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Original Article

Omicron respiratory threat in renal transplant recipients

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Abstract

Background: Omicron was identified as one of the worrisome strains of corona virus. Renal transplant recipients (RTRs) are classified as high-risk groups due to immunosuppressed conditions. Thus, this study was conducted with the aim of comparing these patients infected with the Omicron variant with the general population infected with this variant compare.

Methods: 62 RTRs infected with the Omicron strain and 60 patients with non-RTRs who were hospitalized from 2021 to 2022 at the peak of Omicron in Tehran, Shiraz and Babol, Iran were included in the study. The two groups were compared regarding clinical findings, laboratory results, pulmonary manifestations on high-resolution computed tomography (HRCT), and adverse effects.

Results: In both groups the most common respiratory symptoms were similar. The ground glass opacity was the most frequent finding on CT scan and was seen in 86 cases (70.5%). There was a reduced absolute lymphocyte count (ALC) and platelet count (85.4% and 41.9%, respectively) in RTRs and the rise of creatinine levels was more in RTRs than those in non-RTRs (79% versus 31.6%). the disease severity (16.1% versus 5%, P = 0.008) and adverse outcomes, such as mechanical ventilation (MV) (12.9% versus 0%, P = 0.004), and the mortality rate was significantly higher in RTRs than the general population.

Conclusion: There was no significant difference in clinical symptoms between two groups except diarrhea. MV, ICU admission and mortality were significantly higher in RTRs under prolonged immunosuppression.

Keywords: Omicron, Renal transplant recipients, Immunosuppression.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, has posed a major challenge to the global health situation as one of the largest epidemics of the 21st century and has spread rapidly around the world since its emergence in December 2019 (1). According to the World Health Organization (WHO), this disease has infected more than 260 million people and killed more than 5 million (2). Since its inception, the virus has evolved and emerged in various forms based on mutations. To better monitor and prioritize these new variants, WHO has divided them into three categories, which are variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs) (3). Five VOCs have been identified, all of which have caused a new wave of pandemics and caused thousands of deaths in different countries and around the world. The last variant in this category is called Omicron (B.1.1.529) and was first discovered on November 24, 2021, in South Africa. This substance was classified as a (VOC) due to concerns from WHO about increased transmission rates, increased susceptibility to organ transplantation, and evasion of immune responses induced by vaccination (4-6).

This disease can have different consequences depending on the patient's condition such as age, underlying diseases such as cardiovascular diseases, cerebrovascular disease, abnormal inflammatory markers such as low absolute lymphocyte count, or increased D-dimer (7, 8). Thus, the mortality rate based on these factors can cover a wide range, as according to a report from China, this rate for hospitalized patients can range between 11 and 45%, depending on their conditions (7-9). This disease has also had a major impact on organ transplant programs, as patients receiving organ transplants, including kidney transplants, are at a higher risk of infection with COVID-19 (10, 11). Considering the advantages that kidney transplantation has in improving the quality of life and reducing the mortality of patients compared to other alternative treatments, as well as the reports that the mortality rate of patients on the kidney transplant waiting list has increased 2.2-fold since the COVID-19 pandemic, show that since the epidemic of COVID-19, the death rate of patients on the waiting list for kidney transplantation has increased 2.2 times, the need to perform a kidney transplant is urgent despite the risks it can pose to the patient (12-15). However, kidney transplant patients are at higher risk and have a higher mortality rate than the general population after contracting the COVID-19 virus due to their suppressed immune system, as well as other conditions such as decreased kidney function and high blood pressure or even diabetes (10, 11, 16). On the other hand, it has been observed that the covid-19 virus can cause kidney injury due to its affinity for angiotensin 2 converting enzyme receptors (17, 18). According to various reports, the frequency of acute kidney injury after Covid-19 has been up to 36.4% in critical cases (19, 20). This, along with the detection of viral RNA in urine and kidney tissue, as well as the observation of viral invasion of proximal tubule cells and podocytes, indicates the probability of direct damage to the kidney by the Covid-19 virus (21, 22). Despite the high importance of these issues and previous confirmations on the effect of MERS and SARS viruses on the outcome of kidney transplant patients, there is still limited information about risk factors, clinical manifestations, diagnostic difficulties, treatment protocols, and outcomes of RTRs infected with Omicron strain, which is the aim of our study (23, 24).

