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Evaluation of patients with hepatic cirrhosis due to etiology for the complication

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ABSTRACT

Objectives: Hepatic cirrhosis is a disease with high mortality. The leading causes of morbidity and mortality in patients with hepatic cirrhosis are disease-associated complications. We aimed to describe the association between the difference in laboratory parameters, complications, and commonly known causes of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (NASH), and autoimmune hepatitis.

Methods: We investigated 541 patients with different etiologies of cirrhosis who applied to a gastroenterology clinic from 2009 to 2018 in Florance Nightingale Hospital. All patients were divided into five groups according to the etiology of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, and autoimmune hepatitis. Biochemical and metabolic parameters were evaluated between five groups.

Results: 83 patients with alcoholic liver disease, 242 patients with hepatitis B-associated cirrhosis, 112 patients with hepatitis C-associated cirrhosis, 77 patients with NASH, and 27 patients with autoimmune hepatitis were enrolled. Laboratory parameters due to the etiology of hepatic cirrhosis are shown in Table 2. Ascites and hepatic encephalopathy were statistically higher in alcoholic liver disease, hepatitis B, and NASH cirrhosis, while esophageal variceal bleeding was higher in NASH and autoimmune hepatitis. Spontaneous bacterial peritonitis was statistically higher only in cirrhosis due to autoimmune hepatitis.

Conclusion: It is very important to assign complications that may develop in liver cirrhosis and manage them by etiology.

Keywords: Cirrhosis, Mortality, Etiology

Cirrhosis is the late stage of progressive hepatic fibrosis caused by various liver diseases. It is the 11th most common cause of death and accounts for 3.5% of all-cause mortalities.[1] There are many causes of liver disease which can result in cirrhosis. The epidemiology of liver cirrhosis can be different with socioeconomic conditions. The significant causes of cirrhosis in European and American countries are chronic hepatitis C and alcoholic liver disease.[2-3] Chronic hepatitis B is the primary etiology of cirrhosis in Turkey.[4] Chronic hepatitis C, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and autoimmune hepatitis are the other causes of cirrhosis in Turkey.

The clinical manifestations of cirrhosis include nonspecific symptoms such as weight loss, weakness, fatigue, and complications of hepatic decompensation such as esophageal varices bleeding, ascites, and confusion due to hepatic encephalopathy. Laboratory abnormalities can be elevated serum bilirubin, abnor-

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mal aminotransferases, elevated alkaline phosphatase/gamma-glutamyl transpeptidase, a prolonged prothrombin time/elevated international normalized ratio (INR), hyponatremia, hypoalbuminemia, and thrombocytopenia.

Laboratory parameters and complications can be different depending on the etiology of cirrhosis. Therefore, we aimed to describe the association between the difference in laboratory parameters, complications, and commonly known causes of cirrhosis, such as hepatitis B, hepatitis C, alcoholic liver disease (ALD), and autoimmune hepatitis.

METHODS

Study Participants

The Haseki Training and Research Hospital Ethics Committee, University of Health Sciences, Istanbul, Turkey, approved the study. This retrospective cohort study was conducted following principles of good clinical practice and the declaration of Helsinki. We investigated 541 patients (409 men and 132 women) with different etiologies of cirrhosis who applied to the gastroenterology clinic from 2009 to 2018 in Florance Nightingale Hospital. Patients under 18 years, patients with cardiovascular disease (congenital heart disease, valvular heart disease, coronary heart disease), severe lung disease, thrombo-embolism, kidney disease, and active infection were excluded.

The current study was organized using a computerized database in Florance Nightingale Hospital. Data for the study analyses were derived from the electronic hospital management system dispensing records and Florance Nightingale Hospital profile databases. Standardized data collection includes patient demographic information, medical history, abdominal ultrasound, and laboratory examination. Demographic data, medical history, vital signs at admission, medication, and final diagnosis were obtained from patients' electronic medical records.

