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Original Article

Evaluating the Correlation of Hemostatic and Endocrine Parameters with Child-Turcotte-Pugh Scoring in Patients with Non-Alcoholic Liver Cirrhosis

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Abstract

Background: Liver cirrhosis is one of the most significant causes of death in many regions worldwide. This study aimed to assess the correlation of hemostatic and endocrine parameters with Child-Turcotte-Pugh (CTP) scoring in patients with non-alcoholic liver cirrhosis.

Materials and Methods: This study included 59 patients monitored for non-alcoholic liver cirrhosis in a gastroenterology clinic from January 2018 to February 2019. The subjects were grouped according to the CTP scores, and their adrenocorticotropic hormone (ACTH), cortisol, dehydroepiandrosterone sulfate (DHEA-SO4), progesterone, growth hormone (GH), insulin-like growth factor-1 (IGF-1), GH/IGF-1 ratio, fibrinogen, D-dimer, and D-dimer/fibrinogen ratio were measured.

Results: According to CTP scoring, 20.3% of patients were CTP-A (n=12), 35.6% were CTP-B (n=21), and 44.1% were CTP-C (n=26). There were statistically significant differences for IGF-1, DHEA-SO4, and GH/IGF-1 ratios between CTP-A and CTP-B groups ($P=0.002$, $P=0.043$, $P=0.038$, respectively). Additionally, there were statistically significant differences between the CTP-B and CTP-C groups for D-dimer and GH values ($P=0.024$, $P=0.006$, respectively). There were statistically significant differences for D-dimer, GH, IGF-1, and D-dimer/fibrinogen ratio between the CTP-A and CTP-C groups ($P<0.001$, $P=0.016$, $P=0.002$, $P=0.031$, respectively).

Conclusion: Severe hemostatic and endocrine complications develop in patients with liver cirrhosis due to non-alcoholic causes. Additionally, it seems that using D-dimer and D-dimer/fibrinogen ratio, along with fibrinogen level, can be beneficial in showing liver damage in these patients.

Keywords: Non-alcohol-related liver cirrhosis, Child-Turcotte-Pugh score, D-dimer, Fibrinogen, D-dimer/fibrinogen ratio

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Introduction

Liver cirrhosis is a progressive disease occurring as a result of widespread hepatocellular necrosis in the liver structure, regeneration, nodular formation and disruption, and changes in fibrosis tissue (1). It is one of the most significant causes of death in many regions in the world. Liver cirrhosis caused by chronic liver disease developing linked to hepatitis B virus (HBV) and hepatitis C virus (HCV) is a significant cause of mortality and morbidity in Turkey. The Child-Turcotte-Pugh (CTP) scoring is used to classify liver cirrhosis (2, 3).

In patients, the disease process is mostly life-threatening and rapid and if there is no intervention, complications which may result in death are observed. Among these complications are endocrine and hematologic complications. Cortisol and sex steroids secreted from the adrenal glands circulate in blood linked to proteins synthesized in the liver. The liver is a major metabolism site where the ketone groups and unsaturated rings of these hormones with steroid structure are reduced, and later made water soluble with conjugation, and can be excreted from the body (4). Hence, liver failure may cause serious complications linked to steroid hormone deficiencies. Although many studies have evaluated the relationship between liver disease and adrenal gland functions, most of them have been performed in patients with cirrhosis linked to alcohol (5).

In many liver diseases, noticeable hemostatic defects and thrombo-hemorrhagic tendency are encountered as complications of liver injury. Diagnosis is important as these changes may affect the progression of the specific liver disease and are mostly correctable if correctly identified. Apart from Factor VIII and von Willebrand factor, nearly all regulators and clotting proteins in the coagulation system are synthesized by the liver. Defects in the synthetic functions of the liver cause significant

hemostatic disorders (6).

In this study, we divided the patients with liver cirrhosis linked to non-alcoholic causes according to the CTP classification and evaluated the hemostatic and endocrine parameter values between these groups.

Materials and Methods

This study included 59 patients (20 females, 39 males) monitored with liver cirrhosis linked to non-alcoholic causes in the Gastroenterology Clinic of Van Yüzüncü Yıl University Faculty of Medicine Hospital from January 2018 to February 2019. Patient information and laboratory data were retrospectively obtained from the archive records of the hospital information processing unit. The research protocol was approved by the Research Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine. Patients participating in the study were informed about the study aims and a consent was obtained from all subjects.

Patients were diagnosed with liver cirrhosis linked to non-alcoholic causes by clinical, laboratory and/or liver biopsies. Also, they were classified according to the CTP scoring (Table 1). After identifying ascites, encephalopathy, total bilirubin, albumin, and PT extension duration (INR value), the equivalent points were added to calculate the CTP score. Patients were divided into three groups according to CTP classification as follows: CTP-A: 5-6 points, CTP-B: 7-9 points, and CTP-C: 10-15 points.

