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Coronavirus Pandemic

Real-life outcomes of COVID-19 vaccination in kidney transplant patients: a single-center experience

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Abstract

Introduction: In this study, it was aimed to investigate the clinical (real-life) impact of the vaccination protocol on patients undergoing kidney transplantation during the COVID-19 pandemic.

Methodology: A total of 260 patients who underwent kidney transplantation between June 2012 and May 2022 were retrospectively evaluated. Patients chose vaccination Sinovac-CoronaVac (CoronaVac) and/or BNT162b2 (Biontech), the first vaccine available in the country) in line with the regulations and recommendations of the Ministry of Health. The relationship between vaccination, hospitalization, and mortality in cases diagnosed with COVID-19 was investigated. The prevalence of COVID-19 in patients, the rate of hospital admission, and the mortality of patients before and after the national vaccination program were examined.

Results: The study included a total of 260 kidney transplant patients (Female, n = 107 (41%); male, n = 153 (59%). The mean age of patients was 38.42 (11-75). A total of 108 (41.5%) patients were diagnosed with COVID-19. Seven (6.5%) patients died and 221 (85%) patients were vaccinated after the national vaccination program. During the follow-up period, 108 (41.5%) patients were diagnosed with COVID-19. There was no significant difference in terms of hospitalization between two groups. However, there was a significant difference in terms of admission to intensive care unit and mortality ($p < 0.001$).

Conclusions: The majority of cases that died were unvaccinated. However, repeated vaccinations may not adequately protect all transplant recipients. There is a need to develop personalized treatment and prevention strategies in transplantation cases.

Key words: COVID-19; kidney transplant recipients; vaccine.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is a highly pathogenic and contagious virus and resulted in a global pandemic [1]. Transmission occurs primarily by droplets, direct contact, or contaminated surfaces. It can be seen on a wide spectrum, ranging from a flu-like presentation in the general population to non-life-threatening pneumonia or pneumonia progressing to adult respiratory distress syndrome (ARDS) requiring advanced life support [2-4].

The rate of mortality has been reported to be higher in the presence of comorbidities such as advanced age, cardiovascular diseases, diabetes, chronic kidney disease, chronic lung diseases, and hypertension. Mortality rates due to COVID-19 pneumonia in kidney transplant patients are known to be much higher than in the normal population [5,6]. The most effective approach for preventing and defeating COVID-19 disease is vaccination. Current guidelines recommend vaccination of transplant candidates and recipients [7]. The response to vaccination in solid organ transplantation (Tx) patients is expected to be lower than in the normal population. This has been demonstrated in many studies in the literature. These valuable studies are usually related to antibody titers against spike protein. However, to our knowledge, there are not many studies at this level on the results of current vaccination protocols in clinical practice (real life) [7].

This study aims to investigate the clinical effect of the vaccination protocol on patients who have undergone kidney transplantation during the COVID-19 pandemic.

Methodology

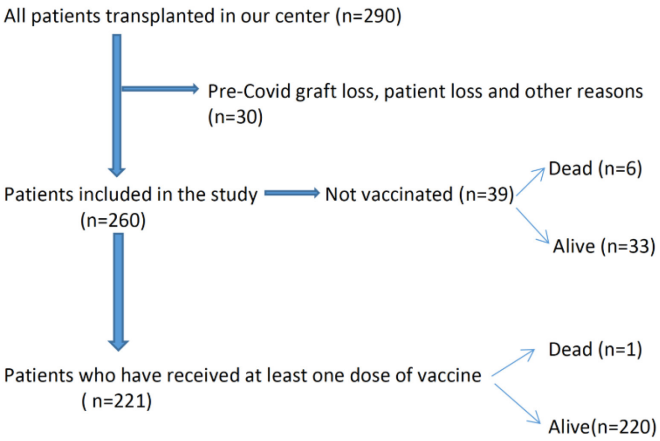
Study Design and Participants

Patients who underwent kidney transplantation between June 2012 and May 2022 were retrospectively evaluated. Cases with graft loss and/or mortality before the pandemic and cases diagnosed with COVID-19 (2 cases) during the vaccination protocol were excluded from the study (Figure 1). New transplants were mostly terminated during the peak of the pandemic between March 2020 and March 2022. Pre-transplant vaccination was recommended for patients undergoing kidney transplantation during the vaccination period. The first dose of vaccine was recommended in the third month after COVID-19 infection in unvaccinated transplant cases who were diagnosed with COVID-19.

