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Original Article

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Kidney Transplantation in Patients Recovered from Coronavirus Disease 2019

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ABSTRACT

Objective: There is limited information about kidney transplant recipients who recovered from the Coronavirus disease 2019. This study is conducted to investigate the safety of transplantation in this patient population.
Methods: Nineteen patients with prior coronavirus disease 2019 were included. We present demographics, clinical characteristics, laboratory findings, and immunosuppressive regimen. Graft functions and patient and allograft outcomes were compared to 19 kidney transplant recipients who did not have coronavirus disease 2019.
Results: The median age of participants was 38 (interquartile range, 26-51) years. Most of the recipients were men (n = 30, 78.9%). The most common presenting symptoms of kidney transplant recipients with prior coronavirus disease 2019 were fever (36.8%), fatigue (21.1%), dyspnea (15.8%), cough (10.5%), and myalgia (5.3%). Eight patients (42.2%) were hospitalized, while none required intensive care unit admission and mechanical ventilation. The median wait time for transplantation after the initial diagnosis of coronavirus disease 2019 was 82 days (interquartile range, 57-172). Most recipients in both groups received antithymocyte globulin as an induction agent. Standard doses of maintenance immunosuppression consisting of tacrolimus, mycophenolate derivatives, and corticosteroids were administered. During a follow-up duration of 85 (interquartile range, 39-154) and 134 (interquartile range, 56-240) days for patients and controls, respectively, the rate of complications and graft functions were not statistically significant between groups. Graft and patient survival was 100%.
Conclusion: Our study results support the safety of kidney transplantation in patients with prior coronavirus disease 2019. Transplant candidates and donors should be carefully screened for coronavirus disease 2019. We suggest continuing the standard doses of induction and maintenance immunosuppression, especially in patients who recovered without pulmonary sequelae.
Keywords: Immunosuppression, kidney transplantation, kidney transplant recipients, SARS-CoV-2, the coronavirus disease 2019

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) became a global public health emergency promptly after the first case was reported in December 2019 in Wuhan, China.[1] It was declared a pandemic on March 11, 2020, by the World Health Organization.[2]

The clinical course varies from asymptomatic infection to severe disease. Among 1.3 million cases reported to the United States Centers for Disease Control and Prevention, 14% were hospitalized, 2% were admitted to the intensive care unit (ICU), and 5% died.[3]

The mortality rate is higher in COVID-19 patients with chronic kidney disease (CKD) compared to the healthy population. The European database collecting clinical information of patients on kidney replacement therapy with COVID-19 (ERACODA) collaboration data showed

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that the 28-day probability of death was 21.3% and 25.0% in kidney transplant recipients (KTRs) and dialysis patients, respectively.[4]

The recently reported data from Türkiye showed that ICU admission and in-hospital mortality rate among hemodialysis patients were 25.4% and 16.2%. The corresponding values for KTRs were 21% and 11.1%, respectively.[5]

Coronavirus disease 2019 affected kidney transplant programs negatively. Many centers suspended living donor kidney transplantation (LDKT) and restricted deceased donor kidney transplantation (DDKT) in the early phase of the pandemic in fear of possible severe disease course in KTRs. As a result, kidney transplantation rates dropped abruptly.[6]

On the other hand, it was shown that waitlisted patients infected with COVID-19 were hospitalized and died more frequently compared to infected KTRs.[7] Another study revealed that mortality on the kidney transplant waitlist increased by 43%.[8]

Administration of newly developed vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and accumulating experience in the management of KTR infected with SARS-CoV-2 enabled many centers to resume transplantation activities.[9] An emerging issue with transplantation activities in the COVID-19 era is managing transplantation candidates with prior COVID-19 infection.

