Comparison Omicron in renal transplant recipients and general population: a case-control study

Mana Baziboroun
Babol University of Medical Sciences
Mojtaba Shafiekhani
Abu-Ali Sina Hospital, Shiraz University of Medical Sciences
Masoumeh Asgharpour
Rouhani Hospital of Medical Sciences
Zahra Zare
Abu-Ali Sina Hospital, Shiraz University of Medical Sciences
Hamed Nikoupour
Abu-Ali Sina Hospital, Shiraz University of Medical Sciences
Jamshid Roozbeh
Abu-Ali Sina Hospital, Shiraz University of Medical Sciences
Elmira Mahmoudi Chalmiani
Shahid Beheshti University of Medical Science
Farshid Oliaie
Babol University of Medical Sciences
Roghayeh Akbari (Roghayeh.akbari@yahoo.com)
Babol University of Medical Sciences
Sara Abolghasemi
Shahid Beheshti University of Medical Science

Research Article

Keywords: Omicron, Renal Transplant recipients, Immunosuppression, adverse outcomes

Posted Date: January 6th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2400099/v1

Abstract

Background

Omicron was introduced as one of the variants of concern covid-19. Due to their immunosuppressed condition, renal transplant recipients (RTRs) are a vulnerable group. Thus, the present study was conducted to compare RTRs and non-RTRs infected with Omicron, with a special focus on clinical symptoms, imaging characteristics, disease severity, and outcomes.

Methods

The case group included 62 RTRs infected with the Omicron strain and the control group included 60 patients non-RTRs infected with the Omicron strain were hospitalized from December 22, 2021, to March 20, 2022 at the peak of Omicron in Tehran, Shiraz and Babol, Iran. RTRs with Omicron were compared to healthy controls in terms of their clinical symptoms, laboratory results, patterns of lung involvement on high resolution computed tomography (HRCT) and unfavorable outcomes, including rates of ICU hospitalization, mechanical ventilation (MV) use, and mortality.

Results

Among the clinical symptoms, significantly more people in the case group experienced diarrhea (P = 0.045). The most common symptoms were the same in both groups, but the order in the case group was fever (58%), chills (54.8%), dry cough (46.7%), and dyspnea (43.5%) and in the control group was dry cough (58.3%), fever (45%), chills (40%), and dyspnea (40%). Overall, the prevalence of pulmonary involvement was greater in the control group. It was shown that RTRs had a reduced absolute lymphocyte count (ALC) and platelet count. As a result, RTRs' creatinine levels rose more than those of non-RTRs. There was a statistically significant difference between the RTRs and control groups in terms of ICU admission, mechanical ventilation (MV), length of hospital stay, and mortality as unfavorable outcomes.

Conclusion

In conclusion, clinical symptoms were not significantly different except diarrhea. The severity based on CDC criteria and risk of adverse outcomes, such as MV, ICU admission, and mortality, were significantly different between RTRs under prolonged immunosuppression and the control group.

Introduction

As one of the biggest epidemics of the 21st century, the severe acute respiratory syndrome of the coronavirus-2, which causes the disease of COVID-19, has faced a great challenge to the health situation of the world, and since its appearance in December 2019, it has spread rapidly throughout the world (1).

According to the statistics of the World Health Organization, this disease has infected more than 260 million people and has also caused the death of more than 5 million people (2). Since the emergence of this virus, it has evolved based on the mutations created in it, and different types of it have appeared. For better monitoring and prioritization of these new types, the World Health Organization 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 epidemics and caused the death of thousands of people in different countries and around the world. The last type of this category is called Omicron (B.1.1.529) and was discovered for the first time on November 24, 2021, in South Africa. According to the World Health Organization's concerns regarding the increase in the transmission rate, higher affinity for transplants, as well as evasion of the immune responses created by the injection of the vaccine, it was introduced as one of the VOCs (4–6).

This disease can have different consequences according to 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). Such that the mortality rate according to these factors can include a wide range, as according to a report from China, this rate can be between 11 and 45 percent for hospitalized patients, depending on their conditions (7–9).

This disease has also had a strong impact on organ transplant programs because 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 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 necessary despite the risks it can bring to the patient (12–15). However, kidney transplant patients due to the suppression of their immune system, as well as being accompanied by other conditions such as reduced kidney function and high blood pressure or even diabetes, are at a higher risk and have a higher death rate than normal people after contracting the COVID-19 virus (10, 11, 16). On the other hand, it has been seen that the covid-19 virus can cause kidney damage due to its affinity for angiotensin 2 converting enzyme receptors (17, 18). According to various reports, the frequency of acute kidney injury after contracting Covid-19 has been up to 36.4% in critical cases(19, 20)

This issue, along with detecting the presence of viral RNA in urine and kidney tissue, as well as observing the invasion of the virus into the cells of the proximal tubules and podocytes, indicates the possibility 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 problems, treatment protocols, and outcomes of RTRs infected with Omicron strain, which is the aim of our study (23, 24).

