

Clinical and paraclinical findings and outcomes of COVID-19 infection in patients with kidney transplantation in affiliated hospitals of Babol University of Medical Sciences

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Abstract

Background: The COVID-19 pandemic significantly threatens immunocompromised patients. We aimed to investigate the clinical and paraclinical findings and consequences of COVID-19 in kidney transplantation recipients.

Methods: In this retrospective study, kidney transplant recipients admitted to Ayatollah Rouhani, Shahid Beheshti, and Shahid Yahyanejad referral hospitals of Babol, North of Iran, with a diagnosis of COVID-19, were examined. Information such as demographic and laboratory findings, clinical symptoms, and treatments received was entered into pre-prepared questionnaires.

Results: Out of the 35 patients included in the study, 19 (54.3%) were males, and 16 (45.7%) were females. The mean age of patients was 47.46 ± 11.28 . Among the clinical symptoms, cough and decreased level of consciousness were associated with a higher mortality rate ($P = 0.02$). Furthermore, the mortality rate was found to be 17.1%. C-reactive protein (CRP) level, oxygen saturation percentage, and diffuse lung involvement were significantly associated with COVID-19 mortality ($p < 0.05$). In this study, no correlation was found between the amount of Cr and the outcome of COVID-19 disease ($P = 0.66$), and also, no significant relationship was found between the amount of BUN and the outcome of COVID-19 ($P = 0.46$). Even the patient who was admitted with a Cr of 6.4 did not die and was discharged with a Cr of 3.4.

Conclusion: Due to the higher mortality rate in transplant patients with COVID-19, the need for more clinically severe treatment and intensification of care in this group of patients is essential.

Keywords: Kidney transplantation, COVID-19, COVID-19 mortality, COVID-19 therapy.

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Coronavirus 2019 (COVID-19) is a clinical syndrome caused by coronavirus infection with severe acute respiratory syndrome 2 (SARS-COV-2) (1). Manifestations of this infection range from mild illnesses to acute respiratory distress syndrome (ARDS) and an inflammatory syndrome characterized by multifocal dysfunction and death (2, 3). Chronic kidney disease (CKD) is a general term used for various disorders that affect the structure and function of the kidney. CKD involves various pathophysiological processes associated with abnormal kidney function and a progressive decline in the glomerular filtration rate (GFR). CKD stages are defined based on GFR estimation (4, 5). End-stage renal disease (ESRD) is a severe form of CKD. According to one definition, ESRD is an irreversible decrease in kidney function that can lead to death if the patient does not undergo dialysis or kidney transplantation (4, 6). It is estimated that there are currently 1900,000 people in the world with ESRD, of whom 1,455,000 are undergoing hemodialysis (6).

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According to official statistics, in 2008 alone, there were more than 24,000 patients with ESRD in Iran, and the number is still increasing (7, 8). About two-thirds of patients with ESRD undergo hemodialysis, a quarter undergoes kidney transplants, and one-tenth experience peritoneal dialysis (9). Kidney surgery and transplantation is the best choice for patients with end-stage renal disease because it has a higher quality of life and longevity than other treatment options and, in the long run, imposes lower costs on the health care system (10).

Iran, like other countries in the world, is making progress in kidney transplantation, so the highest number of kidney transplants in the Middle East is related to Iran (11). Although kidney transplantation is an excellent way to manage patients with ESRD, it can also have side effects; Complications include cardiovascular complications and type 2 diabetes, infections, osteoporosis, stroke, nutritional problems, and rejection of kidney transplant. Also, consider the need to use immunosuppressive drugs to prevent transplant rejection; These patients are prone to opportunistic and exacerbated infections. Previous experiments with respiratory viruses in transplant recipients have shown that transplant recipients are more susceptible to infections with these agents.

