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COVID-19 IN SOLID ORGAN TRANSPLANT RECIPIENTS: INITIAL REPORT FROM NATIONAL MULTICENTER OBSERVATIONAL STUDY "ROKKOR-RECIPIENT"

S.V. Gautier[1, 2], A.O. Shevchenko[1, 3], O.M. Tsirulnikova[2, 1], S.M. Khomyakov[1], O.N. Kotenko[4], V.E. Vinogradov[4, 5], I.N. Abyzov[6], G.D. Avetisyan[7], A.Yu. Anisimov[8], L.Yu. Artyukhina[4], M.T. Bekov[1], V.A. Berdinsky[4], V.S. Bogdanov[4], A.Yu. Bykov[9], A.Yu. Vinokurov[10], A.Yu. Goncharova[1], D.P. Evdokimov[11], D.V. Ezersky[12], V.E. Zagainov[13], V.M. Zakharevich[1, 2], K.N. Zelenin[14], E.S. Ivanova[4], A.A. Kartashev[1], N.G. Kvadratova[1], I.G. Kim[4], N.N. Koloskova[1], V.L. Korobka[15], I.R. Kurbanuglov[1], M.A. Lysenko[4], I.A. Miloserdov[1, 2], Ya.G. Moisyuk[16], G.V. Nikolaev[17], I.V. Ostrovskaya[4], N.Yu. Petrova[18], A.V. Petryaev[19], A.V. Pinchuk[20], V.S. Platonov[21], V.N. Poptsov[1], Z.A. Porchkhidze[1], D.A. Saydulaev[1], A.D. Sapozhnikov[22], S.B. Semchenko[23], M.M. Skorobogatov[21], V.Yu. Tereshchenko[24], N.F. Frolova[4], D.V. Khalikova[1], T.A. Khalilulin[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation
[2] Sechenov University, Moscow, Russian Federation
[3] Pirogov Medical University, Moscow, Russian Federation
[4] Moscow City Scientific and Practical Center for Nephrology and Transplant Kidney Pathology, City Clinial Hospital No. 52, Moscow, Russian Federation
[5] Research Institute of Health Care Organization and Medical Management, Moscow, Russian Federation
[6] Republican Clinical Hospital, Cheboksary, Russian Federation
[7] Clinical Hospital No. 1, Smolensk, Russian Federation
[8] City Clinical Hospital No. 7, Kazan, Russian Federation
[9] State Novosibirsk Regional Clinical Hospital, Novosibirsk, Russian Federation
[10] Leningrad Regional Clinical Hospital, St. Petersburg, Russian Federation
[11] Regional Clinical Hospital, Krasnoyarsk, Russian Federation
[12] Sergeev Regional Clinical Hospital No. 1, Khabarovsk, Russian Federation
[13] Volga Regional Medical Center, Nizhny Novgorod, Russian Federation
[14] Ministry of Health of the Arkhangelsk Oblast, Arkhangelsk, Russian Federation
[15] Rostov Regional Clinical Hospital, Rostov-on-Don, Russian Federation
[16] Vladimirsky Moscow Regional Research Clinical Institute, Moscow, Russian Federation
[17] Almazov National Medical Research Centre, St. Petersburg, Russian Federation
[18] Saratov Regional Clinical Hospital, Saratov, Russian Federation
[19] Tula Regional Clinical Hospital, Tula, Russian Federation
[20] Sklifosovsky Research Institute of Emergency Care, Moscow, Russian Federation
[21] District Clinical Hospital, Khanty-Mansiysk, Russian Federation
[22] Shumakov National Medical Research Center of Transplantology and Artificial Organs in the city of Volzhsky, Volzhsky, Russian Federation
[23] Center for Organ and Tissue Transplantation, Regional Clinical Hospital No. 1, Tyumen, Russian Federation
[24] Kabanov City Clinical Hospital No. 1, Omsk, Russian Federation

