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Impact of Novel Coronavirus Infection on the Course and Prognosis of Cirrhosis

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Aim: to investigate the impact of COVID-19 on the course and prognosis of cirrhosis.
Materials and methods. This was a cohort study in patients with cirrhosis. We included patients with cirrhosis who underwent a medical examination at our center between September 2019 and March 2020. We determined which of these patients were infected with COVID-19, died of COVID-19, or died of cirrhosis complications within the follow-up period from April 2020 to September 2021. Thereafter, we conducted a second medical examination of these surviving patients with cirrhosis in September to December 2021.
Results. Among the 226 patients included in the study, 57 had COVID-19, among which 19 patients who died of the disease. Acute-on-chronic liver failure (ACLF) developed in 16 (28.1 %) patients with cirrhosis and COVID-19, 13 (81.3 %) of whom died. One of the COVID-19 survivors eventually died of liver decompensation. Twenty patients who did not have COVID-19 died of complications of cirrhosis (ACLF) during the follow-up period. The mortality rate in patients who were infected with COVID-19 was higher than that in patients who were not infected (35.1 % vs. 14.2 %; $p = 0.001$). COVID-19 was an independent risk factor for death in patients with cirrhosis. No liver-specific factors predisposing to COVID-19 infection were identified. A more impaired liver function in the pre-pandemic medical examination was a predisposing factor for death in patients who had COVID-19. Patients who died of COVID-19 had better liver function in the pre-pandemic medical examination than patients without COVID-19 who died of complications of cirrhosis during the follow-up period. The liver-related mortality rate and the incidence of liver decompensation or bleeding from esophageal varices during the follow-up period were not significantly different between patients who recovered from COVID-19 and patients with cirrhosis who did not have COVID-19. Among the analyzed survivors, no significant changes were found in the main indicators of liver function after the follow-up period between patients with and without COVID-19, except for the prothrombin index, which was higher in patients after COVID-19.
Conclusion. COVID-19 worsens the prognosis of patients with cirrhosis but does not substantially affect the course of cirrhosis after the recovery from this infection.
Keywords: COVID-19, SARS-CoV-2, coronavirus, liver, cirrhosis, prognosis
Conflict of interest: the authors declare that there is no conflict of interest.

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Влияние новой коронавирусной инфекции на течение и прогноз цирроза печени

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Цель исследования: изучение влияния COVID-19 на течение и прогноз цирроза печени.
Материалы и методы. В данное когортное исследование были включены пациенты с циррозом печени, проходившие медицинское обследование в период с сентября 2019 по март 2020 г. Было определено, кто из этих пациентов был инфицирован COVID-19, умер от COVID-19 или осложнений цирроза печени в течение периода наблюдения (с апреля 2020 по сентябрь 2021 г.). Далее в сентябре — декабре 2021 г. было проведено повторное медицинское обследование включенных выживших пациентов.
Результаты. Среди 226 включенных пациентов у 57 был выявлен COVID-19, в том числе 19 пациентов умерли от этой болезни. Острая на фоне хронической печеночная недостаточность (ОХПН) развилась у 16 (28,1 %) пациентов с циррозом печени и COVID-19, 13 (81,3 %) из которых умерли. Один из выживших после COVID-19 пациентов в итоге умер от декомпенсации функции печени. Двадцать пациентов, у которых не было COVID-19, умерли от осложнений цирроза печени (ОХПН) в течение периода наблюдения. Уровень смертности у пациентов, инфицированных COVID-19, был выше, чем у не перенесших это заболевание (35,1 % vs. 14,2 %;

p = 0,001). COVID-19 был независимым фактором риска смерти у пациентов с циррозом печени. Специфических для поражения печени факторов, предрасполагающих к заражению COVID-19, выявлено не было. Более значительные нарушения функции печени при медицинском обследовании перед пандемией были фактором риска смерти пациентов, переболевших COVID-19. Пациенты, умершие от COVID-19, имели состояние функции печени при медицинском обследовании перед пандемией лучше, чем пациенты, которые умерли от осложнений цирроза печени в течение периода наблюдения. Смертность из-за декомпенсации функции печени, частота декомпенсации печени и кровотечений из варикозно расширенных вен пищевода в течение периода наблюдения существенно не отличались между пациентами, выздоровевшими от COVID-19, и пациентами с циррозом печени, у которые не переносили эту инфекцию. Среди выживших не выявлено значимой разницы в значении основных показателей функции печени между пациентами, перенесшими и не перенесшими COVID-19, за исключением протромбинового индекса, который был выше у пациентов после COVID-19.
Заключение. COVID-19 ухудшает прогноз пациентов с циррозом печени, но не оказывает существенного влияния на течение цирроза печени после выздоровления от этой инфекции.
Ключевые слова: COVID-19, SARS-CoV-2, коронавирус, печень, цирроз печени, прогноз
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Introduction

Cirrhosis is a risk factor for an unfavorable course of coronavirus disease (COVID-19). Patients with cirrhosis are more likely to have a severe course of the disease, to be hospitalized [1], and to have a poor prognosis [2–6]. The liver is one of the targets of COVID-19, resulting in the development of inflammation, thrombosis, vasculitis, and drug-induced and other damage to the organ [7–11]. According to a meta-analysis study, alterations in the results of biochemical liver tests were observed in almost 50 % of patients with COVID-19 in the general population and were associated with more severe disease and a higher risk of death [12]. Liver cells express more receptors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cirrhosis than normal liver cells, and this is more pronounced in decompensated cirrhosis than in compensated cirrhosis [13]. These receptors were reported to be expressed in large amounts in hepatocyte progenitor cells responsible for liver regeneration in cirrhosis [14]. The mortality rate of patients with cirrhosis has increased during the COVID-19 pandemic [15]. A previous study reported no significant difference in mortality between COVID-19-infected and uninfected hospitalized patients with cirrhosis; however, only 37 patients with COVID-19 and cirrhosis were analyzed in this study [16]. Conversely, an analysis of mortality during the first 2.5 months of the pandemic among US veterans with cirrhosis showed that the mortality rate was higher in patients who were infected with COVID-19 than in those who were not infected [17]. Thus, the impact of COVID-19 on the overall prognosis of patients with cirrhosis remains unclear.

The aim of the study: to assess how COVID-19 affects the course and prognosis of a general cohort of patients with cirrhosis during a long-term follow-up.

Materials and methods

This cohort study was approved by the ethics committee of Sechenov University (Protocol No. 20-21 dated 18.11.2021) and was conducted in accordance with the Helsinki Declaration of the World Medical Association.

This study included patients with cirrhosis who were residents of Moscow; underwent a medical examination at the Clinic for Internal Diseases, Gastroenterology, and Hepatology of Sechenov University between September 2019 and March 2020 (before the pandemic); were not liver transplant recipients; and were alive as of April 1, 2020 (the beginning of the COVID-19 pandemic in Russia). The patients were divided into two cohorts: those who were infected with COVID-19 during the follow-up period (April 2020 to September 2021) and those who were not infected.

The diagnosis of cirrhosis was established on the basis of biopsy findings or a combination of clinical, laboratory, and instrumental findings. All patients received standard-of-care treatment for cirrhosis according to etiology and complications [18, 19].

A COVID-19 case was defined as a positive PCR test result for SARS-CoV-2 in oropharyngeal or nasopharyngeal swab samples and the presence of symptoms or signs of COVID-19 (e. g., fever, weakness, cough, shortness of breath, anosmia, and ageusia).

The primary outcome was death from all causes during the follow-up period. The secondary outcomes were the incidence of liver decompensation or bleeding from esophageal varices during the observation period and changes in liver function indicators (e. g., Child — Pugh Score) during the observation period (first observation point — between September 2019 and March 2020; second observation point — between September and December 2021) in surviving patients.

