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ORIGINAL ARTICLE

The impact of chronic viral hepatitis on COVID-19: clinical course and risk factors for poor outcome

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Summary

Introduction/Aim: The impact of chronic viral hepatitis on COVID-19 has not been fully clarified yet. The aim of this paper was to analyze the clinical features, course and outcome of COVID-19 in patients with chronic viral hepatitis and to determine the risk factors for unfavorable outcome.

Methods: A case-control study was conducted in which the case group included patients with chronic viral hepatitis suffering from COVID-19, while the control group included patients with chronic liver diseases of other etiologies; the patients were matched according to the stage of the liver disease. All subjects were treated at the Clinic for Infectious and Tropical Diseases in Belgrade from 1st March 2020 to 1st March 1 2022.

Results: Seventy-five patients with chronic liver diseases suffering from COVID-19 were analyzed – 25 with chronic viral hepatitis (13 HBV, 12 HCV) - case group, and 50 in the control group. In the case group, there were more males (76% vs. 72%) and younger patients (53.5±15.1 vs. 57.9±13.4 years), whereas in the control group there were more overweight patients (36% vs. 20%). In relation to comorbidities, there were more subjects with endocrinological diseases in the control group. The groups did not differ in terms of the severity of clinical features and the outcome of COVID-19. Risk factors for severe form of COVID-19 and lethal outcome were: cirrhosis, active liver disease, high fever, dyspnea, whereas vaccination was a protective factor against COVID-19.

Conclusion: The course and outcome of COVID-19 is similar in people with chronic liver diseases. Risk factors for poor outcome include advanced liver disease and dyspnea, while vaccination is a protective factor.

Keywords: chronic viral hepatitis, COVID-19, risk factors, outcome

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INTRODUCTION

Corona Virus Disease of 2019 (COVID-19) presents a global public health challenge. Since the year 2019, when the first cases emerged, the World Health Organization (WHO) has reported the number of nearly 773 million infected individuals around the globe, and the number of 7 million people who have died (1). The first cases in Serbia were detected in March 2020 and more than 2.6 million people have been infected so far, while 18.000 people have died (1,2). The clinical spectrum of COVID-19 ranges from asymptomatic form (some reports say up to 40% of the people infected) to critical and fatal illness. The percentage of severe disease cases is estimated to be in the range of 15 to 20% of symptomatic infections in unvaccinated individuals, and the overall case fatality rate is 2.3% (3). Many underlying medical conditions which increase the risk for the severe form of COVID-19 and lethal outcome have been identified so far. Experts from Centers for Disease Control and Prevention (CDC) have compiled a list of underlying medical conditions: various chronic lung diseases (asthma, bronchiectasis, interstitial lung disease, pulmonary embolism, etc.), hematologic malignancies, neuropsychiatric conditions (cerebrovascular disease, dementia, schizophrenia), people receiving dialysis, diabetes mellitus, heart conditions (such as heart failure, coronary artery disease, cardiomyopathies), obesity (body mass index - BMI >30 kg/m^2), primary immunodeficiencies and HIV, pregnancy, and recent pregnancy (4). When it comes to chronic liver diseases (CLDs), risk factors that could be important are cirrhosis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and autoimmune hepatitis. Regarding chronic viral infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), those conclusions are not quite clear. This is why in order to define chronic viral hepatitis as an underlying medical condition or a risk factor for severe form of COVID-19 there has to be more proof and more researches (5,6). Reasons for possible severe form of COVID-19 and poor outcome in patients with chronic viral hepatitis include: coexisting direct damage to the liver by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and viral hepatitis, disturbed gut microbiota in these patients, immune system disorders (especially regulatory T cells), the impact of prescribed medications, extrahepatic manifestations of chronic HBV and HCV infections, and their effects on other organ systems (7-9). The main problem of the impact of COVID-19 epidemic on chronic viral hepatitis is postponed diagnosis and initiation of the treatment, along with impossibility of regular check-ups due to the pandemic. As a consequence, individuals more frequently progress to terminal phases of liver disease, such as cirrhosis and hepatocellular carcinoma (10). In addition, there is global inability to achieve the WHO goal for controlling viral hepatitis by 2030 (11).

