Clinical Kidney Journal, 2022, vol. 15, no. 5, 999–1006

https://doi.org/10.1093/ckj/sfac045
Advance Access Publication Date: 14 February 2022
Original Article

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

ORIGINAL ARTICLE

Middle-term outcomes in renal transplant recipients with COVID-19: a national, multicenter, controlled study

Ozgur Akin Oto[1], Savas Ozturk[1], Mustafa Arici[2], Arzu Velioğlu[3], Belda Dursun[4], Nurana Guller[1], İdris Şahin[5], Zeynep Ebru Eser[6], Saime Paydaş[7], Sinan Trabulus[8], Sümeyra Koyuncu[9], Murathan Uyar[10], Zeynep Ural[11], Rezzan Eren Sadioğlu[12], Hamad Dheir[13], Neriman Sıla Koç[2], Hakan Özer[14], Beyza Algül Durak[15], Cuma Bülent Gül[16], Umut Kasapoğlu[17], Ebru Gök Oğuz[18], Mehmet Tanrısev[19], Gülşah Şaşak Kuzgun[20], Safak Mirioglu[21], Erkan Dervişoğlu[22], Ertuğrul Erken[23], Numan Görgülü[24], Sultan Özkurt[25], Zeki Aydın[26], İlhan Kurultak[27], Melike Betül Öğütmen[28], Serkan Bakırdöğen[29], Burcu Kaya[3], Serhat Karadağ[30], Memnune Sena Ulu[31], Özkan Güngör[23], Elif Arı Bakır[32], Ali Rıza Odabaş[33], Nurhan Seyahi[8], Alaattin Yıldız[1] and Kenan Ateş[12]

[1]Department of Internal Medicine, Division of Nephrology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [3]Department of Internal Medicine, Division of Nephrology, Marmara University, School of Medicine, Istanbul, Turkey, [4]Department of Internal Medicine, Division of Nephrology, Pamukkale University, Faculty of Medicine, Denizli, Turkey, [5]Department of Internal Medicine, Nephrology Division, Inonu University, Faculty of Medicine, Malatya, Turkey, [6]Department of Internal Medicine, Division of Nephrology, Mersin University, Mersin Faculty of Medicine, Mersin, Turkey, [7]Department of Internal Medicine, Division of Nephrology, Çukurova University Faculty of Medicine, Adana, Turkey, [8]Department of Internal Medicine, Division of Nephrology, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey, [9]Department of Internal Medicine, Division of Nephrology, Erciyes University, Erciyes Faculty of Medicine, Kayseri, Turkey, [10]Department of Internal Medicine, Division of Nephrology, Yeni Yüzyıl University, Gaziosmanpaşa Hospital, Istanbul, Turkey, [11]Department of İnternal Medicine, Division of Nephrology Gazi University, Faculty of Medicine, Ankara, Turkey, [12]Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey, [13]Department of Internal Medicine, Division of Nephrology, Sakarya University Training and Research Hospital, Sakarya, Turkey, [14]Division of Nephrology, Konya Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey, [15]Department of Nephrology, Ankara Bilkent City Hospital, Ankara, Turkey , [16]Department of

Received: 22.10.2021; Editorial decision: 2.2.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Nephrology, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Istanbul, Turkey, [17]Department of Nephrology, University of Health Sciences, Bakirkoy Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey, [18]Department of Nephrology, University of Health Sciences, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey, [19]Department of Nephrology, University of Health Sciences, Izmir Faculty of Medicine, Tepecik Training and Research Hospital, Izmir, Turkey, [20]Department of Nephrology, Goztepe Prof Dr Suleyman Yalcin City Hospital, Istanbul, Turkey, [21]Division of Nephrology, Department of Internal Medicine, Bezmialem Vakif University School of Medicine, Istanbul, Turkey, [22]Department of Internal Medicine, Division of Nephrology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, [23] Department of Nephrology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey, [24]Department of Nephrology, University of Health Sciences, Bagcilar Training and Research Hospital, Istanbul, Turkey, [25]Department of Internal Medicine, Division of Nephrology, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Turkey, [26]Department of Nephrology, University of Health Sciences, Darıca Farabi Training and Research Hospital, Darica, Turkey, [27]Department of Internal Medicine, Division of Nephrology, Trakya University, Faculty of Medicine, Edirne, Turkey, [28]Department of Nephrology, University of Health Sciences, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey, [29]Department of Internal Medicine, Division of Nephrology, Canakkale Onsekiz Mart University, School of Medicine, Canakkale, Turkey, [30]Department of Nephrology, University of Health Sciences, Haseki Training and Research Hospital, Istanbul, Turkey, [31]Department of Internal Medicine, Division of Nephrology, Bahçeşehir University, Faculty of Medicine, Istanbul, Turkey, [32]Department of Internal Medicine, Division of Nephrology University of Health Sciences, Kartal Training Hospital, Istanbul, Turkey and [33]Department of Nephrology, University of Health Sciences, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey

Correspondence to: Mustafa Arici; E-mail: aricim@gmail.com

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

ABSTRACT

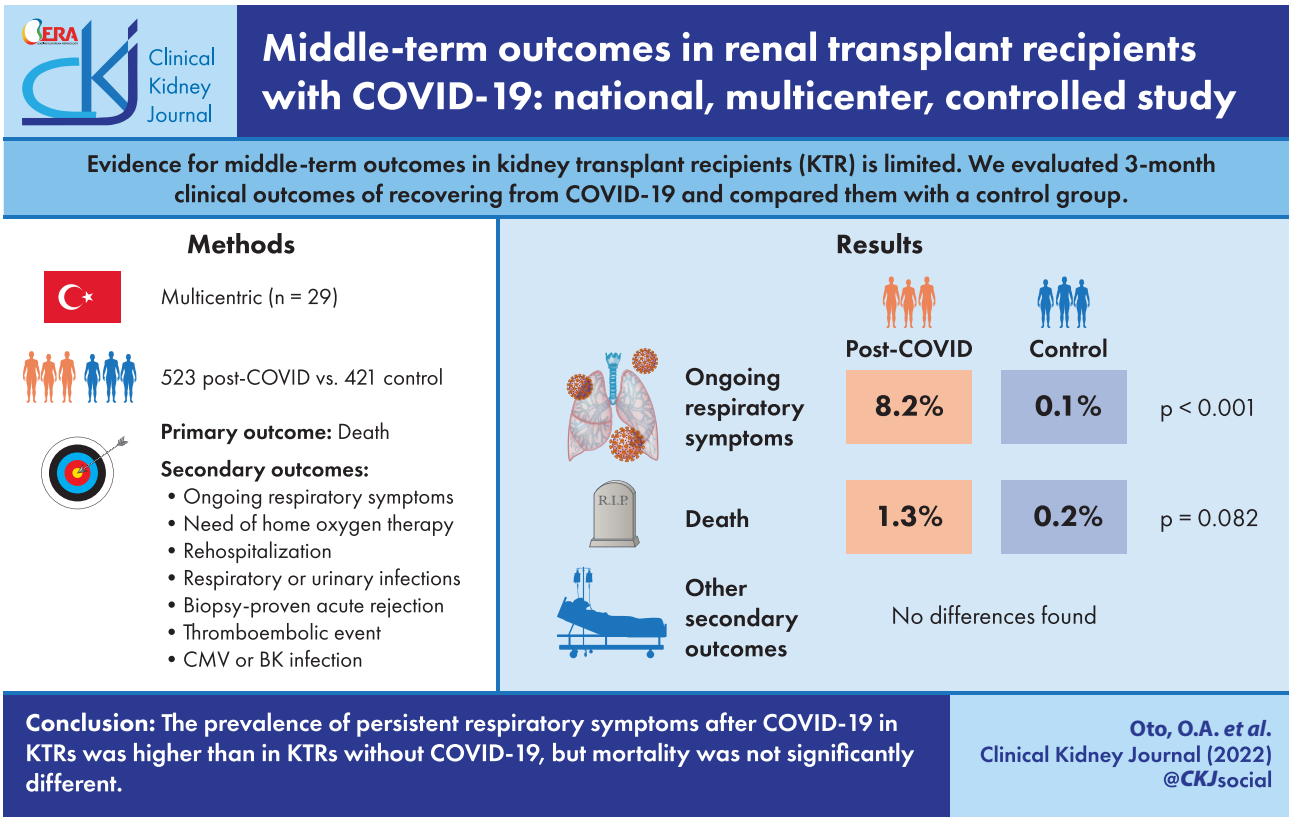
Background. In this study, we evaluated 3-month clinical outcomes of kidney transplant recipients (KTR) recovering from COVID-19 and compared them with a control group.

Method. The primary endpoint was death in the third month. Secondary endpoints were ongoing respiratory symptoms, need for home oxygen therapy, rehospitalization for any reason, lower respiratory tract infection, urinary tract infection, biopsy-proven acute rejection, venous/arterial thromboembolic event, cytomegalovirus (CMV) infection/disease and BK viruria/viremia at 3 months.

Results. A total of 944 KTR from 29 different centers were included in this study (523 patients in the COVID-19 group; 421 patients in the control group). The mean age was 46 ± 12 years (interquartile range 37–55) and 532 (56.4%) of them were male. Total number of deaths was 8 [7 (1.3%) in COVID-19 group, 1 (0.2%) in control group; $P = 0.082$]. The proportion of patients with ongoing respiratory symptoms [43 (8.2%) versus 4 (1.0%); $P < 0.001$] was statistically significantly higher in the COVID-19 group compared with the control group. There was no significant difference between the two groups in terms of other secondary endpoints.

Conclusion. The prevalence of ongoing respiratory symptoms increased in the first 3 months post-COVID in KTRs who have recovered from COVID-19, but mortality was not significantly different.

