https://doi.org/10.23873/2074-0506-2021-13-4-339-355

Clinical characteristics and outcomes of COVID-19 in kidney transplant recipients

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Abstract

Introduction. *The pandemic caused by the SARS-CoV-2 coronavirus is characterized by significant morbidity and mortality. Kidney transplant recipients are at high risk of a more severe course of coronavirus infection due to ongoing immunosuppression, a high comorbidity index, and elder age.*

Aim*. To investigate the features of the clinical course, the treatment applied and also the outcomes of the new coronavirus infection in patients after kidney transplantation.*

Material and methods*. The retrospective study included 69 adult kidney transplant recipients continuously followed-up by our transplant nephrology service and who fell ill with COVID-19 from April 2020 till February 2021. The comparison study of the clinical pattern, laboratory and instrumental test results, treatment features and outcomes was made.*

Results*. The most common clinical symptoms were hyperthermia (85.5%, n=59), weakness (65.2%, n=45) and cough (52.2%, n=36), other*

symptoms were significantly less common. In 89.5% of cases (n=60), the virus ribonucleic acid was detected at least once by polymerase chain reaction; in 10.5% of cases (n=7), the polymerase chain reaction results were negative. According to CT, the extent of lung tissue lesion was identified as CT1 stage in 28 patients (46.7%), CT2 stage in 24 (40%); and only in 8 (13%) patients the lesion was assessed as CT3. Later on the number of patients with more than 50% lung damage–increased to 16 (26.7%) and in 1 case the severity of lung tissue damage was consistent with CT4.

Typical features for all patients were anemia and lymphopenia of varying severity, hypoproteinemia, increased serum creatinine and urea, C-reactive protein, ferritin, procalcitonin and D-dimer in the laboratory test results. The treatment included antiviral, antibacterial, anticoagulant therapy, corticosteroids, biological anti-cytokine drugs. In 95% of cases (n=66), the maintenance immunosuppressive therapy was changed up to complete withdrawal of the certain components.

The patient survival rate with a functioning graft was 76.8% (n=53), the graft loss was observed in 4.3% of cases (n=3), and the lethal outcome was reported in 18.8% (n=13). The cause of death was a severe respiratory distress syndrome with multiple organ dysfunction complicated by sepsis and septic shock in 8 patients (61.5%). Invasive ventilation and hemodialysis were associated with 17.2 ($p<0.00001$) and 21.5 ($p<0.0006$) times higher risk of death, respectively.

Conclusions. *Severe lymphopenia is associated with a clinical worsening of the COVID-19 course. Predictors of fatal outcome were identified as follows: bacterial sepsis, invasive ventilation, the need for renal replacement therapy ($p<0.00001$). Immunosuppression adjustment should be personalized considering the severity of infection, age, comorbidities, post-transplant timeframe, and the risk of rejection.*

Keywords: COVID-19, kidney transplant, immunosuppression, outcomes, survival

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Kantariya RO, Moysyuk YaG, Prokopenko EI, Karapityan AR, Ammosov AA, Makevnina AV, et al. Clinical characteristics and outcomes of COVID-19 in kidney transplant recipients. *Transplantologiya. The Russian Journal of Transplantation.* 2021;13(4):339–355. (In Russ.). https://doi.org/10.23873/2074-0506-2021-13-4-339-355

AKI, acute kidney Injury

ALT, alanine aminotransferase

APTT, activated partial thromboplastin time

ARDS, Acute Respiratory Distress Syndrome

AST, aspartate aminotransferase

CI, confidence interval

CKD, chronic kidney disease

CNI, calcineurin inhibitor

CRF, chronic renal failure

CVD, cardiovascular disease

DM, diabetes mellitus

GFR, glomerular filtration rate

IL-6, interleukin-6

INR, international normalized ratio

KT, kidney transplantation

LDH, lactate dehydrogenase

MSCT, multispiral computed tomography

MV, mechanical ventilation (of lungs)

PCR, polymerase chain reaction

PTDM, post-transplant diabetes mellitus

RDS, respiratory distress syndrome

RNA, ribonucleic acid

RRT, renal replacement therapy

Introduction

The 2019 coronavirus disease pandemic (COVID-19) caused by the SARS-CoV-2 coronavirus with high morbidity and mortality rates has become a serious challenge for the whole world and caused a shortage of medical resources in many countries. Since the first cases appeared in the Chinese province of Wuhan in December 2019, the disease has spread around the world. On March 11, 2020 The World Health Organization declared a global pandemic.

The model of COVID-19 spread and progression differs from the models of Middle East respiratory syndrome (MERS-CoV, 2012) and severe respiratory syndrome (SARS-CoV, 2002-2003). The ribonucleic acid (RNA)-dependent RNA polymerase of SARS-CoV-2 allowed mutations that allow the virus to evade the immune response and adapt to the human body, which was not observed with the MERS-CoV [1].

In general, the published large case series confirm a high mortality rate in patients hospitalized with COVID-19. Thus, clinical outcomes were evaluated in 5,700 hospitalized patients [2]. The authors reported that 21% of the recipients died, with 12.2% receiving invasive mechanical ventilation (MV) and 3.2% receiving renal replacement therapy (RRT). The mortality rate among those requiring mechanical ventilation was 88.1%. In another cohort of 1,150 patients admitted with COVID-19, 22% were in critical condition, 39% of patients died, 79% of patients received MV, and 31% needed RRT [3]. Elderly age, chronic heart and lung diseases, and high levels of interleukin-6 (IL-6) and D-

dimer were associated with a poor outcome. Undoubtedly, the highest mortality rate, reaching 40-50%, was observed in patients hospitalized in the Intensive Care Unit [4, 5].