Various case reports of successful kidney transplantation to recipients with a history of COVID-19 have been published recently. All reports underlined the importance of the resolution of symptoms and detection of negative SARS-CoV-2 reverse-transcription polymerase chain reaction (SARS-CoV-2 RT-PCR) assay before proceeding to transplantation and suggested leaving an interval between infection and transplantation.[10-12]

There are many questions to be answered about kidney transplantation in patients with prior COVID-19. Decisions about the timing of transplantation, choice of induction therapies, and maintenance immunosuppression are crucial. The impact of COVID-19 on long-term graft outcomes and risk of recurrence are uncertain. There is concern about future infectious complications, which may become more frequent after the obligatory use of anti-cytokines and high-dose corticosteroids to treat the hyperinflammatory state related to COVID-19.

This study investigates the clinical course of COVID-19, allograft functions, complications and allograft, and patient survival of KTRs with prior COVID-19.

MAIN POINTS

- The main issues to be decided in kidney transplant recipients with prior coronavirus disease 2019 are the timing of transplantation, choice of induction therapies, and maintenance immunosuppression. The impact of coronavirus disease 2019 on long-term graft outcome, infectious complications, and risk of recurrence are uncertain.
- Nineteen patients with prior coronavirus disease 2019 were compared to 19 kidney transplant recipients without a history of coronavirus disease in terms of graft functions and patient and allograft outcomes.
- Most recipients in both groups received antithymocyte globulin as an induction agent. Standard doses of maintenance immunosuppression consisting of tacrolimus, mycophenolate derivatives, and corticosteroids were administered.
- The rate of complications and graft functions were not statistically significant between groups with a graft and patient survival of 100%.
- According to the study results, kidney transplantation in patients with prior coronavirus disease 2019 seems safe. We suggest continuing the standard doses of induction and maintenance immunosuppression.

METHODS

The retrospective study was conducted at 4 centers in Türkiye.

All kidney transplants were performed in accordance with the Declaration of Istanbul.[13] Informed consent was taken from all recipients and donors prior to transplantation. The study was approved by the ethics committee of Istanbul University (Approval number: 19.08.2021-411645). All participants gave informed consent to participate in the study.

Subjects

Kidney transplant recipients infected with COVID-19 before transplantation between February 2020 and May 2021 were included. The control group consisted of age and sex-matched recipients who were transplanted at the same period as the patient group and did not have COVID-19. Recipients between 18 and 70 years of age were included. Patients with active infection and malignancy were excluded. Also, KTRs from the control group diagnosed with COVID-19 after transplantation were excluded. The study was performed in 4 transplantation centers in Türkiye. Nineteen KTRs were present in each group.

The diagnosis of COVID-19 was made by compatible clinical symptoms, positive SARS-CoV-2 RT-PCR assay of the nasopharyngeal swab, and/or radiological findings showing typical ground glass appearance on computed tomography scan of the chest. In all patients, data regarding demographics, clinical findings, dialysis duration, body mass index (BMI), comorbidities including hypertension (HT), diabetes mellitus (DM), obesity, chronic obstructive pulmonary disease (COPD), previous heart disease, presenting symptoms (fever, fatigue, dyspnea, cough, myalgias) and radiologic findings of COVID-19, clinical course of COVID-19 (hospitalization, length of hospital stay, need for ICU, need for mechanical ventilation, and treatment), transplantation characteristics [number of human leucocyte antigen (HLA) mismatches, presence of donor-specific

antibodies (DSAs), history of COVID-19 infection of the donor, donor source, number of transplantations, induction, and maintenance immunosuppression (IS)], post-transplant complications including acute T-cell rejection (TCR), antibody-mediated rejection, acute tubular necrosis (ATN), infection, and recurrence of COVID-19), laboratory findings (serum creatinine values at hospital discharge, at first and third months after transplantation, and at last patient visit), and median wait time for transplantation after initial diagnosis of COVID-19 were collected. Patient and allograft survival were recorded.

Outcomes

Patient and allograft survival and graft functions were defined as study outcomes.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 26.0. (IBM SPSS Corp.; Armonk, NY, USA) Histogram of the sample data, quintile-quintile plot, Kolmogorov–Smirnov, and Shapiro–Wilk tests were used to test the normality of the data. Categorical variables were summarized by numbers and percentages. Continuous variables are summarized with means and SDs or medians and interquartile range (IQR) where appropriate. Chi-square and Fisher's exact tests were performed for categorical variables. The Mann–Whitney *U*-test was used for quantitative variables with a nonparametric distribution. A *P*-value of less than .05 is considered significant.

