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ХРОНИЧЕСКИЕ ЗАБОЛЕВАНИЯ ПЕЧЕНИ И COVID-19: БАЗА ДАННЫХ МНОГОПРОФИЛЬНОГО СТАЦИОНАРА

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Chronic Liver Diseases and COVID-19: Database of General Hospital

Резюме

Пациенты с хроническими заболеваниями печени (ХЗП) относятся к группе высокого риска инфицирования и тяжелого течения COVID-19 (Corona Virus Disease, коронавирусная инфекция 2019 года). **Цель**: создание базы данных (БД) пациентов с ХЗП, включающей анализ частоты выявления маркеров SARS-CoV-2, причин госпитализации, оценку 30-дневной летальности при наличии маркеров COVID-19 и в отсутствии инфекции. **Материалы и методы.** Проведено одномоментное ретроспективное обсервационное сравнительное исследование, результатом которого стало создание БД. Проанализированы 693 электронные медицинские карты пациентов с ХЗП различной этиологии, госпитализированных в терапевтические отделения ГКБ им. В.М. Буянова ДЗМ за период 01.04.2020–01.10.2021 гг. Анализ включал следующие параметры: пол, возраст, этиологию заболевания, причины госпитализации, наличие рибонуклеиновой кислоты (РНК) SARS-CoV-2 в мазке слизистой носа и ротоглотки, антител к SARS-CoV-2 иммуноглобулинов классов M, G (IgM, IgG), исход заболевания (30-дневная летальность). **Результаты.** Маркеры перенесенной новой коронавирусной инфекции (IgG) обнаружены у 268 (38,7 %), РНК SARS-CoV-2 выявлена у 67 (9,7 %). При анализе причин госпитализации установлено преобладание отечно-асцитического синдрома (64,5 %), нарастание печеночной энцефалопатии (31,6 %) и увеличение количества случаев тромбоза воротной вены (ТВВ) (8,9 %). При оценке 30-дневной летальности выявлены достоверные различия у пациентов с алкогольной болезнью печени (АБП), хроническими вирусными гепатитами (ХВГ) при наличии маркеров COVID-19 и в случаях их отсутствия. **Заключение.** Маркеры SARS-CoV-2 обнаружены у 335 (48,3 %) пациентов с ХЗП. Основная причина госпитализации — появление/нарастание отечно-асцитического синдрома, в том числе вследствие ТВВ. 30-дневная летальность в постковидном периоде достоверно выше при АБП в сравнении с пациентами без перенесенного COVID-19 (218 (34,9 %) и 300 (25,3 %), соответственно, p = 0,0246).

Ключевые слова: *COVID-19, хронические заболевания печени, база данных, летальность, алкогольная болезнь печени*

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Конфликт интересов
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Abstract
Patients with chronic liver diseases (CLD) are at high risk of infection and severe COVID-19 (Corona Virus Disease). **Aim:** to create a database of patients with CLD, including an analysis of the frequency of detection of SARS-CoV-2 markers, the causes of hospitalization, an assessment of 30-day mortality in the presence of COVID-19 markers and in the absence of infection. **Materials and methods.** A one-time retrospective observational comparative study was conducted, the result of which was the creation of a database. 693 electronic case hystories of patients with CLD of various etiologies hospitalized in the V.M. Buyanov State Clinical Hospital for the period 01.04.2020–01.10.2021 were analyzed. The analysis included the following parameters: gender, age, etiology of the disease, reasons for hospitalization, the presence of ribonucleic acid (RNA) SARS-CoV-2 in a smear of the nasal mucosa and oropharynx, antibodies to SARS-CoV-2 immunoglobulins of classes M, G (IgM, IgG), the outcome of the disease (30-day mortality). **Results.** Markers of past new coronavirus infection (IgG) were detected in 268 (38,7 %), SARS-CoV-2 RNA was detected in 67 (9,7 %). The analysis of the causes of hospitalization revealed the predominance of edematous ascitic syndrome (64,5 %), an increase in hepatic encephalopathy (31,6 %) and an increase in the number of cases of portal vein thrombosis (PVT) (8,9 %). When assessing the 30-day mortality, significant differences were found in patients with Alcohol-related liver disease (ARLD), chronic viral hepatitis in the presence of COVID-19 markers and in cases of their absence. **Conclusion**. SARS-CoV-2 markers were found in 335 (48,3 %) of patients with CLD. The main reason for hospitalization is the appearance /increase of edematous ascitic syndrome, including due to PVT. 30-day mortality in the postcovid period is significantly higher (p = 0,0246) in ARLD compared with patients without COVID-19 (218 (34,9 %) и 300 (25,3 %), respectively, p = 0,0246).

