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COVID-19 in Patients with Primary Biliary Cholangitis

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The aim of the study. To analyze the course of COVID-19 infection in patients with primary biliary cholangitis (PBC).
Materials and methods. In a single-center retrospective study, survey and analysis of medical records of 144 patients with PBC was carried out.
Results. All patients (n = 144) received basic therapy with ursodeoxycholic acid (UDCA), 5 of them received fibrates as well. Response to therapy (EASL criteria) was obtained in 30 people.
Between March 2020 and March 2021, 50 patients (34.7 %) suffered COVID-19, with mean age of 58.8 ± 10.7 years, 16 of which were diagnosed with liver cirrhosis. Mild COVID-19 was observed in 34 (68 %) people, moderate course — in 14 (28 %), severe — in 2 (4 %), cases of extremely severe course were not recorded. 12 patients were hospitalized, 8 of which received oxygen therapy due to a decrease in SpO_2 < 94 %, there was no need for the use of other methods of oxygen therapy in any case. The duration of hospitalization was 11.4 ± 5.7 days. There was a higher initial activity of serum alkaline phosphatase (1.8 ± 1.0 versus 1.7 ± 1.4 times of the upper limit of normal, M ± SD, p = 0.04) in patients with COVID-19 infection and lack of UDCA therapy effectiveness was more prominent (40 % vs. 19.1 % of cases, p = 0.04) compared with patients who did not have COVID-19. There were no significant differences in characteristics of the course of PBC (stage, response to therapy) and age in correlation with severity of the course of COVID-19. Among hospitalized patients and those in need of oxygen support, large proportion were older patients (58.3 % and 62.5 %, respectively) and patients with concomitant diseases (62.5 % and 75 %, respectively). Patients who hadn`t previously responded to UDCA therapy were more likely to require oxygen support compared to patients responding to basic therapy (p < 0.01).
Conclusion. PBC is not a risk factor for severe COVID-19. A protective effect of UDCA in SARS-CoV-2 infection is possible, which requires further investigation.
Keywords: primary biliary cholangitis, COVID-19, coronavirus infection, liver disease, ursodeoxycholic acid
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COVID-19 у пациентов с первичным билиарным холангитом

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Цель исследования. Проанализировать течение COVID-19 у пациентов с первичным билиарным холангитом (ПБХ).
Материалы и методы. В одноцентровом ретроспективном исследовании проведен опрос и анализ медицинской документации 144 пациентов с ПБХ.
Результаты. Все пациенты (n = 144) получали базисную терапию урсодезоксихолевой кислотой (УДХК), 5 из них – также фибраты. Ответ на терапию (критерии EASL) достигнут у 30 человек.
В период с марта 2020 по март 2021 г. COVID-19 перенесли 50 пациентов (34,7 %), средний возраст составил 58,8 ± 10,7 года, из них цирроз печени определен у 16 человек. Легкое течение COVID-19 наблюдалось у 34 (68 %) человек, среднетяжелое течение — у 14 (28 %), тяжелое — у 2-х (4 %), случаев крайне тяжелого течения не зафиксировано. Госпитализированы 12 пациентов, из них 8 получали кислородотерапию в связи со снижением SpO_2 < 94 %, потребности в применении других методов оксигенотерапии не было ни в одном случае. Длительность госпитализации составила в среднем 11,4 ± 5,7 суток. При COVID-19 наблюдалась более высокая исходная активность сывороточной щелочной фосфатазы (1,8 ± 1,0 против 1,7 ± 1,4 кратности

верхнему пределу нормы, M ± SD, $p = 0,04$) и чаще встречалась неэффективность терапии УДХК (40 % против 19,1 % случаев, $p = 0,04$) в сравнении с пациентами, не болевшими COVID-19. Не получено достоверных различий в характеристиках течения ПБХ (стадии, ответе на терапию) и по возрасту в зависимости от тяжести течения COVID-19. Среди госпитализированных пациентов и нуждающихся в кислородной поддержке большую долю составили пациенты старшего возраста (58,3 и 62,5 % соответственно) и с наличием сопутствующих заболеваний (62,5 и 75 % соответственно). Пациенты, ранее не ответившие на терапию УДХК, чаще нуждались в кислородной поддержке в сравнении с пациентами, отвечающими на базисную терапию ($p < 0,01$).
Выводы. ПБХ не является фактором риска тяжелого течения COVID-19. Возможен протективный эффект приема УДХК при инфекции SARS-CoV-2, что требует дальнейшего изучения.
Ключевые слова: первичный билиарный холангит, COVID-19, новая коронавирусная инфекция, заболевания печени, урсодезоксихолевая кислота
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Introduction

