Comparison of the Different Medications for COVID-19 in Kidney Transplant Recipients

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Abstract

Background We analyzed the effects of small-molecule antiviral treatment for coronavirus disease-2019 (COVID-19) Omicron strain in kidney transplant recipients. Methods We enrolled 140 kidney transplant patients admitted for COVID-19-related pneumonia were treated using small-molecule antivirals. Patients were divided into three groups: azvudine (n=62), paxlovid (n=49), and a combination of azvudine+paxlovid (A+P, n=29). Differences in clinical outcomes owing to COVID-19 infections were compared among three groups. Results Paxlovid group had a higher proportion of comorbid diabetes than the other two groups (P=0.032). There were differences in the clinical typing of the coronavirus , with the highest proportion of heavy and critical cases in the A+P group (35.5%). The immunosuppression prior to infection did not differ among the groups; however, after adjusting for immunosuppression during antiviral treatment, differences were observed. Of the 140 patients, 125 (89.29%) had fever, 114 (81.43%) had cough, and 66 (47.1%) had malaise. Combination of two or more symptoms were found in 90% patients. Mean length of hospitalization was slightly longer in the combination group than in the azvudine and paxlovid groups. Four deaths, all in the A+P group; five cases of loss of function, two in the paxlovid group and three in the A+P group; and acute kidney injury occurred in 30 patients with 7 in the azvudine, 17 in paxlovid, and 6 in A+P groups. Conclusion The use of small-molecule medications may be the optimal treatment approach; however, they should be modified based on the patients' conditions, such as clinical symptoms, laboratory results, paraclinicals, and examinations.

Introduction

Since 2019, the world has seen a rapid and wavelike spread of the coronavirus disease 2019 (COVID-19). Between 2019 and December 2022, more than 650 million confirmed cases and over 6.6 million deaths were reported globally. The original strain of COVID-19 was Alpha B.1.1.7. Beta B.1.351 variant was first reported in South Africa in May 2020, whereas the Gamma P.1 variant was isolated by Brazilian scholars for the first time in November 2020. The Delta B.1.617.2 variant was first isolated in October 2020 in India [1,2]. Lambda variant first appeared in Peru in December 2020 and has since spread to at least 41 countries and regions worldwide [3]. The Omicron variant originally reported in Southern Africa spread globally at a significantly higher rate than the Delta variant in November 2021. It has proven to be the dominant influenza strain in most parts of the world. Initially, the dominant Delta variant appeared to cause more severe disease while spreading at a lower speed than the current B.1.1.529. However, Omicron variant is more transmissible, spreads faster, and has a shorter incubation period [4]. The aerosol of the variant can survive after a long period, among the Omicron identified, BA. One variant can survive for 193.5 h on the surface of plastic products, which is 3.5 and 1.7 times longer than the original and Delta strains, respectively [5-6]. Immune escape and breakthrough infections can occur easily in vaccinated populations after infection with Omicron subvariants [7].

New neutralizing antibodies are used in antiviral therapies [8]. Currently, the most widely used long-acting neutralizing antibodies are tixagevimab and cilgavimab [9,10]. Besides the immediate protection against

COVID-19 from monoclonal antibodies (mAbs), an increasing number of antiviral drugs have been effective in the treatment of patients with COVID-19 [11-15]. The US FDA emergency use authorized paxlovid, a co-packaging box consisting of nirmatrelivr and the viral protease enhancer ritonavir (Pfizer Pharmaceutical Co., Ltd.) for the treatment of COVID-19 on November 22, 2021. Paxlovid acts on the main protease of SARS-CoV-2, inhibiting the processing of protein precursors mediated by this enzyme and viral replication, and significantly reduces mortality. Nirmatrelivr has a significant antiviral activity, and reduces the viral load most rapidly and has similar antiviral activity for α, γ, δ, λ, and Omicron variants [16]. Azvudine (2'-deoxy-2'-β-fluoro-4'-azidocytidine) (FNC) is the first SARS CoV-2 small-molecule drug developed and successfully marketed in China. The target of Azvudine is RdRp, which is a pathway that increases the indications for anti-HIV drug-based COVID-19 treatment. In a phase III clinical trial, 40% patients with COVID-19 showed alleviated clinical symptoms 1 week after receiving azvudine treatment, while the proportion of patients receiving placebo was only 11% [23].