Data on COVID-19 cases, patient death and its cause, and complications of cirrhosis were obtained from the Unified Medical Information and Analytical System, which collects almost all medical information of Moscow residents.

Statistical analysis was performed with STATISTICA 10 software (StatSoft Inc., USA). The data were represented as median [interquartile range]. The difference between continuous variables was assessed with Mann — Whitney test. Fisher's exact test was used to assess the difference between categorical variables. Survival was assessed using the Kaplan — Meier estimator and Cox test. A Cox regression model was used to assess the influence of factors on patient survival and hazard ratio (HR). P-value ≤ 0.05 was considered significant.

Results

Among the 226 patients with cirrhosis included in the study, 57 were infected with COVID-19 during the follow-up period. Of these patients, 19 died of COVID-19 and one died of liver decompensation that occurred after recovering from COVID-19. Among 169 patients with cirrhosis who did not have COVID-19, 24 died during the follow-up period (Fig. 1, Table 1): 20 died of acute-on-chronic liver failure (ACLF), two died of complications of concomitant cancer, one patient died of heart failure, and one person died of alcohol intoxication. The mortality rate was higher in patients who were infected with COVID-19 than in those who were not (35.1 % vs. 14.2 %; $p = 0.001$). This was true for patients with compensated (Child — Pugh Class A; 23.3 % vs. 4.5 %; p = 0.006) and decompensated (Child — Pugh Class B or C; 44.4 % vs. 24.7 %; $p = 0.046$) cirrhosis in the pre-pandemic medical examination.

COVID-19 was an independent determinant of death in patients with cirrhosis (Table 2).

Among patients with cirrhosis, COVID-19 was mild in 20 (35.1 %) cases, moderate — in 12 (21.1 %) cases, and severe — in 25 (43.8 %) cases. Of patients with cirrhosis who had COVID-19, 33 (57.9 %) required hospitalization, including 20 (35.1 %) who needed intensive care unit admission. A third of group of patients with cirrhosis who had COVID-19 required mechanical ventilation, and all these patients died. The most common COVID-19 symptoms were fever, shortness of

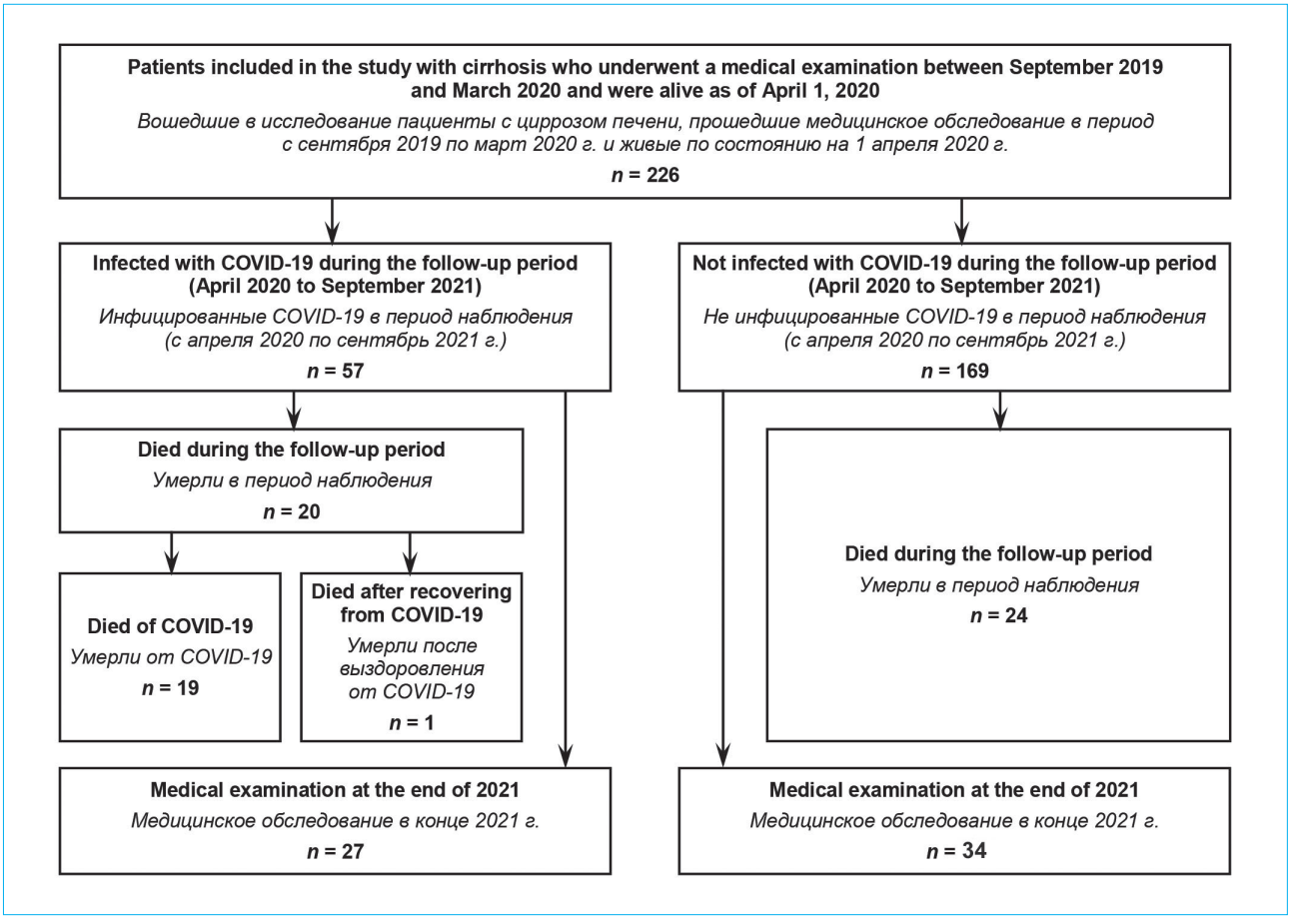

Figure 1. Study flowchart

Рисунок 1. Потоковая диаграмма исследования

Table 1. Main indicators of liver function in patients with cirrhosis in the pre-pandemic medical examination

Таблица 1. Основные показатели функции печени у больных циррозом печени при медицинском обследовании до пандемии