Methods

Study setting: This multi-center study was conducted at three tertiary hospitals related to Medical Sciences in Iran named Shahid Namazi in Shiraz, Shahid Labafinejad in Tehran and Shahid Beheshti and Ayatolah Rouhani in Babol.

Study population: In this case-control study, a total of 122 patients were studied, considering the inclusion and exclusion criteria. The case group consisted of renal transplant recipients (RTRs) with Omicron strain of COVID-19 pneumonia and the control group consisted of non-renal transplant patients infected with the Omicron strain. The entire study population was selected from patients who were hospitalized from December 22, 2021, to March 20, 2022. Infection with COVID-19 in the study population was confirmed by reverse transcription-polymerase chain reaction (RT-PCR), and high-resolution computed tomography (HRCT). Since it was impossible to determine the viral genome sequence by PCR for all patients and the study period coincided with the peak of the Omicron strain in Iran, the study population was infected with Omicron.

Study design: In this case-control study, demographic characteristics underlying diseases, drug history, clinical manifestations, laboratory findings, radiological findings, received treatment, and outcomes due to covid-19 during the hospitalization were analyzed and compared between case and control groups.

Outcomes and severity: The primary outcome of the study was patient status at discharge including expiratory time partial recovery, and complete recovery. In addition, other outcomes including ICU admission, endotracheal intubation, and dialysis were also examined, and compared. To examine and compare the severity of the Covid-19 disease in the two groups, based on CDC criteria, patients were divided into 4 groups: mild, moderate, severe and critical and compared with each other.

Other variables: Underlying diseases including hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cancer, and cerebrovascular accident (CVA) were examined and compared between cases and control groups. Clinical signs and symptoms of the disease such as dry cough, fever, chills, shortness of breath, muscle pain, loss of appetite, etc. were recorded on admission and during hospitalization by taking a history and examination. Laboratory tests were routinely performed, and serum and urine markers were measured. These included white blood cell (WBC) count, neutrophil, lymphocyte, hemoglobin, platelet, C - reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatinine, D-dimer, albumin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)

and alanine aminotransferase. Also, an RT-PCR test was performed for some patients.

One of the procedures performed on all patients was a high-resolution CT scan of the lungs upon admission. All patients' HRCTs were interpreted by licensed radiologists. HRCT findings that could indicate lung involvement were carefully observed and various patterns of involvement were recorded. These included bilateral, unilateral, multifocal, diffuse, peripheral, basal, consolidation, cavity, effusion, and ground-glass opacity (GGO). Based on the established protocols, patients received the necessary treatments, including supportive care, immunosuppressive therapy, antiviral therapy, etc., and the types of treatments received were evaluated in both groups.

Data collection and statistical analysis: Data collection including demographic information, underlying diseases, medication history, clinical manifestations, paraclinical findings, treatments received, and disease outcomes was performed by recording information in a checklist. All statistical analyses were performed with SPSS software (IBM SPSS Statistics 26) and a p-value less than 0.05 was considered significant. T-test was used to compare quantitative data and chi-square test was used for qualitative data. Also, logistic regression test was used to examine the factors affecting the study results.

Results

Demographic features, vaccination history, and underlying disease: In this study, 122 patients with the Omicron coronavirus strain were studied. An attempt was made to have equal numbers of individuals in both the case and control groups, so 50.8% had a history of kidney transplantation (62/122) and 49.2% had no history of kidney transplantation (60/122). In the gender distribution of these 122 participants, 73 patients were males and 49 patients were females. Also, the gender distribution in both the case and control groups was not clearly different, and 64.5% of the case group and 55% of the control group were men. As shown in table 1, an attempt was made to match the age of the patients in the two groups. In all three centers, the most common immunosuppressive drugs fort rejection prevention in RTRs were calcineurin inhibitors (Tacrolimus), antimetabolites (cellcept), and corticosteroids (prednisolone). All patients were reviewed for vaccination history, and 79% of RTRs (49/62) and 78.3% of the control group had received at least the first dose of the vaccine. Also, 75.8% of KTRs (62/47) and 65% of the control group (60/39) had received at least two doses of the vaccine. Finally, only 31.1% of all patients had received all three doses of the vaccine, and their distribution percentages in the two groups did not differ significantly.Various vaccines were used to vaccinate patients, including AstraZeneca, Sputnik, Sinopharm, Iran-Cuba, and Barkat. There was no significant difference between the two groups in terms of receiving the first, second and third doses of the vaccine. The most common underlying diseases in the case group were hypertension 37% and diabetes mellitus at 20.9%. In the control group, hypertension, diabetes mellitus, and ischemic heart disease were the most common underlying diseases with 50%, 43.3%, and 41.6%, respectively. Other underlying diseases are shown in table 1.