Key word: *COVID-19, chronic liver disease, database, mortality, alcoholic liver disease*

Conflict of interests
The authors declare no conflict of interests

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ACE2 — angiotensin-converting enzyme 2; AILDs — autoimmune liver diseases; ALD — alcoholic liver disease; CD147 — cluster of differentiation 147; CHB — chronic hepatitis B; CHC — chronic hepatitis C; CLDs — chronic liver diseases; COVID-19 — coronavirus disease 2019; CVH — chronic viral hepatitis; DB — database; DILI — drug-induced liver injury; EV — esophageal varices; GIB — gastrointestinal bleeding; HA — hepatitis A; HCC — hepatocellular carcinoma; LC — liver cirrhosis; MELD — model for end-stage liver disease; n — normal; NAFLD — non-alcoholic fatty liver disease; PVT — portal vein thrombosis; SARS-CoV-2 — severe acute respiratory syndrome coronavirus

Relevance

COVID-19 remains relevant due to its high prevalence and great importance for public health all around the world.

SARS-CoV-2 can infect various organs and systems of the body, including gastrointestinal tract and liver (epithelial cells, hepatocytes, cholangiocytes). SARS-CoV-2 spike protein targets are angiotensin-converting enzyme 2 (ACE2) and cluster of differentiation 147 (CD147). ACE2 is a widespread membrane-bound monocarboxypeptidase involved in the processing of many peptides, including angiotensin II. CD147 is a transmembrane glycoprotein. In the pathogenesis of SARS-CoV-2 infection, ACE2 and CD147 proteins function as “receptors” for the penetration of SARS-CoV-2 into the host cell [1, 2].

Chronic liver diseases (CLDs) are characterized by increased expression of hepatocyte ACE2, thereby potentially increasing the rate of SARS-CoV-2 entry into hepatocytes. S. Casey et al., 2020 [3], found a significant increase in ACE2 levels in the cases of liver cirrhosis (LC). Thus, the direct mechanism of liver damage in COVID-19 and CLDs is associated with the presence of a SARS-CoV-2 receptor in organ cells. This confirms virus detection in hepatocytes obtained during autopsy of patients with COVID-19 and LC [4].

In addition to the direct cytotoxic effect of the virus on cholangiocytes and hepatocytes, other mechanisms of liver damage are also distinguished: Immune-mediated damage as a result of a systemic inflammatory response; drug-induced damage (hepatotoxic effect of antibacterial and antiviral drugs, non-steroidal anti-inflammatory

Table 1. Characteristics of included patients

Etiology of CLD	Number of patients, n	Пол/Gender		Average age (years)
		Men (n)	Women (n)	
Alcoholic liver disease	420	240	180	50,4
Non-alcoholic fatty liver disease	24	7	17	56,4
Chronic hepatitis B, chronic hepatitis C	40	19	21	58,7
Autoimmune liver disease	24	3	21	54,3
Drug induced liver injury	19	9	10	57,3
Alcoholic liver disease + / Non-alcoholic fatty liver disease	65	31	34	56,4
Alcoholic liver disease + chronic hepatitis B, chronic hepatitis C	92	68	24	49,4
Rare diseases	9	3	6	48,4

Note: Rare diseases: cirrhosis of liver unspecified, combination of autoimmune hepatitis with HBV, HCV, Wilson-Konovalov's disease, glycogen storage disease, Crigler-Najjer syndrome 2

drugs, glucocorticoids, etc.); ischemia as a result of microangiopathy, microthrombosis with underlying endothelial dysfunction [5].