Parameter / *Показатель*	**COVID-19 group *Группа COVID-19* (*n* = 57)**	**Non-COVID group *Группа без COVID-19* (*n* = 169)**	***p***
Age, years *Возраст, лет*	59 [52–68]	56 [46–64]	0.029
Body mass index, kg/m^2 *Индекс массы тела, кг/м^2*	28.1 [25.2–34.0]	27.0 [22.8–30.2]	0.164
Males/Females *Мужчины/Женщины*	27/30	74/95	0.375
Etiology of cirrhosis, *n* (%) *Этиология цирроза, n (%)*			
alcoholic liver disease *алкогольная болезнь печени*	23 (40.4 %)	63 (37.3 %)	> 0.050
metabolically associated fatty liver disease *метаболически-ассоциированная болезнь печени*	2 (3.5 %)	8 (4.7 %)	
autoimmune hepatitis *аутоиммунный гепатит*	2 (3.5 %)	7 (4.1 %)	
primary biliary cholangitis *первичный билиарный холангит*	4 (7.0 %)	16 (9.5 %)	
primary sclerosing cholangitis *первичный склерозирующий холангит*	3 (5.3 %)	3 (1.8 %)	
HBV *вирусный гепатит B*	1 (1.8 %)	7 (4.1 %)	
HCV *вирусный гепатит C*	15 (26.3 %)	34 (20.1 %)	
mixed *смешанная*	5 (8.8 %)	26 (15.4 %)	
other and unkown *другая и неизвестная*	2 (3.5 %)	5 (3.0 %)	
Child — Pugh Score *Шкала Чайлда — Пью*	6 [5–9]	6 [5–9]	0.756
Class according to Child — Pugh Scale, A/B + C, *n* *Классы по шкале Чайлда — Пью, A/B+C, n*	30/16 + 11	88/45 + 36	0.532
Diabetes mellitus, *n* (%) *Сахарный диабет, n (%)*	18 (31.6 %)	30 (17.8 %)	0.024
Malignant neoplasms, *n* (%) *Злокачественные образования, n (%)*	2 (3.5 %)	10 (5.9 %)	0.378
Chronic obstructive pulmonary disease, *n* (%) *Хроническая обструктивная болезнь легких, n (%)*	2 (3.5 %)	7 (4.1 %)	0.594
Bronchial asthma, *n* (%) *Бронхиальная астма, n (%)*	1 (1.8 %)	4 (2.4 %)	0.628
Esophageal varices (Grade 1), *n* (%) *Варикозное расширение вен пищевода (степень 1), n (%)*	15 (26.3 %)	57 (33.7 %)	0.192
Esophageal varices (Grade 2–3), *n* (%) *Варикозное расширение вен пищевода (степень 2–3), n (%)*	22 (38.8 %)	46 (27.2 %)	0.075
Ligation of esophageal varices, *n* (%) *Лигирование вен пищевода, n (%)*	10 (17.5 %)	27 (16.0 %)	0.463
History of bleeding from esophageal varices, *n* (%) *Кровотечение из вен пищевода в анамнезе, n (%)*	3 (5.3 %)	18 (10.7 %)	0.173
Minimal hepatic encephalopathy, *n* (%) *Минимальная печеночная энцефалопатия, n (%)*	9 (15.8 %)	23 (13.6 %)	0.415
Overt hepatic encephalopathy (Grade 1–2), *n* (%) *Явная печеночная энцефалопатия (степень 1–2), n (%)*	16 (28.1 %)	43 (25.4 %)	0.409

Continuation of Table 1. Main indicators of liver function in patients with cirrhosis in the pre-pandemic medical examination

Продолжение таблицы 1. Основные показатели функции печени у больных циррозом печени при медицинском обследовании до пандемии

Ascites, *n* (%) *Асцит, n (%)*	24 (42.1 %)	72 (42.4 %)	0.537
Ascites (Grade 1), *n* (%) *Асцит (степень 1), n (%)*	13 (22.8 %)	39 (23.1 %)	0.562
Ascites (Grade 2–3), *n* (%) *Асцит (степень 2–3), n (%)*	11 (19.3 %)	33 (19.5 %)	0.569
Red blood cells, $\times 10^{12}$ cell/L *Эритроциты, $\times 10^{12}$ кл./л*	4.1 [3.8–4.6]	4.2 [3.7–4.8]	0.838
Neutrophils, $\times 10^{9}$ cell/L *Нейтрофилы, $\times 10^{9}$ кл./л*	2.6 [1.8–3.6]	2.9 [2.0–4.0]	0.146
Lymphocytes, $\times 10^{9}$ cell/L *Лимфоциты, $\times 10^{9}$ кл./л*	1.3 [0.9–1.9]	1.2 [0.9–1.9]	0.765
Platelets, $\times 10^{9}$ cell/L *Тромбоциты, $\times 10^{9}$ кл./л*	114 [66–145]	109 [73–162]	0.580
Serum total protein, g/L *Общий белок, г/л*	71.9 [68.5–76.2]	73.5 [67.7–76.9]	0.552
Serum albumin, g/L *Альбумин, г/л*	37.0 [33.3–39.9]	37.9 [32.3–41.6]	0.300
Serum total bilirubin, μmol/L *Общий билирубин, мкмоль/л*	28.3 [17.5–41.4]	25.9 [16.9–45.8]	0.966
Serum direct bilirubin, μmol/L *Прямой билирубин, мкмоль/л*	11.1 [6.1–16.6]	8.9 [5.7–21.7]	0.700
Prothrombin index, % *Протромбиновый индекс, %*	74 [62–84]	75 [61–83]	0.876
Fibrinogen, g/L *Фибриноген, г/л*	3.0 [2.2–3.7]	2.8 [2.2–3.4]	0.241
Serum creatinine, μmol/L *Креатинин, мкмоль/л*	80 [68–96]	80 [70–94]	0.939
Serum iron, μmol/L *Железо, мкмоль/л*	18.0 [11.4–23.9]	17.8 [12.1–26.5]	0.465
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	34 [22–50]	40 [25–56]	0.296
Aspartate aminotransferase, U/L Аспартатаминотрансфераза, МЕ/л	43 [33–70]	50 [34–81]	0.219
Gamma glutamyl transferase, U/L *Гамма-глутамилтрансфераза, МЕ/л*	71 [33–165]	87 [35–204]	0.460
Alkaline phosphatase, U/L *Щелочная фосфатаза, МЕ/л*	244 [202–372]	270 [193–384]	0.947
Cholinesterase, U/L *Холинэстераза, МЕ/л*	5118 [3203–6947]	5090 [3116–7176]	0.983
Splenic length, cm *Длина селезенки, см*	14.2 [13.2–16.6]	13.9 [11.7–16.0]	0.147

Note: * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: * (здесь и далее в таблице) – в квадратных скобках приведен межквартильный размах.

breath, and dry cough. The extreme (maximum or minimum) values of laboratory parameters in patients with cirrhosis and COVID-19 are shown in Table 3. Among patients with cirrhosis who had COVID-19, pulmonary embolism occurred in two (3.5 %) patients, hepatorenal syndrome – in 2 (3.5 %), bleeding from esophageal varices – in 2 (3.5 %), and systemic bacterial infection (with the pathogen detected in blood) – in 5 (8.8 %) patients. ACLF developed in 16 (28.1 %) patients with cirrhosis and COVID-19, 13 (81.3 %) of whom died. Among patients with cirrhosis who died of COVID-19, those who developed ACLF accounted for 64.8 %.

Patients with cirrhosis who were infected with COVID-19 were more likely to have diabetes and to be older than those who were not. No significant differences were found in other comorbidities and in the results of liver function tests in the pre-pandemic medical examination between patients with cirrhosis who had COVID-19 and those who did not have COVID-19 (Table 1).

Patients with cirrhosis who died of COVID-19 had lower RBC count and serum albumin and

Table 2. Predictors of death in patients with liver cirrhosis during the observation period
Таблица 2. Предикторы смерти больных циррозом печени за период наблюдения

Factor / *Предиктор*	***p***	**Hazard ration *Относительный риск***
COVID-19	0.024	2.11 (95 % CI: 1.10–4.05)
Age / *Возраст*	0.002	1.05 (95 % CI: 1.02–1.09)
Diabetes mellitus / *Сахарный диабет*	0.209	
Malignant neoplasm / *Злокачественное новообразование*	0.007	4.44 (95 % CI: 1.50–13.2)
Pre-pandemic medical examination data / *Данные медицинского осмотра до пандемии*		
Serum albumin / *Альбумин*	0.364	
Total serum bilirubin / *Общий билирубин*	0.503	
Prothrombin index / *Протромбиновый индекс*	0.171	
Alanine aminotransferase / *Аланинаминотрансфераза*	0.863	
Aspartate aminotransferase / *Аспартатаминотрансфераза*	0.863	
Hepatic encephalopathy / *Печеночная энцефалопатия*	0.289	
Ascites grade / *Степень асцита*	0.002	1.80 (95 % CI: 1.25–2.58)

Table 3. Symptoms of COVID-19 and minimum/maximum laboratory values during COVID-19 infection in patients with cirrhosis (n = 57)
Таблица 3. Симптомы COVID-19 и минимальные/максимальные лабораторные показатели во время COVID-19 у пациентов с циррозом печени (n = 57)