Clinical manifestations: Among clinical manifestations, diarrhea and anorexia were significantly more common in the case group, while nausea and vomiting were significantly more common in the control group. In both groups, the most common symptoms were similar but they are in the case group was fever (58%), chills (54.8%), dry cough (46.7%), and shortness of breath (43.5%) and in the control group was dry cough (58.3%), fever (45%), chills (40%), and shortness of breath (40%). Muscle pain sore throat, rhinorrhea, headache, and chest pain were also symptoms in both groups, but they were less common. Clinical manifestations of both groups are shown in table 2.

Table 1. Demographic characteristics, vaccination history, and underlying diseases in renal transplant recipients (RTRs) and non-Renal transplant recipients (non-RTRs) infected with Omicron strain.

Variable	Case group (RTRs)	Control group	All patients	P-value
Demographic characteristics--no./total no. (%)				
Male	40/62 (64.5)	33/60 (55)	73/122 (59.8)	0.284
Female	22/62 (35.4)	27/60 (45)	49/122 (40.2)	
Age > 50 years	30/62 (48.3)	41/60 (68.3)	71/122 (58.2)	
Case	_	_	62/122 (50.8)	
Control	_	_	60/122 (40.2)	

Vaccination history--no./total no. (%)				
First dose of vaccination	49/62 (79)	47/60 (78.3)	92/122 (75.4)	
Second dose of vaccination	47/62 (75.8)	39/60 (65)	86/122 (70.5)	
Third dose of vaccination	21/62 (33.8)	17/60 (28.3)	38/122 (31.1)	
Underlying Diseases -– no./total no. (%)				
Hypertension	23/62 (37)	30/60 (50)	53/122 (43.4)	0.151
Diabetes	13/62 (20.9)	26/60 (43.3)	39/122 (32)	0.008
Cardiovascular disease	2/62 (3.2)	25/60 (41.6)	27/122 (22.1)	0.000
Kidney diseases	3/62 (4.8)	4/60 (6.6)	7/122 (5.7)	
Respiratory disorder	0/62 (0)	4/60 (6.6)	4/122 (3.3)	
Cancer	0/62 (0)	3/60 (5)	3/122 (2.5)	
Neurologic disorder	0/62 (0)	1/60 (1.6)	1/122 (0.8)	

Table 2. Clinical manifestations in Renal transplant recipients (RTRs) and non-Renal transplant recipients (non-RTRs) infected with Omicron strain.

Variable	Case group (RTRs)	Control group	All patients	P-value
Clinical manifestation--no./total no. (%)				
Dry cough	29/62 (46.7)	35/60 (58.3)	64/122 (52.5%)	0.201
Fever	36/62 (58)	27/60 (45)	63/122 (51.6%)	0.149
Chills	34/62 (54.8)	24/60 (40)	58/122 (47.5%)	0.141
Dyspnea	27/62 (43.5)	24/60 (40)	51/122 (41.8%)	0.691
Myalgia	22/62 (35.4)	14/60 (23.3)	36/122 (29.5%)	0.141
Loss of appetite	23/62 (37)	12/60 (20)	35/122 (28.7%)	0.037
Sore throat	13/62 (20.9)	9/60 (15)	22/122 (18%)	0.391
Headache	9/62 (14.5)	4/60 (6.6)	13/122 (10.7%)	0.160
Rhinorrhea	8/62 (12.9)	5/60 (8.3)	13/122 (10.7%)	0.413
Diarrhea	4/62 (6.4)	0/60 (0)	4/122 (3.3%)	0.045
Nausea vomiting	0/62 (0)	4/60 (6.6)	4/122 (3.3%)	0.039
Chest pain	1/62 (1.6)	2/60 (3.3)	3/122 (2.5%)	0.540

