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COVID-19 Seroprevalence in Cirrhotic Patients and Effect of COVID-19 Infection on Liver Cirrhosis by Clinical Form in the Postinfectious Period

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ABSTRACT

Introduction: There are very few studies demonstrating the seroprevalence of coronavirus disease-2019 (COVID-19) in patients with cirrhosis worldwide and in Turkey. This study aimed to investigate the seroprevalence of COVID-19 in patients with cirrhosis and its effect on liver cirrhosis by clinical form in the postinfectious period.

Methods: The study included 174 patients with cirrhosis. Patients with COVID-19 were identified using anti-severe acute respiratory syndrome-coronavirus-2-immunoglobulin G (SARS-CoV-2-IgG) and COVID-19 polymerase chain reaction assays and were divided into symptomatic and asymptomatic groups. The last polyclinic records of the patients before infection or testing were determined as 1st examination and the date of blood collection for anti-SARS-CoV-2-IgG was determined as the 2nd examination. Examination findings and liver tests of the patients in both periods were recorded; Child-Pugh Score (CPS) and Model for End Stage Liver Disease (MELD)-Na scores were calculated. Additionally, patients were evaluated for newly developed hepatic decompensation.

Results: The seropositivity of anti-SARS-CoV-2-IgG was detected in 35.6% of our patients, and the rate of those who had symptomatic COVID-19 infection was 23.6%, whereas the rate of those who had asymptomatic infection was 12%. There was no significant difference in liver tests, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients, and new decompensation was found in 9.6% of patients with COVID-19 infection.

Conclusion: The incidence of COVID-19 among patients with liver cirrhosis is notably high. Although high decompensation rates were reported in the acute phase of the disease, such rates were not observed in the postinfectious period. Ultimately, our results indicated no significant difference in the course of existing liver disease according to clinical form.

Keywords: COVID-19, liver cirrhosis, seroprevalence

Introduction

Although coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is primarily a respiratory infection, it can also affect other organs and systems directly or indirectly through some biological processes. It has been reported that 14-53% of these patients have elevated liver enzymes (1,2).

Various liver and/or biliary tract diseases due to vascular or circulatory problems have been reported, as well as inflammatory, infectious, autoimmunity, or drug-related liver diseases that may occur in relation to COVID-19 infection (2). Studies have reported that among COVID-19 patients, 2-11% have pre-existing and diagnosed liver disease, of which 0.3-2.4% are cases of liver cirrhosis (1,3).

COVID-19 infection in patients with chronic liver disease may result in the development of serious clinical problems, such as acute insufficiency or decompensation of liver cirrhosis with a chronic background (2). Deficiencies in natural and acquired immunity in patients with cirrhosis increase the tendency to infections, and this is more evident in severe cases (4).

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Serological tests in COVID-19 infection are used as diagnostic tools to determine previous and active infection in both symptomatic and asymptomatic patients (5). Seroprevalence studies are used to estimate the extent of COVID-19, which can be useful in detecting asymptomatic patients (6). Few studies have shown the seroprevalence of COVID-19 in patients with liver cirrhosis worldwide or in Turkey. At this point, the finalization of the research initiated during the pandemic process is an important issue in the fight against this health problem that may recur in the future.

This study aimed to investigate the seroprevalence of COVID-19 in patients with liver cirrhosis, the seropositivity rate of symptomatic and asymptomatic COVID-19 patients, and whether there is a difference between the clinical forms of the disease and how it affects pre-existing liver disease in the postinfectious period. The study was conducted during the circulation of the Delta variant and before the vaccination period.

Methods

Study Population

The study included 174 patients with liver cirrhosis who were under follow-up at the İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department Gastroenterology, between December 2020 and June 2021. All patients included in the study were monitored in our clinic and diagnosed with cirrhosis based on the evaluation of previous clinical, radiological, histochemical, and laboratory parameters, and they were followed up with this diagnosis. Patients were included in the study irrespective of the cause of cirrhosis, treatment applied, or other accompanying diseases. Patients who received one or more doses of the COVID-19 vaccine were excluded from the study.

