



ORIGINAL ARTICLE

Medicine Science 2022;11(3):1172-5

## The course of COVID-19 in kidney transplant patients and review of the literature

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Received 18 January 2022; Accepted 04 April 2022

Available online 08.08.2022 with doi: 10.5455/medscience.2022.01.013

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### Abstract

It was aimed to investigate the course of coronavirus disease 2019 (COVID-19) in patients with kidney transplants in a single center. Nine COVID-19 patients with kidney transplants were evaluated concerning demographic, physician examination, clinical and laboratory characteristics, and outcome. Patients' mean age was 50.7±9.22 years. Of nine patients, five (55.6%) were male. As accompanying disorders, diabetes mellitus and hypertension were present in two (22.2%) and seven patients (77.8%), respectively. Four (44.4%) patients required hospitalization in the intensive care unit (ICU). The mean length of stay in ICU was 1.67±2.5 days. While three (33.3%) were required for non-invasive mechanical ventilation, four (44.4%) patients needed to be supported with invasive mechanical ventilation. Although five patients (55.6%) were discharged with recovery, four (44.4%) died. In kidney transplant patients, COVID-19 has a high mortality rate. Close follow-up and early treatment of these patients are important.

**Keywords:** COVID-19, kidney transplantation, mortality

### Introduction

Coronavirus-2019 disease (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a serious global threat to human health and has led to the deaths of nearly 6.029.852 individuals from the end of 2019 to the present [1]. Infections tend to be more serious in organ transplant patients, and patients transmit the virus for a longer period of time [2]. Based on the large series investigating COVID-19 disease and kidney transplantation, it has been demonstrated that COVID-19 has a more serious course in such patients, and the admissions to intensive care units (ICU) and mortality rates are higher [3]. In line with this information, we aimed to investigate the course of COVID-19 in kidney transplant patients hospitalized in our facility.

### Materials and Methods

This study was conducted in the university hospital of Medical School at Usak University, between 20<sup>th</sup> March 2020 and 30<sup>th</sup> January 2021. The patients with kidney transplantation with positive SARS-CoV-2 detected through the reverse transcriptase-polymerase chain reaction (RT-PCR) test and followed-up due to COVID-19 disease were included in the analysis. The data of nine patients were obtained from the hospital automation system. The study was approved by the local ethical committee of Usak University School of Medicine. The patients with COVID-19 admitted to the pandemic clinics and intensive care unit (ICU) in our facility had undergone kidney transplantation in other centres. The patients were evaluated in terms of age, gender, height, weight, body mass index (BMI), the existence of accompanying comorbid diseases, and type and duration of the transplantation. The patients' complaints at the time of admission to the hospital, vital signs on admission, such laboratory findings as biochemistry, blood gas, complete urinalysis, hemogram, procalcitonin, lactate dehydrogenase (LDH), D-Dimer, ferritin, and hemostasis parameters on the first admission to the hospital, thorax computed tomography (CT) findings, immunosuppressive therapy

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administered to each patient, COVID-19 treatment, antibiotic therapy, need for renal replacement, length of stay in the hospital and ICU, the requirement for non-invasive and invasive mechanical ventilation, and mortality rates were evaluated retrospectively.

### Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 22.0 software package was used to perform the statistical analyses (SPSS Inc., Chicago, IL, USA). The distributions within the normal limits were determined through the Kolmogorov-Smirnov and Shapiro-Wilk tests. The data were expressed as mean, frequency, and percentages.

### Results

The mean age of nine patients was calculated as 50.7±9.21 years. Of nine patients, five (55.6%) and four (44.4%) were male and female, respectively. The mean BMI scores were 25.82±5.21 kg/m<sup>2</sup>. As accompanying disorders, there was diabetes mellitus (DM) in two (22.2%) and hypertension (HT) in seven (77.8%) patients. Given the tabulation of other accompanying disorders, we detected that there were two (22.2%) patients with heart disease, two (22.2%) with chronic obstructive pulmonary disease (COPD), one (11.1%) patient with asthma, and one (11.1%) patient with familial Mediterranean fever (FMF). The etiologies of kidney diseases detected were as follows: HT in four (44.4%) patients, DM, and HT in two (22.2%), FMF in one (11.1%), pyelonephritis in one (11.1%), and unknown etiology in one (11.1%) patient. The mean transplantation time was 7.63±4.31 years. Of nine patients, seven and two patients had a history of transplantation from a related living donor and cadavers, respectively.

