COVID-19 Infection in Heart Transplant Recipients: Results of a Six-Month Prospective Survey-Based Study

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Abstract- Solid-organ transplantation recipients were assumed highly vulnerable to coronavirus disease 2019 (COVID-19). However, the results of previous studies in patients with orthotopic heart transplantation (OHT) under immunosuppressive therapy are contradictory. Therefore, we aimed to assess the prevalence of COVID-19 infection and associated risk factors, along with the six-month outcomes in COVID-19 positive OHT patients. This single-center telephone-based survey was conducted on OHT patients. Using a detailed questionnaire, exposure to COVID-19, related symptoms, and preventive self-care measures were collected. Outcomes of COVID-19-positive patients were reassessed using another survey six months later. 118 OHT patients (male: n=87, 73.7%) were included with a mean age of 45.3±13.1 years. Sixteen patients (13.5%) reported one or more symptoms compatible with COVID-19, of whom 12 (10.2%) tested positive. Our results indicated no statistically significant association between COVID-19 and comorbidities. Poor adherence to self-care measures and contact with positive index cases were both significantly associated with COVID-19 infection (P<0.001). A later six months follow-up showed that two out of 12 (16.6%) COVID-19 positive OHT patients died. There was no statistically significant difference between the prevalence of COVID-19 in our patients compared to Iran's general population (P=0.152). Non-compliance with personal protective protocols and a history of contact with COVID-19 cases were the most risk factors for COVID-19 infection in OHT patients.

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Keywords: Coronavirus disease 2019 (COVID-19); Heart transplantation; Immunosuppression; Preventive self-care measures; Telephone-based survey

Introduction

In December 2019, the first case of human coronavirus pneumonia was reported in Wuhan, China (1). In March 2020, the World Health Organization (WHO) announced Coronavirus disease 2019 (COVID-19) as a pandemic (2), and soon it became a global concern that has caused at least 68 million additional poverty years and more than 4.3 million years of life lost across 150 countries (3). Clinical manifestations of the disease may range from mild to severe cases, with a need for mechanical ventilation in some cases (4,5). Mortality is high in the elderly and patients with comorbidities, including diabetes mellitus, hypertension, and chronic kidney and cardiovascular disease (6). Patients with a history of heart transplants in this regard were found particularly at risk due to long-term immunosuppression and frequent comorbidities (7,8).

Patients with a history of solid organ transplantation require immunosuppressive therapy (9-12). The effects of receiving such treatments on the course of COVID-19 is a controversial debate since, although adequate immune response seems vital in the early phase of the disease,

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immunosuppressant therapy is indeed considered a potential treatment in the cytokine storm phase (13) and is the second most prescribed category of medications for COVID-19 (14). Therefore, it is unknown whether treatment with immunosuppressive drugs serves as a predisposing or protective factor in these patients (15).

To address the existing debates in this regard, we aimed to assess the prevalence, symptoms, predisposing factors, and six-month outcomes of COVID-19 infection in a group of OHT patients in our center.

Materials and Methods

Ethical considerations

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. The hospital database of all patients with a history of heart transplantation was assessed, and their contact information, including telephone numbers, was collected. In our center, written informed consent was obtained from each patient with a history of heart transplantation to access specific medical information for research purposes. In addition, the research process and the purpose of this study were described to patients during the phone call.

Study design and participants

This cross-sectional telephone-based survey was conducted in Imam Khomeini Hospital Complex, from July 10, 2020, to August 10, 2020. The contact information of 154 OHT patients was available on the database, and among these patients, 118 patients answered the phone call and were included in the study. Confirmed COVID-19 patients were followed six months later through a telephone survey. Figure 1 illustrates the study selection flowchart.

