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OLGU SUNUMU / CASE REPORT

Clinical follow up of renal transplant recipients with COVID-19: a case series

COVID-19'lu böbrek nakli alıcılarının klinik takibi: bir vaka serisi

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Abstract

COVID-19 has been recognized to become a worldwide health concern at an alarming rate over time and to be more progressive and fatal in specific risk populations. This study aims to determine the clinical features of COVID-19 in kidney transplant recipients (KTRxs) and contribute to the regulation of these patients' immunosuppressive treatments and COVID-19 treatment protocols. The trial comprised eleven KTRxs with COVID-19. Immunosuppressive treatments such as antimetabolite cessation, calcineurin inhibitor dosage adjustments based on blood levels, and low-dose corticosteroids were all controlled. All patients received antiviral medication and low-molecular-weight-heparin (LMWH) as part of initial treatment. The steroid dose was then raised, and anti-cytokine therapies were provided in the setting of clinical worsening. The mean age of the patients was 50.3±11.2 years and 8 (73%) of them were male. The average time since transplantion was 6.82±3.34 years. Due to COVID-19 progression, the steroid dosage was raised in eight patients, anakinra and tocilizumab was added in five and one of the patients respectively. In five (%45) patients, the need for critical care arose and plasmapheresis was used in three of them. At the end of the follow-up, nine of our patients had made a complete recovery, whereas two (18.2%) had perished. Consistent with the literature, the data in presented study may also support the severe and fatal course of COVID-19 in KTRxs. It may be proposed that KTRxs with COVID-19 should be admitted to the hospital and constantly monitored, and certain effective management techniques should be initiated early depending on clinical circumstances.

Keywords:. COVID-19, ICU, immunosuppression, mortality, kidney transplant recipients

Öz

COVID-19'un zaman içinde endişe verici oranda küresel bir sağlık sorunu haline geldiği ve belirli risk gruplarında daha ilerleyici ve ölümcül olduğu gözlenmiştir. Bu çalışma, böbrek nakli (RTx) alıcılarında COVID-19'un klinik özelliklerini belirlemeyi ve bu hastaların immünosupresif tedavileri ile COVID-19 tedavi protokollerinin düzenlenmesine katkıda bulunmayı amaçlamaktadır. Çalışmamıza, COVID-19'lu 11 RTx hastası dahil edildi. İmmünosupresif ilaçlar yattığı sürece "antimetabolitlerin kesilmesi, kalsinörin inhibitörerinin kan seviyelerine göre doz ayarlamaları ve kortikosteroidlerin dozunun azaltılması" şeklinde düzenlenerek uygulandı. Hastaneye yatış sonrası ilk basamakta antiviral ilaçlar ve düşük moleküler ağırlıklı heparin verildi. Steroid dozu daha sonra yükseltildi ve klinik kötüleşme durumunda anti-sitokin tedavileri sağlandı. Hastalarımızın yaş ortalaması 50,3±11,2 iken, 8'i (%73) erkekti. Transplantasyondan başvuru zamanına kadar geçen ortalama süre 6,82±3,34 yıldı. Takip sürecimizde COVID-19 progresyonu nedeniyle 8 hastada steroid dozu artırıldı, 5 hastada anakinra ve 1 hastada ise tocilizumab tedaviye eklendi. 5 hastada (%45) yoğun bakım ihtiyacı ortaya çıktı ve bunlardan 3'ne plazmaferez uygulandı. Takip sonunda 9 hastamız tamamen iyileşirken, 2 hastamız (%18,2) öldü. Böbrek nakil alıcılarında COVID-19'un ağır ve ölümcül seyrettiğini literatürle uyumlu şekilde bizim çalışmamızdaki veriler de desteklemektedir. Bu nedenle COVID-19'lu böbrek nakil alıcılarının hastaneye yatırılarak yakından izlenmesi ve klinik koşullara bağlı olarak etkili yönetim tekniklerinin erkenden başlatılması önerilebilir.