Respiratory failure and hypoxemia are the main manifestations of COVID-19, and kidney involvement is also common [17, 18]. Solid organ transplant recipients (SPTR) are at high risk of infections, including COVID-19, by various pathogens owing to long-term immunosuppressive medication.

Regarding the treatment of kidney transplant recipients (KTR) infected with COVID-19, one of the challenges is protecting the function of the transplanted kidney while adjusting the immunosuppressant. No consensus exists on the adjustment of immunosuppressive drug doses in confirmed COVID-19 KTRs. Although immunosuppression may prevent an effective T cell response against COVID-19, it also helps to control the inflammatory reaction, which is an important cause of COVID-19 disease progression and death [19]. Another challenge in the treatment of COVID-19 after transplantation is that it is neither normal nor standard. Therefore, investigating kidney transplant patients with COVID-19 and administering small-molecule drugs therapy can pave the way for better prognosis of KTR. Since the COVID-19 outbreak, we have taken the lead in conducting clinical trials on small-molecule drugs for COVID-19 in China.

MATERIALS AND METHODS

Study protocol

One hundred and forty post-renal transplant patients hospitalized at the Third People's Hospital of Shenzhen for COVID-19 and treated using small-molecule antivirals between December 2022 and January 2023 were included. Patients were divided into azvudine, paxlovid, and azvudine + paxlovid (A+P) groups, according to their treatment status. By comparing the general condition, immunomodulatory treatment, clinical regression, and occurrence of adverse outcomes, such as death, ICU admission, and graft inactivation between the different treatment groups, we provided insights into the management of the novel coronavirus-related pneumonia in patients after kidney transplantation.

This study was strictly conducted per the guidelines of the Declaration of Helsinki of the World Medical Association (2000), and it was approved and supervised by the ethics committee of the Third People's Hospital of Shenzhen (approval number 2023-036-02).

Study inclusion and exclusion criteria

Inclusion criteria were age [?]18 years, organ transplantation prior to COVID-19 diagnosis, and hospitalization between December 2022 and January 2023.

The exclusion criteria were as follows: age < 18 years, graft failure before the diagnosis of COVID-19-related pneumonia, discontinued immunosuppression, and no small-molecule antiviral therapy.

Treatment program

Azvudine Group: Azvudine (1 mg/tablet; Henan Real Technology Biological Co. Ltd.) 5 mg orally once daily for 5 days.

Paxlovid Group: Nirmatrelvir and ritonavir (150 and 100 mg tablets, respectively Pfizer), with a standard

authorized dose of 300 mg and 100 mg, respectively (two nirmatrelvir tablets and one ritonavir tablet), every 12 h with or without food for 5 days; the real dose of paxlovid was adjusted based on the patient's renal allograft function.

Group A+P: Azvudine orally for 3-5 days at 5 mg daily, subsequently switched to paxlovid if the disease worsened or the viral load increased, based on the standard regimen.

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: Main manifestation was upper respiratory tract infection, such as dry throat, sore throat, cough, and fever.

Medium COVID-19: Persistent high fever for >3 days and/or cough and shortness of breath; respiratory rate (RR) <30 breaths/min and oxygen saturation > 93% when air is inhaled at rest. Characteristics of COVID-19 infection based on imaging of pneumonic manifestations

Heavy COVID-19: Any of the following criteria were met and could not be explained by anything other than COVID-19 infection (i) shortness of breath with RR[?]30 beats/min; (ii) oxygen saturation at rest [?]93% on air inhalation; (iii) arterial blood oxygen partial pressure (PaO2)/inhaled oxygen concentration (FiO2)[?]300 mmHg; (iv) Progressive clinical symptoms with significant progression of >50% of the lesion within 24–48 h on lung imaging.

Critical COVID-19: One of the following conditions was met: (i) respiratory failure that required mechanical ventilation, (ii) shock, and (iii) ICU monitoring and treatment combined with other organ failure.

Statistical analysis

Non-normally distributed measures were expressed as medians, interquartile ranges, and non-parametric tests were used for comparison between groups, whereas count data were expressed as frequencies (composition ratio) and chi-squared tests were used for comparison between groups. Kaplan–Meier curves were plotted to compare the occurrence of adverse outcomes such as death and graft failure between the groups. Differences in the occurrence of adverse outcomes between treatment modalities were analyzed using multifactorial logistic regression. All statistical analyses were performed using SPSS (22.0) software.