Encephalopathy diagnosis was assessed clinically. Patients were divided into Stage 1, Stage 2, Stage 3, and Stage 4. According to CTP scoring, those without encephalopathy are given 1 point, stage 1-2 (moderate) are given 2 points, and stage 3-4 (advanced) are given 3 points.

The presence of ascites was determined with ultrasonography. If there were no ascites, 1 point was given; if low-moderate ascites 2 points, and if severe ascites 3 points.

Patients provided blood for tests at 07:00 in the morning. Nearly 15 cc of intravenous blood was taken for total bilirubin, albumin, adrenocorticotropic hormone (ACTH), cortisol, DHEA-SO4, progesterone, growth hormone (GH), insulin-like growth factor-1 (IGF-1), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer. Blood taken for ACTH measurements was placed in EDTA hemogram tubes on ice and examined in the biochemistry laboratory. Coagulation blood samples like aPTT, PT, fibrinogen, and D-dimer were placed in sodium citrate tubes and examined in the hematology laboratory; other tests were placed in biochemistry tubes and studied in the biochemistry laboratory. Serum samples for cortisol, DHEA-S, progesterone, GH, and IGF-1 were studied with standard methods using an Architect-I4000SR device with the chemiluminescence method. Serum samples for ACTH were studied with standard methods using an Immulite-2000 device with the chemiluminescence method.

Table 1. Child-Turcotte-Pugh Classification

Parameter	Points Assigned		
	1	2	3
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (s)	<4	4-6	>6

CTP-A, 5-6 points (well compensated); CTP-B, 7-9 points (significant functional compromise); CTP-C, 10-15 points (decompensated)

GH ensures IGF-1 synthesis in the liver. As IGF-1 levels fall in chronic liver failure, the GH feedback mechanism is disrupted and an increase is observed in GH levels. As increased GH levels may be a marker of reduced liver reserves. Furthermore, the GH/IGF-1 ratio was calculated to assess the pituitary-liver axis.

Fibrinogen and other coagulation factors are synthesized in the liver. In chronic liver diseases, reduction in clotting factors, dysfibrinogenemia, thrombocytopenia, DIC-linked hemostatic disorders, and D-dimer elevation may be observed. Increased D-dimer and reduced fibrinogen levels may show liver reserves. Hence, D-dimer/fibrinogen ratios were calculated in patients with liver cirrhosis linked to non-alcoholic causes.

Statistical Analysis

Study results were uploaded from the prepared forms to the Statistical Package for the Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, USA) computer program for statistical analysis. Comparison of groups was performed with the unpaired *t* test, with correlations between variables analyzed with the Pearson correlation analysis. Variations before and after treatment were compared with the paired samples *t* test. To compare frequencies between groups, the chi-square test was used. Results are given as mean ± standard deviation and $P<0.05$ was considered as statistically significant.

Results

The study included 59 patients (males: n=39 [66.1%] vs. females: n=20 [33.9%]) monitored for liver cirrhosis linked to non-alcoholic causes. The mean age of patients was 52.2±15.5 years for males and 48.2±15.3 years for females.

The most common non-alcoholic cause of liver cirrhosis in our patients was viral hepatitis (72.87%), followed by cryptogenic hepatitis, autoimmune hepatitis, cardiogenic causes, Budd-Chiari syndrome, primary biliary cirrhosis, and metastasis (Table 2).

According to CTP scoring, 20.3% of patients were CTP-A (n=12), 35.6% were CTP-B (n=21), and 44.1% were CTP-C (n=26).

Table 2. Distribution of Patients According to Etiology and Gender

Etiology	Males (n)	Females (n)	Total (n)	%
Hepatitis B virus + hepatitis D virus	13	8	21	35,59
Hepatitis B virus	13	4	17	28,81
Hepatitis C virus	3	1	4	6,78
Hepatitis B virus + hepatitis C virus	1	0	1	1.69
Cryptogenic cirrhosis	3	2	5	8.47
Budd-Chiari syndrome	1	1	2	3.38
Cardiogenic cirrhosis	3	0	3	5.08
Autoimmune hepatitis	2	2	4	6,78
Metastasis	0	1	1	1.69
Primary biliary cirrhosis	0	1	1	1.69
Total (n)	**39**	**20**	**59**	**100**

n: number of patients.

