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CASE REPORT

COVID-19 in Kidney Transplant Recipients, Single Center Study From Turkey

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Abstract

In December 2019, an outbreak of COVID-19, caused by a novel SARS-CoV-2, occurred in Wuhan. Currently, COVID-19 has spread widely around the World. Although immunosuppression is associated with a severe course of covid infection, information on the first presentation, clinical findings and outcomes of COVID-19 disease in patients with kidney transplantation is limited.

This study included kidney transplant recipients who were radiological and/or serological diagnosed COVID-19 in University of Health Sciences, Haydarpasa Numune Education and Research Hospital. Data from 5 patients were reviewed retrospectively.

Four patients were female and the median age was 46. Four recipients had hypertension, 1 had diabetes mellitus. All the patients were taking tacrolimus except one at the time of COVID-19 diagnosis, and all of them were also taking either mycophenolate mofetil or mycophenolic acid. One patient was taking mTOR inhibitor.The most common presenting symptom was cough. All of the patients had multifocal bilateral ground-glass opacity which was compatible with viral infection with Thorax CT scans. Three patients were lymphopenic. The primary change in immunosuppression in the majority of patients was complete cessation of either mycophenolate mofetil or mycophenolic acid while reducing the tacrolimus. The mTor inhibitor dose of the patient receiving antimetabolite with mTor inhibitor was maintained. All of the patients received hydroxychloroquine (HCQ), azithromycin and ceftriaxone as treatment. Two patients recieved oseltamivir treatment. One patient was treated with azithromycin, hydroxychloroquine, ceftriaxone, favipiravir and vitamin C combination. During the follow-up, none of them had acute kidney injury and needed for intensive care.

In our study, among 5 kidney transplant recipients with COVID-19, overall presentation was similar to that reported from other countries. All of our patients experienced a favorable outcome with our current treatment strategy but the small group cohort makes it difficult to say any conclusions about safety and tolerability of our protocol.

Keywords: COVID-19; Coronaviruses; kidney; transplantation.

In December 2019, cases of pneumonia of unknown cause were reported in Wuhan, Hubei Province, China which was later confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical condition caused by SARS-CoV-2 was referred to as coronavirus disease 2019 (COVID-19) [1]. January 2020, the World health organization (WHO) announced COVID-19 disease as a pandemic disease [2]. The disease was confirmed to have reached Turkey on 11 March 2020, after a man who had returned to Turkey from Europe, tested positive. The first death due to COVID-19 in the country occurred on 15 March 2020 and by 1 April it was confirmed that COVID-19

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had spread all over Turkey [3, 4]. Since that time, Istanbul has become the epicenter of COVID-19 in Turkey, with approximately 60% of confirmed COVID-19 cases as of May 10, 2020.

The relative importance of different underlying health conditions is unclear, such as immunosuppression in solid organ transplantation. As a population living with immunosuppression, the clinical manifestations, treatment and prognosis of COVID-19 pneumonia for kidney transplant recipients may differ from those of the general population[5].

International data regarding the management and prognosis for kidney transplant recipients with COVID-19 has been limited to case reports. The largest case series to date of kidney transplant recipients with COVID-19 was from USA, New York [6].

Herein we report our initial series of COVID-19 in kidney transplant recipients and present their characteristics. Also, we describe our experience with managing patients with kidney disease during the current COVID-19 pandemic in Istanbul, with particular attention to kidney transplant recipients.

Materials and Methods

This study included kidney transplant recipients who were clinically diagnosed and/or confirmed COVID-19 in University of Health Sciences, Haydarpasa Numune Training and Research Hospital between April 2020 and May 2020. Data from 5 patients were reviewed in institutional medical records retrospectively.

According to the "COVID-19 Diagnosis and Treatment Guide" printed by the Turkish Ministry of Health, patients were separated into three groups by their clinical presentation. Mild illness presented with symptoms such as fever, cough, sore throat, and nasal congestion, with or without mild pneumonia together with a respiratory rate <30/min and an oxygen saturation above 90% while breathing room air. The severe illness was defined with widespread findings of pneumonia in chest radiography or computed tomography (CT). Critical illness defines the requirement of the intensive care unit (ICU) [4].