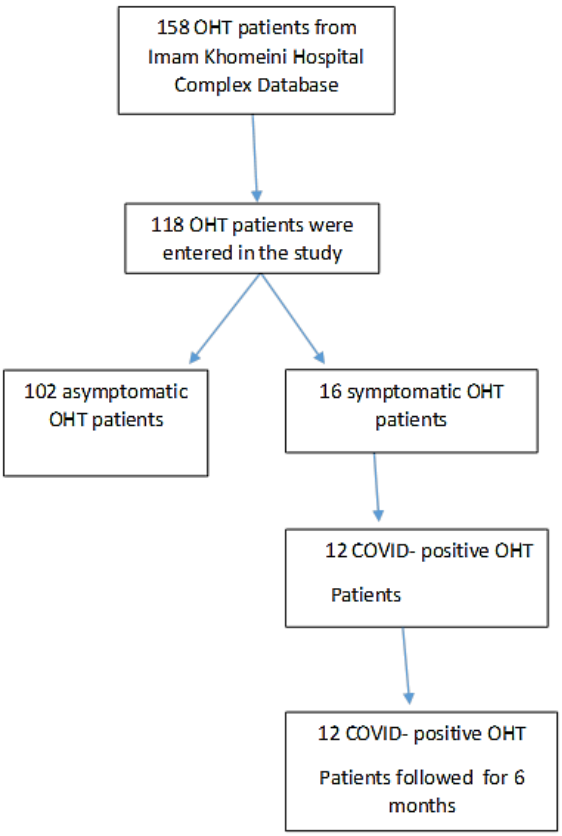

Figure 1. Patient selection flowchart

Demographic data, comorbidities, years from heart transplantation, and the last echocardiographic findings were extracted from the database. A pre-designed questionnaire (see appendix 1) was used for data

collection. Detailed history including the onset of new symptoms such as fever, cough, dyspnea, myalgia, chest pain, anosmia, gastrointestinal symptoms (diarrhea, abdominal pain), and recent worsening of function class (FC) during the time from the first official announcement of COVID-19 infection in Iran (February 2020) to the time of the phone interview was taken from each patient. The history of confirmed laboratory (RT-PCR) and imaging diagnosis of COVID-19 infection in the patient or any family member and the information regarding hospital admission during this time were recorded.

Another questionnaire was used to investigate preventive self-care measures and the history of any exposure to confirmed COVID-19 patients. The original and detailed version of this questionnaire has been developed by Mohammadzadeh *et al*., (16). According to their classification of self-care measures against COVID-19 infection, level 0 indicates no change in the daily routine activity and attitude; level 1 indicates minimal self-care measures, including slight changes in daily routine activity and attitude (occasional hand washing and wearing a mask), level 2 indicates adherence to protective measures based on the WHO recommendations with social distancing, level 3 indicates adherence to protective behaviors plus staying at home. Level 4 indicates level 3 measures plus applying the measures to family members.

The severity of confirmed COVID-19 infection was classified as mild when the patient was only quarantined at home without requiring hospital admission, as moderate when the patient was hospitalized in the general ward, and as severe when the patient was admitted to the intensive care unit (ICU) (17).

Statistical analysis

Categorical variables are presented as frequency and percentage. $\chi 2$ or the Fisher's exact test was used to compare categorical variables between the groups. Continuous variables are expressed as mean and standard deviation (SD). After normality testing, the independent-sample t-test or Mann-Whitney U test was applied to compare continuous variables between the groups depending on their distribution. Also, a one-sample t-test was applied to statistically compare the prevalence of COVID-19 in our population with the prevalence of the COVID-19 in the general population extracted from the serological surveillance program conducted simultaneously with the data extraction of this research (18). *P* of less than 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp).

Results

A total of 118 OHT patients participated in this telephone survey. The mean age of the study participants was 45.3±13.1 years (range: 14-68), and 87 patients (73.7%) were male. The mean time from OHT was 5.5±3.5 years. At least one established risk factor was present in 48 patients (40.7%). Dyslipidemia, diabetes mellitus, hypertension, and cigarette smoking were found in 31 (26.3%), 26 (22%), 26 (22%), and 4 (3.4%) patients, respectively. Twenty-six patients (22%) had a history of cardiac allograft rejection. Mycophenolate mofetil was the primary immunosuppressive drug among the subjects. Other drugs, including cyclosporine (Sandimmune), tacrolimus (Prograf), and prednisolone, were used in 56 (47.5%), 48 (40.7%), and 26 (22.0%) of the OHT patients, respectively. No significant difference was found regarding age, gender, time from heart transplantation, history of rejection, and traditional cardiovascular risk factors between confirmed COVID-19 positive and unknown COVID-19 status cases. Also, there was no significant difference between the two groups regarding the type of immunosuppressive drugs. The results of the last echocardiography (before the telephone survey) showed a mean left ventricular ejection fraction (LVEF) of 47.6%±7.9% (range: 20-60%) and a mean systolic pulmonary artery pressure (sPAP) of 28.9±5.9 mmHg. LVEF and sPAP had no difference between patients with confirmed COVID-19 and the others (*P*:0.691 and 0.670, respectively) (Table 1).