Laboratory Measurements

Routine blood samples were drawn between 6:00 am and 7:00 am, in the morning. After a 12-hour fasting period, blood samples were drawn and analyzed immediately afterward. Alanine transaminase (ALT), aspartate transaminase (AST), serum albumin (ALB), bilirubin, prothrombin time (PT), total cholesterol (TC), triglyceride, low-density lipoprotein (LDL), high-density lipoprotein, white blood cell (WBC) count, red blood cell (RBC) count, platelet count, blood glucose, hemogram were analyzed in the laboratory of Florance Nightingale Hospital, University of Bilim. The laboratory findings were obtained from the patient's electronic medical records at the hospital. Biochemical parameters were performed for all participants.

All patients were divided into five groups such as hepatitis B, hepatitis C, alcoholic liver disease ALD, NASH, and autoimmune hepatitis according to the etiology of cirrhosis. Viral hepatitis was diagnosed with positive hepatitis serology (positive hepatitis B surface antigen for more than six months or positive hepatitis C virus). ALD was diagnosed with a history of alcohol intake (more than 21 units of alcohol per week for males and 14 units per week for females). NASH was diagnosed in patients with the presence of hepatic steatosis on imaging or histology in the absence of significant alcohol consumption. Autoimmune hepatitis was diagnosed with positive autoimmune antibodies. Biochemical and metabolic parameters were evaluated between five groups.

Paracentesis was performed in patients with ascites, and serum ascites albumin gradient was measured. Neutrophil levels in ascites fluid were examined in the laboratory, and values above 250/mm3 were evaluated as peritonitis. A gastroenterologist performed endoscopy, and the presence of esophageal varices was examined. Endoscopic band ligation and medical treatment were applied to patients hospitalized due to variceal bleeding.

Statistical Analysis

Data are expressed as the mean ± standard deviation. A statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Basic descriptive statistics, including the means, standard deviations, ranges, and percentages, were measured. The normality of the distribution was examined using the Kolmogorov–Smirnov test. The Mann compared

Table 1. Frequency of cirrhosis patients according to etiology

	Frequency	Percent (%)
Alcoholic Liver Disease	83	15
Hepatitis B Virus	242	44,7
Hepatitis C Virus	112	20,7
Nonalcoholic Steatohepatitis	77	14,2
Autoimmune Hepatitis	27	5,9

Table 2. Comparison of laboratory parameters related to the etiology of hepatic cirrhosis

	Alcoholic Liver Disease Group 1	Hepatitis B Virus Group 2	Hepatitis C Virus Group 3	Nonalcoholic Steatohepatitis Group 4	Autoimmune Hepatitis Group 5	P value
Age	54,7±7,9	53,2±7,6	55,9±7,4	59,1±7,1	45,6±13,9	IV, VI, VII, IX,X
Glucose	120,4±45,3	111,3±42,2	112,8±39,5	126,7±47,9	94,6±20,9	IV, VI, VII,IX,X
Body Mass Index	27,8±4,2	27,3±3,8	27,8±4,7	30,4±5,1	26,8±5,2	III, VI, VIII, X
MELD Score	17,1±4,7	14,9±5,9	15,2±5,3	15,8±4,8	18,7±4,9	VII
CHILD Score	9,2±1,9	8,2±2,5	8.6±2.2	8.3±1.9	9.5±1.8	NS
Hemoglobin	11.1±2.2	12.4±2.3	11.7±2.2	11.3±2.1	10.2±1.9	I, VI, VII
Platelet	121593±116491	96698±57580	89650±48927	96884±42746	139429±93565	NS
INR	1,6±0,3	1,6±0,5	1,6±0,5	1,6±0,3	1,6±0,4	NS
AST	59,8±37,7	78,1±69	84,9±55,7	48,6±25,1	118,5±88,4	IV, VI, VIII, X
ALT	39,6±24,9	55,9±52,8	56,3±38,9	32,1±24,9	74,8±56,1	VI. VIII, X
ALP	170,1±126	157,7±112,5	130,4±78,1	128,5±80,8	296,2±212,3	IV.VII.IX.X
GGT	99,5±90,1	107,9±158,2	80,3±79,8	117,1±246,8	214,6±290,2	IV.VII.IX
Albumin	3±0,5	3,2±0,7	3±0,6	2,9±0,6	2,8±0,5	NS
Total Bilirubin	4,4±4,6	3,8±5,2	3,8±4,2	3,1±3,6	8,9±8,9	IV.VII.IX.X
Creatinine	1±0,4	0,9±0,4	0,9±0,7	1±0,5	0,8±0,9	NS
Total cholesterol	141,7±54,5	138,1±50,1	122,9±46,6	127,9±41,1	140,1±69,7	NS
TSH	2,8±2,5	1,9±1,5	2,5±2,9	2,5±2,6	1,8±1,1	NS
AFP	25,3±116,3	54,9±144,9	42,7±89,8	6,9±12,3	9,9±34,3	NS