This study was approved by the Institutional Ethics Committee of the Ministry of Health and our hospital with file number 279. The study protocol was in accordance with the Declaration of Helsinki (8). The etiology of primary renal failure, comorbidities, immunosuppressive agents used, and demographic data including age and gender were recorded. A widespread vaccination policy against COVID-19 in Turkey was initiated in January 2021 with Sinovac-CoronaVac (CoronaVac). Afterward, COVID-19 mRNA vaccine BNT162b2 (Biontech) was added and continued. The mandatory vaccination policy was not implemented in accordance with regulations. Patients were recommended to be vaccinated. Patients made their choice of vaccine in line with the regulations and the recommendations of the Ministry of Health. First, two doses were planned for the vaccine candidates, one at least four weeks apart. However, There was no clear protocol for immunocompromised patients in the guidelines of the Ministry. The decision is up to the judgment of the clinician. COVID-19 was diagnosed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab sample. In our hospital, all patients with symptoms suggestive of COVID-19 such as fever, shortness of breath, cough, loss of smell/taste, abdominal pain, diarrhea, nausea, vomiting, myalgia, fatigue, and arthralgia were also evaluated with computed tomography (CT) of the chest. The presence of ground-glass opacities and consolidation areas was defined as COVID-19 pneumonia. Patients with the above-mentioned findings but whose diagnosis of COVID-19 was not confirmed by repeated PCR tests were excluded from this study.

Patients who were admitted to the hospital due to COVID-19 and who needed intensive care were evaluated. The relationship between vaccination and hospitalization due to COVID-19 and mortality of patients was evaluated. The prevalence of COVID-19, hospitalization, and mortality of patients before and after the vaccination policy were examined.

Figure 1. Distribution of patients.



Patients' Drug and Other Therapy

Intensive care and oxygen needs, mechanical ventilation status, mask oxygen needs and Continuous Positive Airway Pressure (CPAP) needs of the patients were evaluated. Hydroxychloroquine, favipiravir, dexamethasone, and antibiotic therapy for secondary infection or prophylaxis were used for medical treatment. Worsening of symptoms and laboratory tests such as a dramatic increase in C-reactive protein (CRP), ferritin and D-dimer levels, and lung involvement on CT were accepted as indications for hospitalization. Transplant patients with COVID-19 were treated outside the transplant unit at a specific clinic for patients with COVID-19. Treatment was organized by clinicians at the COVID-19 clinic in consultation with a nephrologist and transplant surgeon. Immunosuppressive agents such as calcineurin inhibitors (tacrolimus and cyclosporine), anti-metabolite agents (mycophenolate mofetil, mycophenolic acid) and steroids were revised. This revision was also applied to vaccinated patients. First, antimetabolite agents were discontinued. The steroid dose (prednisolone) was doubled (from 5 mg/day to 10 mg/day). Inflammation parameters (CRP, procalcitonin), renal function tests and immunosuppressive agents were closely monitored. Immunosuppressive drugs other than steroids were discontinued in patients who did not respond to treatment.

Statistical Analysis

All statistical analyses were performed using the IBM SPSS software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Continuous variables were presented as a median and interquartile range, whereas categorical variables were presented as counts and percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were compared using Student's *t*-test or Mann-Whitney U test according to the data distribution. Categorical variables were compared with chi-square or Fisher's exact tests whenever appropriate. Significant results in univariate analysis were analyzed using multivariate regression analysis. The effect size was adjusted for all variables with a significance level of $p < 0.05$.

