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Research Article

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Clinical characteristics and outcomes of hospitalized kidney transplant recipients with COVID-19 infection in China during the Omicron wave: a single-center cohort study

Duo LV[1,2*], Xishao XIE[3,4,5,6,7*], Qinyun YANG[8], Zhimin CHEN[3,4,5,6,7], Guangjun LIU[3,4,5,6,7], Wenhan PENG[3,4,5,6,7], Rending WANG[3,4,5,6,7], Hongfeng HUANG[3,4,5,6,7], Jianghua CHEN[3,4,5,6,7], Jianyong WU[3,4,5,6,7]✉

[1]*Department of Clinical Pharmacy, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[2]*Zhejiang Provincial Key Laboratory for Drug Evaluation and Clinical Research, Hangzhou 310003, China*
[3]*Kidney Disease Center, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[4]*Key Laboratory of Kidney Disease Prevention and Control Technology, Zhejiang Province, Hangzhou 310003, China*
[5]*Institute of Nephrology, Zhejiang University, Hangzhou 310003, China*
[6]*Zhejiang Clinical Research Center of Kidney and Urinary System Disease, Hangzhou 310003, China*
[7]*The Third Grade Laboratory under the National State, Administration of Traditional Chinese Medicine, Hangzhou 310003, China*
[8]*Information Center, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*

Abstract: Background: Following the short-term outbreak of coronavirus disease 2019 (COVID-19) in December 2022 in China, clinical data on kidney transplant recipients (KTRs) with COVID-19 are lacking. Methods: We conducted a single-center retrospective study to describe the clinical features, complications, and mortality rates of hospitalized KTRs infected with COVID-19 between Dec. 16, 2022 and Jan. 31, 2023. The patients were followed up until Mar. 31, 2023. Results: A total of 324 KTRs with COVID-19 were included. The median age was 49 years. The median time between the onset of symptoms and admission was 13 d. Molnupiravir, azvudine, and nirmatrelvir/ritonavir were administered to 67 (20.7%), 11 (3.4%), and 148 (45.7%) patients, respectively. Twenty-nine (9.0%) patients were treated with more than one antiviral agent. Forty-eight (14.8%) patients were treated with tocilizumab and 53 (16.4%) patients received baricitinib therapy. The acute kidney injury (AKI) occurred in 81 (25.0%) patients and 39 (12.0%) patients were admitted to intensive care units. Fungal infections were observed in 55 (17.0%) patients. Fifty (15.4%) patients lost their graft. The 28-d mortality rate of patients was 9.0% and 42 (13.0%) patients died by the end of follow-up. Multivariate Cox regression analysis identified that cerebrovascular disease, AKI incidence, interleukin (IL)-6 level of >6.8 pg/mL, daily dose of corticosteroids of >50 mg, and fungal infection were all associated with an increased risk of death for hospitalized patients. Conclusions: Our findings demonstrate that hospitalized KTRs with COVID-19 are at high risk of mortality. The administration of immunomodulators or the late application of antiviral drugs does not improve patient survival, while higher doses of corticosteroids may increase the death risk.

Key words: Coronavirus disease 2019 (COVID-19); Kidney transplant; Hospitalization; Mortality

1 Introduction

Since its emergence in December 2019, coronavirus disease 2019 (COVID-19) has developed into a sustained global pandemic and resulted in millions of deaths around the world. Although the majority of patients infected with COVID-19 experience mild symptoms, patients of advanced age or those with underlying conditions, such as diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, or immunosuppression, are at an increased risk of severe disease and death (Talic et al., 2021; COVID-19 Excess Mortality Collaborators, 2022). For example, several studies reported a significantly higher mortality rate among kidney transplant recipients (KTRs) after COVID-19 infection compared with the general population (Azzi et al., 2021; Kremer et al., 2021; Nimmo et al., 2022). The epidemic prevention policy for

✉ Jianyong WU, wujianyong1964@zju.edu.cn
* The two authors contributed equally to this work
Jianyong WU, https://orcid.org/0000-0003-0957-2630

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COVID-19 in China is distinct from that in most countries. Over the past three years, the devastating effects of the global COVID-19 virus mutants and several waves of pandemics have largely avoided China. The available data on COVID-19 infections among KTRs in this country have been limited to a few case reports from the early stage of the viral outbreak and epidemic (Zhu et al., 2020; Zhang et al., 2022). Despite the wide promotion of COVID-19 vaccination among the population, the vaccination rate remains relatively low in KTRs.

As the primary virus strain gradually mutated into the less virulent Omicron variant, epidemic prevention policies were changed in December 2022, which led to a short-term outbreak of COVID-19 in China, with the main responsible strains of BA.5.2 and BF.7. Due to the unique demographic and distribution characteristics of the Chinese population, the outbreak had distinct features compared with those in other countries. It started in early December 2022 and concluded by the end of January 2023. It resulted in a significant number of hospitalized KTRs with COVID-19 infection, while the outcomes and contributing factors remain unclear. Thus, we performed a retrospective study to summarize the clinical features, complications, and mortality rates of hospitalized KTRs with COVID-19 in this period. Our study aims to provide valuable insights into the impact of the COVID-19 outbreak on KTRs in China.

