Comparative study of COVID-19 infection in renal transplant recipients and non transplant recipients

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Abstract

To analyse the difference in COVID-19 infection between kidney transplant patients and non-transplant patients. We included post-transplant patients with COVID-19 infection who attended Shenzhen No. 3 Hospital from December 2022 to February 2023, and enrolled the general population with COVID-19 infection who were hospitalized during the same period, matched by age and gender. They were divided into Kidney Transplant Recipients group (KTR) (n=194) and Non-Kidney Transplant Recipients Group(NKTR)(n=516) and the basic information, clinical symptoms, laboratory data, treatments and outcomes of these two groups were compared. The proportion of the renal transplant population classified as severe and critical was 15.5%, which was significantly higher than that in NKTR group (P < 0.05); the proportion of patients with pneumonia was also significantly higher than that in NKTR group. The mean maximum fever temperature was slightly higher in the NKTR(P<0.001);Kidney transplant population having lower absolute lymphocyte counts on admission and 7 days after admission than the general population, with statistically significant differences(P<0.001, P¡0.001). The use of intravenous hormones was significantly higher (42.8% vs. 6.0%, p=0.000), as was the use of small molecules such as Azvudine and Paxlovid, compared to the general population. A total of 10 patients in the included population required ICU admission, all in the KTR group; six patients experienced death, also in the renal transplant group. Conclusion: Post-transplant COVID-19 infections are more severe and require hormonal and small molecule antiviral therapy, and the prognosis is worse than in the general population.

INTRODUCTION

Since 2019, the world has seen a rapid and wavelike spread of the coronavirus disease 2019(COVID-19). From 2019 to December 2022, more than 650 million confirmed cases and more than 6.6 million deaths have been reported globally. The Omicron variants originally reported in Southern Africa have spread globally at a significantly higher rate than the Delta variant in November 2021. It already proved to be the dominant influenza strain in most parts of the world at present[1].

Compared to the general population, Kidney transplant recipients(KTRs) are susceptible to multiple infectious diseases because they need to take immunosuppressive medication after kidney transplantation surgery[2-5]. KTRs always suffer from chronic illness such as high blood pressure or various chronic kidney disorder. As a result, they have higher rates of critically ill patients and mortality rates than the general population which call for high attention from experts in the field of kidney transplantation[6].

According to the researches by Montefiore Medical Center in New York and Columbia University Kidney Transplantation Project, the overall performance of COVID-19 in KTR is similar to that of the general population. The most common symptoms are fever, cough, dyspnea, fatigue, diarrhea and myalgia[7-8]. While a another previous researches showed that KTR may face more severe challenges than non-transplant patients. Based on a recent meta-analysis, transplant patients with COVID-19 had a higher risk (+57%) of intensive care unit admission than non-transplant patients[9]. In addition, research has shown that KTRs,

as well as other solid organ transplant recipients (SOTR), the incidence of pneumonia after infection with Omicron was significantly higher than that of ordinary population, resulting the increased proportion of abnormal chest CT imaging. While there may not be significant differences in X-ray radiation detection, as for scattered and slight ground glass like shadow changes, the ordinary posterior anterior combined with lateral chest X-ray is difficult to detect [10].

Most KTRs have 2-3 high-risk factors, which belong to the category of high risk groups that exhibit severe or critically severe conditions, which call for immediately antiviral treatment according to the Diagnosis and Treatment scheme of COVID-19 (Version X) of China[2]. New neutralizing antibodies and antiviral drugs have been used in antiviral therapy nowadays[11-16]. The former includes tixagevimab and cilgavimab as well[17-18]. The latter includes Paxlovid, Azvudine (2'-deoxy-2'-β-fluoro-4'-azidocytidine) (FNC), nematvir, ritonavir, molnupiravir and so on[19].

To compare the differences of the diagnosis and treatment of KTRs and the general population infected with Omicron, we collected 194 kidney transplant patients (KTRs) and 516 patients in the general population who were followed up from December 2022 to January 2023 at The Third People's Hospital of Shenzhen.