This retrospective study was conducted before the initiation of vaccination and the emergence of the omicron variant, during which the delta variant was predominant. The course and seroprevalence of COVID-19 in patients with liver cirrhosis may vary depending on vaccination and novel variants.

Blood samples were collected from all patients on the day of the examination for antibodies against SARS-CoV-2 infection [anti-SARS-CoV-2 NCP ELISA immunoglobulin G (IgG), Euroimmun AG, Lübeck, Germany], and then serum samples were separated from these blood samples and stored at -20 °C. Patients were asked whether they had COVID-19 and the symptoms associated with COVID-19.

In patients who reported having a symptomatic COVID-19 infection, this was confirmed by checking the polymerase chain reaction (PCR) test results through the central public health results system. The severity of symptoms and whether patients were hospitalized in the inpatient or intensive care unit were also assessed, and patients were classified into the symptomatic group (group 1).

Patients who neither reported a history of COVID-19-related symptoms nor received a previous diagnosis of COVID-19 based on PCR test results but tested positive for anti-SARS-CoV-2-IgG were considered to have had an asymptomatic COVID-19 infection, and they were categorized as the asymptomatic group (group 2).

Those who did not report any COVID-19-related symptoms, whose PCR test results were negative, and who tested seronegative for anti-SARS-CoV-2-IgG in the antibody test were classified as patients who did not have a COVID-19 infection (group 3).

The last clinical records of the patients included in the study before infection or testing were taken as pre-COVID-19 (1st examination), and the date of blood collection for anti-SARS-CoV-2-IgG was considered the post-COVID-19 examination date (2nd examination).

Current examination findings, complete blood counts, liver function tests [alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, prothrombin time, alkaline phosphatase and gamma-glutamyl transferase (GGT)], and radiological examinations of the patients in both examination periods were recorded, and Child-Pugh Score (CPS), Model for End Stage Liver Disease (MELD)-Na scores, and neutrophil/lymphocyte ratios were calculated from these data.

In patients with cirrhosis, the occurrence of one or more of the symptoms of ascites, variceal bleeding, icterus, and hepatic encephalopathy that were not previously present was defined as decompensation, and EASL-CLIF criteria were used for the definition of acute insufficiency on a chronic basis (7).

Ethics Approval

This study was approved by the Ethics Committee of İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 83088843-604.01.01-73299, date: 16.07.2020). Informed consent was obtained from the patients.

Statistical Analysis

The demographic and clinical characteristics of the patients evaluated in the study were analyzed using descriptive statistics, such as numbers, percentages, means, standard deviations, and medians. Average data, such as age and MELD-Na score, which were normally distributed between cases with and without COVID-19, were evaluated using the Independent groups t-test. Mean blood values that were not normally distributed between patients with and without COVID-19 were evaluated using the Mann-Whitney U test. Proportional data according to disease severity groups were analyzed using chi-square analysis and Fisher's exact test between cases with and without COVID-19, as well as between symptomatic and asymptomatic COVID-19 infection. In this study, the change in normally distributed mean data, such as the MELD-Na score and hemoglobin, before and after COVID-19 was assessed using Paired Samples t-test. The conformity of the data to the normal distribution was checked using the kurtosis and skewness coefficients (±1.5). The significance level for all analyses was set up $p<0.05$ and IBM SPSS 22.0 (IBM SPSS Statistics for Windows, version 22.0. IBM Corp. (Armonk, NY, USA) software was used in the analysis.

Results

Of cirrhotic patients (n=174) included in the study, 79 were female and 95 were male, with ages ranging from 21 to 85 (median: 61.0, interquartile range: 50-68). Viral hepatitis is the leading cause of cirrhosis, and the other etiologic causes are presented in Table 1. One hundred thirteen

(64.9%) patients had class A cirrhosis, fifty (28.7%) had class B cirrhosis, and eleven (6.3%) had class C cirrhosis. In 61 of the patients (35%), there were diseases other than cirrhosis related to one or more organs or systems. The accompanying comorbid conditions are shown in Table 2.

