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Changes in Kidney Graft Function in COVID-19 Convalescents

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ABSTRACT

Background. Kidney transplant recipients (KTRs) are at an increased risk of infection with severe acute respiratory syndrome coronavirus 2, with mortality from 13% to over 30%. However, data concerning the influence of COVID-19 on long-term graft function in convalescents is lacking. The aim of this study was to evaluate the influence of COVID-19 on graft function at 6 months after recovery.

Methods. A longitudinal controlled study was conducted in a group of 1058 KTRs. Of 180 patients with COVID-19 in the past, 77 KTRs (45 male) with a mean age 50.57 ± 13.37 years, Charlson Comorbidity Index of 3 (median; interquartile range [IQR], 3-5), Fragility Score of 3 (median; IQR, 3-3), and minimum 6 months after acute COVID-19 were included. The most common symptoms were weakness (75.33%), fever (74.03%), cough (51.95%), and loss of appetite (48.05%). Thirty-three patients were hospitalized; none required invasive ventilation therapy, but 16 required oxygen support. The treatment of COVID-19 included antibiotics (38.96%), thromboprophylaxis (25.97%), and nonsteroidal anti-inflammatory drugs, or paracetamol (25.97%).

Results. The median (IQR) values of serum creatinine 3 months before the onset and 6 months after COVID-19 were 1.25 (0.98-1.86) and 1.26 (1.03-1.78) mg/dL (nonsignificant difference); in strata analysis, there were also no differences with regards to patients with higher and lower comorbidity ($3 < \text{Charlson Comorbidity Index} < 3$) and fragility ($3 < \text{Fragility Score} < 3$). Furthermore, creatinine concentration in KTRs and controls did not differ.

Conclusions. In the group of KTRs with a mild course of COVID-19, no negative impact of the infection on graft function was observed 6 months after transplantation.

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has several manifestations. The most common manifestation is respiratory failure, but acute kidney injury is also widespread. Some reports showed evidence of viral tropism to the renal system [1]. The exact mechanism of virus-associated kidney damage is not fully known. The pathophysiology of this phenomenon can be explained by multiple mechanisms. A direct damaging factor may be the binding of the spike protein to *ace2*, endothelial dysfunction, coagulopathy, or cytokine storm. An intermediate cause of renal failure may include the systemic effects of COVID-19, such as volume depletion due to fever or gastrointestinal symptoms, and nephrotoxic medications [2]. Acute kidney injury may be a complication of COVID-19 in kidney transplant recipients (KTRs), not only due to the severity of systemic viral infection and the treatment itself but also due to direct mechanisms like

glomerulopathy, endothelial dysfunction, complement activation, and coagulopathy including thrombotic microangiopathy [3]. Renal impairment in COVID-19 is associated with increased mortality [4]. Depending on the study population, fatality ranges from 13% [5] to over 30% [6–8]. KTRs are a special group at an increased risk of infection due to immunosuppression and preexisting renal impairment. The risk of SARS-CoV-2 infection and complications in KTRs remains

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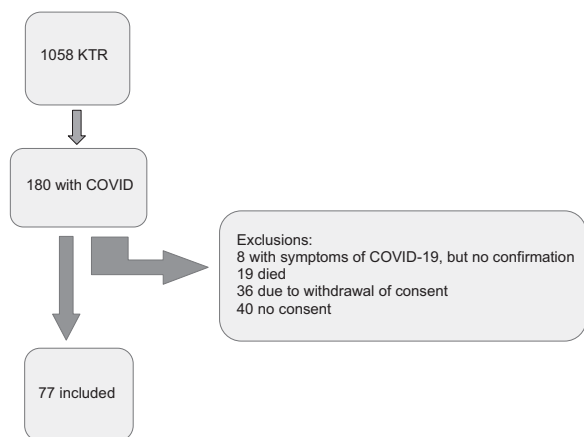


Fig 1. Flowchart of patient recruitment to the study. KTR, kidney transplant recipient.

high, even after widespread vaccination against COVID-19. As our previous studies have shown, the immune response and humoral protection appear in a limited form in only about half of vaccinated KTRs [9,10].

