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Clinical course and outcomes of COVID-19 infection in liver transplant recipients: single-center cross-sectional study

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Abstract

Background. *The novel coronavirus infection (COVID-19) pandemic has had a significant impact on all areas of health care system, including organ donation and transplantation. Despite this, there were no large Russian studies of COVID-19 course and outcomes in liver transplant recipients.*

The study purpose *was to determine prevalence, clinical course, severity, outcomes of COVID-19, as well as to assess the safety and efficiency of vaccination for disease prevention in liver transplant recipients.*

Material and methods. *260 recipients (71% of all patients at risk of COVID-19 disease) who underwent liver transplantation at State Research Center – Burnasyan Federal Medical Biophysical Center from May 2010 to September 2021 were included in a single-center cross-sectional study. Data collection was performed during a telephone or face-to-face interview from September 6, 2021 to September 20, 2021. If*

patients were hospitalized with COVID-19, we also analyzed the results of laboratory and instrumental tests, other medical documentation.

Results. *By mid-September 2021, the incidence of COVID-19 after liver transplantation was 31% (75 cases in 260 recipients). Asymptomatic course was observed in 11 (15%) patients. Hospitalization was required in 18 (28%) cases. In one case, COVID-19 infection was the cause of death. Mortality and death rate in the study cohort were 1% (1/75) and 0.4% (1/260), respectively. Risk factors that statistically significantly increased the likelihood of infection with SARS-CoV-2 were contact with the patient (OR: 12.9; 95% CI: 6.6 - 25.0) and non-compliance with non-specific prophylaxis measures (OR: 2.0; 95 % CI: 1.1 - 3.7). The recipient's age of 60 years or more significantly increased the risk of severe infection (OR 5.0; 95% CI: 1.3 - 18.7). None of the immunosuppressive therapy regimens significantly increased the risk of severe disease. Tacrolimus monotherapy or in combination with other drugs reduced the risk of severe COVID-19 (OR: 0.2; 95% CI: 0.1 - 0.95). Vaccination against SARS-CoV-2, which was performed in 42 (17%) recipients, did not cause serious adverse events and significantly reduced the risk of COVID-19 disease (OR: 7.2; 95% CI: 1.7 - 31.3). The detection rate of specific IgG antibodies to SARS-CoV-2 was 94% in recipients who had undergone the disease and 45% among those vaccinated ($p<0.001$). The achieved level of herd immunity against COVID-19 in the analyzed cohort was 48%.*

Conclusion. *Adult liver transplant recipients are not at an excessive risk of COVID-19 disease. Compliance with preventive measures and vaccination can significantly reduce the risks of infection and severe infection. There is no objective evidence that immunosuppressive therapy increases the risk of severe COVID-19 in liver transplant recipients. In*

the context of the ongoing COVID-19 pandemic, tacrolimus monotherapy may be considered as a safe regimen of maintenance immunosuppression.

Keywords: liver transplantation, COVID-19, vaccination, immunosuppressive therapy

Conflict of interests Authors declare no conflict of interest

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95% CI, 95% confidence interval

AIH, autoimmune hepatitis

CT, computed tomography

CyA, cyclosporine A

Eve, everolimus

FFP, fresh frozen plasma

GCS, glucocorticosteroids

IQR, interquartile range

LC, liver cirrhosis

MLV, mechanical lung ventilation

MPA, mycophenolates

OR, odds ratios

PBC, primary biliary cirrhosis

PSC, primary sclerosing cholangitis

Tac, tacrolimus

Introduction

Over the past decades, the pandemic of a new coronavirus infection has become one of the most global challenges for the health systems of

many countries [1, 2]. The spread of COVID-19 has had a significant negative impact on the activity of donor and transplant programs around the world [3, 4]. The inability to ensure the proper level of infectious safety of transplanted organs in new, constantly changing conditions, as well as the inevitable need for the use of immunosuppressive therapy in the postoperative period, often led to a complete discontinuation of transplantations in a number of centers. The conversion of a number of large clinics to infectious diseases hospitals, the involvement of doctors and nursing staff in the treatment of patients with COVID-19, isolation after contact with infected people, and morbidity among employees also significantly complicated and changed the established working order of donor and transplant teams [5].

However, after some time, most of the transplant centers managed to adapt to the new conditions and continue working. According to the Russian Society of Transplantology, in 2020 [6] compared to 2019 [7], the number of organ transplants in Russia decreased by 19% (from 2,427 to 1,960), and the number of effective post-mortem donors decreased by 23% (from 732 to 564), which cannot be considered a critical decrease.

Despite the fact that during the first wave of COVID-19, an infectious disease hospital was deployed in the Burnasyan Federal Medical Biophysical Center of the Russian Federation to treat patients with a new coronavirus infection, the organizational measures taken made it possible to prevent a discontinuation of the transplantation and donation program activities and generally maintain a rhythmic pace of operations. Active tactics to identify possible SARS-CoV-2 virus infection in recipients, living related and post-mortem donors; as well as to keep a strict compliance with the epidemiological regime, made it possible to avoid COVID-19 outbreaks among patients in the immediate post-transplant period.