These infections in transplant recipients progress faster to complications such as pneumonia and severe forms and have more prolonged viral excretion than non-transplant recipients. According to previous coronavirus pandemics (6, 7), COVID-19 poses a significant threat to immunocompromised patients. Recent studies have reported that kidney transplant recipients are at high risk of developing severe COVID-19 pneumonia with a mortality rate of 20-32% (12, 13) versus 1-14% (14, 15). In a study in April 2021, Craig-Schapiro et al. examined 80 patients with kidney transplants with COVID-19, of which 65% needed hospitalization, and in 4 (5%) patients, kidney transplants were rejected. The mortality rate of COVID-19 in this group was 16% (16). In this study, for the first time in this region, we aimed to investigate the clinical and paraclinical findings and consequences of COVID-19 in kidney transplantation recipients in affiliated hospitals of Babol University of Medical Sciences.

Methods

This research is a descriptive-analytical study performed by the available sampling method. It includes all the patients referred to the affiliated hospitals of Babol University of Medical Sciences from February 2020 to September 2021, who had a history of kidney transplants, and were infected

with this disease during the COVID-19 pandemic. Inclusion criteria were a history of kidney transplantation, in which the transplanted kidney has a normal function and confirmation of infection with COVID-19 based on RT-PCR and radiologic findings.

In the present study, which was designed retrospectively, the records of kidney transplant recipients who were diagnosed with COVID-19 (based on the corresponding clinical findings including fever, cough, shortness of breath, myalgia, diarrhea, nausea and vomiting, chills, sore throat, feeling of heaviness on the chest, runny nose, weakness and lethargy, sputum, loss of smell and loss of taste, skin lesions, etc., along with evidence of pulmonary involvement consistent with positive nasopharyngeal PCR test) admitted to the affiliated hospitals of Babol University of Medical Sciences were investigated and information such as demographic findings (age, sex, time since kidney transplant, history of other chronic diseases, history of smoking, alcohol and drugs), laboratory findings (Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Interleukin (IL)-6, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Ferritin, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine (Cr), and liver function test (LFT)) radiological changes such as ground glass opacities, reticular changes, clinical symptoms (cough, shortness of breath) were included in pre-prepared questionnaires.

Also, patients' clinical history, medications, ICU admission, and mortality were recorded. Then, the information of the study participants was coded and statistically analyzed using SPSS software Version 22.0. Descriptive statistics indices such as mean, standard deviation, frequency, and percentage were studied for the study variables. Also, Student's t- and Chi-square tests were used to study the correlations of variables. A p-less than 0.05 was considered statistically significant.

Results

After applying the inclusion and exclusion criteria, 35 patients were included, of which 19 (54.3%) were males. The mean age of patients was 47.46 ± 11.28 , ranged 23 to 65 years. This study divided patients into two groups under 40 years and over 40 years. Of the 11 patients under the age of 40, all were discharged in good general condition, and of the 24 patients over the age of 40, 18 were discharged, and 6 died.

The evaluation of the outcome of COVID-19 in kidney transplant patients according to demographic characteristics is presented in table 1. In the examination of clinical

symptoms, the following items were obtained: fever in 24 (68.6%), cough in 20 (57.1%), myalgia in 19 (54.3%), dyspnea in 18 (51.4%), anorexia in 16 (45.7%), chills in 16 (45.7%), weakness in 15 (42.9%), nausea in 14 (40%), tachypnea in 6 (17.1%), diarrhea in 6 (17.1%), vomiting and

sore throat in 3 (8.6%) each, decreased level of consciousness and headache in 2 (5.7%) patients each (5.7%). The evaluation of the outcome of Covid-19 in kidney transplant patients according to clinical symptoms is represented in table 2.