The following data were recorded from patient charts: baseline characteristics (gender, age, comorbidities, donor type, transplantation time, tobacco use, maintenance immunosuppression), laboratory parameters (White blood cell count (WBC), absolute neutrophil count, absolute lymphocyte count, eosinophil count, serum albümin, hemoglobin (hb), ferritin, d-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatinine level) physical examination findings and symptoms on the date of the first examination in the emergency room and also COVID, Nephrology outpatient clinics. Thorax CT was performed at the first presentation of the patients. Nasopharyngeal/oropharyngeal swab test was performed to confirming the SARS-CoV-2 infection. Clinical follow-up, change in immunosuppression, the treatment and outcomes were recorded. Ethics committee approval was received from the Ethics Committee of University of Health Sciences, Haydarpasa Numune Training and Research Hospital.

Results

The baseline characteristics of patients are shown in Table 1 (page11-12). All but one of the patients were living donor kidney transplantation. Among the patients who were transplanted from live donors, two received kidneys from the mother, one from her husband and one from her son. The most common presenting symptom was cough, which was reported in all cases, followed by dyspnea, which was present in four (80%) cases. Interestingly, only two patients had fever (%40).

All of the patients had multifocal bilateral ground-glass opacity which was compatible with viral infection with Thorax CT scans. According to initial blood test results, the median absolute lymphocyte count was 900 per mm^3 (range, 520-1920). Three patients (60%) were lymphopenic. None of them had an eosinophil count above 230 per mm^3. Inflammatory markers were measured, and 5 (100%) had CRP levels higher than 0,5 mg per deciliter (upper limit), 4 (80 %) had d-dimer levels higher than 500 ng/ml. We observed a wide variation in admission values for ferritin (median 162 ng/ml; range, 32-4923). Allograft function was stable in all of the patients. The severity of the disease was severe in 1 and mild in 4 patients.

The primary change in immunosuppression in the majority of patients was complete cessation of either mycophenolate mofetil (MMF) or mycophenolic acid (MPA) (4 patients, %80) while reducing the tacrolimus (4 patients, %80) with a goal trough of 4–6 ng/ml. The mTOR inhibitor dose of the patient receiving antimetabolite with mTor inhibitor was maintained (with a goal trough of 3–5 ng/ml) but the dose of antimetabolite was reduced. All patients were under prednisolone maintenance therapy and the current dose was maintained.

All of the patients received hydroxychloroquine (HCQ), azithromycin as treatment. One patient who had a severe infection (the patient presented with tachypnea, 02 de-

Table 1. Clinical Features and Outcomes in Kidney Transplant Recipients

Characteristics			
Baseline characteristics			
Woman, n (%)	4 (%80)		
Age (years)	59 ± 14 (mean ± SD), Range 35-67		
Time since transplant (mo)	93 ± 113 (mean ± SD), Range 3-240		
Deceased donor,n (%)	1 (%20)		
Previous history, n (%)			
Hypertension	4 (%80)		
Diabetes	1 (%20)		
Heart Disease/ Cancer / COPD	0 (%0) / 0 (%0) / 0 (%0)		
Tobacco use	0 (%0)		
Maintenance immunosuppression, n (%)			
CNI	4 (%80)		
mTOR	1 (%20)		
Mycophenolate	5 (%100)		
Steroids	5 (%100)		
Belatacept	0 (%0)		
Admission clinical presentation, n (%)			
Fever	2 (%40)		
Cough	5 (%100)		
Dyspnea	4 (%80)		
Fatigue	1 (%20)		
Gastrointestinal symptoms	1 (%20)		
Initial Thorax CT, n (%)			
Bilateral ground-glass opacity	5 (%100)		
Unilateral ground-glass opacity	0 (%0)		
Linear subsegmental density	1 (%20)		
Pleural effusion	0 (%0)		
Laboratory tests on diagnosis (Median (range))			
White blood cell count, (per mm3)	6000 (3880-9900)		
Lymphocyte count, (per mm3)	900 (520-1920)		
Eosinophil count, (per mm3)	0 (0-220)		
Platelet count, (per mm3)	248 000 (198 000-320 000)		
Hemoglobin (g/dl)	11 (10,6-15)		
Ferritin, (ng/ml)	162 (32-4923)		
d-dimer, (ng/ml)	1090 (400-1820)		
C-reactive protein, (mg/dl)	2,9 (0,8-9,4)		
Lactate dehydrogenase, (IU/l) (n=4)	218 (207-332)		
Albumin, (mg/dl)	3,9 (3,7-4,1)		
Serum creatinine, (mg/dl)	1 (0,7-1,48)		
eGFR (MDRD) (ml/min/1.73 m^2)	54 (46-71)		
Change in immunosuppression n (%)	**Withdrawned**	**Maintained**	**Reduced**
CNI (n=4)	0 (%0)	0 (%0)	4 (%100)
mTOR (n=1)	0 (%0)	1 (%100)	0 (%0)
Mycophenolate (n=5)	4 (%80)	0 (%0)	1 (%20)
Steroids (n=5)	0 (%0)	5 (%100)	0 (%0)
Specific treatment n (%)			
Hydroxychloroquine	5 (%100)		
Azithromycin	5 (%100)		
Favipiravir	1 (%20)		
Vitamin C	1 (%20)		
Outcomes at a median of 12 days (range, 7–13) n (%)			
Death	0 (%0)		
Intubation	0 (%0)		
Renal replacement therapy	0 (%0)		
Acute renal injury/Rejection	0 (%0)		
Discharged from hospital	5 (%100)		