However, from the beginning of April 2020, the Center started receiving reports of COVID-19 from previously operated patients. The dynamics of new cases of infection among recipients corresponded to the morbidity rate about the country – the peak of infections occurred in October-November, 2020.

The wave-like course of COVID-19 morbidity in the world and in Russia, the regular identification of new strains of the virus, as well as the pandemic duration, which is currently approaching two years, make it highly likely that it will not be possible to achieve elimination of the virus from the population in the next few years. Therefore, of particular relevance are the studies aimed at investigating the typical features of COVID-19 spread and course in cohorts of transplant candidates and organ transplant recipients, assessing the safety and efficacy of various preventive and therapeutic strategies, long-term effects, and the history of the disease.

These circumstances made it necessary to conduct our own study aimed primarily at obtaining objective data on the prevalence and course of COVID-19 in liver recipients, as well as identifying specific factors that affect the risk of infection and the severity of the disease. In addition, an equally important task was to evaluate the safety and clinical efficacy of SARS-CoV-2 vaccines in a cohort of liver transplant recipients.

Material and methods

Study design

A single-center cross-sectional study was initiated on September 1, 2021. Data was collected during a telephone or face-to-face survey of patients in the period from 6 to 20 of September, 2021. Patients were interviewed by seven employees of the Center for Surgery and Transplantology using a pre-formed list of questions presented in the

form of an electronic Google Forms. This made it possible to unify the work, reduce the time required for conducting the study, and automatically obtain a set of data suitable for immediate statistical processing. For correct interpretation of medical data, patients were asked for electronic copies of the results of laboratory and instrumental tests, written epicrisis, if inpatient treatment was undertaken. Demographic data on recipients and donors, information on the specificities of operations and the course of the postoperative period necessary for analysis were obtained from the scientific register of liver transplants, which is kept at the Center.

Study cohort formation

When forming the study cohort (Fig. 1), at the first stage, the recipients (62 cases) who died before the start of the COVID-19 pandemic (before 01.02.2020) in the Russian Federation were excluded. From 01.02.2020 to 6.09.2021 (the pandemic period), 16 deaths were reported; these cases were analyzed separately. One hundred and nine patients were lost for contacts or refused to participate in the study, and 245 recipients answered the survey questions.

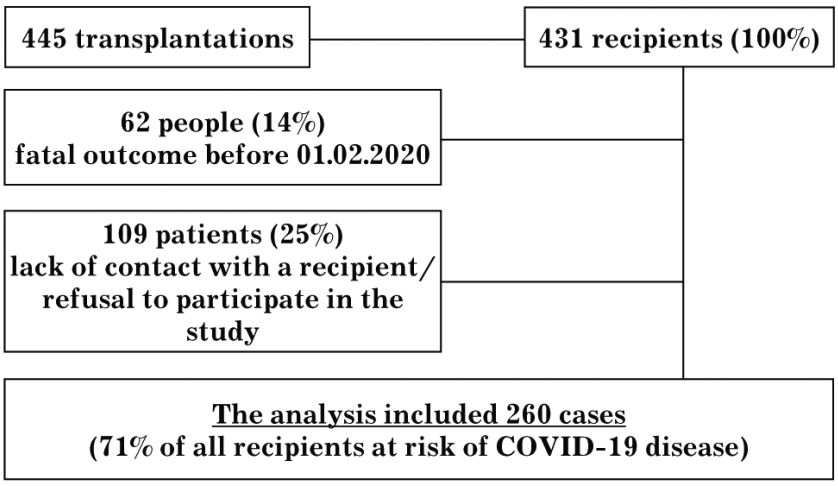

Fig. 1. Forming the study cohort

In total, data on 260 recipients were collected and analyzed, representing 71% of all recipients at risk of COVID-19. In one case, a fatal outcome occurred after a telephone interview.

Criteria used to diagnose COVID-19

The group of COVID-19 survivors included the patients who were diagnosed with the disease when seeking doctor's advice at a medical facility. In addition, a patient was considered to have had COVID-19 if at least once a positive PCR test result was obtained and/or specific anti-SARS-CoV-2 virus antibodies were identified, and/or there was a typical X-ray pattern of "covid" pneumonia on computed tomography. The results of all tests, including those initiated by the patients themselves, were taken into account.

Demographic characteristics of the cohort under study

At the time of registration of outcomes, the median age of recipients was 50 years (from 21 to 72 years). There were 129 (50%) women and 131 (50%) men among them. Transplantation was performed for liver cirrhosis (LC) of viral etiology in 42% of cases, for primary biliary cirrhosis or primary sclerosing cholangitis in 16%, for hepatocellular carcinoma on the background of LC in 14%, for LC of unclear etiology in 7%, for LC in the outcome of autoimmune hepatitis in 3%. A liver graft was transplanted from a related donor to 183 (70%) patients patients, and from a postmortem donor to 77 (30%) patients

The median time elapsed after liver transplantation was 4 years (from 1 month to 10 years; the interquartile range: from 1-6 years. Meanwhile, the proportions of patients at different terms after surgery were comparable (Fig. 2).