Renal transplant recipients, as well as those of other solid organs, are at a high risk of a severe course of coronavirus disease. Obviously, for this category of patients, the risk is associated with continuous immunosuppressive therapy, a high comorbidity index, often elderly age, and the presence of concomitant chronic inflammatory diseases. Data have been published indicating high early mortality rates in renal transplant recipients, significantly exceeding those in general population [6, 7]. Obviously, the immunodeficiency status leading to an impaired immunological response to viral pathogens [8], the presence of a complex of concomitant diseases, worsen the COVID-19 prognosis in patients with transplanted organs [4, 5]. In TANGO multi-center study [9], the early mortality rate was 32% among hospitalized kidney transplant recipients with COVID-19 that was similar to the data of single-center reports where that parameter ranged from 24 to 30% [4, 6, 7, 10, 11]. The study identified several risk factors for COVID-19-related death: old age, hypertension disease, diabetes mellitus (DM), and cardiovascular diseases (CVD) [7, 8, 12]. In the largest OpenSAFELY the COVID-19 mortality in solid organ recipients was also associated with old age, arterial hypertension, DM, and CVD [5-7].

The clinical variability of COVID-19 manifestations is a specific feature of patients after kidney transplantation (KT), which complicates the clinical management, in particular, limits the possibility of timely prescribing antimicrobial therapy, adjusting the immunosuppression. Often, the results of early testing for SARS-CoV-2 RNA in infected patients may be negative, and only later become positive [1].

However, the most frequent clinical manifestations of COVID-19 seen in patients after KT were respiratory syndrome, fever, fatigue, and lack of taste sensations when eating. The severity of the disease ranged from mild forms to hospitalization and death. For example, a multi-center cohort study in Spain examined the risk factors for death and acute respiratory distress syndrome (ARDS) in 104 kidney transplant recipients hospitalized between March 4 and April 17, 2020. Forty seven patients developed ARDS. Obesity was associated with the development of ARDS (odds ratio [OR] 2.63; p=0.04). Mortality was higher in elderly patients compared to younger patients (the mean age was 55 years old in survivors, and 70.8 years old in those deceased, p<0.001), and in patients with the previous history of lung disease (OR 2.89, p=0.009). Higher baseline levels of lactate dehydrogenase (LDH) (257 versus 358 IU/mL, p=0.001) at admission and ARDS were predictors of mortality [13].

The COVID-19 pandemic prompted the decision to suspend many organ transplant programs, especially in Europe, both due to a lack of medical resources and due to fears of recipient infection in the early postoperative period [14].

A large population report OpenSAFELY demonstrated that the cohort with the highest risk of hospital death due to COVID-19 was renal transplant recipients in the early post-transplant period. So, in 12 Spanish transplant centers between March 17 and April 18, 2020, 502 kidney transplant recipients with COVID-19 were followed, 24 of them underwent KT less than 60 days before they were diagnosed with COVID-19. The mortality rate from COVID-19 in recipients who fell ill during the first 60 days after KT was 45.8%, which was significantly higher than the corresponding parameter outside the COVID-19 pandemic. Compared to the survivors, the deceased patients were older and infection occurred in the early post-transplant period; patients were

more likely to require mechanical ventilation and less likely to be treated with high doses of steroids. Obviously, recipients are at a high risk of severe viral infection if infected in the early postoperative period as the immunosuppressive therapy used at this time is of maximum intensity [15].

It is still unclear whether immunosuppressive treatment in solid organ recipients is an independent risk factor for COVID-19-related mortality. However, the conventional approach is to reduce the maintenance immunosuppressive therapy in patients with COVID-19, and the degree of reduction in immunosuppression depends on the severity of the viral disease. The experience of a large transplant Center in Sweden in the management of solid organ recipients with COVID-19 was presented. The study included 53 patients with transplanted organs: with a transplanted kidney (n=31), transplanted liver (n=8), transplanted heart (n=5), transplanted lung (n=5), transplanted liver and kidney (n=3), and 1 patient with transplanted kidney after heart transplantation. COVID-19 was diagnosed in patients between February 21, 2020, and June 22, 2020; 55% of recipients had a mild course of the disease, 13% had a moderate course of the disease, 19% had a severe course of the disease, and 13% had an extremely severe course of the disease. Eight patients needed intensive care; 37 patients (70%) were hospitalized, of whom 13 were treated on an outpatient basis at the initial stage of the disease. Antimetabolites and calcineurin inhibitors (CNI) were discontinued (or the drug doses were reduced) in 2/3 of the recipients; 73% of patients received low-molecular-weight heparin, and no one received antiviral drugs. Five hospitalized patients (13.5%) died, and this is probably one of the lowest mortality rates in COVID-19 patients after organ transplantation. Overall survival in the cohort was 90.5%; there were no rejection episodes. The main treatment measures for COVID-19 after

organ transplantation in the above-mentioned study were the reduction of immunosuppression and the use of anticoagulant drugs [16].