Laboratory and radiographic findings: Laboratory and radiographic findings of the patients are shown in table 3. Based on laboratory tests, WBC was normal in most patients (72.1%), and the distribution of leukopenia (WBC<4000/mm^3) in the RTRs and the control group was 25.8% and 13.3%, respectively, and the distribution of leukocytosis (WBC>11000/mm^3) in the RTRs and the control group was 6.4% and 10%, respectively. Neutrophilia (PMN>60%) was observed in 93.5% of patients in the case group, and 85% of patients, in the control group. An increase in inflammatory factors was observed in both groups with a high percentage, and in total, 74.4% of patients had an increase in ESR (ESR>20), and 86.9% of patients had an increase in CRP (CRP>10).

To assess renal function, BUN and creatinine were measured. BUN was elevated in 86% of RTRs and 70% of

the controls (BUN>20), while creatinine elevation (creatinine>1.4) was more than twice as high in RTRs as in the controls, while in the case group, a 49% increase in creatinine (79%) was observed, and in the controls only a 19% increase in creatinine was observed. (31.6%). liver enzymes and serum albumin were measured to evaluate liver function. In RTRs, decreased albumin, increased AST, and increased ALT (Alb<3.5, AST>33, ALT>35) were observed in 26.7%, 25.85, and 17.7% of patients, respectively, while in the control group, these percentages were 7.3%, 44. 8% and 27.5%, respectively. (P-value: 0.02) Among the patients' non-contrast CT scan findings, ground glass opacities were the most frequent finding. The HRCT of 86(70.5%)patients showed ground glass shadows that its distribution was no significant difference in the case and control groups and it was 66.1% and 75% respectively (p-value: 0.28). As shown in table 4, bilateral involvement, peripheral involvement, basal involvement, and diffuse involvement were the views that differed significantly between the case and control groups.

Treatment, outcome, and severity: The most commonly used drug for treating COVID-19 and relieving its symptoms was remdesivir, which was prescribed to 97 (79.5%) patients. Also, 6 (4.9%) patients received Tocilizumab, 5(4.1%) patients received Baricitinib, and 2(1.6%) patients received Everolimus. Except for Baricitinib, which none of the RTRs received, there was no significant difference between the drugs received in the two groups. ICU admission was slightly higher in the case group than in the control group (p-value: 0.05), with 9.6% of RTRs (6/62) and of 1.6% non-RTRs (1/60) being admitted to the ICU. Among the 62 RTRs, 8 patients required intubation, while none of the non-RTRs required this invasive breathing procedure. Statistically, the need for intubation was significantly higher in RTRs patients than in non-RTRs (P= 0.004). Also, the need for dialysis was significantly higher in RTRs, with only 3(5%) patients in non-RTRs undergoing dialysis compared to 10 (16.1%) patients in RTRs (p-value: 0.04). The discharge status of the patients was such that 73.8% recovered completely (90/122), 20.5% recovered partially (25/122) and 5.7% dided. (7/122). All patients who died were from RTR, while none of the patients in the control group died. Outcomes of patients in both groups are was shown in table 4 and figure 1. Based on CDC criteria, patients were divided into 4 groups: mild, moderate, severe, and critical. Overall, the highest frequency of disease severity was mild with 52.3% (57/109) followed by severe with 22.9% (25/109). In RTRs, the disease was significantly more severe and the percentage of patients with severe and critical disease was significantly higher than the control group. Thus, there was only 1 critical non-RTR (1.8%) compared to 7 critical RTRs (13.2%), and compared to 17 severe RTRs (32%), there were only 8 severe non-RTRs (14.3%). as shown in table 5 and figure 2.

Table 3. Laboratory and radiography findings in Renal transplant recipients (RTRs) and non-Renal transplant recipients (non-RTR) infected with Omicron strain.