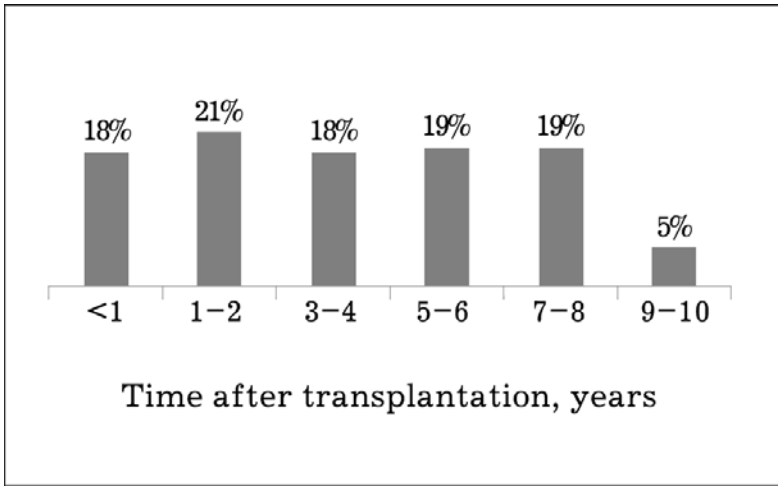

Fig. 2. Distribution of patients of the study cohort in regard with the period after liver transplantation

Patients of the study cohort during the pandemic lived in all federal districts of the Russian Federation (Fig. 3), mainly in the Central, Far Eastern and North Caucasus regions.

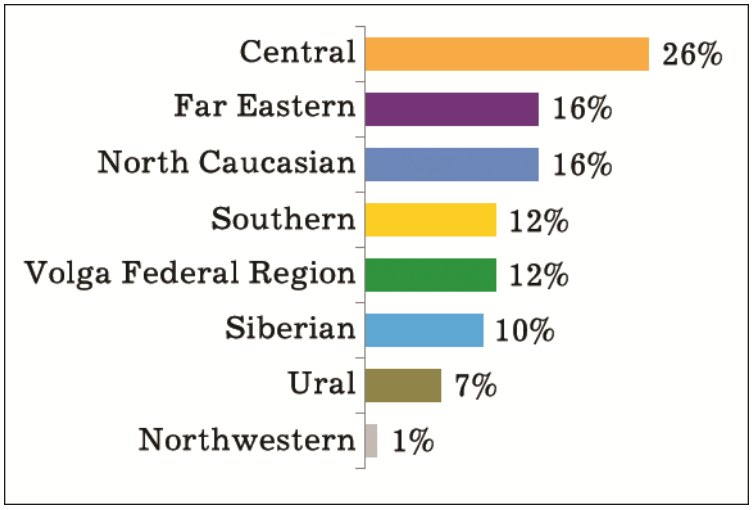

Fig. 3. Permanent residence (Federal Regions of the Russian Federation) of recipients during the COVID-19 pandemic

Forty two (17%) liver recipients lived permanently in Moscow or the Moscow region during the pandemic.

Statistical data processing

To describe the quantitative variables, the median, interquartile range (IQR), and minimum and maximum values were calculated. For qualitative parameters, absolute frequencies were presented; relative frequencies expressed as a percentage were given, where appropriate. The nonparametric two-way Mann–Whitney test was used to determine the differences between two independent groups by quantitative characteristics, and the Chi-square test was used for qualitative characteristics. When calculating the odds ratio (OR) of an event occurring, a 95% confidence interval (95% CI) was shown. Calculations were performed using the Statistica 12 software package (StatSoft Inc., USA).

Results

Prevalence and risk factors of COVID-19 after liver transplantation

In the period from 01.02.2020 to COVID 06.09.2021, 91 (37%) of the 245 recipients surveyed were diagnosed with COVID-19 infection. Meanwhile, 75 (31%) patients sustained the disease after transplantation, and 16 (6%) patients did before surgery.

Among 185 patients operated on before the start of the COVID pandemic, COVID-19 was reported in 66 (36%) people. Of 59 patients who underwent transplantation after 01.02.2020, infection was diagnosed in 9 (15%) cases in the post-transplant period. The dynamics of new COVID-19 cases by month in the study cohort and among the population of the Russian Federation is shown in Figure 4.