In the grouping according to the outpatient clinic query, COVID-19 PCR result screening based on public health center test data, and anti-SARS-CoV-2-IgG results, 41 of the patients (23.6%) (66% of COVID-19 positive patients) had symptomatic COVID-19 infection (group 1). Additionally, 21 patients (12%) (34% of COVID-19 positive patients) had asymptomatic COVID-19 infection (group 2), whereas 112 patients (64.4%) have not had COVID-19 (group 3) (Figure 1).

No significant differences were observed between patients with or without COVID-19 in terms of demographic characteristics, cirrhosis etiology, and severity of liver disease (Table 3).

At this stage of the study, 62 patients who had COVID-19 infection were evaluated within themselves, and how the clinical status and liver tests of those with symptomatic or asymptomatic infections changed compared with pre-COVID-19 and whether asymptomatic COVID-19 infection had an aggravating effect on liver disease in cirrhotic patients (Table 4, 5).

No significant difference was observed between symptomatic and asymptomatic patients with COVID-19 in terms of demographic characteristics and severity of liver disease. In the etiological comparison of both groups, the rates of viral hepatitis in the symptomatic patient group and cryptogenic cirrhosis in the asymptomatic patient group were significantly higher (Table 4).

No significant difference was observed in liver test results, neutrophil-to-lymphocyte ratio, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients with COVID-19 (Table 5).

Among patients with cirrhosis who had symptomatic COVID-19, 61.2% had respiratory symptoms, such as cough and shortness of breath, 32.2% had fever, 29% had myalgia, 19.3% had gastrointestinal

Table 1. The causes of cirrhosis in patients

Etiology	n (%)
Viral hepatitis	56 (32.2)
Alcoholic liver disease	10 (5.7)
Autoimmune hepatitis	6 (3.4)
Wilson's disease	6 (3.4)
PBC, PSK	7 (4)
Fatty Liver	33 (19)
Chronic liver disease with vascular disease	15 (8.6)
Others	9 (5.2)
Cryptogenic	32 (18.4)

PBC: Primary biliary cholangitis, PSK: Primary sclerosing cholangitis

Table 2. Other accompanying system diseases of the patients

	n (%)
Diabetes	15 (8.6)
Hypertension	13 (7.5)
Cardiovascular system diseases	12 (6.9)
Neurological diseases	1 (0.6)
Renal diseases	6 (3.4)
Rheumatological diseases	5 (2.9)
Gastrointestinal diseases	3 (1.7)
Pulmoner diseases	1 (0.6)
Oncological disease (except hepatocellular carcinoma)	2 (1.1)
Others	3 (1.7)
Total	61