RESULTS

One hundred and forty patients with pneumonia due to novel coronavirus after renal transplantation were included in the analysis. Sixty-two patients were classified into the azvudine group, 49 into the paxlovid group, and 29 into the combined group of the two antivirals (Figure 1). The mean age was 47.3 ± 11.3 years, and 90 cases (64.3%) were male patients. Eight patients (5.7%) were vaccinated. Based on the diagnostic criteria in the Chinese Novel Coronavirus Infection Treatment Protocol (Trial Version 10), 1 (0.7%) of the included patients was light, 112 (80.0%) were medium, 23 (16.4%) were heavy, and 4 (2.9%) were critical.

Basic population information

The mean age of the A+P group was 52 years (42.5, 59.0), which was higher than that of the azvudine and paxlovid groups (P=0.025). There were no significant differences in the sex composition among the three groups. In terms of comorbidities, there was no significant difference between the three groups in terms of comorbidity with hypertension and coronary artery disease; however, the paxlovid group had a higher proportion of comorbid diabetes than the other two groups (P=0.032). There were differences in the clinical typing of the novel coronavirus among the three groups, with the highest proportion of severe and critical cases in the A+P group (35.5 %). The basic patient profiles are shown in Table 1.

Immunomodulation-related treatment and adjustment of immunosuppressive drugs

The dose, type, and hormone use of immunosuppressants after renal transplantation did not differ significantly among the three groups (Table 1 in the Appendix). A comparison of immunomodulatory treatments between the three groups showed that the use of propyl globulin was highest in the A+P group, with 41.4% of patients using propyl globulin, followed by the paxlovid group, and lowest in the azvudine group (P=0.030). Intravenous hormone use also differed among the three groups (P=0.001), with the highest use in the A+P group (75.9 %) and the lowest in the azvudine group (37.1 %). The use of monoclonal antibodies did not differ significantly among the three groups (P=0.171). With regard to dose adjustment of immunosuppressive agents, the A+P group had a higher rate of dose reduction and discontinuation of CNI-based immunosuppressive agents than the paxlovid and azvudine groups, whereas there was no significant difference between the three groups regarding dose reduction and discontinuation of MMF-based immunosuppressive agents (Table 2).

The absolute values of the change in immunosuppressive concentration before and after pneumonia treatment were 1.7 (2.5, 4.5) in the azvudine group, 2.1 (0.7, 3.3) in the paxlovid group, and 2.4 (1.4, 2.1) in the A+P group, with no statistical difference between the three groups, according to a non-parametric test(P=0.343).

Characteristics of Omicron infection

Of the 140 patients, 125 (89.3%) had fever, 114 (81.4%) had cough, and 66 (47.1%) had malaise. Ninety percent of the patients had a combination of two or more symptoms. There was no significant difference in the frequency of symptoms between the treatment groups except for nausea and vomiting, which were more common in the two-drug combination groups. In terms of length of hospitalization, the mean length of stay was slightly longer in the combination therapy group than in the azvudine and paxlovid groups. Other comparisons between the groups are presented in Appendix Table 2.

Changes in laboratory test data before and after treatment of the novel coronavirus infection

This study compared changes in clinical data at admission, 7 days after admission, and at discharge for three treatment modalities, including inflammation-related indicators, such as interleukin 6, CRP, PCT, T-lymphocyte counts, absolute lymphocyte levels, novel coronavirus N-gene CT levels, and ORF1ab-gene CT levels. Differences between the three groups were found in absolute T-lymphocyte levels 7 days after admission and at discharge (P= 0.015, P=0.004) and lymphocyte counts at admission, 7 days after admission, and at discharge (P=0.032, P=0.000, P=0.000), with no significant differences in other clinical data between the three groups.

The changes in CRP, IL6 and PCT levels at admission, 7 days after admission, and at discharge are shown in Figure 2.

Changes in T-lymphocyte count and absolute lymphocyte values at admission, 7 days after admission, and at discharge are shown in Figure 2.

Changes in the CT values of the N gene and those of the ORF 1ab gene for the novel coronavirus nucleic acid test are shown in detail in Figure 2.

