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COVID-19 Disease in Kidney Transplant Recipients

Enfermedad por COVID-19 en receptores de trasplante renal

Abdullah Simsek[1], Nizameddin Koca[2]

ABSTRACT

Aim: Coronavirus infection can lead to severe acute respiratory distress syndrome. Information on COVİD-19 infection in patients with kidney transplants (KT) is lacking yet. In our study, clinical, radiological, laboratory features and clinical course of COVİD-19 infection in these patients were investigated. **Methods**: We retrospectively investigated KT recipient patients with COVID-19 diagnosed between March 15, 2020, and December 15, 2020. Clinical, radiological, laboratory features and clinical course of COVID-19 infection in these patients were recorded. **Results:** We identified 23 KT recipient patients with COVID-19 infection.

Eighteen KT patients (78.3%) had positive reverse transcription polymerase chain reaction (RT-PCR) results for COVID-19, 5 patients (21.7%) were negative. Twelve KT patients (52.2%) were male and 11 (47.8%) were female. Fifteen of the KT patients (65.2%) had comorbidity. Thorax computed tomography showed infiltrations in 21 KT patients (91.3%). There were 14 patients (60.8%) with glomerular filtration rate (GFR) below 60 ml/min, who were considered acute renal failure. One patient needed plasma treatment, 2 needed hemodialysis. Mortality rate was 26%. **Conclusion:** COVİD-19 infection causes kidney failure in patients with kidney transplant. Mortality is high in kidney transplant patients with COVİD-19 infection. Suggested poor prognostic factors increasing death risk are being 60 years or older, recent transplantation, low oxygen saturation level, high WBC count, high CRP level, high troponin level, high D-dimer level, high creatinine level, low GFR value, low sodium level.

KEYWORDS: kidney transplantation; COVID-19; clinical course

RESUMEN

Objetivo: La infección por coronavirus puede conducir al síndrome de dificultad respiratoria aguda grave. Aún falta información sobre la infección por COVID-19 en pacientes con trasplante renal (TR). En nuestro estudio, se investigaron las características clínicas, radiológicas, de laboratorio y el curso clínico de la infección por COVID-19 en estos pacientes. **Métodos:** investigamos retrospectivamente a los pacientes receptores de TR con COVID-19 diagnosticados entre el 15 de marzo de 2020 y el 15 de diciembre de 2020. Se registraron las características clínicas, radiológicas, de laboratorio y el curso clínico de la infección por COVID-19 en estos pacientes. **Resultados:** Identificamos 23 pacientes receptores de TR con infección por COVID-19. Dieciocho pacientes con TR (78,3%) tuvieron resultados positivos de la reacción en cadena de la polimerasa con transcripción inversa (RT-PCR) para COVID-19, 5 pacientes (21,7%) tuvieron resultados negativos. Doce pacientes con TR (52,2%) eran hombres y 11 (47,8%) mujeres. Quince de los pacientes con TR (65,2%) presentaban comorbilidad. La tomografía computarizada de tórax mostró infiltraciones en 21 pacientes

1) Department of Chest Diseases, Saglık Bilimleri University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey
2) Department of Internal Medicine, Saglık Bilimleri University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

Correspondencia:
Abdullah Simsek
jorgericof@yahoo.com
abdullahsimsek1@yahoo.com.tr

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con TR (91,3%). Hubo 14 pacientes (60,8%) con tasa de filtración glomerular (TFG) por debajo de 60 ml/min, que se consideraron insuficiencia renal aguda. Un paciente necesitó tratamiento con plasma, 2 necesitaron hemodiálisis. La tasa de mortalidad fue del 26%. **Conclusión**: La infección por COVİD-19 provoca insuficiencia renal en pacientes con trasplante renal. La mortalidad es alta en pacientes trasplantados de riñón con infección por COVİD-19. Los factores de mal pronóstico sugeridos para aumentar el riesgo de muerte son tener 60 años o más, trasplante reciente, nivel bajo de saturación de oxígeno, recuento alto de glóbulos blancos, nivel alto de PCR, nivel alto de troponina, nivel alto de dímero D, nivel alto de creatinina, valor bajo de GFR, nivel bajo de sodio.