The multicenter cohort study using open online survey resulted in the development of the international registry of patients with CLDs and confirmed SARS-CoV-2 infection (n = 220,727). Patients with CLDs were found to have an increased risk of severe COVID-19 and poor outcome. When assessing 30-day mortality, the authors found that patients infected with SARS-CoV-2 had a 2.38-fold higher risk of adverse outcome than patients with LC with no COVID-19 [6].

Objective of our study: the development of a database (DB) of patients with CLDs, including the analysis of the frequency of SARS-CoV-2 markers detection, reasons for hospitalization, assessment of 30-day mortality depending on gender, age and etiology of liver disease.

Compliance with ethical standards: the study protocol No. 213 dated December 13, 2021, was approved by the local ethics committee of N. N. Pirogov Russian National Research Medical University (N. N. Pirogov Medical University of the Ministry of Health of Russia).

Materials and METHODS

To develop a DB, 693 electronic medical records of patients with CLDs of various etiology were analyzed; these patients were hospitalized into N. N. Buyanov City Clinical Hospital of Moscow Health Department (a multidisciplinary hospital that is not a COVID hospital) for the period 04/01/2020–10/01/2021. The range of liver diseases included the following: alcoholic liver disease (ALD), chronic viral hepatitis (CVH), non-alcoholic fatty liver disease (NAFLD), drug-induced liver disease (DILI), autoimmune liver diseases (AILDs), accumulation diseases (Wilson — Konovalov, glycogen liver disease). The DB also included 1 patient after liver transplantation for LC as an outcome of autoimmune hepatitis (AIH). Patients vaccinated against COVID-19 were not included in this study. The following parameters were evaluated: gender, age, etiology of the disease, reasons for hospitalization, presence of SARS-CoV-2 RNA in nasal and oropharyngeal mucosal smear and antibodies to SARS-CoV-2 immunoglobulins of classes M, G (IgM, IgG), disease outcome (30-day mortality).

Statistical processing was carried out using Statistica 13.0 and Python3 software. Nonparametric statistical methods were used: for the analysis of qualitative features — $\chi 2$ test and Fisher's exact test; for comparing two independent values — the Mann — Whitney test, as well as the Spearman's correlation coefficient (Spearman's r).

Results

Comparing the data on the detection of new cases of COVID-19 in Moscow and the detection of SARS-CoV-2 RNA in patients with CLDs in hospital for the same period of time revealed moderate positive correlation (Spearman's r — 0.56) (Figure 1).

The markers of the past novel coronavirus infection were found in 268 patients (38.7 %); SARS-CoV-2 RNA was detected on days 1–7 of hospitalization in 67 (9.7 %) patients. The etiology of CLDs in patients included in the sample (n = 335) is presented in Figure 2.

Detection rate of SARS-CoV-2 RNA, past infection markers (IgG), as well as 30-day mortality in these groups of patients with CLDs of various etiologies is presented in Table 2.

The group of patients with ALD and markers of past infection (SARS-CoV-2 IgG) was the largest one (218/270). In this group, alcoholic hepatitis (AH) was diagnosed in 23 (10.6 %) cases, severe AH with cirrhosis — in 53 cases (24.3 %), and decompensated LC — in 142 cases (65.1 %). The main complications of ABP are shown in Figure 3.