2. Method

2.1 Study design and participants

This study retrospectively collected post-transplant patients with novel coronavirus infection who attended Shenzhen No. 3 Hospital from December 2022 to February 2023, and enrolled the general population with novel coronavirus infection who were hospitalized or treated as outpatients during the same period, matched by age and gender. The characteristics of infection and prognosis after novel coronavirus infection were compared between the renal transplantation population and the general population.This study was approved and supervised by the ethics committee of the Third People's Hospital of Shenzhen (approval number 2023-036-02) and registered in Clinical Trials(NCT05926076).

2.2 Inclusion and exclusion criteria for the study population

Inclusion criteria:

Confirmed novel coronavirus infection between December 2022 to February 2023,

Exclusion criteria:

Age less than 18; failure of the transplanted kidney before the new coronavirus infection; exclusion of oral immunosuppressed and other types of organ transplant recipients from the non-renal transplant population

2.3 Data collection

Age, BMI, underlying comorbidities and other basic information were collected retrospectively from the two groups. The medical records were used to collect information about the patients' new coronavirus infection, such as the time of onset of symptoms, time of diagnosis, time of conversion and common symptoms such as fever, cough, nasal congestion and runny nose, muscle aches and pains.

2.4 Diagnostic criteria

The diagnostic criteria were based on the Chinese Novel Coronavirus Infection Treatment Protocol (Trial Version 10). Positive nucleic acid or antigen was diagnosed as Coronavirus infection. Patients were divided into four categories according to their severity as follows: Mild COVID-19, Medium COVID-19,Heavy COVID-19,Critical COVID-19

2.5 Statistical analysis

Normally distributed measures were expressed as mean ± standard deviation and t-tests were used for comparisons between groups; non-normally distributed measures were expressed as median (interquartile range) and non-parametric tests were used for comparisons between groups. Frequency (expressed as proportion)

was used for count data and the chi-squared test was used for comparisons between groups. Multifactor logistic regression analysis was used to compare differences in the occurrence of symptoms after novel coronavirus infection between the two groups. In addition, Kaplan-Meier curves for the occurrence of adverse outcomes in the two populations were plotted to compare the occurrence of adverse outcomes between the two groups. All statistical analyses were performed with SPSS (22.0) software.

3. Results

3.1 Basic information

A total of 710 patients with novel coronavirus infection were included in this study, including 194 kidney transplant patients (KTR) and 516 patients from the general population (NKTR)(Figure1), with a mean age of 48.8+-11.0 years, the youngest being 21 years and the oldest 80 years. Of these, 482 were male (67.9%), 411 were mild (57.9%), 261 were moderate (36.8%) and 38 were severe and critical (5.4%).
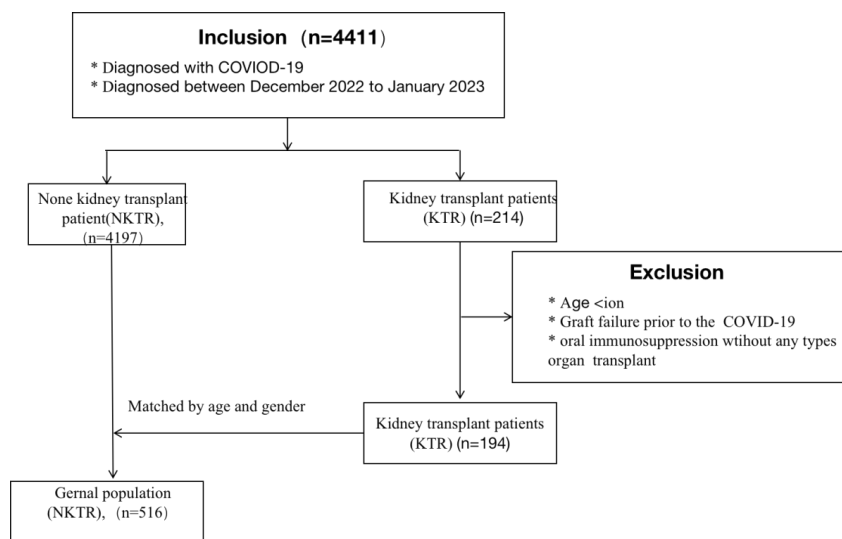