PALABRAS CLAVE: trasplante renal; COVID-19; curso clínico

INTRODUCTION

COVID-19 is highly contagious and in some cases, it can progress rapidly to severe acute respiratory syndrome. Patients with COVID-19 infection over the age of 60 were reported to have a higher mortality rate (1,2), and the case fatality rate was close to 8-10% (1,2). Comorbidities cause increased mortality with multiorgan dysfunction (3,4).

The effect of chronic immunosuppression on the course of COVID-19 infection is unknown.

Despite widespread concerns about the high prevalence and potential for severity of COVID-19 among transplant recipients, data on these patients are lacking. There are currently few studies on COVID-19 infection in kidney transplant (KT) recipients.

In this study, clinical and radiological laboratory findings of patients with KT diagnosed with COVID-19 infection in our clinic were retrospectively analyzed.

METHODS

We retrospectively investigated KT recipient patients with COVID-19 diagnosed between March 15, 2020, and December 15, 2020. For this study, approval was obtained from the clinical research ethics committee of the higher specialized education and research hospital. Ethics committee approval code: 2011-KAEK-25 2020/12-13.

Clinical, radiological, laboratory features of COVID-19 infection in these patients were recorded.

Treatments given and responses to treatment, length of stay (LOS) in hospital, whether convalescent plasma therapy was needed, the need for dialysis, intensive care and intubation was determined. And mortality rates were also recorded.

Radiological involvement of the lung was graded as mild, moderate, or severe.

Glomerular filtration rate (GFR) was calculated by MDRD formula.

Patients' follow-up for 3 months after discharge were also examined, and it was also recorded whether the COVID-19 infection had recurred or if there were complications due to COVID-19 infection.

RESULTS

Between March 2020 and December 2020, 23 KT patients diagnosed with COVID-19 and treated in our hospital were included in our study. Five of the patients (21.8%) underwent outpatient treatment and follow-up and 18 patients (78.2%) were hospitalized.

Donor characteristics

Eighteen of KT donors were deceased, 5 were living. All 5 living donors were relatives of recipients, of which 1 was father, 1 mother, 1 husband, 1 wife, 1 daughter.

Kidney transplant recipients patients with COVID-19 infection

Twelve of the 23 KT patients (52.2 %) were male and 11 (47.8%) were female.

Kidney transplant patients' ages ranged from 29 to 73. Mean age of them was 48.2 +/- 13.8 years (mean +/- SD).

Time to diagnosis of COVID-19 after KT ranged from 1 year to 16 years (median 6.1 years); 8.7% (2 patients) were diagnosed during the first year after transplant. Fifteen patients (65.2%) had comorbidity, while no comorbidities were observed in 8 (34,8%) patients. Comorbid diseases and their incidence in KT patients are shown in **Table 1.** Twenty-one patients (91.3%) had complaints in the anamnesis and physical examination, and only 2 (8.7%) were asymptomatic.

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Table 1. Comorbid diseases and their incidence in renal transplant patients at diagnosis

	HT	DM	CAD	COPD	Liver Ca	FMF	Chronic DVT	Neurogenic bladder	Ankylosing spondylitis	Scoliosis
n (%)	9 (39,1)	7 (30,3)	3 (13)	2 (8,7)	1 (4,3)	1 (4,3)	1 (4,3)	1 (4,3)	1 (4,3)	1 (4,3)

Ca: Carcinoma; **CAD:** Coronary Artery Disease; **COPD:** Chronic Obstructive Pulmonary Disease; **DM:** Diabetus Mellitus; **DVT:** Deep Venous Thrombosis; **FMF:** Familial Mediterranean Fever; **HT:** Hypertension

One of the asymptomatic patients was found to have a positive RT-PCR results for COVID-19, which was required during the international departure procedure, and the other routinely requested PCR test was positive before the surgical correction of umbilical hernia. Incidence of other complaints is shown in the **Table 2.**