Variable	Case group (RTRs)	Control group	Total	P-value
Laboratory finding—no./total no. (%)				
leukopenia (WBC < 4k/mm3)	16/62 (25.8)	8/60 (13.3)	24/122 (19.7)	
Normal WBC (4k<WBC<11k/mm3)	42/62 (67.7)	46/60 (76.6)	88/122 (72.1)	
leukocytosis (WBC > 11k/mm3)	4/62 (6.4)	6/60 (10)	10/122 (8.2)	
Neutrophilia (PMN > 60%)	58/62 (93.5)	51/60 (85)	109/122 (90.8)	0.287
Lymphopenia (Lymphocyte < 20)	53/62 (85.4)	38/59 (64.4)	91/121 (75.2)	0.007
low hemoglobin (Hb < 14)	57/62 (91.9)	51/59 (86.4)	108/121 (88.5)	0.329
Thrombocytopenia (Plt < 150k)	26/62 (41.9)	16/59 (27.1)	42/121 (34.7)	0.087
Increased ESR (ESR > 20)	47/57 (82.4)	40/60 (66.6)	87/117 (74.4)	0.051
Increased C-reactive protein (CRP > 10)	52/62 (83.8)	54/60 (70)	106/122 (86.9)	0.316
Uremia (blood urea nitrogen > 20)	53/61 (86.8)	42/60 (70)	95/121 (78.5)	0.024

Variable	Case group (RTRs)	Control group	Total	P-value
Creatinuria (Creatine > 1.4)	49/62 (79)	19/60 (31.6)	68/122 (55.7)	
Increased D-dimer (D-dimer > 500)	50/62 (80.6)	58/60 (96.6)	108/122 (88.5)	0.006
Decreased Albumin (Alb < 3.5)	15/56 (26.7)	3/41 (7.3)	18/97 (18.6)	0.015
Increased lactate dehydrogenase (LDH > 480)	35/58 (60.3)	43/58 (74.1)	78/116 (67.2)	0.114
Increased aspartate aminotransferase (AST > 33)	16/62 (25.8)	26/58 (44.8)	42/120 (35)	0.029
Increased alanine transaminase (ALT > 35)	11/62 (17.7)	16/58 (27.5)	27/120 (22.5)	0.197
Chest CT scan patterns—no./total no. (%)				
Ground glass	41/62 (66.1)	45/60 (75)	86/122 (70.5)	0.283
Bilateral	22/62 (35.5)	41/60 (68.3)	63/122 (51)	0.000
Peripheral	19/62 (30.6)	30/60 (50)	49/122 (40.2)	0.029
Basal	5/62 (8)	24/60 (40)	29/122 (23.8)	0.000
Consolidation	14/62 (22.5)	7/60 (11.6)	21/122 (17.2)	0.110
Unilateral	11/62 (17.7)	4/60 (6.6)	15/122 (12.3)	0.063
Multifocal	6/62 (9.6)	4/60 (6.6)	10/122 (8.2)	0.544
Diffuse	5/62 (8)	0/60 (0)	5/122 (4.1)	0.025
Cavity	1/62 (1.6)	2/60 (3.3)	3/122 (2.5)	0.540
Effusion	2/62 (3.2)	1/60 (1.6)	3/122 (2.5)	0.578

Table 4. Treatment and outcomes in renal transplant recipients (RTRs) and non-Renal transplant recipients (non-RTRs) infected with Omicron strain.

Variable	Case	Control	Total	P-value
Treatment for COVID-19—no./total no. (%)				
Remdesivir	50/62 (80.6)	47/60 (78.3)	97/122 (79.5)	0.752
Tocilizumab	4/62 (6.4)	2/60 (3.3)	6/122 (4.9)	0.426
Baricitinib	0/62 (0)	5/60 (8.3)	5/122 (4.1)	0.020
Everolimus	2/62 (3.2)	0/60 (0)	2/122 (1.6)	0.161
Outcomes—no./total no. (%)				
ICU admission	6/62 (9.6)	1/60 (1.6)	7/122 (5.7)	0.057
Intubation	8/62 (12.9)	0/60 (0)	8/122 (6.6)	0.004
Dialysis	10/62 (16.1)	3/60 (5)	13/122 (10.7)	0.046
Complete improvement	42/62 (67.7)	48/60 (80)	90/122 (73.8)	
Partial improvement	13/62 (20.9)	12/60 (20)	25/122 (20.5)	
Expire	7/62 (11.2)	0/60 (0)	7/122 (5.7)	

Table 1. Severity of disease according to CDC criteria in renal transplant recipients (RTRs) and non-Renal transplant recipients (non-RTRs) infected with Omicron strain.