We herein present our initial report from "ROKKOR-recipient", a national multicenter observational study. The prevalence, risk factors, clinical manifestations and outcomes of the novel coronavirus disease 2019 (COVID-19) in solid organ transplant recipients receiving immunosuppressive therapy were investigated. The study enrolled 251 COVID-19 patients (220 kidney recipients, 7 liver recipients, 1 liver-kidney recipient, and 23 heart recipients). The subjects came from 20 regions in Russia. The symptoms, clinical presentation, imaging and lab test results,

Corresponding author: Alexey Shevchenko. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (495) 190-35-62. E-mail: alxxshevchenko@aol.com

therapy and outcomes of COVID-19 were described. It was established that solid organ transplant recipients with COVID-19 have a higher risk of developing adverse events. Predictors of adverse events include associated cardiovascular diseases, pulmonary diseases, diabetes, and kidney failure. Symptoms of the disease include dyspnea, rash and catarrhal signs, as well as initial low blood oxygen saturation (SpO_2 <92%), leukocytosis (white blood cell count >10×10^9/L), elevated creatinine levels (>130 μmol/L) and a marked decrease in glomerular filtration rate, requiring hemodialysis. Performing organ transplant surgery in COVID-19 does not increase the risk of adverse events but could save the lives of waitlisted terminally ill patients.

Keywords: organ transplantation, pandemic, COVID-19, SARS-CoV-2, risk factors, Russian Transplant Society.

INTRODUCTION

In the first half of 2020, the unprecedented magnitude and impact of the pandemic caused by the new SARS-CoV-2 coronavirus reached, with few exceptions, virtually every country in the world. By the end of July 2020, there have been more than 16 million cases and over 650,000 deaths. In Russia, between January 31 and July 17, 2020, 759,203 confirmed COVID-19 cases were detected, and 12,123 deaths were recorded [1]. The high rate of spread of the virus is caused by asymptomatic carrier state, high contagiosity, and long-term preservation in the environment. About 20% of patients need hospitalization, while mortality varies greatly from country to country and depends on a number of factors, ranging from 1 to 15.2% [2, 3].

The infection caused by the new SARS-CoV-2 coronavirus is a poorly studied disorder; despite the huge spread of coronavirus disease in the world, the number of observations in the recipients of transplanted organs is low. An important feature of this category of patients is the permanent risk of developing the transplant rejection which implies the need for immunosuppressive therapy. The patients of transplanted organs – heart, liver, kidneys – who are forced to receive immunosuppressive therapy for life and have a number of concomitant diseases are a group of potentially high risk of severe complications of COVID-19 [4, 5].

By early 2020, against the backdrop of the development of domestic transplantology, a large population of patients with transplanted organ had formed in the Russian Federation. Heart, liver and kidney transplantations allows to save life, to restore the ability of patients in critical, life-threatening conditions, to achieve physical and social rehabilitation. Recipients have a number of features due to physiology of transplanted organs and the need for life-long immunosuppressive therapy, which can have an unpredictable impact on the risk of SARS-CoV-2 virus infection and the clinical course of COVID-19 disease. In particular, immunosuppression increases the probability of infectious diseases [6] but reduces the risk of developing acute inflammatory response ("cytokine storm"); moreover, there is an assumption that calcineurin inhibitors which are the basis of complex immunosuppressive therapy, can inhibit intracellular replication of coronavirus [7].

The COVID-19 pandemic is dangerous not only for organ recipients, but also for severe patients with terminal heart, liver and kidney diseases included in the waiting list [8], and clinical data are needed to assess the risk-benefit ratio of surgery.

Under the auspices of the Russian Transplantology Society, the national multicenter study entitled "Prevalence and Features of the Clinical Course of Coronavirus Infection in Heart, Kidney, Liver Recipients" (ROK-KOR-Recipient) was organized to study the incidence, risk factors, clinical manifestations, and outcomes of the new coronavirus infection (COVID-19) in the recipients of the solid organs (heart, kidney, liver) receiving immunosuppressive therapy.