Figure 1 Flowchart of the inclusion and exclusion criteria

There was no statistical difference in the age and gender composition of the patients in the renal transplant group compared with those in the non-transplant group. There was a difference in vaccination between the two groups, with the vaccination rate in the general population being 67.2%, significantly higher than in the renal transplant group ($P < 0.05$). In addition, 66.0% of patients in the renal transplant group had hypertension and 24.7% had diabetes mellitus, which were higher than those in the non-renal transplant group ($P < 0.05$); the proportion of the renal transplant population classified as severe and critical was 15.5%, which was significantly higher than that in the non-renal transplant group ($P < 0.05$); the proportion of patients with pneumonia was also significantly higher than that in the non-renal transplant group. Baseline patient profiles are shown in Table 1

Table 1 Comparison of basic information between the two groups

	Group-NKTR (N=516)	Group-KTR (N=194)	P
Age,y,Mean±SD	48.0±11.1	47.3±10.7	0.467
BMI,Kg/m^2,Mean±SD	24.1±3.8	22.2±3.0	0.000
Female,n(%)	355(68.8%)	127(65.5%)	0.396
Degree of education, n(%)			

3

Junior high school and below	157(30.4%)	54(27.8%)	0.254
High school or technical secondary school	112(21.7%)	53(27.3%)	
Bachelor's degree or college degree	218(42.2%)	81(41.8%)	
Master degree or above	29(5.6%)	6(3.1%)	
Vaccination	347(67.2%)	9(4.6%)	0.000
Hypertension,n(%)	93(18.0%)	128(66.0%)	0.000
Diabetes,n(%)	54(10.5%)	48(24.7%)	0.000
CHD*,n(%)	21(4.1%)	10(5.2%)	0.528
Tumour,n(%)	41(7.9%)	3(1.5%)	0.002
Pneumonia ,n(%)	265(51.4%)	169(87.1%)	0.000
Novel coronavirus infection typing,n(%)			
light	399(77.3%)	12(6.2%)	0.000
medium	109(21.1%)	152(78.4%)	
heavy	8(1.6%)	26(13.4%)	
critical	0(0.0%)	4(2.1%)	