In the Russian literature, the experience of treating COVID-19 patients − kidney transplant recipients has been presented in a few publications [17-19].

The aim of our study was to study the typical features of the new coronavirus infection clinical course in patients after KT in our own case series.

Material and methods

Clinical characteristics of patients

The retrospective study included 69 kidney transplant patients who were regularly followed-up at the Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy and who developed COVID-19 in April 2020–February 2021. The study group included 36 men (52.2%) and 33 women (47.6%). The causes of stage 5 chronic kidney disease (CKD) were following: chronic glomerulonephritis in 33 patients (47.8%), diabetic nephropathy in 10 (14.5%), polycystic kidney disease in 9 (13.0%), urinary system abnormalities in 4 (5.8%), gouty nephropathy in 3 (4.3%), hypertensive nephrosclerosis in 2 (2.9%), chronic pyelonephritis in 2 (2.9%), chronic tubulointerstitial nephritis in 2 (2.9%), ischemic kidney disease in 1 (1.4%), glomerulonephritis in relation to systemic vasculitis in 1 (1.4%), Alport syndrome in 1 (1.4%), kidney amyloidosis in 1 patient (1.4%).

The characteristics of the patients included in the study are presented in the Table 1. All comorbidities and complications listed in this table were diagnosed in patients prior to COVID-19 development. The median age of patients at the time of the onset of coronavirus infection clinical

symptoms was 55.2 [43.3;61.6] years, and the median follow-up period after KT was 69.4 [23.5;107.2] months. The absolute majority of recipients received three-component immunosuppression based on tacrolimus or cyclosporine in combination with mycophenolates and oral corticosteroids. 18.8% of the recipients had a history of cured acute rejection, while 4.3% of the recipients had a chronic rejection history. A significant portion of patients, in addition to kidney disease that had led to end-stage chronic renal failure (CRF), had various combinations of other diseases/conditions that could aggravate the course of coronavirus infection: arterial hypertension, post-transplant DM, cardiovascular and oncological complications. In the postoperative period (prior to the development of a new coronavirus infection), 42% of recipients had various viral infections: active cytomegalovirus infection, viral hepatitis, infection caused by Epstein–Barr virus. By the time of SARS-CoV-2 infection, 27.5% of patients had had a chronic graft dysfunction. The Charlson Comorbidity Index was used to assess the patient's co-existence of two or more diseases related to each other by a single pathogenetic mechanism or coinciding in time [20]. The median comorbidity index in the entire cohort of patients was 4 [3;6].

Table 1. Characteristics of renal transplant recipients with COVID-19

Parameter	Value
Age at KT, years	48.1 [38.4;55.1]
Age at the time of onset of COVID-19 symptoms, years	55.2 [43.3;61.6]
Time after KT by the moment of the onset of COVID-19 symptoms, months	69.4 [23.5;107.2]
Retransplantation patients, n (%)	9 (13)
Patients with immediate graft function, n (%)	53 (76.8)
Immunosuppression: tacrolimus cyclosporine A without CNI, n (%)	 57 (82.6) 11 (15.9) 1 (1.4)
History of acute graft rejection, n (%)	13 (18.8)
Chronic graft rejection, n (%)	3 (4.3)
Urological complications after KT, n (%)	7 (10.1)

Arterial hypertension, n (%)	49 (71)
Viral complications after KT (before the development of COVID-19), n (%)	29 (42)
Post-transplant diabetes mellitus (PTDM), total on insulin, n (%)	 22 (31.9) 6 (27.3)
Total patients with diabetes mellitus (PTDM and diabetes mellitus as the CRF cause), n (%)	32 (46.4)
Cardiovascular complications after KT, n (%)	14 (20.3)
Cancer complications after KT, n (%)	5 (7.2)
Graft dysfunction (serum creatinine>150 μmol/L) at the onset of COVID-19 symptoms, n (%)	19 (27.5)
Comorbidity Index, score	4 [3;6]

Sixty recipients (85.5%) were treated for COVID-19 in hospital, and 9 (14.5%) received an outpatient treatment.

The clinical data and the laboratory and instrumental test results for processing and analysis were obtained from "Everest" Medical Information System of Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy (MONIKI), as well as from the abstracts of medical records and outpatient charts of patients regularly followed-up in our Institute after transplantation, but receiving treatment for COVID-19 in other hospitals.

Methods for diagnosing COVID-19

The diagnosis of a new coronavirus infection was confirmed by detecting the SARS-CoV-2 RNA in oropharyngeal and nasopharyngeal swab samples using a real-time reverse transcriptase-polymerase chain reaction (PCR) and/or identifying the lung pattern typical of viral pneumonia on chest computed tomography. In case of PCR negative results, an additional argument to confirm the COVID-19 diagnosis was the detection of SARS-CoV-2-specific antibodies of IgM class and an increase of the IgG antibody titer over time.

Treatment was given in accordance with the clinical guidelines of the Russian Federation Healthcare Ministry currently valid at the time of the disease.

Methods of statistical processing

Statistical analysis was performed using the BioStat 7.3 statistical software package. The data obtained were evaluated using descriptive statistics methods. To assess clinical and laboratory parameters, the median and the interquartile ranges were calculated, including the 25th and 75th percentiles. Statistical significance of differences between the two groups was assessed using the nonparametric Mann-Whitney test. Regression logistic analysis was used to identify independent predictors of a poor outcome. All differences were considered statistically significant at $p<0.05$.