Data concerning the influence of COVID-19 on long-term health consequences in KTRs are scarce. The aim of the study was to evaluate the impact of SARS-CoV-2 infection on graft function at 6 months after recovery.

MATERIALS AND METHODS

Study Population

An observational longitudinal controlled study was conducted in a group of 1058 kidney transplant recipients under the care of our department. They were screened between January 1 and June 1, 2021 for a history of COVID-19. All cases of COVID-19 were diagnosed before the vaccination was initiated. We excluded the following patients: 1. those who did not agree to take part in the study, 2. those in whom COVID-19 was not confirmed with reverse transcriptase polymerase chain reaction tests from nasopharyngeal/oropharyngeal swabs, antigen tests or elevated levels of SARS-CoV-2 IgG antibodies, 3. those who died within 6 months of infection, and 4. those whose creatinine level was not measured in the laboratory of Clinical University Center either before or 6 months after infection (Fig 1). The control group consisted of KTRs who were not diagnosed with COVID-19 of the same age and sex and with similar comorbidities and fragility. Ethics approval for the study was obtained at the Medical University of Gdańsk (NKBBN/2014/2021). The study is part of the COVID-19 in Nephrology project focusing on the nephrological aspects of COVID-19 (COViNEPH).

Data Collection

KTRs were interviewed retrospectively for COVID-19 symptoms and treatment. Other information about demographic and clinical characteristics and comorbidities according to the Charlson Comorbidity Index [11] was obtained from the electronic patient data. The level of clinical frailty was calculated with the Clinical Frailty Score before and 6 months after COVID-19 recovery retrospectively for all participants. The Rockwood Clinical Frailty Scale (FS) is a judgment-based tool with scores from 1 to 9, where 1 = very fit, active, and motivated; 2 = well, no active disease symptoms, active occasionally; 3 = managing

well, medical problems are well-controlled, not regularly active; 4 = vulnerable, not dependent on others for daily help, symptoms limit activities; 5 = mildly frail, more evident slowing, need help in finances, transportation, heavy housework, medications; 6 = moderately frail, need help with all outside activities and with keeping house; 7 = severely frail, completely dependent for personal care; 8 = very severely frail, completely dependent, approaching the end of life; 9 = terminally ill, people with life expectancy <6 months, who are not otherwise evidently frail. Patients scoring 1 to 3 on the FS are defined as not frail. Participants from the control group were screened retrospectively for a non-positive reverse transcriptase polymerase chain reaction SARS-CoV-2 test during the observation period. Creatinine serum concentrations were measured using an enzymatic method during regular visits to the outpatient clinic; estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation formula.