The aim of this paper is to analyze clinical presentation, course and outcome of COVID-19 in patients with chronic viral hepatitis in comparison with patients with liver disease of another etiology. It is also investigated which risk factors are responsible for severe form and poor outcome of COVID-19 in patients with chronic viral hepatitis.

MATERIAL AND METHODS

In order to find answers, a retrospective study was conducted including patients with confirmed COVID-19 who had been previously diagnosed with CLD and had been followed for at least six months. They were hospitalized due to COVID-19 at the Department of Hepatology of the Clinic for Infectious and Tropical Diseases, the University Clinical Center of Serbia between 1st March, 2020 and 1st March, 2022. The treatment of COVID-19 was conducted in accordance with the Serbian National Treatment Protocol for COVID-19 Patients (12) and the recommendations of the European Centre for Disease Prevention and Control (ECDC) (13).

In the first part of the study, where the influence of viral etiology of CLD on the clinical presentation, clinical course, and outcome of COVID-19 was examined, a matched case-control study was conducted. The case group was made out of patients with chronic viral hepatitis (chronic hepatitis B or C) infected with SARS-CoV-2. The inclusion criteria were defined as follows: at least a six-month follow-up of chronic hepatitis B or C infection before COVID-19; the stage (presence or absence of liver fibrosis and the degree of fibrosis) and the activity of liver disease were known; COVID-19 was confirmed by PCR test; patients gave a written informed consent for being included in the study. The exclusion criteria were defined as follows: diagnosed or previously treated hepatocellular carcinoma, liver transplantation, and HIV co-infection. The control group was made from patients with previously diagnosed CLD of another etiology infected with COVID-19. They were matched with patients from the case group according to the severity of CLD (presence or absence of cirrhosis), which had been clearly defined as a negative prognostic factor in previously conducted researches. The same inclusion and exclusion criteria were applied to the control group. For every patient in the case group two patients from the control group were selected (ratio 2:1) to ensure a higher power of the study. When it comes to non-infective liver disease, the following were included: autoimmune liver disease (autoimmune hepatitis, primary biliary cholangitis - PBC, primary sclerosing cholangitis - PSC), ALD, metabolic liver disease, hereditary liver disease (hemochromatosis, Wilson disease, deficit of alfa-1 trypsin) or CLD of unknown origin (individuals who had had elevated liver enzymes more than 2x UNL for more than 6 months but without confirmed diagnosis even after complete diagnostics had been performed).

In the second part of the study, risk factors for severe clinical course and poor outcome of COVID-19 were examined in patients with chronic viral hepatitis (the study group). The severity of COVID-19 was determined based on the severity of pneumonia and the need for oxygen support in the following way: absence of pneumonia, mild pneumonia with no need for oxygen support, moderate pneumonia (involving less than 50% of lung parenchyma) requiring oxygen support, severe pneumonia (involving more than 50% lung parenchyma) requiring oxygen support, and critically ill patients treated in the intensive care unit (ICU) requiring high-flow oxygen support, non-invasive, or invasive mechanical ventilation. Risk factors that were analyzed were as follows: age and gender, constitution, severity of chronic hepatitis (assessed through the stage of liver fibrosis and the activity of the disease), comorbidity diseases previously defined as risk factors (heart diseases - cardiomyopathies, heart arrhythmias; endocrine diseases - thyroid disease, diabetes mellitus, chronic lung disease - asthma, chronic bronchitis, emphysem, chronic kidney disease, malignancy - carcinomas, hematologic malignancies), applied therapy for COVID-19 (antivirals, corticosteroids, immunomodulators), previous vaccination against SARS-CoV-2, symptoms and signs of COVID-19 (high fever, weakness and malaise, cough, dyspnea, diarrhea, vomiting). Neurological diseases as risk factors were not included, because none of the patients had any. The use of antibiotics, anticoagulants, or vitamins was not analyzed, as all patients received these medications. The study was approved by the Ethical Board of the University Clinical Centre of Serbia, under the reference number 87/3.

Statistical analysis

Methods of descriptive and analytic statistics were used. When it comes to statistical tests for comparing two groups of patients the following tests were used: Student's t-test, the Mann–Whitney U test, chi square test. The value $p<0.05$ was considered to indicate statistical significance. The statistical analyses were performed using the IBM SPSS software v21.