	Severity	Non-KTRs (Control)	RTRs (Case)	Total	P-value
		no./total no. (%)			
Disease severity based on CDC criteria	**mild**	35/56 (62.5)	22/53 (41.5)	57/109 (52.3)	0.008
	Moderate	12/56 (21.4)	7/53 (13.2)	19/109 (17.4)	
	Severe	8/56 (14.3)	17/53 (32)	25/109 (22.9)	
	Critical	1/56 (1.8)	7/53 (13.2)	8/109 (7.3)	

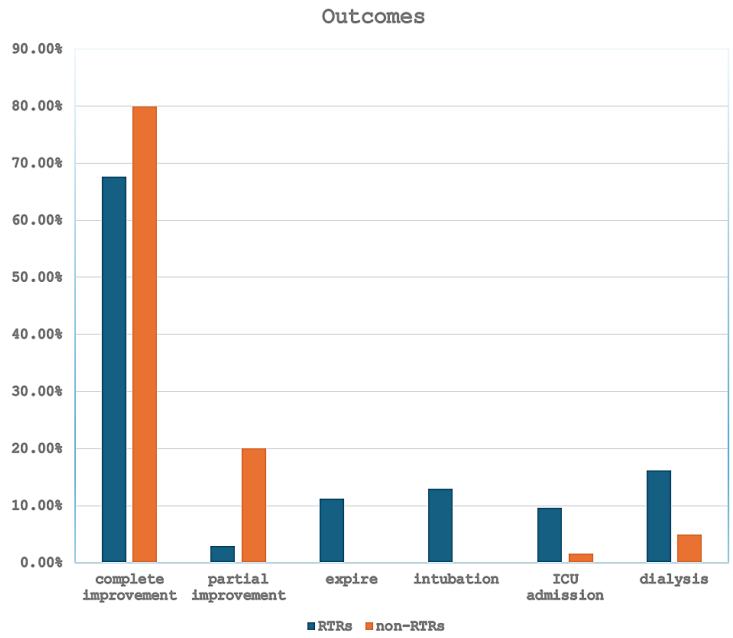

Figure 1. Outcomes in renal transplant recipients (RTRs) and non-RTRs infected with Omicron strain.

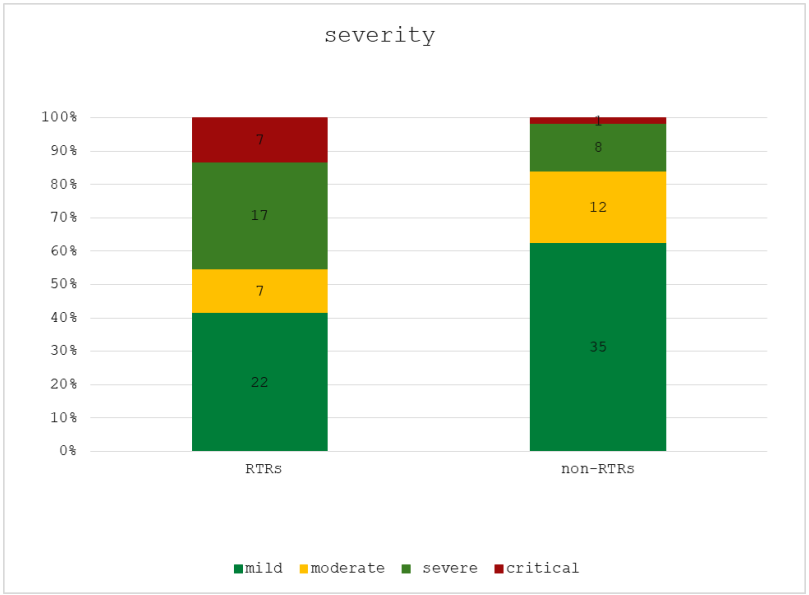

Figure 2. Disease severity based on CDC criteria in renal transplant recipients (RTRs) and non-RTRs infected with Omicron strain.

