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OF MEDICINE

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Paper Accepted[1]

ISSN Online 2406-0895

Original Article / Оригинални рад

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Outcome of COVID-19 infection in patients with kidney transplant in the first two years of the pandemic – our experience with the use of tocilizumab and monoclonal antiSARS-CoV-2 antibodies

Исход инфекције ковида 19 у болесника са трансплантираним бубрегом у прве две године пандемије – наша искуства са освртом на примену тоцилизумаба и моноклонских *antiSARS-CoV*-2 антитела

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Received: June 9, 2026
Revised: August 4, 2026
Accepted: August 28, 2026
Online First: September 9, 2026
DOI: https://doi.org/10.2298/SARH260609071P

[1]**Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
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When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

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SUMMARY

Introduction/Objective Kidney transplant recipients were at higher risk for COVID-19–associated complications and mortality. The goal was to examine the frequency and outcomes of COVID-19 infection among patients under our center's control, as well as the effects of tocilizumab and anti-SARS-CoV-2 antibodies.

Methods We analyzed a cohort of 220 kidney transplant patients monitored at our center who experienced COVID-19 infection between March 2020 and March 2022.

Results In the period of two years, 55 pts contracted COVID-19 (25%). The average age of the infected was 48.38 years old. In 24% of patients during COVID-19 infection the immunosuppressive therapy did not change. Because of pneumonia development 33% of patients have been hospitalized. Of all infected patients, tocilizumab was used in 7% of patients, of whom three died. AntiSARS-COV-2 mAb was used in 24% of patients, no fatalities were reported. Antivirotic (favipiravir) was used in 4% of patients, in one case fatal. CRRT/HD was applied in 5.5% of patients. Out of all infected, death occurred in 14.5% of patients. The cause of death was severe acute respiratory syndrome (50%), cardiac arrest (25%), or multiorgan failure (25%). All of these patients had serious comorbidities, or were late admitted to the transplant center.

Conclusions The therapeutic use of mAb was reliable, with a significant positive effect on achieving a milder clinical form and shorter duration of the disease. The main risk factors of adverse outcomes of COVID-19 infection in kidney transplant recipients were serious comorbidities and late admission to the transplant center.

Keywords: kidney transplant; COVID-19 infection; anti-SARS-CoV-2 antibodies

САЖЕТАК

Увод/Циљ Инфекција ковида 19 код болесника са трансплантираним бубрегом је била повезана са већим ризиком од компликација и морталитета. Циљ рада је био да се испита учесталост и исход инфекције ковида 19 код болесника контролисаних у нашем центру, као и ефекат тоцилизумаба и *anti-SARS-COV*-2 моноклонских антитела (мАТ).

Методе Од укупно 220 болесника са трансплантираним бубрегом, испитали смо 55 болесника који су развили инфекцију ковида 19 у прве две године пандемије.

Резултати Од укупног броја контролисаних, у прве две године пандемије 55 болесника је имало инфекцију ковида 19 (25%). Просечна старост оболелих је била 48,38 година. Имуносупресивна терапија није мењана у 24% болесника. Због развоја пнеумоније 33% болесника је било хоспитализовано. Посматрајући све оболеле, тоцилизумаб је примењен у 7% болесника, од којих су три преминула. *AntiSARS-COV*-2 мАТ су примењена у 24% болесника, није било смртних исхода. Антивирусни лек (фавипиравир) је примењен у 4% болесника, у једном случају настаје фатални исход. Континуирана терапија замене бубрежне функције/хемодијализа је примењена у 5,5% болесника. Од укупног броја оболелих од ковида 19, смртни исход је наступио у 14,5%, а узрок је био тежак акутни респираторни синдром (50%), срчани застој (25%) или мултиорганска слабост (25%).

Закључак Примена мАб била је поуздана, са значајним позитивним ефектом на постизање блажег клиничког тока и краћег трајања болести. Главни фактори ризика за неповољне исходе инфекције ковида 19 код прималаца трансплантираног бубрега били су озбиљни коморбидитети и касно јављање у цен-тар за трансплантацију у развијеној фази болести.

Кључне речи: трансплантација бубрега; инфекција ковида 19; *antiSARS-COV*-2 антитела

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had led to unprecedented challenges for healthcare systems worldwide. The pandemic rapidly spread worldwide after the first

reported case of COVID-19 in Wuhan, China, in late December 2019, prompting the World Health Organization (WHO) to declare it a global pandemic on 11 March 2020. Since the initial phase, substantial progress in clinical research had led to a better understanding of SARS-CoV-2, and multiple medical therapies to treat the disease emerged [1, 2, 3].

