

# Clinical course of COVID-19 infection in liver transplant patients

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In the presence of chronic liver diseases, the post-infectious period of COVID-19 is difficult and potentially mortal. The impact of COVID-19 on liver transplant patients has not been thoroughly investigated.

**OBJECTIVE** — to study the characteristics of the clinical course of COVID-19 in liver transplant patients.

**MATERIALS AND METHODS.** At the end of December 2014, the first successful liver transplant operation in Georgia was performed at the Batumi Referral Hospital of the Autonomous Republic of Adjara. To date, a total of surgical interventions have been conducted, including 42 surgeries since the beginning of the pandemic. We analysed

The incidence of COVID-19 infection in the cohort of 88 patients throughout their hospital stay after liver transplant and at the late postoperative period was analysed, as well as the characteristics of the clinical course of COVID-19. To prevent COVID-19 transmission within the hospital, a special protocol been developed: to ensure that the patient is safely isolated from contact with the source of infection. In the postoperative period, all patients received immunosuppressive therapy. To monitor the course of the disease, an interdisciplinary team was created, which consisted of a transplant surgeon, hepatologist, gastroenterologist, infectious disease specialist, therapist, and immunologist. The consultation was held at the place of residence and treatment of a patient.

**RESULTS.** No cases of COVID-19 infection were reported among patients at the hospital where the liver transplant was conducted. In the late period, COVID-19 was registered in 17 (19.3%) patients, of whom one (5.9%) died from the infection. One patient was infected with COVID-19 twice. We have identified four variants of the clinical course of COVID-19: mild (23.5%) — without any symptoms except for mild respiratory symptoms; aggravated (41.2%) — mild respiratory symptoms and dyspeptic symptoms without significant changes in clinical diagnostic parameters; moderate (29.4%) — cough without sputum, hyperthermia for three days, decreased sense of smell, the presence of dyspeptic symptoms, increased average values of biochemical parameters (alanine aminotransferase, aspartate aminotransferase,  $\gamma$ -glutamyl transpeptidase, alkaline phosphatase, total bilirubin); severe (5.9%) — development of multiple organ failure.

**CONCLUSIONS.** The implemented set of preventive measures ensured the patient's protection from COVID-19 infection in all cases during their hospital stay. In liver transplant patients.

## KEYWORDS

liver transplantation, COVID-19, prevention, frequency, clinical course.

**ARTICLE** • Received 2023-10-11 • Received in revised form 2023-11-21

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Severe acute respiratory syndrome (SARS) is a clinical disease of infectious etiology that has recently been reported in the literature [4]. The disease is believed to have first originated

in Guangdong Province in China, but has rapidly spread to other parts of the world, including Asia, North America, and Europe [12]. The World Health Organisation (WHO) identifies suspected

and probable SARS cases based on clinical and epidemiological case definitions [11]. A suspected case is someone who presents with fever and cough, has a history of contact with a suspected or probable case of acute respiratory infection (ARI) within 10 days before the onset of illness or travel history to an ARI-affected region, or lives in an affected area. A probable case is someone who fits the above-mentioned criteria and has pulmonary infiltrates on a chest radiograph. The incubation period ranges from 2 to 11 days. The disease usually begins with fever, headache, and myalgia, which may progress to lower respiratory tract symptoms that in some cases require mechanical ventilation. The causative agent of SARS has been speculated to be a novel coronavirus and is probably transmitted by airborne droplets [1, 2, 7].

Clinical studies have shown that the liver is one of the targets of coronavirus infection. The infectious agent uses the receptors expressed in the hepatocytes to invade the cell and impair its function. In the presence of chronic liver diseases, the post-infectious period of coronavirus disease 2019 (COVID-19) is difficult and potentially mortal. The impact of COVID-19 on liver transplant patients has not been thoroughly investigated.

**OBJECTIVE** — to study the characteristics of the clinical course of COVID-19 in liver transplant patients.

## Materials and methods

At the end of December 2014, the first successful liver transplant operation in Georgia was performed at the Batumi Referral Hospital of the Autonomous Republic of Adjara. To date, a total of 88 surgical interventions have been conducted, including 42 surgeries since the beginning of the pandemic. We analysed the incidence of COVID-19 infection in this cohort of patients throughout their hospital stay and the late postoperative period, as well as focused on the characteristics of the clinical course of COVID-19.

To prevent COVID-19 transmission within the hospital, we followed a special protocol that was developed by different transplant teams in South Korea and India (including our active participation). The protocol consists of the following guidelines:

1. Two days before liver transplantation, the surgical block is closed.
2. The recipient and the donor are placed in specially designated rooms, where they are tested twice using polymerase chain reaction (PCR).
3. The medical personnel involved in the specified surgical intervention must undergo PCR testing before surgery.

4. Regardless of the duration of the operation, the medical personnel are not allowed to leave the operating room and come into contact with other staff members until the end of the operation.

5. After the operation, the patient is transferred to an intensive care unit and is isolated from other patients, and only specially assigned medical personnel wearing the required gear are allowed to interact with the patient.

6. The donor and recipient are prohibited from contacting their relatives and friends.

In the postoperative period, all patients received immunosuppressive therapy.