mand and diffuse-severe Thorax CT lesions) were treated with azithromycin, HCQ, favipiravir, low-molecular-weight heparin, n-acetylcysteine and vitamin C (1,5 gr/day intravenously). All patients had an electrocardiogram (ECG) performed before initiation of therapy. Daily ECG of the patients was taken and QTc levels were recorded. The QTc levels were appropriate.

The patients were followed up in the clinic (inpatient) for an average of 12 days. None of them had acute kidney injury and needed intensive care. All of the patients were discharged from the hospital after the recovery.

Discussion

The sudden spread of COVID-19 throughout the globe has resulted in early uncertainty in the identification and management of this disease. Although the general understanding of the clinical presentation of COVID-19 is improving, information about selected patient groups who may warrant special consideration, such as kidney transplant recipients, remains limited [7]. The immune response of kidney transplant recipients is significantly suppressed due to the long-term use of immunosuppressive agents. This means that some of the clinical manifestations of COVID-19 infection in this population may be distinctive and that treatment methods for COVID-19 pneumonia require careful consideration [8]. Although our cohort is small, here, we present a series of 5 cases of COVID-19 in kidney transplant recipients at our center who required hospitalization.

The study included three positive cases confirmed with the rRT-PCR method and two negative cases who had typical CT findings of viral pneumonia and COVID-19 contact history. Cases had been reported that rRT-PCR test is negative but medical histories, clinical and also CT scans are compatible with COVID-19 [9]. The false negativity rate of rRT-PCR test was reported to reach 30% [10]. In another study, a retrospective analysis showed that the sensitivity of initial CT was 97.2%, whereas initial rRT-PCR sensitivity was 83.3%, with 6 initially missed cases [11]. This may be related to sample collection, Pharyngeal, oral and nasal samplings are easier methods to collect, whereas lower respiratory tract sampling is relatively difficult to perform, with medical staff susceptible to get infected. The sensitivity of the rRTPCR kit can also contribute to false negatives [12]. In summary, CT scan seems to be also another sensitive method for virus detection, whereas rRT-PCR may produce false-negative results. According to multiple study, the investigators recommend that patients with positive imaging findings but negative rRT-PCR results should be isolated and rRT-PCR repeated to avoid misdiagnosis [11].

Regarding the cases discussed before this study, overall clinical characteristics of kidney recipients (symptoms, laboratory examinations, and thorax CT) were similar to those of other non-transplanted adult patients with COVID-19 pneumonia [8]. According to Nair et al similar to those of the general population, the most frequent presenting symptoms were fever, myalgia, and cough [13]. In our study, the symptom of fever was less common than in other studies. This may be due to the steroid regimen that masking the fever symptom. In other studies, some patients are followed up with steroid-free regimens. While other studies had patients who were followed up with steroid-free regimens, all patients were using steroids in our study.

Older age, accompanying chronic illnesses, lymphopenia, and elevated procalcitonin and d-dimer levels were found to be related to severe disease and mortality [14]. In our study, comorbidities with the highest frequency were as follows: hypertension (4,%80), diabetes (1, %20) The severity of the disease was mild in four of the cases, only in one case it was more severe. But none of the patients were classified as critically ill. All of them were healed and discharged from the hospital.