Symptoms / *Симптомы*		**Number of patients, *n* (%) *Количество пациентов, n (%)***
Fever / *Лихорадка*		57 (100.0 %)
Dry cough / *Сухой кашель*		28 (49.1 %)
Cough with sputum / *Кашель с мокротой*		8 (14.0 %)
Rhinorrhea / *Насморк*		7 (12.3 %)
Sore throat / *Боль в горле*		9 (15.8 %)
Shortness of breath / *Одышка*		25 (43.9 %)
Anosmia / *Потеря обоняния*		3 (5.3 %)
Ageusia / *Потеря вкуса*		2 (3.5 %)
Diarrhea / *Диарея*		2 (3.5 %)
Parameter / *Показатель*	**Number of patients *Количество пациентов***	**Minimum laboratory valuesduring having COVID-19* *Минимальные значения лабораторных показателей во время COVID-19****
Gamma glutamyl transferase, U/L *Гамма-глутамилтрансфераза, МЕ/л*	33	108 [95–125]
Lymphocytes, × 10^9 cell/L *Лимфоциты, × 10^9 кл./л*	31	0.5 [0.3–1.0]
Platelets, × 10^9 cell/L *Тромбоциты, × 10^9 кл./л*	33	67 [32–90]
Serum total protein, g/L *Общий белок, г/л*	23	56.5 [48.0–64.8]
Serum albumin, g/L *Альбумин, г/л*	18	26.5 [23.0–30.0]
Neutrophils, × 10^9 cell/L *Нейтрофилы, × 10^9 кл./л*	31	4.4 [2.2–9.9]
C-reactive protein, mg/L *С-реактивный белок, мг/л*	31	32.0 [13.5–100.0]
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	33	43 [25–54]
Aspartate aminotransferase, U/L *Аспартатаминотрансфераза, МЕ/л*	33	73 [43–97]
Gamma glutamyl transferase, U/L *Гамма-глутамилтрансфераза, МЕ/л*	8	66 [32–99]
Щелочная фосфатаза, МЕ/л Alkaline phosphatase, U/L	13	109 [93–188]

Continuation of Table 3. Symptoms of COVID-19 and minimum/maximum laboratory values during COVID-19 infection in patients with cirrhosis (n = 57)

Продолжение таблицы 3. Симптомы COVID-19 и минимальные/максимальные лабораторные показатели во время COVID-19 у пациентов с циррозом печени (n = 57)

Serum creatinine, μmol/L *Креатинин, мкмоль/л*	33	100 [71–132]
Total serum bilirubin, μmol/L *Общий билирубин, мкмоль/л*	27	55.2 [15.0–83.0]
Fibrinogen, g/L *Фибриноген, г/л*	21	3.7 [2.5–4.6]
D-dimer, ng/mL *D-димер, нг/мл*	18	1288 [745–3865]
Lactate dehydrogenase, U/L *Лактатдегидрогеназа, МЕ/л*	15	750 [329–1314]

Note: * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: * (здесь и далее в таблице) – в квадратных скобках приведен межквартильный размах.

cholinesterase levels; higher serum levels of direct bilirubin, aspartate aminotransferase, and gamma-glutamyl transpeptidase; higher Child – Pugh scores; and more severe ascites in the pre-pandemic medical examination than those who were alive after COVID-19 at the end of the follow-up period (the only patient who died of cirrhosis decompensation after recovering from COVID-19 was excluded from this analysis) (Table 4). Among these results, only a reduced serum albumin level was an independent predictor of death from COVID-19 (HR = 0.92; 95 % CI: 0.86–0.98; p = 0.017). The mortality rate in patients with COVID-19 who had hypoalbuminemia in the pre-pandemic medical examination was 52.9 %, whereas it was only 25.0 % in those with normal albumin levels (p = 0.042). Moreover, all patients who had normal albumin levels during the pre-pandemic medical examination and died of COVID-19 developed hypoalbuminemia before death. In contrast, among patients with normal baseline albumin levels who recovered from COVID-19, only one patient had hypoalbuminemia during the COVID-19 infection.

Patients with cirrhosis who died of COVID-19 during the follow-up period had better liver function (based on the Child – Pugh scale) in the pre-pandemic medical examination than those who died of cirrhosis complications during the same period (Table 5).

The liver-related mortality rate (7.2 % vs. 4.2 % per patient-years; p = 0.509), incidence of liver decompensation (0.26 vs. 0.24 per patient-years; p = 0.497), and incidence of bleeding from esophageal varices (0.00 vs. 0.08 per patient-years; p = 0.192) during the follow-up period were not significantly different between patients who recovered from COVID-19 and patients with cirrhosis who did not have COVID-19.

We invited all surviving patients to attend an express medical examination in September 2021. Among them, 27 patients who recovered from COVID-19 (post-COVID-19 group; the characteristics of COVID-19 in these patients are presented in Table 6) and 34 patients who did not have COVID-19 (non-COVID-19 group) responded to the invitation. The rest of the patients declined owing to fear of COVID-19 infection or for other reasons. No significant differences between these groups of patients were observed in sex distribution, age, etiology of cirrhosis, and values of liver function indicators in the pre-pandemic medical examination (Table 7). The time interval between the two medical examinations was 23.8 [22.1–25.8] months in the post-COVID-19 group and 23.2 [19.4–24.5] months in the non-COVID-19 group (p = 0.068). The second medical examination was performed at an average of 8.4 [3.1–13.3] months after COVID-19 infection in the post-COVID-19 group. At the time of the second medical examination (end of 2021), the indicators of liver function showed no significant differences between the post-COVID-19 and non-COVID-19 groups, except for the prothrombin index, which was higher in the post-COVID-19 group than in the non-COVID-19 group (Table 7).

Discussion

The presence of cirrhosis is a predisposing factor for an unfavorable course of COVID-19 [1]. Several factors have been found to predict death in patients with cirrhosis who had COVID-19, including poor liver function [2]. However, COVID-19 itself impairs liver function and this liver dysfunction is associated with a poor prognosis even in patients without pre-existing liver disease [7–11]. Thus, the examination of liver function in patients with cirrhosis who had been infected with COVID-19, as performed in previous studies [2–6], cannot establish the liver function status before COVID-19, as it has already been altered by the infection. Thus, previous studies have not analyzed how pre-existing

Table 4. Main liver function tests during pre-pandemic medical examination in patients with cirrhosis who subsequently died from COVID-19 or survived COVID-19

Таблица 4. Основные показатели функции печени во время медицинского обследования до пандемии у пациентов с циррозом, в дальнейшем умерших от COVID-19 или выживших после COVID-19