CHD*, Coronary heart disease

3.2 Comparison of post-infection symptoms

By comparing the occurrence of various symptoms in the two groups, it was found that there were differences in the symptoms of the two groups after infection with the novel coronavirus. Taking into account the differences in baseline conditions between the two groups, factors that differed between the two groups, such as whether they had been vaccinated, combined with hypertension, diabetes, tumours and novel coronavirus infection typing, were adjusted using multi-factor logistic regression and a forest plot of the adjusted ORs was drawn. The results showed that the renal transplant population was less likely to have shortness of breath (OR: 0.315, 95% CI: 0.178-0.557, P =0.000), cough (OR: 0.445, 95% CI: 0.228-0.868, P =0.018) and headache (OR: 0.445, 95% CI: 0.215-0.921, P =0.029) than the general population. As shown in Figure 2, although there was no difference in the incidence of febrile symptoms between the two groups, there were differences in maximum temperature and number of days of fever. The mean maximum fever temperature in the general population group was 38.87°C, slightly higher than in the renal transplant group (38.46°C), with a statistically significant difference between the two groups (P <0.001); whereas the duration of fever in the two groups was not significantly different by non-parametric tests.
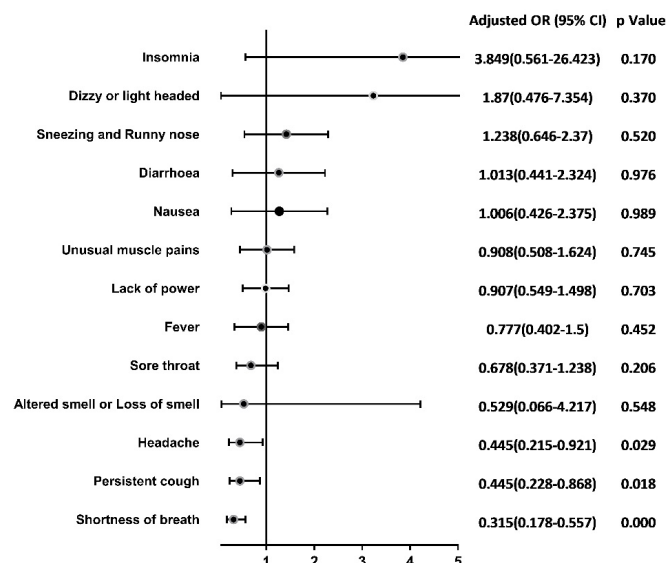
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	Adjusted OR (95% CI)	p Value
Insomnia	3.849(0.561-26.423)	0.170
Dizzy or light headed	1.87(0.476-7.354)	0.370
Sneezing and Runny nose	1.238(0.646-2.37)	0.520
Diarrhoea	1.013(0.441-2.324)	0.976
Nausea	1.006(0.426-2.375)	0.989
Unusual muscle pains	0.908(0.508-1.624)	0.745
Lack of power	0.907(0.549-1.498)	0.703
Fever	0.777(0.402-1.5)	0.452
Sore throat	0.678(0.371-1.238)	0.206
Altered smell or Loss of smell	0.529(0.066-4.217)	0.548
Headache	0.445(0.215-0.921)	0.029
Persistent cough	0.445(0.228-0.868)	0.018
Shortness of breath	0.315(0.178-0.557)	0.000

Figure 2 Comparison of symptoms between the two groups

3.3 Changes in laboratory test data

To further investigate the infection characteristics of the two populations after novel coronavirus infection, we compared the changes in validation-related indicators at admission, 7 days after admission and at discharge in the two populations of moderately, severely and critically ill patients. The results showed that there were no significant differences in C-reactive protein (CRP) and interleukin-6 (IL-6) levels between the two groups at different time points, whereas procalcitonin (PCT) levels were different between the two groups at admission, 7 days after admission and at discharge, and were significantly higher in renal transplant patients than in the general population, with statistically significant differences($P < 0.001, P ¡0.001, P ¡0.001$)). Absolute lymphocyte counts also differed between the two groups, with the kidney transplant population having lower absolute lymphocyte counts on admission and 7 days after admission than the general population, with statistically significant differences($P < 0.001$, $P ¡0.001$). Lymphocyte counts were also lower in the kidney transplant population than in the general population, and the difference was statistically significant($P<0.001$).

The changes in T-lymphocyte count and absolute lymphocyte values at admission, 7 days after admission, and at discharge are shown in Figure 3.