Results

The study included 260 kidney transplant patients (female, n = 107 (41%); male, n = 153 (59%)). The mean age was 38.42 (11-75). One hundred eight (41.5%) patients were diagnosed with COVID-19. The median time between kidney transplantation and diagnosis of COVID-19 was 74 (24-142) months. The most common cause of kidney failure was hypertension (HT/ n = 69 (26.5%)). After the national vaccination program (NVP), 221 (85%) patients were vaccinated with the coronavirus vaccine (Table 1). Thirty-nine (15%) patients refused to be vaccinated. There was no significant difference between the vaccinated and unvaccinated patients in terms of the immunosuppression protocol. During the follow-up period, 108 (41.5%) patients were diagnosed with COVID-19. Among these patients, 65 (60.2%) were diagnosed with COVID-19 after the National Vaccination Program (NVP). 56 of these patients (51.8%) were included in NVP afterward. However, 9 (8.3%) patients refused to be vaccinated. Before NVP, 43 (39.8%) patients were diagnosed with COVID-19. 38 (35.2%) of these patients received at least one dose of vaccine after COVID-19 infection. 5 (4.6%) patients, who were diagnosed with COVID-19 after NVP, were not vaccinated. The total number of patients who were not vaccinated or diagnosed with COVID-19 before

Table 1. Demographic and clinical characteristics of vaccinated and not vaccinated kidney transplant patients.

Characteristic	All patients	Vaccinated	Not vaccinated	*p* value
	n = 260	221 (85%)	39 (15%)	
Age	38.42 (11-75)	39.41 (17-75)	31.5 (11-75)	> 0.05
Gender, n (%)				
Female	107 (41%)	92 (41.6%)	15 (38.5%)	0.711
Male	153 (59%)	129 (58.4%)	24 (61.5%)	
Primary kidney disease				
Diabetes mellitus	46 (17.7%)	39 (17.6%)	7 (17.9%)	-
Hypertension	69 (26.5%)	63 (28.5%)	6 (15.4%)	0.08
CGN	28 (10.8%)	26 (10%)	2 (5%)	0.274
Urologic disease	29 (11.2%)	25 (11.3)	4 (10.2%)	-
ADPCKD	5 (1.9%)	5 (2.2%)	0 (0%)	-
Nephrotic syndrome	38 (14.6%)	34 (15.4%)	4 (10.2%)	-
Nephronophthisis	14 (5.4%)	6 (2.7%)	8 (20.5%)	**0.001**
Other	16 (6.2%)	11 (5%)	5 (12.8%)	0.036
Etiology unknown	15 (5.7%)	12 (5.4%)	3 (7.7%)	-
Immunosuppressive drugs				
Tacrolimus	257 (98.8%)	218 (98.6%)	39 (100%)	-
Cyclosporine	3 (1.2%)	3 (1.3%)	0 (0%)	-
Mycophenolate mofetil	154 (59.2%)	134 (60.6%)	20 (51.3%)	-
Mycophenolate sodium	104 (40%)	85 (38.4%)	19 (48.7%)	-
Everolimus	2 (0.7%)	2 (0.9%)	0 (0%)	-
Prednisolone	260 (100%)	221 (100%)	39 (100%)	-
Covid-19 positive	108 (41.5%)	94 (42.5%)	14 (35.9%)	0.43
After NVP	65 (25%)	56 (25.3%)	9 (23%)	-
Before NVP	43 (16.5%)	38 (17.1%)	5 (12.8%)	0.843
Admitted to hospital, n (%)	49 (18.8%)	42 (19%)	7 (17.9%)	-
LOHS (Mean)	12.5	11.6	17.6	0.595
ICU admission, n (%)	8 (3 %)	2 (0.9%)	6 (15.4%)	**< 0.001**
Dead	7 (2.7%)	1 (0.5%)	6 (15.4%)	**< 0.001**
Death before NVP	3 (1.16%)	0	3 (7.7%)	**0.003**
Death after NVP	4 (1.54%)	1 (0.05 %)	3 (7.7%)	**0.011**

CGN: chronic glomerulonephritis; ADPCDK: autosomal dominant polycystic kidney disease; LOHS: length of hospital stay; ICU: Intensive care unit; NVP: national vaccination policy.

vaccination was 65 (60.2%; 14 of these cases were non-vaccinated cases. Among the remaining 51 patients, 43 were diagnosed with COVID-19 before NVP, and 8 were diagnosed with COVID-19 after NVP). Forty-nine (45.4%) patients were admitted to the hospital. Among these, the number of vaccinated and unvaccinated patients was 42 (38.9%) and 7 (6.5%), respectively. The rate of admission to the intensive care unit was 2 (1.9%) and 6 (5.6%) for vaccinated and unvaccinated cases, respectively. This was statistically significant when all patients were included in the analysis ($p < 0.001$). Seven patients (6.5%) died during the pandemic. Six of the dead patients (5.6%; 15.4% of the patients who were not vaccinated) were not vaccinated ($p < 0.001$). The number of cases who died before and after NVP were 3 (2.8%; 7% of cases diagnosed with COVID-19 before NVP) and 4 (3.7%; 6.2% of cases diagnosed with COVID-19 after NVP), respectively (Table 2).