RESULTS

Patient Characteristics

Nineteen patients with prior COVID-19 and 20 COVID-19 naïve controls were examined. One KTR from the control group infected with COVID-19 after kidney transplantation and still under treatment was excluded. A total of 38 KTRs (19 patients, 19 controls) were included. The median age of participants was 38 (IQR, 26-51) years. Most of the recipients were men (n = 30, 78.9%). The study groups mainly comprised normal-weight individuals with a median BMI of 25 kg/m^2 (IQR, 21.5-28.5). The most frequent etiology of end-stage kidney disease (ESKD) was chronic glomerulonephritis in 12 recipients (31.6%), followed by 11 (28.9%) recipients in whom the etiology was unknown. Fifteen recipients (39.5%) underwent transplantation preemptively. The median dialysis vintage was 7 months (IQR, 2-24). A high prevalence of comorbidities was observed, HT being the most common (78.9%), followed by previous cardiac disease (13.2%), DM (10.5%), obesity (10.5%), and COPD (2.6%). There were 7 recipients (18.4%) without comorbidities. The baseline characteristics were similar between patients and controls (Table 1).

Presentation and Clinical Course of Coronavirus Disease 2019

The most common presenting symptoms were fever in 7 (36.8%), fatigue in 4 (21.1%), dyspnea in 3 (15.8%), cough in 2 (10.5%)

Table 1. Demographics and Clinical Characteristics of Study Groups

	COVID-19 Positive	COVID-19 Negative	
	n = 19	n = 19	*P*
Recipient age, years, median (IQR 25-75)	37 (26-49)	44 (27-51)	.413
Gender, n (%)			
Female	4 (21.1)	4 (21.1)	1
Recipient BMI, median (IQR 25-75)	24 (21-27)	25 (21.8-29.8)	.393
Etiology of ESKD, n (%)			
Hypertensive nephrosclerosis	1 (5.3)	1 (5.3)	.489
Diabetic nephropathy	3 (15.8)	1 (5.3)	
Chronic glomerulonephritis	4 (21.1)	8 (42.1)	
Others	6 (31.6)	3 (15.8)	
Unknown	5 (26.3)	6 (31.6)	
Dialysis vintage, year, median (IQR 25-75)	15.5 (4.5-60.8)	4 (2-21)	.163
Re-transplantation, n (%)	4 (21.1)	2 (10.5)	.66
Comorbidities, n (%)			
HT	15 (78.9)	15 (78.9)	1
DM	3 (15.8)	1 (5.3)	.604
Obesity	2 (10.5)	2 (10.5)	1
Previous heart disease	4 (21.1)	1 (5.3)	0.34
COPD	0	1 (5.3)	1
Donor source, n (%)			
Living	19 (100)	18 (94.7)	1
Deceased donor	0	1 (5.3)	
HLA-MM, median (IQR 25-75)	3 (1-3)	3 (0-5)	.074
Occurrence of DSAs, n (%)	0	2 (10.5)	.486
Induction, n (%)			
ATG	15 (78.9)	18 (94.7)	.321
Basiliximab	1 (5.3)	0	
Maintenance IS, n (%)			
Tacrolimus	19 (100)	19 (100)	1
Mycophenolate derivates	18 (94.7)	18 (94.7)	
Azathioprine	1 (5.3)	1 (5.3)	
Steroid	19 (100)	19 (100)	
Post-transplant complications, n (%)			
T-cell rejection	0	1 (5.3)	1
Antibody mediated rej.	0	0	–
Tubular necrosis	0	1 (5.3)	1
İnfection	0	2 (10.5)	.486
Post-transplant follow-up, days, median (IQR 25-75)	85 (39-154)	134 (56-240)	.062
Serum creatinine (mg/dL), median (IQR 25-75)			
At discharge	1.3 (1-1.7)	1.4 (1-2)	.378
At first month	1.3 (1-1.8)	1.5 (1.1-1.8)	.595
At third month	1.2 (0.9-2)	1.5 (1.2-1.8)	.728
At last follow-up	1.2 (0.9-1.6)	1.4 (1-1.7)	.523
Patient survival, n (%)	19 (100)	19 (100)	1
Allograft survival, n (%)	19 (100)	19 (100)	1