Materials And Methods

Study setting

The present study was conducted at three tertiary hospitals in Iran named Shahid Namazi in Shiraz, Shahid Labafinejad in Tehran and Shahid Beheshti and Ayatolah Rohani in Babol .This study was approved by the Medical Ethics Committee of Babol University of Medical Sciences (approval number: IR.MUBABOL.HRI.REC.1401.086).

Study Population

A total of 122 patients were included in this case-control study considering the inclusion and exclusion criteria. The case group included renal transplant recipients (RTRs) infected with Omicron strain and the control group included non-RTRs infected with Omicron strain. All study populations were selected from patients who were hospitalized from December 22, 2021, to March 20, 2022.

The infection with COVID-19 was confirmed in the study population with reverse transcription-polymerase chain reaction (RT-PCR), and high resolution computed tomography (HRCT). Since the study period coincided with the peak of the Omicron strain in Iran, the study population was considered to be infected with Omicron.

Study Design

In this case-control study, after obtaining informed consent from all patients, demographic features, 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 the patient's condition at discharge including expiration, partial improvement, and complete improvement. In addition, other outcomes including ICU admission, intubation, and dialysis were investigated examined, and compared.

To investigate and compare the severity of the Covid-19 disease in two groups, based on the CDC criteria, the 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 clinical symptoms of the disease such as dry cough, fever, chills, dyspnea, myalgia, loss of appetite, etc. were recorded on admission and during hospitalization by history taking and examination.

Laboratory tests were performed routinely and urine and serum markers were measured. Including 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 for all patients was a high-resolution CT scan of the lungs upon admission. All patients' HRCTs were interpreted by certified radiologists. HRCT findings that can indicate lung involvement were carefully observed and various patterns of involvement were recorded. Including patterns of bilateral, unilateral, multifocal, diffuse, peripheral, basal, consolidation, cavity, effusion, and ground-glass opacity (GGO).

Based on the established protocols, the patients received the necessary treatments, including supportive treatments, 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, drug history, clinical manifestations, Para clinical findings, received treatments, and disease outcomes were done by recording information in a checklist.

All statistical analyzes 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, a logistic regression test was used to check the factors affecting the results of the study.

Results

Demographic features, vaccination history, and underlying disease

In this study, 122 patients with the Coronavirus Omicron strain were included. The effort was to make the number of people in both case and control groups equal, therefore 50.8% had a history of kidney transplantation (62/122) and 49.2% didn't have kidney transplantation (60/122). In the sex distribution of these 122 participants, 73 patients were men and 49 patients were women. 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, it was tried to match the age of the patients in the two groups.

All patients were checked 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 vaccine. Finally, only 31.1% of all patients had received all three doses of the vaccine, and their distribution percentages were not significantly different in the two groups. Various vaccines including AstraZeneca, Sputnik, Sinopharm, Iran-Cuba, and Barkat were used to vaccinate the patients. There was no significant difference between 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 at 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. As shown in Table 1, there were a few other underlying diseases such as CKD, COPD, Cancer, and a history of CVA.

Table 1
Demographic characteristics, vaccination history, and underlying diseases in RTRs and 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. (%)				
HTN	23/62 (37)	30/60 (50)	53/122 (43.4)	0.151
DM	13/62 (20.9)	26/60 (43.3)	39/122 (32)	0.008
IHD	2/62 (3.2)	25/60 (41.6)	27/122 (22.1)	0.000
CKD	3/62 (4.8)	4/60 (6.6)	7/122 (5.7)	
COPD	0/62 (0)	4/60 (6.6)	4/122 (3.3)	
Cancer	0/62 (0)	3/60 (5)	3/122 (2.5)	
CVA	0/62 (0)	1/60 (1.6)	1/122 (0.8)	

Clinical Manifestations

Among the clinical manifestations, diarrhea and Loss of appetite were significantly more in the case group, while nausea and vomiting were significantly more in the control group. The most common symptoms were the same in both groups, but the order in the case group was fever (58%), chills (54.8%), dry cough (46.7%), and dyspnea (43.5%) and in the control group was dry cough (58.3%), fever (45%), chills (40%), and dyspnea (40%).

Myalgia, sore throat, rhinorrhea, headache, and chest pain were also symptoms of both groups but they were less common. Clinical manifestations of both group was demonstrated in Table 2.