Table 2. Rate of complaints detected in kidney transplant patients with COVID-19 infection at diagnosis

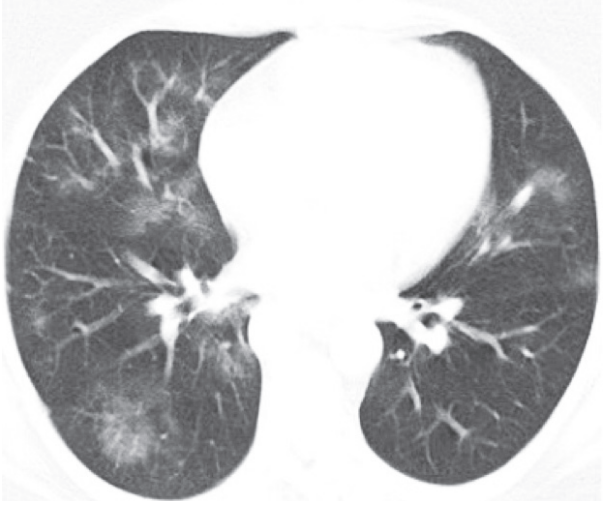
	Cough	Dyspnea	Fatigue	Fever	Joint Pain	Anorexia	Sore Throat	Myalgia	Headache	Diarrhea	Nasal congestion	Taste inability+ Anosmia	Uncons-ciousness
n (%)	11 (47,8)	7 (30,4)	7 (30,4)	6 (26,1)	4 (17,4)	2 (8,7)	2 (8,7)	2 (8,7)	2 (8,7)	2 (8,7)	1 (4,3)	1 (4,3)	1 (4,3)

Fourteen patients (60.9%) had good general physical condition, 6 (26.1%) had moderate and it was poor in 3 (13%). Oxygen saturation values measured with pulse oximeter in 10 patients (43.5%) were 93% or below, and in the remaining (56.5%) they were normal. 18 patients (78.3%) had positive RT-PCR results for COVID-19; 5 patients (21.7%) had negative tests. In those whose PCR test was negative, the diagnosis of COVID-19 was made due to the presence of clinical and especially typical tomographic findings. Laboratory findings of KT patients with COVID-19 are shown in **Table 3**.

Thorax CT showed infiltrations in 21 KT patients (91.3%); 2 patients (8.7%) had no infiltrations. Radiological involvement was mild in 9 patients (42.9%), moderate in 7 patients (33.3%), and severe in 5 patients (23.8%). Bilateral pulmonary infiltrates were seen in 17 of 21 patients (81%). Ipsilateral pulmonary infiltrates were observed in 4 patients (19%), 3 of these were in the right lung and 1 was in the left lung (**Figure 1**, that was obtained from the archive of our hospital).

There were 14 patients (60.8%) with GFR below 60 ml/min, who were considered in acute renal failure (ARF). GFR of the patients at the time of admission to the hospital is shown **Table 4**. Of the

Figure 1. A kidney transplant recipient patient with COVID-19 Thorax CT: bilateral ground glass opacities (from archive of our hospital)



23 patients, 7 already had previously diagnosed chronic renal failure. Therefore, ARF was detected in 7 (43.7%) of 16 patients with previously normal renal function and in all 7 (100%) patients with pre-existing chronic renal failure. The antiviral treatment given to KT patients with COVID-19 is shown in **Table 5**. The number and rates of laboratory tests that return to normal levels with treatment in KT patients with COVID-19 is listed in **Table 6.**

Table 3. Laboratory findings of kidney transplant patients with COVID-19 at diagnosis