As to the symptoms, there were seven (77.8%) patients with shortness of breath, three (33.3%) with fever, six (66.7%) with fatigue, one (11.1%) with diarrhea, and seven (77.8%) with cough. As the most common symptoms, shortness of breath and cough were observed. Seven (77.8%) patients were detected to have respiratory distress on admission. In terms of the laboratory findings, four (44.4%) patients displayed lymphopenia, and five

(55.6%) were with increased LDH. The data of the laboratory findings are presented in Table 1. The patients were also evaluated in terms of disease severity. The patients with mild clinical symptoms without dyspnea or any sign of viral pneumonia on thorax CT findings were defined as those with mild disease. However, those with the symptoms like fever and cough, dyspnea, and signs of viral pneumonia on thorax CT findings were categorized as those with moderate disease, and the cases requiring oxygen support on admission and bilateral diffuse involvement on thorax CT were with severe disease. Considering the CT findings and clinical findings; mild COVID-19 involvement was found in one patient, moderate and severe COVID-19 involvements were also determined in five and three patients, respectively. Of these patients, seven exhibited the classical CT findings of COVID-19 infection, and the probable CT findings of COVID-19 disease were found in one patient. PCR test findings of eight (88.9%) patients were positive. One patient with a negative PCR test was considered to have COVID-19 based on thorax CT findings. Although three patients (33.3%) developed acute kidney injury during the hospitalization, the renal replacement therapy was administered only in one patient. Additionally, seven (77.8%) patients required oxygen support, and four (44.4%) patients were also required for the hospitalization in ICU. Considering the mean length of stay in ICU and the mean hospitalization time, the mean rates were detected as 1.67±2.5 days and 10.33±8.19 days, respectively. Although the need for invasive mechanical ventilation developed in four (44.4%) patients, three (33.3%) patients showed requirements for non-invasive mechanical ventilation. While five patients (55.6%) were discharged from the hospital with recovery, four (44.4%) patients (all male) died within the study period, each was hospitalized in ICU and followed up through intubation. Of these patients, the first (60 years) patient was with COPD and severe lung involvement on thoracic CT; the second (49 years) having coronary artery disease (CAD) and HT displayed severe lung involvement; the third was a 58-year-old individual with CAD and HT along with moderate lung involvement; however, the fourth (43 years) with HT had moderate lung involvement and received hemodialysis treatment. The laboratory findings, such as lymphopenia, and elevation in CRP, D-dimer, and LDH were found in all these patients.

**Table 1.** Laboratory Findings of Patients Undergoing Renal Transplantation

	1	2	3	4	5	6	7	8	9
Age (years)	50	60	49	58	62	51	32	51	43
Gender	F	M	M	M	F	M	F	F	M
BMI (kg/)	25.00	22.50	23.90	27.00	19.50	25.80	22.90	38.00	27.80
Basal creatinine value (0.7-1.3 mg/dL)	1.02	1.47	1.05	1.22	1.53	1.54	0.79	0.95	2.54
Creatinine value on admission (0.7-1.3 mg/dL)	0.98	1.22	1.01	1.42	3.98	1.34	1.09	1.18	6.31
GFR on admission (90-120 mL/min)	67.76	64.04	86.93	54.06	11.44	60.90	67.11	53.36	9.90
Creatinine value during follow up (0.7-1.3 mg/dL)	1.10	1.78	Unknown	1.04	0.94	1.31	Unknown	0.83	3.75
WBC (4-10.5 10 <sup>3</sup> /μL)	6.09	10.16	4.18	5.50	11.44	6.35	7.48	6.48	6.94
ALC (0.8-4 10 <sup>3</sup> /μL)	1.55	0.46	0.59	1.03	1.21	1.67	0.51	1.12	0.37
Hgb (14-18 g/dL)	9.60	10.80	14.30	12.80	13.10	14	10.70	15.10	9.80
LDH(100-250 U/L)	478	484	Unknown	495	201	184	180	371	345
CRP (0.1-5 mg/L)	92.60	165.70	81.60	39.60	53.40	2.30	29.70	44	85.10
D-Dimer (0-550 ng/mL)	1791	4381	867.30	3398	1216	505	1684	368.9	34.50
Ferritin (18.5-306 μg/L)	217	Unknown	993.20	187.40	1650	331.30	31.20	444.10	7

ALC: Absolute lymphocyte count, BMI: Body mass index, CRP: C-reactive protein, F: Female GFR: Glomerular filtration rate, Hgb: Hemoglobin, LDH: Lactate dehydrogenase, M: Male, WBC: White blood cell

All hospitalized patients received a combined treatment of favipiravir, low-molecular-weight heparin (LMWH), and corticosteroid against COVID-19 infection. As well as one patient administered with immune plasma therapy, eight (88.8%) were detected to receive antibiotic treatment.