Table 2
Clinical manifestations in RTRs and 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 Radiography Findings

Laboratory and radiography findings of the patients was 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 control group was 25.8% and 13.3%, respectively, and the distribution of leukocytosis (WBC > 11000/mm^3) in the RTRs and control group was 6.4% and 10%, respectively. Neutrophilia (PMN > 60%) was detected in 93.5% of patients in the case group, and 85% of patients, in the control group.

An increase in inflammatory factors was detected 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 evaluate kidney function, BUN and Creatinine were measured. BUN in 86% of RTRs and 70% of the control group was increased (BUN > 20), while the increase in creatinine (creatinine > 1.4) in RTRs was more than twice as high as in the control group, compared to 49 increase in creatinine in the case group (79%), only 19 increase in creatinine was detected in the control group (31.6%).

To check liver function, blood albumin level and liver enzymes were measured. In RTRs, decreased albumin, increased AST, and increased ALT (Alb < 3.5, AST > 33, ALT > 35) were detected 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.

Among the non-contrast CT scan findings of the patients, the ground glass opacity was the most frequent, and the HRCT of 86 patients (70.5%) showed ground glass shadows that its distribution in the case and control groups was not significantly different and was 66.1% and 75% respectively. As shown in Table 4, bilateral involvement, peripheral involvement, basal involvement, and diffuse involvement were the views that were significantly different in the case and control groups.

Table 3
Laboratory and radiography findings in RTRs and non-RTRs infected with Omicronstrain.

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 CRP (CRP > 10)	52/62 (83.8)	54/60 (70)	106/122 (86.9)	0.316
Uremia (BUN > 20)	53/61 (86.8)	42/60 (70)	95/121 (78.5)	0.024
Creatinuria (Cr > 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

Variable	Case group (RTRs)	Control group	Total	P-value
Laboratory finding—no./total no. (%)				
Decreased Alb (Alb < 3.5)	15/56 (26.7)	3/41 (7.3)	18/97 (18.6)	0.015
Increased LDH (LDH > 480)	35/58 (60.3)	43/58 (74.1)	78/116 (67.2)	0.114
Increased AST (AST > 33)	16/62 (25.8)	26/58 (44.8)	42/120 (35)	0.029
Increased ALT (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

Treatment, Outcome, And Severity

The most drugs that were used to treat Covid-19 and alleviate its symptoms was Remdesivir, which was prescribed to 97 patients (79.5%). Also, 6 patients (4.9%) received Tocilizumab, 5 patients (4.1%) received Baricitinib, and 2 patients (1.6%) received Everolimus. There was no significant difference between the drugs received in the two groups except Baricitinib, which none of the RTRs received.

ICU admission in the case group was significantly higher than the control group (P-value: 0.057), as 9.6% RTRs (6/62) and 1.6% non-RTRs (1/60) admitted to the ICU. Among the 62 RTRs, 8 patients required

intubation, while none of the non-RTRs needed this invasive method of breathing. Statistically, the need for intubation in RTRs patients was significantly higher than in non-RTRs (p-value = 0.004). Also, the need for dialysis was significantly higher in RTRs, and compared to dialysis in 10 patients (16.1%) in RTRs, only 3 patients (5%) in non-RTRs underwent dialysis (P-value: 0.046). The discharge status of patients was such that 73.8% recovered completely (90/122), 20.5% recovered partially (25/122) and 5.7% expired (7/122). All the expired patients were from the RTRs and none of the control group patients expired. Outcomes of patients in both groups was shown in Table 4 and Fig. 1.

Table 4
Treatment and outcomes in RTRs and 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)	

Based on CDC criteria, patients were divided into 4 groups: mild, moderate, severe, and critical. In total, the highest frequency in terms of patient 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 who were involved in severe and critical disease was significantly higher than the control group. In this way, compared to 7 critical RTRs (13.2%), there was only 1 critical non-RTR (1.8%) and compared to 17 severe RTRs (32%), there were only 8 severe non-RTRs (14.3%). as shown in Table 5 and Fig. 2.

Table 5
Disease severity based on CDC criteria in RTRs and 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)	

Discussion

COVID-19 is a public health emergency, and kidney transplant recipients have a significant chance of contracting a severe illness as a result. The present study was conducted to compare RTRs and non-RTRs infected with COVID-19, with a special focus on clinical symptoms, imaging characteristics, disease severity, and outcomes during the Omicron epidemic.

The most prevalent comorbidity among patients with kidney disease was hypertension. No significant correlation existed between HTN and RTRs. The Benoteman et al. cohort study revealed that hypertension was the most prevalent comorbidity among RTRs infected with COVID-19, and a Turkish study identified hypertension and diabetes as the most prevalent comorbidities among patients with kidney disease (25–27). Due to the underlying disease, routine use of steroids and CNIs, and lower glomerular filtration rate (GFR), these results were anticipated.