GRAPHICAL ABSTRACT



Keywords: COVID-19, kidney transplantation, mortality, outcome, registry

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly turned into a global pandemic after emerging in China in December 2019. It has been shown that approximately 20% of COVID-19 patients have moderate to severe clinical manifestations and 5% progress to critical illness [1]. Solid-organ transplant recipients have an increased vulnerability due to chronic immunosuppression and concomitant comorbidities, and the overall clinical course is worse than that of the general population [2–4]. Similarly, mortality rates in kidney transplant recipients (KTRs) were reported to be higher than in non-transplant patient groups [5, 6].

KTR may have different complications from non-transplant patient groups in the post-disease period. In KTRs that survive COVID-19, graft functions may be adversely affected by ischemic, inflammatory and nephrotoxic damage during the disease process. In addition, KTRs with COVID-19 are at higher immunological risk in the course of the disease due to drug and dose changes in immunosuppressive regimens, transfusion of blood products and virus-related immunomodulation [7].

Evidence for middle-term outcomes in KTRs recovering from COVID-19 is very limited. Therefore, in this nationwide multicenter retrospective observational study, we included a cohort of KTRs after recovery from COVID-19 with at least 3 months of follow-up and with an aim to identify the clinical outcomes and to compare them with the control group.

MATERIALS AND METHODS

This retrospective cohort study, which was carried out following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [8], was approved by the Ethics Committee of Health Sciences University Haseki Training and Research Hospital (Number: 255–2020).

Population and setting

This multicenter study included KTRs aged 18 years and older who recovered from confirmed COVID-19. Recovery from COVID-19 was defined as no symptoms or presence of mild symptoms and/or a negative polymerase chain reaction (PCR) test at the end of 14 days after diagnosis. A control group was also formed from KTR patients in the same center who did not have COVID-19. To select the control group, we included the next KTR patient without COVID-19 who was transplanted at the same center and on similar dates as KTR with COVID-19. We have created a web-based database to collect detailed national data on KTR patients with COVID-19, which was supported by the Turkish Society of Nephrology. The data of patients enrolled in the database between 15 March 2021 and 11 June 2021 were included in this study. We only included patients whose diagnosis of COVID-19 was confirmed by a nasopharyngeal swab positive reverse transcriptase-polymerase chain reaction (RT-PCR)

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

test. Patients in the active period of COVID-19 who were still positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR and/or still receiving antiviral therapy for COVID-19, SARS-CoV-2 RT-PCR negative COVID-19 patients and patients who lack outcome data were excluded.

Measurements and definitions

We recorded demographic data, reported comorbidities, non-immunosuppressive medications, primary kidney diseases, body mass index (BMI), the data regarding transplantation (donor type, duration of transplantation, immunosuppressive medication), COVID-19-related symptoms, complications during the treatment [need for intensive care and renal replacement therapy (RRT), presence of acute kidney injury (AKI)], the COVID-19 treatment information and treatment changes. We collected data for laboratory tests [hemogram, serum creatinine, electrolytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin, C-reactive protein (CRP), ferritin, urinalysis, quantitative proteinuria] at the last routine control before the development of COVID-19 and during the enrollment. The same laboratory tests were also performed in the control group. COVID-19 severity was classified according to the suggestions in our national guideline [9]. The clinical severity of COVID-19 was defined based on the clinical presentation of COVID-19 at hospital admission and divided into four categories. 1—Mild disease: patients without shortness of breath, or any signs of viral pneumonia on chest computed tomography (CT). 2—Moderate disease: patients with symptoms such as fever and cough, shortness of breath and viral pneumonia in chest CT. 3—Severe disease: patients who need oxygen support at admission. 4—Critical disease: patients who are hypoxic at admission (arterial oxygen saturation <90%) and require close follow-up and/or need an intensive care unit (ICU). AKI was defined by the following criteria determined by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [10]: increase in serum creatinine ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or increase in serum creatinine to >1.5 times the baseline creatinine levels within 7 days.

Follow-up and outcome

The primary endpoint in the study was death in the third month. The secondary endpoints were ongoing respiratory symptoms, need for home oxygen therapy, rehospitalization for any reason, lower respiratory tract infection, urinary system infection, biopsy-proven acute rejection, venous/arterial thromboembolic event, cytomegalovirus (CMV) infection/disease BK viruria/viremia. Persistent cough and/or shortness of breath were defined as ongoing respiratory symptoms. For the control group, primary and secondary endpoints were also questioned during the same period (3 months).

Statistical analyses

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. We used visual methods (histograms and probability plots) and Kolmogorov–Smirnov tests to decide the normality of the variables. For descriptive statistics, we used numbers and percentages for categorical variables and median and interquartile ranges (25–75%) for numerical variables. We used the Chi-squared test for two- or multiple-group comparisons of categorical variables. Independent *t*-test or Mann–Whitney U test, if appropriate, was used for comparison of numerical variables. Analysis of variance test was used for numerical variables with normal distribution and Kruskal–Wallis test was used for numerical variables that did not show normal distribution. We used the Bonferroni corrected Mann–Whitney U test for subgroup analyses of variables that did not show normal distribution in *post hoc* analyses, and the Bonferroni corrected Chi-squared test for subgroup analyses of categorical variables. $P < 0.05$ was considered as the significance level.