Results

The period from the onset of clinical symptoms to patient hospital admission was 7 [4; 10] days, at a minimum on the day of clinical manifestation, and a maximum on day 39 (late patient's seeking for medical care).

Among kidney transplant patients with COVID-19, only 27.5% had a history of confirmed contact with people infected with SARS-CoV-2. The most common clinical symptoms of new coronavirus infection in patients with a renal allograft were hyperthermia, general weakness at the onset of the disease, cough and shortness of breath, but also, although significantly less often, anosmia, chest pain, vomiting and/or diarrhea (Table 2).

Table 2. Epidemiological data and early clinical symptoms in renal transplant recipients with SARS-CoV-2 infection

Risk factors and symptoms	Number of patients (n=69)
Confirmed contact with SARS-CoV-2 source, n (%)	19 (27.5)
Hyperthermia at the onset of the disease, n (%)	59 (85.5)
General weakness at the onset of the disease, n (%)	45 (65.2)
Cough, n (%)	36 (52.2)
Dyspnea, n (%)	19 (27.5)
Chest pain, n (%)	5 (7.2)
Anosmia, n (%)	10 (14.5)
Vomiting and/or diarrhea, n (%)	5 (7.2)

Upon hospital admission, all patients showed the signs of lung tissue damage of varied severity, but most of the patients had the lung tissue damage of up to 50% (CT1 and CT2), and only in 13% of patient had the lesion consistent with CT3 severity assessment at the time of hospital admission. In the course of further follow-up, despite the treatment, more cases with CT3 occurred, and a patient with CT4 appeared (Table 3).

Table 3. Multispiral chest computed tomography results of hospitalized kidney recipients with COVID-19

The severity of lung damage by CT assessment on admission to hospital (for 60 patients), n (%)	CT1	28 (46.7)
	CT2	24 (40)
	CT3	8 (13.3)
	CT4	0
The maximum severity of lung damage by CT assessment (for 60 patients), n (%)	CT1	24 (40)
	CT2	19 (31.7)
	CT3	16 (26.7)
	CT4	1 (1.7)

The median number of positive PCR tests per patient was 1 with a minimum of 0 and a maximum of 3. PCR test results were unavailable in 2 patients; 60 of 67 patients (89.5%) had the virus RNA in at least one swab sample, and 7 patients (10.5%) had negative PCR results in all swab samples.

In patients with SARS-CoV-2 infection, the peak period of the disease (the time of maximum clinical and laboratory manifestations/patterns) was characterized by the following abnormalities in laboratory parameters: decreased hemoglobin and absolute lymphocyte count, total protein and serum albumin, increased creatinine, urea, LDH, blood glucose, C-reactive protein, ferritin, procalcitonin and D-dimer (Table 4).

Table 4. Clinical and laboratory parameters in renal transplant recipients in the peak period of SARS-CoV-2 infection

Clinical and laboratory parameters	Value
The number of positive PCR results for SARS-CoV-2, median (min;max), n=67	1 (0;3)
Hemoglobin, g/L, n=69	111.5 [95.7;130.3]
Leukocytes, $*10^9$/L, n=69	8.660 [6.750;15.600]
Granulocytes, $*10^9$/L, n=69	2.000 [0.675;3.500]
Lymphocytes, $*10^9$/L, n=69	0.500 [0.132;1.200]
Platelets, $*10^9$/L, n=69	174.0 [121.0;202.0]
Bilirubin, μmol/L, n=69	11.0 [8.0;15.0]
ALT, U/L, n=69	31.0 [19.7;54.0]
AST, U/L, n=69	32.0 [21.0;51.0]
Total protein, g/L, n=69	59.5 [53.3;64.3]
Albumen, g/L, n=69	32.5 [30.8;38.8]
Lactate dehydrogenase, U/L, n=69	339.7 [224.6;588.5]
Blood glucose, mmol/L, n=69	7.10 [6.00;11.00]
Urea, mmol/L, n=69	14.4 [9.5;19.2]
Blood creatinine, μmol/L, n=69	169.0 [126.0;260.5]
GFR, ml/min/1.73 m^{2} (creatinine clearance), n=69	38.1 [22.1;56.6]
C-reactive protein, mg/L, n=69	34.9 [12.9;97.8]
Ferritin, μg/L, n=69	647.0 [300.0;985.0]
Troponin I, ng/mL, n=61	0.150 [0.035;1.840]
Procalcitonin, ng/mL, n=69	1.050 [0.240;10.000]
Activated partial thromboplastin time, sec, n=69	30.0 [26.5;35.0]
INR, n=69	1.200 [1.038;1.330]
D-dimer, ng/mL, n=69	632.0 [347.5;3630.3]

Notes: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; INR, International Normalized Ratio

A number of patients developed serious complications: bacterial sepsis in 8 of 69 patients (11.6%), pseudomembranous colitis in 3 (4.3%),

myocardial infarction in 5 (7.2%), myocarditis in 5 (7.2%), and lower limb vascular thrombosis in 2 (2.9%) patients.