Parameter / *Показатель*	**Died from COVID-19 *Умерли от COVID-19* (n = 19)**	**Survivors of COVID-19 *Выжили после COVID-19* (n = 37)**	***p***
Age, years *Возраст, лет*	63 [57–71]*	59 [49–67]	0.113
Body mass index, kg/m² *Индекс массы тела, кг/м²*	28.0 [24.8–30.1]	28.2 [25.5–34.0]	0.644
Males/Females *Мужчины/Женщины*	11/8	19/18	0.390
Etiology of cirrhosis, *n* (%) *Этиология цирроза, n (%)*			
alcoholic liver disease *алкогольная болезнь печени*	8 (42.1 %)	14 (37.8 %)	> 0.050
metabolically associated fatty liver disease *метаболически-ассоциированная болезнь печени*	0	2 (5.4 %)	
autoimmune hepatitis *аутоиммунный гепатит*	0	2 (5.4 %)	
primary biliary cholangitis *первичный билиарный холангит*	3 (15.8 %)	1 (2.7 %)	
primary sclerosing cholangitis *первичный склерозирующий холангит*	2 (10.5 %)	1 (2.7 %)	
HBV *вирусный гепатит B*	0	1 (2.7 %)	
HCV *вирусный гепатит C*	3 (15.8 %)	12 (32.4 %)	
mixed *смешанная*	2 (10.5 %)	3 (8.1 %)	
other and unkown *другая и неизвестная*	1 (5.3 %)	1 (2.7 %)	
Child — Pugh Score *Шкала Чайлда — Пью*	8 [6–10]	6 [5–7]	0.015
Class according to Child — Pugh Scale, A/B + C, *n* *Классы по шкале Чайлда — Пью, A/B + C, n*	7/5 + 7	22/11 + 4	0.093
Diabetes mellitus, *n* (%) *Сахарный диабет, n (%)*	6 (31.6 %)	12 (32.4 %)	0.598
Malignant neoplasms, *n* (%) *Злокачественные образования, n (%)*	1 (5.3 %)	1 (2.7 %)	0.568
Chronic obstructive pulmonary disease, *n* (%) *Хроническая обструктивная болезнь легких, n (%)*	1 (5.3 %)	1 (2.7 %)	0.568
Bronchial asthma, *n* (%) *Бронхиальная астма, n (%)*	0	1 (2.7 %)	0.661
Esophageal varices (Grade 1), n (%) *Варикозное расширение вен пищевода (степень 1), n (%)*	6 (31.6 %)	9 (24.3 %)	0.391
Esophageal varices (Grade 2–3), *n* (%) *Варикозное расширение вен пищевода (степень 2–3), n (%)*	7 (36.8 %)	15 (40.5 %)	0.511
Ligation of esophageal varices, *n* (%) *Лигирование вен пищевода, n (%)*	6 (31.6 %)	4 (10.8 %)	0.063
History of bleeding from esophageal varices, *n* (%) *Кровотечение из вен пищевода в анамнезе, n (%)*	0	3 (8.1 %)	0.280
Minimal hepatic encephalopathy, *n* (%) *Минимальная печеночная энцефалопатия, n (%)*	5 (26.3 %)	4 (10.8 %)	0.134
Overt hepatic encephalopathy (Grade 1–2), n (%) *Явная печеночная энцефалопатия (степень 1–2), n (%)*	5 (26.3 %)	10 (27.0 %)	0.609

Continuation of Table 4. Main liver function tests during pre-pandemic medical examination in patients with cirrhosis who subsequently died from COVID-19 or survived COVID-19

Продолжение таблицы 4. Основные показатели функции печени во время медицинского обследования до пандемии у пациентов с циррозом, в дальнейшем умерших от COVID-19 или выживших после COVID-19

Ascites, *n* (%) *Асцит, n (%)*	11 (57.9 %)	13 (35.1 %)	0.090
Ascites (Grade 1), *n* (%) *Асцит (степень 1), n (%)*	4 (21.0 %)	9 (24.3 %)	0.532
Ascites (Grade 2–3), *n* (%) *Асцит (степень 2–3), n (%)*	7 (36.8 %)	4 (10.8 %)	0.027
Red blood cells, × 10^{12} cell/L *Эритроциты, × 10^{12} кл./л*	3.9 [3.2–4.1]	4.4 [3.9–4.8]	0.010
Neutrophils, × 10^{9} cell/L *Нейтрофилы, × 10^{9} кл./л*	2.4 [2.0–3.5]	2.6 [1.4–3.6]	0.675
Lymphocytes, × 10^{9} cell/L *Лимфоциты, × 10^{9} кл./л*	1.2 [0.8–1.6]	1.3 [1.0–1.9]	0.499
Platelets, × 10^{9} cell/L *Тромбоциты, × 10^{9} кл./л*	119 [80–159]	102 [64–144]	0.446
Serum total protein, g/L *Общий белок, г/л*	73.3 [65.2–77.4]	71.7 [68.5–74.9]	0.484
Serum albumin, g/L *Альбумин, г/л*	35.7 [31.2–36.3]	38.3 [35.6–41.8]	0.014
Serum total bilirubin, μmol/L *Общий билирубин, мкмоль/л*	32.7 [22.6–55.6]	26.2 [14.8–35.0]	0.098
Serum direct bilirubin, μmol/L *Прямой билирубин, мкмоль/л*	13.9 [10.0–26.9]	9.5 [6.0–14.2]	0.036
Prothrombin index, % *Протромбиновый индекс, %*	70 [54–87]	74 [68–83]	0.530
Fibrinogen, g/L *Фибриноген, г/л*	3.1 [2.1–3.7]	2.9 [2.2–3.5]	0.990
Serum creatinine, μmol/L *Креатинин, мкмоль/л*	82 [68–88]	78 [68–101]	0.726
Serum iron, μmol/L *Железо, мкмоль/л*	19.2 [12.1–24.2]	17.2 [10.6–23.3]	0.418
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	43 [25–59]	30 [22–41]	0.109
Aspartate aminotransferase, U/L Аспартатаминотрансфераза, МЕ/л	60 [42–99]	39 [33–55]	0.029
Gamma glutamyl transferase, U/L *Гамма-глутамилтрансфераза, МЕ/л*	121 [68–225]	48 [32–110]	0.043
Alkaline phosphatase, U/L *Щелочная фосфатаза, МЕ/л*	268 [223–562]	242 [192–334]	0.110
Cholinesterase, U/L *Холинэстераза, МЕ/л*	3200 [2962–3951]	5708 [4606–7031]	0.003
Splenic length, cm *Длина селезенки, см*	14.5 [13.1–15.2]	14.0 [13.5–17.0]	0.882

Note: * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: * (здесь и далее в таблице) – в квадратных скобках приведен межквартильный размах.

cirrhosis-associated liver dysfunction is associated with the risk of COVID-19 and the risk of death from this disease. Addressing this issue was one of the goals of our study.

Ideally, assessment of liver function in patients with cirrhosis would take into account data obtained immediately before the onset of COVID-19 disease; however, in most cases this was not possible. Therefore, we collected the data of patients who underwent a medical examination in our clinic 7 months before the onset of the pandemic and followed up these patients during the three main waves of COVID-19 in Moscow.

We found no liver-dependent factors predisposing to COVID-19 infection.

COVID-19 in patients with cirrhosis was often severe and associated with a high mortality rate, as described in previous studies [2–4]. Among the indicators of cirrhosis-related liver dysfunction, only decreased serum albumin level was an independent predictor of death from COVID-19 in our study. In another study, patients without cirrhosis who

Table 5. Main liver function tests during pre-pandemic medical examination in patients who subsequently died from COVID-19 and in those who died from complications of cirrhosis

Таблица 5. Основные показатели функции печени при медицинском обследовании до пандемии у пациентов, впоследствии умерших от COVID-19 и от осложнений цирроза печени