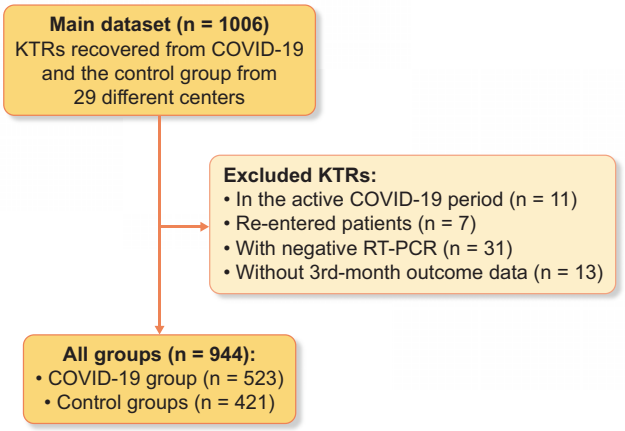


FIGURE 1: Flowchart of the study. KTR, kidney transplant recipient; RT-PCR, reverse transcriptase-polymerase chain reaction.

RESULTS

Demographic, clinical and laboratory characteristics of groups

There were a total of 1006 patients in the raw data; 11 patients in the active COVID-19 period, 7 re-entered patients, 31 patients with negative RT-PCR and 13 patients without third month outcome data were excluded. A total of 944 (523 COVID-19 patients, 421 controls) KTRs from 29 different centers were included in the study (Figure 1). The mean ± SD age was 46 ± 12 years, the male/female ratio was 532/412 (56.4/43.6%). Age, gender, immunosuppressive medications, other medications (antihypertensive, antidiabetics, etc.), smoking habits, transplantation durations, donor type and other baseline parameters were generally similar in both groups (Table 1). However, chronic obstructive pulmonary disease (COPD) was significantly more frequent in the COVID-19 group compared with the control group (3.8% versus 1.4%, respectively, $P = 0.026$). Compared with the control group, in the COVID-19 group; BMI, serum creatinine, amount of proteinuria, and ferritin, CRP, LDH, AST and ALT levels were significantly higher, whereas serum albumin and hemoglobin levels, and leukocyte and lymphocyte counts were significantly lower (Table 1). Other comorbidities and medication data of the study groups are shown in Supplementary data, Table S2.

Presentation, treatment regimes and complications of COVID-19 patients during the active period

The most common symptoms at admission were myalgia (68.0%) and cough (63.8%), followed by fever (63.7%) and dys-

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

Table 1. Baseline characteristics, lab tests, medication and follow-up parameters of the study groups

		All patients N: 944	COVID-19 group N: 523	Control group N: 421	P
Age, years, mean ± SD		46.0 ± 12.0	45.0 ± 12.0	46.0 ± 12.0	0.726
Gender, *n*/*N* (%)[a]	Male	532/944 (56.4)	303/523(57.9)	229/421 (54.4)	0.276
Smoking status, *n* (%)	Never smoked	621/885 (70.2)	339/494 (68.6)	282/391 (72.1)	0.410
	Current smoker	25/885 (2.8)	13/494 (2.6)	12/391 (3.1)	
	Former smoked	239/885 (27.0)	142/494 (28.7)	97/391 (24.8)	
Tx duration, years, median (IQR)		6.0 (3.0–11.1)	6.6 (3.0–11.2)	6.0 (3.0–11.0)	0.414
Donor type, *n* (%)	Living non-related	90/944 (9.5)	50/523 (9.6)	40/421 (9.5)	0.068
	Living related	638/944 (67.6)	368/523 (70.4)	270/421 (64.1)	
	Deceased	216/944 (22.9)	105/523 (20.1)	111/421 (26.4)	
BMI kg/m^2, median (IQR)		25.7 (23.8–28.1)	25.9 (23.7–28.4)	25.43 (22.9–27.9)	0.019
Systolic BP, mmHg, median (IQR)		130.0 (120.0–135.0)	130.0 (120.0–133.0)	130.0 (120.0–135.0)	0.464
Diastolic BP, mmHg, median (IQR)		80.0 (70.0–85.0)	80.0 (70.0–85.0)	80.0 (74.0–85.0)	0.488
Creatinine, mg/dl, median (IQR)		1.3 (1.0–1.6)	1.3 (1.0–1.7)	1.2 (1.0–1.5)	<0.001
AST, U/L, median (IQR)		17.0 (14.0–22.0)	17.5 (14.0–24.0)	17.0 (13.0–21.0)	0.018
ALT, U/L, median (IQR)		17.0 (12.0–22.0)	17.0 (13.0–24.0)	16.0 (12.0–21.0)	0.039
LDH, U/L, median (IQR)		200.0 (163.0–247.0)	206.0 (166.0–254.0)	193.0 (160.0–236.0)	0.014
Albumin, g/dL, median (IQR)		4.2 (4.0–4.5)	4.2 (3.9–4.5)	4.3 (4.0–4.6)	0.001
Ferritin, ng/mL, median (IQR)		120.0 (43.1–295.9)	136.0 (5.0–327.5)	98.5 (38.0–252.0)	0.022
CRP, mg/L, median (IQR)		3.9 (2.1–10.0)	15.0 (2.0–16.2)	3.1 (1.7–5.6)	<0.001
Leukocyte counts/mm^3, median (IQR)		7400 (5895–9255)	7200 (5600–8903)	7600 (6100–9480)	0.008
Neutrophil counts/mm^3, median (IQR)		4640 (3540–5960)	4600 (3500–5800)	4700 (3600–6270)	0.124
Lymphocyte counts (/mm^3), median (IQR)		1775 (1185–2375)	1600(1100–2300)	1900 (1340–2500)	<0.001
Proteinuria (mg/mg), median (IQR)		228.1 (117.5–564.9)	280.0 (127.5–700.7)	188.2 (103.7–467.5)	0.001
Hemoglobin (g/dL), median (IQR)		12.9 (11.3–14.2)	12.8 (11.1–14.0)	13.0 (11.6–14.4)	0.013