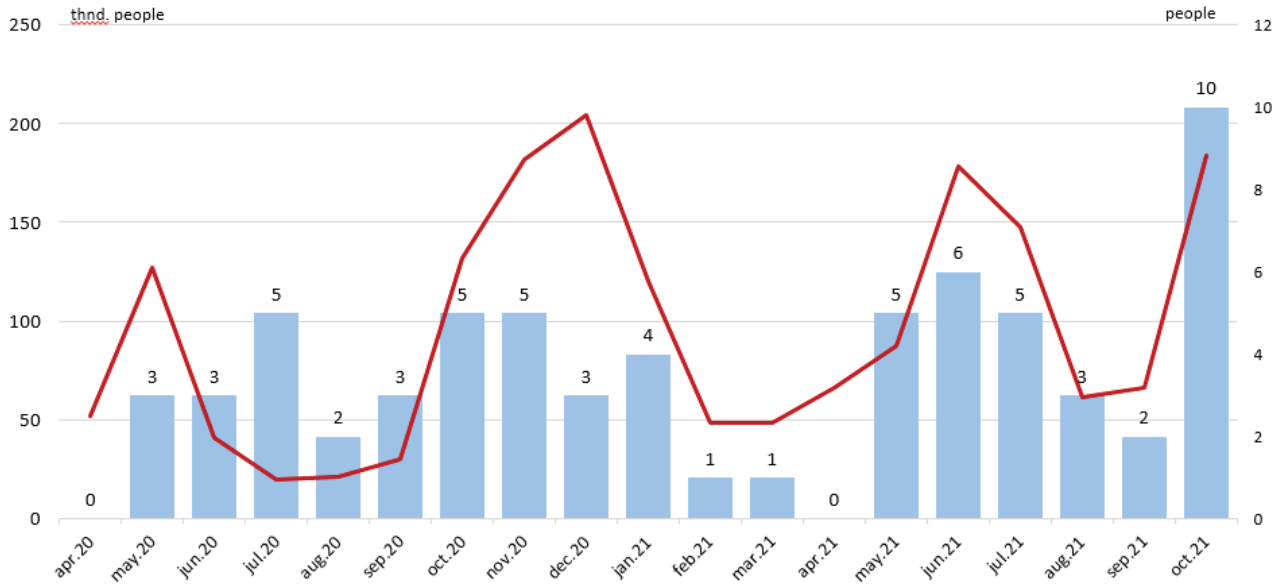

Figure 1. *Number of new cases COVID-19 in Moscow, thnd people, and number of patients with CLD + RNA SARS-CoV-2*
Columns (light blue) — number of patients with RNA SARS-CoV-2
Red line — number of new cases COVID-19 in Moscow, thnd people [7]