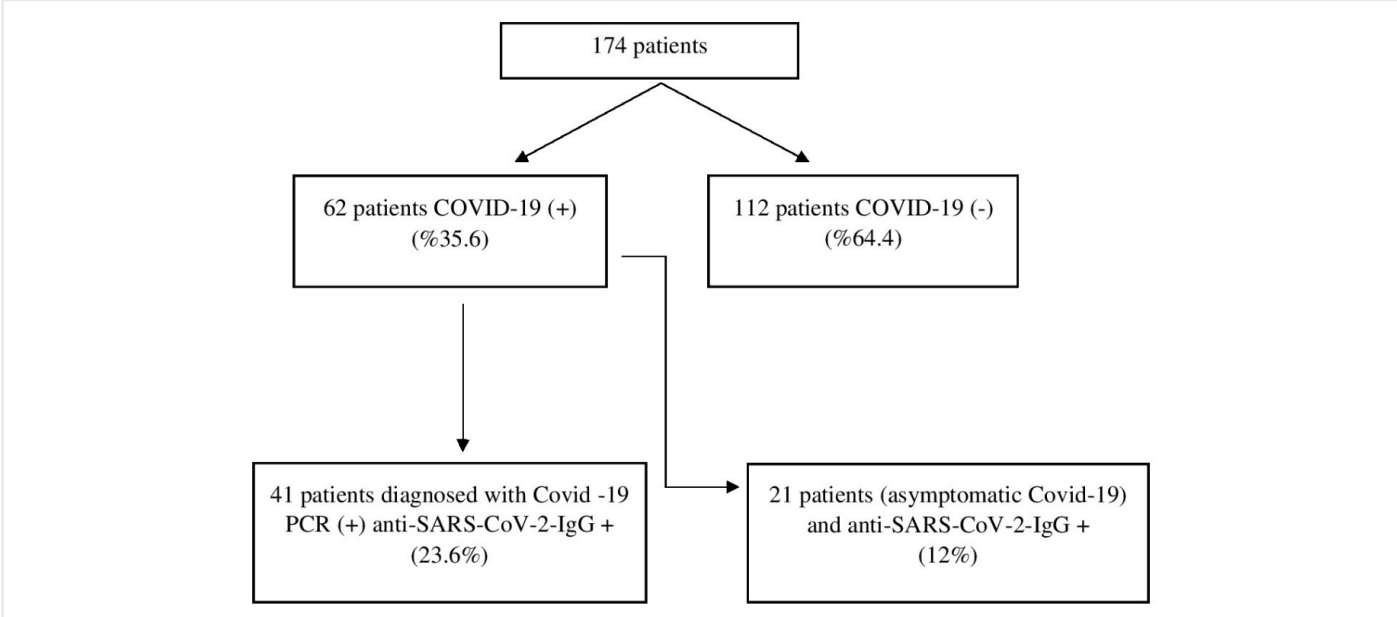

Figure 1. Flow chart of patient inclusion
COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, SARS-CoV-2-IgG: Severe acute respiratory syndrome-coronavirus-2-immunoglobulin G

Table 3. Demographic characteristics and liver disease status of patients with and without COVID-19

		COVID-19 (-) (n=112)	COVID-19 (+), (n=62)	p
Age (mean/SD)		59.05/14.18	57.16/10.19	0.356
Gender (n, %)	Male	62/55.4	33/53.2	0.787
	Female	50/44.6	29/46.8	
Etiological diagnosis (n, %)	Viral hepatitis	35/30.4	21/33.9	0.686
	Autoimmune hepatitis	4/3.6	2/3.2	
	Alcoholic cirrhosis	8/7.1	2/3.2	
	Cryptogenic cirrhosis	25/41.1	7/35.5	
	Fatty liver	20	13	
	Other reasons	30	17	
CPS (n, %)	A	67/59.8	46/74.2	0.163
	B	36/32.1	14/22.6	
	C	9/8.0	2/3.2	

CPS: Child-Pugh Score, SD: Standard deviation, COVID-19: Coronavirus disease-2019

Table 4. Characteristics of symptomatic and asymptomatic COVID-19 cases

		Symptomatic, (n=41)	Asymptomatic, (n=21)	p
Age (mean/SD)		56.3±9.3	58.8±11.8	0.14
Gender (n, %)	Male	23	10	0.5
	Female	18	11	
Etiological diagnosis (n, %)	Viral hepatitis	19	2	0.003
	Autoimmune hepatitis	2	0	0.54
	Alcoholic cirrhosis	1	1	0.61
	Cryptogenic cirrhosis	1	6	0.002
	Fatty liver	9	4	0.79
	Other reasons	9	8	0.17
CPS (n, %)	A	33	14	0.3
	B	7	6	
	C	1	1	

CPS: Child-Pugh Score, SD: Standard deviation, COVID-19: Coronavirus disease-2019

symptoms, such as abdominal pain and diarrhea, and 16.1% had other symptoms, such as headache and loss of smell. Of patients with cirrhosis and symptomatic COVID-19, 51.7% received outpatient treatment, 38.7% received inpatient treatment, and 9.6% required intensive care unit treatment.

Among the COVID-19 seropositive patients, new decompensation was seen in 6 patients (9.6%). The clinical features of patients who developed decompensation are presented in Table 6.

Discussion

In this study, we found anti-SARS-CoV-2 IgG seropositivity in 35.6% of patients with cirrhosis. The rate of COVID-19 infection with symptoms was 23.6%, and the rate of asymptomatic patients was 12%. When the literature is searched, different incidence and prevalence rates related to COVID-19 are encountered in studies conducted in various regions and at different times in patients with liver cirrhosis. In two studies conducted on hospitalized patients, the incidence of COVID-19 in patients with cirrhosis was 6.6% and 16.8%, respectively (8,9). In the seroprevalence study of Del Zompo et al. (5) in patients with cirrhosis, the rate of asymptomatic COVID-19 was found to be 1.9%. In our study, the rate of COVID-19 infection was quite high in patients with cirrhosis. The longer study period compared with other studies may have caused this rate to be higher. However, reasons such as the overpopulation of İstanbul, the lifting of curfews during the study period, and the lack of vaccination may have increased the risk and incidence of COVID-19 transmission.