P-values presented from the Chi-squared test, Fisher's exact test, *t*-test or Mann–Whitney U test.

[a]Compared with female gender.

IQR, interquartile range; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

pnea (38.0%). Most of the patients (66.0%) had a mild disease at the time of admission (Supplementary data, Table S1). The majority of the patients received favipiravir (87.5%) as antiviral treatment. A smaller subset of the patients also received tocilizumab (3.9%) or anakinra (3.1%). Almost none of the glucocorticoids (0.4%) were stopped during the active period of the disease, but the dose was temporarily increased in 43.6% of the patients. Most patients discontinued mycophenolic acid treatments (65.6%) (Supplementary data, Table S3). Chest CT revealed viral pneumonia findings in 72.9% of the COVID-19 patients. A total of 290 COVID-19 patients (55.4%) were hospitalized, 31 patients (10.7%) were followed in the ICU. Nine of 31 patients needed invasive mechanical ventilation. The length of stay in the hospital was 10 [interquartile range (IQR) 6–15] days. AKI was developed in 114 patients (39.4%) and RRT was required in 15 (5.2%) patients. SARS-CoV-2 RT-PCR-positive reinfection was reported in 6 (1.2%) patients after a median of 42 (IQR 31–89) days. In the first month, the proportion of ongoing respiratory symptoms [93 (17.8%) versus 5 (1.2%), respectively; $P < 0.001$)] and the development of lower respiratory tract infection rates [36 (6.9%) versus 5 (1.2%), respectively; $P < 0.001$] were statistically significantly higher in the COVID-19 group compared with the control group. The CRP level and proteinuria were significantly higher, while the hemoglobin and albumin levels were significantly lower in the COVID-19 patient group than in the control group. Both groups were comparable in terms of creatinine levels (Supplementary data, Table S4).

Clinical and laboratory characteristics of groups according to primary and secondary outcomes

Table 2 shows the outcomes and biochemical parameters during 3 months of follow-up. The CRP level was significantly higher, while the hemoglobin level was significantly lower in the COVID-19 patient group compared with the control group in the third month. Both groups were comparable in terms of systolic blood pressure, diastolic blood pressure, creatinine levels, albumin levels and amount of proteinuria. More deaths occurred in the COVID-19 group compared with the control group, but the difference was not statistically significant [7 (1.3%) versus 1 (0.2%), respectively; $P = 0.082$]. The proportion of ongoing respiratory symptoms [43 (8.2%) versus 4 (1.0%), respectively; $P < 0.001$] was statistically significantly higher in the COVID-19 group. Although it did not reach statistical significance, a trend towards an increase in the development of lower respiratory tract infection was detected in the COVID-19 group compared with the control group ($P = 0.05$). There was no statistically significant difference between the two groups in terms of the need for home oxygen therapy, rehospitalization, urinary tract infection, acute rejection, venous/arterial thromboembolic event, CMV infection/disease or BK virus infection. When comparing the control group, the frequency of hypertension, BMI, creatinine, AST, ALT, LDH, ferritin, CRP and proteinuria was higher, whereas the serum albumin levels, lymphocyte and hemoglobin were lower in the inpatient group. (Supplementary data, Table S5).

