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COVID-19 in chronic liver patients; great danger for cirrhosis patiens

Kronik karaciğer hastalarında COVID-19; siroz hastaları için büyük tehlike

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ABSTRACT

Aim: The aim of this study; to investigate the clinical course and mortality of COVID-19 in chronic liver patients with and without cirrhosis and to determine decompensation rates during COVID'19 in cirrhotic patients.

Materials and Methods: 96 patients with chronic liver disease (30 of them cirrhosis) and 153 patients without any comorbid disease were included in this study. It was examined whether there was a difference among these patient groups in terms of severity and mortality of COVID-19.

Results: Severe COVID-19 developed in 46.6% (14/30) cirrhotic patients, in 15.1% (10/66) non-cirrhotic patients, and in 12.4% (19/153) patients with no chronic liver disease (p<0.001). Although mortality was seen in 26.7% (8/30) cirrhotic patients and 1.3% (2/153) of the patients with no chronic liver disease, none of the patients in non-cirrhotic group was died. The rate of mortality in the cirrhotic patient group was statistically significantly higher than in the control group (26.6% vs 1.3%; p<0.001). In the patients with cirrhosis, the Child-Pugh score increased from 6.4 to 8 (p=0.004) and the MELD score from 10.4 to 15.8 during the course of COVID-19 (p<0.001).

Conclusion: As a result of our study; we conclude that in patients with chronic liver disease, the risk of developing severe COVID-19 and death is similar to patients without liver disease if the patient does not have cirrhosis. This shows us that preserved hepatic reserve can tolerate inflammation. However, we determined that COVID-19 developing in cirrhotic patients was more severe than in patients without cirrhosis and its mortality was quite high. The results of this study showed us that COVID-19 is an increased risk factor for mortality in patients with cirrhosis, as in other chronic diseases.

Keywords: COVID-19; chronic liver disease; cirrhosis; prognosis; mortality.

ÖZ

Amaç: *Sirozu olan ve olmayan kronik karaciğer hastalarında COVID-19'un klinik seyrini ve mortalitesini araştırmak ve sirotik hastalarda COVID'19 sırasında kompansasyon oranlarını belirlemek.*

Gereç ve Yöntem: *Bu çalışmaya, kronik karaciğer hastalığı olan 96 hasta ile (30 tanesi sirotik) herhangi bir komorbid hastalığı bulunmayan 153 hasta alındı. Bu hasta grupları arasında COVID-19'un şiddeti ve mortalitesi açısından fark olup olmadığı incelendi.*

Bulgular: *Sirotik hastaların %46,6'sında (14/30) non-sirotik hastaların %15,1'inde (10/66), kronik karaciğer hastalığı olmayan hastaların %12,4'ünde (19/153)'ünde ağır COVID-19 gelişti (p<0.001). Sirotik hastaların %26,6'sında (8/30) ölüm görülmesine rağmen, kronik karaciğer hastalığı olanlarda ölüm oranı %1,3 (2/153) oldu. Sirotik olmayak kronik karaciğer hastalarında ise mortalite görülmedi. Sirotik hastalarda ölüm oranı kontrol grubundaki hastalara göre anlamlı derecede yüksekti (%26,6'ya karşı %1,3; p<0.001). Sirotik hastaların COVID-19 sırasında Child-Pugh skoru 6,4'ten 8'e (p=0.004) MELD skoru ise 10,4'ten 15,8'e yükseldi (p<0.001).*

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Sonuç: *Çalışmamız sonucunda; kronik karaciğer hastalarında, eğer hastanın sirozu yoksa ağır COVID-19 gelişme ve ölüm riskinin karaciğer hastalığı olmayan hastalarla benzer olduğu sonucuna ulaştık. Bu bize korunmuş hepatik rezervin, inflamasyonu tolere edebildiğini gösteriyor. Fakat sirotik hastalarda gelişen COVID-19'un, sirozu olmayan hastalara göre daha ağır seyrettiğini ve mortalitesinin oldukça yüksek olduğunu belirledik. Bu çalışmanın sonuçları bize sirozlu hastalarda COVID-19'un diğer kronik hastalıklarda olduğu gibi mortalite için artmış bir risk faktörü olduğunu gösterdi.*

Anahtar Sözcükler: *COVID-19; kronik karaciğer hastalığı; siroz; prognoz; mortalite.*

INTRODUCTION

The novel coronavirus-2019 disease (COVID-19), caused by the SARS-CoV-2 virus, basically affects the upper respiratory tract and lungs. While most patients can recover with mild symptoms, in those of advanced age or in high-risk groups, acute respiratory distress syndrome associated with severe pneumonia can lead to sepsis, septic shock and multiorgan dysfunction, and ultimately death. Since the end of 2019, the COVID-19 pandemic has caused at least 170 million cases and 3.5 million deaths worldwide at the time of writing (1).