Kidney transplant recipients (KTRs) remained at higher risk for COVID 19–associated complications and mortality. Compared with matched nontransplant patients, kidney transplant recipients experience a doubling of risk of COVID-19–related death, especially when considering age, body mass index, and other major comorbidities. Therefore, the identification of early interventions that can halt the progression from mild or moderate to severe COVID-19 is especially important in this vulnerable population [4, 5].

KTRs were vulnerable to infections due to their ongoing immunosuppressive therapy, impaired vaccine response, presence of other comorbidities, and, in some cases, impaired kidney-graft function. Identifying modifiable risk factors that increased the susceptibility to severe COVID-19 could help target prevention and treatment strategies, thus improving future outcomes in this population [2].

Age and comorbidities are known risk factors associated with COVID-19 severity and higher mortality in the general population and among solid organ (SOT) recipients [6, 7].

Numerous therapeutic interventions have been tested to control the spread of the COVID19 infection. However, to this date, no specific agent had been found that guarantees safe and effective control of COVID-19. Monoclonal antibodies (mAbs) such as casirivimab, imdevimab, bamlanivimab, etesevimab, sotrovimab, and tocilizumab have gotten emergency use authorization for COVID-19-infected patients. These mAbs targeted the proteins of SARS-CoV-2 that helped the virus bind to human cells. Additionally, some of them also reduced the

action of cytokines, thereby minimizing the inflammatory reactions considered to be responsible for COVID-19 complications [8–13].

Bamlanivimab and casirivimab-imdevimab prevented viral entry into host cells by blocking the binding of the spike protein to the cell surface angiotensin-converting enzyme 2 (ACE2) receptor. These drugs, combined with immunosuppression reduction for outpatient treatment of mild to moderate COVID-19 in kidney transplant recipients, were safe and had good outcomes [4]. Tocilizumab represented a valuable therapeutic option for managing COVID-19 complications, particularly in patients at risk of cytokine storm syndrome. The mechanism of action of tocilizumab involves binding to interleukin-6 receptors, inhibiting pro-inflammatory responses in a variety of cells, including lymphocytes, monocytes, fibroblasts, and B-cells [10–19].

Modifications of the immunosuppressive regimen were a part of the therapeutic prescription in SOT recipients who developed COVID-19 infection. These include suspending antimetabolites and/or reducing calcineurin inhibitor dosing in asymptomatic patients and patients not requiring hospitalization. In COVID-19 infected patients needing low-flow oxygen, a dose reduction of the metabolite and/or reduction of calcineurin inhibitors or mTOR inhibitor levels might be necessary. In more severe cases, some centers applied a more significant immunosuppression reduction strategy, with temporary discontinuation of all immunosuppressive drugs, except steroids. This strategy needed to be balanced with a potential increased risk for the development of acute rejection and/or graft loss. However, other experts proposed continuation of calcineurin inhibitors (particularly cyclosporine) during advanced disease to control the inflammatory phase. In any case, the complex management of immunosuppression during the course of infection should have been discussed in a multidisciplinary approach by transplant physicians, ICU doctors, and transplant infectious diseases specialists [14].

The goal of this study was to examine the frequency and outcome of the COVID-19 infection within patients controlled at our center, as well as the effect of tocilizumab and antiSARS-COV-2 antibodies.

METHODS

We performed a retrospective, single-center study of adult kidney transplant (KT) recipients with a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 or positive SARS-CoV-2 antigen test, from 1st March 2020, to 28th February 2022, at the University Clinical Center of Vojvodina. Informed consent was obtained in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

At the time of data collection, 220 KT recipients were followed up at our center. All had a functional kidney transplant. We defined adult KT recipients with PCR- or AG-test confirmed SARS-CoV-2 infection. SARS-CoV-2 RT-PCR testing was performed on nasopharyngeal swab samples. ELISA measured IgM and IgG antibodies for SARS-CoV-2 spike RBD.

Demographic and clinical data, including transplant characteristics, comorbidities, immunosuppressive therapy, hospital admission in the ICU, treatment with mAbs/antivirals, AKI, renal replacement therapy (RRT), and all-cause mortality rates were registered. All cases were followed up for at least 60 days after diagnosis.

All of the data were gathered from patients, medical documentation during the treatment of COVID-19 infection, as well as during further treatment.