RESULTS

The study included 75 patients with CLD infected with COVID-19. The case group included 25 patients with chronic viral hepatitis: 13 (52%) with chronic HBV infection and 12 (48%) with chronic HCV infection. The other 50 patients had CLD of another etiology (the control group): 8 (16%) with autoimmune liver disease, 10 (20%) with ALD, 24 (48%) with NAFLD, and 8 (16%) with CLD of an unknown origine. The patients included in the study group were younger (53.5±15.1 years vs. 57.9±13.4 years), but a statistical difference was not reached ($p=0.754$). The male gender dominated in both groups, but there were still more individuals of male gender in the study group - ratio 3.2:1 vs. 2.8:1, respectively. In both groups, 64% of patients did not have cirrhosis, while 36% had diagnosed liver cirrhosis. Liver enzymes were found to be more elevated in the control group than in the study group (70% vs. 52%), but without significant difference ($p=0.315$). In terms of comorbidities that can impact the clinical course of COVID-19, the only notable difference was observed in endocrinological diseases, which had a higher prevalence in the group with nonviral liver diseases. There was no significant difference between the groups in terms of cardiovascular diseases, chronic lung diseases, chronic kidney diseases and malignancy. There was a higher percentage of vaccinated individuals in the group of patients with chronic viral hepatitis (40% vs. 22%), but without statistical significance ($p=0.102$). The main characteristics of patients are presented in **Table 1**.

COVID-19

Regarding symptoms and signs of COVID-19, there was a similar clinical course observed in both groups of patients with CLD. Therefore, there was no statistically significant difference ($p>0.05$) between the duration of the disease before hospital admission, the duration of hospital treatment, taste and smell loss, weakness and malaise, the presence of cough and a sense of dyspnea, diarrhoea and vomiting. On the other hand, a higher degree of body temperature was noted among patients with chronic viral hepatitis (38.7±0.9°C vs. 38.2±0.6°C) and it was a statistically significant difference ($p=0.036$). As for COVID-19 severity, the majority of patients in both groups had mild or moderate pneumonia (60% and 68%, respectively), and one-third of the patients had severe pneumonia or were critically ill, requiring treatment in the ICU. The difference in severity of COVID-19 in the case group and the control group was not statistically significant ($p=0.578$). When it comes to COVID-19 treatment, corticosteroids were used slightly more often in the control group (78% vs. 68%), such as immunomodulatory therapy - tocilizumab (55% vs. 48%). This difference was not statistically significant ($p=0.348$ and $p=0.126$, respectively). Antibiotics were used in all patients with pneumonia in both groups. The treatment with antibiotics, antivirals, vitamins C and D and anticoagulants was almost identical in both groups, without significant statistical difference ($p>0.05$). In the study group, there were more vaccinated patients (40%) compared to the control group (22%), although the difference did not reach statistical significance ($p=0.102$). Among vaccinated patients, the majority (61.9%) got an inactivated vaccine, 28.5% got an mRNA vaccine, and the remaining 9.6% got an adenovirus viral vector vaccine. Clinical characteristics and outcome of COVID-19 are presented in **Table 2**.

Table 1. The main characteristics of the subjects included in the study (n=75)

Variables	Patients with chronic viral hepatitis (case group); n=25	Patients with chronic nonviral liver diseases (control group); n=50	P value
Gender			
Male	19 (76%)	36 (72%)	0.712
Female	6 (24%)	14 (28%)	
Average age, y	53.5±15.1	57.9±13.4	0.754
Constitution			
Average constitution (BMI 18.5-24.9 kg/m^2)	17 (68%)	30 (60%)	0.212
Underweight (BMI <18.5 kg/m^2)	3 (12%)	2 (4%)	
Overweight (BMI>25 kg/m^2)	5 (20%)	18 (36%)	
Stage of liver disease			
No cirrhosis	16 (64%)	32 (64%)	1.000
Liver cirrhosis	9 (36%)	18 (36%)	
[a]Presence of active liver disease*			
Normal values of transaminases	12 (48%)	15 (30%)	0.315
Values of transaminases increased two- to three-times UNL	6 (24%)	16 (32%)	
Values of transaminases increased more than three-times UNL	7 (28%)	19 (38%)	
[b]Comorbidites			
Heart diseases (cardiomyopathy, arrhythmia)	10 (40%)	25 (50%)	0.413
Chronic lung disease (asthma, chronic bronchitis, emphysema)	2 (8%)	2 (4%)	0.665
Endocrine diseases (diabetes mellitus, thyroid disease)	3 (12%)	21 (42%)	**0.009**
Chronic kidney disease	2 (8%)	4 (8%)	1.000
Malignancy (carcinomas, hematologic malignancies)	5 (20%)	3 (6%)	0.108
Vaccinated against COVID-19	10 (40%)	11 (22%)	0.102