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

Table 2. Outcomes and biochemical parameters at 3 month follow-up

	All patients	COVID-19 patients	Control group	P
Death, *n*/*N* (%)	8/944 (0.8)	7/523 (1.3)	1/421 (0.2)	0.082
Ongoing respiratory symptoms, *n*/*N* (%)	47/944 (5.0)	43/523 (8.2)	4/421 (1.0)	<0.001
Need for home oxygen therapy, *n*/*N* (%)	5/944 (0.5)	5/523 (1.0)	0/421 (0.0)	0.069
Re-hospitalization for any reason, *n*/*N* (%)	71/944 (7.5)	41/523 (7.8)	30/421 (7.1)	0.679
Lower respiratory tract infection, *n*/*N* (%)	12/944 (1.3)	10/523 (1.9)	2/421 (0.5)	0.050
Urinary tract infection, *n*/*N* (%)	47/944 (5.0)	26/523 (5.0)	21/421 (5.0)	0.991
Acute rejection (biopsy proven), *n*/*N* (%)	10/944 (1.1)	6/523 (1.1)	4/421 (1.0)	1.000
Venous or arterial thromboembolic event, *n*/*N* (%)	5/944 (0.5)	5/523 (1.0)	0/421 (0.0)	0.069
CMV infection/disease, *n*/*N* (%)	8/944 (0.8)	6/523 (1.1)	2/421 (0.5)	0.310
BK virus infection, *n*/*N* (%)	13/944 (1.4)	6/523 (1.1)	7/421 (1.7)	0.499
Hematuria, *n*/*N* (%)	40/369 (10.8)	22/195 (11.3)	18/174 (10.3)	0.773
Pyuria, *n*/*N* (%)	65/368 (17.7)	35/195 (17.9)	30/173 (17.3)	0.879
BMI (kg/m^2), median (IQR)	25.6 (23.4–27.9)	25.7 (24.1–28.3)	25.5 (22.7–27.5)	0.133
Systolic blood pressure, mmHg, median (IQR)	130.0 (120.0–132.0)	130.0 (120.0–132.0)	130.0 (120.0–134.0)	0.890
Diastolic blood pressure, mmHg, median (IQR)	80.0 (70.0–85.0)	80.0 (70.0–84.0)	80.0 (75.0–85.0)	0.501
Creatinine, mg/dL, median (IQR)	1.3 (1.0–1.7)	1.3 (1.0–1.7)	1.2 (1.0–1.6)	0.230
Albumin, g/dL, median (IQR)	4.2 (4.0–4.5)	4.2 (3.9–4.5)	4.2 (4.0–4.5)	0.527
CRP, mg/L, median (IQR)	3.3 (2.0–6.0)	4.1 (2.5–7.4)	3.0 (2.0–5.0)	0.021
Hemoglobin, g/dL, median (IQR)	12.9 (11.4–14.2)	12.8 (11.2–14.1)	13.0 (11.7–14.4)	0.005
Proteinuria, mg/mg, median (IQR)	234.0 (115.1–600.0)	257.5 (115.0–616.0)	201.5 (115.5–458.1)	0.434

P-values presented from the Chi-squared test, Fisher's exact test, or Mann–Whitney U test.
IQR, interquartile range; BMI, body mass index; CMV, cytomegalovirus; CRP, C-reactive protein.

Clinical and laboratory characteristics according to mortality

Those who died had older age, severe COVID-19 clinic at the time of admission, needed hospitalization, required ICU, required RRT during the hospital follow-up period, required rehospitalization, ongoing respiratory symptoms, had lower respiratory infection and needed home oxygen therapy (Table 3). There was no statistically significant difference between the dead and the survivors in terms of donor type, transplantation duration, smoking habit, gender, CMV infection/disease, acute rejection, BK infection, venous/arterial thromboembolic event and urinary system infection.

DISCUSSION

In this multicenter, retrospective, controlled follow-up study of KTRs recovering from COVID-19, although it did not reach statistical significance, the number of patients who died in the post-COVID era was higher than in the control group. We found persistence of respiratory symptoms without increased risk of acute rejection, BK and CMV infection, thromboembolic event or urinary tract infection. As far as we know, this is the first controlled follow-up study in KTRs who have recovered from COVID-19.

There are growing concerns about possible long-term sequelae of COVID-19 [11]. The inflammatory damage and severe tissue sequelae characteristic of particularly severe forms of the disease may affect multiple organ systems. Some patients who recovered from COVID-19 develop persistent or new symptoms lasting weeks or months. This condition is defined as 'long COVID', 'Long Haulers' or 'Post COVID syndrome' [12].

Several publications showed that COVID-19 causes significant pulmonary sequelae. Although it was not a controlled study and was not conducted specifically for the transplant population, in a follow-up study evaluating recovery from COVID-19 in 478 patients, the incidence of new-onset dyspnea was 16%. Also, 4 months after hospitalization for COVID-19, a proportion of patients developed previously unreported symptoms and lung scan abnormalities were common in this group [13]. Similarly, in another study, dyspnea, chest pain and cough were found in 37, 16 and 14% of patients between 3 weeks and 3 months, after discharge of hospital admission by COVID-19, respectively [14]. In our patient group, the rate of patients with persistent respiratory symptoms was lower than in the literature. This may be related to the fact that many of our patients had mild COVID-19 or our patients were relatively young. The mean age was 60.9 ± 16.1 in the study of Morin *et al*. and between 49 ± 15 and 63.2 ± 15.7 in the review of Cares-Marambio *et al*. [13, 14]. However, the mean age in our study was 46.0 ± 12.0 years. In addition, we found that death was more common in the patient group whose respiratory symptoms continued. However, we do not have enough evidence to state that the deaths are related to COVID-19. This result may be an important finding emphasizing that the patient group with persistent respiratory symptoms should be followed closely after discharge.