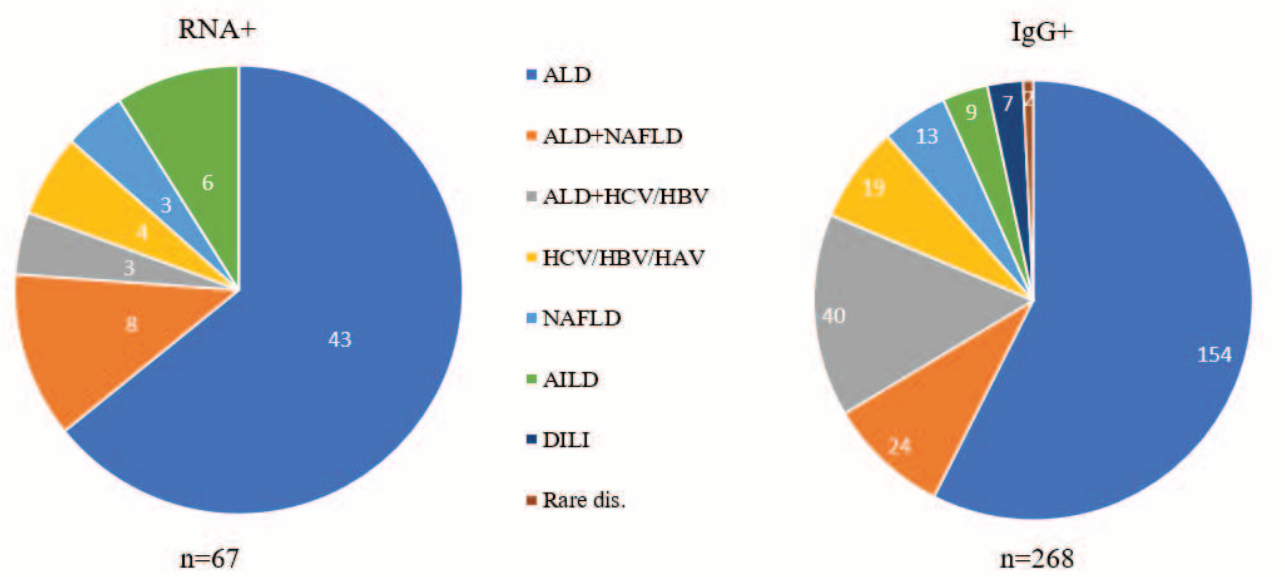

Figure 2. *Etiological structure of chronic liver diseases (CLD) for patients with COVID-19*
Note: Rare diseases: cirrhosis of liver unspecified, combination of autoimmune hepatitis with HBV, HCV; ALD — alcoholic liver disease; NAFLD — non-alcoholic fatty liver disease; HBV — chronic hepatitis B; HCV — chronic hepatitis C; AILD — autoimmune liver disease; DILI — drug induced liver injury

Table 2. *COVID-19 markers, 30-day mortality in CLD of various etiologies*

Etiology of CLD	n	Patients with CLD without markers COVID-19		RNA SARS-CoV-2			IgG SARS-CoV-2		
		n	30-day mortality (%)	n	30-day mortality (%)	P1	n	30-day mortality (%)	P2
ALD	570	300/570	25,3	52/570	59,6	<0,0001	218/570	34,9	0,025
NAFLD	40	18/40	0	3/40	0	1,0	19/40	5	1,0
HBV, HCV	132	66/132	7,6	7/132	42,9	0,0021	59/132	8,5	0,818
AILD	24	9/24	11,1	6/24	0	1,0	9/24	22,2	1,0

Note: P1 — difference between CLD patients without COVID-19 markers and those with SARS-CoV-2 RNA; P2 — difference between CLD patients without COVID-19 markers and those with SARS-CoV-2 IgG