ATG, anti-thymocyte globulin; BMI, body mass index; COPD, chronic obstructive lung disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; DSA, donor-specific antibody; ESKD, end-stage kidney disease; HLA-MM, human leukocyte antigen mismatch; HT, hypertension; IS, immunosuppression; IQR, interquartile range.

patients, and myalgia in 1 (5.3%) patient. Coronavirus disease 2019 pneumonia was detected in 13 (68.4%) of the patients. Eight patients (42.2%) were hospitalized, while none required ICU admission and mechanical ventilation. The median length of hospital stay was 10 days (IQR, 8-12). A substantial number of patients were treated with favipiravir (n = 13, 68.4%). Eight donors (42.2%) were diagnosed with COVID-19 concomitantly. Data regarding COVID-19 infection are presented in Table 2.

Laboratory Variables

The median serum creatinine values of the patients with prior COVID-19 were 1.3 mg/dL (IQR, 1-1.7), 1.3 mg/dL (IQR, 1-1.8), and 1.2 mg/dL (0.9-2) at discharge, first and third months, respectively. The corresponding values for the control group were 1.4 mg/dL (IQR, 1-2), 1.5 mg/dL (IQR, 1.1-1.8), and 1.5 mg/dL (IQR, 1.2-1.8).

Transplantation Characteristics

Among the study group, only 1 participant (2.6%) from the COVID-19 naive control group received a graft from a deceased donor. Four recipients had kidneys from living unrelated donors. One of the living unrelated donors was the spouse of the recipient, while the other 3 living unrelated donors donated their kidneys as part of the paired donor kidney exchange program. According to the program, 3 first-degree relatives of the recipients donated their kidneys in exchange.

Table 2. Clinical Characteristics of Patients with Prior COVID-19

COVID-19 symptoms, n (%)	
Fever	7 (36.8)
Dyspnea	3 (15.8)
Myalgia	1 (5.3)
Fatigue	4 (21.1)
Cough	2 (10.5)
Hospitalized patients, n (%)	8 (42.2)
Length of hospitalization, median (IQR 25-75)	10 (8-12)
Need for ICU, n (%)	0
Need for Intubation, n (%)	0
Medications, n (%)	
Favipiravir	13 (68.4)
Antibiotics	5 (26.3)
Anticytokin	0
Anticoagulants	6 (31.6)
The duration between COVID-19 diagnosis to transplantation, median (IQR 25-75)	82 (57-172)
Donor COVID-19 status, n (%)	8 (42.2)

COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range.

All living-related donors were first- or second-degree relatives of recipients. Four (21.1%) patients with prior COVID-19 and 2 (10.5%) controls received second transplants, which was not statistically significant. The median numbers of HLA mismatches were 3 (IQR 1-3) and 3 (0-5) in patients and controls, respectively. Donor-specific antibodies were detected in 2 controls, while none of the patients with prior COVID-19 had DSA's. Statistically significant differences were not found between the groups regarding the number of HLA mismatches and the presence of DSAs. The majority of the recipients in both groups became antithymocyte globulin (ATG) as induction agent [n = 15 (78.9%) and n = 18 (94.7%) in patient and control groups, respectively], while basiliximab was administered to 1 recipient (5.3%) in the patient group. Standard doses of maintenance IS consisting of tacrolimus, mycophenolate derivatives, and corticosteroids were administered at transplantation, while 1 exceptional patient (5.3%) in each group became azathioprine. The induction and maintenance treatments were similar in both groups. Neither patients nor controls were vaccinated, as the research was conducted in pre-vaccination era.