Other than the lungs, COVID-19 also affects other systems. Angiotensin converting enzyme 2 (ACE2) receptors, by which the virus enters cells, are also found in hepatocytes and cholangiocytes (2). In addition, the cytokine storm formed with the effect of several inflammatory mediators such as interleukin-1 (IL-1) and IL-6, interferon-γ, and granulocyte colony stimulating factor, which emerge during the course of COVID-19, causes liver damage (3). Intrahepatic immune activation, microvascular thrombosis, and intestinal-liver perturbation have also been held responsible (4-6).

A more severe COVID-19 course and mortality have been reported at higher rates in patients with chronic diseases such as hypertension, diabetes and chronic obstructive pulmonary disease (COPD) (7-9).

The aim of our study was to investigate the clinical course of COVID-19 in patients with chronic liver disease. In this patient group, we tried to answer the question of whether the rate of development of severe COVID-19 and mortality are different from patients without liver disease. In addition, we examined whether patients with cirrhosis, known to have decreased liver reserve, pose a risk such as hypertension and diabetes, which are reported to have a more severe course of COVID-19 in the literature.

MATERIALS and METHODS

A total of 249 COVID-19 patients, who admitted our hospital between April and November 2020, with positive PCR tests were recruited in this study. Of these patients, 96 had previously known chronic liver disease. As the control group, 153 patients in the similar age group but without any chronic disease were included.

Patients with chronic liver disease; they were divided into two groups as patients with cirrhosis and those without cirrhosis. It was statistically examined whether there was a difference between the patients in the control group and patients with chronic liver disease (cirrhotic and non-cirrhotic) between the development of severe COVID-19 and mortality.

During the treatment of COVID-19, patient's data belongs to liver dysfunction, coagulation disorders, and decompensation symptoms such as ascite, encephalopathy, and hepatorenal syndrome were recorded. The Child-Pugh and MELD scores of patients with cirrhosis before Covid-19 were compared with the Child-Pugh and MELD scores during Covid-19 infection. Child-Pugh and MELD scores were calculated based on clinical and laboratory data for cirrhotic patients every 3 days while they were hospitalized. The mean values of these scores were used in statistical analysis. It was attempted to determine how much decompensation developed in cirrhotic patients. The decompensation criteria were defined based on the ACLF and APASL criteria (jaundice [serum bilirubin >85umol/L] and/or coagulopathy [international normalised ratio, INR>1.5] complicated by ascite or encephalopathy within 4 weeks) (10). Evaluation was also made of whether more severe COVID-19 and mortality developed in chronic liver disease patients with or without cirrhosis.

In accordance with the guideline recommendations, patients who did not have lung infiltration but had symptoms such as fever, headache, cough, loss of taste and smell, widespread body pain, diarrhea, and patients with lung infiltration but with oxygen saturation >92% were considered mild COVID-19.

Oxygen saturation is below 92% despite supplementation with oxygen, who needs non-invasive or mechanical ventilation, has a PaO 2

/FiO 2 ratio of <300 mm according to blood gas analysis, a respiratory rate >30 breaths/minute or lung infiltrates >50%. Also patients with septic shock or multi-organ failure were considered severe COVID-19 (11). Thus, liver functions and other laboratory parameters of patients with severe and mild COVID-19 were compared.

Ethics committee approval was obtained from the ethics committee of our hospital for the study, dated 16/10/2020, number 611.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS for Windows v. 26.0 software (SPSS Inc., Chicago, IL, USA). The distribution of continuous data was assessed with the Shapiro-Wilk test, variation coefficient, skewness and kurtosis. Continuous variables were stated as mean ± standard deviation (SD), or median, minimum and maximum values and categorical variables as number (n) and percentage (%). The difference in the distribution of categorical data between the groups was analyzed with the Chi-square test. One-way ANOVA test was applied to determine the difference between the patients with chronic liver disease (cirrhotic and non-cirrhotic) and the patients in the control group, such as demographic data such as age and gender, length of hospital stay, mild and severe COVID-19 development rate, mortality. In the initial comparisons between the mild and severe COVID-19 groups, the Student's t-test was applied to parameters with normal distribution, and the Mann Whitney U-test to parameters not showing normal distribution. In the comparisons of patients with and without liver disease and cirrhotic patients, in groups with homogeneity of variances, the one-way Anova test was applied. To determine from which group the difference originated, Bonferroni correction was used. In groups where variances were not homogenously distributed, the Welch ANOVA or Kruskal Wallis tests were applied. Paired t-test or Wilcoxon test was used to determine the difference between MELD and Child-Pugh scores before and during COVID-19 in patients with cirrhosis. In all the tests, a two-tailed p value of <0.05 was accepted as statistically significant.