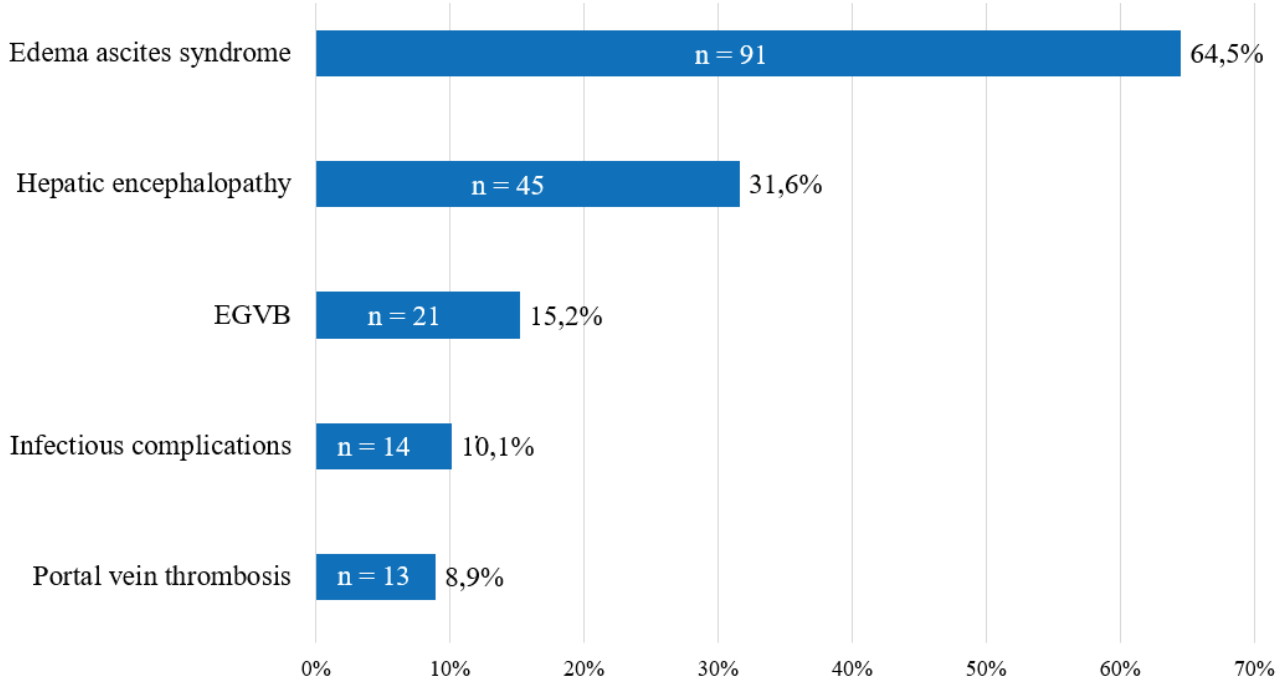

Figure 3. *Complications of cirrhosis in ALD*
Note: EGVB — esophagogastric variceal bleeding

The assessment of 30-day mortality revealed significant differences in patients with ALD and CVH in the presence of COVID-19 markers and in cases of their absence. 30-day mortality in patients with NAFLD, AILDs with the presence of SARS-CoV-2 RNA/IgG was also higher (Table 2), however, no significant differences were found due to their small number.

In the patients of the analyzed group, 11 (1.6 %) cases of hepatocellular carcinoma (HCC) were found: 8 (72.7 %) cases in the outcome of CVH; 2 (18.1 %) — with ABP; 1 (9.1 %) — with a combination of ABP + NAFLD.

Results and Discussion

The results presented demonstrate the differences in the course and outcomes of CLDs with underlying COVID-19.

When analyzing the causes of hospitalization, special attention should be paid to the prevailing edematous-ascitic syndrome, as well as to increased number of the cases of portal vein thrombosis (PVT).

Thromboses of various locations are one of the frequent complications of novel coronavirus infection, both during acute infection phase and in the post-COVID period. According to a meta-analysis, the incidence of thrombotic complications in COVID-19 ranges from 7 to 40 % [8]. The most common locations of thrombosis are deep veins of lower legs that in several cases can be complicated with the development of pulmonary embolism.

According to the American Association for the Study of Liver Diseases [9], the incidence of PVT among patients with LC with no COVID-19 is 0.6–26.0 % depending on its Child-Pugh severity class. However, the incidence of PVT in the post-COVID period is not assessed yet. According to our study, it was 8.9 %.

The second most common reason for hospitalization was the onset/exacerbation of hepatic encephalopathy. There are published data on the correlation of hyperammonemia with the severity of COVID-19 and inflammatory markers (C-reactive protein, leukocytes, ferritin); it can be used as a predictor of the severity of new coronavirus infection [10].

The patients with CLDs, especially at the stage of cirrhosis, are more susceptible to infections, including COVID-19, due to their systemic immunodeficiency. When comparing the data obtained regarding the frequency of detecting COVID-19 markers in hospital patients and in the general population of Moscow as of October 1, 2021 [7], the higher frequency was established in hospital patients infected with CLDs (38.7 % vs 12.9 %, respectively). It should be emphasized that patients with different chronic diseases belong to the risk group due to frequent hospitalizations, as well as to numerous contacts with possible sources of infection (other patients, medical staff, pharmacists) in outpatient healthcare system.