Table 1. Evaluation of the outcome of COVID-19 in kidney transplant patients according to demographic characteristics

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Age, years	≤ 40	11 (100)	0	0.14
	> 40	18 (75)	6 (25)	
Gender	Man	17 (89.5)	2 (10.5)	0.37
	Female	12 (75)	4 (25)	
Years after transplantation, years	< 5	15 (93.8)	1 (6.3)	0.28
	5-10	9 (75)	3 (25)	
	> 10	5 (71.4)	2 (28.6)	
Days of hospitalization, days	≤ 10	17 (94.4)	1 (5.6)	0.08
	> 10	12 (70.6)	5 (29.4)	
Smoking	Yes	2 (66.7)	1 (33.3)	0.44
	No	27 (84.4)	5 (15.6)	

Table 2. Evaluation of the outcome of COVID-19 in kidney transplant patients according to clinical symptoms

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Fever	Yes	18 (75)	6 (25)	0.14
	No	11 (100)	0	
Chills	Yes	11 (68.8)	5 (31.3)	0.07
	No	18 (94.7)	1 (3.5)	
Cough	Yes	14 (70)	6 (30)	0.02
	No	15 (100)	0	
Dyspnea	Yes	13 (2.7)	5 (27.8)	0.17
	No	16 (94.1)	1 (5.9)	
Nausea	Yes	13 (92.9)	1 (1.7)	0.36
	No	16 (2.8)	5 (23.8)	
Tachypnea	Yes	4 (66.7)	2 (33.3)	0.26
	No	25 (2.9)	4 (13.8)	
Myalgia	Yes	14 (73.7)	5 (3.3)	0.18
	No	15 (8.9)	1 (3.6)	

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Weakness	Yes	14 (3.9)	1 (6.7)	0.20
	No	15 (75)	5 (25)	
Diarrhea	Yes	5 (83.3)	1 (16.7)	1.00
	No	24 (82.8)	5 (2.17)	
Vomiting	Yes	3 (100)	0	1.00
	No	26 (3.8)	6 (18.8)	
Loss of consciousness	Yes	0	2 (100)	0.02
	No	29 (87.9)	4 (1.12)	
Anorexia	Yes	14 (87.5)	2 (12.5)	0.66
	No	15 (78.9)	4 (21.1)	
Headache	Yes	2 (100)	0	1.00
	No	27 (81.8)	6 (2.2)	
Sore throat	Yes	3 (100)	0	1.00
	No	26 (3.8)	6 (18.8)	

In the evaluation of the medication used, 29 (82.9%) patients used mycophenolate mofetil, 22 (62.9%) used cyclosporine, 10 (28.6%) used tacrolimus, and 2 (5.7%) used azathioprine. In the study of the final consequences of the disease in 29 patients who received mycophenolate mofetil, 24 (82.8%) were discharged, and 5 (17.2%) died. Furthermore, among 6 patients who did not take this medication, 5 patients (83.3%) were discharged, and 1 (16.7%) patient died, and no significant difference was found between the two groups in terms of outcome (P= 1.00). Table 3 shows the outcome of COVID-19 in kidney

transplant patients by type of immunosuppressive drug used after transplantation. The underlying disease was assessed in the patients: 23 (65.7%) patients had diabetes, 23 (65.7%) hypertension, 8 (22.9%) cardiovascular diseases, 2 (5.7%) with a history of stroke, 3 (8.6%) chronic lung disease, and 1 patient (2.9%) had hypothyroidism. Eighteen patients with diabetes (78.3%) were discharged, and 5 (21.7%) died. Also, no correlation was found between the outcome of COVID-19 patients and diabetes (P= 0.64). The evaluation of the outcome of COVID-19 in kidney transplant patients according to the underlying disease is presented in table 4.

Table 3. Evaluation of the outcome of COVID-19 in kidney transplant patients by type of immunosuppressive drug used after transplantation

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Mycophenolate mofetil	Yes	24 (82.8)	5 (17.2)	1.00
	No	5 (83.3)	1 (16.7)	
Cyclosporine	Yes	18 (81.8)	4 (18.2)	1.00
	No	11 (84.6)	2 (15.4)	
Tacrolimus	Yes	9 (90)	1 (10)	0.64
	No	20 (80)	5 (20)	
Azathioprine	Yes	2 (100)	0	1.00
	No	27 (81.8)	6 (18.2)	