RESULTS

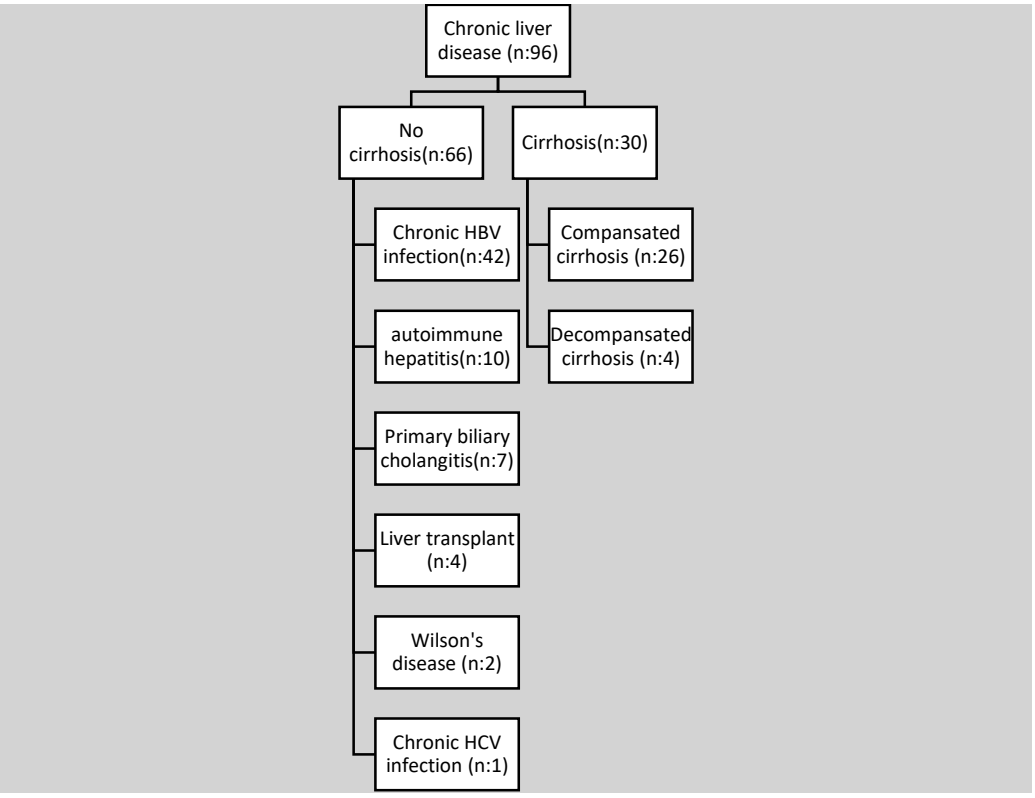
A total of 249 patients were included in our study. 153 of these patients constituted the control group without any chronic disease. 96 patients also had known chronic liver disease. While 26 (86.7%) patients with cirrhosis had compensated liver cirrhosis; 4 patients (13.3%) had decompensated liver cirrhosis. The most common etiologic cause in patients with non-cirrhotic chronic liver disease; chronic HBV infection (n=42). Other etiologic causes were autoimmune hepatitis (n=10), primary biliary cholangitis (n=7), liver transplantation (n=4), Wilson's disease (n=2) and chronic HCV infection (Table-1).

While the mean age of patients with cirrhosis was 65.8±14.0 (42-90), the mean age of patients with chronic liver disease without cirrhosis was 40.9±14.1 (20-75). The mean age of the control group was 53.1±10.7 (23-68). The total patient group comprised 130 (52.2%) females and 119 (47.8%) males. Severe COVID-19 developed in 14/30 (46.6%) cirrhotic patients, and in 10/66 (15.1%) non-cirrhotic patients. Severe COVID-19 developed in 19 (12.4%) patients in the control group (p<0.001). Mortality occurred in 8 patients with cirrhosis, all of whom died due to severe respiratory failure related to COVID-19. In the control group of 153 patients, mortality was seen in 2 patients. The rate of mortality in the cirrhotic patient group was statistically significantly higher than in the control group (26.6% vs 1.3%; p<0.001). The length of stay in hospital was longer in the patients with cirrhosis (16.6 days vs.8.2 days) (Table-2).