However, the results of our study did not show this. In accordance with symptoms reported in immunocompromised patients in a recent systematic review (28), fever, cough, and chills were found to be the most common clinical manifestations of RTRs in our study. In some other studies, however, fever was less common among RTRs (29). According to a recent study, solid organ transplant recipients exhibited greater dyspnea than the general population; likewise, in our study, dyspnea was higher in RTRs than in the control group (28). The cytokine release syndrome (CRS), which has been proposed as a destructive mechanism in COVID-19, can cause lung inflammation. Consequently, preventing or reducing cytokine release will reduce organ damage (30).

We found a significant difference between the two study groups in terms of gastrointestinal symptoms. Recent research (31) revealed that diarrhea is a common clinical manifestation of SARS-CoV-2 infection in RTRs, with a prevalence significantly higher than that of the general population. It is hypothesized that immunosuppressive agents exacerbate gastrointestinal (GI) symptoms, making them more prevalent in

RTRs infected with COVID-19 than in the general population (31); however, in other studies, GI symptoms were a less common symptom among RTRs (32).

RTRs may be more susceptible to infection due to their immunosuppression and burden of comorbidities, including diabetes, HTN, and cardiovascular disease. Although the definitive effect of immunosuppression on host immune response is unknown yet, it has been speculated that chronic immunosuppression may play a role as a protector against hyper-inflammatory response and cytokine storm severity in RTRs with COVID-19 (33); thus the possibility of subsequent respiratory damage resulting from elevated cytokines would be mitigated.

Because of this, it is assumed that infection with COVID-19 might not result in worse consequences in patients under immunosuppression agents chronically. Additionally, the protective role of chronic use of CNIs has been suggested in COVID-19-infected patients (34).

On the other hand, being on chronic immunosuppression, especially at the first phase of infection, has been thought to increase morbidity and mortality owing to the altered immune system during the early episode of SARS-CoV-2 infection, during which a strong response is required to overcome viral replication and disease progression; moreover, immunosuppression puts individuals at higher risk of 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 either decreasing the dosage of CNIs or discontinuing them together, and we did so based on the severity of illness in each patient at the time of hospitalization (33).

However, in our study, despite a remarkable dose reduction of IS medications through the admission period, none of the KTRs experienced allograft rejection, as none of them developed progressive kidney failure and renal replacement therapy requirements and gradually recovered without antirejection t. The simultaneous increase of corticosteroids to stress dose in the context of decreasing or discontinuing CNIs and antimetabolites may have modulated the absence of rejection. Patients who had to stop CNIs due to a severe infection have also been hypothesized to benefit from anti-inflammatory drugs' protective effect against rejection (36). It is important; case-by-case immunosuppressive management should be evaluated for each KTR infected with COVID-19.

In-hospital mortality, ICU admission, and MV requirements were significantly different between RTRs and non-RTRs, according to our findings. Due to the immune suppression caused by antirejection protocols, RTRs are generally more susceptible to bacterial superinfection. In this group of ICU-admitted patients, a higher mortality rate may have been caused by concurrent superinfection. In addition to a higher burden of comorbidities, single-functioning kidneys, and worse laboratory parameters in these patients, the higher mortality rate in RTRs could be attributed to ineffective immune function during the early phase of infection, when a strong immune response is required to suppress viral replication and overload. In the study we conducted in 2020, the mortality rate and ICU admission rate were 41.6% (10/24) and 50% (12/24), respectively, in RTRs (37). This difference can be due to the experience of the treatment staff, drugs and vaccination. Unlike our study, previous observational studies (27, 32, 38), found no significant difference between RTRs and non-RTRs in terms of mortality and adverse outcomes (death or ICU

admission). In our study, severe to critical situations were more detected in patients with kidney disease compared to patients without underlying kidney disease. The most drugs that were used to treat Covid-19 and alleviate its symptoms was Remdesivir, which was prescribed to 97 patients (79.5%). Also, 6 patients (4.9%) received Tocilizumab, 5 patients (4.1%) received Baricitinib, and 2 patients (1.6%) received Everolimus.

