COVID-19 mortality in patients after orthotopic heart transplantation: A single-center one-year observational study

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INTRODUCTION

Reports on transplant patients affected by SARS-CoV-2 suggest that not only the immunosuppressive regimen but also comorbidities and advanced age influence the clinical course of the infection [1]. Based on the available case series, reports, and meta-analyses, the COVID-19 mortality rate in solid organ transplant patients is higher than in the general population. We aimed to assess COVID-19 mortality and morbidity in heart transplant (HTx) recipients who were under the surveillance of one Polish center.

METHODS

This was a one-year prospective clinical observational study from a single transplant center regarding susceptibility to SARS-CoV-2. Patients were analyzed from March 2020 to March 2021. The data were collected during hospitalization, home medical visits, phone calls, and from the open database of the National Health Fund. All patients signed written informed consent to participate in the study.

The patients were considered infected if they had positive results of reverse transcription-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 whole group of patients comprised 540 patients after HTx (112 patients ≤1 year and 428 patients >1 year after HTx), and among them there were 50 SARS-CoV-2 infected patients, including 10 patients ≤1 year after HTx.

Forty patients (80%) received tacrolimus, including 12 patients (24%) on monotherapy, 27 patients (54%) in combination with mycophenolate mofetil, and one patient (5%) in combination with everolimus. Eight patients (16%) received cyclosporine A, including 6 subjects (12%) who received cyclosporine A in combination with mycophenolate mofetil and 2 subjects (10%) took it in monotherapy. One patient received everolimus with mycophenolate mofetil, and another patient was given sirolimus in combination with mycophenolate mofetil.

Patients up to one year after transplantation were administered prednisone as the basic regimen in tapered doses. All patients were given statins and acetylsalicylic acid (75 mg/day).

As antiviral and antibacterial prophylaxis, all patients were administered valganciclovir up to day 110 and sulfamethoxazole-trimethoprim up to 6 months after transplantation.

Table 1 shows clinical and laboratory parameters.

The Bioethics Committee of the Medical University of Silesia approved the study (decision no. PCN/CMN/0022/KB1/30/21).

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were presented as the mean and standard deviation for normally distributed data or median with lower and upper quartiles. The Shapiro-Wilk test was used to verify the normal distribution of data. The Chi^2 test

Table 1. Clinical patient characteristics

	Whole group (n = 50)	Survivors (n = 44)	Deceased (n = 6)	*P*-value
Age, years, mean (SD)	57.1 (12.2)	56.5 (12)	61.32 (13.5)	0.405
Female sex, n (%)	10 (20)	9 (20.5)	1 (16.7)	0.91
Time from HTx to infection, years, median (IQR)	7.01 (0.38–12.5)	7.43 (2.12–26.4)	3.93 (0.38–12.25)	0.51
Infection-to-death time, days, median (IQR)	38.0 (28–47)	NA	38.0 (28–47)	NA
Patients hospitalized for COVID-19, n (%)	14 (28)	8 (18.2)	6 (100)	<0.001
Hospitalization for COVID-19, days, mean (SD)	21.3 (10.94)	20.75 (10.63)	25.33 (15.19)	0.517
Hypertension, n (%)	40 (80)	36 (81.8)	4 (66.7)	0.3
Bodyweight, kg, mean (SD)	81.45 (14.3)	81.18 (13.9)	83.47 (15.71)	0.71
Height, cm, mean (SD)	173.18 (7.57)	173.9 (7.81)	172.33 (5.47)	0.71
BMI, kg/m^2, mean (SD)	26.94 (4.07)	26.77 (3.81)	28.15 (5.61)	0.44
Active cancer, n (%)	0 (0)	0 (0)	0 (0)	NA
Previous cancer, n (%)	3 (6)	3 (6.8)	0 (0)	0.499
Previous TIA, n (%)	2 (4)	2 (4.5)	0 (0)	0.585
Previous stroke, n (%)	6 (12)	6 (13.6)	0 (0)	0.322
Impaired glucose metabolism				0.454
None, n (%)	17 (34)	14 (31.8)	3 (50)	
Glucose intolerance, n (%)	8 (16)	8 (18.2)	0 (0)	
Diabetes, n (%)	24 (48)	21 (47.7)	3 (50)	
COPD, n (%)	3 (6)	2 (4.5)	1 (16.7)	0.26
Graft vasculopathy, n (%)	9 (18)	8 (18.2)	1 (16.7)	0.9
Previous PTCA, n (%)	6 (12)	5 (11.4)	1 (16.7)	0.74
Chronic renal failure, n (%)	36 (72)	30 (68.2)	6 (100)	0.116
Chronic dialysis, n (%)	6 (12)	3 (6.8)	3 (50)	0.02
Dialyses in the course of COVID-19, n (%)	7 (14)	3 (6.8)	4 (66.7)	<0.001
NYHA I, n (%)	44	41 (93.2)	3 (50)	0.008
NYHA II, n (%)	4	3 (6.8)	1 (16.7)	
NYHA III, n (%)	1	0 (0)	1 (16.7)	
NYHA IV, n (%)	1	0 (0)	1 (16.7)	
LVEF, % (median, IQR)	55.9 (45–60)	56 (55–60)	55 (45–58)	0.31
Leukocyte count before the SARS-CoV-2 infection, ×10^9/l, median (IQR)	6.74 (5.6–10.12)	6.57 (5.6–7.84)	7.96 (5.95–10.12)	0.261
Leukocyte count after the SARS-CoV-2 infection, ×10^9/l, mean (SD)	6.29 (1.92)	6.33 (1.8)	5.99 (2.64)	0.737
Lymphocyte count before the SARS-CoV-2 infection, ×10^3/ /μl, median (IQR)	1.37 (0.27–1.93)	1.49 (1.12–1.93)	0.46 (0.27–0.65)	0.063
Creatinine level before the SARS-CoV-2 infection, μmol/l, median (IQR)	129.7 (95.47–354)	120.5 (95.47–156)	197.5 (164–354)	0.014
Creatinine after the SARS-CoV-2 infection, μmol/l, median (IQR)	121.6 (87.0–244.5)	114.0 (87.0–144)	177.5 (109–244.5)	0.256
Acute cellular rejection treatment one year before the SARS--CoV-2 infection, n (%)	6 (12)	6 (13.6)	0 (0)	0.31
Peripheral vascular disease, n (%)	6 (12)	4 (9.1)	2 (33.3)	0.099
Therapy with the lymphocyte depleting agent 6 months before the SARS-CoV-2 infection	None	None	None	NA
Bacterial or viral infection requiring hospitalization or during hospitalization for other reasons one year before the SARS-CoV-2 infection, n (%)	6 (12)	4 (9.1)	2 (33.3)	0.099
Past CMV infection, n (%)	7 (14)	6 (13.6)	1 (16.7)	0.86
Active CMV infection, n (%)	0 (0)	0 (0)	0 (0)	NA
Past HBV infection, n (%)	3 (6)	3 (6.8)	0 (0)	0.504
Past HCV infection, n (%)	2 (4)	2 (4.5)	0 (0)	0.58