Anahtar kelimeler: COVID-19, YBÜ, immunosuppresyon, mortalite, böbrek nakil alıcıları

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019[1]. Since then, the disease has spread at an alarming rate over the world, prompting the World Health Organization (WHO) to designate the outbreak a pandemic in March 2020. According to current data, the overall number of cases in the COVID-19 pandemic worldwide is estimated to be around 500 million; the total number of deaths has been reported to be around 6 million, making COVID-19 a global health disaster[2]. The spread of SARS-CoV-2 occurs through close contact and respiratory droplets during an incubation period that can last up to 2 to 14 days. Respiratory symptoms, ranging from mild symptoms to critical illness requiring mechanical ventilation, are the most common clinical features of COVID-19; however, immunocompromised patients may present with atypical symptoms[3,4]. The Centers for Disease Control and Prevention (CDC) classifies immunocompromised patients, including patients requiring immunosuppression following kidney transplantation in the high risk group for severe COVID-19[3]. Kidney transplant recipients (KTRxs) are considered immunocompromised hosts for COVID-19 infection due to their long-term exposure to immunosuppressive drugs and their potential risk of persistent chronic kidney disease. In reality, the SARS pandemic was said to have had a significant impact on KTRx, and numerous solid organ transplant patients perished as a result of both SARS and MERS epidemics[5-7]. However, although different studies have been conducted on the risk factors, clinical presentation, diagnostic problems, therapeutic protocols and results of KTRx infected with SARS-CoV-2, a common consensus has not been established yet, the data and recommendations are mostly based on expert opinion. We aim to contribute to the literature by sharing our clinical experience in KTRx patients with this case series.

MATERIALS AND METHODS

Study design and participants

This case series included eleven patients who were admitted to a tertiary center between August 1 and December 15, 2020, had a history of kidney transplantation, were on immunosuppressive treatment regimens, and were diagnosed with COVID-19.

Ethical approval for the study was obtained in accordance with ethic commitee of Health Ministry Republic of Turkish and local ethical commitee of Cukurova University (Ethics Committee No:59/12.02.2021). An informed consent statement was required to participate. All procedures performed in the study involving human participants were in accordance with the ethical standards of the hospital, national research committee and the 1964 Helsinki declaration.

Follow-up and outcomes

Cinical data collected prospectively and immunsupressive drugs censored due to previously published scientific articles and recommendations of Health Ministrial Authorities. In all patients, we used the following protocol for immunosuppressive drug regimen management: discontinuation of antimetabolite drugs (mycophenolate mofetil (MMP), azothiopurine), and dose adjustment in calcineurin inhibitor (CNI) therapy to be slightly below the recommended target blood level (3-5 ng/ml for tacrolimus, 50-75 ng/ml for cyclosporine Co)[8]. We held the steroid dose except an oxygen saturation of 93% or less in room air[9,10].

In all patients, a conventional antiviral and LMWH treatment is prescribed. As antiviral therapy, ten patients received favipiravir and one patient received remdesivir. Patients who experienced clinical deterioration due to COVID-19 (an increase in oxygen requirement or progressive pulmonary involvement on chest X-Ray and no signs of bacterial infection) in minimum 7 days after symptom onset and in the absence of fever for at least 72 hours, were given anti-cytokines. Anakinra (an interleukin-1 receptor antagonist, twice a day) and tocilizumab (an interleukin-6 receptor antagonist, at intervals of 12 to 24 hours at 200 mg.) were ordered as anti-cytokines[10,11]. Respiratory support treatments for patients in need of oxygen was categorized as conventional oxygen therapy (Nasal cannula, face mask, mask with reservoir), high flow nasal cannulation and non-invasive mechanical ventilation[12]. With conventional oxygen therapy, it was aimed to keep the oxygen saturation above 92% with low flow (< 15 L/min) methods or high flow nasal cannula. In cases where oxygenation cannot be corrected by these methods; with a high flow nasal cannula system, the flow was increased (maximum 60

L/min) and oxygen was administered so that FiO2 < 60%[12].

All patients' clinical tracing was taken very closely. The amount of oxygen need required on a daily basis was calculated and documented. Detailed data about comorbidities and previous health was revealed with either anamnesis or according to retrospective investigation of health system data; complete blood count, lymphocyte count, and certain biomarkers (CRP, Ferritin, D-dimer, procalcitonin, LDH) were monitored at regular intervals. The patients were tracked until discharge or death. The primary goal of the study is to determine clinical characteristics and the mortality of COVID-19 in KTRxs.

Statistical analysis

Descriptive statistics were performed due to the small sample size. Descriptive statistics for continuous variables are given as mean±standard deviation while for categorical variables it is given as frequency and percentages.

RESULTS

In this study, we examined 11 KTRxs hospitalized for COVID-19 in a a tertiary university hospital. The mean age of the participants was 50.3±11.2 years and 8 (73%) were male. The mean time since transplantation was 6.82±3.34 years, the mean baseline creatinine value was 1.34±0.53, and the mean baseline eGFR was 57.8±27.1. Accompanying co-morbid diseases were DM in 6 patients (55%), HT in 5 patients (45%), asthma in 2 patients (18%).