2 Materials and methods

2.1 Study population

This retrospective observational cohort study enrolled all KTRs with COVID-19 infection who were hospitalized in the First Affiliated Hospital of Zhejiang University in China between Dec. 16, 2022 and Jan. 31, 2023. Only KTRs who received kidneys from deceased or living donors after 2010 were included. The diagnosis of COVID-19 infection was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) analysis. The basic hospital admission criteria were as follows: computed tomography (CT) or X-ray infiltrates of the lungs, requirement of oxygen therapy, and emergence of complications (i.e., renal dysfunction or secondary bacterial infection). Patients with an age of <18 years and graft failure, or those required to return to dialysis before COVID-19 infection were excluded.

2.2 Data collection

All data were collected from our hospital databases and patients' clinical records. The recorded baseline demographic and clinical data included age, sex, body mass index (BMI), time after transplantation, transplant type, maintenance immunosuppression regimen, prior history of acute rejection of less than one year, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination status, and time from symptom onset to admission. Further collected data included the prior history of comorbid conditions before admission, such as diabetes, hypertension, cardiovascular disease (history of angina, myocardial infarction, coronary artery disease, or valvular heart disease), cerebrovascular disease (cerebral hemorrhage or infarction), chronic pulmonary disease (bronchiectasis, asthma, chronic bronchitis, or obstructive pulmonary disease), peripheral vascular disease, malignancy, and history of cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection of less than six months. The basal creatinine and glomerular filtration rate (GFR) prior to COVID-19 infection and the laboratory data on admission were recorded. Severe COVID-19 was defined according to the COVID-19 treatment guidelines of the National Institutes of Health (US) (2021): individuals with blood oxygen saturation (SpO_2) of <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of <300 mmHg (1 mmHg=0.133 kPa), a respiratory rate of >30 breaths/min, or lung infiltrates of >50%.

The data on medical treatments during hospitalization were extracted from the available medical records. As different types of corticosteroids are used during hospitalization, such as prednisone, methylprednisolone, and dexamethasone, all corticosteroid types were converted to equal doses of methylprednisolone for statistical convenience. The clinical variables and outcomes included acute kidney injury (AKI), need for renal replacement therapy (RRT), mechanical ventilation requirement, intensive care unit (ICU) admission, thrombogenesis, and fungal infection. AKI was defined as an increase in serum creatinine of >50% according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. The severity of the

AKI episode of index admission for COVID-19 was graded using the KDIGO definition. Patients were followed up from the date of hospital admission to the date of death or the end of the study (Mar. 31, 2023).

2.3 Statistical analysis

Continuous variables were presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), while categorical variables were presented as frequencies with percentages. Differences between survivors and non-survivors were analyzed by the *t*-test for normally distributed continuous data, the Mann-Whitney *U* test for skewed continuous data, and Chi-squared and Fisher's exact tests for categorical data. Survival was analyzed using the Kaplan-Meier method. Univariate and multivariate Cox regression models were utilized to explore the risk factors associated with mortality. Due to the limited number of death events and to avoid overfitting in the model, a backward stepwise selection method was implemented. Only covariates with a P value of <0.05 in the univariate models were selected for the last multivariate Cox regression models. The cutoffs of continuous variables were confirmed by receiver operating characteristic curves. A forest plot was generated to display the results of the multivariate Cox model. All statistical analyses were performed using R version 3.1.3 (R Development Core Team, Vienna, Austria). Throughout this paper, we refer to statistical significance as a two-sided P value of <0.05.