The specific COVID-19 treatment depended on the timing of the pandemic; a protocol according to the national guide for treatment was applied and was furthermore changed during the pandemic [20].

Statistical analyses were conducted using RStudio 2025.05.0+496 "Mariposa Orchid" Release. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are reported as mean ± standard deviation (SD), and as a median with interquartile range (IQR; Q1–Q3); range is provided for all continuous variables. Continuous variables were compared between independent groups using the Student's t-test or Wilcoxon rank-sum test, as appropriate, while categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All statistical tests were two-tailed, and an alpha level of 0.05 was set as the significance threshold. No imputation was performed for missing data.

RESULTS

Out of 220 KTRs that are under our supervision at the University Clinical Center of Vojvodina, in the first two years of the COVID19 pandemic, 55 (25%) patients had been infected with COVID19. In the first year, 23 patients were infected, while in the second year, 32 patients were infected.

Baseline characteristics of kidney transplant recipients with COVID-19 infection are shown in Table 1. The average age of those infected was 48.38 years old (the youngest being 26 years old, the oldest 71 years old), with the greatest percentage ranging from 41 to 65 years old (60%), followed by the age group ranging from 26 to 40 years old (27%), ending with the age group of patients over 65 years old (13%) (Figure 1).

A total of 53% of those infected received a transplant from a living-related donor, and 47% from a deceased donor. The average time from kidney transplant to COVID-19 infection was 8.13 years; 40% of patients were infected in the first 5 years after kidney transplant (Tables 1 and 2; Figure 2); 67% were male.

All patients were on triple immunosuppressive therapy (calcineurin inhibitor, antimetabolite, corticosteroid). In 24% of the patients who had lighter clinical manifestations of the infection and were treated in home conditions, during the COVID-19 infection, immunosuppressive therapy was not changed; in 67% of all patients, antimetabolite therapy was excluded (mycophenolate mofetil/mycophenolate sodium/azathioprine), the corticosteroid dose was increased, CNI dose was decreased by 25–50%.

Considering specific antiviral therapeutic protocol out of the total number of those infected (55), 36 (65.5%) did not receive tocilizumab, an anti-SARS-CoV-2 monoclonal antibody or antiviral treatment; antiSARS-CoV-2 monoclonal antibody (bamlanivimab or casirivimab-imdevimab (REGEN-COV)) was used in 13 (23.6%) patients, from whom only two had been hospitalized with pneumonia, and in this group of patients, there were no fatal outcomes; tocilizumab was used with four (7.3%) patients treated at the hospital (in which three of the cases ended up lethal). Antiviral (favipiravir) was used with two (3.6%) patients, where in one case, there was a fatal outcome (Figure 3).

The average value of serum creatinine before the patients had been infected with COVID-19 was 144 μmol/l, min:90 μmol/l, max:300 μmol/l. Three hospitalized patients (5.5% of those infected) experienced significant deterioration of transplanted kidney function, and therefore, they received renal function replacement therapy. All three of the patients developed multi-organ dysfunction syndrome and had, consequently passed away. The rest of the patients did not develop a significant decrease in graft function during the course of the illness, nor did they

develop a month after the negative COVID-19 PCR test. The average serum creatinine after overcoming COVID-19 infection (n = 47) was 138.7 μmol/l (min: 88 μmol/l, max: 330 μmol/l) (Figure 4).

All of the patients were put back on immunosuppressive therapy after their inflammatory parameters and number of lymphocytes stabilized.

Out of all the ill (n = 55), fatal outcome occurred in eight (14.5%) patients, that is, when considering all of the patients being monitored after a KT (220), a fatal outcome caused by COVID-19 infection during the first two years of the pandemic was 3.6% (Table 2). All of the deceased patients were hospitalized at the time of their death. Regarding specific therapy one patient received favipavir; three patients received tocilizumab; four patients did not receive tocilizumab/anti-SARS-CoV-2 mAb/antiviral; three patients received renal replacement therapy. Patients who received casirivimab-imdevimab (n = 12) or bamlanivimab (n = 1) did not succumb to death. There is a statistically significant difference in survival between patients who received anti-SARS-CoV-2 mAb and patients who received tocilizumab $p < 0.05$). The average age of patients who had a lethal outcome is 62.5 years old ($p < 0.05$), 75% of whom were male patients. Every patient with a fatal outcome received a cadaveric renal transplant.