In the present study, the relationship between oxygen therapy and the outcome of the disease was investigated. All 4 patients who used nasal cannula were discharged. Also, no statistically significant relationship was found between oxygen intake through a nasal cannula and the type of disease outcome ($P = 1.00$). Of the 32 patients treated with oxygen masks, 27 (84.4%) were discharged, and 5 (15.6%) died. There was no significant relationship between this type of oxygen intake and the outcome of the disease ($P = 0.44$). Additional information in this section is presented in table 5. Among the 8 people with diffuse lung involvement,

2 (25%) were discharged, and 6 (75%) died. Of the four patients with upper peripheral involvement, all four were discharged. Also, all 21 (100%) patients with middle lung peripheral involvement were discharged. Two patients with lower peripheral involvement were both discharged. Diffuse pulmonary involvement was significantly associated with mortality ($p < 0.001$). Ground-glass opacity was found in different views of lung involvement in 34 patients, of which 28 (82.4%) were discharged, and 6 (17.6%) died. No significant difference was found between the two groups ($P = 1.00$) (table 6).

Table 4. Evaluation of the outcome of COVID-19 in kidney transplant patients according to the underlying disease

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Diabetes	Yes	18 (3.78)	5 (21/7)	0.64
	No	11 (91.7)	1 (3.8)	
Blood pressure	Yes	18 (3.78)	5 (21/7)	0.64
	No	11 (91.7)	1 (3.8)	
Heart disease	Yes	5 (62.5)	3 (37.5)	0.11
	No	24 (88.9)	3 (1/11)	
Stroke	Yes	1 (50)	1 (50)	0.31
	No	28 (8/84)	5 (2.15)	
Chronic lung disease	Yes	2 (66.7)	1 (33.3)	0.44
	No	27 (84/4)	5 (15.6)	
Hypothyroidism	Yes	1 (100)	0	1.00
	No	28 (82/4)	6 (17.6)	

Table 5. Evaluation of the outcome of COVID-19 in kidney transplant patients in terms of oxygen uptake

Variables		Outcome		P-value
		Discharged, n (%)	Death, n (%)	
Nasal cannula	Yes	4 (100)	0	1.00
	No	25 (80.6)	6 (19.4)	
Simple mask	Yes	27 (84.4)	5 (15.6)	0.44
	No	2 (66.7)	1 (33.3)	
Reserve bag	Yes	9 (75)	3 (25)	0.39
	No	20 (87)	3 (13)	
BiPAP	Yes	3 (42.9)	4 (57.1)	0.009
	No	26 (92.9)	2 (7.1)	
Intubation	Yes	0	5 (100)	0.001
	No	29 (96.7)	1 (3.3)	

BiPAP, Bilevel positive airway pressure

Table 6. Evaluation of the outcome of COVID-19 in kidney transplant patients according to lung involvement

Variables	Outcome		P-value	
	Discharged, n (%)	Death, n (%)		
Pulmonary involvement area	Diffuse	2 (25)	6 (75)	<0.001
	Upper peripheral	4 (100)	0	
	Middle peripheral	21 (100)	0	
	Inferior peripheral	2 (100)	0	
Pattern of pulmonary involvement	Ground-glass opacity	28 (82.4)	6 (17.6)	1.00
	Interlobular septal thickening	9 (64.3)	5 (35.7)	0.02
	Centrilobular nodule	1 (50)	1 (50)	0.31
	Crazy Paving	8 (72.7)	3 (27.3)	0.35
	Consolidation	10 (66.7)	5 (33.3)	0.06
Oxygen saturation during hospitalization, percentage	> 94	13 (100)	0	0.004
	90-94	11 (91.7)	1 (8.3)	
	< 90	5 (50)	5 (50)	
Lung involvement, percentage	23.79±17.14	53.33±17.51	<0.001	
Hospitalization in the ICU	2 (28.6)	5 (71.4)	<0.001	

ICU, Intensive care unit

Investigating the relationship between medications taken during hospitalization and the outcome of the disease, we found no significant relationship between the use of the following drugs and the outcome of COVID-19 disease (table 7). The relationship between patients' paraclinical features and the disease outcome was investigated. Based on the number of white blood cells, patients were divided into three groups: less than 4,500/ μ L, between 4,500 and 11,000/ μ L, and more than 11,000/ μ L. In this study, no

significant difference was found between different groups based on the number of WBCs and the outcome of COVID-19 disease (P= 0.85) (table 8). In this study, no correlation was found between the amount of Cr and the outcome of COVID-19 disease (P = 0.66), and also, no significant relationship was found between the amount of BUN and the outcome of COVID-19 (P = 0.46). Even the patient who was admitted with a Cr of 6.4 did not die and was discharged with a cr of 3.4 (table 8.).