MATERIALS AND METHODS

Russian federal and regional centers providing medical assistance to recipients of transplanted organs in the conditions of the COVID-19 pandemic participated in the study. The inclusion criteria were the presence of a transplant organ, liver, kidney or heart, and the detected COVID-19 as well as the patient's informed consent to data processing.

The diagnosis of coronavirus infection caused by COVID-19 required either laboratory confirmation or the presence of characteristic clinical signs, including pneumonia [9], corresponding to the following ICD-10 codes: U07.1, U07.2, J12–J18. For laboratory diagnostics of SARS-CoV-2 virus infection, a viral RNA was isolated by polymerase chain reaction in samples taken from mucous membranes. The clinical criteria included signs of acute respiratory infection and respiratory failure as well as the oxygen saturation reduction at breathing atmospheric air (SpO_2 <92%) and characteristic changes detected by computer tomography of chest organs (ground glass attenuation), presence of reticular changes, consolidation sites and pulmonary tissue consolidations).

To determine the COVID-19 severity, the classification presented in the "Provisional Methodological Recommendations for Diagnosis, Prevention and Treatment of the New Coronavirus Infection of the Ministry if Health of the Russian Federation" [9] (Table 1) was used.

The study protocol included the collection and analysis of demographic and anthropometric data, as well as complaints, physical, laboratory and instrumental exa-

minations, transplant anamnesis, prescribed therapy and clinical outcomes of coronavirus infection. All recipients received immunosuppressive therapy with account for individual characteristics (individual tolerability, infection severity, risk of development of rejection etc.) as well as symptomatic and other pathogenetically based therapy determined by current clinical recommendations and treatment protocols considering clinical status.

The study results were statistically processed with the SPSS 18.0 software package (SPSS Inc., USA). Shapiro–Wilk W test was used to verify the normality of distribution. The significance of differences in the quantitative indicators meeting the normal distribution criteria was determined by Student's t-test, in other cases by Mann–Whitney U test. The groups were compared by non-parametric characteristics by Pearson chi-squared test (with observations in the group ≥10) and Fisher's exact test (with observations in the group <10). In all methods of statistical analysis, differences in $p < 0.05$ were considered to be significant.

Table 1

COVID-19 severity classification ("Temporary guidelines for the diagnosis, prevention and treatment of a new coronavirus infection of the Ministry of health of the Russian Federation" [9])

Severity	Criteria
Mild	t <38 °C, cough, weakness, throat pain Absence of criteria for medium and severe course
Medium	t >38 °C RR >22 Dyspnea at physical load Pneumonia at CT SpO_2 <95% CRP >10 mg/l
Severe	RR >30 SpO_2 ≤93% PaO_2/FiO_2 ≤300 mm Hg Progressing changes in lungs by radiology, CT (increase in lung changes by more than 50% in 24–48 h) Decreased level of consciousness, agitation Unstable hemodynamics (systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg, urine output <20 ml/h) Arterial blood lactate >2 mmol/l qSOFA >2 points
Extremely severe	ARF, respiratory support needed (ALV) TSS MOSF

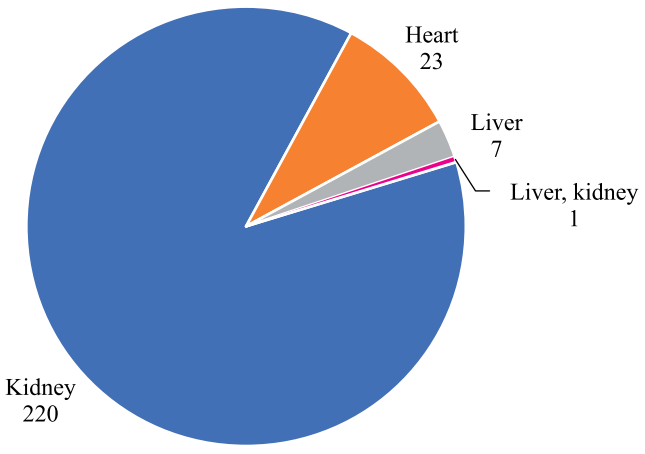

Fig. 1. Distribution of patients by transplanted organ

RESULTS

Between 01.04.2020 and 17.07.2020, 251 recipients with COVID-19 were identified and monitored in 20 regions of the Russian Federation, most of them in Moscow (66.9%)), Moscow region (5.6%), Leningrad region (4%) and Nizhny Novgorod region (4.0%) (Table 2).