whereas, in a recently conducted case-control study, in terms of COVID-19 infection severity, no significant difference was detected between the two groups (32). but, in another case-control study, severe to critical situations were more detected in patients with kidney disease compared to patients without underlying kidney disease (27). Our results showed that among RTRs, AKI was more common than among controls. A recent study (38) also found that the prevalence of AKI in RTRs was substantially higher than in the general population. During the progression of COVID-19 infection, RTRs are predisposed to AKI etiologies like acute rejection, hemodynamic imbalance, volume depletion, medication toxicity, and high fever (39). Thus, complications may arise more frequently in RTRs than in the general population from prerenal azotemia, acute tubular necrosis, or other potential etiologies of AKI. Reasons include immunosuppression, decreased medication 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 research found that the prevalence of thrombocytopenia and lymphopenia was much lower in patients without any underlying kidney illness compared to those with RTRs, Chronic kidney disease (CKD), and end-stage renal disease (ESRD) (27). Additionally, immunocompromised organ transplant recipients with COVID-19 were found to frequently have lymphocytopenia (41). RTRs may have lower lymphocyte and platelet counts because of chronic disease and the usage of immunosuppressive agents such as antimetabolites (42). There was no statistically significant difference in C-reactive protein levels between the two groups (27), despite previous case-control studies showing a greater increase in C-reactive protein in RTRs compared with their control group (32).

About 70% of patients in both groups displayed GGO, a highly suggestive pattern of COVID-19 pneumonia, on CT scan, with no statistically significant difference between the two groups. Findings associated with severe to critical clinical conditions (cavity, linear opacity, bronchiectasis, and consolidation alone) were not significantly different between the two groups and were within the same ballpark as those seen in studies of the general population (43, 44).

Among critically ill patients, pleural effusion (23%), an extra pulmonary lesion suggestive of severe inflammation and viral load (43), was usually more common. Another study found that while it was present in all of the RTRs, it was much higher in the control group. Neither group showed statistically significant differences in our investigation. Immunosuppressive drugs may prevent cytokine release, which is thought to cause pleural effusion, explaining why this finding is absent 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 the ratios did

not agree with those found in earlier research (43, 44). The prevalence of pulmonary involvement was higher in the control group as a whole.

There are some limitations to our study. We had a limited number of participants in our study, and we only followed them for a brief period. Secondly, there wasn't enough useful information to go around because our facility doesn't have many registry databases.

Conclusion

According to our knowledge, this case-control study for the first time comparing RTRs under chronic immunosuppression to the general population in Omicron pandemic. Identified substantial differences in severity, patterns of pulmonary involvement, risk of MV, ICU admission, length of hospital stay, and mortality. Clinical symptoms were not significantly different except diarrhea. Reassuring and deducible from findings necessitates additional research with higher sample sizes.

Abbreviations

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)

Declarations

Acknowledgements: The study has not previously been published. The present study was supported by Babol University of Medical Sciences and we thank the Clinical Research Development Unit of Rouhani Hospital.

Author contributions: ZZ, RA and SA have made substantial contributions to conception and design of the study. ZZ, RA, SA, MSH, MA, ZZ, HN, JR, EMch and FO: acquisition of data, analysis and interpretation of data. All authors contributed substantially to its revision and All authors read and approved the final manuscript.

Funding: This Study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets used and analyzed during the current study are available with author Roghaye Akbari,MD.

Ethics approval and Informed consent to participate:

This study was approved by the Medical Ethics Committee of Babol University of Medical Sciences (approval number: IR.MUBABOL.HRI.REC.1401.086). Were explained to the participants and they were assured that all their information would was kept confidential. Informed consent was also obtained from all patients (from legal representative/guardians of the illiterate participants). All methods were performed following the relevant guidelines and regulations.

Consent for publication: not applicable.

Competing interests: The authors report no proprietary or commercial conflicts of interest with respect to any product mentioned or concept discussed in this article.

Author details .1:Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.2:Infectious Disease and Tropical Medicine Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran.3: Shiraz Transplant Center, Abu-Ali Sina Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.4:Shiraz Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.5:Department of Nephrology, Rouhani Hospital of Medical Sciences, Babol, Iran

References

1. WHO. Coronavirus disease 2019 (COVID-19) Situation Report 2022 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. WHO. Coronavirus disease (COVID-19) pandemic 2021 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
3. WHO. Tracking SARS-CoV-2 variants 2022 [Available from: https://www.who.int/activities/tracking-SARS-CoV-2-variants.
4. He X, Hong W, Pan X, Lu G, Wei X. SARS-CoV-2 Omicron variant: characteristics and prevention. MedComm. 2021;2(4):838-45.
5. Ingraham NE, Ingbar DH. The omicron variant of SARS-CoV-2: Understanding the known and living with unknowns. Clinical and translational medicine. 2021;11(12):e685.
6. Agency UHS. COVID-19 variants: genomically confirmed case numbers: UK Health Security Agency; 2021 [updated 24 June, 2022. Available from: https://www.gov.uk/government/publications/covid-19-variants-genomically-confirmed-case-numbers.
7. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020;46(5):846-8.
8. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. European Respiratory Journal. 2020;55(5).
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet.

2020;395(10229):1054-62.