UNL - upper normal limit; [a]values of liver enzymes during follow up period before COVID-19; [b]presence of listed diseases

Table 2. COVID-19 in patients with chronic viral hepatitis (the case group) and with nonviral chronic liver disease (the control group)

Variables	Patients with chronic viral hepatitis (case group); n=25	Patients with nonviral chronic liver disease (control group); n=50	P value
[a]Clinical characteristics			
Fever	38.7±0.9°C	38.2±0.6°C	**0.036**
The loss of smell and taste	1 (4%)	3 (6%)	0.716
Weakness and malaise	15 (60%)	37 (74%)	0.215
Cough	14 (56%)	36 (72%)	0.166
Dyspnea	9 (36%)	18 (36%)	1.00
Vomitting	5 (20%)	5 (10%)	0.230
Diarrhea	4 (16%)	6 (12%)	0.631
Severity of disease			
No pneumonia	2 (8%)	3 (6%)	0.578
Mild pneumonia	3 (12%)	13 (26%)	
Moderate to severe pneumonia	12 (48%)	20 (40%)	
Severe pneumonia	3 (12%)	2 (4%)	
Critically ill	5 (20%)	12 (24%)	
[a]Treatment model			
Antiviral therapy applied	6 (24%)	15 (30%)	0.585
Corticosteroids applied	17 (68%)	39 (78%)	0.348
Tocilizumab applied	12 (48%)	15 (55.6%)	0.126
Antibiotics applied	23 (92%)	47 (94%)	0.743
Vitamin C or D applied	22 (88%)	43 (86%)	0.810
Anticoagulants applied	20 (80%)	45 (90%)	0.230
[a]Vaccination	10 (40%)	11 (22%)	0.102
Outcome			
Recovered	19 (76%)	37 (74%)	0.851
Died	6 (24%)	13 (26%)	

[a]the number of patients with listed characteristics

In terms of the outcome in the study group, the lethal outcome occurred in 6 patients (24%), while 19 patients completely recovered (76%). When it comes to patients with nonviral CLDs, 13 (26%) succumbed, while 37 (74%) recovered. The difference in the lethality rate was not significant (p=0.851). Further analysis showed that the majority of patients who died in both groups had liver cirrhosis and that difference was statistically proven. Thus, 5 (55.6%) out of 9 patients with viral cirrhosis died, while in those without cirrhosis only 1 (6.3%) died; p=0.006. In the control group, 12 (66.7%) out of 18 patients with cirrhosis died, and only 1 (3.1%) without cirrhosis died (p<0.001).

Risk factors for severe clinical course of COVID-19 and lethal outcome in patients with chronic viral hepatitis

Out of 25 patients with chronic viral hepatitis (designated as the study group), 16 individuals (64%) experienced a mild or moderately severe clinical form of COVID-19 and successfully recovered, while the remaining 9 patients (36%) faced a severe clinical presentation of COVID-19, resulting in either a critical condition or fatality. The presence of liver cirrhosis (66.7% vs. 18.8%, p=0.025) and active CLD (66.7% vs. 25%, p=0.041) were identified as statistically significant risk factors for the severe form of COVID-19 and fatal outcome. When it comes to clinical signs and symptoms of COVID-19, patients with dyspnea had significantly more severe clinical course and lethal outcome, in comparision with those without dyspnea (66.7% vs. 18.8%, p=0.025), while in respect to the presence of cough this difference was not noted (56.3% vs. 36.6%, p=0.648). Differences in other signs and symptoms between the groups were not registered. Severe clinical presentation and poor outcomes were more frequently observed in patients with comorbidities, and if there was no application of antivirals or immunomodulatory therapy, but without statistical significance (p>0.05). On the other hand, COVID-19 vaccination was shown to be a significant protective factor. Vaccinated patients with chronic viral hepatitis that had mild or moderate clinical courses of COVID-19 were registered in 56.3%, while there were 10% of vaccinated patients who had severe clinical presentation and lethal outcome (p=0.027). The analyzed risk factors are shown in **Table 3**.