The cause of death was severe acute respiratory syndrome in four patients (50%), multiorgan dysfunction syndrome in two patients (25%). All of the patients with fatal outcomes had serious comorbidities (congestive heart failure, diabetes mellitus, liver insufficiency, systemic lupus erythematosus). In two of the fatal outcomes, besides the comorbidity, the factor of late presentation to the hospital (> 7 days after disease beginning) without timely exclusion of antimetabolites and inclusion of the right therapy also took effect. Therefore, patients were hospitalized with well-developed massive pneumonia and signs of severe global respiratory insufficiency (Figure 5).

Statistically significant difference for death in patients with cardiomyopathy, hypertension, and late referral was confirmed compared to patients without these characteristics, $p < 0.05$ (Table 2).

DISCUSSION

In our study, we monitored 220 KRTs with a functioning graft. Between March 1st 2020., when the first patient in Serbia was diagnosed with COVID19, and March 1st 2022. Out of all monitored KTRs, 55 (25%) were infected with COVID-19. The average age of those infected was 48.38 years old, 47% of patients received a deceased donor graft, 67% were male, and the average time period between the transplant and the infection of COVID-19 was 8.13 years. It was similar to a nationwide observational study of Swedish authors [2].

In our study, all of the patients were on triple immunosuppressive therapy, while 61% of patients in the group of Swedish authors were treated with three immunosuppressants as maintenance therapy [2]. Like most transplant centers, we modified immunosuppression in kidney transplant recipients with COVID-19 infection; in 76% of the patients, the antimetabolite was excluded immediately upon COVID-19 diagnosis, the dose of corticosteroids was increased, while the CNI dose was decreased by 20–25% [4].

The number of hospitalized patients in the Swedish study was 6.7% of all that have been monitored, which was less when compared to the results of our study: 18 patients (8.2%) (5.5% of patients in the first year, 2.7% of patients in the second year). In comparison to the group monitored by Swedish authors, the difference could be explained by better application of methods to reduce viral transmission, and thus the occurrence of infection. In our study, the most common group of infected patients was within a period of 1–5 years after transplantation

(40%), which could be explained by the fact that the highest dosage of immunosuppressants was being used [2].

Swedish authors did not confirm a significant effect of comorbidities as independent risk factors, besides heart failure, but they confirmed a significant effect of DM as a primary diagnosis, as well as the effect of severe arterial hypertension. In our study, primarily cognitive heart insufficiency, diabetes mellitus, systemic lupus erythematosus and liver insufficiency had a significant effect of comorbidities on the unfortunate outcome of the disease [2].

In our study, as well as in other studies, we found that bamlinivimab or casirivimab-imdevimab combined with immunosuppression reduction for outpatient treatment of mild to moderate COVID-19 infection in kidney transplant recipients was safe and associated with good outcomes. Only two of the 13 patients treated with mAbs required hospitalization for COVID-19 because they developed pneumonia. Similar data was obtained from Wangs work, whose results showed a positive effect of mAbs use with the need for hospitalization in only four out of 27 patients treated with mAbs, without fatal outcome [4, 5, 6, 7, 16].

In a systematic review and meta-analysis by Gatti and authors, the clinical outcome of COVID-19 infection in SOT recipients compared to generalized population was tested. However, in some studies, SOT recipients affected by COVID-19 showed a higher risk of mortality compared with the general population, especially with the presence of comorbidities (i.e., hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease) combined with old age. In our study, all of the patients who had a fatal outcome had some of the severe comorbidities (hypertension, diabetes mellitus, cardiovascular disease, congestive heart failure, systemic lupus erythematosus) [21].

Dazinger-Isakov and authors found that the mortality ranged from 9 to 46%, with most in the 18–30% range depending on the cohort and circumstance, when analyzing the impact of

COVID-19 infection in SOT recipients. They also stated that many studies addressed risk factors for mortality with age, underlying cardiovascular or lung disease [14]. In our study, the mortality rate was 3.6% of all monitored KTRs, but all monitored were only KTRs.

In the French study, which included the first 2 months of the pandemic, it stated a high percentage of patients who developed AKI (45.8%), while using RRT in 13.2% of the cases [22, 23]. In our study, AKI developed in 5.5% of those ill, and all of them were on RRT. As in our study, factors combined with mortality were age (over 60 years old), male gender, arterial hypertension, cardiovascular diseases, and DM. However, in the said study, it had not been proven that kidney transplant recipients are an independent factor combined with mortality.