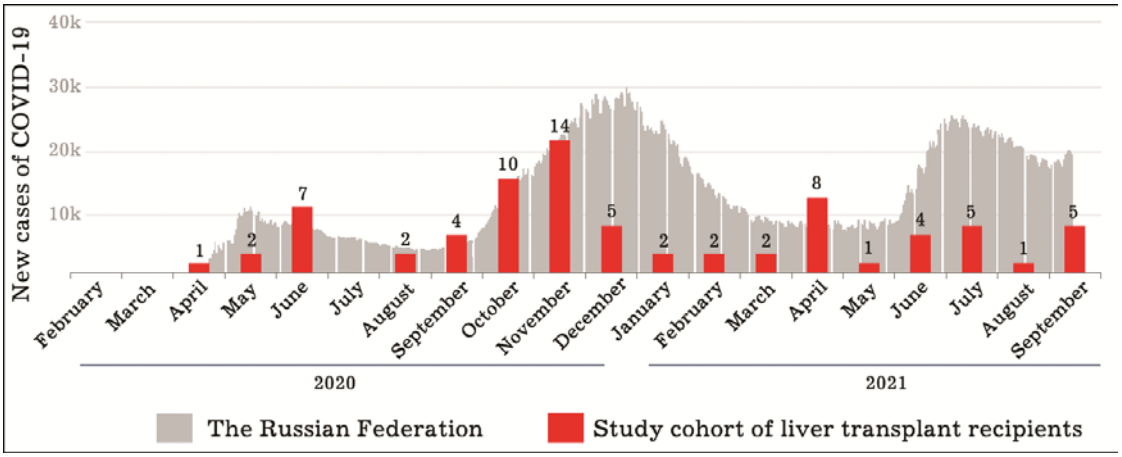

Fig. 4. Dynamics of new cases of COVID-19 among patients of the study cohort and the population of the Russian Federation in the period from February 2020 to September 2021

The significance of potential risk factors for SARS-CoV-2 infection after liver transplantation was evaluated by comparing groups of patients who had (n=75) and did not have (n=154) COVID-19 (Table 1).

Table 1. Significance of potential risk factors for SARS-CoV-2 infection

Risk factor of infection	Not sick (n=154)	COVID-19 after transplantation (n=75)	p	Odds ratio (95% CI)
Contact with an infected individual, n (%)	23 (15)	52 (69)	<0.001	12.9 (6.6-25.0)
Neglect of preventive measures, n (%)	32 (21)	26 (35)	0.024	2.0 (1.1-3.7)
Moving outside the region of residence, n (%)	64 (42)	34 (45)	0.588	1.2 (0.7-2.0)
Age 60 and over, n (%)	32 (21)	12 (16)	0.389	0.7 (0.4-1.5)
Residence in Moscow or the Moscow region, n (%)	32 (21)	10 (13)	0.172	0.6 (0.3-1.3)
Time after transplantation less than 1 year, n (%)	21 (14)	4 (5)	0.059	0.4 (0.2-1.1)

Thus, the chance of getting COVID-19 was statistically significantly higher in case of contact with an infected person (usually one of the patient's family members) and in case of non-compliance with the non-specific prevention measures. It should be emphasized that the compliance with preventive measures was assessed by the patients themselves, so the significance of this factor may be underestimated.

Clinical symptoms, diagnostic test results, duration and severity of COVID-19 after liver transplantation

Of the 75 recipients who underwent COVID-19 after liver transplantation, PCR testing was performed in 61 (81%) cases, blood tests for specific anti-SARS-CoV-2 antibodies were performed in 45 (60%) cases, and chest computed tomography was performed in 32 (43%) patients. The test results are shown in Fig. 5.

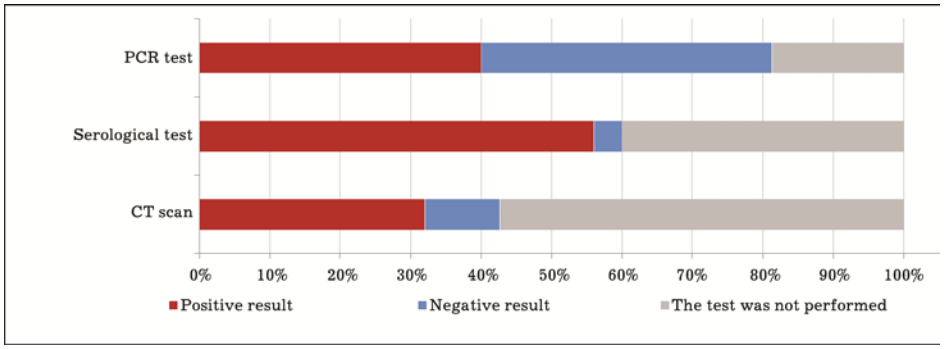

Fig. 5. Frequency and results of diagnostic tests in liver transplant recipients with COVID-19 infection (n=75)

Among 24 patients who showed signs of viral pneumonia ("ground-glass" opacities) at computed tomography, the affected area was less than 25% in 17 people, 25-50% in 6 patients, and exceeded 75% only in one case.

In 11 (15%) cases, the infection was asymptomatic. The remaining patients reported at least one of the disease symptoms, the symptom incidence is shown in Fig. 6.