Suspicious symptoms related to COVID-19 infection were present in 16 patients (13.5%). A diagnosis of COVID-19 was made in 12 out of 16 symptomatic patients (10.2%), of whom eight (66.7%) were stable and were advised to stay at home, and four (33.3%) were hospitalized. None of the patients with a confirmed COVID-19 infection was admitted to the ICU at presentation. Dyspnea was the most common symptom in four (33.3%) of the OHT patients with confirmed COVID-19 infection, followed by myalgia (25%), anosmia (25%), fever (16.7%), cough (16.7%), and chest pain (8.3%) (Table 2).

Data showed that COVID-19 infection was present in at least one family or household member in 9 (75%) patients, all in the COVID-19 positive group. Three (25%) of COVID-19 positive patients had no history of any exposure to the virus. Preventive self-care was reclassified as follows: "level 0" and "level 1" were considered "low self-care," and levels 2, 3, and 4 were

considered "high self-care." Two (1.7%) patients reported low self-care measures, both had a history of confirmed COVID-19 infection, 106 (98.3%) patients had high self-care, and ten patients became infected by COVID-19. Data analyses showed that preventive self-care measures and exposure to COVID-19 infection had a significant association with COVID-19 infection (P<0.001, OR: 1.2, CI: 1.02-2.54 and P-value <0.001, OR: 4.0, CI: 1.50-10.65, respectively) (Table 3).

Lastly, using a one-sample t-test to statistically compare the prevalence of COVID-19 in OHT patients in this study with that in Iran's general population at the time of this study (14.2%) yielded insignificant (P=0.152).

Definition of self-care levels: 0: no change in daily activity or behaviors or protection, 1: minimal self-care measures such as occasional hand washing or mask-wearing, 2: protective measures based on WHO recommendation with social distancing, 3: level 2 measures plus staying at home, 4: level 3 measures plus applying the measures to family members.

Telephone follow-up was done six months later, which revealed that two out of 12 (16.6%) OHT patients with COVID-19 had died. One patient had prolonged hospitalization and was transferred to ICU, and finally died three weeks after admission due to COVID-19. The other patient had died five months after the first telephone contact due to reinfection with COVID-19. The remaining four symptomatic patients without confirmed COVID-19 infection were doing well at the time of telephone follow-up.

Table 1. Baseline demographic and clinical characteristics of heart transplant patients

	Total (n=118)	COVID-19 Positive (n=12)	Others* (n=106)	*P*
Age (Years)	45.3±13.1	43.2±3.3	45.5±1.4	0.618
Gender (Male)	87 (73.7%)	8 (66%)	79 (75.5%)	0.728
Time from Heart Transplantation (Years)	5.5±3.5	7.0±1.3	5.3±0.3	0.231
LVEF (%)	47.6±7.9	48.7±2.0	47.6±0.8	0.691
sPAP (mmHg)	28.9±5.9	28.3±1.2	28.9±0.6	0.670
Comorbidities				
Diabetes mellitus	26 (22.0%)	3 (25.9%)	23 (21.7%)	0.519
Dyslipidemia	31 (26.3%)	4 (33.3%)	27 (25.5%)	0.558
Hypertension	26 (22.0%)	4 (33.3%)	22 (20.7%)	0.462
Smoking	4 (3.4%)	1 (8.3%)	3 (2.8%)	0.386
History of Rejection	26 (22.0%)	5 (41.7%)	21 (19.8%)	0.134
Drugs				
Mycophenolate Mofetil	114 (96.6%)	12 (100%)	102 (96.2%)	0.494
Cyclosporine	56 (47.5%)	7 (58.3%)	49 (46.2%)	0.426
Tacrolimus	48 (40.7%)	3 (25.0%)	45 (42.5%)	0.243
Prednisolone	26 (22.0%)	3 (25.0%)	23 (21.7%)	0.794

*Asymptomatic or negative PCR

**Data are shown as mean ±SD and number (percentage).

LVEF: Left ventricular ejection fraction, s PAP: Systolic Pulmonary arterial pressure

Table 2. Symptoms of COVID-19 infection, methods of diagnosis, and admission rate because of COVID-19 in heart transplant patients

	Total (n=118)	COVID-19 positive (n=12)
Symptoms		
Dyspnea	7 (5.9%)	4 (33.3%)
Cough	4 (3.4%)	2 (16.7%)
Myalgia	4 (3.4%)	3 (25.0%)
Anosmia	3 (2.5%)	3 (25.0%)
Fever	2 (1.7%)	2 (16.7%)
Chest pain	2 (1.7%)	1 (8.3%)
Method of Diagnosis		
RT-PCR	12(10.1%)	8 (66.7%)
Both RT-PCR and chest CT	4(3.3%)	4 (33.3%)
Admission		
Quarantine	8(6.7%)	8 (66.7%)
Hospitalized in the ward	4(3.3%)	4 (33.3%)