Patients' immunosuppression treatment modalities administered before the hospitalization were detected to be as follows: Three (33.3%) patients were treated with mycophenolic acid, tacrolimus, and prednisolone, one with mycophenolic acid, sirolimus, and prednisolone, three (33.3%) with tacrolimus and prednisolone, one with cyclosporine and prednisolone, and one patient also with

mycophenolic acid and prednisolone. During the treatment period, the treatment regimes with mycophenolic acid and cyclosporine were found to be discontinued in four patients and one patient, respectively. The reason of cyclosporine discontinuation was the patient could not tolerate the drug because of nausea and vomiting. In two patients, however, the existing medications were continued. While the treatment with prednisolone was continued in two patients at the same dose, the treatment was changed into a regime with iv methylprednisolone in seven patients. The methylprednisolone treatment was given to the patients at a dose of 40-80 mg/day.

**Table 2.** Mortality rates in studies performed in different centers

The centers where the study was performed	Study Authors/References	Patients' Number	Number of Dying Pati-ents	Mortality(%)
A retrospective study invol-ving 34 centers in Turkey	Oto OA, Ozturk S, Turgutalp K, Arici M, et al. Predicting the outcome of COVID-19infection in kidney transplant recipients. <i>BMC Nephrology</i> (2021) 22:100	109	14	12.8
Montefiore Medical Center (Bronx, New York, USA)	Akalın E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. <i>N Engl J Med</i> 2020; 382:2475-2477	36	10	28
Abrishami et al. (Iran)	Abrishami A, Samavat S, Behnam B, et al. Clinical Course, Imaging Features, and Outcomes of COVID-19 in Kidney Transplant Recipients. <i>Euro-pean Urology</i> 78 (2020); 281-286	12	8	66.7
Sánchez-Álvarez et al. (Spain)	Sánchez-Álvarez JE, Fontán MP, Martín CJ, et al. Status of SARS-CoV-2 infection in patients on renal replacement therapy. Report of the COVID-19 Registry of the Spanish Society of Nephrology (SEN). <i>Nefrologia</i> . 2020;(x x).	122	53	43
Ravanan et al. (England)	Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: a national cohort study. <i>Am J Transplant</i> . 2020. doi:10.1111/ajt.16247	489	128	26
Cravedi et al. (USA-Italy-Spain)	Cravedi P, Mothi SS, Azzi Y, et al. COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium. <i>Am J Transplant</i> . 2020;(June):1-9.	144	46	32
Kates et al. (USA)	Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: A multi-center cohort study. <i>Clin Infect Dis</i> . 2020.	318	57	18
Lubetzky et al. (New York, USA)	Lubetzky M, Aull MJ, Craig-Schapiro R, et al. Kidney allograft recipients, immunosuppression, and coronavirus disease-2019: a report of consecutive cases from a New York City transp-lant center. <i>Nephrol Dial Transplant</i> . 2020;35(7):1250-1261.	39	7	18
Demir et al. (Istanbul, Turkey)	Demir E, Uyar M, Parmaksiz E, et al. COVID-19 in kidney transplant recipients: A multicenter experience in Istanbul. <i>Transpl Infect Dis</i> . 2020;(June):1-9.	40	5	13
Bossini et al. (Brescia, Italy)	Bossini N, Alberici F, Delbarba E, et al. Kidney transplant patients with SARS-CoV-2 infection: The Brescia Renal COVID task force experien-ce. <i>Am J Transplant</i> . 2020;(June):1-11.	42	15	36
Mohamed et al. (London, Eng-land)	Mohamed IH, Chowdary PB, Shetty S, et al. Outcomes of Renal Transplant Recipients With SARS-CoV-2 Infection in the Eye of the Storm. <i>Transplantation</i> . 2020;Publish Ah.	25	9	36
Elias et al. (Paris, France)	Elias M, Pievani D,Randoux C, Louis K , et al. COVID-19 Infection in Kidney Transplant Recipients: Disease Incidence and Clinical Outcomes. <i>JASN</i> 31: 2413–2423, 2020.	66	16	24