DISCUSSION

CLDs generally present a risk factor for a severe form of COVID-19. Previous studies analyzing the etiology of CLD in relation to the course and outcome of COVID-19 have shown an increased risk in ALD, NAFLD and autoimmune hepatitis, while this relation is not so clear for chronic viral hepatitis (7,14,15). It was clearly defined that the severity of CLD had a direct influence on severity of COVID-19 and lethal outcome. It was demonstrated that liver cirrhosis carried a 3,31-4,90 times higher 30-day mortality rate. In addition, the lethality rate for those with decompensated liver cirrhosis was 43-63% (6,14,16). People with advanced liver diseases have a higher expression of the ACE2 receptor in the respiratory tract because the ACE2 gene is interferon-inducible. This could lead to a more severe form of COVID-19 in these individuals. Additionally, people with cirrhosis of the liver experience immune dysregulation known as cirrhosis-associated immune dysfunction (CAID), which affects both innate and acquired immune responses. This dysregulation causes damage to the synthesis and

Tabela 3. Risk factors for severe form of COVID-19 and lethal outcome

Risk factors	Patients with mild or moderate clinical course of COVID-19; n=16	Patients with severe clinical course or lethal outcome: n=9	P value
Gender - male	13 (81.3%)	6 (66.7%)	0.363
Constitution - overweight (BMI>25 kg/m^2)	3 (18.8%)	2 (22.2%)	0.835
Age >65 years	5 (31.3%)	2 (22.2%)	0.501
Severity of chronic liver disease - cirrhosis	3 (18.8%)	6 (66.7%)	**0.025**
[a]Active liver disease	4 (25%)	6 (66.7%)	**0.041**
[b]Comorbidities – one or more	9 (56.3%)	6 (66.7%)	0.470
Vaccination – not carried out	7 (43.8%)	8 (88.9%)	**0.027**
Fever >38°C	14 (87.5%)	7 (77.8%)	0.458
Weakness and malaise	10 (62.5%)	5 (55.6%)	0.530
Cough	9 (56.3%)	5 (55.6%)	0.648
Dyspnea	3 (33.3%)	6 (66.7%)	**0.025**
Dyarrhea and vomitting	3 (18.8%)	4 (44.4%)	0.181
Antiviral therapy – not applied	11 (68.8%)	8 (88.9%)	0.267
Corticosteroids – not applied	6 (37.5%)	2 (22.2%)	0.374
Tocilizumab – not applied	8 (50%)	5 (55.6%)	0.560

[a]prior to the occurence of COVID-19; [b]Heart diseases (hypertension, cardiomyopathies, heart arrhythmias), endocrine diseases (thyroid disease, diabetes mellitus), chronic lung disease (asthma, chronic bronchitis, emphysema), chronic kidney disease, malignancy (carcinomas, hematologic malignancies)

function of pattern recognition receptors (PRRs) and toll-like receptors (TLRs), disrupts the function of neutrophils and macrophages, leads to various T lymphocyte defects (such as CD4 and CD8 relationship disorder), and results in B lymphocyte hyperactivity. The function of the complement system (C3, C4, C5a) is also disturbed. Such immune disorders manifest, on one hand, as immunodeficiency (characterized by reduced bacterial opsonization, phagocytosis, and T lymphocyte-dependent antigen responses) and, on the other hand, as increased systemic inflammation (indicated by elevated serum levels of TNF-α, IL-1β, IL-6, IL-17, IL-18, and IFN-γ), resulting in a 2.6 times higher risk of sepsis. Consequently, the risk of a cytokine storm during COVID-19 is higher in people with advanced liver diseases, as well as the risk of the most severe form of respiratory complication, acute respiratory distress syndrome (ARDS) (17). Unrelated to COVID-19, advanced liver disease and cirrhosis were previously recognized as significant predisposing factors for ARDS because liver damage activates and enhances inflammation in the pulmonary intravascular compartment and lower respiratory tract, leading to important changes in the structure and/or functions of the lung (18).

