	Symptomatic Survivors (78 Patients), *n* (%)	Deceased (10 Patients), *n* (%)
Rhinitis	19 (24.4)	1 (1)
Cough	22 (28.2)	5 (5)
Sore throat	10 (12.8)	1 (1)
Shivers	5 (6.4)	0
Fever	37 (47.4)	5 (50)
Loss of smell and/or taste	20 (25.6)	2 (20)
Weakness	60 (76.9)	10 (100)
Headache	12 (15.4)	0
Earache	2 (2.6)	0
Muscle aches	16 (20.5)	0
Gastrointestinal symptoms	10 (12.8)	1 (10)
Chest pain	3 (3.8)	0
Dyspnea	10 (12.8)	9 (90)
Respiratory failure	7 (9)	10 (100)

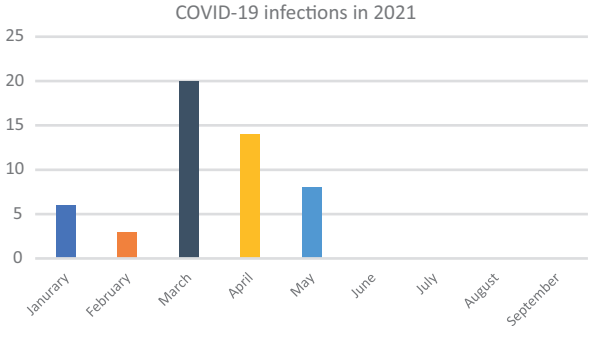

Fig 2. COVID-19 infections in 2021 in patients after orthotopic heart transplantation.

of the immunosuppressive regime during booster vaccination in nonresponders might also be considered.

CONCLUSION

We observed high susceptibility to COVID-19 in HTx recipients. A majority of patients infected in 2021 did not receive the vaccination. Vaccination do not fully protect against severe COVID-19 in this group of patients. Markers of vaccination efficacy are needed.

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