10. Michaels MG, La Hoz RM, Danziger-Isakov L, Blumberg EA, Kumar D, Green M, et al. Coronavirus disease 2019: implications of emerging infections for transplantation. American Journal of Transplantation. 2020;20(7):1768-72.
11. Milloy M, Wood E. Withdrawal from methadone in US prisons: cruel and unusual? The Lancet. 2015;386(9991):316-8.
12. Schnuelle P, Lorenz D, Trede M, Van Der Woude F. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. Journal of the American Society of Nephrology. 1998;9(11):2135-41.
13. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. Jama. 1993;270(11):1339-43.
14. Chiu M-C. Suggested management of immunocompromized kidney patients suffering from SARS. Pediatric Nephrology. 2003;18(12):1204-5.
15. Boyarsky BJ, Werbel WA, Durand CM, Avery RK, Jackson KR, Kernodle AB, et al. Early national and center-level changes to kidney transplantation in the United States during the COVID-19 epidemic. American Journal of Transplantation. 2020;20(11):3131-9.
16. Fishman JA. Infection in solid-organ transplant recipients. New England Journal of Medicine. 2007;357(25):2601-14.
17. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney international. 1996;50(1):235-42.
18. Kostro J, Hellmann A, Kobiela J, Skóra I, Lichodziejewska-Niemierko M, Dębska-Ślizień A, et al., editors. Quality of life after kidney transplantation: a prospective study. Transplantation proceedings; 2016: Elsevier.
19. Sharifi-Razavi A, Sedaghat Z, Baziboroun M, Karimi N. COVID-19 accompanied with intracerebral hemorrhage: A case series. Archives of Clinical Infectious Diseases. 2020;15(4).
20. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. Critical Care. 2020;24(1):1-8.
21. D'Marco L, Puchades MJ, Romero-Parra M, Gimenez-Civera E, Soler MJ, Ortiz A, et al. Coronavirus disease 2019 in chronic kidney disease. Clinical kidney journal. 2020;13(3):297-306.
22. Sperati CJ. Coronavirus: kidney damage caused by COVID-19. John Hopkins Medicine 2022 [updated March 1, 2022. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/coronavirus-kidney-damage-caused-by-covid19.
23. Kumar D, Tellier R, Draker R, Levy G, Humar A. Severe Acute Respiratory Syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening. American Journal of Transplantation. 2003;3(8):977-81.
24. AlGhamdi M, Mushtaq F, Awn N, Shalhoub S. MERS CoV infection in two renal transplant recipients: case report. American Journal of Transplantation. 2015;15(4):1101-4.

25. Ozturk S, Turgutalp K, Arici M, Odabas A, Altiparmak M, Aydin Z, et al. Mortality analysis of COVID-19 infection in chronic kidney disease. 2020.
26. Benotmane I, Perrin P, Vargas GG, Bassand X, Keller N, Lavaux T, et al. Biomarkers of cytokine release syndrome predict disease severity and mortality from COVID-19 in kidney transplant recipients. Transplantation. 2021;105(1):158-69.
27. Ozturk S, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. Nephrology Dialysis Transplantation. 2020;35(12):2083-95.
28. Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. Journal of Infection. 2021;82(3):329-38.
29. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. New England Journal of Medicine. 2020;382(25):2475-7.
30. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clinical immunology. 2020;215:108427.
31. Caillard S, Anglicheau D, Matignon M, Durrbach A, Greze C, Frimat L, et al. An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants. Kidney international. 2020;98(6):1549-58.
32. Monfared A, Akhondzadeh L, Mousazadeh M, Jafari A, Khosravi M, Lebadi M, et al. COVID-19 in renal transplant recipients and general population: a comparative study of clinical, laboratory, and radiological features, severity, and outcome. Virology Journal. 2021;18(1):1-14.
33. Chen TY, Farghaly S, Cham S, Tatem LL, Sin JH, Rauda R, et al. COVID-19 pneumonia in kidney transplant recipients: focus on immunosuppression management. Transplant Infectious Disease. 2020;22(5):e13378.
34. Hage R, Steinack C, Gautschi F, Schuurmans MM. Transplant drugs against SARS, MERS and COVID-19. Transplantology. 2020;1(2):71-84.
35. Andersen KM, Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, et al. Association between chronic use of immunosuppresive drugs and clinical outcomes from coronavirus disease 2019 (COVID-19) hospitalization: a retrospective cohort study in a large US health system. Clinical Infectious Diseases. 2021;73(11):e4124-e30.
36. Maggiore U, Abramowicz D, Crespo M, Mariat C, Mjoen G, Peruzzi L, et al. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. Oxford University Press; 2020. p. 899-904.
37. Abolghasemi S, Mardani M, Sali S, Honarvar N, Baziboroun M. COVID-19 and kidney transplant recipients. Transplant Infectious Disease. 2020;22(6):e13413.
38. Aziz F, Mandelbrot D, Singh T, Parajuli S, Garg N, Mohamed M, et al., editors. Early report on published outcomes in kidney transplant recipients compared to nontransplant patients infected with

coronavirus disease 2019. Transplantation Proceedings; 2020: Elsevier.