## Discussion

Given the distribution of the cases with COVID-19, the rates of male patients and mean ages are seen to be higher among solid organ transplant recipients, compared to the normal population [4,5]. In a study investigating 12 kidney transplant patients diagnosed with COVID-19 from Iran, the rates of male patients and mean age were stated as 75% and 47.66±1.35 years (ranging between 29-66 years) [6]. However, in another cohort study including 229 kidney

transplant patients diagnosed with COVID-19 in New York, the proportion of both genders was reported as 62%, and the median age was measured as 59 years (range between 49-68 yrs) [7]. In the multicenter study investigating 109 hospitalized kidney transplant patients diagnosed with COVID-19 from Turkey, 57.8% of the patients were male, and the mean age was reported as 48.4±12.4 years [8]. In our study, however, the mean age of nine patients was 50.67±9.21 years, and five (55.6%) and four (44.9%) patients were male and female, respectively. In terms of mean age level

and gender difference, there was a male predominance among our patients, and the mean age level was also consistent with the findings reported in the literature. And according to registry report of Turkish Society of Nephrology in 2020, there is a male predominance (%56) among prevalent kidney transplant patients [9]. Heart disease, HT, DM, obesity, and chronic kidney disease (CKD) have been reported among the common accompanying diseases [7-8,10-11]. In terms of accompanying diseases in our study, seven (77.8%) and two (22.2%) patients had HT, and DM, respectively. The distribution of other comorbidities was also as follows: Two (22.2%) patients had heart disease, and two (22.2%) were with COPD. The mean BMI scores of nine patients were  $25.82 \pm 5.21$  kg/m<sup>2</sup>. Of nine patients, five had a BMI score of  $\geq 25$  kg/m<sup>2</sup>. A previous study based on the French solid organ transplant (SOT) registry demonstrated that obesity is a risk factor for the development of severe disease [10].

Additionally, acute kidney injuries (AKI) developed in three (33.3%) of our patients. Two of our patients developing acute kidney injuries died, and one of the two patients had to receive renal replacement therapy due to acute kidney injury. The relatively increased risk of acute kidney injury, requirements for dialysis, hospitalization in ICU, and mortality was reported in kidney transplant patients compared to other patients [3]. In recent multi-center studies including a high number of patients, the rate of kidney transplant patients with COVID-19 and developing AKI was stated to be 42.2-52% [8-10]. On the other hand, in another single-center study with 20 kidney transplant patients from Italy, the incidence of AKI was found as 30% [12].

Based on the literature, lymphopenia, and elevated levels of CRP and LDH were reported as the common laboratory findings in kidney transplant patients [5,7-8,10-11]. In our study, in four of the deceased patients, it was found that the levels of CRP and LDH were elevated, and three had lymphopenia.

The mortality rate in kidney transplant patients due to COVID-19 is higher than that in the normal population and varies between 12.8 and 67% in studies performed in different centers [5-8,10-14]. In our study, the mortality rate was found as 44.4% with the deaths of four patients, and the findings are summarized in Table 2. In a multi-centric study conducted in Turkey, the mortality rate was reported as 12.8% in kidney transplant patients, and the rate was stated as 2.49% in the general population [8]. We consider that the reason for the higher mortality rate was associated with the low number of our participants, and our study is of a single-centered design; additionally, kidney transplantations cannot be performed in our center, and the patients included in the study received the post-transplant followed-ups in the units where the kidney transplants had been carried out. The patients undergoing kidney transplants and followed-up in other centers after the transplants were admitted to our hospital due to COVID-19 infection. In another study including a small number of participants (n=12) from Iran, eight patients were reported to die, and the mortality rate was found as 66.7% [6]. However, the mortality rates in different studies including the number of patients  $\leq 20$  differ between 25-30% [5,12-14].

In our study, mycophenolic acid and cyclosporine were discontinued in four patients and one patient, respectively. In addition, two patients kept on receiving their current medications. In previous

studies, although anti-metabolite medications were discontinued in 68-93% of the cases, the calcineurin inhibitors were reported to be discontinued, or the doses were reduced in 13.9-28.7% of the cases [7,10-11]. Such treatments modalities differ from one country to another and even from one center to another.

## Conclusion

In both previous studies and our study, it was seen that COVID-19 infection has higher mortality in the kidney transplant group with accompanying comorbid diseases.

## Conflict of interests

*The authors declare that there is no conflict of interest in the study.*

## Financial Disclosure

*The authors declare that they have received no financial support for the study.*

## Ethical approval

*The study was approved by the local ethical committee of Usak University School of Medicine. Ethical committee approval number is E.22949*

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