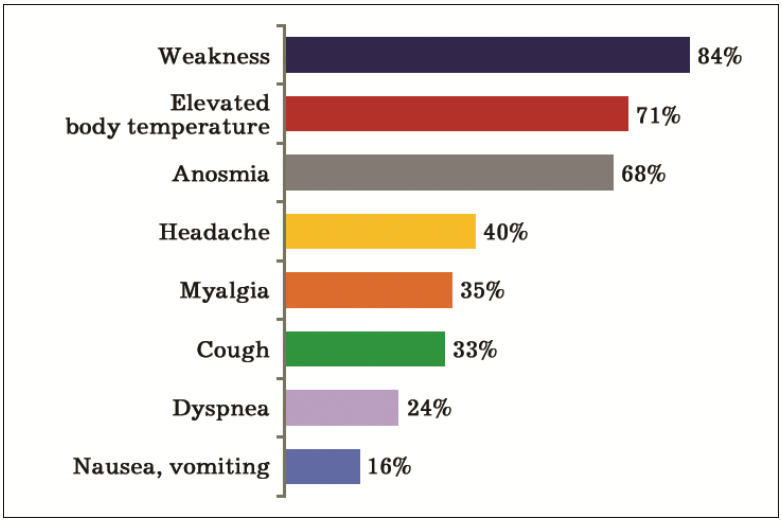

Fig. 6. Incidence of individual symptoms in COVID-19 disease (n=64, cases of asymptomatic course are excluded)

The severity of the temperature response in COVID-19 is shown in Fig. 7.

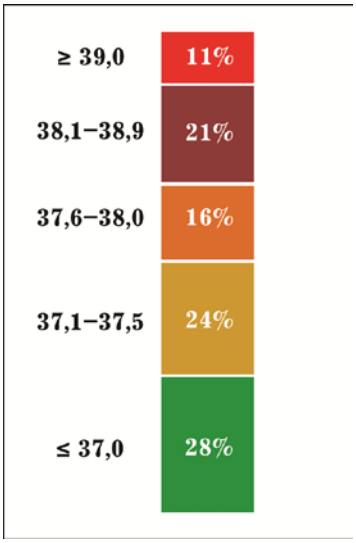

Fig. 7. Distribution of liver transplant recipients in regard with the maximum body temperature in COVID-19 disease (n=64, cases of asymptomatic course are excluded)

The COVID-19 severity was assessed according to the definition in the current valid version of the recommendations of the Russian Federation Health Ministry at the moment of assessment [8] Thirty eight (50%) patients had a mild course of the infection, moderate to severe infection was reported in 20 (27%) patients, severe course was observed in 5 (7%), extremely severe infection was seen in one case (1%).

In most cases of COVID-19, with the exception of the asymptomatic form, in 43 (68%) patients, the clinical manifestations of infection regressed within two weeks; 15 (24%) patients recovered within two to four weeks; and symptoms persisted for more than one month in 5 (8%) patients.

Immunosuppressive therapy, treatment, outcomes, and risk factors of severe COVID-19

It is obvious that one of the main factors that can affect both the severity of the course and the outcome of COVID-19 in the study cohort could be immunosuppressive therapy. In the course of the study, the current frequency of using individual immunosuppressive drugs and their combinations was established. Of the 245 patients surveyed, 176 (72%) received monotherapy, 60 (25%) followed a two–component protocol, and 7 (2%) followed a three-component protocol of maintenance immunosuppression.

In this study, in order to determine the significance of factors (including those related to immunosuppressive therapy) that could potentially lead to a more severe course of COVID-19, the patients who had had the disease were divided into two groups: the first group included cases of asymptomatic and mild course (n=49), the second group comprised the cases of moderate, severe and extremely severe course

(n=26). The frequency of using individual immunosuppressive regimens for varying severity of COVID-19 in liver recipients is shown in table 2.

Table 2. Frequency of using immunosuppressive therapy regimens in COVID-19 of different severity

Immunosuppression regimen	Asymptomatic and mild course (n=49)	Moderate, severe and extremely severe course (n=26)	p	Odds ratio (95% CI)
Monotherapy, n (%)	**38 (78)**	**19 (73)**	**0.667**	**0.8 (0.3-2.4)**
Tacrolimus (Tac), n	36	15	0.164	0.5 (0.2-1.3)
Everolimus (Eve), n	1	3	0.082	6.2 (0.6-63.5)
Cyclosporin A (CyA), n	1	1	0.645	1.9 (0.1-32.0)
Dual-component protocol, n (%)	**8 (18)**	**7 (27)**	**0.275**	**1.9 (0.6-6.0)**
Tac+Eve, n	5	2	0.722	0.7 (0.1-4.1)
Tac+Glucocorticosteroids (Ster), n	2	2	0.508	2.0 (0.3-14.8)
Tac+Mycophenolates (MPA), n	1	1	0.645	1.9 (0.1-32.0)
CyA+MPA, n	-	2	-	-
Three-component protocol, n (%)	**2 (4)**	**-**	**-**	**-**
Tac+MPA+Ster, n	2	-	-	-

It should be noted that 34 (14%) recipients reported that they had changed the immunosuppressive therapy regimen since the beginning of the pandemic. In most cases (n=18), changes were determined by paramedical motives, and consisted in replacing the drug with one trade name for another. Eight patients underwent a planned correction, namely, a gradual withdrawal of glucocorticosteroids. In five cases, changes were dictated by clinically significant toxicity of calcineurin inhibitors (nephrotoxicity in 3 cases, neurotoxicity in 2 cases). Three patients underwent enhanced immunosuppressive therapy due to a suspected or

proven graft rejection. In no case of COVID-19 in liver recipients, was the immunosuppressive therapy regimen changed.