The mean age of patients who died due to COVID-19 and were discharged was 49.1 (40-59) and 39.6 (11-75) years, respectively ($p = 0.084$). Among the deceased patients, 2 were female and 5 were male. The most common comorbidity in the deceased patients was hypertension ($p = 0.036$) (Table 2). In addition, fever, cough, and shortness of breath were the prominent symptoms in all of these patients. After the initiation of NVP, 221 (85%) patients received at least one dose of vaccine. The most frequently applied vaccine protocol was the double-dose Biontech protocol. The number of cases vaccinated before kidney transplantation was 32. Eight of these cases were diagnosed with COVID-19 (Table 3). The number of patients who refused or could not be vaccinated during the pandemic was 39. Six of the deaths were in this group. Three of these cases died before NVP due to COVID-19. Three of the 4 patients who died after NVP were unvaccinated, and one patient had received two doses of CoronaVac and a single dose of Biontech vaccine. However, it had been more than 6 months since the last dose of the vaccine. Forty-three of the patients who received the Corona vaccine were diagnosed with COVID-19 after vaccination. These patients accounted for 25.3% of patients who were

Table 2. Demographic and clinical characteristics of COVID-19 positive kidney transplant patients.

Characteristic	All patients	Death	Discharged	*p* value
	n = 108	7 (6.5%)	101 (93.5%)	
Age	40 (11-75)	49.1 (40-59)	39.6 (11-75)	0.084
Gender, n (%)				
Female	44 (40.7%)	2 (28.6%)	42 (41.6%)	0.69
Male	64 (59.3%)	5 (71.4%)	59 (58.4%)	
Coexisting disorder				
Diabetes mellitus	20 (18.3%)	3 (42.3%)	17 (16.8%)	0.117
Hypertension	33 (30.6%)	4 (57.1%)	29 (28.7%)	0.199
CAH	23 (27.8%)	4 (57.1%)	19 (18.8%)	**0.036**
COPD	1 (0.9%)	1 (14.3%)	0	0.065
AHUS	1 (0.9%)	1 (14.3%)	0	0.065
Immunosuppressive drugs				
Tacrolimus	106 (98.1%)	7 (100%)	99 (98%)	-
Cyclosporine	2 (1.8%%)	0	2 (1.9%)	-
Mycophenolate mofetil	64 (59.3%)	5 (71.4%)	59 (58.4%)	-
Mycophenolate sodium	44 (40.7%)	2 (28.6%)	42 (41.6%)	-
Symptoms on admission, n (%)				
Fever	51 (47.2%)	7 (100%)	44 (43.5%)	**0.004**
Cough	57 (52.8%)	7 (100%)	50 (49.5%)	**0.014**
Dyspnea	35 (32.4%)	7 (100%)	28 (27.7%)	**0.001**
Myalgia or arthralgia	65 (60.2%)	4 (57.1%)	61 (60.4%)	-
Diarrhea	17 (15.7%)	0 (0%)	17 (16.8%)	-
Vaccinated before TX	8 (7.4%)	0 (0%)	8 (7.9%)	-
Admitted to hospital, n (%)	42 (38.9%)	7 (100%)	35 (34.6%)	**0.003**
LOHS (Mean)	12.5 ± 13	20.7 ± 27	5.6 ± 8.4	**0.001**
ICU admission, n (%)	8 (7.4%)	7 (100%)	1 (0.01%)	**0.001**
Covid-19 / vaccine relationship				
Before the vaccine or not vaccinated	65 (60.2%)	6 (85.7%)	59 (58.4%)	0.240
*< 6 months	28 (25.9%)	0	28 (27.7%)	0.187
**> 6 months	15 (13.9%)	1 (14.3%)	14 (13.9%)	-
Not vaccinated	14 (12.9%)	6 (85.7%)	8 (7.9%)	**0.001**
Death before NVP	3 (2.8%)	3 (42.9%)	0	
Death after NVP	4 (3.7%)	4 (57.1%)	0	