With regards to prognostic blood tests including lymphocyte counts and serum levels of d-dimer, ferritin, albumin is likely to be valuable. In our patients, among the biomarkers of inflammation measured at presentation, although almost slightly elevated. In a study of kidney transplant recipients, it had been reported that the worsening of these inflammatory markers may determine the prognosis [15]. There was no such change in the biomarkers of our patients. By determining the severity of the disease and the prognosis of the patients, we think these tests will be valuable when making immunosuppressive and COVID-19 specific treatment decisions.

When studies and case reports involving kidney recipients are examined, it is seen that mortality rates vary between 6 and 30% [6, 7, 13, 15-17]. When the outbreak first emerged, the overall mortality rates of the general population reported in China were between 4- 15% [18]. A study from Italy reported that the in-hospital mortality was 15% [19]. In a recent study involving 5,700 patients in New York, US, the mortality rate was reported as 21% [20]. The preliminary results of the study which was performed in our country, the mortality rate of hospitalized patients were found at 3.8%. Immunosuppressed patients were commonly presented with atypical or attenuated signs and symptoms of infection, often leading to late presentations, or missed diagnoses, more severe illness and potentially leading more

severe illness to worse outcomes overall. Besides the other studies, our patients' lower mortality rate can be explained as follows; a low number of patients in critical condition, low comorbid diseases of patients and relatively low age. Also, criteria for hospitalization, ICU admission, discharge and treatment of COVID-19 are likely to be different between countries. Larger studies are warranted to fully understand mortality risk and prognostic factors of transplant recipients with COVID-19.

The ideal treatment for kidney transplant recipients with COVID-19 remains uncertain at present. Treatment consists of two arms, immunosuppressive treatment management and COVID-19 specific treatments.

Managing immunosuppression in these patients is challenging and the patient's age, the severity of COVID-19 infection, associated comorbidities, and also posttransplant period should have to be taken into account. In kidney transplant recipients with mild to moderate infections, the usual practice is to continue or make reductions in the dose of immunosuppressive drugs, but this approach might favor high mortality in patients admitted to hospital with COVID-19 infection [15]. The Columbia University COVID-19 protocol is to withdraw the antimetabolite [7]. The patient reported from Wuhan recovered after cessation of immunosuppression and treatment with methylprednisolone, intravenous Ig, and IFNa [8]. Brazilian investigators reduced tacrolimus to reach through levels of 3-5 ng/mL, withdrawn MMF/MPA and doubled prednisone dose on their study [21]. According to the Spain based study, their policy is to temporarily discontinue immunosuppressants in admitted patients (MMF/MPA and/or mTOR-i in all patients, and CNI if lopinavir/ritonavir is prescribed due to interactions). Maintenance immunosuppression is based on prednisone (15-20mg/day) until improvement [16]. In the study of Montagud - Marrahi et al. based in the USA, immunosuppressive management included the withdrawal of an antimetabolite in 24 of 28 patients (86%). In addition, tacrolimus was withheld in 6 of the 28 severely ill patients (21%) [6]. The impact of the approach is not clear. There is concern that immunosuppression may be associated with poor virologic control, leading to more severe disease and more prolonged viral shedding. Conversely, reducing immunosuppression may not only lead to acute rejection but may cause an immune reconstitution-like reaction with a paradoxical worsening of disease [22]. Our general approach was to hold the antimetabolite while reducing the tacrolimus (with a goal trough of 4–6 ng/ml), mTor inhibitör (with a goal trough of 3–5 ng/ml) and the baseline prednisone in those individuals who were on maintenance prednisone.