In the meta-analysis conducted by Sah et al. (10), the estimated rate of asymptomatic COVID-19 infection among patients with COVID-19 infection was reported as 36.9%. In a study conducted by Brozat et al. (11), 62.5% of 70 patients with COVID-19-positive cirrhosis were found to have symptoms and 37.5% had asymptomatic infections. Respiratory symptoms and fever are observed most frequently in patients with symptomatic infection (11).

In our study, 66% of patients with COVID-19-positive cirrhosis had symptoms and 34% were asymptomatic, which is similar to the results of both the general COVID-19 population and Brozat et al. (11). Additionally,

Table 5. Laboratory parameters and liver disease status of symptomatic and asymptomatic patients before and after COVID-19

	Symptomatic (n=41)		Asymptomatic (n=21)		sPRE-asPRE	sPOS-asPOS
	Pre-COVID	Post-COVID	Pre-COVID	Post-COVID	p	p
Hgb (g/dL)	12.3±2.1	12.1±2.1	11.9±2.6	11.9±2.3	0.6	0.6
WBC (µL)	5.06±1.8	5.09±2.0	5.57±1.8	5.13±0.18	0.9	0.6
Neutrophils (µL)	2.9 (1.9)	2.7 (2)	3.2 (1.7)	2.9 (1.5)	0.2	1
Lymphocyte (µL)	1.2 (0.7)	1.1 (0.8)	1.3 (1)	1.3 (1)	0.9	0.7
Neutrophils/lymphocyte ratio	2.3 (1.8)	2.4 (1.8)	2.2 (1.9)	2.3 (2.1)	0.4	0.5
Platelet (µL)	97 (91)	106 (64)	118 (112)	108 (129)	0.1	1
ALT (IU/L)	27 (23)	28 (20)	24 (22)	22 (11)	0.4	0.1
n (%), normal ALT	76	78	81	85	0.6	0.4
AST (IU/L)	34 (26)	35 (17)	27 (24)	30 (21)	0.5	0.1
n (%), normal AST	63	66	66	76	0.8	0.4
Total bilirubin level (mg/dL)	0.9 (0.9)	0.9 (1.1)	1.2 (2)	1.2 (2.1)	0.1	0.4
Alkaline phosphatase (IU/L)	102 (62)	106 (74)	94 (69)	98 (69)	0.2	0.5
GGT (IU/L)	61 (69)	61 (77)	49 (93)	44 (109)	0.5	0.1
Albumin (g/dL)	3.9±0.6	3.7±0.7	3.9±0.5	3.7±0.6	0.5	0.4
INR	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	1.2 (0.4)	0.8	1
Creatinine (mg/dL)	0.7 (0.2)	0.7 (0.3)	0.8±0.4	0.7 (0.3)	1	0.7
CPS						
A	33	28	13	15		
B	7	9	7	4	0.2	0.9
C	1	4	1	2		
MELD-Na	11 (5)	10 (7)	10.5 (6)	10.5 (9)	0.8	0.8

Hgb: Hemoglobin, WBC: White blood cell, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, CPS: Child-Pugh Score, MELD: Model for End Stage Liver Disease, sPRE: Symptomatic patients before COVID-19, asPRE: Asymptomatic patients before COVID-19, sPOS: Symptomatic patients after COVID-19, asPOS: Asymptomatic patients after COVID-19, COVID-19: Coronavirus disease-2019

Table 6. COVID-19 seropositive patients developing hepatic decompensation

	Total (n=62)	Symptomatic, (n=41)	Asymptomatic, (n=21)
Decompensation	6 (9.6%)	4 (6.4%)	2 (3.2%)
Newly developed ascite	3 (4.8%)	3 (4.8%)	0
Hepatic encephalopathy	3 (4.8%)	1 (1.6%)	2 (3.2%)

COVID-19: Coronavirus disease-2019

respiratory symptoms and fever are in the first place in symptomatic patients. In our study, 51.7% of patients with cirrhosis and symptomatic COVID-19 received outpatient treatment, 38.7% received inpatient treatment, and 9.6% received intensive care unit treatment. These rates show that approximately half of the patients with COVID-19 with cirrhosis are hospitalized. According to data from the Turkish Ministry of Health, 21.1% of patients with COVID-19 were treated in hospital wards and 7.4% in intensive care units (12). Compared with these rates, the rate of hospitalized patients with cirrhosis due to COVID-19 seems to be higher than that of the general population.