3 Results

3.1 Patient characteristics

A total of 324 KTRs with COVID-19 infection were admitted to our hospital between Dec. 16, 2022 and Jan. 31, 2023. The baseline characteristics of the overall cohort are shown in Table 1. The median age was 49 years (IQR, 38–56 years), 192 (59.3%) patients were male, and the median BMI was 22.6 kg/m^2 (IQR, 19.8–25.0 kg/m^2). The median time since transplantation was 41.7 months (IQR, 13.0–74.6 months) and 77 (23.8%) patients underwent transplantation of less than one year before their current COVID-19 infection. Two hundred forty (74.1%) transplanted kidneys were sourced from deceased donors and 84 (25.9%) originated from living donors. The most prevalent comorbidities were diabetes (27.5%), hypertension (75.3%), cardiovascular disease (41.4%), peripheral vascular disease (12.7%), and a history of respiratory disease (15.7%). Eight (2.5%) and 63 (19.4%) patients had a history of CMV and EBV infection during the six months preceding COVID-19 infection, respectively. Only 25 (7.7%) patients received the anti-SARS-CoV-2 vaccine before infection. The maintenance immunosuppression regimens included antimetabolites, calcineurin inhibitors (CNIs), mammalian target of rapamycin inhibitor (mTORi), and corticosteroids, taken by 97.8%, 99.4%, 6.8%, and 97.2% of patients, respectively. The median time between the onset of symptoms and admission was 13 d (IQR, 7–16 d). The laboratory results on admission are presented in Table 2. The basal median creatinine level before infection was 1.6 mg/dL (IQR, 1.2–2.0 mg/dL). The median creatinine level on admission was 1.8 mg/dL (IQR, 1.3–2.5 mg/dL) and the median GFR was 40.7 mL/min (IQR, 25.1–59.6 mL/min). The mean hemoglobin and serum albumin levels were (116.1±22.0) g/L and (35.4±4.7) g/L, respectively. The median levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were 19.7 mg/mL (IQR, 7.5–49.2 mg/mL) and 6.2 pg/mL (IQR, 4.3–12.6 pg/mL), respectively. The median D-dimer level was 602 μg/L (IQR, 344–1385 μg/L). The median neutrophil and lymphocyte counts were 4.64×10^9 L^{-1} (IQR, 2.85×10^9–7.86×10^9 L^{-1}) and 0.46×10^9 L^{-1} (IQR, 0.28×10^9–0.80×10^9 L^{-1}), respectively. The median neutrophil/lymphocyte ratio (NLR) was 9.0 (IQR, 4.7–18.7).

3.2 In-hospital treatment

The in-hospital treatment of the enrolled patients is shown in Table 3. Two hundred and one (62.0%) patients received antiviral therapy. The median time between the onset of symptoms and antiviral therapy was 14 d (IQR, 8–20 d). Molnupiravir, azvudine, and nirmatrelvir/ritonavir were administered to 67 (20.7%), 11 (3.4%), and 148 (45.7%) patients, respectively. Twenty-nine (9.0%) patients were treated with more than one antiviral agent. Forty-eight (14.8%) patients were treated with tocilizumab, 53 (16.4%) patients received baricitinib therapy, and immunoglobulin was used in 68 (21.0%) patients. The median dose of corticosteroids was 40.0 mg/d (IQR, 29.4–57.9 mg/d). For the maintenance immunosuppression agents, antimetabolites, CNIs, and mTORi were withdrawn in 85.5%

Table 1 Baseline characteristics of hospitalized kidney transplant recipients with COVID-19

Characteristics	Total (*n*=324)	Survivor (*n*=282)	Non-survivor (*n*=42)	*P* value
Age (year)	49 (38–56)	48 (38–55)	53 (45–60)	0.018
Male	192 (59.3%)	169 (59.9%)	23 (54.8%)	0.640
Body mass index (kg/m^2)	22.6 (19.8–25.0)	22.6 (19.8–24.8)	22.0 (19.5–25.4)	0.861
Time after transplantation (month)	41.7 (13.0–74.6)	42.5 (14.2–73.6)	25.4 (9.8–83.2)	0.223
<1 year since transplant to COVID-19 symptom onset	77 (23.8%)	63 (22.3%)	14 (33.3%)	0.172
Previous transplantation	9 (2.8%)	6 (2.1%)	3 (7.1%)	0.180
Time from symptoms onset to admission (d)	13 (7–16)	13 (7–17)	13 (5–15)	0.521
Type of donor				0.016
Deceased	240 (74.1%)	202 (71.6%)	38 (90.5%)	
Living	84 (25.9%)	80 (28.4%)	4 (9.5%)	
Comorbidities				
Diabetes mellitus	89 (27.5%)	72 (25.5%)	17 (40.5%)	0.066
Hypertension	244 (75.3%)	208 (73.8%)	36 (85.7%)	0.138
Cardiovascular disease	134 (41.4%)	111 (39.4%)	23 (54.8%)	0.085
Cerebrovascular disease	11 (3.4%)	7 (2.5%)	4 (9.5%)	0.058
Peripheral vascular disease	41 (12.7%)	30 (10.6%)	11 (26.2%)	0.010
Respiratory disease	51 (15.7%)	41 (14.5%)	10 (23.8%)	0.190
Malignancy	16 (4.9%)	13 (4.6%)	3 (7.1%)	0.745
CMV infection	8 (2.5%)	6 (2.1%)	2 (4.8%)	0.622
EBV infection	63 (19.4%)	50 (17.7%)	13 (31.0%)	0.070
Vaccination status	25 (7.7%)	25 (8.9%)	0	0.089
COVID-19 RT-PCR cycle threshold	29 (26–33)	30 (27–33)	28 (25–30)	0.004
Baseline immunosuppreCion				
Antimetabolite	317 (97.8%)	276 (97.9%)	41 (97.6%)	0.923
CNI	322 (99.4%)	281 (99.6%)	41 (97.6%)	0.611
mTORi	22 (6.8%)	19 (6.7%)	3 (7.1%)	1.000
Corticosteroids	315 (97.2%)	275 (97.5%)	40 (95.2%)	0.737
Severe COVID	69 (21.3%)	55 (19.5%)	14 (33.3%)	0.066

Data are expressed as median (interquartile range) or frequency (percentage). COVID-19: coronavirus disease 2019; CMV: cytomegalovirus; EBV: Epstein-Barr virus; RT-PCR: reverse transcription-polymerase chain reaction; CNI: calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor.