In this study, COVID-19 patients with chronic viral hepatitis were mostly male and slightly younger than those with a nonviral cause of CLD. This finding was expected since the transmission of chronic viral hepatitis nowadays is mostly by means of intravenous drug use (HCV infection) or through sexual transmission (HBV infection) (19). The patients with nonviral cause of CLD were more often overweight (36% *vs*. 20%), and had more common endocrinological diseases (42% *vs*. 12%). The explanation lies in the fact that almost half of the patients in this group had NAFLD, and obesity and diabetes mellitus are primary risk factors for NAFLD. Although the sample of patients is too small to evaluate the prevalence of NAFLD in Serbia, it is important to note that the representation of these exceeds the prevalence in Europe which is 25% (20). No significant differences were registered between the examined groups regarding other comorbidities (cardiac, pulmonary, malignancies, chronic kidney diseases) that could have an impact on the course and outcome of COVID-19. There was no statistical difference in vaccination rate either. However, there is a notable difference in the vaccination rate, favoring the group with chronic viral hepatitis (40% *vs*. 22%). This can be explained by the fact that these patients were treated by infectiologists, who are well-known for advocating vaccination. Unfortunately, the total percentage of those vaccinated against COVID-19 in this study is low (only 28%). This low rate of vaccination is in collision with recommendations of the European Association for the Study of the Liver (EASL) as the most important organisation in Europe when it comes to liver diseases (21). The low number of vaccinated patients can be explained by the fact that the majority of included patients were treated at the beginning of the COVID-19 pandemic, before the introduction of vaccines. In the period when the vaccine became available, patients hesitated to get vaccinated for various reasons. A Chinese study from 2022 demonstrated that more than two-thirds of patients with advanced liver disease were unvaccinated. Besides fear and lack of support, a significant number of them did not want to disclose the reason for such a decision (22).

In addition to fever, which was a symptom in almost all patients, the dominant complaints were the feeling of weakness and malaise, as well as cough, which were reported by more than half of the respondents. The loss of smell and taste, gastrointestinal problems, dyspnea and skin rashes were rare in included patients. This distribution of COVID-19 symptoms is similar in patients without chronic liver disease (15,23,24). Almost a third of the patients (32%) with chronic viral hepatitis had severe pneumonia or were critically ill, but there was no statistically significant difference when compared to the control group. During SARS-CoV-2 infection, the largest number of patients had viral pneumonia, while the prevalence of bacterial superinfection was around 10% and was related to the severity of COVID-19. The greatest risk was found in patients who required treatment in the intensive care unit (25). However, given that people with advanced liver diseases are prone to bacterial infections, a higher percentage of superinfections can be expected in them during COVID-19, which is the main reason why the majority of patients in our study received antibiotic therapy.

When comparing the frequency of patients with severe COVID-19 in terms of the general distribution of disease severity, as expected, there was a higher percentage of severe cases in both groups compared to the general population. Thus, in the study published by Chinese Center for Disease Control and Prevention which included 44,500 patients, the percentage of people with severe pneumonia or critically ill was 19% (26). The reason for this might be the fact that the Chinese study included persons with confirmed COVID-19, disregarding the fact whether they were in need of hospitalization or not. In a study conducted in the UK analysing hospitalized patients with COVID-19, the majority had comorbidities and the rate of severe disease (26%) was similar to the one in our study. The main comorbidities in the UK study were chronic cardiac disease (30.9%), diabetes mellitus (20.7%), chronic pulmonary disease including asthma (32.2%) and chronic kidney disease (16.2%) (27).