Another result observed in our study was that the symptomatic infection rate was significantly higher in patients with liver cirrhosis due to chronic viral hepatitis, whereas the asymptomatic infection rate was significantly higher in patients with cryptogenic cirrhosis. Studies investigating the effect of viral hepatitis on COVID-19 have reported that COVID-19 infection progresses with more severe symptoms in this patient group. It has been stated that impaired intestinal flora in patients with viral hepatitis plays a role in the development of this condition (13,14). There are no studies or subgroup analyses on the relationship between cryptogenic cirrhosis and COVID-19 infection. It is not possible to determine from the current literature whether the reason for the high rate of asymptomatic infection in this patient group is a coincidence or if there is another reason.

Many studies and meta-analyses have evaluated the impact of COVID-19 infection on liver function. It has been reported that approximately half of patients with COVID-19 have elevated liver enzyme levels upon admission to the hospital, and similarly, aminotransferase levels are increased in patients with previous chronic liver disease (15,16). In the

follow-up of patients with COVID-19 with hepatic dysfunction until the second month after discharge, high aminotransferase and GGT levels decrease over time, and a longer follow-up period is recommended in some patients (17). In our study, the reason why there was no significant difference in liver function tests in both the asymptomatic and symptomatic groups before and after COVID-19 infection was thought to be that the tests returned to normal over time in the post-infection period.

There are many factors associated with liver injury during COVID-19. These include the direct cytopathogenic effects of the virus, abnormal immune responses associated with cytokine storms, vascular changes due to coagulopathy, hepatic ischemia/hypoxia-related injury, reactivation of existing liver disease, and drug-induced liver injury. Coronavirus directly causes liver damage through the use of the angiotensin-converting enzyme 2 receptor for cell entry, which is expressed mainly in cholangiocytes and less frequently in hepatocytes (3,14).

In the study of Moon et al. (18) in patients with cirrhosis who were followed up for COVID-19, hepatic decompensation was observed in 36.9% of the patients. New ascites formation or worsening of existing ascites developed in 27.2% of the patients, hepatic encephalopathy in 16.9%, spontaneous bacterial peritonitis in 2.9%, and variceal bleeding in 1%. In our study, no significant differences were observed in liver test results, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients with COVID-19. On the other hand, 9.6% of the 62 patients with COVID-19 developed new decompensation. The lack of a significant difference in these results between the asymptomatic and symptomatic groups before and after COVID-19 infection may be explained by the fact that CPS A class patients constituted the majority in both groups, and the liver functions of these patients were largely preserved.

Study Limitations

The small patient population, especially in patients with decompensated liver cirrhosis, the single-center design, and the absence of a control group are considered important limitations of our study. Additionally, the retrospective nature of the study and the possibility that patients showed mild symptoms such as weakness, fatigue, and subfebrile fever and did not remember them may have affected the ratio of symptomatic to asymptomatic patients.

Conclusion

As a result of, the incidence of COVID-19 infection among patients with liver cirrhosis is notably high, with approximately half of these patients requiring hospitalization and some of them had to be treated in intensive care unit. There is no significant differences in the course of existing liver disease according to the clinical form of the disease. Although high decompensation rates were reported in the acute phase of the disease, such rates were not observed in the post-infection period. Nevertheless, hepatic decompensation can also develop in this patient group, and considering the magnitude of the impact of hepatic decompensation in terms of patient and healthcare costs, close follow-up of patients in this regard is of great importance.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 83088843-604.01.01-73299, date: 16.07.2020).

Informed Consent: Informed consent was obtained from the patients.

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