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; * : *< 6 months: within six months after vaccination; ** > 6 months: more than six months after vaccination; LOHS: length of hospital stay.

vaccinated without a previous COVID-19 diagnosis (170 cases). Comparison of cases with and without COVID-19 diagnosis after vaccination showed no significant difference in terms of age (cases with COVID-19: 38.67 ± 14.8; cases without COVID-19: 38.2 ± 11.9; $p = 0.853$), gender (cases with COVID-19: 27/M; 16/F, cases without COVID-19: 74/M; 53/F, $p = 0.720$), and presence of chronic obstructive pulmonary disease (COPD: cases with COVID-19: 1/43; cases without COVID-19: 0/127 $p = 0.253$). However, a significant difference was present in favor of cases who were diagnosed with COVID-19 after vaccination in terms of the presence of DM (cases with COVID-19: 8/43; cases without COVID-19: 0/127 $p < 0.001$), presence of HT (cases with COVID-19: 8/43; cases without COVID-19: 1/127 $p < 0.001$) and CAD (cases with COVID-19: 10/43; cases without COVID-19: 0/127 $p < 0.001$). While these results were significant in univariate analyses, they were not statistically significant in multivariate analyses. Twenty-eight of these cases were diagnosed with COVID-19 within six months of vaccination and 15 patients were diagnosed with COVID-19 after six months. None of the twenty-eight patients died. Only 3 of the cases who were diagnosed with COVID-19 after vaccination were hospitalized. One patient had acute rejection due to immunosuppression revision and had a partial response to steroid treatment. However, the other patient died. The deceased patient was diagnosed with COVID-19 more than six months after vaccination.

Discussion

In this study, a significant decrease was not observed between the vaccinated and unvaccinated patients in terms of the frequency of COVID-19 after NVP. There was no significant difference in the rate of hospital admission between the vaccinated and unvaccinated groups. However, the rates of intensive care admission and death were higher in the unvaccinated group. COVID-19-related deaths also continued after NVP. The majority of these patients were in the unvaccinated group. When we compared kidney transplant patients diagnosed with COVID-19 in terms of mortality and survival, mortality was clinically significantly higher in unvaccinated patients or patients diagnosed with COVID-19 before vaccination. However, this was not statistically significant. In a multi-center study involving 47 centers, mortality rates in the control group and transplant group before NVP were found to be 4% and 11%, respectively [9]. In another study with 20 patients who received a double dose of CoronaVac vaccine, the rate of mortality was not statistically significant compared to 63 unvaccinated patients. However, the rate of intensive care unit admission and the need for non-invasive mechanical ventilation were significantly higher in the unvaccinated group [10]. In an Israeli study that included 308 transplant patients to whom two doses of Biontech vaccine were administered, Anti-Spike antibodies tested sero-positive in only 112 patients (36.4%). In this study, advanced age, maintenance of anti-metabolite therapy, high blood calcineurin inhibitor levels, and a history of kidney transplantation within the last three months were significantly associated with sero-negativity [7]. Response to vaccination in solid organ transplantation is expected to be low. Current guidelines recommend vaccination of transplant candidates and recipients against SARS-CoV-2 [11-14]. In a study by Bertrand *et al*, the antibody response of the 1st and 2nd doses of Biontech vaccine was investigated in kidney transplant patients. In renal transplantation patients, antibody response was rarely induced after the first vaccine and antibody response was observed in only 17.8% of patients after the second dose. Anti-spike T cell-specific response was observed in 51.1% of cases after the second dose [15]. These results are in contrast with the robust and early-induced immunity observed during mRNA vaccine trials, which showed 100% anti-spike seroconversion after vaccination with mRNA-127312 or Biontech [16,17]. So, what might be the real-life counterpart of low antibody response to vaccination after kidney transplant? COVID-19 was diagnosed in 43 patients who were vaccinated with at least one dose of COVID-19 vaccine. This number of patients represents 25.3% of previously vaccinated cases (170

Table 3. Vaccine type and COVID-19 relationship.