The changes in CRP, IL6 and PCT levels at admission, 7 days after admission, and at discharge are shown in Figure 4.
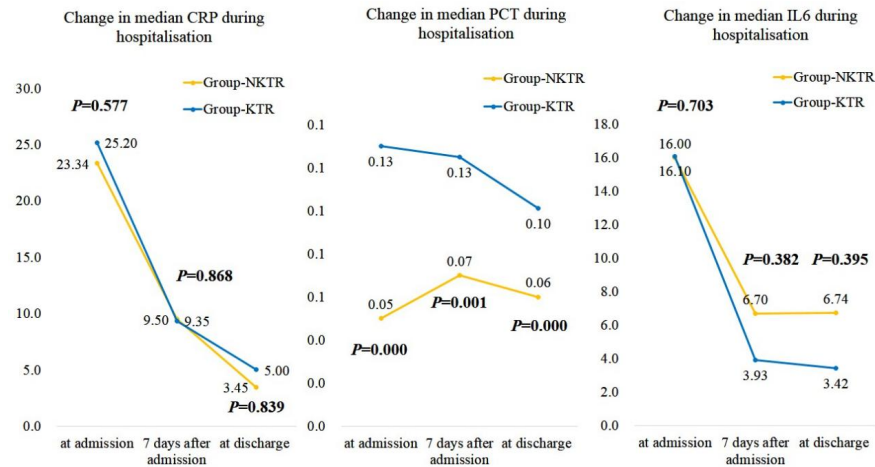
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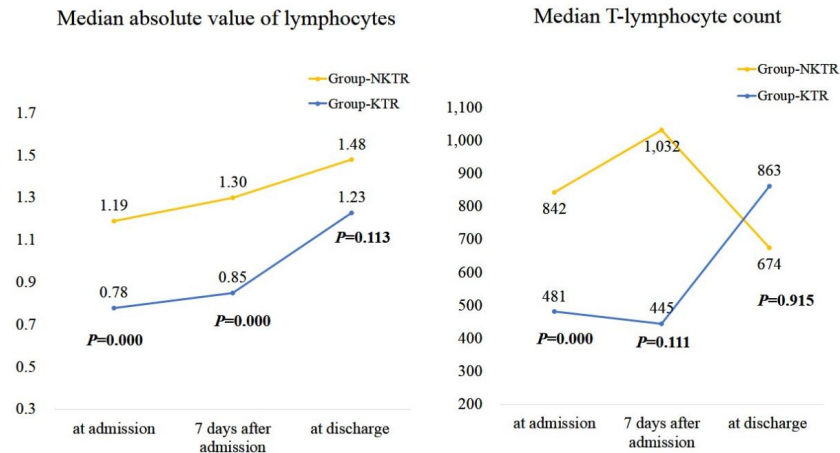Figure 3. Trends in lymphocyte changes during hospitalization

Figure 4. Trends in C-reactive protein (CRP), IL6 and PCT changes during hospitalization

3.4 Comparison of treatment of novel coronavirus infections

The use of intravenous hormones was significantly higher (42.8% vs. 6.0%, p=0.000), as was the use of small molecules such as Azvudine and Paxlovid, compared to the general population. The use of monoclonal antibodies and proglobulin was also higher than in the general population. However, the rate of oxygenation was significantly higher in the general population than in the renal transplant population.

In terms of overall length of illness, the time from symptom onset to hospital discharge was significantly longer in renal transplant patients than in the general population, with a statistically significant difference (p =0.000); renal transplant patients also had a slightly delayed visit to the hospital, with a longer time from symptom onset to admission than in the general population, again with a statistically significant difference (p =0.000). See Table 2 for details.

Table 2 Comparison of treatment and duration of illness

	Group-NKTR (N=516)	Group-KTR (N=194)	Total	P
Intravenous hormones, n (%)	31(6.0%)	83(42.8%)	114(16.1%)	0.000
Azvudine, n (%)	77(14.9%)	112(57.7%)	189(26.6%)	0.000
Paxlovid, n (%)	125(24.2%)	77(39.7%)	202(28.5%)	0.000
Monoclonal antibodies, n (%)	0(0.0%)	8(4.1%)	8(1.1%)	0.000
Proglobulin, n (%)	5(1.0%)	35(18.0%)	40(5.6%)	0.000
Oxygenation, n (%)	239(46.3%)	17(8.8%)	256(36.1%)	0.000
Time O to P*, d, median (IQR)	0.0(0.0,4.0)	0.0(0.0,3.0)	0.0(0.0,4.0)	0.481
Time O to N*, d, median (IQR)	9.0(12.0,16.0)	15.0(20.5,25.8)	10.0(14.0,21.0)	0.000
Time O to D*, d, median (IQR)	9.0(12.0,16.0)	18.8(24.0,29.0)	9.0(14.0,21.0)	0.000
Time O to A*, d, median (IQR)	2.0(5.0,8.0)	7.0(11.0,16.0)	2.0(6.0,10.0)	0.000
Days of hospitalization, d, median (IQR)	4.0(7.0,9.0)	8.0(11.0,16.0)	5.0(7.0,11.0)	0.000