* Data are shown as numbers (percentage)

Table 3. Comparison of self-care measures and different types of contact with COVID-19

	Total (n=118)	COVID-19 Positive (n=12)	Others* (n=106)	*P*
Level of self-care				<0.001
Level 0	0 (0%)	0 (0%)	0 (0%)	
Level 1	2 (1.7%)	2 (16.7%)	0 (0%)	
Level 2	55 (46.6%)	7 (58.3%)	48 (45.3%)	
Level 3	20 (16.9%)	1 (8.3%)	19 (17.9%)	
Level 4	41 (34.7%)	2 (16.7%)	39 (36.8%)	
Type of self-care				0.010
Low self-care	2 (1.7%)	2 (16.7%)	0 (0%)	
High self-care	116 (98.3%)	10 (83.3%)	106 (100%)	
Contact with COVID-19				<0.001
No contact	109 (92.4%)	3 (25.0%)	106 (100%)	
Contact in the community	7 (5.9%)	7 (58.3%)	0 (0%)	
Contact with household member	2 (1.7%)	2 (16.7%)	0 (0%)	
Exposure to COVID-19				<0.001
No exposure	109 (92.4%)	3 (25.0%)	106 (100%)	
Any exposure	9 (7.6%)	9 (75.0%)	0 (0%)	

*Asymptomatic patients or negative PCR
**Data are shown as mean ±SD and number (percentage)

Discussion

The purpose of the present study was to elucidate any clinical or demographic characteristics in the heart transplant recipients that may predispose them to COVID-19 infection and alter their outcome. Infection is the most common complication in patients with solid organ transplantation (19,20). Similarly, OHT patients have a higher risk of infection and adverse outcomes due to the use of immunosuppressive drugs along with other comorbidities; however, the prognosis and fatality rate of COVID-19 in these patients are not consistent in different studies. Currently, three phases are considered for the course of COVID-19 infection, including pulmonary, proinflammatory, and prothrombic (21). It is known that COVID-19 may cause a severe inflammatory response in the late phases, clinically distinguished by a cytokine storm (22). Since OHT patients are under long-term immunosuppressive treatment, the course of this disease was assumed unpredictable and yielded various pursuits to address the needs of this vulnerable group of population (23).

Of 118 OHT patients that participated in the present study, 12 (10.1%) were affected by COVID-19 infection, among which eight (66.6%) were male, similar to the results of previous studies (24,25), and no statistically significant demographical difference was present between those affected by COVID-19 and unknown COVID-19 status cases in our study. Also, the prevalence of COVID-19 in our studied population is lower than in the general Iranian population (18); however, this difference is statistically insignificant and might be due to our limited sample size. Therefore, no generalization is statistically approvable. It is to mention that other studies with larger sample sizes assessing the prevalence of COVID-19 in solid organ transplant recipients have estimated a prevalence of as high as two folds rates in these patients compared to the general population (8,26). Yet still, this controversy prompts further works to sum up, the literature in this regard.

Severe manifestations of COVID-19 infection in the general population are associated with advanced age and comorbidities such as diabetes, hypertension, and cardiac and renal disease (6). Our study found no association between COVID-19 infection and gender, cardiovascular risk factors (diabetes, hypertension, and dyslipidemia), LVEF, and sPAP. Moreover, there was no significant difference in the history of allograft rejection, duration of transplantation, and type and dose of immunosuppressive drugs between the patients with a confirmed COVID-19 infection and those with no confirmed infection. This is contrary to previous findings, suggesting significant

correlations between in-hospital morality of heart transplant patients affected by COVID-19 with underlying comorbidities including diabetes mellitus, extracardiac arteriopathy, previous percutaneous coronary intervention, and cardiac allograft vasculopathy, lower glomerular filtration rate (23). Future works with larger sample sizes are required to arrange further conclusions on this debate.

Previous studies did not directly compare patients with and without COVID-19 infection since the prevalence of asymptomatic infection may be as high as 20% (27). As this study was telephone-based, we could not estimate the accurate prevalence of COVID-19 in OHT patients since asymptomatic carriers were not detected. However, we attempted to increase our precision by using a detailed questionnaire to thoroughly investigate any related symptoms, and those COVID-19 positive patients in the initial survey were followed up for six months. Similar works were as well conducted using documented records in order to avoid imposing unnecessary exposure to patients. However, they were multicentered or nationwide to overcome the potential flaws of this type of data (7,8). These multicenter approaches will be beneficial in presenting more accurate estimates on the course of COVID-19 in OHT patients in Iran.