Table 2 Biochemical characteristics of hospitalized kidney transplant recipients with COVID-19

Characteristics	Total (*n*=324)	Survivor (*n*=282)	Non-survivor (*n*=42)	*P* value
Creatinine before infection (mg/dL)	1.6 (1.2–2.0)	1.5 (1.2–1.9)	1.8 (1.4–2.6)	0.018
Creatinine on admission (mg/dL)	1.8 (1.3–2.5)	1.7 (1.2–2.4)	2.6 (1.8–3.6)	<0.001
GFR on admission (mL/min)	40.7 (25.1–59.6)	44.2 (28.8–60.5)	24.3 (16.1–39.8)	<0.001
IL-6 (pg/mL)	6.2 (4.3–12.6)	5.8 (4.2–10.4)	10.0 (7.2–81.2)	<0.001
D-Dimer (μg/L)	602 (344–1385)	550 (320–1183)	1258 (710–3031)	<0.001
C-reactive protein (mg/mL)	19.7 (7.5–49.2)	18.2 (6.6–46.1)	30.7 (14.4–62.3)	0.011
Neutrophil (×10^9 L^{-1})	4.64 (2.85–7.86)	4.58 (2.78–7.59)	5.76 (3.70–11.05)	0.024
Serum albumin (g/L)	35.4±4.7	35.9±4.6	32.4±3.9	<0.001
Hemoglobin (g/L)	116.1±22.0	117.7±21.8	105.3±20.6	0.001
Lymphocyte (×10^9 L^{-1})	0.46 (0.28–0.80)	0.49 (0.31–0.86)	0.28 (0.17–0.54)	<0.001
NLR	9.0 (4.7–18.7)	8.5 (4.2–16.6)	19.1 (9.1–51.7)	<0.001

Data are expressed as median (interquartile range) or mean±standard deviation (SD). COVID-19: coronavirus disease 2019; GFR: glomerular filtration rate; IL-6: interleukin-6; NLR: neutrophil/lymphocyte ratio.

(271 of 317), 32.3% (104 of 322), and 63.6% (14 of 22) of patients, respectively. Anticoagulant agents were administered to 139 (42.9%) patients.

3.3 Clinical course and outcomes

The clinical course during hospitalization and the outcomes are shown in Table 4. A total of 98.5% (319 of 324) of patients received nasal oxygen therapy on admission. AKI occurred in 81 (25.0%) patients and RRT was needed for 35 (10.8%) patients. During hospitalization, a total of 39 (12.0%) patients were admitted to the ICU. Mechanical ventilation was necessary for 34 (10.5%) patients and 6 (1.9%) patients received extracorporeal membrane oxygenation (ECMO) therapy. Thrombosis events occurred in 15 (4.6%) patients, in which 13 patients presented with lower limb venous thrombosis and two patients were diagnosed with pulmonary embolism. Fungal infections occurred in 55 (17.0%) patients. Fifty (15.4%) patients lost their graft. The Kaplan-Meier plots of patient survival are provided in Fig. 1. The 28-d mortality rate of patients was 9.0% and 42 (13.0%) patients deceased at the end of follow-up.

3.4 Risk factors for mortality

The differences in baseline characteristics between survivors and non-survivors are presented in Table 1. In brief, the patients who died were generally

Table 3 Clinical treatment modalities of hospitalized kidney transplant recipients with COVID-19

Treatment modality	Total (*n*=324)	Survivor (*n*=282)	Non-survivor (*n*=42)	*P* value
Antiviral therapy				
None	123 (38.0%)	120 (42.6%)	3 (7.1%)	<0.001
Molnupiravir	67 (20.7%)	55 (19.5%)	12 (28.6%)	0.250
Azvudine	11 (3.4%)	9 (3.2%)	2 (4.8%)	0.946
Nirmatrelvir/ritonavir	148 (45.7%)	113 (40.1%)	35 (83.3%)	<0.001
Combined antiviral therapy	29 (9.0%)	18 (6.4%)	11 (26.2%)	<0.001
Other COVID-19 treatment				
Baricitinib	53 (16.4%)	44 (15.6%)	9 (21.4%)	0.466
Tocilizumab	48 (14.8%)	30 (10.6%)	18 (42.9%)	<0.001
Immunoglobulin	68 (21.0%)	44 (15.6%)	24 (57.1%)	<0.001
Corticosteroids (mg/d)	40.0 (29.4–57.9)	40.0 (27.7–55.3)	62.7 (47.9–85.6)	<0.001
Immunosuppression management				
Antimetabolite withdraw	271 (85.5%)	235 (83.3%)	36 (85.7%)	0.868
CNI withdraw	104 (32.3%)	79 (28.0%)	25 (59.5%)	<0.001
mTORi withdraw	14 (63.6%)	13 (68.4%)	1 (33.3%)	1.000
Anticoagulant	139 (42.9%)	104 (36.9%)	35 (83.3%)	<0.001

Data are expressed as frequency (percentage) or median (interquartile range). COVID-19: coronavirus disease 2019; CNI: calcineurin inhibitor; mTORi: mammalian target of rapamycin inhibitor.