The median wait time for transplantation after the initial diagnosis of COVID-19 was 82 days (IQR, 57-172). The clinical resolution was observed in all COVID-19 positive patients, and each patient was tested for COVID-19 via the SARS-CoV-2 RT-PCR assay of the nasopharyngeal swab at admission. Transplantation characteristics are shown in Table 1.

Complications after Transplantation

During post-transplant follow-up, recipients experienced various complications. One KTR with acute TCR and 1 with ATN were detected among the controls. Also, 2 recipients were diagnosed with a urinary infection in the control group. The patients with prior COVID-19 infection were closely monitored for reinfection, which was detected in 1 patient 78 days post-transplantation. The rate of complications was not statistically significant between groups, as shown in Table 1.

Outcome

Statistically significant differences between the groups regarding allograft functions were not observed. After a median follow-up time of 85 (IQR, 39-154) days for patients and 134 (IQR, 56-240) days for controls, graft and patient survival was 100% (Table 1). One year after transplantation, graft and patient survival were re-evaluated, revealing that all participants were alive with functioning grafts.

DISCUSSION

The delay of transplantation activities in the early days of the pandemic resulted in a sudden fall in transplantation rates and a subsequent increase in the number of waiting patients. This circumstance may be associated with poor outcomes in transplant candidates.[14]

The mortality of transplant patients with COVID-19 was 18-43%, significantly higher than that of the general population.[15]

Also, the mortality seems to be higher in early KTRs according to a recent report, which showed a mortality rate of 46% in patients with COVID-19 within the first 60 days of transplantation.[16] Data on the survival of KTRs and dialysis patients, on the other hand, showed that KTRs might have better survival than patients on dialysis.[4,17]

A simulation, which predicts mortality in case of postponing or resuming kidney transplantation, was built to help decision-making in transplantation during COVID-19. According to the results, most scenarios with different patient and disease parameters showed that pursuing transplantation is associated with better survival.[18]

Parallel to the spread of COVID-19 and the growing number of affected people, there will be more recipients and donors undergoing kidney transplantation who recovered from COVID-19.

Here, we reported 19 KTRs who recovered from COVID-19 compared with 19 KTRs transplanted during the same period and did not have the infection. Our study results support the safety of kidney transplantation in patients with prior COVID-19 infection.

A crucial decision before transplanting patients with prior COVID-19 is the use of induction and maintenance treatments. A few studies suggest that IS intensity and induction therapy with depleting agents were not associated with mortality.[19,20] Fewer KTRs during the pandemic were treated with depleting agents than the number of patients before the pandemic. However, the use of depleting agents during the pandemic was associated with a decreased rate of rejection, and mortality was not increased.[21] Considering these reports, we continued to use induction and maintenance IS treatments as per the recipient's immune risk evaluation due to concerns over the risk of acute rejection. This approach may be further supported by the absence of rejection and infectious complications in our patient group during the study period.

All patients with prior COVID-19 infection were asymptomatic and had a negative SARS-CoV-2 RT-PCR test before transplantation. The diagnostic test of choice for COVID-19 is the SARS-CoV-2 RT-PCR assay of the nasopharyngeal swab. It is recommended that both donor and recipient should have a minimum of 1 negative SARS-CoV-2 RT-PCR assay result in 48 hours before transplantation.[22] Routine screening with non-contrast CT imaging of the chest is controversial.[23] Therefore, we preferred not to routinely screen recipients by non-contrast CT. The median duration between the initial diagnosis of COVID-19 to kidney transplantation was 82 days. The 2 recent studies from the USA and India reported 71 and 60 days wait times, respectively.[24,25] Although precise data are lacking, the wait time after infection is suggested to be at least 4-6 weeks.[26] As complete recovery from COVID-19 is an essential requirement for transplantation and an interwall between infection and transplantation is deemed necessary, a significant obstacle would have been the occurrence of the long COVID syndrome among our patients, defined as symptoms present beyond 4 weeks after the initial presentation, including fatigue, dyspnea, cardiac involvement, joint pain and neuropsychological disorders.[27]

The persistence of COVID-19 in the body and T-cells dysfunction are 2 of many putative pathophysiologic mechanisms of this chronic and disabling condition.[27] The requirements for kidney transplantation preparation and the timing of transplantation in kidney transplant candidates with long COVID syndrome are unknown, but it is clear that great caution should be exercised.