Hydroxychloroquine was used in 21 of 69 recipients (30.4%) (who became ill in spring and summer of 2020; later the drug was discontinued), antiviral drugs were used in 16 (23.2%) patients, antibiotics in 59 (85.5%), parenteral corticosteroids (methylprednisolone, dexamethasone) were administered in 33 (47.8%). Biological anti–cytokine agents were given to 11 of 69 (15.9%), including tocilizumab to 7 patients, baricitinib to 2, levilimab to 1, olokizumab followed by tocilizumab to 1 patient. Fifty two (75.4%) of 69 patients received unfractionated or low-molecular-weight heparin, 4 (5.8%) received oral anticoagulants, and 13 (18.8%) received insulin. Twenty (29%) of 69 patients received no oxygen therapy, 23 patients (33.3%) were given humidified oxygen through a nasal cannula, 12 patients (17.4%) received noninvasive ventilation, and 14 patients (20.3%) received invasive ventilation. Six (8.7%) of 69 patients required RRT due to severe renal graft dysfunction; 5 of these 6 patients died, and one recovered with restoring the graft function.

In a majority of patients: 66 (95.6%) of 69, the maintenance immunosuppressive therapy was somehow adjusted. In a majority of patients: 66 (95.6%) of 69, the maintenance immunosuppressive therapy was somehow adjusted. The dose of CNI was kept unchanged in 14 recipients (20.3%) of 69, was decreased with reducing target concentrations in 46 (66.7%), CNIs were completely canceled in 9 (13%). The dose of mycophenolates did not change in 5 recipients (7.6%), was decreased in 14 (20.3%), and was completely withdrawn in 47 (68.1%). Everolimus was discontinued in all three patients treated with that drug. Oral corticosteroids were given in the same dose to 24 (34.8%) recipients of 69, in an increased dose to 44 (63.8%); only one patient (1.4%) had

oral corticosteroids withdrawn owing to the intravenous use of methylprednisolone.

Fifty three (76.8%) of 69 patients survived with a functioning graft, 3 (4.3%) survived with lost graft function, and 13 (18.8%) died. The cause of death in all patients was a severe respiratory distress syndrome (RDS) with multiple organ dysfunction, which was complicated by sepsis and septic shock in 8 patients (61.5%).

Patients with a poor COVID-19 outcome were slightly older and had a longer post-transplant period at the time of the disease compared to the surviving patients, but the differences in these parameters were not statistically significant (Table 5). In the group of deceased patients, the Comorbidity Index was significantly higher, and there were also more patients with DM. Some clinical cases displayed a severe COVID-19 developed in the early postoperative period after KT, especially during treatment for rejection. One patient from our case series was histologically diagnosed with humoral rejection on day 30 after repeated cadaveric kidney allotransplantation. Anti-crisis therapy was performed according to the standard scheme: plasmapheresis, rituximab, intravenous immunoglobulin. However, on day 11 after the therapy completion, the patient showed the signs of respiratory viral infection. PCR test of nasopharyngeal swab sample confirmed COVID-19. Subsequently, there was a rapid development of ARDS, the patient died on the 3rd day of hospitalization in the Intensive Care Unit.

Table 5. Demographic characteristics and comorbidity status in the survived and deceased renal transplant recipients with COVID-19

Parameter/group	Survived, n=56	Deceased, n=13	p
Age at the time of KT, years	47.4 [36.7;4.8]	51.3 [39.9;58.4]	0.104
Age at the time of the onset of COVID-19symptoms, years	54.5 [42.7;61.3]	58.8 [45.9;63.9]	0.177
Time after KT by the moment of the onset of COVID-19 symptoms, months	70.3 [29.9;108.7]	42.4 [2.4;99.7]	0.510
Comorbidity Index, score	4 [3;5]	5 [4;6.5]	0.047
Diabetes mellitus, n (%)	14 (25.3)	8 (61.5)	0.019

At the peak of the disease, the patients who later died compared to the survivors, had significantly lower levels of hemoglobin, lymphocytes, platelets, GFR, total protein and albumin, and higher values of white blood cells, lactate dehydrogenase, blood glucose, creatinine, and urea, C-reactive protein, ferritin, procalcitonin, activated partial thromboplastin time (APTT), INR, and D-dimer (table. 6).

Table 6. Laboratory parameters, severity biomarkers in survived and deceased renal transplant recipients with COVID-19

Parameter/group	Survived, n=56	Deceased, n=13	p
Hemoglobin	112.4 [100.0;132.0]	81.0 [73.9;106.4]	0.004
Leukocytes	8.000 [6.670;10.600]	17.700 [12.675;24.460]	0.001
Lymphocytes	0.629 [0.170;1.500]	0.256 [0.065;0.515]	0.040
Granulocytes	2.450 [0.700;3.800]	0.829 [0.623;2.145]	0.118
Platelets	178.5 [148.8;212.5]	119.0 [102.0;142.5]	0.001
LDH	280.0 [220.0;479.0]	843.3 [450.0;1087.5]	0.021
Blood glucose	6.89 [5.87;8.20]	11.07 [6.30;17.69]	0.045
Creatinine	146.0 [116.7;220.3]	374.0 [193.7;545.5]	0.001
Urea	12.5 [8.9;16.6]	26.1 [17.4;33.8]	0.0001
GFR	42.4 [26.9;61.0]	13.0 [8.5;29.1]	0.0001
Total protein	61.0 [56.8;65.0]	48.2 [44.2;56.1]	0.002
Albumen	34.0 [31.2;39.6]	31.0 [26.8;32.4]	0.043
Bilirubin	11.17 [7.90;14.41]	10.70 [8.47;16.70]	0.620
ALT	33.2 [20.3;54.0]	23.5 [17.8;56.1]	0.409