Discussion

COVID-19 is a public health emergency, and kidney transplant recipients are at significantly increased risk of severe disease as a result. A recent study has been conducted to compare RTRs and non-RTRs with Omicron strain of COVID-19 pneumonia with a particular special focus on clinical symptoms, imaging findings, disease severity and outcome. The most common comorbidity among patients with kidney disease was hypertension. There was no significant association between HTN and RTRs. The cohort study by Benotman et al. showed that hypertension was the most common comorbidity among RTRs infected with COVID-19, and a study in Turkey identified hypertension and diabetes as the most common comorbidities among kidney patients (25-27). These results were expected given, routine use of steroids and CNIs, and lower glomerular filtration rate (GFR), these results were anticipated.

However, our study results did not show this. Consistent with the symptoms reported in immunocompromised patients in a recent systematic review (28), fever, cough, and chills were the most common clinical manifestations of RTRs in our study. However, in some other studies, fever was observed less frequently among RTRs (29). According to a recent study, solid organ transplant recipients had more shortness of breath than the general population, Contrary to the findings of our study, shortness of breath was more common in RTRs. (28). Cytokine release syndrome (CRS), which has been proposed as a damaging mechanism in COVID-19, can cause lung inflammation. Therefore, preventing or reducing cytokine release reduces organ damage (30). We observed a significant difference in gastrointestinal symptoms between the two study groups. Recent research (31) has shown that diarrhea is a common clinical manifestation of SARS-CoV-2 infection in RTRs, with a significantly higher prevalence than in the general population. Immunosuppressive drugs are assumed to deteriorate gastrointestinal (GI) problems, makes them more common in RTRs than in non-RTRs; however, insome research, GI symptoms were a less common symptom among RTRs (32). RTRs may be susceptible to infections due to immunosuppression and underlying diseases such as HTN, diabetes, and cardiovascular disease Although the definitive effect of immunosuppression on the host immune response is still unknown, it is thought that chronic immunosuppression may act as a suppoter against the excessive inflammatory response and severity of the cytokine storm in RTRs with COVID-19 (33); thus the possibility of subsequent respiratory damage resulting from elevated cytokines would be mitigated. Both innate and adaptive immunity are activated after COVID and are essential for viral clearance.24, 25 Immunosuppressive agents administered after KT affect both innate and adaptive immunity and may disrupt immune control of viral replication (34). For this reason, it is hypothesized that COVID-19 pneumonia may not lead to worse outcomes in patients on chronic immunosuppressive agents. On the other hand, chronic immunosuppression, especially at the early phase of infection, is thought to increase morbidity and mortality due to changes in the immune system during the early episode of SARS-CoV-2 infection, during which a robust. Response is required to overcome viral replication and disease progression; In addition, immunosuppression places individuals at greater risk for secondary infections (33, 35). In our study, we aimed to minimize the negative effects of CNIs and antimetabolites on the clinical course of viral pneumonia by reducing or discontinuing their doses and we did this based on the severity of each person's illness (33). However, in our study, despite a significant reduction in the dose of IS drugs during the hospitalization period, none of the KTRs experienced allograft rejection, as none of them developed progressive kidney failure and renal replacement therapy and gradually recovered without the need for anti-rejection therapy. The concomitant increase in the dose of corticosteroids in the context of reduction or discontinuation of CNIs and antimetabolites may have moderated the lack of rejection. It has also been hypothesized that Patients who had to discontinue CNIs due to a severe infection benefit from the protective effect of anti-inflammatory drugs against graft rejection (36). Individual management of immunosuppressive agents is important in KTRs with COVID-19. According to our findings, the rates of hospital mortality, ICU admission, and MV requirements were different between RTRs and non-RTRs. Due to the immune suppression caused by antirejection protocols, RTRs are generally more susceptible to secondary bacterial infection. In this group of patients admitted to the ICU, the higher mortality rate may be due to concurrent secondary infection.