Parameter / *Показатель*	**Died from COVID-19 *Умерли от COVID-19* (n = 19)**	**Died from cirrhosis complications *Умерли от осложнений цирроза* (n = 20)**	***p***
Age, years *Возраст, лет*	63 [57–71]*	67 [58–74]	0.967
Body mass index, kg/m² *Индекс массы тела, кг/м²*	28.0 [24.8–30.1]	26.4 [23.9–28.1]	0.470
Males/Females *Мужчины/Женщины*	11/8	11/9	0.556
Etiology of cirrhosis, *n* (%) *Этиология цирроза, n (%)*			
alcoholic liver disease *алкогольная болезнь печени*	8 (42.1 %)	14 (70.0 %)	> 0.050
metabolically associated fatty liver disease *метаболически-ассоциированная болезнь печени*	0	1 (5.0 %)	
autoimmune hepatitis *первичный билиарный холангит*	0	0	
primary biliary cholangitis *первичный билиарный холангит*	3 (15.8 %)	3 (15.0 %)	
primary sclerosing cholangitis *первичный склерозирующий холангит*	2 (10.5 %)	0	
HBV *Вирусный гепатит B*	0	0	
HCV *Вирусный гепатит C*	3 (15.8 %)	0	
mixed *смешанная*	2 (10.5 %)	2 (10.0 %)	
other and unkown *другая и неизвестная*	1 (5.3 %)	0	
Child — Pugh Score *Шкала Чайлда — Пью*	8 [6–10]	10 [8–11]	0.035
Class according to Child — Pugh Scale, A/B + C, *n* *Классы по шкале Чайлда — Пью, A/B + C, n*	7/5 + 7	1/6 + 13	0.018
Diabetes mellitus, *n* (%) *Сахарный диабет, n (%)*	6 (31.6 %)	5 (25.0 %)	0.460
Malignant neoplasms, *n* (%) *Злокачественные образования, n (%)*	1 (5.3 %)	2 (10.0 %)	0.520
Chronic obstructive pulmonary disease, *n* (%) *Хроническая обструктивная болезнь легких, n (%)*	1 (5.3 %)	3 (15.0 %)	0.322
Bronchial asthma, *n* (%) *Бронхиальная астма, n (%)*	0	0	–
Esophageal varices (Grade 1), *n* (%) *Варикозное расширение вен пищевода (степень 1), n (%)*	6 (31.6 %)	6 (30.0 %)	0.594
Esophageal varices (Grade 2–3), *n* (%) *Варикозное расширение вен пищевода (степень 2–3), n (%)*	7 (36.8 %)	9 (45.0 %)	0.424
Ligation of esophageal varices, *n* (%) *Лигирование вен пищевода, n (%)*	6 (31.6 %)	2 (10.0 %)	0.101
History of bleeding from esophageal varices, *n* (%) *Кровотечение из вен пищевода в анамнезе, n (%)*	0	1 (5.0 %)	0.513
Minimal hepatic encephalopathy, *n* (%) *Минимальная печеночная энцефалопатия, n (%)*	5 (26.3 %)	2 (10.0 %)	0.182

Continuation of Table 5. Main liver function tests during pre-pandemic medical examination in patients who subsequently died from COVID-19 and in those who died from complications of cirrhosis

Продолжение таблицы 5. Основные показатели функции печени при медицинском обследовании до пандемии у пациентов, впоследствии умерших от COVID-19 и от осложнений цирроза печени

Ascites, *n* (%) *Асцит, n (%)*	11 (57.9 %)	17 (85.0 %)	0.063
Ascites (Grade 1), *n* (%) *Асцит (степень 1), n (%)*	4 (21.0 %)	5 (25.0 %)	0.535
Ascites (Grade 2–3), *n* (%) *Асцит (степень 2–3), n (%)*	7 (36.8 %)	12 (60.0 %)	0.130
Red blood cells, × 10^{12} cell/L *Эритроциты, × 10^{12} кл./л*	3.9 [3.2–4.1]	3.7 [3.2–4.2]	0.729
Neutrophils, × 10^{9} cell/L *Нейтрофилы, × 10^{9} кл./л*	2.4 [2.0–3.5]*	3.2 [2.4–3.9]*	0.244
Lymphocytes, × 10^{9} cell/L *Лимфоциты, × 10^{9} кл./л*	1.2 [0.8–1.6]	1.1 [0.8–1.6]	0.752
Platelets, × 10^{9} cell/L *Тромбоциты, × 10^{9} кл./л*	119 [80–159]	99 [62–145]*	0.341
Serum total protein, g/L *Общий белок, г/л*	73.3 [65.2–77.4]	67.9 [62.2–75.1]	0.105
Serum albumin, g/L *Альбумин, г/л*	35.7 [31.2–36.3]*	31.5 [27.0–36.1]	0.377
Serum total bilirubin, μmol/L *Общий билирубин, мкмоль/л*	32.7 [22.6–55.6]	54.9 [32.9–95.9]	0.021
Serum direct bilirubin, μmol/L *Прямой билирубин, мкмоль/л*	13.9 [10.0–26.9]	22.4 [15.6–41.4]	0.028
Prothrombin index, % *Протромбиновый индекс, %*	70 [54–87]*	57 [53–67]*	0.143
Fibrinogen, g/L *Фибриноген, г/л*	3.1 [2.1–3.7]	2.3 [1.6–3.0]	0.049
Serum creatinine, μmol/L *Креатинин, мкмоль/л*	82 [68–88]	84 [69–97]	0.593
Serum iron, μmol/L *Железо, мкмоль/л*	4.8 [4.5–5.9]	5.3 [4.7–6.8]	0.379
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	19.2 [12.1–24.2]	21.7 [14.2–26.7]	0.471
Aspartate aminotransferase, U/L Аспартатаминотрансфераза, МЕ/л	43 [25–59]	33 [24–54]	0.624
Gamma glutamyl transferase, U/L *Гамма-глутамилтрансфераза, МЕ/л*	60 [42–99]	75 [40–99]	0.728
Alkaline phosphatase, U/L *Щелочная фосфатаза, МЕ/л*	121 [68–225]	121 [47–392]	0.729
Cholinesterase, U/L *Холинэстераза, МЕ/л*	268 [223–562]	338 [258–512]	0.613
Splenic length, cm *Длина селезенки, см*	3200 [2962–3951]	2742 [2474–4151]	0.633
Длина селезенки, см *Splenic length, cm*	14.5 [13.1–15.2]	14.8 [128.8–16.0]	0.764

Note: * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: * (здесь и далее в таблице) – в квадратных скобках приведен межквартильный размах.

had hypoalbuminemia at the time of hospitalization for COVID-19 had a poor prognosis [20]. In our study, all patients who had normal albumin levels during the pre-pandemic medical examination and died of COVID-19 developed hypoalbuminemia before death. In contrast, among patients with normal baseline albumin levels who recovered from COVID-19, only one patient developed hypoalbuminemia during the COVID-19 infection. Previous studies have reported that albumin can bind and neutralize the coronavirus spike protein [20] and downregulates the expression of ACE2 (the target receptor of COVID-19) [21]. The deficiency in circulating albumin in patients with Child – Pugh class B and C cirrhosis and the reduced ability of the liver to form new albumin molecules to replace those used to neutralize coronavirus proteins in patients with Child – Pugh class A cirrhosis are possible reasons for the high mortality rate in patients with cirrhosis who were infected with COVID-19.

Table 6. Symptoms of COVID-19 and minimum/maximum laboratory values during COVID-19 infection in patients with cirrhosis who recovered from COVID-19 and in whom changes in liver function values were assessed in the study (n = 27)

Таблица 6. Симптомы COVID-19 и минимальные/максимальные значения лабораторных показателей при инфекции COVID-19 у пациентов с циррозом печени, функция печени которых была оценена после перенесенного COVID-19 (n = 27)

Course of COVID-19 / *Течение COVID-19*	
Mild course / *Легкое течение*	14 (51.9 %)
Moderate course / *Средней тяжести*	8 (29.6 %)
Severe course / *Тяжелое течение*	5 (18.5 %)
Hospitalization / *Госпитализация*	11 (40.7 %)
Admission in the intensive care unit *Госпитализация в отделение интенсивной терапии*	1 (3.7 %)
Mechanical ventilation / *Потребность в ИВЛ*	0
Acute-on-chronic liver failure *Острая на фоне хронической печеночная недостаточность*	2 (7.4 %)
Symptoms / *Симптомы*	
Fever / *Лихорадка*	
Dry cough / *Сухой кашель*	15 (55.6 %)
Cough with sputum / *Кашель с мокротой*	4 (14.8 %)
Rhinorrhea / *Насморк*	6 (22.2 %)
Sore throat / *Боль в горле*	6 (22.2 %)
Shortness of breath / *Одышка*	9 (33.3 %)
Anosmia / *Потеря обоняния*	3 (11.1 %)
Ageusia / *Потеря вкуса*	2 (7.4 %)
Diarrhea / *Диарея*	1 (3.7 %)
Minimum laboratory valuesduring having COVID-19* *Минимальные значения лабораторных показателей во время COVID-19**	
Hemoglobin, g/L *Гемоглобин, г/л*	113 [96–132]
Lymphocytes, × 10^9 cell/L *Лимфоциты, × 10^9 кл./л*	0.6 [0.4–0.8]
Platelets, × 10^9 cell/L *Тромбоциты, × 10^9 кл./л*	74 [41–93]
Serum total protein, g/L *Общий белок, г/л*	59 [57–69]
Serum albumin, g/L *Альбумин, г/л*	30 [30–34]
Maximum laboratory valuesduring having COVID-19 *Максимальные значения лабораторных показателей во время COVID-19*	
Neutrophils, × 10^9 cell/L *Нейтрофилы, × 10^9 кл./л*	2.5 [1.7–6.8]
C-reactive protein, mg/L *С-реактивный белок, мг/л*	20 [11–29]
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	27 [22–44]
Aspartate aminotransferase, U/L *Аспартатаминотрансфераза, МЕ/л*	43 [36–63]
Serum creatinine, μmol/L *Креатинин, мкмоль/л*	82 [63–99]
Total serum bilirubin, μmol/L *Общий билирубин, мкмоль/л*	15 [14–34]