The novel SARS-CoV-2 coronavirus infection (COVID-19) can be described as a multisystem disease that can cause acute liver damage or decompensation of pre-existing liver disease. The mechanism of liver damage in COVID-19 is multifactorial. SARS-CoV-2 can have a direct damaging effect by penetration the liver through cholangiocytes or via intestinal translocation. Indirect effects of the virus are mediated through systemic inflammation with dysregulation of the immune response, hypoxia of mixed genesis, ischemic damage as a consequence of coagulopathy or the development of endothelitis, right ventricular failure, worsening of the course of pre-existing liver diseases, and in some cases, drug-induced liver damage [1].

Patients with chronic liver disease, cirrhosis, and hepatocellular carcinoma have a high risk of severe COVID-19 and death [2–4].

The results of an evaluation of large international multicenter patient registries with chronic liver disease and COVID-19 showed that mortality due to COVID-19 is associated with the initial severity of liver disease and the presence of alcoholic and liver disease. Decompensated liver cirrhosis is a particularly high-risk group: mortality exceeds 30 % [5].

There are only limited data on the course of COVID-19 in autoimmune liver disease (AILD) in the global literature. An international study combining data from 3 large-scale registries analyzed a large cohort of patients with AILD and COVID-19 between March and October 2020: 70 patients with autoimmune hepatitis (AIH), 19 with primary biliary cholangitis (PBC), 19 with primary sclerosing cholangitis (PSC), and 16 with variant syndromes. The authors found no difference in the incidence of serious adverse outcomes of SARS-CoV-2 infection between patients with AILD and other liver diseases. However, patients with AIH were more likely to be in need of hospitalization than patients without liver disease, although there was no increased risk of transfer to the intensive care unit or death. In the meantime, independent mortality-related risk factors were found to be age and initial severity of liver disease, but not immunosuppressive therapy [6].

In a multinational European COVID-19 study published in June 2021 [7], patients with AILD showed a low incidence of COVID-19 (2.2 %), which is comparable to the general population. Between cases with COVID-19 ($n = 39$) and without COVID-19 ($n = 1730$), there were no differences in terms of age, sex, smoking, type of AILD, status after liver transplantation, the presence of concomitant diseases or liver cirrhosis. These results suggest, that patients with AILD do not appear to be at increased risk of COVID-19 contamination.

Aim of the study: To analyze the course of COVID-19 in patients with primary biliary cholangitis (PBC).

Materials and methods

As part of the retrospective study, a survey and analysis of medical documentation in the period from March 2020 to March 2021 of patients with PBC under observation at the Scientific, Clinical and Educational Center for Gastroenterology and Hepatology of St. Petersburg University was conducted. The cohort included 144 people, all women, 12 (8.3 %) of the them had PBC with signs of autoimmune hepatitis. During the observation period, 50 patients with PBC (34.7 %) had coronavirus infection. The main characteristics of patients, their course of PBC and basic therapy are shown in Table 1.

Results

Mild COVID-19 was observed in 34 (68 %) people, moderate course — in 14 (28 %), severe — in 2 (4 %), cases of extremely severe course were not recorded. Lung damage according to computed tomography (CT) was detected in 14 patients (among them, 8 had less than 25% lung volume involvement,

Table 1. Characteristics of patients and the course of PBC

Characteristics		PBC (n = 144)
Aged (y., $M \pm SD$)		58.8 ± 10.7
Comorbidities, n (%)		62 (43.1)
Early/late stages PBC*, n (%)		75 (52.1)/ 51 (35.4)
Cirrhosis, n (%)		45 (31.2)
– Child-Pugh:	A, n (%)	28 (62.2)
	B, n (%)	14 (31.1)
	C, n (%)	3 (6.7)
– including a history of decompensation, n (%)		13 (28.9)
"Responders" to UDCA (EASL), n (%)		73 (50.7)
Basic therapy:		
– UDCA		106 (73.6)
– UDCA + fibrate		8 (5.5)
– UDCA + GCS (systemic and topical)		12 (8.3)
– UDCA + GCS + AZA		3 (2.1)