Table 4 Clinical course and complications of kidney transplant recipients with COVID-19 during hospitalization

Course and complication	Total (*n*=324)	Survivor (*n*=282)	Non-survivor (*n*=42)	*P* value
Acute kidney injury	81 (25.0%)	51 (18.1%)	30 (71.4%)	<0.001
Stage 1	36 (44.4%)	32 (62.7%)	4 (13.3%)	
Stage 2	7 (8.6%)	6 (11.8%)	1 (3.3%)	
Stage 3	38 (46.9%)	13 (25.5%)	25 (83.3%)	
RRT	35 (10.8%)	9 (3.2%)	26 (61.9%)	<0.001
Admission to ICU	39 (12.0%)	7 (2.5%)	32 (76.2%)	<0.001
Ventilation requirement	34 (10.5%)	5 (1.8%)	29 (69.0%)	<0.001
ECMO	6 (1.9%)	1 (0.4%)	5 (11.9%)	<0.001
Thrombosis	15 (4.6%)	4 (1.4%)	11 (26.2%)	<0.001
Fungal infection	55 (17.0%)	30 (10.6%)	25 (59.5%)	<0.001

Data are expressed as frequency (percentage). COVID-19: coronavirus disease 2019; RRT: renal replacement therapy; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

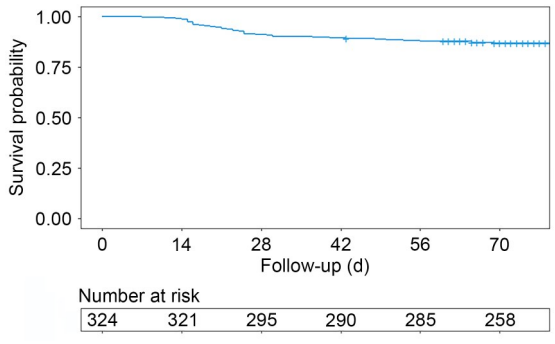

Fig. 1 Kaplan-Meier survival curve for hospitalized kidney transplant recipients with coronavirus disease 2019 (COVID-19).

older (median, 53 vs. 48 years; *P*=0.018), received more kidneys from deceased donors (90.5% vs. 71.6%; *P*=0.016), and presented with a higher prevalence of peripheral vascular disease (26.2% vs. 10.6%; *P*=0.010) than survivors. Non-survivors had significantly worse results in most laboratory indicators compared to survivors (Table 2). In terms of treatment (Table 3), more patients in the non-survivor group received antiviral medication (92.9% vs. 57.4%; *P*<0.001), tocilizumab (42.9% vs. 10.6%; *P*<0.001), and immunoglobulin (57.1% vs. 15.6%; *P*<0.001) therapies. The average daily dose of corticosteroids was also higher in the non-survivor group (median, 62.7 vs. 40.0 mg; *P*<0.001). For the comorbidities and outcomes, a higher proportion of patients in the non-survivor group developed AKI (71.4% vs. 18.1%; *P*<0.001) and needed RRT (61.9% vs. 3.2%; *P*<0.001). The majority of patients in the non-survivor group were admitted to the ICU (76.2% vs. 2.5%; *P*<0.001) and needed mechanical ventilation (69.0% vs. 1.8%; *P*<0.001) during hospitalization. Furthermore, there were more occurrences of thromboembolic events (26.2% vs. 1.4%; *P*<0.001) and fungal infections (59.5% vs. 10.6%; *P*<0.001) during hospitalization in the non-survivor group (Table 4).

The univariate analysis showed that multiple potential factors were associated with mortality (Table S1). After adjusting for potential factors by the backward stepwise selection method, only certain variables, such as cerebrovascular disease, peripheral vascular disease, neutrophil/lymphocyte ratio, hemoglobin, IL-6 level, antiviral therapy, use of tocilizumab, incidence of AKI, fungal infection, and daily dose of corticosteroids, were included in the final model. The multivariate Cox regression analysis identified that cerebrovascular disease, incidence of AKI, IL-6 level of >6.8 pg/mL, daily dose of corticosteroids of >50 mg, and fungal infection were associated with death in hospitalized patients (Fig. 2).