Note: * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: * (здесь и далее в таблице) — в квадратных скобках приведен межквартильный размах.

Table 7. Changes in the values of the main indicators of liver function in patients with cirrhosis between the pre-pandemic medical examination and the examination at the end of 2021

Таблица 7. Сравнение значений основных показателей функции печени у больных циррозом печени до пандемии и в конце 2021 г.

Parameter / *Показатель*	**Patients with cirrhosis who survived after COVID-19 *Пациенты с циррозом, которые пережили COVID-19* (*n* = 27)**		**Patients with cirrhosis who did not have COVID-19 *Пациенты с циррозом, которые не имели COVID-19* (*n* = 34)**		***p* (difference between the groups at the PPME) *(разница между группами перед пандемией)***	***p* (difference between the groups at the E2021) *(разница между группами на конец 2021 г.)***
	PPME *ДО*	**E2021 *К2021***	**PPME *ДО***	**E2021 *К2021***		
Child — Pugh Score *Шкала Чайлда — Пью*	5 [5–7]*	6 [5–7]	6 [5–8]	6 [5–8]	0.542	0.495
Class according to Child — Pugh Scale, A/B + C, *n* *Классы по шкале Чайлда — Пью, A/B + C, n*	18/7 + 2	19/8 + 0	18/10 + 6	19/12 + 3	0.206	0.186
Hepatic encephalopathy, *n* (%) *Печеночная энцефалопатия, n (%)*	8 (29.6 %)	8 (29.6 %)	15 (44.1 %)	13 (38.2 %)	0.186	0.403
Ascites, *n* (%) *Асцит, n (%)*	8 (29.6 %)	8 (29.6 %)	17 (50.0 %)	17 (50.0 %)	0.089	0.089
Ascites (Grade 1), *n* (%) *Асцит (степень 1), n (%)*	7 (25.9 %)	6 (22.2 %)	13 (38.2 %)	8 (23.5 %)	0.230	0.617
Ascites (Grade 2–3), *n* (%) *Асцит (степень 2–3), n (%)*	1 (3.7 %)	2 (7.4 %)	4 (11.8 %)	9 (26.5 %)	0.231	0.053
Serum total protein, g/L *Общий белок, г/л*	72 [69–76]	69 [67–75]	72 [68–76]	69 [65–72]	0.561	0.518
Serum albumin, g/L *Альбумин, г/л*	39 [36–42]	38 [35–43]	38 [32–41]	38 [32–44]	0.459	0.947
Serum total bilirubin, umol/L *Общий билирубин, мкмоль/л*	25 [15–31]	23 [14–29]	20 [14–47]	22 [15–36]	0.647	0.994
Прямой билирубин, мкмоль/л *Serum direct bilirubin, umol/L*	7 [6–12]	7 [5–13]	7 [5–19]	7 [4–12]	0.777	0.650
Prothrombin index, % *Протромбиновый индекс, %*	75 [68–84]	82 [76–86]	71 [62–83]	68 [59–82]	0.313	0.003
Serum creatinine, umol/L *Креатинин, мкмоль/л*	82 [67–102]	82 [63–93]	81 [69–96]	84 [67–98]	0.908	0.403
Alanine aminotransferase, U/L *Аланинаминотрансфераза, МЕ/л*	34 [25–44]	31 [22–52]	42 [27–51]	22 [19–32]	0.278	0.053
Aspartate aminotransferase, U/L *Аспартатаминотрансфераза, МЕ/л*	39 [33–62]	42 [28–53]	54 [36–89]	34 [29–41]	0.061	0.467
Splenic length, cm *Длина селезенки, см*	13.9 [12.9–16.0]	14.2 [12.8–16.5]	14.9 [12.9–16.7]	15.0 [12.0–17.0]	0.453	0.935
General information about analyzed patients by groups *Общая информация об анализируемых пациентах по группам*						
Age, years *Возраст, лет*	59 [51–67]		57 [44–67]		0.228	
Males/Females *Мужчины/Женщины*	13/14		11/23		0.161	

Continuation of Table 7. Changes in the values of the main indicators of liver function in patients with cirrhosis between the pre-pandemic medical examination and the examination at the end of 2021

Продолжение таблицы 7. Сравнение значений основных показателей функции печени у больных циррозом печени до пандемии и в конце 2021 г.

Etiology of cirrhosis, *n* (%) *Этиология цирроза, n (%)*			
alcoholic liver disease *алкогольная болезнь печени*	7 (25.9 %)	10 (29.4 %)	>0.050
metabolically associated fatty liver disease *метаболически-ассоциированная болезнь печени*	2 (7.4 %)	1 (2.9 %)	
autoimmune hepatitis *аутоиммунный гепатит*	2 (7.4 %)	0	
primary biliary cholangitis *первичный билиарный холангит*	1 (3.7 %)	5 (14.7 %)	
primary sclerosing cholangitis *первичный склерозирующий холангит*	1 (3.7 %)	0	
HBV *вирусный гепатит B*	1 (3.7 %)	0	
HCV *вирусный гепатит C*	10 (37.0 %)	8 (23.5 %)	
mixed *смешанная*	3 (11.1 %)	6 (17.6 %)	
other and unkown *другая и неизвестная*	0	4 (11.8 %)	
Diabetes mellitus, *n* (%) *Сахарный диабет, n (%)*	10 (37.0 %)	6 (17.6 %)	0.079
Malignant neoplasms, *n* (%) *Злокачественные образования, n (%)*	1 (3.7 %)	0	0.443

Note: PPME — pre-pandemic medical examination; E2021 — an the end of 2021; * (hereinafter in the table), interquartile range is given in square brackets.

Примечание: ДО — до пандемии; К2021 — в конце 2021 г.; * (здесь и далее в таблице) — в квадратных скобках приведен интерквантильный интервал.

In our study, the pre-pandemic liver function was better in patients who died of COVID-19 than in those who died of complications of cirrhosis. COVID-19 infection was found to be an independent risk factor for death in patients with cirrhosis. Thus, COVID-19 is an important cause of death in patients with cirrhosis, who might have better survival chances without the pandemic.

A previous study showed that there was no significant difference in prognosis between hospitalized cirrhosis patients with and without COVID-19 [16]. However, the hospitalization of a patient with cirrhosis itself is associated with a poor prognosis. In our study, we evaluated all patients with cirrhosis, both hospitalized and non-hospitalized. The prognosis of cirrhosis patients with COVID-19 was significantly worse than that of those who did not have it in this case.

Our study showed that COVID-19 worsens the prognosis of patients with cirrhosis and that hypoalbuminemia is the main predictor of death in these patients. This is in agreement with previously published data [2–6]. However, in contrast to previous studies, we assessed the impact of baseline (before the COVID-19 pandemic) liver function in patients with cirrhosis on the outcome of COVID-19, which is one of the strengths of our study.