Table 1. Characteristics of the Study Population

Characteristics	COVID-19	Control
<i>n</i>	77	71
Age, years, mean ± SD	50.57 ± 13.37	51.03 ± 14.61
Male sex, <i>n</i> (%)	45 (58.44)	37 (52.11)
Primary nephropathy, <i>n</i> (%)		
Glomerulonephritis	25 (32.9)	19 (33.3)
Pyelonephritis	2 (2.6)	1 (1.8)
Interstitial nephritis	3 (4.0)	2 (3.5)
Congenital kidney disease	4 (5.3)	4 (7.0)
Diabetic nephropathy	2 (2.6)	2 (3.5)
Hereditary nephropathies	13 (17.1)	6 (10.5)
Other or unknown	27 (35.5)	23 (40.4)
No data	1	14
Transplantation vintage, months, median (IQR)	60 (13-110)	72 (34-138)
Donor		
Living, <i>n</i> (%)	7 (9.1)	7 (10.8)
Deceased, <i>n</i> (%)	70 (90.9)	58 (89.2)
No data, <i>n</i>	0	6
Immunosuppression protocol, <i>n</i> (%)		
TAC ± MMF/MPS ± steroids	45 (58.4)	44 (62.0)
CYS ± MMF/MPS ± steroids	17 (22.1)	17 (23.9)
Protocol without steroids	3 (3.9)	1 (1.4)
Protocol without MMF/MPS	11 (14.3)	8 (11.2)
Other	1 (1.3)	1 (1.4)
Baseline proteinuria, <i>n</i> (%)		
8 (10.4)	8 (10.4)	14 (19.7)
No data, <i>n</i>	3	0
Follow-up proteinuria, <i>n</i> (%)		
9 (11.7)	9 (11.7)	16 (22.5)
No data, <i>n</i>	3	2
Baseline FS, <i>n</i> (%)		
=3	65 (84.42)	49 (69.01)
≥3	12 (15.58)	22 (30.99)
Follow-up FS, <i>n</i> (%)		
=3	57 (74.03)	48 (67.61)
≥3	20 (25.97)	23 (32.39)
Baseline CCI, <i>n</i> (%)		
≤3	19 (24.68)	22 (30.99)
≥3	58 (75.33)	49 (69.01)
Follow-up CCI, <i>n</i> (%)		
≤3	19 (24.68)	22 (30.99)
≥3	58 (75.33)	49 (69.01)

CCI, Charlson Comorbidity Index; CYS, cyclosporine; FS, Clinical Frailty Score; IQR, interquartile range; MMF/MPS, mycophenolate mofetil or mycophenolate sodium; TAC, tacrolimus; SD, standard deviation.

Table 2. Creatinine Levels in the Group of Convalescents and Control Before COVID-19 and 6 Months After Infection

	COVID-19 Baseline	Follow-Up	P Value	Control Baseline	Follow-Up	P Value
Creatinine						
Median (IQR)	1.25 (0.98-1.86)	1.26 (1.03-1.78)	.17	1.28 (1.05-1.67)	1.29 (1.05-1.72)	.73
eGFR CKD-EPI						
Median (IQR)	61 (37-77)	58 (40-76)	.51	57 (40-72)	57 (39-68)	.54
CCI						
Median (IQR)	3 (3-5)	3 (3-5)		3 (2-6)	3 (2-6)	
FS						
Median (IQR)	3 (3-3)	3 (3-4)		3 (3-4)	3 (3-4)	
FS						
=3	1.25 (0.98-1.78)	1.26 (1.03-1.78)	.35	1.24 (1.05-1.56)	1.27 (1.08-1.65)	.74
>3	1.24 (0.98-1.94)	1.22 (1.04-2.16)	.19	1.48 (0.94-2.08)	1.36 (1.05-2.15)	.19
CCI						
<3	1.37 (1.09-1.95)	1.54 (1.08-1.83)	.60	1.41 (1.10-1.65)	1.45 (1.14-1.70)	.27
≥3	1.20 (0.92-1.78)	1.22 (1.00-1.78)	.19	1.24 (1.04-1.67)	1.25 (1.01-1.72)	.75

CCI, Charlson Comorbidity Index; eGFR CKD-EPI, estimated glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration equation formula; FS, Clinical Frailty Score; IQR, interquartile range.

Statistical Analysis

Descriptive statistics were used to report the characteristics of patients. Normally distributed values are shown as mean \pm standard deviation and abnormally distributed values as median (interquartile range). The main outcome measure was an increase or decrease in creatinine levels of patients after COVID-19. *t* Tests or Wilcoxon signed rank tests were used to compare continuous variables where appropriate. $P < .05$ was considered statistically significant. Data were evaluated using the STATISTICA (v12.0, Stat Soft Inc, Kraków, Poland) software package.