Severe acute respiratory syndrome coronavirus 2 IgG and IgM antibodies were tested before transplantation in 9 and 6 KTRs from the patient group, respectively. There are various assays with different technologies to measure antibody response against SARS-CoV-2, and effort is made to develop and validate new antibody detection assays.[28] However, their applicability to the transplant population has yet to be discovered. For this reason, we decided not to use the antibody results for COVID-19 diagnosis and further treatment decisions.

The median follow-up time of patients with prior COVID-19 and controls were 85 and 134 days, respectively.

There were no differences in graft functions and patient and allograft survival between the groups, similar to the study of Santeusanio et al.[24] They reported losing one patient. In our study, patient and allograft survival was 100% similar to the study of Kute et al.[25] Also, one year after transplantation, graft and patient survival were reevaluated, revealing that all participants were alive with functioning grafts.

Although very pleasing, the absence of mortality requires further discussion. This may be associated with the relatively better health of transplant recipients in our study, indicated by younger age, a low number of diabetic patients, and an abundance of living donor transplantation. Our patients were relatively younger, with a median age of 37 (IQR, 26-49) compared to studies subjecting patients with CKD or on dialysis diagnosed with COVID-19.[5,29] The younger age of KTRs in Türkiye may explain this discrepancy. All recipients in the patient group underwent LDKT. The ratio of DDKT in Türkiye is almost 5:1. However, our study group almost consisted only of recipients with living donors, representing the dramatic fall in DDKT during COVID-19 in our country.[30]

One patient was diagnosed with COVID-19 after 78 days post-transplant. He was 24 years old and underwent second

kidney transplantation from a living donor in March 2021. His initial COVID-19 diagnosis was in September 2020, and his SARS-CoV-2 RT-PCR assay of the nasopharyngeal swab was negative before transplantation. As highlighted in the study by Ghorbani et al, given that more than 90 days had passed from the initial COVID-19 diagnosis and an infection-free state was evident by a negative RT-PCR test, we assumed that it was reinfection with SARS-CoV-2.[31] There are concerns about the duration and effectiveness of protective antibodies, and the outcome of reinfection in transplant patients are not reported yet. We repeatedly underscore the importance of vaccination and adherence to protective measures in follow-up visits.

As far as we know this is the third study of recipients with a history of COVID-19 and the second study on this subject with a control group.[24,25] Compatible with the other 2 studies, we waited for a minimum of 4 weeks from the diagnosis of COVID-19 to transplantation, continued to use standard doses of induction and maintenance IS, and observed good patient and allograft survival rates with no rejections and infectious complications. Larger studies may reduce confusion and help to build safe practice patterns in this fragile patient group.

Limitations

The study's major limitations are low patient and control numbers and short follow-up time. As most of the study participants underwent living donor transplantation, our results may not be generalized for deceased donor KTRs. Severe acute respiratory syndrome coronavirus 2 antibody levels of the patients were not available. In addition, power analysis for calculating the study cohort was not performed prior to the study, so types I and II errors may have occurred.

CONCLUSION

Our results suggest that transplanting patients with prior COVID-19 infection using standard induction and maintenance treatments and follow-up routines is associated with similar outcomes to those of COVID-19 naive patients.

Ethics Committee Approval: All kidney transplants were performed in accordance with the Declaration of Helsinki and the Declaration of Istanbul. The study was approved by the ethics committee of Istanbul University (Date: 19.08.2021, Approval number: 411645)

Informed Consent: Written informed was taken from all recipients and donors prior to transplantation.

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