MMP, ± tacrolimus and ± prednisolone was the immunosuppressive therapy of nine patients at the outset, whereas tacrolimus and ± prednisolone was the treatment of one patient, and cyclosporine and ± prednisolone was the treatment of another patient. The most common presenting symptom was dyspnea in six (55%) of the patients. It was followed by fever in five (45%), malaise in four (36%) and cough in four (36%). The average time from the onset of symptoms to the admission was three days (2-5 days) (Table 1). At the time of admission, ten (91%) of the patients had positive Covid 19 Real-Time-Polymerase-Chain-Reaction (RT-PCR) test and all patients had pulmonary involvement compatible with COVID-19 infection. Pulmonary involvement was bilateral in eight (73%) patients and unilateral in three (27%) patients in computerized tomography. A patient with a compatible symptoms with COVID-19 was diagnosed with COVID-19 with rapid antigen test positivity despite RT-PCR (-) and unilateral atypical radiological involvement. Progression in pulmonary involvement on computerized tomography was observed in six (55%) of eight patients with bilateral lung involvement.

The most prevalent laboratory abnormalities at admission were raised lactate dehydrogenase (LDH) level (n:73%), lymphopenia (n:6, 55%), elevated D-Dimer (n:6, 55%), and elevated ferritin (n:5, 45%), respectively. C-reactive protein (CRP) was increased in all patients. Four (80%) of the patients hospitalized to the critical care unit had lymphopenia, one (20%) had increased D-Dimer, and four (80%) had radiographic progression. The laboratory findings of our patients are examined broadly in Table 1.

LMWH was administered to all of our hospitalized patients; as antiviral therapy favipiravir was given to ten (91%) patients, and remdesivir was given to one (9%) patient. Prednisolone therapy was assessed on a patient-by-patient basis, with the duration and clinical progression of the disease taken into account. The maintenance steroid dose was maintained in the early stages of the illness, but it was raised in individuals whose oxygen saturation dropped to 93% or below. In eight (73%) of the patients, the dose of systemic steroid medication was raised. Due to impairment in exclusion of subsequent bacterial infection, antibacterial medication was added to the existing treatment in eight (73%) patients. Tocilizumab and anakinra were administered in one (9%) and five (45%) patients, respectively, throughout clinical follow-up. Three (27%) patients in the intensive care unit had further plasmapheresis (ICU). Five (45 %) of the patients who had hypoxemia during their hospital stay received low-flow oxygen support. Four of the five patients eventually received high-flow oxygen treatment owing to increasing oxygen needs, however three patients did not respond to high-flow oxygen therapy and respiratory support was alternated with NIMV. However, these three patients did not react to NIMV during follow-up, and IMV was used to give respiratory support. Two of the three intubated patients died.

In the ICU, a total of five (45%) patients were followed up; four (36%) owing to respiratory failure + hypoxemia and one (9%) due to acute myocardial infarction. Except for one patient with acute coronary syndrome, none of the patients experienced any acute problems throughout their clinical follow-up. The average hospital stay was 21 days, while the

average length of hospital stay in the ICU was 20 days. Complete recovery was obtained in 9 (82%) patients at the end of follow-up to discharge/death, whereas two (18%) patients with IMV in the ICU died. Table 2 provides detailed information on follow-up and treatment processes during the hospital stay.

Table 1. Baseline and hospital admission clinical and laboratory findings of the cases