Note: UDCA — ursodeoxycholic acid, GCS — glucocorticosteroids, AZA — azathioprine EASL — European Association for the Study of the Liver; * According to EASL [8]: The early stage of PBC is defined as mild fibrosis or its absence according to morphological research, liver stiffness according to transient elastography of 9.6 kPa, serum albumin and bilirubin levels within reference values. The late stage of PBC is defined as the presence of bridging fibrosis or cirrhosis according to morphological studies, liver stiffness according to transient elastography of 9.6 kPa, a decrease in serum albumin levels and / or an increase in serum bilirubin levels.

and the remaining 6 had 25-50% of lung volume involved). Symptomatic treatment was carried out in 26 patients, in 9 cases anticoagulants were additionally prescribed, in 2 — hydroxychloroquine. Anti-inflammatory therapy with glucocorticosteroids was conducted in 4 cases, and Janus-kinase inhibitor therapy was required in 1 case. Antibacterial therapy was received by 17 patients.

Eight patients (out of 12 hospitalized) received respiratory support due to a decrease in SpO_2 < 94 % by oxygen insufflation through nasal catheters. There was no need in invasive methods of respiratory support in any case. The duration of hospitalization was from 5 to 18 days (an average of 11.4 ± 5.7 days). In 1 case, a 72-year-old patient with cirrhosis class C according to Child-Pugh hospitalized due to deterioration of the underlying disease, intrahospital new coronavirus infection occurred, that led to fatal outcome from terminal liver failure, which was confirmed by the pathology examination. Notably, the infection proceeded in a mild form without significant damage to the lungs and respiratory failure.

Between patients with PBC who have had COVID-19 and patients who didn't have COVID-19, there are no differences in age, stage of PBC, the presence of comorbidities and liver cirrhosis, as well as ongoing basic therapy with PBC (Table 2). However, patients with PBC and COVID-19 before SARS-CoV-2 infection are more likely to have higher serum levels of alkaline phosphate (ALP) and more often face ineffectiveness of basis therapy with ursodeoxycholic acid (UDCA).

The prevalence of individual comorbidities varied significantly in patients with different COVID-19 disease course. Thus, extrahepatic autoimmune diseases (9 — autoimmune thyroiditis, 1 — systemic scleroderma, 1 — rheumatoid arthritis, 3 — vitiligo) with a mild course of a new coronavirus infection were detected in 11 patients (32.35 %), while with moderate severity — only in 2 (14.29 %), and in severe course of the disease they did not occur. On the contrary, diabetes mellitus was more often observed in patients with moderate course of COVID-19 2 (14.28 %) cases versus 1 (2.94 %) with mild disease). Chronic lung disease and hypertension in mild and moderate COVID-19 were detected with comparable frequency: in 2 (5.88 %) and 1 (7.14 %), as well as 8 (23.53 %) and 4 (28.57 %), respectively. Severe course was observed in 1 patient with arterial hypertension and 1 patient without concomitant pathology.

We found serum ALP levels to be lower within 3 to 4 months after COVID-19 compared to the levels before and during SARS-CoV-2 infection (Fig.). There was no correlation between serum ALP activity and drugs used to treat SARS-CoV-2 infection.

Among hospitalized patients (n = 12) and patients in need of oxygen support (n = 8), a large

Table 2. Initial course of PBC and basic therapy in post- and non-COVID-19 patients

Indicators	Non-COVID-19 (n = 94)	COVID-19 (n = 50)	p
Aged (y., $M \pm SD$)	57.8 ± 10.3	58.3 ± 11.1	0.84
Comorbidities, n (%)	35 (37.2)	25 (50)	0.12
Early/late stages PBC, n (%)	48 (51.1) / 32 (34)	27 (54) / 19 (38)	0.89
Cirrhosis, n (%)	29 (30.9)	16 (32)	0.18
– including a history of decompensation, n (%)	9 (31)	4 (25)	0.67
Non-responders to UDCA (EASL), n (%)	18 (19.1)	20 (40)	0.04
Basic therapy:			0.13
– UDCA, n (%)	69 (73.4)	35 (70)	
– UDCA + fibrate, n (%)	3 (3.2)	5 (10)	
– UDCA + GCS, n (%)	6 (6.4)	5 (10)	
– UDHC + AZA, n (%)	1 (1.1)	2 (4)	
The level of AP, the multiplicity of the upper limit of the norm, $M \pm SD$	1.7 ± 1.4	1.8 ± 1.0	0.04

proportion were patients older than 60 years (58.3 % and 62.5 %, respectively) and with the presence of concomitant diseases (66.7 % and 75 %, respectively). We found no significant differences in the need for hospitalization and oxygen support among patients with and without liver cirrhosis.