	Minimum	Maximum	Mean	Patient number higher than normal n (%)	Patient number lower than normal n (%)
WBC count (/µL)	4420	20200	9141	7 (30,4)	
Platelet count (/µL)	83000	368000	207304	-	3 (13)
Hemoglobin (g/dl)	8,6	20	12,5	1 (4,3)	11 (47,8)
Lymphocyte count (/µL)	530	3050	1116	-	12 (52,2)
Lymphocyte %	2,8	28,1	13,4	-	17 (73,9)
Leucocyte count (/µL)	3,5	18,7	7,4	5 (21,7)	-
Leucocyte %	59,4	93	79,4	16 (69,6)	-
Eosinophil count (/µL)	0,00	0,16	0,03	-	-
Eosinophil %	0	3	0,36	-	-
Basophil count (/µL)	0	0,21	0,02	-	-
Basophil %	0,1	1	0,21	-	-
CRP (mg/L)	3,1	199	48	20 (87)	-
Ferritin (ml/ng)	19	7265	1009,6	14 (60,9)	-
D-dimer (µg/mL)	0,19	16,3	1,7	11 (47,8)	-
LDH (IU/l)	16	523	291,6	8 (34,8)	6 (26,1)
Troponin (ng/ml)	3	98,2	29,6	11 (47,8)	-
Fibrinogen (mg/dl)	252	900	469,1	15 (71,4)	-
Creatinine (mg/dl)	0,49	6	2,3	12 (52,2)	-
AST (IU/L)	7	58	21,5	1 (4,3)	-
ALT (IU/L)	5,4	37	16,3	-	-
Sodium (mEq/L)	116	150	134,5	1 (4,3)	10 (43,5)
Potasium (mEq/L)	3,48	5,95	4,71	1 (4,3)	3 (3)

Table 4. Glomerular Filtration Rates (GFR) of the kidney transplant patients with COVID-19 at diagnosis

	GFR ≥ 90ml/min	GFR: 60-89ml/min	GFR: 30-59ml/min	GFR: 15-29ml/min	GFR<15ml/min
n (%)	3 (13)	6 (26)	5 (21,7)	4 (17,4)	5 (21,7)

Table 5. The antiviral treatment given to kidney transplant patients with COVID-19 infection

	Favipravir	**HCQ**	**HCQ + Favipravir**	**Tocilizumab**
n (%)	8 (34,7)	5 (21,7)	5 (21,7)	1 (4,3)

HCQ: Hydroxychloroquine

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Table 6. The number and rates of laboratory tests that return to normal levels with treatment in kidney transplant patients with COVID-19

	WBC	Lymphocyte count	CRP	Ferritin	D-dimer	LDH	Fibrinogen	Sodium
n (%)	4 (57,1)	2 (16,6)	9 (45)	4 (28,5)	5 (45,4)	6 (75)	6 (40)	6 (60)

Hemodialysis (HD) was performed in one patient who developed acute renal failure, HD was planned for another patient but that patient died before HD. Clinical course of KT patients with COVID-19 while they were being treated in hospital is shown in **Table 7**. Convalescent plasma treatment was given to 1 patient (4.3%), and six patients died (None of them received treatment for rejection or recent increase in immunosuppression for any reason). Mortality rate was 26%. Four (66.6%) of the deceased patients and 3 (17.6%) of the living patients were 60 years or older. Clinical and laboratory features of deceased and survivor patients is shown in **Table 8**. Length of stay in the hospital ranged from 1 to 30 days. Average LOS was 9.4 days.

During the 3-months follow-up after COVİD-19 infection, it was learned that acute renal failure, which developed due to COVİD-19 infection in one of the patients, continued after discharge and therefore a second KT had to be performed in an external center. One patient had to be hospitalized in the service several times since renal failure continued after discharge. And in another patient, the COVID-19 infection recurred 3 months after the first COVİD-19 infection. In this recurrent infection, the disease was clinically and radiologically much severe than the first episode (RT-PCR result for COVID-19 was positive in both infections).