AST	27.9 [21.0;47.0]	47.6 [27.9;76.7]	0.103
C-reactive protein	29.9 [11.7;69.0]	168.6 [64.9;291.0]	0.00008
Ferritin	503 [260;762]	3313 [902;8299]	0.027
Procalcitonin	0.450 [0.163;4.185]	14.00 [2.235;34.45]	0.003
Troponin	0.625 [0.045;1,325]	0.060 [0.035;8.590]	0.905
APTT	29.6 [25.1;32.4]	41.1 [37.8;73.9]	0.0003
INR	1.170 [1.030;1.300]	1.420 [1.240;1.980]	0.001
D-dimer	500 [245;2405]	3507 [2076;7215]	0.008

In the peak period of the disease, the renal transplant recipients who survived COVID-19 had a statistically significantly lower degree of lung tissue damage according to multislice computed tomography (MSCT) results compared to the patients who died (Table 7).

Table 7. Chest multispiral CT characteristics in survived and deceased patients with COVID-19*after kidney transplantation

Parameter/group		Survived, n=47	Deceased, n=13	p
The maximum severity of lung damage by CT assessment (for n=60), n (%)	CT1	24	0	<0.001
	CT2	15	3	
	CT3	8	9	
	CT4	0	1	

Note: the CT data were available for 47 of 56 survived patients

In the group with a poor outcome of the new coronavirus infection, more patients developed bacterial complications, bacterial sepsis, fungal complications, had myocardial infarction and myocarditis. These patients were more likely to require invasive MV and RRT, and they were more likely to have their CNI canceled (Table 8).

Table 8. Complications and treatment features in the groups of survived and deceased renal transplant recipients with COVID-19

Parameter/group	Survived, n=56	Deceased, n=13	p
Bacterial complications, n (%)	9 (16.1)	8 (61.5)	0.002
Bacterial sepsis, n (%)	0	8 (61.5)	<0.00001
Fungal complications, n (%)	2 (3.6)	3 (23.1)	0.043
Myocardial infarction, n (%)	1 (1.8)	4 (30.8)	0.004
Myocarditis, n (%)	2 (3.6)	3 (23.1)	0.043
Invasive MV, n (%)	3 (5.4)	12 (92.3)	<0.00001
The need for hemodialysis, n (%)	1 (1.8)	5 (38.5)	0.001
Biological therapy, n (%)	7 (12.5%)	4 (30.8%)	0.199
Withdrawal of CNI (for n=63), n (%)	3 (5.4)	6 (12)	0.002

The groups of survivors and deceased patients did not differ significantly in the frequency of taking hydroxychloroquine, antibiotics, anticoagulants, mycophenolate withdrawal, in increasing the dose of oral steroids, parenteral use of additional steroids, and the use of biological agents.

Multivariate regression analysis identified the independent predictors of death: bacterial sepsis, invasive mechanical ventilation, severe renal graft dysfunction with the need for hemodialysis treatment (Table 9).

Table 9. Mortality predictors in renal transplant recipients with COVID-19 (logistic regression analysis)

Predictor	OR	95% CI	p
Bacterial sepsis − no	0.385	0.193-0.765	<0.00001
Invasive MV − yes	17.231	5.667-52.388	<0.00001
Hemodialysis − yes	21.538	2.744-169.074	0.0006

Note: OR, odds ratio, CI, confidence interval

Invasive mechanical ventilation increased the risk of death by 17.2 times, and hemodialysis did by 21.5 times. Since no patients survived bacterial sepsis that developed in patients with COVID-19 infection, it is impossible to calculate the direct risk. For this reason, we determined a

protective value: the absence of sepsis reduced the risk of patient death by 2.6 times.

Discussion

In 2019, a new threat to the health and life of patients with transplanted organs emerged. It is known that COVID-19 is much more severe in patients after solid organ transplantation. They are subject to longer hospital stay and have poorer outcomes of treatment compared to patients in general population [9].

As previously reported, SARS-CoV-2 is transmitted from asymptomatic individuals in most cases [1]. In our study, most of the affected recipients had no known epidemiological contacts, only 27.5% had contact with infected individuals. The most frequent symptoms reported on admission to the hospital were fever, cough, shortness of breath, and one third of patients were admitted with gastrointestinal complaints, which did not differ significantly from general COVID-19 population [12, 21].

Abnormal X-ray findings preceded the development of hypoxemia in the same way as in the general COVID-19 population of patients [22], although it is commonly assumed that patients receiving immunosuppressants may develop ARDS in the early period of the disease. In our patients, the ARDS progression was mostly associated with the development of systemic inflammation and the addition of bacterial infection. Apparently, infection with other viruses affecting the respiratory system may also play a role, but for a number of reasons, testing for these viruses was not performed in our patients. One study reported that 22.4% of those infected with SARS-CoV-2 (11 of 40) also had other respiratory viruses identified; and of 127 patients with other viruses, 11 (8.66%) had a SARS-COV-2 co-infection [1].