According to the results obtained by T. Marjot et al., 2021 [11], the patients with LC had the increased risk of adverse outcomes when infected with SARS-CoV-2. Mortality in the group of LC patients with COVID-19

differed depending on LC stage according to the Child-Pugh scale: it was 19 % in class A cirrhosis (n = 33), 35 % in class B (n = 44), 51 % in class C (n = 46). In this study, the main cause of death was COVID-19-associated lung injury (71 %, n = 87), however, 19 % (n = 23) of deaths were due to liver cirrhosis-related complications. The analysis of these cases also demonstrated a significant impact of the coronavirus infection on the course of CLDs. The incidence of acute liver decompensation in this cohort was 46 % (n = 179).

The DB presented demonstrates a high incidence of adverse outcomes in patients with CLDs with novel coronavirus infection, as well as higher mortality in the post-COVID period. This dependence can be reliably traced in the group of patients with ALD.

There are published data on the immunomodulatory effect of the long-term consumption of alcohol in high doses that, when an individual is infected with SARS-CoV-2, can contribute to the development of other infections, as well as of the acute respiratory distress syndrome [12]. When comparing the outcomes in patients with alcoholic LC and in patients with LC of mixed origin (alcoholic + CHC/CHB), mortality in the post-COVID period was higher in the ALD group (Figure 4) and amounted to (42.2 % and 5.0 %, respectively).

In addition, the analysis of data from the international registry [11] established a higher incidence of adverse outcomes in ALD during COVID-19 in comparison with CLDs of other etiologies.

Among the patients with CHC and CHB after novel coronavirus infection, the 30-day mortality rate was higher (8.5 %) than in patients with viral CLDs with no coronavirus infection (7.6 %), however, it was significantly lower than in the patients with ALD (34.9 %). However, there were no significant differences in this parameter in patients with CHC, apparently due to the small size of the sample. Meanwhile, A. A. Butt et al., 2021 [13], obtained similar results for CHC with and without COVID-19; significant differences in 30-day mortality were revealed only at the cirrhosis stage.

According to A. A. Saryglar et al., 2022 [14], the patients with CHB (n = 46, including 16 patients at cirrhosis stage) who received antiviral therapy with entecavir demonstrated a mild course of novel coronavirus infection in most cases (87 %). No fatal outcomes were registered; this fact is also consistent with the data obtained by J. Zhu et al., 2021 [15]. However, the mechanism of the possible protective effect of HBV AVT on the signs of COVID-19 was not clarified.

However, considering the specific features of COVID-19 course in elderly people vaccinated against hepatitis A (HA) that was characterized by extremely low mortality (1.8 %), it was suggested that immunity against HA can provide protection against COVID-19 [16]. The presented literature data and our own observations revealed "specific" interviral interactions in CVH and GA [17] that require further investigation.

The mortality in the group of patients with AILDs in the post-COVID period did not differ from this parameter in patients with no COVID-19 markers; this fact was also demonstrated in the study by T. Marjot et al., 2021 [11].