At this time there are no medical therapies that have been definitively shown to improve outcomes in patients with COVID-19. Several drugs have demonstrated in vitro activity against the SARS-CoV-2 virus or potential clinical benefits in observational or small, nonrandomized studies. Adequately powered randomized clinical trials are currently enrolling and needed to establish the efficacy of these proposed therapies. There is yet no proven treatment for COVID-19. The most frequently used agents both in Turkey and all over the world are chloroquine, HCQ, azithromycin, lopinavir/ ritonavir, favipiravir and remdesivir. The reported clinical benefits of the combination of HCQ and azithromycin for patients with COVID-19 based on nonrandomized trials with small numbers of participants (<100 patients) [23]. Favipiravir is a RNA-dependent RNA polymerase inhibitor with broad-spectrum antiviral activity; however, demonstrated high EC50 (decreased potency) against SARS-CoV-2 but was effective in protecting mice against Ebola virüs despite similarly high EC50 values [24]. Currently being evaluated in Clinical Trial for Patients with COVID-19. All of our hospitalized patients were treated with HCQ and azithromycin. One patient who had a severe infection (the patient presented with tachypnea, 02 demand and diffuse-severe Thorax CT lesions) were treated with azithromycin, HCQ, ceftriaxone, favipiravir and vitamin C combination. As we applied this treatment to our patients, there was no or acute kidney injury or death due to COVID-19.

The most important limiting factor in our study was the lack of data specific to retrospective studies. The number of patients included in the study was small, which may have reduced the effectiveness of the statistical results.

In conclusion, among 5 kidney transplant recipients at our center with COVID-19, the overall presentation was similar to that reported from other countries. All of our patients experienced a favorable outcome with our current treatment strategy but the small group cohort makes it difficult to say any conclusions about the safety and tolerability of our protocol. Large scale studies are needed to define the risk factors and proper treatment for COVID-19 in transplant recipients.

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References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9. [CrossRef]
2. WHO. Novel coronavirus (2019-nCoV) situation report -2. Lyon, France, January 22, 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/330761/nCoVsitrep22Jan2020-eng.pdf?sequence=1&isAllowed=y. Accessed Oct 25, 2022.
3. Cakir Z, Savas H. A mathematical modelling approach in the spread of the novel 2019 Coronavirus SARS-CoV-2 (COVID-19) pandemic. Electron J Gen Med 2020;17:em205. [CrossRef]
4. Republic of Turkish Ministry of Health. COVID-19. Covid-19 (SARS-CoV-2 Infection Guide). Study of Scientific Board. 14 April 2020.
5. Michaels MG, La Hoz RM, Danziger-Isakov L, Blumberg EA, Kumar D, Green M, et al. Coronavirus disease 2019: Implications of emerging infections for transplantation. Am J Transplant 2020;20:1768–72. [CrossRef]
6. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. N Engl J Med 2020;382:2475–7. [CrossRef]
7. Columbia University Kidney Transplant Program. Early description of Coronavirus 2019 disease in kidney transplant recipients in New York. J Am Soc Nephrol 2020;31:1150–6. [CrossRef]
8. Zhu L, Xu X, Ma K, Yang J, Guan H, Chen S, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020;20:1859–63. [CrossRef]
9. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020;295:202–7. [CrossRef]
10. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. MedRxiv 2020. [CrossRef]
11. Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol 2020;126:108961. [CrossRef]
12. Tian HY. 2019-nCoV: New challenges from coronavirus. Zhonghua Yu Fang Yi Xue Za Zhi [Article in Chinese] 2020;54:E001.
13. Nair V, Jandovitz N, Hirsch JS, Nair G, Abate M, Bhaskaran M, et al. COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:1819–25. [CrossRef]
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054–62. [CrossRef]
15. Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. Kidney Int 2020;97:1076–82. [CrossRef]
16. Montagud-Marrahi E, Cofan F, Torregrosa JV, Cucchiari D, Ventura-Aguiar P, Revuelta I, et al. Preliminary data on outcomes of SARS-CoV-2 infection in a Spanish single center cohort of kidney recipients. Am J Transplant 2020;20:2958–9. [CrossRef]
17. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. Management of patients on dialysis and with kidney transplantation during the SARS-CoV-2 (COVID-19) pandemic in Brescia, Italy. Kidney Int Rep 2020;5:580–5. [CrossRef]
18. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020;368:m1091. [CrossRef]
19. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries 2020;14:125–8. [CrossRef]
20. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052–9.
21. Machado DJB, Ianhez LE. COVID-19 pneumonia in kidney transplant recipients-Where we are? Transpl Infect Dis 2020;22:e13306. [CrossRef]
22. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant 2020;20:1800–8. [CrossRef]
23. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus Disease 2019 (COVID-19): A review. JAMA 2020;323:1824–36. [CrossRef]
24. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71.