The application of antiviral drugs in the study and control groups was 25% and 40%, respectively. This low percentage of antiviral therapy could be explained by the fact that antivirals became available in Serbia almost a year after the beginning of the study. In addition, the average duration of the illness before hospitalization was 6.5 days and the introduction of antivirals was advised until the fifth day of the illness. The other limitation for the application of antivirals was a warning that special caution was

needed in advanced liver diseases (12). Medications that decrease the possibility of the development of the cytokine storm (corticosteroids and tocilizumab) were used a bit more often in the control group of patients with nonviral CLD. We believe that the reason could be fear of worsening of other viral infections, such as chronic HBV and HCV infections. Almost the same lethality rate was registered in both the study and the control groups (24% and 26%, respectively). Similar lethality rate (20%) was noted analyzing 745 persons with CLD from the International registry of Great Britain in a study conducted by Major et al. In this study, it was also pointed out that there was a significantly higher percentage of deaths among people with liver cirrhosis (with Child-Pugh class C as much as 51% *vs.* 8% among those without cirrhosis), and the same conclusion was noted with our patients as well (14).

Risk factors for the development of severe COVID-19 and lethal outcome in patients with chronic viral hepatitis in our study were as follows: diagnosis of liver cirrhosis, active CLD, and dyspnea. These findings are consistent with previously published studies of other authors. Liver cirrhosis causes higher mortality rate probably due to CAID that leads to higher sensitivity to infection and aberrant inflammatory response during infection. All of this results in increased sensitivity, not only to bacterial and fungal infections, but also to viral infections such as SARS-CoV-2 infection (28,29). Active CLD with increased liver enzymes during continued follow up of our patients prior to COVID-19, was also a significant risk factor for adverse outcome. Elevated transaminases in chronic viral hepatitis are related to inflammatory process in the liver and necrosis of hepatocytes. During inflammatory process proinflammatory cytokines are released, also known as hepatokines (TNFα, IL-6, IL-1A, IL-33, pro-IL-18) leading to the development of cytokine storm in COVID-19 (30). Hepatocyte necrosis culminates in decreasing hepatic reserve making the liver more susceptible to injury in COVID-19. Liver injury itself influences the choice and dosage of drugs used in COVID-19 treatment (antivirals, antibiotics, anticoagulant therapy, analgopyretics, etc.) and also affects metabolism of the applied drugs (31).

In our study, vaccination against SARS-CoV-2 was noted as a protective factor for course and clinical outcome of COVID-19 in patients with chronic viral hepatitis. It was clearly demonstrated that aforementioned vaccines (inactivated, mRNA, vector with adenovirus as a carrier) had protective effect on all aspects of COVID-19, such as the infection itself, the need for hospitalization and oxygen support, the admission to ICU and overall mortality (32). Surprisingly, the administration of antivirals for COVID-19 in our study did not have a positive effect on the course and outcome of COVID-19. This might be accounted for by the fact that most of our patients (83.3%) were treated with favipiravir. Recently published meta-analysis conducted by Batool et al. showed that the administration of favipiravir was safe, but not efficient enough in COVID-19 treatment. This meta-analysis included 1,448 patients from eight randomized control trials (RCTs) and it showed that favipiravir did not exert any beneficial impact on reducing ICU admission, the need for oxygen therapy, and time to viral clearance (33). At the same time, antiviral therapy was mainly applied in our patients with liver cirrhosis which in itself was a negative prognostic factor for poor outcome of COVID-19 (6,14,34).

To our knowledge, this is the first study conducted in Serbia that analyzed the impact of chronic viral hepatitis on COVID-19. The characteristics of COVID-19 in these patients were compared with matched controls who had CLD of some other, non-infectious etiology, and the risk factors for a severe clinical course and poor outcome were analyzed, which gives special significance to the results obtained. The authors are fully aware of the limitations of the study. It included only hospitalized patients, and not those treated in outpatient settings, leading to a selection bias. This also leads to reporting bias, with over-representation of the cases with more progressive liver disease, or more severe COVID-19. All in all, a higher number of participants would certainly have increased the strength of the study and potentially discovered some other risk factors. Regardless of these imperfections, the authors believe that none of these facts have brought the study's validity into question.