Of the 64 patients who had clinical manifestations of COVID-19, 18 (28%) needed hospitalization, including to the intensive care unit in two cases. The remaining patients were treated on an outpatient basis or did not seek for medical help from medical organizations. Oxygen support was required to 6 patients, mechanical lung ventilation was required in one case, extracorporeal membrane oxygenation was not performed in any case. There were no cases of recurrent COVID-19 after a previous infection.

Figure 8 shows the frequency of administering individual groups of drugs to liver recipients for the treatment of COVID-19 and the need for oxygen support.

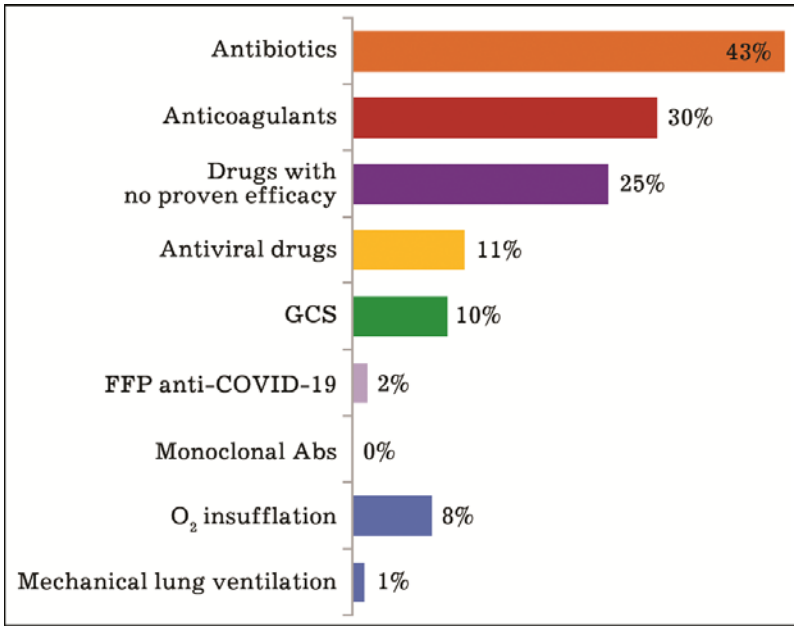

Fig. 8. Frequency of prescribing certain groups of drugs for the treatment of COVID-19 and the need for oxygen support (n = 64)

It should be emphasized that in the vast majority of cases, drugs without proven efficacy were used by patients on their own initiative.

The results of the analyzed statistical significance of possible risk factors for severe COVID-19 in liver recipients are shown in Table 3.

Table 3. Potential risk factors for severe COVID-19 course and the analysis of their statistical significance

Risk factor for severe COVID-19 course of	Asymptomatic and mild (n=49)	Moderate, severe and extremely severe course (n = 26)	p	Odds ratio (95% CI)
Age 60 and over, n (%)	**4 (8)**	**8 (31)**	**0.012**	**5.0 (1.3-18.7)**
Hepatocellular carcinoma as an indication for transplantation, n (%)	4 (8)	5 (19)	0.161	2.7 (0.7-11.0)
PBC, PSC or AIH, n (%)	9 (18)	4 (15)	0.746	0.8 (0.2-2.9)
Time after transplantation less than 1 year, n (%)	7 (14)	6 (23)	0.339	1.8 (0.5-6.1)
Disease after April 1, 2021: high probability of infection with the δ-strain of SARS-CoV-2, n (%)	16 (33)	7 (27)	0.609	0.8 (0.3-2.2)
Dual- or three-component immunosuppressive therapy protocol, n (%)	10 (20)	7 (26)	0.522	1.4 (0.5-4.4)
GCS*, n (%)	4 (8)	2 (8)	0.943	1.5 (0.2-5.5)
MPA *, n (%)	4 (8)	3 (12)	0.633	1.5 (0.3-7.1)
Eve *, n (%)	6 (12)	5 (19)	0.416	1.7 (0.5-6.2)
CyA *, n (%)	12)	3 (12)	0.082	6.3 (0.6-63.5)
Tacrolimus*, n (%)	**46 (94)**	**20 (77)**	**0.032**	**0.2 (0.1-0.95)**

Note: * − as monotherapy or in combination with other immunosuppressive drugs;

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis

Thus, among the factors considered, a significant negative impact on the severity of the COVID-19 course in liver recipients was posed by patient's elderly age (60 or more years). At the same time, the inclusion of tacrolimus in the immunosuppression regimen as monotherapy or in

combination with any other drugs significantly reduced the chances of a severe course of the disease.