Features	Patients										
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**Case 10**	**Case 11**
Age (Years)	56	52	66	52	39	40	59	51	64	45	29
Gender	M	F	M	M	M	M	M	F	F	M	M
Transplant Time	2013	2012	2012	2012	2020	2007	2013	2003	2013	2020	2012
Comorbidities	Asthma/ HT	DM/HT	None	DM	None	None	DM	Asthma/ HT	DM/HT	DM/HT	DM
Basal Creatinin	1.65	1.2	0.96	1.1	1.1	2.5	1.2	0.4	1.6	1.5	1.5
e-GFR	29	52	82	48	69	27	58	120	30	67	54
İmmuno-supressive treatment protocoles	MMF/ Tac/ Pred	Cs/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred	Tac/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred	MMF/ Tac/ Pred
Symptoms on admission	Dyspnea fever	Myalgia fatigue	Dyspnea fatigue	Diarrhea cough	Dyspnea fever cough	Fever cough	Dyspne a fever	Dyspnea nausea	Dyspnea fatigue	Fatigue	Fever cough
PCR	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)	(+)	(+)
Hypoxemia	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)
CT Findings	Bilateral typical findings	Bilateral typical findings	Bilateral typical findings	Bilateral typical findings	Bilateral typical findings	Atypical findings	Bilateral typical findings	Bilateral typical findings	Atypical findings	Bilateral typical findings	Atypical findings
The time between syptoms to hospital admission (days)	5	2	4	3	3	2	3	5	2	4	3
WBCx10³/µL	5.2	4.5	10.4	11	6.5	6.7	4.8	8	10.6	1.6	23
Lymphocyte (%) 1.day/lowest/at discharge or ex	1.5/ 0.2/ 0.5	1.1/ 1.8/ 1.9	0.5/ 0.2/ 0.2	0.9/ 1.8/ 1.6	1.3/ 0.9/ 0.6	1.1/ 2/ 1.4	0.6/ 0.2/ 1.1	0.8/ 0.3/ 0.5	1/ 1/ 0.9	0.3/ 0.3/ 1.1	0.9/ 2.4/ 3.4
CRP (mg/L) 1.day/ highest/ at discharge or ex	66/ 106/ 97	13/ 21/ 9	42/ 180/ 36	170/ 45/ 6	11/ 140/ 22	115/ 125/ 21	88/ 260/ 18	45/ 139/ 2,8	11/ 69/ 64	83/ 231/ 12	89/ 137 /32
Ferritin (mg/dL) 1. day/ highest/ at discharge or ex	188/ 2665/ 2655	153/ 234/ 232	528/ 1184/ 753	930/ 1081/ 450	18/ 68/ 189	77/ 169/ 150	846/ 1860/ 342	176/ 654/ 380	42/ 113/ 94	972/ 1624/ 690	552/ 607/ 646
D-Dimer (mg/L)	0.34	0.68	0.36	0.64	0.33	0.78	2.1	0.77	0.59	0.33	0.2
LDH (U/L)	358	199	238	208	263	301	456	520	385	541	514
Radiologic Progression	(+)	(+)	(+)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)

M: Male, F: Female, HT: Hypertension, DM: Diabetes Mellitus, MMF: Mycophenolate Mofetil, Tac: Tacrolimus, Pred: Prednizolone, Cs: Cyclosporine, CT: Computed Tomography, PCR: Polymerase Chain Reaction, Wbc: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Table 2. Treatment and clinical course during hospital stay

Features	Patients										
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**Case 10**	**Case 11**
Antiviral drugs (Favipiravir/ Remdesivir)	(+)/(-)	(+)/(-)	(+)/(-)	(+)/(-)	(+)/(-)	(+)/(-)	(-)/(+)	(+)/(-)	(+)/(-)	(+)/(-)	(+)/(-)
Corticosteroid (additional doses)	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(-)	(-)	(-)
Anakinra	(+)	(+)	(+)	(-)	(+)	(-)	(-)	(+)	(-)	(-)	(-)
Tocilizumab	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)
LMWH	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Antibiotics	(+)	(-)	(+)	(-)	(+)	(+)	(+)	(+)	(-)	(+)	(+)
Plasmapheresis	(+)	(-)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)
HFO2/ NIMV/ Entubation	(+)/ (+)/ (+)	(-)/ (-)/ (-)	(+)/ (+)/ (+)	(-)/ (-)/ (-)	(-)/ (-)/ (-)	(-)/ (-)/ (-)	(+)/ (+)/ (+)	(+)/ (+)/ (-)	(-)/ (-)/ (-)	(-)/ (-)/ (-)	(-)/ (-)/ (-)
ICU stay (day)	10	(-)	2	7	(-)	(-)	75	3	(-)	(-)	(-)
Hospital stay (day)	15	8	13	16	13	4	109	17	9	17	15
At discharge	Exitus	Recover	Exitus	Recover	Recover	Recover	Recover	Recover	Recover	Recover	Recover

LMWH: Low moleculary weight heparine, HFO2: High Flow Oxygen, NİMV: Noninvasive Mechanical Ventilation

All of the ICU patients exhibited dyspnea and bilateral lung involvement at the time of admission, and four of them (80 percent) had lymphopenia. While 1 (20%) of these 5 patients had no additional disease, 2 (40%) had asthma + HT and 2 (40%) had DM. The mean time since transplantion of KRTxs in ICU was 9,4 years. During this period, the patients were supported with oxygen and ventilation support in ICU, as well as additional dose of systemic glucocorticoids and anti-inflammatory agents as IL-1 and IL-6 antagonists. In the follow-up of the patient who was admitted to intensive care due to acute coronary syndrome, neither additional oxygen demand nor other clinical deterioration has developed. Two of the patients who died while being monitored with mechanical ventilators in the ICU were given anakinra therapy; however, those who were given an IL-6 antagonist survived despite their protracted stay in the ICU.