Table 7. Clinical course of kidney transplant patients with COVID-19 while being treated in hospital

	Convalescent Plasma treatment	Need for hemodialysis	Need for intensive care	Intubation	Exitus
n (%)	1 (4,3)	2 (8,7)	6 (26)	6 (26)	6 (26)

Table 8. Clinical and laboratory features of deceased and living kidney transplant patients with COVID-19

	Age (Years)	Transplant Time (Years)	Sat O2 (%)	WBC Count (/µL)	Plt Count (/µL)	Lymp Count (/µL)	CRP (mg/L)	Ferritin (ml/ng)	LDH (IU/l)	Trop (ng/ml)	D-dimer (µg/mL)	Cre (mg/dl)	Na (mEq/L)	K (mEq/L)	GFR ml/min
Deceased (Averages)	60.5	4.1	83.4	11000	168500	1206	106.2	1255	399	67.5	4.8	3	129	5.1	35.5
Survivor (Averages)	43.8	6.8	95.1	8460	221000	1084	27.5	922	253	16.2	0.5	2	136	4.5	51

Cre: Creatinine; **CRP:** C-Reactive Protein; **GFR:** Glomerular Filtration Rate; **K:** Potassium; **LDH:** Lactic Dehydrogenase; **Lymp:** Lymphocyte; **Plt:** Platelet; **Transplant:** Transplantation; **Trop:**Troponin; **WBC:** White Blood Cell

DISCUSSION

SARS-CoV-2 is more contagious than other viruses among populations.

Solid organ transplant recipients are known to be vulnerable to several respiratory virus infections, such as influenza[5] due to a weakened T-cell mediated immune response.[6] The Centers for Disease Control and Prevention include SOT recipients amongst patients at increased risk for severe illness from SARS-CoV-2.[7]

Since this virus is new, we do not have yet clear information about the course of the disease in immunosuppressed patients, the efficacy of the treatments applied in nontransplant patients and the effects of immunosuppression on the course of the disease.[8-9] There is no evidence yet that immunosuppression in COVID-19 infection will adversely affect the course of the disease. Vishnevetsky et al. showed that MERS and Respiratory Syndrome Coronavirus 1 (SARS), which are in the same family as COVID-19, do not increase the poor prognosis of the disease.[10-12] In fact, it is thought that immunosuppression may prevent excessive cytokine release in the case of hyperinflammation.[13] COVID-19 presentation amongst SOT recipients has ranged from mild upper respiratory infection to severe acute respiratory distress and death.[14] In the general population, the disease has been found to be severe in the middle age group and patients with comorbid diseases, whereas such information is still lacking in SOT patients.[15]

Fernandez-Ruiz *et al*.[16] reported on 18 SOT recipients with COVID-19 that the case fatality rate was 27.8% (5/18). They suggests that SARS-CoV-2 infection had a severe course in SOT recipients.[16] Nacif et al analyzed overall SOT cases, found the case fatality rate was 25.6% (10/39).[17] They demonstrated that SOT populations have a higher mortality risk than that in nontransplanted populations. In the studies of Nacif *et al*., Verity et al and Glynn, a significant increase in fatality risk among SOT patients older than 60 years was observed.[1-2, 17]

Kidney transplant patients are seen at high risk for COVİD -19 infection due to immunosuppression and comorbid diseases. [18] Data on COVID-19 in SOT, LT, and KT patients are scarce.[17] A case series showed that children with LTs were not at a higher risk for severe SARS-CoV-2 infection despite being immunosuppressed.[19]

Most of our KT recipients patients with COVID-19 infection had comorbidity (65.2%). Hypertension (39.1%) and DM (30.3%) were the most common comorbidities. In the literature, the presence of comorbidities (older age, HT, DM and cardiovascular disease) that cause immunosuppression in these patients except renal failure has been shown.[20-22] 8.7 % of patients had no complaints in the anamnesis and signs, 91.3% had complaints. While cough (47.8%), dyspnea (30.4%) and fatigue (30.4%) were the most common complaints, fever was detected at a rate of 26.1%. Most of the patients (60.9%) were in good general condition and had normal oxygen saturation levels (56.5%) when they were admitted to the hospital.