COVID-19 associated AKI is common, and has been associated with a higher mortality rate and was an independent risk factor for all-cause in-hospital death in COVID-19 patients. Mortality rate of 14.5% (of all COVID-19 infected KTRs) in our study was similar to the one in Tavareses and the authors work (20%) [24]. Age and comorbidities were known risk factors associated with COVID-19 severity and higher mortality in the general population, as well as among SOT recipients. SOT recipients were predominantly 50 or older and had several comorbidities, including diabetes, hypertension, cardiovascular disease, chronic kidney disease, and obesity, which were associated with worse outcomes after COVID-19. Comorbidities rather than immunosuppression intensity were the main risk factors for impaired outcome in a large cohort [6, 7, 22, 25].

CONCLUSION

A fortunate course of the disease was achieved by timely arrival at the institution of tertiary care that controls kidney transplant patients, with a modification of immunosuppressive therapy, and applying all therapeutic procedures in connection with the COVID19 infection.

Therapeutic usage of bamlanivimab or casirivimab was reliable, with a significant positive effect on achieving mild and shorter courses of the disease, which allowed returning to the usual dosage of immunosuppressive therapy in a shorter amount of time.

The main risk factor for an unfavorable outcome of the COVID19 infection in patients with a kidney transplant was presence of severe comorbidities and late presentation at the transplant center without timely modification of the immunosuppressive therapy and application of adequate therapeutic protocols.

The results obtained offer a critical review for improving the management of kidney transplant recipients for any future pandemic or infectious disease on a larger scale.

Ethics: Before the start of the study, approval was granted by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad, Serbia (Number: 00-50/2).

Conflict of interest: None declared.

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Figure 1. Age of kidney transplant recipients with COVID-19 infection