Table 7. Evaluation of the outcome of COVID-19 in kidney transplant patients according to the treatment received

Variables	Outcome		P-value	
	Discharged, n (%)	Death, n (%)		
Corticosteroids	Yes	19 (76)	6 (24)	0.15
	No	10 (100)	0	
Antiviral	Yes	26 (81.3)	6 (18.8)	1.00
	No	3 (100)	0	
Antibiotics	Yes	25 (80.6)	6 (19.4)	1.00
	No	4 (100)	0	
Anticoagulants	Yes	20 (80)	5 (20)	0.57
	No	9 (90)	1 (10)	
Plasma therapy	Yes	3 (100)	0	1.00
	No	26 (81.3)	6 (18.8)	

Table 8. Evaluation of the outcome of COVID-19 in kidney transplant patients according to paraclinical data

Variables	Outcome		P-value	
	Discharged, n (%)	Death, n (%)		
WBC count, cell/ μ L	< 4,500	7 (77.8)	2 (22.2)	0.85
	4,500-11,000	18 (85.7)	3 (14.3)	
	> 11,000	4 (80)	1 (20)	
Lymphocytes count, cell/ μ L	\leq 1,100	16 (72.7)	6 (27.3)	0.06
	> 1,100	13 (100)	0	
ESR, mm/h	\leq 40	9 (100)	0	0.13
	40-100	14 (70)	6 (30)	
CRP, mg/L	< 20	5 (100)	0	0.01
	20-50	7 (100)	0	
	50-100	11 (73.3)	4 (26.7)	
	> 100	0	2 (100)	
LDH, IU/L	\leq 500	5 (100)	0	0.54
	> 500	13 (72.2)	5 (27.8)	
IL-6, pg/mL	\leq 6	2 (100)	0	1.00
	> 6	10 (90.9)	1 (9.1)	
D-dimer, ng/mL	\leq 500	7 (100)	0	0.41
	> 500	4 (80)	1 (20)	
Cr	<1.5	17 (77.2)	5 (22.7)	0.66
	\geq 1.5	12 (92.9)	1 (7.6)	
BUN	<25	13 (76.4)	4 (23.5)	0.46
	\geq 25	16 (88.8)	2 (11.1)	
NT-proBNP, pg/mL	< 300	3 (100)	0	-
	300-900	1 (100)	0	
	> 900	6 (100)	0	

Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Interleukin (IL)-6, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Ferritin, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine (Cr), and liver function test (LFT).

Discussion

Given previous pandemics, the COVID-19 virus poses a significant threat to immunocompromised patients, and transplant physicians are particularly concerned about the impact of this new infection on this sensitive population. However, the specific effect of long-term immunosuppression on their outcome has not yet been clarified. Besides chronic immunosuppression that may

increase the risk of severe COVID-19, most kidney transplant recipients have chronic diseases, mainly cardiovascular disease and diabetes, which increase the risk of severe disease and lead to severe outcomes, including death (17). Due to the lack of sufficient studies on these patients and the clinical effects and consequences of COVID-19, the present study evaluated the clinical and paraclinical findings and outcomes of COVID-19 in