As expected, a positive history of contact with COVID-19 infection was significantly higher in OHT patients with confirmed COVID-19 infection, although the presence of recall bias in patients with a positive test should be considered. Similarly, the prevalence of COVID-19 infection was significantly higher in patients with a low level of self-care. This finding highlights the importance of adherence to protocols in this group of patients. Zong-Li Ren *et al*., found that patients with a history of OHT were more aware of general precautions and protective measures resulting in lower infection rates in these patients with no mortality (1), which is in accordance with our results, indicating that the majority of our patients were applying self-care measure levels of two or higher.

Dyspnea was the most presented symptom in our patients, and fever and chest pain were the least common manifestations of COVID-19 in our patients. Latif *et al*., and Rasmus Rivinius *et al*., found that shortness of breath and cough were the most common symptoms in their OHT patients, and fever was as well less common in these studies (7,25). The lower prevalence of fever may be due to the effects of immunosuppressive medications and eliminating this symptom to a mostly undetectable level for patients (28,29).

Of the 12 patients with confirmed COVID-19 infection, eight were advised to stay at home, and four were hospitalized in the general wards. Telephone follow-up six months later revealed that two out of 12 patients (16.6%) had died. Latif et al. reported a high mortality rate (25%) in their study (25). Other studies reported mortality rates between 23% (30) to 33.3% (7). The high mortality rate in these studies may be due to neglecting asymptomatic cases at the initial screening. In agreement with our results, another research has identified a COVID-19-related mortality range of 13-30% in patients with solid organ transplantation (31).

Despite weakening the immune system, immunosuppressants can play a protective role against the cytokine storm due to their anti-inflammatory effects (32-34). These drugs may also activate the renin-angiotensin system (RAS) and modify the clinical manifestations of the disease (35-39). Our results indicated that patients were under four groups of medications, including mycophenolate mofetil, cyclosporine, tacrolimus, and prednisolone. No statistically significant difference existed in the incidence of COVID-19 between these groups. In patients with a history of OHT, angiotensin-converting enzyme 2 (ACE2) expression may also be affected, leading to milder forms of COVID-19 infection. A related study on a large cohort in the UK reported milder symptoms in patients under these medications after liver transplant (29). However, the present results in this regard are highly controversial, and further comprehensive works are required to draw conclusions.

Our results indicate that non-compliance with personal protection protocols and a history of contact with COVID-19 infection are the most predisposing factors for this disease in patients with heart transplantation. The importance of adherence to protocols should be overemphasized in this vulnerable group. Eventually, there was no statistically significant difference between the prevalence of COVID-19 in this study and with the general Iranian population.

The data used in this study was obtained using a telephone bases survey; therefore, our estimated prevalence of the COVID-19 is to be generalized with caution since asymptomatic cases were not detected. Also, merely those who were COVID-19 positive in the initial survey were followed up for six months, and the statistical comparison regarding the prevalence was made with those records from other studies. Therefore, more comprehensive study designs are required to comparatively and causally investigate the role of immunosuppressive therapy in the course of COVID-19.

Appendix 1

Questionnaire
First name/ Last name: Sex: Female□ Male□ Age: Resident: Date of OHT: Medications: Prednisolone □ Tacrolimus □ Cyclosporine □ Mycophenolate Mofetil □ Cardiovascular risk factors: Blood pressure: Yes□ No□ Diabetes: Yes□ No□ Cigarettes: Yes□ No□ Hyperlipidemia: Yes□ No□ Rejection history: Yes□ No□ Echocardiographic findings: LVEF: s PAP: 1. Do you have any new symptoms from the time of initial announcement of COVID-19 in Iran until now? No□ Yes□ Dyspnea□ Fever□ Cough □ Myalgia□ Chest pain □ Diarrhea □ abdominal pain □ Increased FC□ 2.Do you have history of COVID-19? No□ Yes □ By PCR□ By PCR and chest CT□ -You are/ were quarantined at home □ -You are/ were hospitalized in the general ward□ -You have/ had hospitalization in the ICU□ -Patient died□ 3. Do you have any history of COVID-19 in the household/family member? No □ Yes□ -She (He) is/ was quarantined at home□ - She (He) is/ was hospitalized in the general ward□ - She (He) is/ was hospitalized in the ICU□ -She (He) is/was died

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