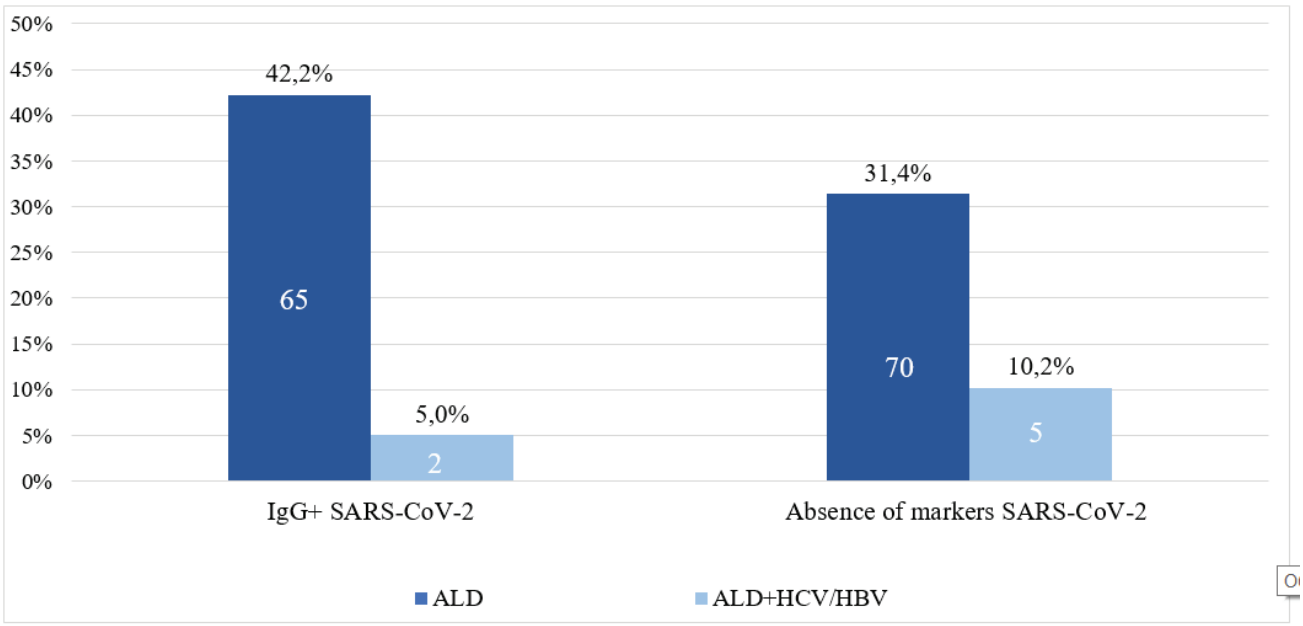

Figure 4. *Mortality of ALD and ALD+HBV/HCV*
Note: ALD — alcoholic liver disease; HBV — chronic hepatitis B; HCV — chronic hepatitis C

We have diagnosed 11 cases of HCC. There are reports of the increased mortality in this group of patients [18]. Meanwhile, it is not excluded that the increased number of adverse outcomes due to HCC may be associated with a delay in the start of anticancer treatment in the context of the redistribution of healthcare system resources during the pandemic. However, the question of the oncogenic effect of SARS-CoV-2 and the development of malignant tumors remains open.

The presented DB and the analysis of several published studies emphasize that CLDs patients are at risk for severe COVID-19 that requires active preventive measures, including mandatory vaccination. Thus, according to J. Ge et al., 2022 [19], vaccination reduced 30-day mortality in patients with LC and COVID-19 (n = 8,218) by 66 %. A. Moon et al., 2022 [20], also mentioned a significant decrease in mortality in vaccinated patients with CLDs, as well as the fact that such patients needed no mechanical ventilation.

Conclusion

Direct cytotoxic effect of SARS-CoV-2 on cholangiocytes and hepatocytes, as well as other mechanisms of negative effect on the course of CLDs, were established. Significant increase in the number of thrombotic complications, including PVT, is observed. The mortality in the patients with CLDs and SARS-CoV-2 RNA or IgG is significantly higher, especially in cases of ALD (59.6 % and 34.9 %, respectively, $p < 0.0001$ and $p = 0.0246$).

There is no idea about the interaction and mutual influence of SARS-CoV-2 and other hepatotropic viruses, as well as about the mechanisms that contribute to the development of autoimmune and oncological diseases. The repeated cases of infection do not exclude the possibility of the long-term persistence of SARS-CoV-2 in human body. It is necessary to continue the study of epidemiological, clinical and pathogenetic specific features of CLDs in patients co-infected with hepatitis viruses and SARS-CoV-2, as well as to perform the follow-up for this cohort in the post-COVID period.

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All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

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