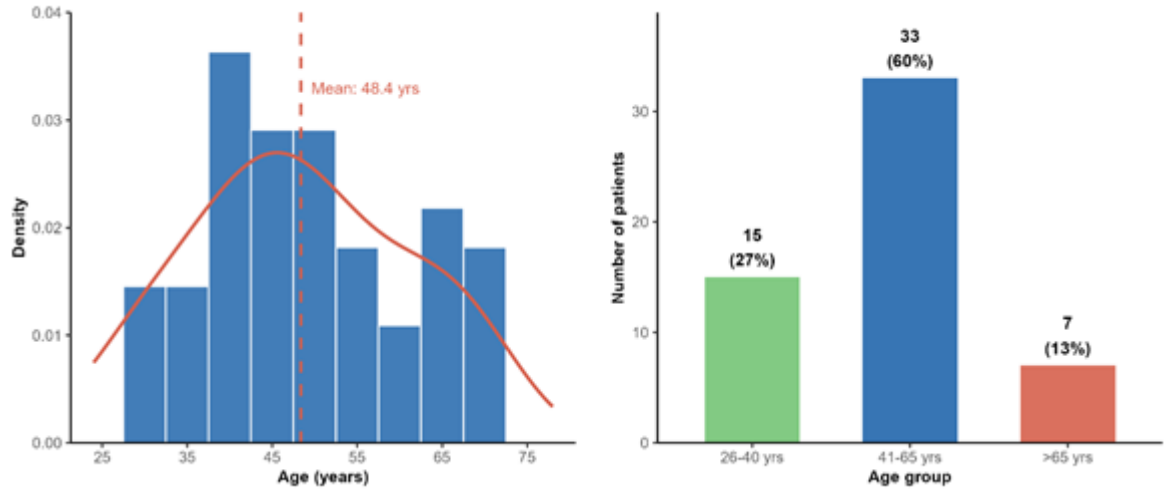

Figure 2. Time between kidney transplant and COVID-19 infection

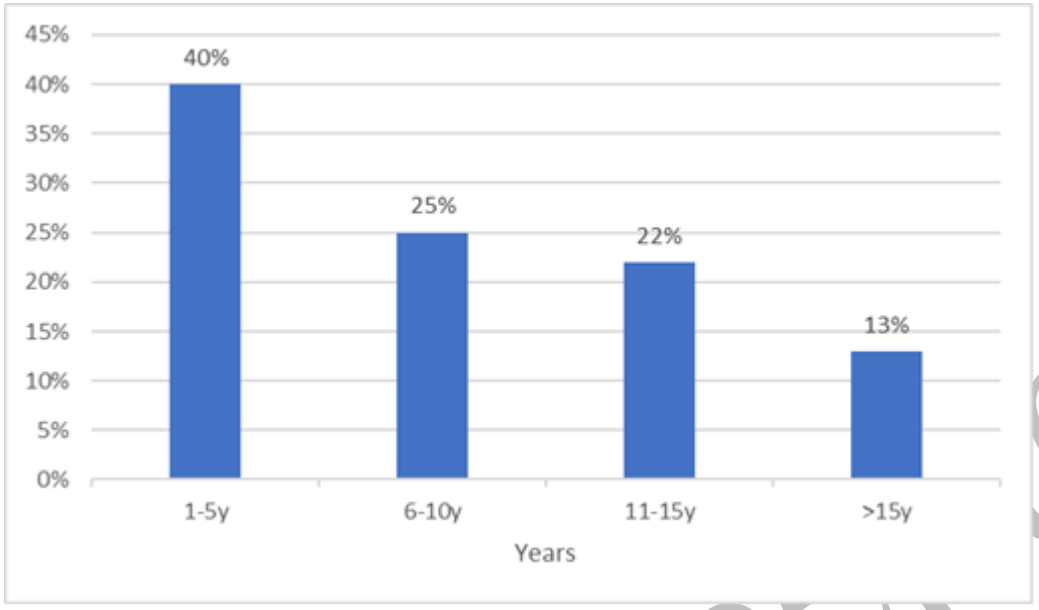

Figure 3. Specific Antiviral Therapeutic Protocols in all patients

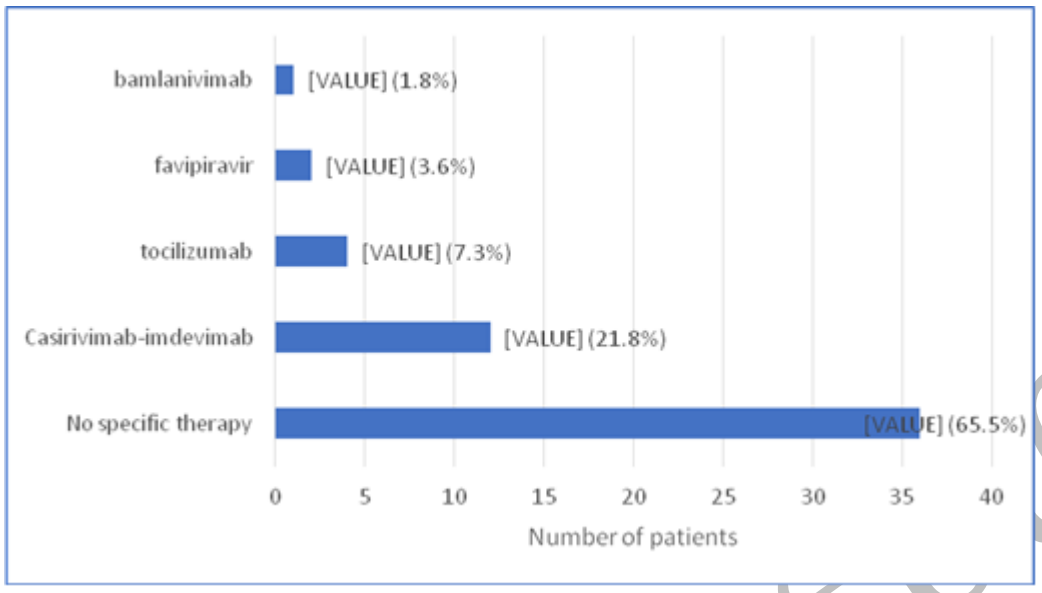

Figure 4. Kidney transplant function before and after COVID-19 in all survived kidney transplant recipients