Significant differences were determined between the laboratory values of patients who had mild and severe Covid-19. While the mean albumin level of patients with mild COVID-19 was 4±0.3 g/dl, it was 2.8±0.5 g/dl in patients with severe COVID-19 (p<0.001). AST level was different in patients with mild and severe COVID-19. (40.4±21.2 vs 84.4±52.7 (IU/L) P=0.039) While the LDH level of patients with mild COVID-19 was 278.2±117.3 IU/L, this value was 374.5±108.9 IU/L in patients with severe COVID-19 (p=0.049). A statistically significant difference was found between the sodium levels of patients with mild and severe COVID-19, although not clinically. (138.9±2.6 vs 134.7±2.1 (mmol/L); p<0.001). Significant differences were found between the markers of inflammation in patients with mild and severe COVID-19. The mean CRP level of patients with mild COVID-19 was 28.7±43.9 mg/L, while the CRP level of patients with severe COVID-19 was 81.0±51.3 mg/L (p=0.010). In parallel, patients with severe COVID-19 had a higher mean ferritin level

(494.3±396.8 µg/L vs 202.7±214.1 µg/L; p=0.036). In severe COVID-19 patients, more severe lymphopenia developed. The mean lymphocyte count of patients with mild COVID-19 was 1461±576 cell/µl; in severe COVID-19 patients it was 702±423 cell/µl (p=0.002). More thrombocytopenia developed in patients with severe COVID-19. (93.4±41.3 103 cell/µl vs 204.6±75.4 103 cell/µl; p<0.001) (Table-3).

Table-1 Distribution of patients with chronic liver disease according to their etiology.



(HBV: Hepatitis B virus, HCV: Hepatitis C virus)

Table-2. Demographic data of cirrhotic and non-cirrhotic liver patients and patients in the control group, the average length of stay in the hospital, and the number of patients who died between groups.

	Cirrhotic patients	**Chronic liver disease patients without cirrhosis**	**Covid-19 patients without liver disease and comorbid conditions**	**P***
Age	**65.8±14.03*** (42-90)	40.94±14.19 (20-75)	53.14±10.77 (23-68)	0.001
Gender				
Female	17 (56.7%)	35 (53%)	78 (51%)	
Male	13 (43.7%)	31 (%7%)	75 (49%)	
Severe Covid-19	**14 (46.6%)***	10 (15.1%)	19 (12.4%)	<0.001
Death	**8* (26.6%)**	0	2 (1.3%)	<0.001
Days of hospitalization	**16.6*** (3-22)	8.2 (6-37)	8.0 (4-19)	0.002

*One-way ANOVA test/ Chi-square test

Table-3. Difference between laboratory parameters of patients with mild and severe Covid-19

Parameters	Mild Covid-19±SD	Severe Covid-19±SD	P*
Albumin (g/dL)	4.00±0.39	2.87±0.57	**<0.001**
ALT(IU/L)	42.12±24.58	62.1±36.94	0.100
AST(IU/L)	40.47±21.26	84.44±52.77	**0.039**
ALP(IU/L)	99.53±38.19	101.12±54.76	0.935
GGT(IU/L)	68.63±48.58	103.45±51.3	0.098
LDH(IU/L)	278.24±117.31	374.55±108.9	**0.049**
T. Bilirubin (mg/dL)	0.91±0.83	1.37±0,34	0.128
INR	1.16±0.10	1.25±0.13	0.059
Sodium(mmol/L)	138.95±2,67	134.78±2.10	**<0.001**
Creatinine(mg/dL)	0.85±0.23	0.83±0.21	0.791
D-Dimer (ng/mL)	289.95±250.88	843.67±546.47	0.016
CRP (mg/L)	28.79±43.99	81.00±51.31	**0.010**
Ferritin (μg/L)	202.74±214.17	494.33±396.82	**0.036**
WBC (cell/μl)	6422±1726	5937±1848	0.504
Lymphocyte (cell/μl)	1461±576	702±423	**0.002**
Platelet (10^3 cell/μl)	204.68±75.43	93.44±41,38	**<0.001**
WBC/Lymphocyte	4.89±1.85	11.41±7.05	**0.001**

(*Student's t-test or Mann Whitney U-test, SD: standard deviation, ; ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; ALP: alkaline phosphatase, GGT: gamma glutamyl transpeptidase WBC: white blood cell)

Of the 26 patients with compensated liver cirrhosis, decompensation developed in 13 (50%). The most frequently observed symptom of decompensation in the cirrhotic patients was ascite, which developed in 38.4% of the patients, followed by coagulopathy in 19.2%. In the patients with cirrhosis, the Child-Pugh score statistically significantly increased from 6.4 to 8 (p=0.004) and the MELD score from 10.4 to 15.8 during the course of COVID-19 (p<0.001).