Adverse complications and graft survival

Rejection occurred in three patients, two in the A+P group and one in the paxlovid group; death occurred in four patients, all in the combination group; graft inactivation occurred in five patients, two in the paxlovid group and three in the A+P group; new-onset urinary albumin positivity occurred in seven patients, four in the azvudine group, two in the paxlovid group and one in the A+P group; and acute kidney injury occurred in 30 patients: 7 in the azvudine group, 17 in the Paxlovid group, and 6 in the A+P group.

Kaplan–Meier survival curves were plotted for the risk of adverse events in the three groups, using ICU admission or death as the observation endpoint, with the lowest incidence of adverse events during the observation period recorded in the azvudine group; however, the difference in risk between the three groups was not statistically significant (log-rank test, P=0.069).

Kaplan–Meier curves were also plotted for graft survival between the three treatment groups, with no graft failure The best graft survival was in the azvudine group, and the lowest graft survival in the A+P group, with a statistical difference between the three groups (log-rank test P=0.037).

In this study, the observed adverse outcomes were ICU admission or death. To examine the differences in the occurrence of adverse outcomes among the three treatment modalities in more detail, we used the occurrence of adverse outcomes as the dependent variable; age, time since kidney transplantation, treatment group, and pneumonia type were the independent variables in a multifactorial logistic regression equation. Differences in the occurrence of adverse outcomes among the three treatment modalities were analyzed after adjusting for other factors. Age (years) and time since transplantation (months) were included in the equation as continuous variables, and the pneumonia subtype (1 for severe or critical, 0 for other) and treatment regimen were categorical variables. The results showed no significant differences in the occurrence of adverse events among the three groups after adjusting for other baseline values (Table 4).

DISCUSSION

In this study, the mean ages of the three groups were 45, 50, and 52 years, respectively, which were much higher than those of the general population (see Table 1). This was because the investigated patients were hospitalized with pneumonia rather than patients with only COVID-19. Moreover, pneumonia mostly occurs in older infected individuals. Although the three groups differed significantly in terms of age (P=0.025), patients with severe symptoms who needed medications were mostly older individuals (Table 1). COVID-19 infection in KTR occurred later than it did in healthy people; furthermore, we indicated the duration of medication and time needed to reveal negative results (Supplementary Table 2).

The Montefiore Medical Center in New York reported 36 KTR confirmed with COVID-19 [21]. Moreover, 15 KTR who required hospitalization due to confirmed COVID-19 were reported by the Columbia University Kidney Transplantation Project [22]. The most common complications were hypertension, diabetes, smoking history, and heart disease. The overall performance of KTRs with COVID-19 was similar to that of the general population. The most common symptoms were fever, cough, dyspnea, fatigue, diarrhea, and myalgia. More than 50% of patients had bilateral or multiple focal ground-glass shadows on the initial chest radiograph. Laboratory examination showed that lymphocyte and platelet counts were decreased, and CD3, CD4, and CD8 cell counts were decreased. Inflammatory markers such as ferritin, C-reactive protein, procalcitonin, and D-dimer had increased [21-22]. In our study, 125 (89.29%) patients had fever, 114 (81.43%) had cough, and 66 (47.1%) had malaise. Ninety percent of patients had a combination of two or more symptoms. There was no significant difference in the frequency of symptoms between the treatment groups, except for nausea and vomiting, which were more common in the two drug combination groups and was statistically different (Supplementary Table 2).

KTRs 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 ICU admission than non-transplant patients [20]. Therefore, there is a need to pay more attention to medication for KTRs with COVID-19. The lymphatic system is rebuilt after an increase in lymphocytes, after which the viral load is decreased. Therefore, the application of small-molecule antiviral drugs is of significance and beneficial for better prognosis.

Small-molecule drugs for the treatment of patients with COVID-19 mainly include two types: those that inhibit COVID-19 and those that control the human cytokine storm. Among these, RdRp and Mp-ro are the main targets of COVID-19 small-molecule drugs. Among the COVID-19 therapeutic drugs currently on the market, Azvudine and Paxlovid are small-molecular drugs targeting RdRp and Mp-ro [Gordon D E, Jang G M, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing[J]. Nature, 2020, 583(7816):1-13.].