	Not vaccinated (n = 39)	B	B + B	B + B + B	C	C + C	C + C + C	C + B	C + C + B	C + C + B + B
Dead (n = 7)	6 (15.4%)	0	0	0	0	0	0	0	1	0
Non-Dead (n = 253)	33 (84.6%)	16 (7.2%)	118 (53.4%)	7 (3.1%)	3 (1.4%)	18 (8.1%)	4 (1.8%)	4 (1.8%)	28 (12.7%)	22 (9.9%)
COVID-19 positive after vaccinated (n = 43)	14 (35.9)	3 (18.7%)	22 (18.6%)	2 (28.6%)	0	1 (5.6%)	0	0	5 (17.9%)	10 (45.5%)
Vaccinated before Tx (n = 32)	-	3	16	0	0	3	1	1	6	2
COVID-19 positive in cases vaccinated before tx (n = 8)	-	0	4	0	0	1	0		1	2

B: Biontech; C: CoronaVac; Tx: Transplantation.

cases) without a COVID-19 diagnosis. Of all cases (260 cases), COVID-19 was diagnosed in 25% (65 cases) of the patients who were not vaccinated yet or unvaccinated. In addition, COVID-19 was observed in 8 (25%) of patients who received pre-transplant vaccination. This may suggest that vaccination was not effective in preventing COVID-19 in our study. Cucchiari *et al.* investigated the cellular and humoral response in kidney transplant patients and reported that humoral or cellular response was observed in 65% of cases. The authors also emphasized that patients may be protected against SARS-CoV-2 even if they do not have S antibodies and the extent to which cellular immunity in the absence of detectable antibodies can prevent severe infection or death from SARS-CoV-2 has not yet been determined and that the definitive answer will only be given by clinical follow-up of these patients [18]. When patients diagnosed with COVID-19 were compared in terms of mortality in the univariate analysis, there was no statistically significant difference between vaccinated and unvaccinated patients. When patients diagnosed with COVID-19 were compared in terms of mortality in the univariate analysis, there was no statistically significant difference between vaccinated and unvaccinated patients. However, the fact that 6 of the 7 patients who died were not vaccinated should be considered clinically. In their study on SARS-CoV-2 sero-negativity after COVID-19 vaccination in kidney transplant patients, Vaiciuniene *et al.* reported that glomerular filtration rate, the level of hemoglobin, and the use of mycophenolate mofetil were effective after vaccination [19]. The hypothesis of our study was based on investigating the real-life clinical outcomes of vaccination. In univariate analysis, we found that DM, HT, and CAD were more common in cases diagnosed with COVID-19 after vaccination, but this could not be confirmed by multivariate analysis. Another study investigated immune response in kidney transplant recipients following the 3rd and 4th doses of heterologous and homologous COVID-19 vaccines. This study showed that 24% and 19% of kidney transplant recipients did not have any detectable spike protein antibodies in response to doses 3 and 4 of the vaccine, respectively. In addition, this study also showed that some of the transplant patients who did not respond to the first 4 doses of vaccine also did not respond significantly to the fifth dose [20]. The presence of spike protein antibodies was not investigated in our study. This is one of the limitations of our study. However, when we retrospectively evaluated our cases, the cases diagnosed with COVID-19 after vaccination were the ones who received four doses of mixed vaccine. This may be due to a possible variant of SARS-CoV-2. However, we do not have data about the type of variant in these infected patients, which was another limitation of our study.

Limitations

The limitations of the study include the retrospective and single-center design, the inability to standardize vaccination protocols in cases of patient preference due to the health policy of the country, and the inability to study anti-spike proteins and SARS-CoV-2 variants although it was not the aim of the study.

Conclusions

The majority of patients who died were unvaccinated. However, repeated vaccinations may not adequately protect all transplant recipients. Vaccination may be recommended to patients before Tx. Antibody formation in the patient, immunosuppressive protocols used, different variants of the disease, patients' hesitation about the safety of vaccination, and the lack of definitive treatment for the disease are some of the difficulties that must be overcome to achieve standardization in Tx patients. Therefore, social distancing and mask use are still important for kidney transplant recipients. There is a need to develop personalized treatment and prevention strategies in transplantation cases.

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