It is unclear whether changes in immunosuppressive therapy during active COVID-19 or possible persistent inflammation during the recovery period are associated with a higher risk of transplant complications such as rejection or infection.

There are several reports that SARS-CoV-2 infection could cause exhaustion of T cells and particularly CD8+ T cells, thus leading to viral replication [15, 16]. We did not detect an increase in the risk of CMV and BK viruria/viremia in our patient group after recovery from COVID-19. This may be related to the short follow-up period. It is unclear whether there will be an increase in the frequency of viral infections in the long term.

Numerous studies have shown evidence of COVID-19-related coagulopathy and an increased risk of arterial and venous thromboembolic events [17–20]. We did not detect a significant increase in thromboembolic phenomena. This may be related to the fact that most of the patients had a mild course of COVID-19.

In immunosuppressed hosts, comorbidities and medications may impair cellular and humoral immunity and limit viral

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

Table 3. Demographic and clinical parameters according to the survival status of all patients at 3 months

		Total N: 944	Survivors N: 936	Nonsurvivors N: 8	P
Study groups, *n/N* (%)	Control group	421/944 (44.6)	420/936 (44.9)	1/8 (12.5)	0.082
	COVID-19 group	523/944 (55.4)	516/936 (55.1)	7/8 (87.5)	
Age, years, median (IQR)		46.0 (37.0–55.0)	46.0 (36.0–55.0)	59.0 (54.0–65.0)	0.001
Gender, *n/N* (%)	Male	532/944 (56.4)	527/936 (56.3)	5/8 (62.5)	1.000
Smoking, *n/N* (%)	Never smoked	621/885 (70.2)	616/877 (70.2)	5/8 (62.5)	0.758
	Current smoker	25/885 (2.8)	25/877 (2.9)	0/8 (0.0)	
	Former smoker	239/885 (2.7)	236/877 (26.9)	3/8 (37.5)	
Tx duration, years, median (IQR)		6.0 (3.0–11.0)	6.0 (3.0–11.0)	8.0 (5.0–10.0)	0.536
Donor type, *n/N* (%)	Living non-related	90/944(9.5)	88/936 (9.4)	2/8 (25.0)	0.071
	Living related	638/944 (67.6)	635/936 (67.8)	3/8 (37.5)	
	Deceased	216/944 (22.9)	213/936 (22.8)	3/8 (37.5)	
Pneumonia finding on CT, *n/N* (%)		317/435 (72.9)	310/428 (72.4)	7/7 (100.0)	0.197
Clinical presentation, *n/N* (%)	Mild disease	345/523 (66.0)	344/516 (66.6)	1/7 (14.4)	<0.001
	Moderate disease	157/523 (30.0)	155/516 (30.0)	2/7 (28.6)	
	Severe-critical disease	21/523(4.0)	17/516 (3.3)	4/7 (57.1)	
Type of treatment, *n/N* (%)	Inpatient	290/523 (55.4)	283/516 (54.8)	7/7 (100.0)	0.019
ICU admission, *n/N* (%)		31/290 (10.7)	25/283 (8.8)	6/7 (85.7)	<0.001
Outcomes at 3 month follow-up, *n/N* (%)	Ongoing respiratory symptoms	47/944 (5.0)	42/936 (4.5)	5/8 (62.5)	<0.001
	Re-hospitalization	5/944 (0.5)	2/936 (0.2)	3/8 (37.5)	<0.001
	Need for home oxygen therapy	71/944 (7.5)	66/936 (7.1)	5/8 (62.5)	<0.001
	Lower respiratory tract infection	12/944 (1.3)	7/936 (0.7)	5/8 (62.5)	<0.001
	Urinary tract infection	47/944 (5.0)	46/936 (4.9)	1/8 (12.5)	1.000
	Acute rejection (biopsy proven)	10/944 (1.1)	9/936 (1.0)	1/8 (12.5)	0.082
	Venous or arterial thromboembolic event	5/944 (0.5)	5/936 (0.5)	0/8 (0.0)	1.000
	CMV infection/disease	8/944 (0.8)	7/936 (0.7)	1/8 (12.5)	0.066
	BK virus infection	13/944 (1.4)	13/936 (1.4)	0/8 (0.0)	1.000

P-values presented from the Chi-squared test Fisher's exact test, or Mann–Whitney U test.
IQR, interquartile range; CMV, cytomegalovirus; ICU, intensive care unit; CT, computed tomography; Tx, transplantation.

clearance in COVID-19 as in other infections [21]. COVID-19 reinfections, which can sometimes be lethal, have been described in the literature [22]. We also detected reinfection in 1.2% of patients.