We administered azvudine, paxlovid, or a combination of both. Paxlovid acts on the main protease of COVID-19, inhibits the processing of protein precursors mediated by this enzyme and viral replication, and significantly reduces mortality. On the other hand, nirmatrelivr has a significant antiviral activity, and is currently reported to reduce viral load most rapidly [16]. However, paxlovid is contraindicated in

patients with severe liver and kidney injury. According to the diagnosis and treatment modality of COVID-19 (Version X), patients with moderate kidney injury should be administered half of nirmatrelivr, whereas patients with severe liver and kidney injury should not use paxlovid because its usage may increase the blood concentration of calcineurin inhibitors, which are essential for KTRs is one aspect. Moreover, paxlovid may cause renal injury. This is consistent with our study. AKI in the paxlovid group was much higher than that in the other two groups (P=0.010), as shown in Table 4. However, to treat COVID-19, small-molecule antiviral drugs are urgently needed. Therefore, we used azvudine as a substitute, when a calcineurin inhibitor acted as an immunosuppressant after kidney transplantation.

The target of Azvudine is RdRp, which is a pathway that increases the indications for anti-HIV drug-based COVID-19 treatment. In a phase III clinical trial, 40% patients with COVID-19 showed alleviated clinical symptoms 1 week after receiving azvudine treatment, whereas the proportion of patients receiving placebo was only 11% [23]. Azvudine does not directly inhibit viral replication. It performs triphosphorylation in cells to produce FNC triphosphate, which then produces broad-spectrum inhibitory activity against not only COVID-19, but also hepatitis C virus (HCV) and enterovirus 71 (EV71). FNC triphosphate has been proven to effectively inhibit COVID-19 in cell cultures and animal models. Azvudine's triphosphorylation product is used as a substrate that combines with the RdRp of COVID-19, resulting in the termination of viral RNA chain synthesis and generation of non-functional viral genomic RNA, thus inhibiting viral replication [24]. However, KTRs infected with COVID-19 present with quite severe symptoms, and azvudine alone is insufficient to achieve treatment outcomes; therefore, we administered paxlovid immediately after the calcineurin inhibitor was withdrawn. Therefore, we grouped the patients into A+P and paxlovid groups (Table 2).

The period of medication for KTRs receiving any of the three groups of small-molecule drugs lasted longer than the recommended time of diagnosis and treatment scheme of COVID-19 (Version X), and was also longer than that of patients with simple pneumonia. This, on the other hand, proves that KTRs with COVID-19 infection presents with more severe symptoms than those pneumonia patients with infection.

According to the changes in laboratory test data before and after treatment with the novel coronavirus (Figures 2), differences between the three groups were found in absolute T-lymphocyte levels 7 days after admission and at discharge (P= 0.015, P=0.004) and lymphocyte counts at admission, 7 days after admission, and at discharge (P=0.032, P=0.000, P=0.000), with no significant differences in other clinical data between the three groups. This showed that there were no differences between the three groups of small-molecule drugs after the removal of the interference factors. In other words, the small-molecule drugs we used were suitable and safe for kidney transplant patients with COVID-19. However, the specific choice of azvudine, paxlovid, or a combination of both must be determined based on the use of immunosuppressants and the patient's symptoms.

We also administered intravenous hormones to improve the treatment effect in patients with severe conditions (Table 2). For the immunosuppressive therapeutic modality, we used triple immunosuppressive agents and antimetabolic drugs for most patients. During the course of treatment, the rate of withdrawal of antimetabolic drugs was higher than that of calcineurin inhibitors, whereas the use of calcineurin inhibitors in the paxlovid and A+P groups was discontinued (Table 2).

CONCLUSION

The use of small-molecule medications may be the optimal treatment approach; however, they should be modified based on the patients' conditions, such as clinical symptoms, laboratory results, paraclinicals, and examinations.

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Table 1 Comparison of basic population information between groups

	Group-A (N=62)	Group-P (N=49)	Group-A+P (N=29)	*P*
Age, median (IQR)	45.0 (40.0,52.0)	50 (39.5,57)	52.0 (42.5,59.0)	0.025
Sex (males), n (%)	41 (66.1%)	28 (57.1%)	21 (72.4%)	0.365
BMI, kg/m^2, median (IQR)	22.4±2.8	21.6±3.4	22.9±2.7	0.346
Kidney transplant to admission time,month, median (IQR)	59.9 (15.5,103.2)	44.1 (15.4,60.6)	29.1 (12.2,77.0)	0.392
Comorbidities				
Hypertension, n (%)	43 (69.4%)	29 (59.2%)	18 (62.1%)	0.519
Coronary artery disease, n (%)	1 (1.6%)	3 (6.1%)	4 (13.8%)	0.072
Diabetes mellitus, n (%)	7 (11.3%)	15 (30.6%)	8 (27.6%)	0.032
eGFR¡30, mL/min per 1.73 m^2, n(%)	11 (11.7%)	10 (20.4%)	4 (13.8%)	0.762
Heavy or critical, n (%)	4 (6.5%)	13 (26.5%)	10 (34.5%)	0.002