To assess the severity of COVID-19 and the degree of liver damage, patients were prescribed the following diagnostic tests: a complete blood count, determination of hemostasis indicators, liver function tests, D-dimer test, blood urea nitrogen test, creatinine test, tacrolimus test, C-reactive protein test, interleukin test,  $\alpha$ -fetoprotein test, assessment of the lung and liver function (CT-scan), and administration of intravenous immunoglobulin (IVIG).

The tasks of the research

1. Analyse the incidence of COVID-19 infection in the cohort of patients throughout their hospital stay.

2. Analyse the incidence of COVID-19 infection in the cohort of patients after their discharge from the hospital.

3. Focus on the characteristics of the clinical course of COVID-19 in liver transplant patients.

To monitor the course of the disease, an interdisciplinary team was created, which consisted of a transplant surgeon, hepatologist, gastroenterologist, infectious disease specialist, therapist, and immunologist. The consultation was held at the place of residence and treatment of a patient with COVID-19.

## Results

No cases of COVID-19 infection were reported among patients at the hospital where the liver transplant was conducted. In the late period, COVID-19 was registered in 17 (19.3 %) patients, of whom one (5.9 %) died from the infection. One patient was infected with COVID-19 twice: the first time in November 2020 and the second time in August 2021.

Based on the course of the disease, patients infected with COVID-19 were divided into four groups.

The first group included 4 (23.5 %) patients who had COVID-19 without any symptoms except for mild respiratory ones, so the clinical diagnostic parameters were within normal limits.

The second group included 7 (41.2 %) patients who had aggravated respiratory symptoms (cough,

runny nose) and dyspeptic symptoms without significant changes in clinical diagnostic parameters.

The third group included 5 (29.4%) patients with a moderate course of the disease, which was manifested by a periodic cough without sputum, hyperthermia (37.2–37.8 °C) for three days, a decreased sense of smell, insomnia, and the presence of dyspeptic symptoms. In this group, the following changes in the average values of biochemical parameters were recorded: an increase in the content of alanine aminotransferase (ALT) to 83 U/l, aspartate aminotransferase (AST) to 74 U/l,  $\gamma$ -glutamyl transpeptidase (GGT) to 102 U/l, alkaline phosphatase (ALP) to 168 U/l, and total bilirubin (TBIL) to 24  $\mu$ mol/l. Hemostasis indicators, tacrolimus levels, and direct bilirubin levels were within normal limits; no infiltrative changes were recorded according to computed tomography.

The fourth group included one (5.9%) patient with a severe course of the disease. He developed multiple organ failure, which became the cause of his death.

Antibiotic therapy was not used in any of the 17 infected patients.

## Discussion

Since the beginning of the pandemic, all fields of medicine, especially transplantology, have faced many challenges. The suspension of organ transplantation due to COVID-19 could have had life-or-death circumstances as it is a life-saving procedure.

In Georgia, liver transplantation commenced about 9 years ago. In total, more than 120 patients have undergone this operation so far, including 42 operations since the beginning of the pandemic. Due to a special protocol that was developed by different transplant teams in South Korea and India (including our active participation), we managed to control the COVID-19 infection and prevent its spread among our patients.

The first case of a liver transplant patient infected with COVID-19 was detected in the United States in March 2020. Subsequently, in October 2020, a similar case was reported in Georgia. Patients with an active immune response or those taking hepatotoxic drugs to treat COVID-19 may experience a decline in liver function as a consequence of viral infection or drug-induced liver damage. However, it turned out that these disorders, as a rule, are transient, mild in nature, and do not require specific treatment, and cases of severe, acute hepatitis are extremely rare [4]. In our study, monitoring of biochemical parameters did not reveal significant changes, with the exception of one patient who died from COVID-19.

COVID-19 can cause three types of liver damage: hepatocellular, cholestatic, and mixed [4]. When the levels of ALT and/or AST are three times the normal value or reach the upper limit, a hepatocyte type of liver damage is determined. When the levels of ALP or GGT are more than twice the upper limit, a cholestatic type of liver damage is noted. Both variants of abnormal values indicate a mixed type of liver damage. Of the 17 patients who underwent liver transplantation and subsequently became infected with COVID-19, only one patient had hepatocellular liver damage. Other authors have similarly observed the absence or moderate damage to the liver parenchyma in COVID-19 cases during liver transplantation [4].

A literature review indicates that COVID-19 has a three-phase course in patients with liver transplantation [8]. In the first phase, patients have mild respiratory symptoms. The second phase is moderate [10], since abdominal symptoms are observed along with the respiratory symptoms. The third phase is the most severe condition, since a systemic syndrome develops. These patients have high levels of interleukins 2, 6, and 7 [9].

The progression from one phase to another is not always noticeable. According to our data, only 5 (29.4%) patients showed progression to the second phase, and 1 (5.9%) to the third.

In our study, the cohort of patients with COVID-19 did not differ significantly from that described in the literature: the average age was  $60.8 \pm 5.24$  years, 68.5% were males, and the average duration of the period before infection with COVID-19 was  $5.72 \pm 1.75$  years [3]. However, the mortality rate (5.9%) was less than the rate observed in a study involving 1481 liver recipients: 17.4% (95% CI: 15.4–19.6%) [3].