DISCUSSION

This study highlighted the clinical characteristics and clinical course of KRTxs hospitalized owing to COVID-19 in a tertiary hospital. The most important data demonstrated by the presented study was that mortality in KRTxs hospitalized due to COVID-19 was 18% and 45% in patients in clinics and in intensive care respectively.

The most common presenting symptoms were dyspnea, fever and cough in our study. In an observational study of KRTxs patients, fever (100%) was the leading symptom; cough (50%) and dyspnea (5%) were more rare[13]. Cough (75%) was the most common symptom whereas fever (62%) and dyspnea (52%) were less commonly documented in a multi-center study enrolling 40 KRTxs[14]. In an other study with KRTxs, fever, cough and myalgia, chills and fatigue were presented as the leading symptoms[15]. The data of our study is compatible with the general literature data.

It has been reported that shows a more aggressive and fatal course of COVID-19 disease especially in certain risk groups such as advanced age and immunosuppression and accompanying comorbid diseases (DM, HT, CVD, cancer etc)[16]. Among three intubated patients in our research; one of the three had DM, the other had HT and asthma, and the third had no concomitant condition. This study revealed that mortality in KRTxs hospitalized due to COVID-

19 was 18% and 45% in the group requiring intensive care. In general population, pooled rates of ICU admission and mortality were 10.9%, 4.3% respectively[17]. Mortality rates in KRTxs has been determined to range from 6% to 25% in various studies[14,18-23]. In a study of Azzi Y. et al. mortality rate was 20.5% for all patients and 37.8% for patients requiring hospitalization in 912 KRTxs with COVID-19[22]. Another research compared the death rates of solid organ transplant recipients with nontransplant patients in the United States and found that transplant patients had a mortality rate of 21.9%, while nontransplant patients had a mortality rate of 14.9%[24]. Though, with limited data, it can be assumed that KRTxs may have a higher mortality than general population.

There is insufficient clinical data to recommend for or against anakinra and its use in the treatment of COVID-19. On the other hand, the guidelines recommend that the use of tocilizumab be limited to clinical studies only. Two of the patients who died while being monitored with mechanical ventilators in the ICU were given anakinra therapy; however, those who were given an IL-6 antagonist survived despite their protracted stay in the ICU in this study. We preferred anakinra because of its shorter half-life[10,11]. Although there may be various factors contributing to mortality in the clinical course, it is thought that this situation needs to be investigated in larger groups.

As the main result of this study; it can be speculated that COVID-19 has a significant death rate in KTRxs. The absence of comorbid disease in one of the patients who died also may serve to support that the course of COVID-19 disease may be more aggressive in KRTxs regardless of comorbidities. Furthermore, we were unable to avoid clinical deterioration and mortality despite the proper administration of steroid, IL-1, and IL-6 antagonists, as well as antiviral and anticoagulant therapy. However, the sample size is too small to draw conclusions.

This study is a case-series from a single center and has some limitations: the sample size is small and the data needs to be verified in larger cohorts. Risk analyzes could not be performed because the number of participants was limited and there was no matched control group. Because only KRTxs hospitalized for COVID-19 were included in the research, these findings cannot be generalized to all KRTxs.

In conclusion, The ideal therapy for SARS-CoV-2-infected KTRx remains unclear, and answers regarding its optimal management still rely on expert opinion. However, COVID-19 may have a high mortality rate in KTRxs. As a result, for this group of individuals, urgent hospitalization, rearrangement of the immunsupressive drug regimens and closer monitoring of clinical course may be preferable. Long-term follow-up is required and multicenter studies are needed to better understand the prognosis and sequelae of COVID-19 in KTRx.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EG, OBT, YS, İH, SP, BK, YT; Veri toplama: EG, OBT, BK, YS; Veri analizi ve yorumlama: EG, OBT, YS, İH, SP, BK, YT; Yazı taslağı: EG, OBT, BK; İçeriğin eleştirel incelenmesi: EG, OBT, YS, İH, SP, BK, YT; Son onay ve sorumluluk: EG, OBT, YS, İH, SP, BK, YT; Teknik ve malzeme desteği: EG, OBT, YS, BK, SP; Süpervizyon: EG, OBT, YS, İH, SP, BK, YT; Fon sağlama (mevcut ise): yok.
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