BMI, body mass index; eGFR, estimated glomerular filtration rate;Severe or critical, based on the diagnostic criteria in the Chinese Novel Coronavirus Infection Treatment Protocol (Trial Version 10), patients were diagnosed as heavy or critical.

Table 2 Immunomodulation-related treatment and adjustment of immunosuppressive drugs

	Group-A (N=62)	Group-P (N=49)	Group-A+P (N=29)	Total (N=140)	*P*
Immunomodulation-related treatments					
Proglobulin, n (%)	10 (16.1%)	11 (22.4%)	12 (41.4%)	33 (23.6%)	0.030

Monoclonal antibodies, n (%)	6 (9.7%)	1 (2%)	1 (3.4%)	8 (5.7%)	0.179
Intravenous hormone use, n (%)	23 (37.1%)	31 (63.3%)	22 (75.9%)	76 (54.3%)	0.001
Immunosuppressant adjustment					
CNI reduction, n (%)	28 (45.2%)	48 (98.0%)	26 (96.3%)	102 (73.9%)	0.000
MMF reduction, n (%)	56 (90.3%)	46 (93.9%)	28 (96.5%)	130 (92.9%)	0.509
CNI deactivation, n (%)	16 (25.8%)	47 (95.9%)	27 (93.1%)	90 (64.3%)	0.000
MMF deactivation, n (%)	53 (85.5%)	38 (77.5%)	27 (93.1%)	118 (84.3%)	0.178
CNI and MMF are both deactivated, n (%)	18 (29.0%)	36 (73.5%)	24 (82.8%)	78 (55.7%)	0.000
Number of days off immunosup-pressive drugs,median (IQR)	7.0 (6.0,9.5)	7.0 (6.0,9.5)	8.5 (7.0,14.0)	7.0 (6.0,10.0)	0.071

Table 3. Occurrence of adverse complications

	Group-A (N=62)	Group-P (N=49)	Group-A+P (N=29)	Total (N=140)	*P*
Graft deactivation	0 (0.00%)	3 (6.12%)	2 (6.9%)	5 (3.57%)	0.049
Dialysis	1 (1.61%)	3 (6.12%)	1 (3.45%)	5 (3.57%)	0.442
AKI	7 (11.29%)	17 (35.42%)	6 (22.22%)	30 (21.9%)	0.010
ICU	1 (1.64%)	6 (12.24%)	3 (10.34%)	10 (7.19%)	0.051
Mechanical Ventilation	1 (1.64%)	3 (6.12%)	3 (10.34%)	7 (5.04%)	0.181

Table 4. Multi-factor logistic regression analysis of the occurrence of adverse events

	β	*S.E.*	Wald	df	Sig.	Exp(B)	95% CI for EXP(B) Lower	95% C Upper
Treatment groups	0.565	0.540	1.097	1	0.295	1.760	0.611	5.067
Transplant time	0.008	0.006	1.910	1	0.167	1.008	0.996	1.021
Age	0.063	0.041	2.430	1	0.119	1.065	0.984	1.153
Novel coronavirus typed as heavy or critical	3.368	0.929	13.129	1	0.000	29.015	4.693	179.38