During the analyzed period, COVID-19 infection caused a fatal outcome in one liver recipient operated on before the start of the pandemic in 2019. Thus, the lethality rate was 1% (1 per 75 cases), and the mortality rate was 0.4% (1 case per 260 cases in the study cohort). Among the remaining 15 deaths that occurred during the pandemic, there were no data on patients being infected with COVID-19 in any case. For more than 2 years after liver transplantation, the causes of death were: relapse and progression of hepatocellular carcinoma (n=3), the graft cirrhosis as a result of the HDV infection recurrence (n=3), lymphoproliferative disease (n=1). For less than 2 years, they were progressive multiple organ failure with severe early liver graft dysfunction (n=4), cholangiogenic sepsis (n=2), hepatic artery thrombosis (n=1), pulmonary embolism (n=1).

Vaccination against COVID-19 and its clinical efficacy in liver recipients

Since the introduction of Russian COVID-19 vaccines into civil circulation COVID and the beginning of widespread vaccination of the Russian Federation population in December 2020, 42 (17%) recipients had been vaccinated before the data were collected for this analysis. Four of them were vaccinated before liver transplantation. Most often, liver recipients were vaccinated with Sputnik V (n=26; 68%). The following vaccines were also used: Sputnik Light (n=4; 10%), EpiVacCorona (n = 4; 10%), CoviVac (n=3; 8%), Moderna (n=1; 3%), USA. The median time elapsed from transplantation to vaccination was 5.5 years (from 3 months to 10.5 years; IQR: 3.5-7.2 years).

Regardless of the vaccinating agent used, the vaccination was not associated by immediate or delayed serious adverse events. Fourteen (37%) patients vaccinated after transplantation reported minimal adverse events: ache at the injection site, a short-term increase in body temperature of no more than 37.5°C, myalgia. In 24 (63%) recipients, the vaccination was asymptomatic.

To assess the clinical effectiveness of vaccination, the recipients were divided into two groups: those who had not been vaccinated (n=191) and those who had been vaccinated, not previously had COVID-19 (n=30). COVID-19 infection was diagnosed in 65 (34%) recipients in the first group, in 2 (7%) patients in the second group, p=0.003; odds ratio 7.2 (95% CI: 1.7–31.3).

Collective immunity, detection of specific anti-SARS-CoV-2 antibodies after vaccination and previous COVID-19 infection.

The level of collective immunity in the study cohort was defined as the proportion of patients who had been ill and/or vaccinated against COVID-19 to the total number of patients. By September 2021, this figure was 48%. The frequency of testing and detection of neutralizing IgG class anti-SARS-CoV-2 antibodies is shown in Table 4.

Table 4. Distribution of liver recipients in regard with the previous COVID-19 infection and vaccination, the frequency of testing and the frequency of detecting the anti-SARS-CoV-2 neutralizing IgG antibodies

COVID-19	**No**	**Yes**	**No**	**Yes**
Vaccination	**No**	**No**	**Yes**	**Yes**
N (% of all patients)	126 (52)	75 (31)	28 (12)	15 (6)
Frequency of testing, n (%)	35 (28)	46 (61)	11 (39)	12 (80)
Positive test rate, n (%)	-	43 (94)	5 (45)	11 (92)

It should be noted that the detection rate of the anti-SARS-CoV-2 neutralizing IgG antibodies was statistically significantly lower in the group of recipients who were vaccinated rather than those who sustained COVID-19: $p<0.001$ when compared to the group of patients who had been ill but not vaccinated, and $p=0.017$ when compared with those who had been ill and vaccinated.

Discussion

Despite a high relevance of these issues at the time of publication, this study was the first in the Russian Federation to assess the prevalence, course, and outcomes of COVID-19 among liver recipients. Taking into account the federal level of the transplant program of the A. I. Burnasyan *Federal Medical Research Center of Federal Medical Biological Agency* and the wide geography of recipients' residence, the results obtained and conclusions drawn can be useful for specialists working in other centers where liver transplantation is performed. It was crucial to include in the analysis the maximum possible number of recipients operated on in the clinic – only such study design allowed us to reliably assess the prevalence, lethality and mortality rates.

The COVID-19 prevalence in the studied cohort of liver recipients was 31%, which is 5 times higher than in the population of the Russian Federation [9]. However, we are not inclined to believe that liver transplant recipients are more likely to be infected with the SARS-CoV-2 virus. The reason for this result was significantly higher testing coverage in the cohort under consideration. As expected, the main risk factor for infection was a contact with an infected person (OR 12.9; 95% CI: 6.6-25.0), usually with someone from the patient's family. This obvious observation emphasizes the particular importance of compliance with

preventive measures by the recipients themselves, and also by their relatives and friends, as well as the need for their early vaccination and subsequent revaccination.