The average age of patients was 48.3 ± 1.5 (13 to 77), 108 (43%) females, 143 (57%) males. The patients included 220 kidney recipients, 7 liver recipients, 1 liver and kidney recipient, 23 heart recipients (Fig. 1).

The average period from organ transplantation to the first clinical signs of COVID-19 was 363.6 ± 265.4 days (2 days to 11.5 years); 12 COVID-19 patients were diagnosed within the first 14 days after transplantation (6 after heart transplant, 6 after kidney transplant).

The most common symptoms of coronavirus infection were general discomfort and fatigue (84.4%), muscle pain (70.1%) and cough (68.9%), while anosmia and

Table 2

Distribution of organs recipients with COVID-19 by region

City, town, oblast (province)	Qty, n
Moscow	168
Moscow Oblast	14
Leningrad Oblast	10
Nizhny Novgorod Oblast	10
Novosibirsk Oblast	9
Omsk Oblast	5
Chuvash Republic	5
Republic of Tatarstan	4
St. Petersburg	4
Khanty-Mansiysk Autonomous District	4
Volgograd Oblast	3
Krasnoyarsk Kraj	3
Tula Oblast	3
Arkhangelsk Oblast	2
Rostov Oblast	2
Voronezh Oblast	1
Saratov Oblast	1
Smolensk Oblast	1
Tyumen Oblast	1
Khabarovsk Krai	1

rash were less frequent (13.5 and 4.4%, respectively), 12.4% of patients were asymptomatic (Table 3).

In most cases, the main clinical manifestation of COVID-19 was pneumonia (78.1%); the signs of extrapulmonary pathology – heart or kidney failure of various degrees of intensity – were observed in 38.3%, in 1.2% the paroxysm of atrial fibrillation developed. The average time from the first symptoms to visiting a doctor for medical treatment was 5.2 ± 3.1 days (1 to 12). At pre-assessment, the temperature above 38.5 °C was observed in 26%, 37–38.5 °C in 69.0%, in 10.8% the high temperature was not noted. In 19.3% of cases, with non-invasive determination SpO_2 <90%, in 41.2% – 90–95%, in 39.5% more than 95% was revealed.

At chest CT performed in 208 (82.9%) recipients, there were no changes (CT-0) in 12 (5.8%), ground-glass opacity which occupied less than 25% of the pulmonary parenchyma (CT-1) was found in 44 (21.2%), 25 to 50% of the pulmonary parenchyma (CT-2) in 52 (25.0%), 50 to 75% of the pulmonary parenchyma (CT-3) in 88 (42.3%), over 75% of the pulmonary parenchyma (CT-4) in 12 (5.8%).

Hospitalized were 233 patients (92.8%), the remaining 18 with a mild or asymptomatic course of coronavirus infection were observed outpatiently. In 39 patients hospitalized with COVID-19 clinical signs, the PCR primary test for virus DNA was negative, while retests were positive.

41 cases (16.3%) met the criteria for mild severity of COVID-19, 82 (32.8%), 60 (24.1%) for moderate, 67 (26.8%) for extreme severity (Fig. 2).

32 (12.8%) patients needed respiratory support (LV) with the average LV time of 9.3 ± 5.5 (3–17) days. 96 (38.3%) patients had non-invasive ventilation, while the remaining 123 had no need for ventilation. In connection with the development of expressed respiratory and heart failure in 4 patients with extremely severe COVID-19 course, the peripheral system of extracorporeal membrane oxygenation (ECMO) was implanted; two of them died on days 6 and 8 after the ECMO implantation, 2 achieved remission.