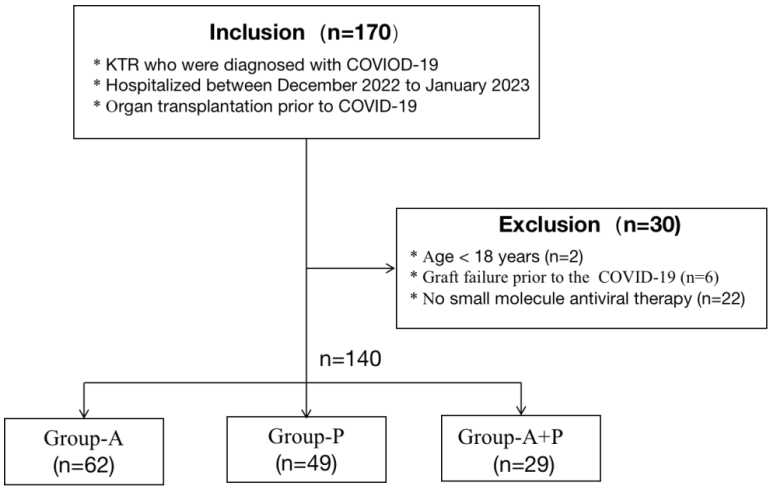


Figure 1 Flowchart of the inclusion and exclusion criteria

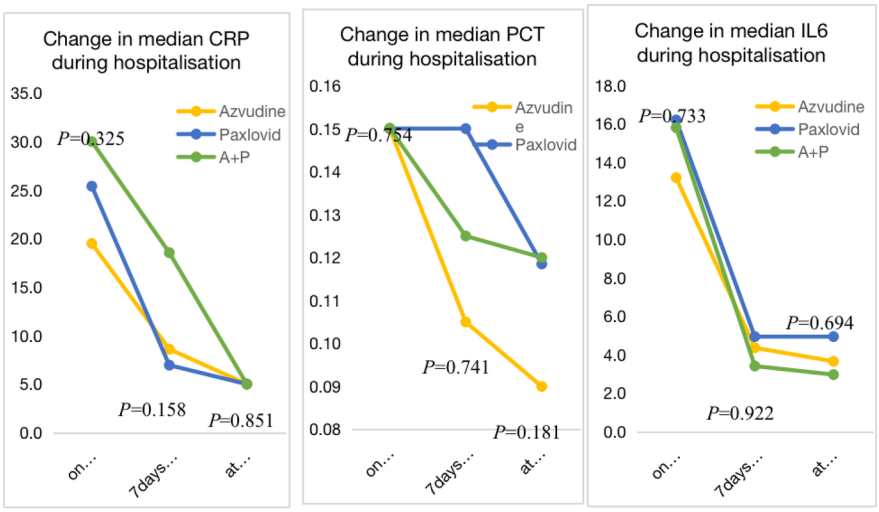


Figure 2 Trends in inflammatory indicators during hospitalization

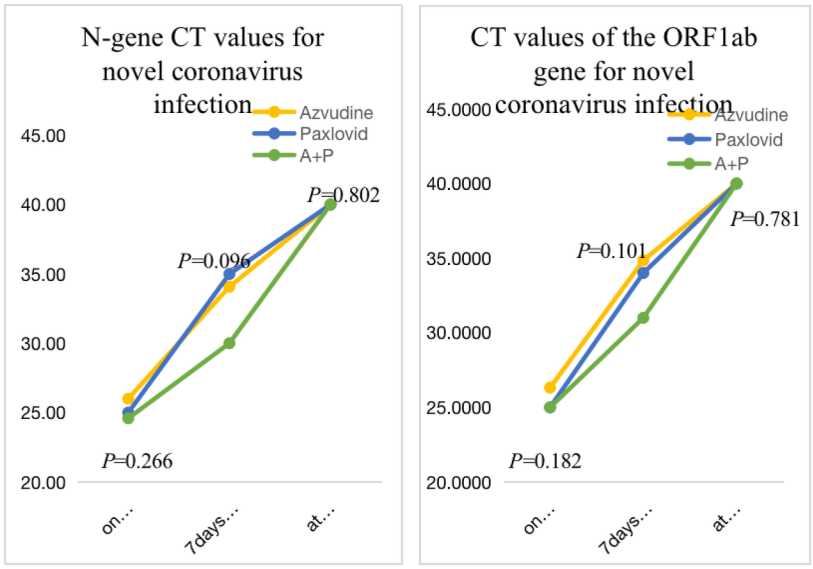


Figure 3 Trends in CT values of novel coronavirus nucleic acid tests during