Patients responding to UDCA therapy were less likely to require oxygen support compared to patients who were unresponsive to UDCA therapy (n = 19 and n = 16, respectively, $p < 0.01$).

Discussion

According to published materials, as of February 16, 2022, SARS-CoV-2 has caused more than 415 million infections worldwide and more than 5.8 million deaths [9].

According to our data, the presence of PBC, regardless of the stage of the disease, is not a risk factor for a more severe course of COVID-19. According to the results of the annual observation, a lethal outcome was recorded in 2.2 % of cases of PBC-related liver cirrhosis, which is significantly lower compared to 32.0 % of deaths due to liver cirrhosis of various etiologies according to T. Marjot et al. [5]. Hospitalization was required more frequently in cases of older patients with comorbidities, which is consistent with the recently published meta-analysis of German researchers [10].

In majority of cases mild to moderate COVID-19 have been reported. Concomitant autoimmune diseases were associated with a milder course, and diabetes mellitus and obesity with moderate severity of the novel coronavirus infection. Diabetes, obesity and hypertension were among the most common diseases reported in hospitalized patients with severe COVID-19 clinical outcomes [11, 12].

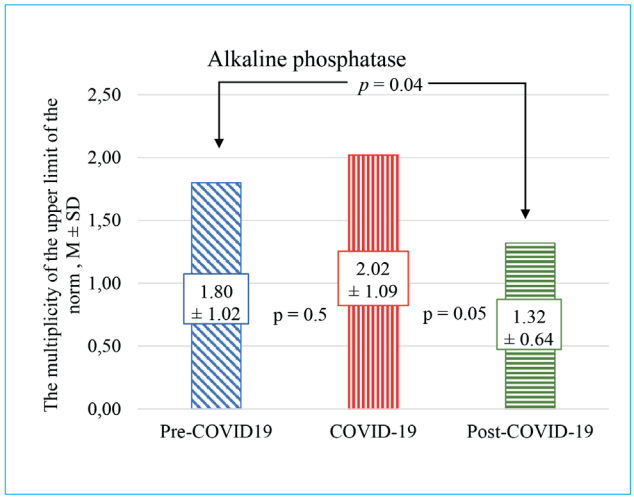

Fig. Differences in serum alkaline phosphatase levels in patients with PBC prior to, during, and after COVID-19 disease

All patients in our study received UDCA therapy. During the pandemic, the possible protective effect of UDCA on the risk of infection and the severity of SARS-CoV-2 infection was repeatedly discussed [13]. Interestingly, according to our data, SARS-CoV-2 infection was more often detected in patients with PBC unresponsive to UDCA therapy and those patients more often required oxygen support when hospitalized for COVID-19.

It has previously been shown that UDCA is able to prevent the introduction of SARS-CoV-2 into a human cell by interacting with the spike protein and SARS-CoV-2 membrane model, by disrupting the interaction between virus with its target cells and preventing the infection [13]. UDCA, an endogenous hydrophilic bile acid, is

an anti-apoptotic agent that has a pleiotropic effect, including anti-inflammatory one. Serum levels of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-2 and IL-6, have been shown to decrease significantly under the action of UDCA [14]. These data allow some authors [15] to consider UDCA as a potential means for controlling cytokine storm in COVID-19. Permanent use of UDCA by patients with PBC may be one of the factors that reduced the incidence of severe COVID-19.

Conclusion

Primary biliary cholangitis is not a risk factor for severe COVID-19. Elderly age and presence of comorbidities in patients with primary biliary cholangitis are defined by us as risk factors of hospitalization due to COVID-19. A protective effect of UDCA on the course of SARS-CoV-2 is possible, which requires further investigation.

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