The average hospital stay was 16.1 ± 1.9 days (7 to 49). By 17.07.2020, 34 (13.5%) of the patient have died against COVID-19 infection, 186 (74.1%) were diagnosed with remission of the infectious disease, 31 (12.4%) continued treatment, 1 kidney recipient has been retransplanted.

Among liver recipients (n = 7) with COVID-19, no one was found to have either rejection or signs of transplant dysfunction; Five patients were discharged with remission, while two patients with the medium severity COVID-19 continue their treatment (hospital stay – 63 and 18 days). In 11 of 23 (47.8%) heart recipients, there were clinical signs of heart failure, and according to the endomyocardial biopsy, acute rejection of heart transplant was detected in only 7 patients – in 5 cases

Table 3

COVID-19 symptoms in organ recipients

Symptom	Rate, %
Tiredness	84.4
Muscle pain	70.1
Cough	68.9
Dyspnea	55.7
Chest discomfort	45.0
Catarrhal signs	30.0
Diarrhea	25.5
Chest pain	24.3
Anosmia	13.5
Rash	4.4
No symptoms	12.4

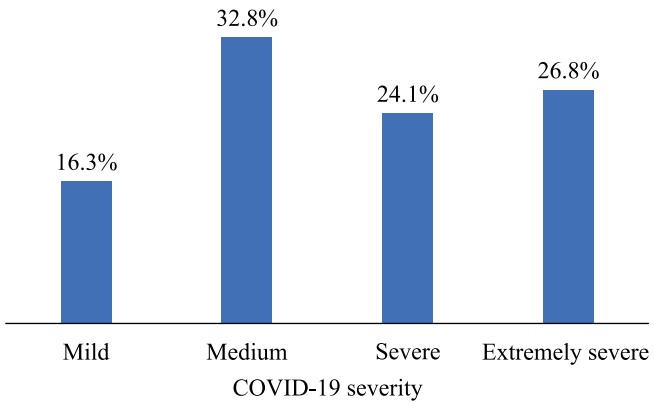

Fig. 2. The The distribution of recipients by COVID-19 severity

there were histologic signs of acute cell rejection, in two acute antibody-mediated rejection. One heart recipient with no sign of a heart transplant rejection died against the background of acute heart and respiratory failure, in all other cases remission was achieved. Of 220 kidney recipients, 78 (35.5%) had a decrease in the glomerular filtration speed of various degrees of expression. 17 cases had signs of acute cellular or antibody-mediated rejection, 2 cases – signs of acute tubular necrosis without signs of rejection. 37 (16.8%) kidney recipients needed substitution therapy. At the coronavirus infection remission, most patients had kidney function regeneration, 3 patients had a persistent loss of transplant function, and 1 had kidney retransplantation.

Table 4 shows average laboratory parameters determined before the pandemic (autumn-winter 2019), at the peak of the virus infection manifestation and a month after the remission.

At the coronavirus infection, lymphocytopenia was noted in 53.9% of patients, thrombocytopenia in 27.1%. The comparative analysis showed that in recipients with the coronavirus infection there was a significant decrease in the average white blood cell levels followed by their recovery (decrease from the initial 10.7 ± 3.3 × 10^9/l to