39. Adapa S, Chenna A, Balla M, Merugu GP, Koduri NM, Daggubati SR, et al. COVID-19 pandemic causing acute kidney injury and impact on patients with chronic kidney disease and renal transplantation. Journal of clinical medicine research. 2020;12(6):352.
40. Zhu L, Gong N, Liu B, Lu X, Chen D, Chen S, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China. European urology. 2020;77(6):748-54.
41. Fishman JA, Grossi PA. Novel Coronavirus-19 (COVID-19) in the immunocompromised transplant recipient:# Flatteningthecurve. Wiley Online Library; 2020. p. 1765-7.
42. Chaudhry ZS, Williams JD, Vahia A, Fadel R, Parraga Acosta T, Prashar R, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: a cohort study. American Journal of Transplantation. 2020;20(11):3051-60.
43. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. AJR Am J Roentgenol. 2020;214(5):1072-7.
44. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative radiology. 2020.

Figures

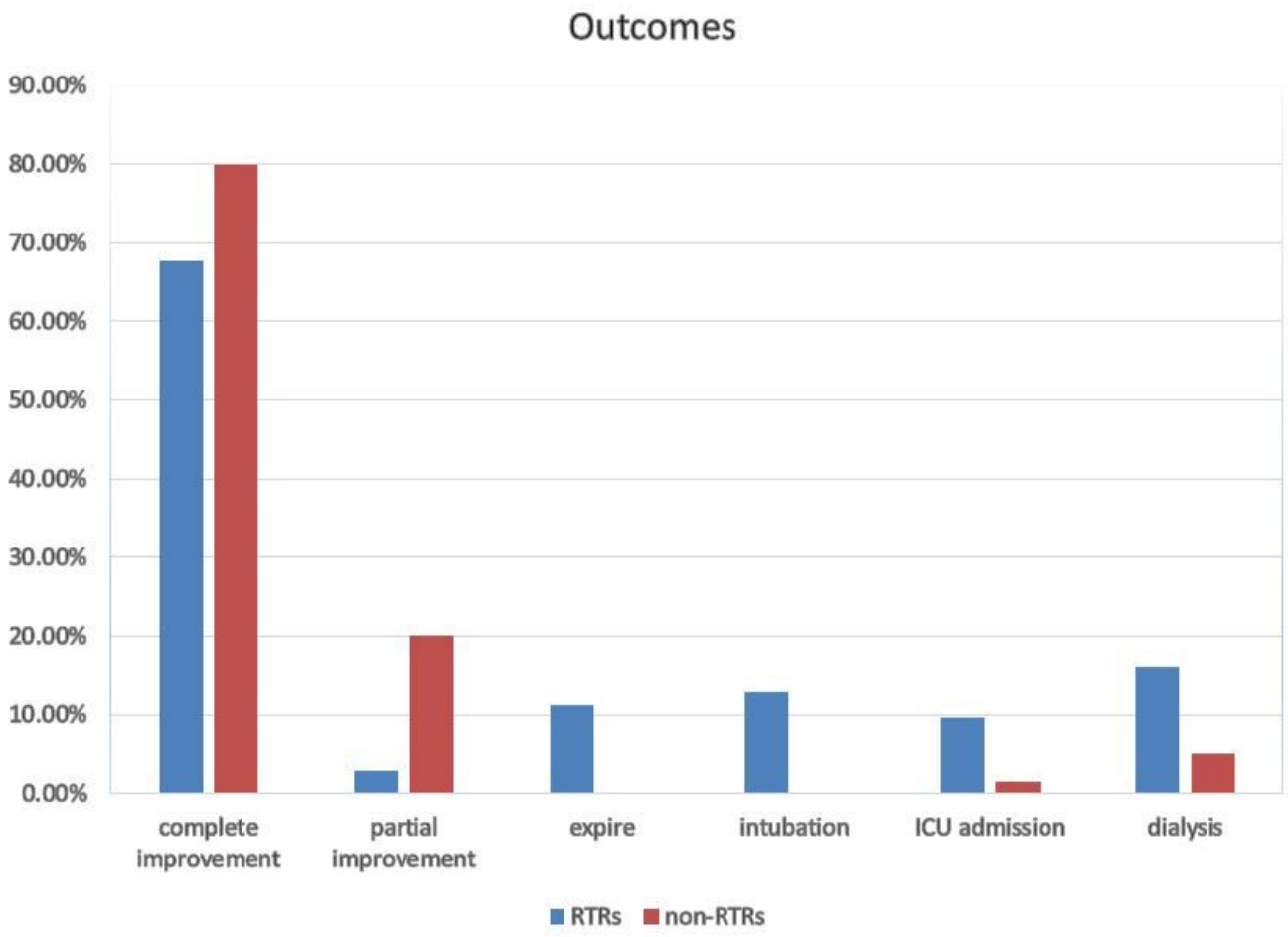

Figure 1

Outcomes in RTRs and non-RTRs infected with Omicron strain.