Statistical significance is shown in bold-faced type ($p < 0.05$). INR= International Normalized Ratio; AST = aspartate aminotransferase; ALT= alanine aminotransferase; ALP= alkaline phosphatase; GGT= gamma-glutamyl transferase ; TSH =thyroid stimulating hormone; AFP= alpha-fetoprotein I Group 1 versus 2, II Group 1 versus 3, III Group 1 versus 4, IV Group 1 versus 5, V Group 2 versus 3, VI Group 2 versus 4, VII Group 2 versus 5, VIII Group 3 versus 4, IX Group 3 versus 5, X Group 4 versus 5 NS not significant

mean values between two independent groups-the Whitney U test for continuous variables and the $\chi 2$ test for categorical parameters; comparisons between more than two subgroups were performed by ANOVA and Kruskal–Wallis h tests. Bivariate correlations were explored by Pearson's (continuous variables). Differences were considered statistically significant if the two-tailed P value was less than 0.05.

RESULTS

541 patients who had either hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, or autoimmune hepatitis as the primary etiology of the cirrhosis were included in the study. 83 patients with alcoholic liver disease, 242 patients with hepatitis B-associated cirrhosis, 112 patients with hepatitis C-associated cirrhosis, 77 patients with NASH, and 27 patients with autoimmune hepatitis were enrolled. The patients were predominantly male except for the cirrhosis from the autoimmune hepatitis cohort, where the female patients were dominant. The mean age and age range of these patients were shown in Table 1 that NASH-associated cirrhosis was more often in the older age group, and autoimmune hepatitis-associated cirrhosis was in the younger age group. The autoimmune hepatitis-associated cirrhosis group decreased glucose levels compared to other groups. NASH had increased glucose levels rather than the hepatitis B-associated cirrhosis group. There was a significant difference in BMI levels between NASH and other groups. NASH had higher BMI levels. The autoimmune hepatitis-associated cirrhosis group had a significantly higher MELD score than hepatitis B-associated cirrhosis. The five groups had no significant difference in CHILD PUGH score, platelet, INR ratio, albumin, creatinine, total cholesterol, TSH, free T4, and free T3. The hepatitis B-associated cirrhosis group had elevated hemoglobin levels compared to ALD, NASH, or autoimmune hepatitis-associated cirrhosis. AST and ALT levels were lower in NASH-associated cirrhosis compared to hepatitis B, hepatitis C, and autoimmune hepatitis-associated cirrhosis patients. There was a significant difference in gamma-glutamyl transferase, alkaline phosphatase, and bilirubin levels between autoimmune hepatitis-associated cirrhosis and other groups (Table 2).

Ascites and hepatic encephalopathy were statistically higher in alcoholic liver disease, hepatitis B, and NASH cirrhosis, while esophageal variceal bleeding was higher in NASH and autoimmune hepatitis (Table 3). Spontaneous bacterial peritonitis was statistically higher only in cirrhosis due to autoimmune hepatitis.

DISCUSSION

We described the laboratory parameters and liver complications of the five most common causes of cirrhosis. We analyzed the liver features of hepatitis B, hepatitis C, alcoholic liver disease (ALD), NASH, and autoimmune hepatitis-associated cirrhosis to distinguish each other.

Autoimmune hepatitis is a chronic progressive liver disease. It is characterized by hyperglobulinemia and a mixed histological infiltrate of plasma cells and lymphocytes, leading to cirrhosis.[5, 6] According to the antibody profile, autoimmune hepatitis can be divided into two subgroups. Autoimmune hepatitis – 1 is characterized by the presence of ANA and/or anti-smooth muscle antibodies (SMA). Autoimmune hepatitis -2 is characterized by the positivity of anti-liver-kidney microsomal antibody type one (LKM1), anti-LKM3, and/or anti-liver cytosol type 1 antibody (LC1). Autoimmune hepatitis affects mainly women.[7] The peak incidence of the disease is in the adolescence of 30-45 years of age. Estrogen plays a vital role in immu-

Table 3. Comparison of etiology-related complication frequency with all cirrhosis cases.