The mortality rate from COVID-19 was similar in patients who had undergone liver transplantation ( $n = 610$ ) and those who had not ( $n = 239,704$ ), with an odds ratio of 0.8 (95% CI: 0.6–1.08,  $P = 0.14$ ). In addition, there was no significant difference in mortality rates between individuals who contracted the infection within one year after transplantation and those who contracted it one year later; odds ratio: 1.5 (95% CI: 0.63–3.56,  $P = 0.35$ ). The cumulative incidence of graft dysfunction was 2–3% (1.3–4.1) [3].

The relatively benign course of COVID-19 in liver transplant patients is likely due to their permanent use of immunosuppressive drugs that suppress the systemic inflammatory effects of the *virus*. According to other studies, it is feasible to prescribe immunosuppressive drugs for the prevention and treatment of the hyperinflammatory

phase of COVID-19, although these drugs suppress the body's immune response against the *virus* and therefore may be harmful in the early stages of COVID-19. All patients in our study were continuously on immunosuppressive medications. We believe that this contributed to their comparatively benign course of COVID-19. However, this issue is still the subject of debate.

Thus, clinical data on the incidence of COVID-19 infection in the liver transplant population are scarce. In these patients, recovery from severe COVID-19-associated pneumonia may depend on the restoration of immune function. The primary components of the therapeutic regimen may consist of low-dose corticosteroids and the temporary withdrawal of immunosuppression. Nevertheless, success in particular situations does not imply the necessity and rationality of a comprehensive approach. In order to determine the clinical characteristics of COVID-19 in recipients, further information regarding cases of immunosuppression must be collected [6].

## Conclusions

The implemented set of preventive measures ensured the patient's protection from COVID-19 infection in all cases during their hospital stay. In liver transplant patients, the clinical course of COVID-19 was relatively favourable and did not result in death in 94.1 % of cases.

## DECLARATION OF INTERESTS

The authors declare that they have no conflicts of interest.

## AUTHORS CONTRIBUTIONS

The authors have contributed equally to conception and design, acquisition and interpretation of data, drafting the article.

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# Перебіг інфекції COVID-19 у пацієнтів, які перенесли трансплантацію печінки

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У разі хронічних захворювань печінки післяінфекційний період при коронавірусній хворобі 2019 (COVID-19) перебігає тяжко і характеризується високою летальністю. Наслідки COVID-19 у пацієнтів, які перенесли трансплантацію печінки, вивчено недостатньо.

**Мета** — вивчити особливості перебігу COVID-19 у пацієнтів, які перенесли трансплантацію печінки.

**Матеріали та методи.** Вивчено частоту інфікування COVID-19 у 88 хворих після трансплантації печінки під час перебування в стаціонарі та у віддалений післяопераційний період, а також особливості клінічного перебігу COVID-19. Для профілактики COVID-19 у лікарні розроблено протокол, що забезпечує надійну ізоляцію хворого від контакту із джерелом інфекції. У післяопераційний період усі хворі отримували імуносупресивну терапію. Моніторинг перебігу COVID-19 здійснював консилиум у складі хірурга-трансплантолога, гепатолога, гастроентеролога, інфекціоніста, терапевта та імунолога за місцем проживання та лікування пацієнта.

**Результати.** Не зафіксовано випадків інфікування пацієнтів COVID-19 у стаціонарі. У віддалений період COVID-19 зареєстровано в 17 (19,3%) пацієнтів, із них 1 (5,9%) помер від інфекції. Один пацієнт інфікувався COVID-19 двічі. Виділено 4 варіанти клінічного перебігу COVID-19: легкий (23,5%) — без будь-яких симптомів, за винятком легких респіраторних, помірної тяжкості (41,2%) — помірні респіраторні симптоми та диспептичні явища без істотних змін клініко-діагностичних показників, середньої тяжкості (29,4%) — кашель без мокротиння, гіпертермія протягом трьох днів, зниження нюху, диспептичні явища, збільшення середніх значень біохімічних показників (аланінамінотрансфераза, аспаратамінотрансфераза,  $\gamma$ -глутамілтранспептидаза, лужна фосфатаза, загальний білірубін), тяжкий (5,9%) — розвиток поліорганної недостатності.

**Висновки.** Розроблений комплекс заходів профілактики забезпечив захист усіх пацієнтів від інфікування коронавірусом під час перебування в стаціонарі. Клінічний перебіг COVID-19 у хворих, які перенесли трансплантацію печінки, відносно сприятливий і у 94,1% випадків не призвів до летального наслідку.

**Ключові слова:** трансплантація печінки, COVID-19, профілактика, частота, клінічний перебіг.

## FOR CITATION

■ Bolkvadze R, Chomakhashvili Z, Nakashidze M, Beridze D, Beridze S, Shanava K, Mikeladze L, Kashibadze K. Clinical course of COVID-19 infection in liver transplant patients. General Surgery (Ukraine). 2023;3-4:35-39. <http://doi.org/10.30978/GS-2023-3-35>.