4 Discussion

In the past three years, the global COVID-19 pandemic has had a limited impact in China, which resulted in a paucity of data on COVID-19-infected patients including KTRs. To address this knowledge gap, we conducted a retrospective study to analyze the hospitalization records of 324 KTRs with COVID-19 who were admitted to our center between Dec. 16, 2022 and Jan. 31, 2023. Our findings provide valuable insights into the clinical characteristics and outcomes of COVID-19 in this vulnerable population in China.

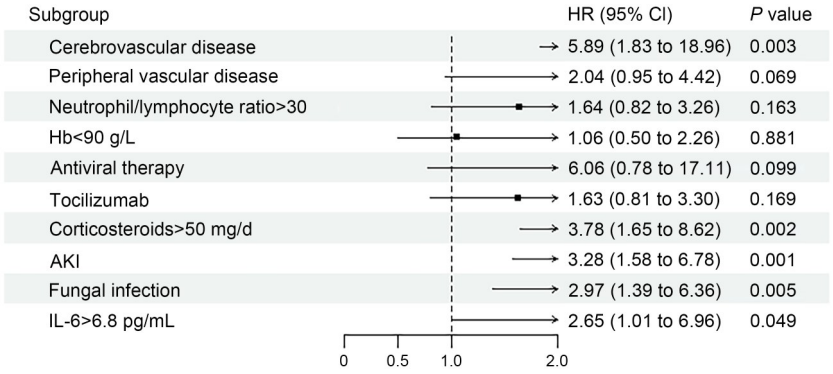

Fig. 2 Multivariate analysis of risk factors for the mortality of hospitalized kidney transplant recipients with COVID-19. COVID-19: coronavirus disease 2019; Hb: hemoglobin; AKI: acute kidney injury; IL-6: interleukin-6; HR: hazard ratio; CI: confidence interval.

During the early stages of the COVID-19 outbreak, particularly before 2021, several studies showed that short-term in-hospital mortality rates in KTRs with COVID-19 were as high as 20%–32% (Kremer et al., 2021; Zhou et al., 2021; Mahalingasivam et al., 2022). With the increasing understanding of the disease, widespread vaccination campaigns, the use of antiviral drugs, and the weakening virulence of SARS-CoV-2 due to continuous mutations, the incidence of severe illness, hospitalization, and mortality rates have significantly decreased in the general population (Ahmad et al., 2023; Nab et al., 2023). However, KTRs continue to face a higher risk of death following COVID-19 infection, with recent studies reporting hospital mortality rates of around 10% or higher in KTRs (Berger et al., 2022; Hajibaratali et al., 2023; Weiss et al., 2023). Consistent with previous studies, we found that the overall mortality rate of hospitalized KTRs after COVID-19 infection was 13%. Although the World Health Organization (WHO) has declared that COVID-19 is no longer a global public health emergency, it is unlikely to disappear and intermittent regional outbreaks may continue. Therefore, the high mortality rate in KTRs following COVID-19 infection warrants our attention and efforts to further improve the outcomes.

AKI is a common complication in patients with COVID-19, with an incidence rate exceeding 20% among hospitalized patients. The incidence could exceed 50% in critically ill patients with underlying conditions such as chronic kidney disease (CKD) and KTRs (Nadim et al., 2020; Chan et al., 2021; Mallhi et al., 2022). AKI has been associated with a significantly higher risk of in-hospital mortality in patients with COVID-19 (Ronco et al., 2020; Ng et al., 2021). The pathophysiology and mechanisms of AKI in patients with COVID-19 are multifactorial and include direct virus-induced kidney injury and indirect mechanisms resulting from the systemic consequences of viral infection (Farkash et al., 2020; Nadim et al., 2020; Su et al., 2020; Bernal et al., 2021). In our cohort, 25.0% (81 of 324) of patients developed AKI, with Stage 3 AKI accounting for 46.9% of all cases. The mortality rate among AKI patients was significantly higher than that among non-AKI patients (37.0% vs. 4.9%; $P<0.001$), and AKI was an independent risk factor for mortality in KTRs (hazard ratio (HR), 3.28; 95% confidence interval (CI), 1.58–6.78; $P=0.001$). Evidence on the recovery of kidney function in KTRs after COVID-19 infection is currently limited. Recent research has reported that patients with COVID-19-associated AKI exhibited persistent elevations of 125% or more in baseline serum creatinine at 365 d compared to non-AKI patients (Tan et al., 2023). Among the 81 patients with AKI in our cohort, 30 patients died, 8 patients lost their graft and needed long-term dialysis after discharge, while 40 patients had creatinine reductions below 1.5 times the baseline level at the end of follow-up. However, for most of these patients, these levels did not recover to baseline. Thus, further follow-up is needed to evaluate long-term kidney function recovery after COVID-19-associated AKI.