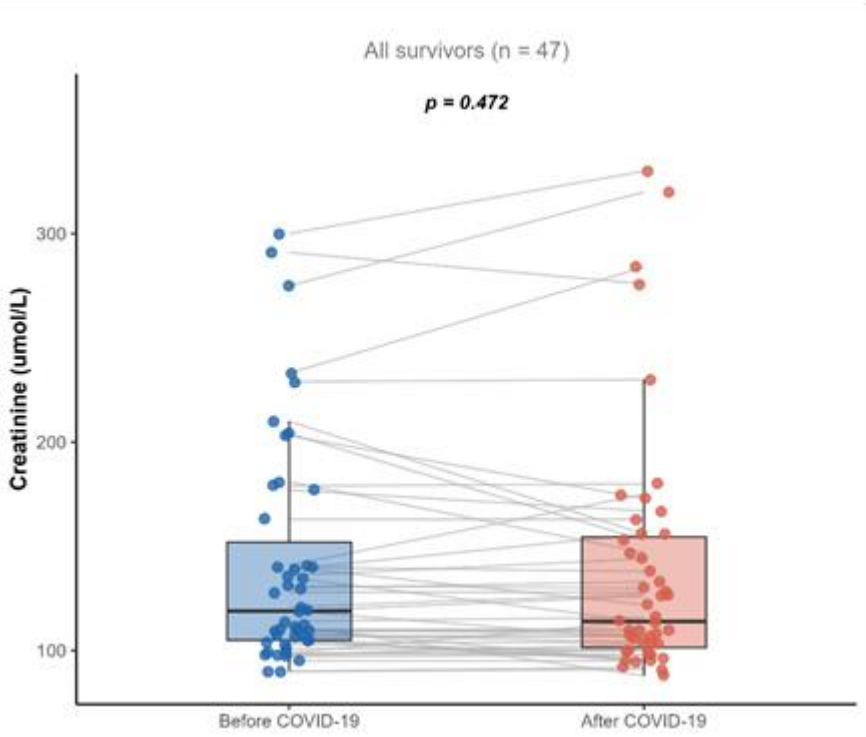

Figure 5. Comorbidities stratified by clinical outcome

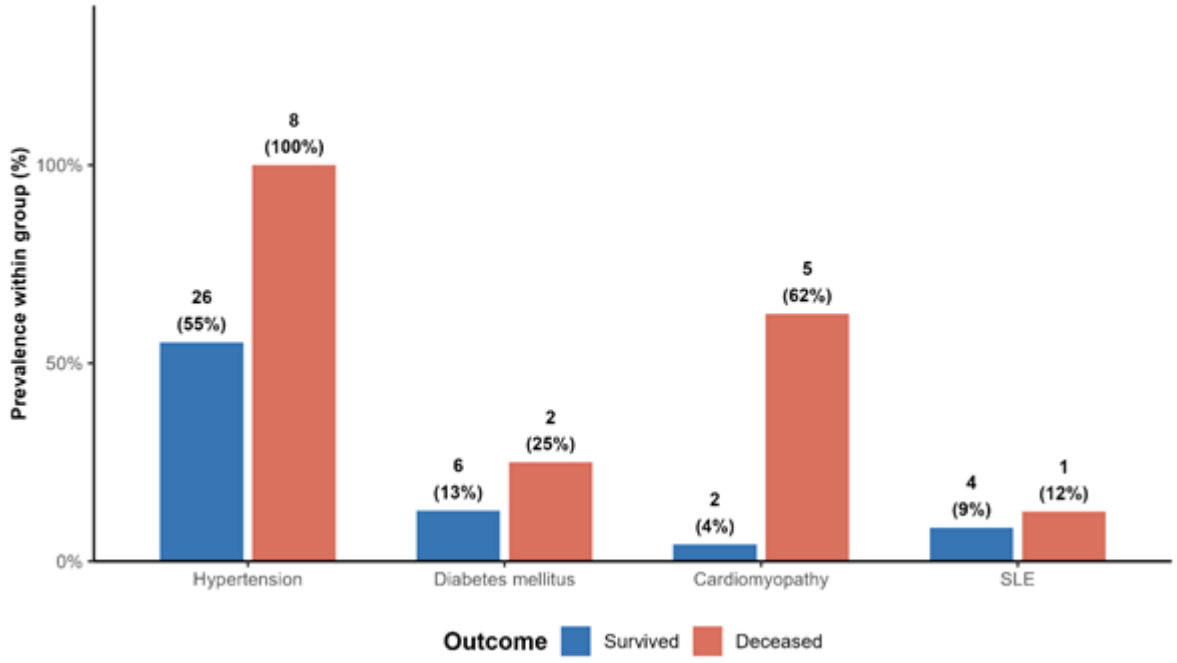

Table 1. Baseline characteristics of kidney transplant recipients with COVID-19 (n = 55)