Time O to P*: Time from symptom onset to positive nucleic acid;

Time O to N*: Time between onset of symptoms and negative nucleic acid test

Time O to D*: Time between onset of symptoms and discharge from hospital

Time O to A*:Time between onset of symptoms and admission to hospital

3.5 Occurrence of adverse outcomes

A total of 10 patients in the included population required ICU admission, all in the renal transplant group; six patients experienced death, also in the renal transplant group. In terms of organ impairment, graft failure occurred in five of the renal transplant patients and liver failure in one of the non-renal transplant patients. Using death or admission to the ICU as the adverse outcome, Kaplan-Meier curves were plotted for the occurrence of adverse outcomes in both groups, and the cumulative risk of adverse events was higher in the renal transplant group than in the non-renal transplant patients, with a statistically significant difference by Log-rank test (p =0.028).(Fgure 5、6)
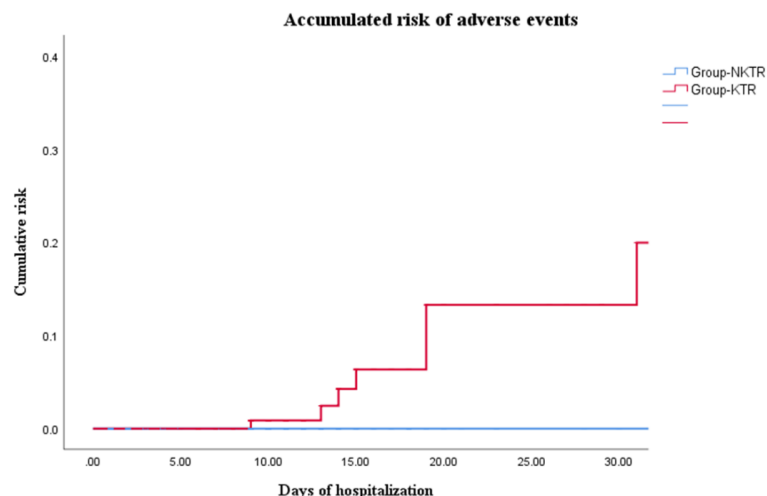
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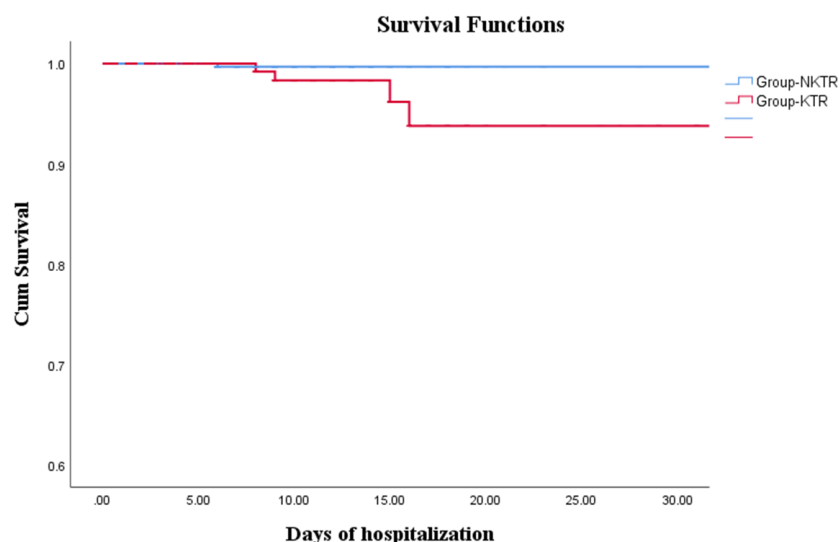Figure 5 Cumulative risk of adverse events between the two groups

Figure6 Cumulative survival rate of organ function between the two groups

Discussion

In order to compare the infection situation between the KTRs and the non-KTRs groups, we conducted a case-control study. Because of the sudden onset and rapid infection of COVID-19, we did not have enough time to prepare for a prospective study. However, we collected a large number of cases, which can also accurately explain the problem.