For many patients with COVID-19, a common feature is known to be the presence of lymphopenia, which is especially pronounced in patients with a severe course of the disease. It is possible that the reduced levels of circulating lymphocytes in patients may reflect the mass migration of lymphocytes to inflamed tissues or the use of steroid therapy. Some studies have reported significant depletion of the T-cell pool in the secondary lymphoid organs of the patients infected with SARS-CoV-2 [23, 24], although the potential mechanisms responsible for this phenomenon are not fully understood. However, in our study, low lymphocyte counts were associated with respiratory decompensation and fatal outcome. Thus, severe lymphopenia is an unfavorable prognostic factor in renal transplant recipients with COVID-19. The deceased patients had also higher leukocyte counts at the peak of the disease compared to the survivors, which, combined with a significantly higher procalcitonin level, probably indicates the addition of bacterial sepsis. The group of our patients with a poor outcome had higher levels of C-reactive protein and ferritin. Similarly, according to literature reports, higher blood levels of inflammatory markers (including C-reactive protein, ferritin, and D-dimer), an increased neutrophil-to-lymphocyte ratio, and high serum levels of proinflammatory cytokines, as well as procalcitonin [25-27] were associated with the disease severity and death.

Patients who died from COVID-19 had had significantly lower platelet levels, higher D-dimer and LDH values, which highly likely suggests the development of systemic microvascular thrombosis contributing to the onset of a fatal outcome. Published data confirm that coronavirus disease is complicated by coagulopathy, namely, disseminated intravascular coagulation in the absence of clinically obvious thromboembolic events [25, 28] at the onset of the disease, although later large-vessel thrombosis may also develop. S. Cui et al.

reported 81 cases of COVID-19-associated venous thrombosis in patients admitted to an Intensive Care Unit, while 40 % of patients among those who had received no thromboprophylaxis died [26]. The presented data once again confirm the importance of administering anticoagulant therapy to patients with COVID-19, and especially to renal transplant recipients, since this group of patients usually has other risk factors for developing thrombotic events.

In our case series, the overall mortality rate of kidney transplant recipients with a new coronavirus infection was 18.8%, which corresponds to publications with similar figures: from 6% to 30% [9, 11, 22, 29]. The death rate from COVID-19 in the general population was 8% in New York, 14% in Italy, and 12% in Spain. In those hospitalized, this value varies significantly, but reaches higher level than that for COVID-19 in general. In the initial study conducted in China, among 191 hospitalized patients, the mortality rate was 28% [30].

We did not find a significant difference in age and duration after KT between the groups with favorable and poor outcomes, although a number of publications have described an older age and shorter time after transplantation as predictors of mortality [12, 14]. This might be explained by a small number of patients in our cohort. Our study confirmed the presence of multiple co-morbidities in renal transplant recipients with COVID-19. Thus, arterial hypertension occurred in 49% of patients, DM in 32%, CVD in 14%; history of viral complications (cytomegalovirus infection, Epstein-Barr virus) was seen in 29% of recipients at different timepoints after transplantation. In the group of deceased recipients, the Comorbidity Index and the proportion of patients suffering from DM were significantly higher.

Patients who died from a novel coronavirus infection had higher serum urea and creatinine levels at the peak of the disease compared to

survivors. Overall, 6 patients developed stage 3 acute kidney injury (AKI) of the graft, 5 of whom died. All these patients underwent RRT: hemodialysis. The causes of AKI in solid organ recipients may vary: there have been discussed acute tubular necrosis, direct cytotoxic effect of coronavirus, development of acute graft rejection due to reduced immunosuppression, and thrombotic microangiopathy [29, 30]. A common hypothesis for the AKI development in patients is the occurrence of an uncontrolled cytokine storm and the development of multiple organ failure associated with COVID-19 [31].

The cause of death in the patients in our study was a severe RDS with a multiple organ dysfunction (including AKI) often complicated by sepsis and septic shock.

As noted above, it is still unclear whether immunosuppressive treatment is an independent risk factor for the severe course and death from coronavirus infection. The initial assumption that an immunodeficiency status restricts the cytokine syndrome and leads to a milder course of the disease [32] was refuted by subsequently obtained data. On the contrary, recipients infected with COVID-19 have a high risk of irreversible complications actually caused by secondary immunodeficiency. Therefore, most of our patients underwent a controlled reduction of immunosuppression. It is noteworthy to mention that in the group of deceased patients there were more patients who underwent a complete withdrawal of CNI. Apparently, this can be explained by the fact that the CNI withdrawal was performed in patients with an initially more severe course of SARS-CoV-2 infection.

Currently, there is very little data available on the optimal treatment of transplant patients who test positive for SARS-CoV-2, including strategies to reduce or modify immunosuppression. The group of transplant doctors from London reduced immunosuppressive therapy

in 27% of patients, completely canceled it in 31%, and did not change it in 5% of patients. The most frequently discontinued was the drug of antimetabolite group (91%). Calcineurin inhibitors were reduced in 32% (65/204) and discontinued in 58% of cases; 7% of patients were converted from tacrolimus or an mTOR inhibitor to cyclosporine. Everolimus was reduced in 7% and discontinued in 67% of cases [33-35].