In this study, the most frequent abnormal laboratory findings were high CRP level (%87), low percentage of lymphocytes (73.9%), high fibrinogen level (71.4%), high ferritin level (60.9%). Thrombocytopenia was seen in 3 patients (13%). Leukocytosis was detected in 69,6% of patients. Radiological involvement was detected in most of the patients (91.3%), and it was bilateral in most (81%). Infiltration was severe in 5 patients (23.8%). Favipravir or/and HQ treatment was used to treat KT patients with COVID-19 in this study.

Acute kidney injury is common in patients with COVID-19 due to multiple factors, including reduced renal perfusion, multiorgan failure, and cytokine storm.[23] Although rates vary, studies have shown that these patients develop a high rate of ARF.[21-24] We found ARF in 60.8% (14 patients) of the patients (determined by GFR). This is a very high rate and is consistent with the literature. Five (21.7%) of them had GFR <15 ml/min indicating very severe renal failure. Two patients required hemodialysis. In our study, the detection of ARF in 43.7% of patients with previously normal renal functions and in all (100%) patients with pre-existing chronic renal failure indicates that COVİD -19 infection is an important condition that threatens kidney function in renal transplant recipients. Kidney transplantation had to be performed again in one of these patients in the follow-up after discharge, while another had to be followed closely due to renal failure after discharge.

Rates of laboratory tests that return to normal levels with treatment, respectively were; LDH (75%), sodium (60%), WBC count (57.1%), CRP and D-dimer (45%). Based on these results, we think that besides acute phase reactants, improvement in sodium level may also be an important marker in showing the response to treatment. One patient (4.3%) required treatment with convalescent plasma, 6 patients (26%) who needed intensive care unfortunately died. Our mortality rate was 26% in hospitalized KT recipients with COVID-19. This ratio is consistent with previous literature findings. Cravedi et al. found mortality rate of 32% (23) and

other reports observed death rates between 24% and 30%.[18, 25-30]

While the average age of the patients who died was 60.5 years old, that of the surviving patients was 43.8. Five patients had comorbidities. The median transplant recipient time before COVID-19 disease was 6.8 years for living patients and 4.1 years for those who died, meaning those with a more recent transplant were more likely to die. The average O2 saturation level of the patients who died was 83.4% and in those who survived it was 95.1%. The mean GFR value of the patients who died was 35.5 ml/min, while that of the surviving patients was 51 ml/min. GFR value was <30 ml/min in 4 (66.6%) of the patients who died, ie severe-very severe renal failure was present. While the mean WBC level was as high as 11000/μL in the deceased, it was at the normal level in the survivors (8460/μL). Creatinine value was higher in the deceased. While the average level of CRP was 27,5mg/L in the living patients, it was very high as 106,2 mg/L in the deceased patients. In addition, the mean value of troponin (67,5 ng/ml) in deceased patients was considerably higher than the value in the survivors (16,2 ng/ml). While the mean D-dimer level in deceased patients was as high as 4.8μg/mL, it was normal (0.5μg/mL) in surviving patients. The mean Ferritin level was also higher in the deceased (1255ml/ng) than in the survivors (922ml/ng). Mean sodium value of those who died was significantly lower (129mEq/L) but it was normal for those who survived (136mEq/L). Contrary to expectations, the mean lymphocyte count was normal (1206/μL) in patients who died. Platelet level was lower than normal in 50% (3 patients) of the KT patients who died. While 5 of those who died had pneumonia, 1 patient did not have pneumonia who was the youngest 44-year-old male patient, had no additional disease other than Familial Mediterrian Fever, and his O2 saturation level was normal (96%). One of the patients who died had KT within the last 1 year before COVID-19 infection was diagnosed, and he had no comorbid disease and his GFR level was normal when he was admitted to the hospital.

CONCLUSION

COVID infection causes kidney failure in patients with kidney transplantation. Mortality is high in kidney transplant patients with covid infection**.** Suggested poor prognostic factors for death are being 60 years or older, recent transplantation, low oxygen saturation level, high WBC count, high CRP level, high troponin level, high D-dimer level, high creatinine level, low GFR value, low sodium level.

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