Transplant recipients with COVID-19 often require the alleviation of immunosuppression to minimize the risk of exacerbated infection. Although there are no specific guidelines or consensus on adjusting immunosuppressive regimens for KTRs after COVID-19 infection, existing studies recommend the discontinuation of antimetabolite agents and the maintenance of low doses of CNIs for mild to moderate symptoms, and the optional administration of high doses of corticosteroids as well as intravenous immunoglobulin in severe cases (Kronbichler et al., 2020; Willicombe et al., 2020; Daoud et al., 2021). In our cohort, 83.6% and 32.1% of patients discontinued antimetabolites and CNIs upon hospital admission, respectively. Patients who discontinued CNIs were mainly those receiving the nirmatrelvir/ritonavir treatment due to adverse drug interactions (Wang et al., 2022). Similar to previous studies (Favà et al., 2020; Gérard et al., 2022; Hajibaratali et al., 2023), we found no significant impact of immunosuppression changes on mortality risk in our cohort. However, it is unclear whether reducing or discontinuing immunosuppressive agents increases the risk of rejection or donor-specific antibody (DSA) production. One study reported a 45% (5 of 11) incidence rate of acute rejection (4 with arteritis) among patients who underwent renal biopsy within one month after COVID-19 infection (Daniel et al., 2021). In contrast, other scholars have suggested that immune function may be more compromised in KTRs with COVID-19, and no increase in the risk of rejection or de novo DSA production has been observed (Masset et al., 2022). In response to this dilemma, we suggest that monitoring and quantifying the SARS-CoV-2-reactive adaptive immune responses can guide the individualized adjustment of the immunosuppression regimen in KTRs after COVID-19 infection

(Hartzell et al., 2020). As such, further studies with long-term follow-up are needed to clarify this issue. The use of corticosteroids in COVID-19 is controversial. Early studies suggested that corticosteroids could reduce the proportion of patients requiring mechanical ventilation and lower mortality rates (Chaudhuri et al., 2021; Wagner et al., 2021). However, more recently, it was found that low doses of corticosteroids might benefit certain patients but higher doses (dexamethasone of >6 mg/d) may significantly increase the risk of death in critically ill patients (Tu et al., 2022; RECOVERY Collaborative Group, 2023). We revealed a significant increase in the mortality risk for patients receiving >50 mg average daily dose of methylprednisolone (HR, 3.78; 95% CI, 1.65–8.62; P=0.002). A potential explanation may lie in that administration of high doses of steroids may lead to further suppression of immune function and an increased risk of opportunistic infections (Gangneux et al., 2022; van Grootveld et al., 2023). In our study, the non-survivor group received a significantly higher daily dose of corticosteroids (median, 62.7 vs. 40.0 mg; P<0.001) and experienced a greater proportion of fungal infections (59.5% vs. 10.6%; P<0.001) than the survivor group. Fungal infection was an independent risk factor for death in KTRs (HR, 2.97; 95% CI, 1.39–6.36; P=0.005). Therefore, high-quality clinical trials are needed to further elucidate the ideal dosage and course of corticosteroids for COVID-19 patients with different characteristics.

The early administration of antiviral drugs is recommended for COVID-19 patients to reduce the risk of severe illness and hospitalization (Avery, 2022; Saravolatz et al., 2023). However, it remains unclear whether such drugs are effective for individuals who are unable to obtain early treatment or when severe symptoms are present. In our study, most patients had difficulty in obtaining effective antiviral drugs in the early stage of infection in outpatient clinics, while antiviral drugs were only administered irregularly to certain hospitalized patients. The median time between symptom onset and antiviral therapy was 14 d in our cohort. Upon hospital admission, patients who received antiviral drug therapy presented worse laboratory indicators, were more likely to be in the ICU, were mechanically ventilated, and needed RRT. Although our multivariate analysis indicated that antiviral drugs seemed to be associated with a higher risk of death (HR, 6.06; 95% CI, 0.78–17.11), it did not reach statistical significance (P=0.099). This may be attributed to the more severe illness of patients receiving antiviral therapy, which led to treatment selection bias, and to the difficulty in managing systemic inflammation and organ damage in the late stage of COVID-19 infection through virus clearance. Considering the significant differences in several parameters between patients who received antiviral therapy and those who did not, we also conducted matched and subgroup analyses on three antiviral drugs, including molnupiravir, azvudine, and nirmatrelvir/ritonavir, which yielded similar results (data not shown). Thus, the late application of antiviral drugs cannot benefit patient survival. Immunomodulators such as IL-6 antagonists (i.e., tocilizumab) and Janus kinase (JAK) inhibitors (i.e., baricitinib) have been reported to improve the outcomes of COVID-19 infection in the general population (Klopfenstein et al., 2022; RECOVERY Collaborative Group, 2022). However, the timing of their administration is critical. Studies have reported that tocilizumab only showed efficacy in patients who presented with symptoms for less than 7 d along with those receiving low-flow nasal cannula oxygen (Gupta et al., 2021; RECOVERY Collaborative Group, 2021). Meanwhile, no improvement in mortality was observed when tocilizumab was administered at the time when high-flow nasal cannula or mechanical ventilation was required (Singh et al., 2021; Richier et al., 2022). For KTRs, two studies reported that tocilizumab was associated with a higher mortality rate, with the multivariate analysis or matching methods not indicating a positive impact of tocilizumab on patient outcome (Pereira et al., 2020; Pérez-Sáez et al., 2020). Similar to previous studies, the patients who received tocilizumab in our cohort had more severe disease and the use of tocilizumab was not associated with a decreased risk of mortality according to the multivariate analysis. Limited research has been conducted on the use of baricitinib in transplant recipients. Mendoza et al. (2023) found that baricitinib did not significantly increase the risk of secondary infection or impact the 90-d mortality rate in transplant recipients, similar to the findings of our study. This suggests that the impact of immunomodulators on KTRs who are already chronically immunosuppressed may be limited. Therefore, more randomized studies are needed to identify subsets of KTRs