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B; HCV, hepatitis C; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; PTCA, percutaneous coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack

was utilized to compare categorical variables, whereas the t-test or the Mann-Whitney U test was applied to compare continuous variables where appropriate. A *P*-value <0.05 was considered statistically significant. SAS software, version 9.4 (SAS Institute Inc., Gary, NC, US) was used for all calculations.

RESULTS AND DISCUSSION

The whole population of patients with COVID-19 included 50 patients (9.23% of all patients). Clinical patient characteristics are given in Table 1.

Patients within the first year after HTx (n = 10) comprised 20% of COVID-19 subjects. The percentage of

SARS-CoV-2 positive patients within the first year after HTx was 8.9% (10/112), and 9.3% (40/428) after the first year following HTx. The death rate was 30% (3/10) within the first year after HTx, and 7.5% (3/40) after the first year following HTx. Four patients, who were intubated due to respiratory failure, died. In one patient, renal replacement therapy *de novo* was introduced. In 3 patients (6%), the left ventricular ejection fraction was already decreased before COVID-19. In none of the patients, left ventricular ejection fraction changed by more than 5% when compared to the baseline examination. In one patient after COVID-19, a significant acute cellular rejection was diagnosed based on elective endomyocardial biopsy. Two patients within the first year after HTx and 5 patients after the first year following Htx were asymptomatic.

Immunosuppressive modifications were performed only in symptomatic patients and included dose reduction of mycophenolate mofetil or cessation and/or additional steroid administration. Dose reduction of mycophenolate mofetil was used in 2 patients (5%), and temporary cessation in 11 patients (37% of the whole group on mycophenolate mofetil). Among the deceased patients, mycophenolate mofetil was used in four subjects. However, it was suspended due to the disease (n = 2). The doses of tacrolimus were not modified and the median whole blood concentration of tacrolimus in survivors was 8.81 ng/ml (interquartile range [IQR]: 6.21–10.52 ng/ml), and 7.2 ng/ml in deceased patients (IQR, 6.17–8.49 ng/ml; $P = 0.493$). The doses of prednisone were not modified due to the disease.

Additional doses of dexamethasone were introduced in two patients (>1 year after HTx). In four patients, convalescent plasma was used, whereas azithromycin was given to four patients. Other antibiotics were administered to three patients. Remdesivir was used in one patient who recovered.

In our study, total mortality of confirmed SARS-CoV-2 infection cases reached only 12%, but it was still unacceptably high when compared to the general population (2.6%) [2].

Notably, the mortality rate in patients within the first year after HTx was four times higher than in the group >1 year after HTx. This could be explained by more potent immunosuppressive treatment and a weakened general condition due to HTx and previous long-standing end-stage heart failure. In particular, we also observed that comorbidities, such as heart or renal failure, resulted in an unfavorable outcome. We found significant differences in the baseline creatinine level in favor of survivors. Also, lower exercise capacity before infection, assessed by the New York Heart Association (NYHA) classification, adversely influenced the outcome. The association between heart failure and adverse outcomes in COVID-19 patients was reported for the general population previously [3, 4].

All the clinical symptoms were typical of the general population. In our group of patients, despite a low number of COVID-19 cases, it was noticeable that the deceased patients had a lower lymphocyte count compared to the survivors.

Article information

Conflict of interest: None declared.

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