Table 4

Dynamics of laboratory parameters in kidney, liver, and heart recipients

Parameter	Initially	COVID-19 manifestation peak	Remission
RBC ($\times 10^{12}$/l)	3.5 ± 0.4	3.5 ± 0.2	3.6 ± 0.3
Hh (g/l)	97.9 ± 8.5	96.2 ± 7.0	108.9 ± 9.8
WBC ($\times 10^9$/l)	10.7 ± 3.3	**6.1 ± 0.7**[1]	9.2 ± 2.8
NEUT ($\times 10^9$/l)	37.6 ± 22.3	49.9 ± 11.6	34.9 ± 21.8
LYM ($\times 10^9$/l)	4.6 ± 3.3	5.1 ± 1.7	5.5 ± 1.1
MON ($\times 10^9$/l)	3.4 ± 1.7	5.9 ± 1.6	6.2 ± 3.2
PLT ($\times 10^9$/l)	233.6 ± 38.7	205.6 ± 22.4	213.3 ± 42.7
Fasting glucose, mmol/l	5.1 ± 1.1	5.6 ± 0.5	5.9 ± 1.5
Albumen, g/l	35.4 ± 2.9	35.6 ± 17.1	37.5 ± 1.8
Total bilirubin, mmol/l	7.6 ± 1.2	**11.6 ± 1.1**[1]	8.0 ± 0.9
AST, U/l	23.4 ± 9.6	**31.6 ± 5.8**[1]	**52.8 ± 13.4**[2]
ALT, U/l	15.3 ± 5.6	**31.9 ± 10.7**[1]	**65.2 ± 15.0**[2]
BUN, mmol/l	9.3 ± 7.3	**20.9 ± 4.4**[1]	15.3 ± 5.2
Creatinine, μmol/l	149.3 ± 18.7	**244.5 ± 32.3**[1]	150.1 ± 14.5
Ca, mmol/l	4.7 ± 0.3	**5.1 ± 1.7**[1]	3.9 ± 0.2
PT, s	14.5 ± 13.4	17.1 ± 12.8	18.1 ± 15.5
D-dimer, ng/ml	203.2 ± 104.2	**1304.3 ± 346.5**[1]	162.2 ± 107.1
APPT, s	30.6 ± 4.8	32.7 ± 3.4	35.9 ± 6.9

Note. The initial value of the indicators meant the values determined in the fall-winter of 2019. [1] – the value of the indicator at the peak of the manifestation of COVID-19 infection significantly differs from the baseline indicators and indicators against the background of remission; [2] – the value of the indicator against the background of remission significantly differs from the baseline values and values at the peak of the manifestation of COVID-19 infection.

$6.1 \pm 0.7 \times 10^9$/l at the coronavirus infection with subsequent recovery to $9.2 \pm 2.8 \times 10^9$/l after the remission onset). Mean levels of total bilirubin, urea, creatinine, potassium, and D-dimer increased at the acute infection and recovered 2–4 weeks after remission. At the same time, the increased mean levels of AST and ALT did not decrease after remission.

Although no effective etiotropic COVID-19 therapy has been available to date, the empirical treatment protocol included minimizing immunosuppressive therapy and prescribing medications with theoretically justified pathogenetic effects. Mycophenolic acid drugs were discontinued in all patients after clinical signs of viral infection were detected. With the viral infection manifested as immunosuppressive therapy, all heart recipients received tacrolimus preparations in monotherapy or in combination with methylprednisolone. Among 228 liver and kidney recipients, 2 (0.9%) received methylprednisolone in monotherapy, 8 (3.5%) received methylprednisolone in combination with everolymus, and 10 (4.4%) received everolymus in combination with cyclosporine or tacrolimus, 17 (7.5%) – cyclosporine in monotherapy or in combination with methylprednisolone, 191 (83.8%) – tacrolimus in monotherapy or in combination with methylprednisolone. Anticoagulant therapy (low molecular weight heparins) was provided to 74 hospitalized patients with D-dimer levels above 300 ng/ml. In addition to immunosuppressive therapy, hydroxychloroquine preparations were administered to 81 patients, preparations of IL-6 receptor antagonists: tocylizumab – 26, arilumab – 8, Janus kinase inhibitor (JAK) tofacitinib – 12, barycytinib – 9, IL-1beta inhibitor kanakinumab – 2, IL-17 inhibitor netakimab – 2, C-5 human complement component inhibitor eculizumab – 2 patients; 45 patients received immunoglobulin intravenously, 64 patients – fresh frozen plasma.