According to our results, there was no statistical difference in the age and gender composition of the patients in the renal transplant group compared with those in the non-transplant group. While there was a difference in vaccination between the two groups, with the vaccination rate in the general population being 67.2%, significantly higher than in the renal transplant group ($P < 0.05$)(Table 1). The difference in vaccination may be one of the reasons of the different complications between the kidney transplant group and the general

8

population group, which also indicates the protective effect of vaccination. As for the general population, the reason for the complications of the non-KTRs group may be that our non-KTRs group is not the general population in general sense, but the people who need to be hospitalized after COVID-19 infection, which is the general population relative to the transplant population. Therefore, our general population group will also have complications.

According to early data from Spain (as of December 2019), it occurs within 60 days after kidney transplantation 46% of patients infected with COVID-19 died[20]. The early symptoms of the solid organ transplantation recipients were concealed due to the use of immunosuppressants, but the later disease progressed rapidly. For example, the incidence of pneumonia, the proportion of transfer to intensive care unit (ICU), and the mortality rate of the solid organ transplantation recipients recipients were increased compared with other COVID-19 infected patients [21]. Among hospitalized recipients of KTRs, the risk of secondary acute kidney injury and dyspnea is 3.78 times and 4.53 times higher than that of normal individuals, respectively, indicating poor prognosis[22].

As shown in Figure 2, there was no difference in the incidence of fever between the two groups, while the highest temperature and the number of days of fever of the two groups are different. The average highest fever temperature of the non-KTRs group is 38.87, slightly higher than that in the KTRs group (38.87). There is also a difference in absolute lymphocyte count between the two groups. The absolute lymphocyte count of the kidney transplant population at admission and 7 days after admission is lower than that of the general population, with a statistically significant difference ($P<0.001$, $P<0.001$). The lymphocyte count of the kidney transplant population is also lower than that of the general population, and the difference is statistically significant ($P<001$). This may be related to the use of immunosuppressants by patients after transplantation.

Due to the use of immunosuppressants, it is difficult for renal transplant recipients to carry out immunotherapy for COVID-19 infection and inflammatory reaction. Monovir is less effective compared to other recommended antiviral drugs, so it is not a first-line recommended medication for the general population. However, this drug is not as effective as solid organ transplant recipients. There was no significant interaction between the immunosuppressive drugs used by the recipient in solid organ transplant recipients[13].

According to the Diagnosis and Treatment scheme of COVID-19 (Version X) of China, the patients infected with Omicron were clinically classified to mild, moderate, severe and critically ill. The first two types, collectively referred to as ordinary patients, were recommended to stay at home and take self isolation and monitoring. Whlie in terms of those with high-risk factors, they were suggested to take antiviral treatment as soon as possible. Most KTRs have 2-3 high-risk factors, which belong to the category of high risk groups that exhibit severe or critically severe conditions. So the antiviral treatment is crucial, as well as the monitoring and maintenance of graft function[2].

Our results indicate that the use of intravenous corticosteroids is significantly higher than that of the general population (42.8% vs 6.0%, p=0.000), and the use of small molecule drugs such as azivudine and combination packaging of nimatevir/ritonavir tablets is also significantly higher than that of the general population. The use of monoclonal antibodies and gamma globulin is also higher than that of the general population.

According to Table 2, the time from symptom onset to discharge in KTRs is significantly longer than that of the general population, with statistical significance (p=0.000). The incubation period of solid organ transplant recipients infected with COVID-19 is 1-14 days, most of them are 3-7 days, and the incubation period is infectious. At present, there is no evidence showed that there is difference between the latency of transplant patients and other COVID-19 infected patients[23]. Typically, the median detoxification period for individuals infected with the Omicron variant is 11.3 days, while for the solid organ transplant recipients, it is extended to 14 days[24].

Conclusion

Post-transplant infections are more severe, require hormonal and small-molecule antiviral therapy, and prog-

nosis is worse than general population.

NOTES

Conflicts of interests:

All authors have no conflicts of interest to declare.

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