The second strength of our study is that it is the first study to assess how COVID-19 affects liver function in surviving patients with cirrhosis. We found that recovery from COVID-19 had no significant effect on most indicators of liver function, except for the prothrombin index, which was higher in patients who had the infection. This may be a manifestation of the procoagulant status that is observed in COVID-19 [22] and post-COVID-19 syndrome [23].

A limitation of this study was that we were unable to examine all surviving patients at the end of the follow-up period, as many of

them refused to visit our clinic owing to fear of COVID-19 infection or for other reasons. Nevertheless, we were able to collect data from sufficiently large groups of patients who showed no significant differences in the pre-pandemic levels of liver function indicators.

Conclusion

COVID-19 worsens the prognosis of patients with cirrhosis but does not substantially affect the course of cirrhosis after the recovery from this infection. The decreased ability of the liver to form albumin may be a major cause of increased mortality from COVID-19 in patients with cirrhosis.

References / Литература

1. *Simon T.G., Hagström H., Sharma R., Söderling J., Roelstraete B., Larsson E., et al.* Risk of severe COVID-19 and mortality in patients with established chronic liver disease: A nationwide matched cohort study. *BMC Gastroenterol*. 2021;21(1):439. DOI: 10.1186/s12876-021-02017-8
2. *Elhence A., Vaishnav M., Biswas S., Anand A., Gunjan D., Kedia S., et al.* Predictors of in-hospital outcomes in patients with cirrhosis and Coronavirus disease-2019. *J Clin Exp Hepatol*. 2021;12(3):876–86. DOI: 10.1016/j.jceh.2021.10.014
3. *Middleton P., Hsu C., Lythgoe M.P.* Clinical outcomes in COVID-19 and cirrhosis: A systematic review and meta-analysis of observational studies. *BMJ Open Gastroenterol*. 2021;8(1):e000739. DOI: 10.1136/bmjgast-2021-000739
4. *Ge J., Pletcher M.J., Lai J.C.; N3C Consortium.* Outcomes of SARS-CoV-2 infection in patients with chronic liver disease and cirrhosis: A National COVID Cohort Collaborative study. *Gastroenterology*. 2021;161(5):1487–501. DOI: 10.1053/j.gastro.2021.07.010
5. *Xiao Y., Wu D., Shi X., Liu S., Hu X., Zhou C., et al.* High Child – Pugh and CRUB65 scores predict mortality of decompensated cirrhosis patients with COVID-19: A 23-center, retrospective study. *Virulence*. 2021;12(1):1199–208. DOI: 10.1080/21505594.2021.1909894
6. *Bajaj J.S., Garcia-Tsao G., Wong F., Biggins S.W., Kamath P.S., McGeorge S., et al.* Cirrhosis is associated with high mortality and readmissions over 90 days regardless of COVID-19: A multicenter cohort. *Liver Transpl*. 2021;27(9):1343–7. DOI: 10.1002/lt.25981
7. *Gaspar R., Castelo Branco C., Macedo G.* Liver and COVID-19: From care of patients with liver diseases to liver injury. *World J Hepatol*. 2021;13(10):1367–77. DOI: 10.4254/wjh.v13.i10.1367
8. *Vairappan B., Wright G., Corrigal D., Ts R.* Liver injury in COVID-19: A direct hit or collateral damage? *Infect Disord Drug Targets*. 2022;22(1):e130921196417. DOI: 10.2174/1871526521666210913110500
9. *Su Y.J., Chang C.W., Chen M.J., Lai Y.C.* Impact of COVID-19 on liver. *World J Clin Cases*. 2021;9(27):7998–8007. DOI: 10.12998/wjcc.v9.i27.7998
10. *Mikolasevic I., Bozic D., Pavić T., Ruzic A., Hauser G., Radic M., et al.* Liver disease in the era of COVID-19: Is the worst yet to come? *World J Gastroenterol*. 2021;27(36):6039–52. DOI: 10.3748/wjg.v27.i36.6039
11. *Gracia-Ramos A.E., Jaquez-Quintana J.O., Contreras-Omaña R., Auron M.* Liver dysfunction and SARS-CoV-2 infection. *World J Gastroenterol*. 2021;27(26):3951–70. DOI: 10.3748/wjg.v27.i26.3951
12. *Del Zompo F., De Siena M., Ianiro G., Gasbarrini A., Pompili M., Ponziani F.R.* Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: Systematic review with meta-analysis. *Eur Rev Med Pharmacol Sci*. 2020;24(24):13072–88. DOI: 10.26355/eurrev_202012_24215
13. *Limon-De La Rosa N., Cervantes-Alvarez E., Navarro-Alvarez N.* Increased hepatic expression of SARS-CoV-2 entry points and proinflammatory cytokines in cirrhosis. *Clin Gastroenterol Hepatol*. 2022;20(1):239–41.e3. DOI: 10.1016/j.cgh.2021.08.053
14. *Seow J.J.W., Pai R., Mishra A., Shepherdson E., Lim T.K.H., Goh B.K.P.* Single-cell RNA-seq reveals angiotensin-converting enzyme 2 and transmembrane serine protease 2 expression in TROP2+ liver progenitor cells: Implications in Coronavirus Disease 2019-associated liver dysfunction. *Front Med (Lausanne)*. 2021;8:603374. DOI: 10.3389/fmed.2021.603374
15. *Kim D., Bonham C.A., Konyn P., Cholankeril G., Ahmed A.* Mortality trends in chronic liver disease and cirrhosis in the United States, before and during COVID-19 pandemic. *Clin Gastroenterol Hepatol*. 2021;19(12):2664–6. DOI: 10.1016/j.cgh.2021.07.009
16. *Bajaj J.S., Garcia-Tsao G., Biggins S.W., Kamath P.S., Wong F., McGeorge S., et al.* Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: Multicentre matched cohort. *Gut*. 2021;70(3):531–6. DOI: 10.1136/gutjnl-2020-322118
17. *Ioannou G.N., Liang P.S., Locke E., Green P., Berry K., O'Hare A.M., et al.* Cirrhosis and severe acute respiratory syndrome coronavirus 2 infection in US veterans: Risk of infection, hospitalization, ventilation, and mortality. *Hepatology*. 2021;74(1):322–35. DOI: 10.1002/hep.31649
18. *European Association for the Study of the Liver.* EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69(2):406–60. DOI: 10.1016/j.jhep.2018.03.024
19. *Yoshiji H., Nagoshi S., Akahane T., Asaoka Y., Ueno Y., Ogawa K., et al.* Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. *J Gastroenterol*. 2021;56(7):593–619. DOI: 10.1007/s00535-021-01788-x
20. *Zekri-Nechar K., Zamorano-León J.J., Segura-Fragoso A., Alcaide J.R., Reche C., Andrés-Castillo A., et al.* Albumin binds COVID-19 spike 1 subunit and predicts in-hospital survival of infected patients-possible alteration by glucose. *J Clin Med*. 2022;11(3):587. DOI: 10.3390/jcm11030587
21. *Rabbani G., Ahn S.N.* Review: Roles of human serum albumin in prediction, diagnoses and treatment of COVID-19. *Int J Biol Macromol*. 2021;193 (Pt A):948–55. DOI: 10.1016/j.ijbiomac.2021.10.095
22. *Hadid T., Kafri Z., Al-Katib A.* Coagulation and anticoagulation in COVID-19. *Blood Rev*. 2021;47:100761. DOI: 10.1016/j.blre.2020.100761
23. *Visco V., Vitale C., Rispoli A., Izzo C., Virtuoso N., Ferruzzi G.J., et al.* Post-COVID-19 syndrome: Involvement and interactions between respiratory, cardiovascular and nervous systems. *J Clin Med*. 2022;11(3):524. DOI: 10.3390/jcm11030524

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