The analysis of adverse events showed that there were no liver recipients among 34 lethal cases, 33 underwent kidney transplantation (15% of all kidney recipients) and 1 – heart transplantation (4.3% of all heart recipients). It was revealed that the main fatal case predictor COVID-19 severity. Thus, according to the constructed prognostic model, in patients with a mild course of coronavirus infection, the expected fatal cases rate was 1.9% (95% CI: 0.1–4.3%), moderate – 9.7% (95% CI: 3.7–15.8%), severe – 11.8 (95% CI: 4.2–19.3%), extremely severe – 50% (95% CI: 32.4–67.6%).

Concomitant diseases were the factors reliably associated with COVID-19 severity and the risk of death of recipients, i. e. coronary heart disease, arterial hypertension, cerebrovascular disease and bronchospasm. As for the symptoms, these were the presence of shortness of breath, rash and catarrhal phenomena, and oxygen saturation at admission SpO_2 <92%, white blood cells $>10 \times 10^9$/l, an increase in creatinine levels of more than 130 μmol/l, and a significant decrease in the glomerular filtration rate requiring hemodialysis. At this, for other clinical and laboratory parameters, including age over

60, gender, the degree of increase in D-dimer levels, hydroxychloroquine preparations, etc., there was no significant relationship with the risk of adverse events against the background of COVID-19.

Between January 29 and July 1, 2020, which coincided with the period of the spread of coronavirus infection in Russia, organ transplantation was performed in 70 of the 251 patients included in the study, 56 kidney recipients, 12 heart recipients, 1 liver recipient, and 1 liver and kidney recipient. In 12 patients (4.8%) the infection was detected within the first 7 days after heart (n = 6) or kidney (n = 6) transplantation. Among the kidney recipients who died due to coronavirus infection, 5 (14.7%) died within 30 days after the kidney transplantation. One patient with COVID-19 diagnosed within a week after kidney transplantation, developed a transplant dysfunction, and on day 8 after the first operation was retransplanted. Comparative analysis did not reveal any reliable differences (p = 0.53) in the number of lethal cases between those who were operated during the COVID-19 pandemic (n = 11, 15.7%) and in 1995 to 2019 (n = 23, 12.7%).

DISCUSSION

The first results of the "ROKKOR-recipient" multicenter national study presented in the article which were obtained by analyzing the data of examination and observations of 251 liver, kidney and heart recipients with COVID-19 from 20 regions of Russia, indicate the importance of prevention and timely detection of coronavirus infection in recipients of transplanted organs. This is evidenced by the relatively high mortality (13.5%) at COVID-19. This is significantly higher than the mortality rates in the general populations of Russia (1.6%), the United States (3.4%) and China (5.4%) [3].

The lack of systematic data prevented a consensus on the impact of coronavirus infection on patients with transplanted organs. For example, one of the first reports by Chinese authors of 2 COVID-19 cases in patients with heart transplants suggested that immunosuppressive therapy may make the disease course easier for recipients and not progressing to the hyperinflammatory response stage [10]. Other Chinese authors in their analysis of the results of a small cohort study [11] concluded that there are no significant features of the course of coronavirus infection in the heart recipients. There exists an empirical hypothesis that calcineurin inhibitor, especially takrolimus, can specifically suppress coronavirus infection [12]. However, our study did not identify a link between various immunosuppressive drugs and the risk of severe course or complications of coronavirus infection. Among recipients with a severe course of coronavirus infection, the average blood concentration of the tacrolimus was lower, the percentage of patients who did not receive calcineurin inhibitor was higher, but this fact may be due to the immunosuppressive therapy reduced by attending physicians in a severe course of infection.