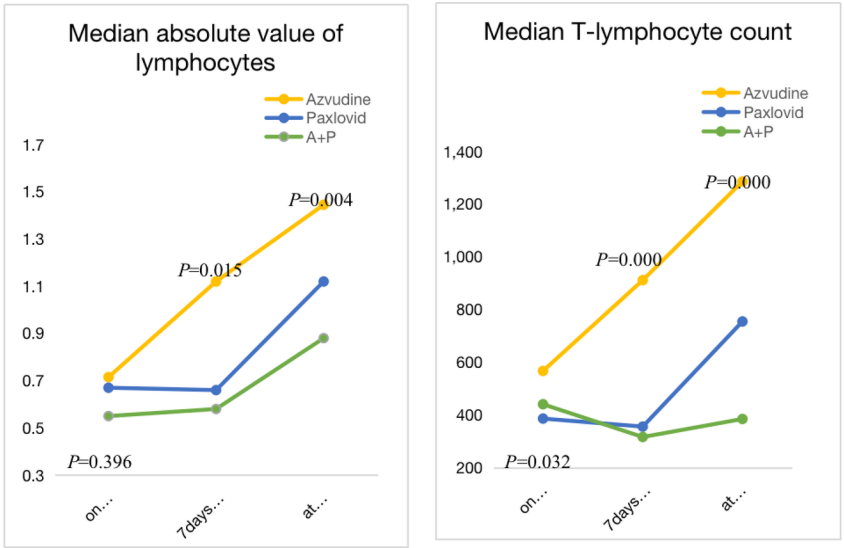
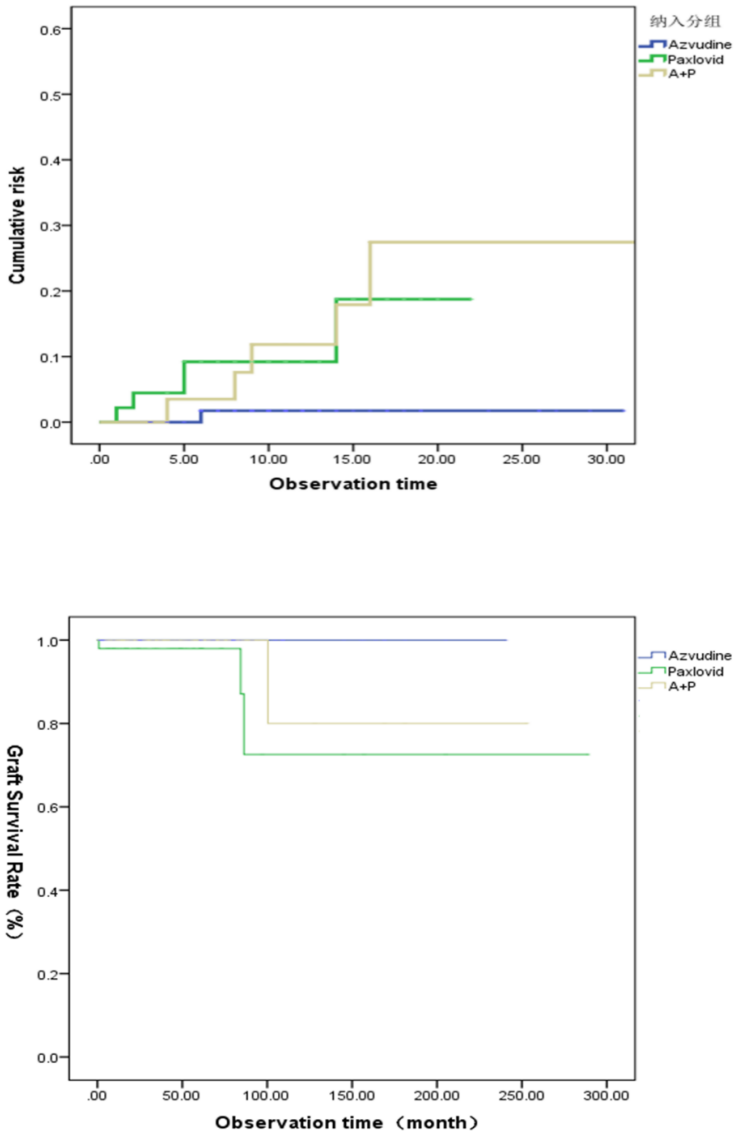


Figure 4. Trends in lymphocyte changes during hospitalization

Figure 2 Trends in Laboratory test indicators during hospitalization



a b

Figure 3. Kaplan-Meier curves for cumulative risk of death or ICU admission(a)and graft survival times (b) between groups.