Corticosteroids have been the cornerstone of many maintenance immunosuppression regimens, and they have also shown unequivocal efficacy in treating patients with severe coronavirus infection in a number of multicenter studies. On the one hand, corticosteroids can reduce the severity of the cytokine storm, on the other, they can suppress the immune response, decrease the clearance of pathogens, if they are administered at early stages of therapy for SARS-CoV-2 or in a mild course of the disease. In our case series, parenteral corticosteroids were administered to 33 hospitalized patients (47.8%). Oral corticosteroids were administered at the previously given dose in 24 of 69 recipients (34.8%), in an increased dose in 44 (63.8%); in one patient (1.4%) only, oral corticosteroids were discontinued against intravenous methylprednisolone therapy.

To date, there is no consensus as to what pharmacotherapy strategy should be followed in the treatment of a new coronavirus infection. Maintenance therapy remains the mainstay of treatment for COVID-19, and currently there are no antiviral drugs with proven efficacy. Most of our patients received hydroxychloroquine, an antimalarial drug with an in vitro activity against SARS-CoV-2, because the Clinical Guidelines of the Russian Federation Healthcare Ministry valid at that time supported this treatment option. However, recent data from a large observational study [29] and a randomized controlled trial [43] have not confirmed a

significant benefit of this drug for the treatment or prevention of COVID-19.

At the beginning of the COVID-19 pandemic, attempts were also made to use antiretroviral drugs. However, the patients taking protease inhibitors have been shown to require an acute reduction of daily doses and extended intervals between CNI doses [44–50]. It was estimated [51] that the half-life of CNI increased 5−20-fold due to systemic inhibition of CYP3A and ABCB1, which led to a dosage regimen of 0.5-1 mg once a week for Tac and 25 mg every 1-2–days for cyclosporin A in kidney and liver transplant recipients. Overall, these data strongly suggest that administration of lopinavir therapy in CNI-treated transplant recipients without a dose adjustment will result in extremely high and persistent blood levels of the drugs and excessive immunosuppression. Often, a preemptive reduction in the dose of cyclosporine or tacrolimus was insufficient [52]. Currently, protease inhibitors are not used in patients with COVID-19, including in patients with transplanted organs.

When signs of systemic hyperinflammation (referred to as a "cytokine storm") developed, anti-interleukin agents were used in most centers. These drugs showed themselves to be particularly effective in patients who experienced an increased need for oxygen support [53-55–]. Tocilizumab, an IL-6 receptor antagonist, was mainly used in our patients (7 patients). IL-6 blockers were used in only 9 patients (13%). Meanwhile, CT3-4 severity was observed in 17 patients, and CT2 was in 19 patients. Theoretically, that was the number of patients who had indications for the administration of IL-6 blockers. According to literature data, this is probably the only group of drugs that improves the disease outcomes in all subpopulations of patients (severe, extremely severe, treated with non-invasive and invasive mechanical ventilation, etc.). We did not find any effect of biological drugs on the outcome, but this may

be due to the fact that there were very few patients who received such therapy in our cohort. In retrospect, we can say that in the presented cohort, at least 50% of patients, those were the patients having CT2-4 severity, could have received IL-6 blockers, but had not received them due to limited access to the latter.

In 2021, the arsenal of SARS-CoV-2 vaccines with high efficacy and low incidence of serious adverse events is being rapidly replenished [56]. Vaccination seems to be the only reliable way to prevent severe forms of COVID-19 and deaths associated with this viral infection in patients with transplanted organs.

Conclusions

1. Among kidney transplant recipients who suffered COVID-19 infection at mean 69.4 months after transplantation, 76.8% survived with a functioning graft, 3 (4.3%) survived with the lost graft function, and 13 (18.8%) died. The cause of death of the patients was severe respiratory distress syndrome with multiple organ dysfunction. There were no differences between the groups of survivors and those who died in terms of their age and time elapsed after transplantation during the entire disease, but the group of those who died had a significantly higher comorbidity index and more patients with diabetes mellitus.

2. The deceased patients compared to the survivors had significantly lower levels of hemoglobin, lymphocytes, platelets, glomerular filtration rate, total protein and albumin at the peak of the disease, and higher values of leukocytes, lactate dehydrogenase, blood glucose, creatinine and urea, C-reactive protein, ferritin, procalcitonin, activated partial thromboplastin time, international normalized ratio, and D-dimer, which confirms the role that is played by the excessive systemic

inflammatory response, specific coagulopathy, sepsis, and graft dysfunction in a poor outcome of the disease.

3. Multivariate regression analysis revealed independent predictors of death in renal transplant recipients with COVID-19: bacterial sepsis, invasive mechanical ventilation, severe renal graft dysfunction with the need for hemodialysis treatment.

4. Modification of immunosuppressive therapy in recipients with COVID-19 is usually necessary, but the decision to reduce the amount of immunosuppression should be personalized, taking into account the severity of the viral infection, the patient's age, co-morbidities, the time after transplantation, and the risk of rejection.

5. Since the efficacy of antiviral and biological therapy for SARS-CoV-2 infection has not been fully established and the mortality risk is extremely high, the prevention of the COVID-19 development in renal transplant recipients through vaccination should be considered the optimal approach, although further clinical studies of both the treatment and prevention strategies are required.

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The article was received on September 7, 2021;
Approved after reviewing September 20, 2021;
Accepted for publication September 29, 2021