patients with kidney transplantation. In this research, fever, cough, and myalgia were the most common clinical symptoms, with a frequency of 68.8%, 57.1%, and 54.3%, respectively. Among the clinical symptoms, cough and decreased level of consciousness were associated with the outcome of the disease and a higher mortality rate. Craig-Schapiro et al. also found fever (71%), cough (59%), then dyspnea (49%), and myalgia as the most common clinical symptoms (16). In the study of Ryan et al., decreased level of consciousness was also recognized as a predictor of adverse outcomes in COVID-19 patients (18). In the present study, the mortality rate in kidney transplant patients with COVID-19 was 17.1%, similar to other studies in this group of patients (16, 19). Age over 65, male gender, and diabetes was also identified as contributing factors to mortality (19). According to available studies, the mortality rate of patients with COVID-19 who did not have a kidney transplant is reported to be one to eight percent. The present study shows the highest rate of COVID-19 mortality in kidney transplant patients. In the study of laboratory factors, all 6 patients who died had CRP above 50, so there was a significant relationship between CRP and the disease outcome ($P=0.01$). Similar results were observed in the research of Zeng F et al. (20) and Mdaghri et al. (19). In a study conducted in 2021 by Smilowitz et al., the mortality rate in patients with high CRP was significantly higher than in patients with low CRP (39.8% vs. 13%) and as a decisive factor indicating mortality. It was known that since high CRP also occurs in a cytokine storm, it can cause increased mortality and out-of-control inflammation in the course of this disease (21). In this study, no correlation was found between the amount of Cr and the outcome of COVID-19 disease ($P=0.66$), and also, no significant relationship was found between the amount of BUN and the outcome of COVID-19 ($P=0.46$). Even the patient who was admitted with a Cr of 6.4 did not die and was discharged with a cr of 3.4. However, in the research of Eli Zolotov and many other studies, mortality in patients with abnormal renal function was higher compared to patients with normal renal function (22).

This study found a significant relationship between intubation and BiPAP use with mortality in COVID-19 patients ($P=0.001$). In Oltean et al., 72.7% of patients who needed intubation died, which confirms the results of the present study. It seems that the higher mortality in these patients is the need for more critically ill patients to use more advanced methods of respiratory support and, as a result, more mortality in these patients (22). Also, more cases of death in patients with lower arterial blood oxygen saturation were reported in the present study and the study of Bentivegna et al. and many other studies, which was due

to the above (23). In the present study, no correlation was found between the number of years of transplantation and the outcome of COVID-19 disease ($p=0.28$).

Also, in Craig-Schapiro et al.'s study, the transplantation duration was not related to the mortality rate of COVID-19 (16). In a study by Nair et al., the most common pattern seen on chest X-rays and CT scans was multifocal patchy ground glass opacities (24). In this study, 34 patients out of 35 had ground-glass opacity, and most of the patients had middle peripheral involvement. However, all 6 deaths in this study occurred in patients with diffuse lung involvement, indicating a direct relationship between the severity of lung involvement and mortality in transplant patients with COVID-19. In the Moroni et al.'s study, diffuse lung involvement cases were found to be associated with adverse outcomes in COVID-19 disease (25). Moreover, in the current study, there was a correlation between the appearance of interlobular septa thickening (ILST) lung involvement with the outcome of the disease, and out of 6 patients who died, 5 had this type of involvement, which was also shown in the study of Zou et al. that it was associated with severe forms of COVID-19 disease (26).

In this study, no significant relationship was found between the treatments used to prevent transplant rejection for patients and the outcome of COVID-19, and in most studies that have been performed so far, no accurate judgment has been made due to the low sample size. In the study of Nair et al., no relationship was found between the drugs used to prevent kidney transplant rejection and the outcome of COVID-19, which was consistent with the results of the present study (24). According to the results of this study, the mortality rate in transplant patients with COVID-19 was 17.1%, and cough and decreased level of consciousness were among the cases with higher mortality in transplant patients with COVID-19. Factors such as the need for intubation and BiPAP, diffuse lung involvement, the appearance of interlobular septal thickening in the lungs, and low oxygen saturation that indicated high disease severity were also found in the present study, which, like previous studies, indicated adverse outcome. No significant relationship was found between kidney transplant treatments and mortality. It is recommended to use more sample size in future studies, and if possible, patients should be followed up for an extended period.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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