	Alcoholic Liver Disease	Hepatitis B Virus	Hepatitis C Virus	Nonalcoholic Steatohepatitis	Autoimmune Hepatitis
Gender M/F	80/3**	208/34**	63/49**	54/23	4/23**
Ascites	77**	157**	81	61**	20
Esophageal varices bleeding	30	68	30	22*	3*
Hepatic encephalopathy	43*	78*	40	41**	12
Spontaneous bacterial peritonitis	8	19	9	4*	3

Statistical significance is shown *p≤0.05 **p<0.001

nology, and increased estrogen levels can inhibit the Th1 response and promote the Th2 response, causing antibody production. Prolactin, growth hormone, and progesterone can regulate the immune system by changing the cytokine secretion and the expression of the estrogen receptor.[8,9] In this study, autoimmune hepatitis-associated cirrhosis presented in the younger age group and was dominant in the female gender due to all these immune system alterations. There was a significant difference in gamma-glutamyl transferase, alkaline phosphatase, and bilirubin levels between autoimmune hepatitis-associated cirrhosis and other groups. Cholestasis in autoimmune hepatitis-associated cirrhosis is more prominent than in other cirrhosis. Autoimmune hepatitis-associated cirrhosis had decreased glucose levels compared to other groups.

Non-alcoholic fatty liver disease (NAFLD) is a chronic progressive liver disease characterized by dysregulated lipid metabolism and chronic inflammation, and it results in fibrosis. NAFLD can progress to NASH and cirrhosis. In this study, the patients who had NASH-associated cirrhosis had significantly higher BMI levels due to dysregulated lipid metabolism. AST and ALT levels were lower in NASH-associated cirrhosis compared to hepatitis B, hepatitis C, and autoimmune hepatitis-associated cirrhosis patients. The patients with NASH-related cirrhosis experienced more frequent hepatic encephalopathy than other patients.

Alcoholic hepatitis is a multisystem disease that occurs in patients who abuse large amounts of alcohol for many years. The development of alcoholic hepatitis is complex and depends on a variety of genetic and environmental factors.[10] Severe alcoholic hepatitis has a high mortality rate with fulminant hepatic failure without liver transplantation.[11] In our study, we observed that the development of ascites and hepatic encephalopathy was statistically higher in patients who developed cirrhosis due to alcoholic hepatitis.

Hepatitis B has an important place in the etiology of chronic hepatitis. It is thought that there are approximately 400 million people infected with HBV.[12] Despite vaccines and new antiviral therapies, HBV infection remains severely underdiagnosed. Few patients eligible for treatment receive antiviral therapy.[13,14] The study determined that viral factors play an essential role in the etiology of hepatic cirrhosis. In our study, 242 patients were diagnosed with hepatitis B-related cirrhosis, and 112 patients were diagnosed with hepatitis C-related cirrhosis. Hepatitis B and C-related cirrhosis were observed to be more common in male patients. Ascite development was higher in hepatitis B-associated cirrhosis.

The etiological causes and frequency of complications of the included patients were evaluated. In conclusion, hepatic cirrhosis is a disease with high mortality. The leading causes of morbidity and mortality in patients with hepatic cirrhosis are disease-associated complications. Therefore, managing complications properly when they develop is very important.

Conflict of Interest

The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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Ethical Approval

This study was accepted by the local Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. This retrospective cohort study was managed according to principles of good clinical practice and the declaration of Helsinki. The ethics committee's approval was obtained from Haseki Training and Research Hospital. (No: 126-2021- 01.12.2021).

Authors' Contribution

Study Conception: TŞ; Study Design: FT; Supervision; FT; Funding: FT; Materials: FT; Data Collection and/or Processing: TŞ; Analysis and/or Data Interpretation: BÇT; Literature Review: BÇT; Critical Review: TŞ; Manuscript preparing: BÇT.

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