RESULTS

Patients

Of 1058 KTRs screened, 180 had COVID-19 symptoms in their history. The patient enrollment process is presented in the flow-chart in Fig 1. All included convalescents ($n = 77$) had a creatinine measurement within the 3 months before and 6 months after SARS-CoV-2 infection. The mean (SD) age of the convalescents was 50.57 ± 13.37 years and 45 were male. Nineteen KTRs had no comorbidities (24.68%), despite chronic kidney disease and kidney transplantation (Charlson Comorbidity Index [CCI] < 3). Sixty-five patients were not frail (FS ≤ 3 ; 84.42%). Table 1 shows the detailed characteristics of the study population. The most common reported symptoms of infection during acute COVID-19 were weakness (75.33%), fever (74.03%), cough (51.95%), and loss of appetite (48.05%). Thirty-three patients were hospitalized (42.86%); none required invasive ventilation therapy, but 16 required oxygen support. The treatment of COVID-19 was based on antibiotics (38.96%), thromboprophylaxis with low-molecular-weight heparin (25.97%), and nonsteroidal anti-inflammatory drugs and/or paracetamol (25.97%). In the control group ($n = 71$) the mean age of participants (37 males) was 51.03 ± 14.61 years. Twenty-two patients had a CCI < 3 (30.99%) and 49 had an FS ≤ 3 (69.01%).

Graft Function

There were no significant changes in graft function before and after COVID-19 in either the median level of creatinine (1.25 vs 1.26 mg/dL) or estimated glomerular filtration rate CKD-EPI results (61 vs 58 mL/min/1.73 m²). The differences were also negligible in the control group, with a median creatinine level of 1.28 mg/dL in the beginning and 1.29 mg/dL after 6 months of the observation period. Details are presented in Table 2.

DISCUSSION

To our knowledge, this is one of the first studies to evaluate long-term graft function in KTRs after SARS-CoV-2 infection. Although we know that the serious sequelae of the disease extend beyond the acute phase of COVID-19 [12], we have not seen statistically significant changes in serum creatinine levels in this group of patients.

In fact, most of the publications are mainly based on in-patient cohort studies and are related to the acute phase of the infection. In a paper from the first few months of the pandemic, 45% of patients presented with acute allograft dysfunction, which highlighted the effect of SARS-CoV-2 infection on kidney function. However, the median follow-up time from presentation was only 25 days (interquartile range, 13-38) [13], and the long-term impact of COVID-19 on kidney function was unclear. In the other few published articles, a cohort study of 104 KTRs showed that although allograft function remained stable after acute COVID-19 in most patients, after 6 months 2 were dialysis dependent and 2 had reached the preterminal stage of chronic allograft nephropathy without dialysis [14].

It is worth underlining that graft function remained stable during the COVID-19 infection in the subpopulation of KTRs with the highest comorbidity index (CCI ≥ 3). Moreover, there was no statistically significant change in graft function in the

most frail subpopulation, which scored >3 on the clinical frailty scales (FS > 3). The percentage of patients with FS >3 increased from 15.58% to 25.97% 6 months after COVID-19 infection. That increase points to the necessity of an early start for physiotherapy and the rehabilitation of post-COVID-19 convalescents.

Our study has limitations: this is a single-center study with a small sample size. Therefore, our results need to be validated by larger prospective cohort studies. Second, we had no information on graft function during coronavirus infection. Certainly, some cases of acute allograft dysfunction had to occur during the early phase of infection and shortly after. We also cannot eliminate some degree of underreporting of COVID-19 in KTRs. Thirdly, the greatest limitation was that we had to exclude 36 patients from our analysis because of withdrawal of consent and a lack of serum creatinine measurement in our center. The reason for the dropout of KTRs from our observation was mainly due to the patient's fear before any medical contact during the epidemic. However, because there were no significant differences in age and sex between the study population and all patients excluded from our analysis, we believe that selection bias was unlikely. It would be interesting to compare kidney function with nontransplant recipients with similar degrees of comorbidity and frailty who had COVID-19. Additionally, further studies focused on the long-term outcomes of COVID-19 and monitoring of all patients who survived the infection are needed.

In conclusion, our analysis reveals that in the group of KTRs with a mild course of COVID-19, no negative effects of the infection on graft function were noticed 6 months after recovery.

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