According to KDIGO guidelines, reduction of immunosuppressants in life-threatening infections in KTRs may be indicated [23]. Although these modifications raise concerns about the increased risk of acute rejection, studies that found no increased risk have been published [24]. Similar findings were found in a study of KTRs with COVID-19. In this study, the intensity and degree of reduction in immunosuppression were not associated with acute allograft rejection [25]. We also did not detect an increase in the risk of acute rejection, which is consistent with the literature. However, the short follow-up period should be considered while interpreting these data.

The results of our study should be evaluated according to their strengths and potential limitations. Among the strengths, to the best of our knowledge, this is the first multicenter, controlled follow-up study involving a large sample of KTRs who survived COVID-19. This study had several limitations. First, this investigation was a retrospective study. Second, simple randomization was used instead of systematic randomization when creating groups. Third, the cause of death of the patients who died was not clear. Fourth, etiological examination (radiological or functional tests) for lung pathologies causing respiratory symptoms was not performed. Fifth, the low number of patients and the low number of primary events were also potential limitations, so statistical significance might not have been determined despite the numerical difference. However, considering the chaotic environments during the pandemic period, these data can be considered close to real practical life data despite all the study's limitations.

In conclusion, the prevalence of persistent respiratory symptoms after COVID-19 in KTRs was higher than in KTRs without COVID-19, but mortality was not significantly different.

SUPPLEMENTARY DATA

The supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022

the Chinese center for disease control and prevention. *JAMA* 2020; 323: 1239–1242
2. Oltean M, Søfteland JM, Bagge J *et al*. COVID-19 in kidney transplant recipients: a systematic review of the case series available three months into the pandemic. *Infect Dis* 2020; 52: 830–837
3. 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. *Am J Transplant* 2020; 20: 3008–3018
4. Kates OS, Haydel BM, Florman SS *et al*. Coronavirus disease 2019 in solid organ transplant: a multicenter cohort study. *Clin Infect Dis* 2021; 73.11: e4090–e4099
5. Caillard S, Chavarot N, Francois H *et al*. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant* 2021; 21: 1295–1303
6. Oto OA, Ozturk S, Turgutalp K *et al*. Predicting the outcome of COVID-19 infection in kidney transplant recipients. *BMC Nephrol* 2021; 22: 100
7. Vanichanan J, Udomkarnjananun S, Avihingsanon Y *et al*. Common viral infections in kidney transplant recipients. *Kidney Res Clin Pract* 2018; 37: 323–337
8. Vandenbroucke JP, von Elm E, Altman DG *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014; 12: 1500–1524
9. Guidance to COVID-19 (SARS-CoV-2 Infection) (Study of Scientific Board) Republic of Turkey, Ministry of Health (published on 14 April 2020)
10. Kellum JA, Lameire N, Aspelin P *et al*. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1–138
11. Wiersinga WJ, Rhodes A, Cheng AC *et al*. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020; 324: 782–793
12. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. *Diabetes Metab Syndr* 2021; 15: 869–875
13. Morin L, Savale L, Pham T *et al*. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021; 325: 1525–1534
14. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R *et al*. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Chron Respir Dis* 2021; 18: 14799731211002240
15. Masset C, Ville S, Halary F *et al*. Resurgence of BK virus following COVID-19 in kidney transplant recipients. *Transpl Infect Dis* 2021; 23: e13465
16. Vabret N, Britton GJ, Gruber C *et al*. Immunology of COVID-19: current state of the science. *Immunity* 2020; 52: 910–941
17. Cui S, Chen S, Li X *et al*. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18: 1421–1424
18. Fogarty H, Townsend L, Ni Cheallaigh C *et al*. COVID19 coagulopathy in Caucasian patients. *Br J Haematol* 2020; 189: 1044–1049
19. Wichmann D, Sperhake JP, Lütgehetmann M *et al*.. Autopsy findings and venous thromboembolism in patients with COVID-19: A Prospective Cohort Study *Ann Intern Med* 2020; 173: 268–277
20. Zhou F, Yu T, Du R *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: 1054–1062
21. Ling Y, Xu S-B, Lin Y-X *et al*. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)* 2020; 133: 1039
22. Ma BM, Hung IFN, Chan GCW *et al*. Case of "relapsing" COVID-19 in a kidney transplant recipient. *Nephrology (Carlton)* 2020; 25: 933–936
23. Kasiske BL, Zeier MG, Chapman JR *et al*. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int* 2010; 77: 299–311
24. Shih C-J, Tarng D-C, Yang W-C *et al*. Immunosuppressant dose reduction and long-term rejection risk in renal transplant recipients with severe bacterial pneumonia. *Singapore Med J* 2014; 55: 372–377
25. Santeusanio AD, Menon MC, Liu C *et al*. Influence of patient characteristics and immunosuppressant management on mortality in kidney transplant recipients hospitalized with coronavirus disease 2019 (COVID-19). *Clin Transplant* 2021; 35: e14221

Downloaded from https://academic.oup.com/ckj/article/15/5/999/6528382 by Ankara University Library (ANK) user on 23 October 2022