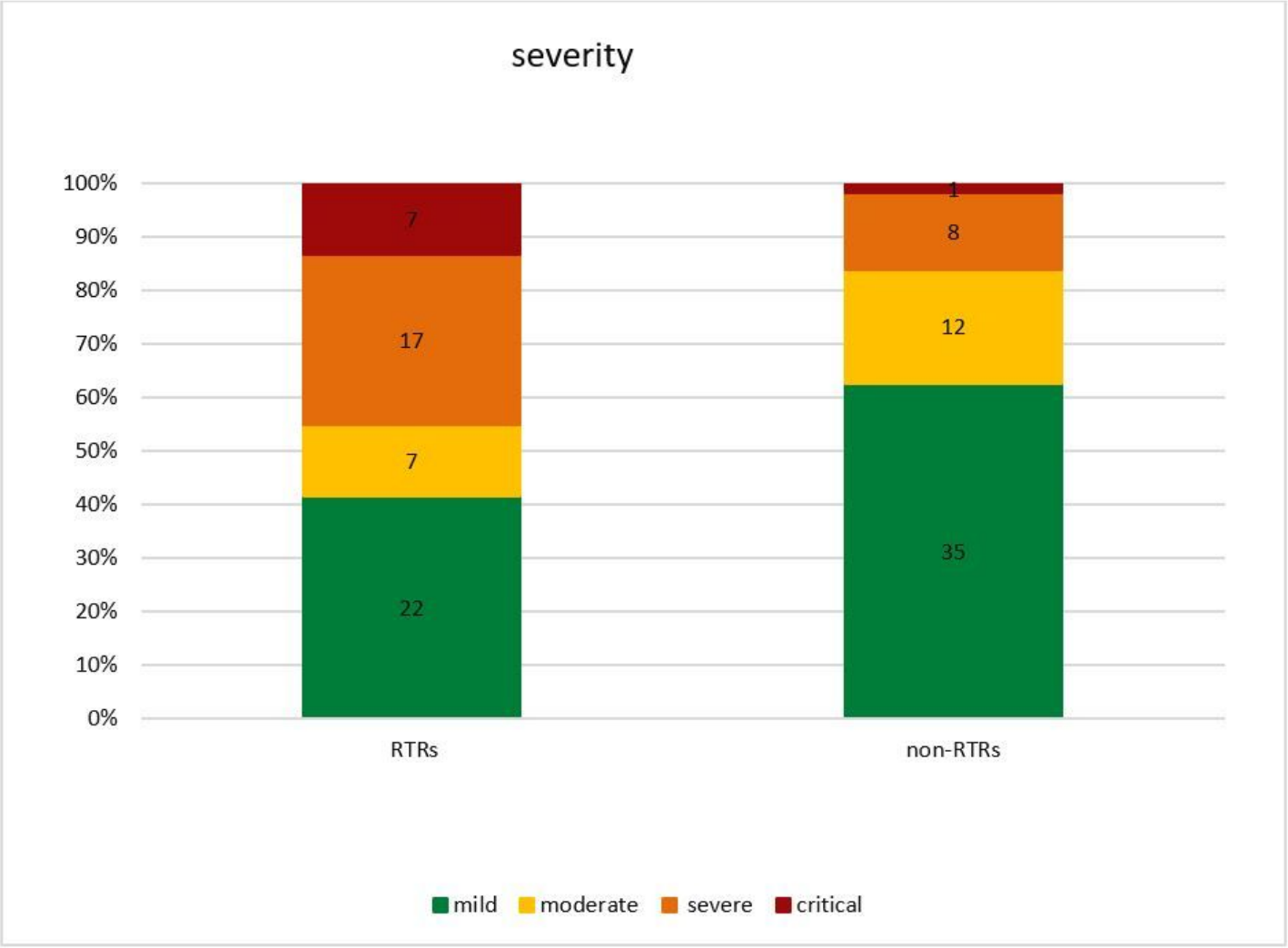

Figure 2

Disease severity based on CDC criteria in RTRs and non-RTRs infected with Omicron strain.