In addition to a higher burden of comorbidities, single-function kidneys, and worse laboratory parameters in these patients, the higher mortality rate in RTRs could be attributed to the dysfunctional immune system in the early phase of infection, when a strong immune response is required to suppress viral replication and overload. In our 2020 study, mortality and ICU admission rates were 41.6% (10/24) and 50% (12/24), respectively, in RTRs (37). This difference could be due to the experience of the treatment staff, medications and vaccination. In contrast to our

research, in previous observational studies (27, 32, 38) no significant differences were observed between RTRs and non-RTRs in terms of mortality and unfavorable outcomes. In the present study, severe to critical illnesses were seen in patients with kidney disease more than patients with no underlying kidney disease. The most commonly used drug to treat Covid-19 and relieve its symptoms was Remdesivir, which was prescribed to 97(79.5%) patients. Also, 6 (4.9%) patients received Tocilizumab, 5(4.1%) patients received Baricitinib, and 2(1.6%) patients received Everolimus.

While in a recent study, no significant difference has been observed between the two groups in terms of the severity of infection (32). However, in another case-control study, more severe conditions were diagnosed in patients with renal disease compared to patients without it. (27). Our results showed that among RTRs, AKI was more common than among controls. A recent study (38) has also found that the prevalence of AKI in RTRs was substantially higher than in the general population. RTRs during the course of infection with COVID-19 are susceptible to causes of AKI such as volume depletion, hemodynamic imbalance, acute rejection and toxicity. (39). Therefore, complications from prerenal azotemia, acute tubular necrosis, or other potential causes of AKI may occur more frequently in RTRs than in the general population. Reasons include immunosuppression, reduced drug tolerance and a single-functioning kidney (40). both lymphopenia and thrombocytopenia, which are markers of low-grade inflammation, were shown to be much more prevalent in RTRs than in non-RTRs. Consistent with our findings, a recent case-control study showed that the prevalence of thrombocytopenia and lymphopenia was much lower in patients with no underlying renal disease compared with those with RTRs, Chronic kidney disease (CKD), and end-stage renal disease (ESRD) (27). In addition, it has been found that immunocompromised transplant recipients with COVID-19 often develop lymphocytopenia. (41). RTRs may have lower lymphocyte and platelet counts due to chronic disease and the use of immunosuppressive agents such as antimetabolites (42). Despite previous case-control studies showing greater elevations in C-reactive protein in transplant patients compared with controls, (32). There was no statistically significant difference in C-reactive protein levels between the two groups (27), Approximately 70% of patients in both groups showed GGO, a pattern highly suggestive of COVID-19 pneumonia, on CT scan, and there was no statistically significant difference between the two groups. Findings associated with severe to critical clinical conditions (cavity, linear opacity, bronchiectasis, and consolidation alone) did not differ significantly between the two groups and were within the same range as observed in general population studies (43, 44). Among the critically ill patients, pleural effusion (23%), an additional lung lesion that severe inflammation and viral load (43), was more common. Another study found that although it occurred in all RTRs, it was much higher in the control group. None of the groups in our study showed a statistically significant difference. Immunosuppressive drugs may prevent cytokine release, which is thought to cause pleural effusion, which explains why this finding was not present in RTRs. The prevalence of bilateral, peripheral, and basal lesions was statistically higher in the control group. As an additional point, the RTRs had a significantly higher prevalence of unilateral and diffuse lesions, and these proportions were not consistent with those found in previous studies (43, 44).

There are limitations to our study. We had a limited number of participants in our study, and only followed them for a short period of time. Second, there was not enough useful information to review because our center does not have many registry databases. In the present study, we compared RTRs with the general papulation during the COVID pandemic with the Omicron strain. Significant differences in the severity and patterns of pulmonary involvement, risk of MV, length of hospital stay, and mortality were identified. Clinical symptoms except for diarrhea, were not significantly different. Further research with larger sample sizes is warranted to confirm and generalize the findings.

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Authors' contribution: Variants of concern (VOCs),Variants of interest (VOIs),Variants under monitoring (VUMs),Renal Transplant Recipients

(RTRs),Reverse transcription-polymerase chain reaction (RT-PCR),High resolution computed tomography (HRCT),Ground-glass opacity (GGO),Glomerular filtration rate (GFR),Intensive care unit (ICU),End-stage renal disease (ESRD), Diabetes mellitus (DM), ,Ischemic heart disease (IHD),, Chronic kidney disease (CKD), ,Chronic obstructive pulmonary disease (COPD), Cerebrovascular accident (CVA).

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