who may benefit from immunomodulators for the treatment of COVID-19.

In accordance with previous research (Fang et al., 2020), we found that preexisting comorbidities (such as cerebrovascular disease and peripheral vascular disease) and increased levels of inflammatory markers (such as IL-6) were associated with an increased risk of mortality. Lymphopenia and a higher NLR have been reported as predictors of mortality in the general population (Tatum et al., 2020; Jimeno et al., 2021). In our cohort, although a lower lymphocyte count and higher NLR were observed in non-survivors, NLR was not associated with mortality after adjustment for other confounders. This may be explained by the fact that lymphopenia is common in KTRs and may not always be linked to COVID-19 infection (Caillard et al., 2020).

There are several limitations to the present study. Firstly, due to its single-center retrospective nature, we only included hospitalized KTRs with moderate or severe COVID-19 and excluded outpatients with mild symptoms. Therefore, the conclusions may not be generalizable to all KTRs infected with COVID-19 but require external validation with larger sample sizes. Secondly, some laboratory indicators, such as D-dimer, ferritin, and tacrolimus blood concentrations, were not included due to the scarcity of these data. Due to the small number of vaccinated patients and the fact that COVID-19 antibodies were not routinely tested in our hospital, SARS-CoV-2-specific immunoglobulin G (IgG) and IgM data among these patients were unavailable. The application of the KDIGO criteria of AKI in clinical practice also has limitations. A considerable number of patients did not undergo creatinine level re-evaluation within 48 h; thus, our definition of AKI may underestimate its true incidence. Thirdly, only baseline data were recorded and included in our analysis, and neither exact information on medication management (such as dose reduction of immunosuppression) nor changes in laboratory parameters over time were considered. Similarly, we only assessed and graded the severity of COVID-19 in patients upon admission, while some patients may still progress to severe illness during hospitalization, which could impact the results. Forthly, during the COVID-19 pandemic, our hospital faced the challenge of admitting a substantial number of KTRs with COVID-19. The surge in such cases overwhelmed the capacity of our department, leading to the necessity to accommodate many patients in other departments. This resulted in different doctors in various departments with varied approaches and dosages when administering drugs such as corticosteroids, antiviral medications, and tocilizumab. Furthermore, irregular pharmaceutical supplies in the hospital might further contribute to significant differences in treatment among these patients. Nonetheless, this situation provided a genuine reflection of the treatment landscape during that period. Lastly, the follow-up time in this study was relatively short, whereas many studies suggest that COVID-19 can cause long-term complications for patients. Therefore, the sustained effects of COVID-19 infection on KTRs require further prolonged observation and follow-up.

5 Conclusions

In summary, our study demonstrates that hospitalized KTRs with COVID-19 are at a high mortality risk. The administration of immunomodulators or late application of antiviral drugs cannot benefit patient survival, while higher doses of corticosteroids may increase the death risk. Therefore, optimizing the drug therapy to improve patient outcomes remains a significant challenge in the management of KTRs with COVID-19.

Data availability statement

The data used or analyzed during this study can be available from the corresponding author on reasonable request.

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Author contributions

Research idea and study design: Duo LV, Jianyong WU, and Jianghua CHEN; Data acquisition: Duo LV, Xishao XIE, Qinyun YANG, Zhimin CHEN, Guangjun LIU, Rending WANG, Wenhan PENG, and Hongfeng HUANG; Data analysis/interpretation and statistical analysis: Duo LV and Xishao XIE; Supervision or mentorship: Jianyong WU and Jianghua CHEN. All the authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Duo LV, Xishao XIE, Qinyun YANG, Zhimin CHEN, Guangjun LIU, Wenhan PENG, Rending WANG, Hongfeng HUANG, Jianghua CHEN, and Jianyong WU declare that they have no conflicts of interest.

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University (expedition review No. 63 in 2023). The Ethics Committee authorized the informed consent waiver. This study was performed in accordance with the Declaration of Helsinki.

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Supplementary information

Table S1