CONCLUSIONS

COVID-19 in patients with chronic viral hepatitis has similar clinical course, severity and possibility of lethal outcome in comparison with patients suffering from some other nonviral CLDs. Administration of antiviral therapy and vaccination against COVID-19 was noted in low rates. Risk factors for severe clinical forms and lethal outcome in patients with chronic viral hepatitis are progressive liver disease (stage of cirrhosis), active necroinflammatory liver disease prior to COVID-19 and the presence of dyspnea. When it comes to protective factors, prior vaccination against SARS-CoV-2 was noted. The obtained results are significant for the prediction of course and outcome of COVID-19 in persons with chronic viral hepatitis, and the identified risk factors will help in their stratification and assessment of the need of hospital treatment. Protective effect of vaccination is also an important finding and should encourage patients with chronic viral hepatitis, and health professionals as well, to promote vaccination. This is in accordance with the recommendations of the most important world associations for liver diseases.

Author Contributions

Ivana Milosevic and Nikola Mitrovic conceived and designed the study. Nikola Mitrovic, Natasa Nikolic, Ana

Filipovic, Ankica Vujovic, Uros Karic and Milos Sabanovic collected the data. Ivana Milosevic, Nikola Mitrovic, Natasa Nikolic, Ana Filipovic, Ankica Vujovic, Uros Karic and Milos Sabanovic analysed and interpreted the data. Nikola Mitrovic, Natasa Nikolic, Ana Filipovic, Ankica Vujovic, Uros Karic and Milos Sabanovic drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Conflict of interest

None to declare

Ethical approval

The study was approved by the Ethical Board of the University Clinical Centre of Serbia, under the reference number 87/3.

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UTICAJ HRONIČNOG VIRUSNOG HEPATITISA NA KOVID-19: KLINIČKI TOK BOLESTI I FAKTORI RIZIKA KOJI UTIČU NA NEPOVOLJAN ISHOD

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Sažetak

Uvod/Cilj rada: Uticaj hroničnih virusnih bolesti jetre na Kovid-19 do sada nije u potpnosti razjašnjen. Cilj rada je da se analizira klinička slika, tok i ishod Kovid-19 kod osoba sa hroničnim virusnim hepatitisima i da se utvrde faktori rizika za nepovoljan ishod.

Metode: Sprovedena je studija slučajeva i kontrola u kojoj su u grupu slučajeva uključene osobe sa hroničnim virusnim hepatitisom obolele od Kovid-19, a u kontrolnu grupu osobe sa hroničnim bolestima jetre neke druge etiologije, pri čemu su mečovani u odnosu na stadijum bolesti jetre. Svi ispitanici su lečeni u odeljenju hepatolgije Infektivne klinike u Beogradu od 1.3.2020. do 1.3.2022. godine.

Rezultati: Analizirano je 75 pacijenta sa hroničnim bolestima jetre obolelih od Kovid-19, i to 25 pacijenata virusne etiologije (13 HBV, 12 HCV) – grupa slučajeva i 50 ispitanika u kontrolnoj grupi. U grupi slučajeva bilo je više osoba muškog pola (76% nasuprot 72%) i bili su mlađeg uzrasta (53.5±15.1 nasuprot 57.9±13.4 godine), dok je u kontrolnoj grupi bilo više gojaznih (36% nasuprot 20%). Kada je reč o komorbiditetima, u kontrolnoj grupi je bilo više ispitanika sa endokrinološkim bolestima. Grupe se nisu razlikovale u pogledu težine kliničke slike i ishoda Kovid-19. Faktori rizika za težak oblik Kovid-19 i smrtni ishod kod ispitanika sa hroničnim virusnim hepatitisima su: ciroza jetre, aktivna bolest jetre, visoka febrilnost, prisustvo dispneje, a protektivan faktor vakcinacija protiv Kovid-19.

Zaključak: Tok i ishod Kovid-19 je sličan kod osoba sa hroničnim bolestima jetre, bilo da je u pitanju virusna etiologija ili neka druga. Najvažniji faktori rizika za nepovoljan ishod su uznaprdovala bolest jetre i dispneja, dok je zaštitni faktor vakcinacija.

Ključne reči: hronični virusni hepatitis, Kovid-19, faktori rizika, ishod

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