The study identified clinical and lab test predictors of severe COVID-19 and death of recipients. It is noteworthy that the association with the rate of adverse events was statistically significant for concomitant diseases (coronary heart disease, arterial hypertension, cerebrovascular disease, bronchospasm, diabetes mellitus, and renal failure) but not for age. In publications, age, along with concomitant cardiovascular and pulmonary diseases, obesity and diabetes mellitus, is presented as a risk factor for severe complications and death of COVID-19 patients [13, 14].

In this regard, the results of a major Russian study carried out on the basis of the I.M. Sechenov First Moscow State Medical University deserve attention. There 1,007 COVID-19 patients were included. The authors showed that acute respiratory distress syndrome caused by SARS-CoV-2 is more common in persons over 40 years of age with cardiovascular disease, type 2 diabetes mellitus and/or obesity [15].

According to the results obtained, the coronavirus infection in the recipients was most frequently expressed as pneumonia, though there was a high rate (38.3%) of extrapulmonary manifestations. The fact that the phenomena of blood insufficiency and kidney failure in most recipients were not related to the rejection of the transplanted organ against the backdrop of the immunosuppression reduction and occurred at COVID-19 remission may indicate a direct viral damage to the targeted organs.

Indeed, the membrane receptors of angiotensin transforming enzyme type 2 (ATE2) are found, besides lungs, on the surface of endothelium cells, smooth muscle cells, cardiomyocytes, etc. [16, 17]. The Russian authors have recently published a description of the clinical case of coronavirus myocardial lesions in an elderly patient with arterial hypertension [18].

Endothelium dysfunction resulted from the direct and indirect effect of coronavirus infection, platelet activation and system inflammatory response suggest a high risk of thrombotic complications [19]. Despite the fact that in the examined COVID-19 patients there was almost 6-times increase in the average levels of D-dimer, we did not identify the relationship between the levels of this marker and the risk of complications. This can be partially explained by the high frequency of empirical use of low-molecular heparin drugs in patients with high risk of developing thrombotic complications [9].

One of the most important issues discussed in various countries is the feasibility of performing organ transplantation in the context of the COVID-19 pandemic. The pandemic has been a major challenge for all national health systems. At the pandemic, the number of patients hospitalized with diseases requiring emergency care and surgical interventions [20, 21] including organ transplants [22] in the world is decreasing.

The risk of infection of organ recipients, especially in the early postoperative period, when maximum immunosuppression is required, is high due to the need for high doses of immunosuppressive medication and the risk of infection from unrecognized sources, donor, medical personnel, objects and food items. In our study, 6 heart recipients and 6 kidney recipients had SARS-CoV-2 virus detected within a week after transplantation, and the infection source remained unknown. This may be partially due to the limited capabilities of the laboratory diagnostics method itself and the probability of getting false negative results of the tests in the toolkit [23]. The donor's role as a source of infection is hardly considered; evidence of the possibility of SARS-CoV-2 virus infection through heart or kidney transplant is currently missing, although the amount of data is limited. At least a study of the biopsy results of four patients has not confirmed this possibility for SARS-CoV-1 virus [24]. It is important to note that our comparative analysis of the results of coronavirus infection in the recipients operated at the outbreak of the epidemic in Russia and in previous years, did not reveal any reliable differences.

Thus, the results of the "ROKKOR-transplant" study indicate that the presence of a transplanted organ increases the risk of adverse events at COVID-19. Risk factors for severe course and lethal cases in organ transplant recipients infected with the SARS-CoV-2 virus are concomitant cardiovascular and pulmonary diseases, diabetes mellitus and renal failure, the presence of dyspnea, rash and catarrhal signs as manifestation symptoms, as well as initially low oxygen saturation (SpO_2 <92%), white blood cells >10 × 10^9/l, an increase in creatinine levels of more than 130 μmol/l, and a significant decrease in the glomerular filtration rate requiring hemodialysis.

The analysis of the data obtained allowed us to draw an important conclusion that performing organ transplant surgery in COVID-19 does not increase the risk of adverse events but could save the lives of waitlisted terminally ill patients.

The authors declare no conflict of interest.

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