Initially, we regarded immunosuppressive therapy as the most important factor that can affect the severity of COVID-19. A detailed analysis of the frequency of the regimens used in groups of patients with severe and asymptomatic/mild disease did not reveal any statistically significant differences. However, it is necessary to interpret this result taking into account the "center effect": in 94% of all patients, steroid-free protocols were used, and 72% of recipients received immunosuppression in the monotherapy regimen. Despite the fact that none of the immunosuppression regimens used showed significant benefits in reducing the risk of severe COVID-19, the use of tacrolimus alone or in combination with other drugs reduced the chances of severe disease (OR: 95% CI: 0.2 0.1–0.95). It should also be noted that recipients aged 60 and over were statistically significantly more likely to have a severe COVID-19 course (OR: 5.0; 95% CI: 1.3-18.7). Similar results were obtained by L.S.Belli et al. [10] in the large-scale European multicenter ELITA/ELTR study.

The clinical course of COVID-19 in liver recipients did not have any specific features. However, cases of asymptomatic infection in the study cohort were significantly less common than in the general population: 15% and 50%, respectively. This result is probably due to the careful collection of medical history when making a patient survey. COVID-19 in severe and extremely severe form was reported in 7% and 1% of the affected recipients. Hospitalization to infectious disease hospitals was required in 28% of cases, but often the admission for inpatient treatment was more often motivated by the concern about the transplanted organ rather than by the objective severity of the patient's

condition. All patients who referred for doctor's advice to a medical facility received treatment in accordance with the clinical guidelines. Meanwhile, a quarter of the affected patients independently took the drugs without proven efficacy on their own. It is important that no monoclonal antibody preparations were used in the treatment of any of the patients, which suggests a low probability of developing a "cytokine storm" among liver recipients. This may be due to the use of maintenance immunosuppressive therapy, in most cases based on tacrolimus.

Respiratory failure and hypoxemia rarely accompanied the COVID-19 course; the need for oxygen insufflation and MLV made 8% and 1%, respectively.

The COVID-19 infection caused a single fatal outcome. Thus, in the analyzed cohort, the lethality from a new coronavirus infection was 1%, and the mortality rate was 0.4%.

Data on the safety and clinical efficacy of vaccination in a cohort of liver recipients should be considered of fundamental importance. For preventive vaccinations, all available vaccines were used (Sputnik V was the most commonly used vaccine, 68%). No serious adverse events were reported in any follow-up. Meantime, the vaccination significantly increased the chances of not getting COVID-19 (OR: 7.2; 95% CI: 1.7–31.3). The obtained result confirms the advisability of vaccination.

At the same time, we noted that the occurrence of specific IgG-class anti-SARS-CoV-2 antibodies after vaccination was twice as rare as after the previous disease: 45% versus 94%, $p<0.001$) This result is quite consistent with the data of world studies [11-13] and, apparently, indicates the suppression of the antibody response due to the use of immunosuppressive therapy. Despite this, we believe it is erroneous and highly dangerous to minimize immunosuppressive therapy before the planned vaccination in order to increase the likelihood of seroconversion.

A possible strategy may be to administer additional booster doses of the vaccine to recipients with careful laboratory monitoring. It would be possible to assess the feasibility of such an approach only in the framework of controlled studies.

As of September 2021, the level of collective immunity to SARS-CoV-2 acquired as a result of a previous illness and/or vaccination was 48% in the study cohort, which roughly corresponds to this figure among the Russian population.

The results obtained suggest that liver recipients are not at an excessive risk of COVID-19 infection. Proper adherence to preventive measures and vaccination can significantly reduce the risk of infection and severe course of infection. There is no objective evidence that taking immunosuppressive therapy increases the risk of severe COVID-19 in liver recipients. In context of the ongoing COVID-19 pandemic, tacrolimus monotherapy may be considered the safest regimen for maintenance immunosuppression. At the same time, aggressive minimization of immunosuppressive therapy in an attempt to reduce infectious risks and/or increase the likelihood of specific antibody formation after vaccination seems to be an extremely dangerous and unjustified approach.

Conclusions

1. The prevalence of COVID-19 infection in the study cohort of liver recipients made 31%: 75 patients of 260. Hospitalization was required in 18 (28%) cases of the disease.

2. Asymptomatic course was observed in 11 (15%) of the infected recipients, 38 (50%) patients had a mild infection, moderate course was

observed in 20 (27%) patients, the infection course was severe in 5 (7%), extremely severe in one case (1%).

3. COVID-19 infection was the cause of death in one recipient: the lethality and mortality rates in the study cohort were 1% and 0.4%, respectively.

4. Risk factors that significantly increased the likelihood of SARS-CoV-2 infection were contact with an infected person (OR: 12.9; 95% CI: 6.6-25.0) and neglect of non-specific prevention measures (OR: 2.0; 95% CI: 1.1-3.7). The recipient's age of 60 years or more significantly increased the risk of severe infection (OR 5.0; 95% CI: 1.3-18.7).

5. Vaccination against SARS-CoV-2 in 42 (17%) liver recipients was not associated with serious adverse events and significantly reduced the risk of COVID-19 (OR: 7.2; 95% CI: 1.7–31.3).

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