DISCUSSION

As a result of this study, the course of COVID-19 in patients with non-cirrhotic chronic liver disease was determined to be similar to that of patients with no chronic liver disease. The risk of severe COVID-19 and mortality was similar in patients with non-cirrhotic chronic liver disease and patients with no chronic liver disease. However, patients with compensated or decompensated cirrhosis of the liver were determined to be at a much greater risk of severe COVID-19 and associated mortality.

The increasing inflammation load in cirrhotic patients cannot be tolerated by the liver, and hepatic decompensation develops rapidly, as a result of which COVID-19 becomes a severe ARDS and multiorgan dysfunction table, resulting in mortality (12).

In the examination of the liver functions of the current study patients, hepatocellular damage was determined to be more evident than cholestatic damage. No significant difference was seen between the mild and severe COVID-19 patients in respect of the change in ALP and

GGT levels, although a difference was seen in that the ALT and AST levels were parallel to the severity of COVID-19. In a study by Tapper et al in 2015, it was reported that hypoxia affected the centrolobular region in the liver first, and with the development of necrosis in this region, ALT and AST elevation developed to exceed a level 20-fold of normal (13).

Mortality rates were higher in the presence of liver cirrhosis in the current study. Decompensation developed in one of every two patients with cirrhosis of the liver. There was a significant increase in the Child-Pugh and MELD scores of these patients and mortality occurred at a high rate in this patient group. The cause of death in these patients was not liver failure, but the very severe course of respiratory failure and the occurrence of hypoxia which could not be corrected despite mechanical ventilation and the development of multiorgan dysfunction associated with hypoxia. This situation could be related to an insufficient immune response in cirrhotic patients.

Parallel results have been obtained in other studies conducted in this context. In a large cohort study, hepatic decompensation developed in 46% of cirrhotic patients, and the initial grade of cirrhosis was shown to be an independent risk factor for COVID-19-related death (14). In another study, the presence of chronic liver disease was emphasized as a serious risk factor in the determination of the course of COVID-19 (15). The effect of chronic liver disease on COVID-19 was investigated in another study, and decompensation was reported at the rate of 20% and mortality at 43%, and the Child-Pugh score was seen to be predominant as a predictive marker of mortality (16).

In a broad-based study, the mortality rate in diabetes and hypertension patients who developed COVID-19 was found to be considerably higher than in COVID-19 patients without comorbid disease (17-18). In our study, we found a higher mortality rate during COVID-19 in cirrhotic patients than in patients without comorbid disease. This result shows us that patients with cirrhosis have an increased risk of mortality during COVID-19, just like diabetes and hypertension.

CONCLUSION

The results of this study showed that if cirrhosis does not develop, patients with a chronic liver disease have a similar risk of severe COVID-19 and mortality as other patients. As cirrhosis has not developed in these patients, it can be said that the increasing inflammation load can be tolerated by the existing hepatic reserve. It is not possible to say the same for cirrhotic patients. When the Child-Pugh and MELD scores increase in patients with cirrhosis of the liver, there is an increased risk of severe COVID-19 and of associated mortality.

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Author Contributions

Idea/Concept: Berat Ebik; **design**: Nazım Ekin; **checking/consultancy:** Ferhat Bacaksız; **data collection and/or processing:** Jihat Kılıç; **analysis and/or interpretation:** Nazım Ekin **literature review:** Jihat Kılıç; **writer of the article:** Berat Ebik; **critical review:** Ferhat Bacaksız; **materials**: Jihat Kılıç.

Ethics committee approval

Ethics committee approval was obtained from the ethics committee of our hospital for the study, dated 16/10/2020, number 611. Written consent was obtained from the patients for the use of pre-study data. The entire work was developed in accordance with the Helsinki Declaration regulation.

Conflict of interest: The authors report no relevant conflict of interest or disclo-sures relevant to this viewpoint.

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