Characteristic	**n = 55 (100%)**
Age (years)	
Mean ± SD	48.4 ± 12.6
Median: Median [Q1–Q3]	Median: 47 [39–58]
Range: Min–Max	Range: 26–71
Age group, n (%)	
26–40 yrs	15 (27%)
41–65 yrs	33 (60%)
> 65 yrs	7 (13%)
Time from transplant to COVID-19 (years)	
Mean ± SD	8.1 ± 5.7
Median: Median [Q1–Q3]	Median: 7 [3–13]
Range: Min–Max	Range: 1–24
Creatinine before COVID-19 (umol/L)	n = 55
Mean ± SD	144.9 ± 54.6
Median: Median [Q1–Q3]	Median: 122 [105–179]
Range: Min–Max	Range: 90–300
Creatinine after COVID-19 (umol/L)	n = 47
Mean ± SD	138.7 ± 58.9
Median: Median [Q1–Q3]	Median: 114 [100–156]
Range: Min–Max	Range: 88–330
Antimetabolite, n (%)	
MMF	47 (85%)
Everolimus	6 (11%)
Azathioprine	2 (3.6%)
Calcineurin inhibitor, n (%)	
Tacrolimus	48 (89%)
Cyclosporine A	6 (11%)
Antimetabolite discontinued, n (%)	37 (67%)
Hypertension, n (%)	34 (62%)
Diabetes mellitus, n (%)	8 (15%)
Cardiomyopathy, n (%)	7 (13%)
Systemic lupus erythematosus, n (%)	5 (9.1%)
Late referral / respiratory insufficiency, n (%)	2 (3.6%)
Hospital admission, n (%)	16 (29%)
Renal replacement therapy (CRRT/HD), n (%)	4 (7.3%)
Casirivimab-imdevimab, n (%)	12 (22%)
Bamlanivimab, n (%)	1 (1.8%)
Tocilizumab, n (%)	4 (7.3%)
Favipiravir, n (%)	2 (3.6%)
Lethal outcome, n (%)	8 (15%)

Table 2. Comparison of survivors and deceased patients

Characteristic	**Overall** n = 55	**Survived** n = 47	**Deceased** n = 8	**p**[1]
Age (years)				< 0.001
Mean ± SD	48.4 ± 12.6	46 ± 11.9	62.6 ± 5.4	
Median: Median [Q1–Q3]	Median: 47 [39–58]	Median: 46 [38–53]	Median: 64.5 [59.5–66.5]	
Age group, n (%)				0.019
26–40 yrs	15 (27%)	15 (32%)	0 (0)	
41–65 yrs	33 (60%)	28 (60%)	5 (63%)	
> 65 yrs	7 (13%)	4 (8.5%)	3 (38%)	
Time from transplant to COVID-19 (years)				0.464
Mean ± SD	8.1 ± 5.7	7.8 ± 5.4	9.8 ± 7.2	
Median: Median [Q1–Q3]	Median: 7 [3–13]	Median: 7 [3–12]	Median: 9 [3–14.5]	
Creatinine before COVID-19 (umol/L)				0.102
Mean ± SD	144.9 ± 54.6	140.6 ± 54.1	170.1 ± 54.4	
Median: Median [Q1–Q3]	Median: 122 [105–179]	Median: 119 [105–163]	Median: 166 [128.5–219]	
Antimetabolite-before COVID-19, n (%)				0.690
MMF	47 (85%)	39 (83%)	8 (100%)	
Everolimus	6 (11%)	6 (13%)	0 (0)	
Azathioprine	2 (3.6%)	2 (4.3%)	0 (0)	
Calcineurin inhibitor-before COVID-19, n (%)				0.213
Tacrolimus	48 (89%)	42 (91%)	6 (75%)	
Cyclosporine A	6 (11%)	4 (8.7%)	2 (25%)	
Antimetabolite discontinued, n (%)	37 (67%)	31 (66%)	6 (75%)	> 0.999
Hypertension, n (%)	34 (62%)	26 (55%)	8 (100%)	0.018
Diabetes mellitus, n (%)	8 (15%)	6 (13%)	2 (25%)	0.329
Cardiomyopathy, n (%)	7 (13%)	2 (4.3%)	5 (63%)	< 0.001
Systemic lupus erythematosus, n (%)	5 (9.1%)	4 (8.5%)	1 (13%)	0.559
Late referral / respiratory insufficiency, n (%)	2 (3.6%)	0 (0)	2 (25%)	0.019
Hospital admission, n (%)	16 (29%)	8 (17%)	8 (100%)	< 0.001
Renal replacement therapy (CRRT/HD), n (%)	4 (7.3%)	1 (2.1%)	3 (38%)	0.008
Casirivimab-imdevimab, n (%)	12 (22%)	12 (26%)	0 (0)	0.178
Bamlanivimab, n (%)	1 (1.8%)	1 (2.1%)	0 (0)	>0.999
Tocilizumab, n (%)	4 (7.3%)	1 (2.1%)	3 (38%)	0.008
Favipiravir, n (%)	2 (3.6%)	1 (2.1%)	1 (13%)	0.272
[1]Wilcoxon rank sum test; Fisher's exact test				