Between the CTP-A and CTP-B groups, there were statistically significant differences in ascites, total bilirubin, albumin, INR, IGF-1, DHEA-SO4, and GH/IGF-1 ratio used in the CTP classification ($P<0.001$, $P=0.004$, $P=0.008$, $P=0.006$, $P=0.002$, $P=0.043$, $P=0.038$, respectively) (Table 3). Between CTP-B and CTP-C groups, there were statistically significant differences for total bilirubin, albumin, D-dimer, and GH ($P=0.035$, $P<0.001$, $P=0.024$, $P=0.006$, respectively) (Table 3). Between CTP-A and CTP-C, there were statistically significant differences between ascites, total bilirubin, albumin, INR, D-dimer, GH, IGF-1, and D-dimer/fibrinogen ratio ($P<0.001$, $P=0.008$, $P<0.001$, $P<0.001$, $P<0.001$, $P=0.016$, $P=0.002$, $P=0.031$, respectively) (Table 3).

Discussion

Chronic liver disease is among the diseases causing significant health problems in Turkey, as in the whole world. Liver cirrhosis is a result of liver injury. The most frequent cause of cirrhosis in the USA is excessive alcohol use, while this is followed by viral infections like HBV and HCV (7). Serious hemostatic and endocrine complications develop in patients with cirrhosis linked to non-alcoholic causes. Additionally, it seems that using D-dimer and D-dimer/fibrinogen ratio, along with fibrinogen level, can be beneficial in showing liver damage in these patients.

In Turkey, HBV and HCV are the most important causes of liver cirrhosis; this is followed by alcohol and other causes (8). In another study in Turkey, Ökten et al (9) investigated a 393-case series of liver cirrhosis in the 4-year period from 1994 to 1997. They identified that 60% of cases were due to viral hepatitis, 11% due to alcohol, 4% due to alcohol + viral hepatitis, and 9% due to other causes (autoimmune hepatitis, biliary cirrhosis, metabolic causes, etc.); meanwhile, 16% received cryptogenic cirrhosis diagnosis and no cause could be found. For viral hepatitis, the HBV rate was 42.6%, HCV rate was 34.5%, and HDV rate was 15.7% (9).

A study by Koruk et al (10) found the mean age was 50.8 years (15-80) in males and 46.7 years (18-73) in females in a liver cirrhosis series of 87 cases including 63 males and 24 females. Distribution according to CTP staging was 18 people in stage A (21%), 38 people in stage B (43%), and 31 people in stage C (36%) (10). When the etiologic distribution of patients was examined, 67 cases had chronic viral hepatitis (77%), 58 had HBV (86%), six had HCV (9%), two had HDV (3%), one had HBV+HCV (1.5%), four had alcohol (5%), one had autoimmunity (1%), one had cardiac (1%), and 14 had cryptogenic causes (16%). In our study, the most common cause of non-alcoholic liver cirrhosis was viral hepatitis (72.87%) followed by cryptogenic hepatitis (8.47%), autoimmune hepatitis (6.78%), cardiogenic causes (5.08%), Budd-Chiari syndrome (3.38%), primary biliary cirrhosis (1.69%), and metastases (1.69%).

Due to the low alcohol consumption in Van region, alcohol-linked liver cirrhosis is rarely observed. Consistent with this data, the dominant high delta hepatitis among cirrhosis patients in our study supports the hypothesis that this infection is a disease due to low socioeconomic level and crowded family structure.

GH stimulates synthesis and secretion of IGF-1 in the liver. In circulation, the increase in IGF-1 is inhibited by GH secretion from the pituitary. While less than 10% of the IGF-1 in circulation is free, 90% is transported with insulin-like growth factor binder protein-3 (IGFBP-3) (11). The liver plays an important role in regulating the IGF system. The liver is the most important source of IGF-1 and IGFBP-3. Studies have found that IGF homeostasis is disrupted in chronic liver disease. However, the role of IGF-1 and IGFBP-3 in the pathogenesis of chronic liver disease has still not been definitely explained (12). In a similar study, serum IGF-1 levels were low in cirrhosis patients, and there are studies proposing that this occurs as a result of GH resistance linked to GH receptor loss in hepatocyte cell membranes (13). Another study identified a reduction in hepatocytes as a result of injury linked to cirrhosis and in GH receptors on hepatocyte cell membranes and as a result, serum IGF-1 level fell (14).

External administration of GH did not increase serum IGF-1 levels in patients with high CTP score, but GH with IGFBP-2 increased in serum in liver cirrhosis patients. This difference is linked to IGFBP-3 synthesis occurring in cells apart from hepatocytes (15).

Increased expression of IGF-1 in the liver and IGF-1R on hepatocytes surfaces was identified with fibrosis developing in liver cirrhosis and this increase was proposed to be a compensatory mechanism considering the proliferation and stimulation of regeneration of hepatocytes with IGF-1 and antifibrinogenic effects. Additionally, the lack of observation of this increase in serum was linked to autocrine effects of IGF-1 in liver injury (16). Due to the reduction in GH clearance in liver

Table 3. Statistical Comparison Analyses Between CTP-A, CTP-B, and CTP-C Groups

	CTP	Number (n)	Mean ± SD	Standard Error of Mean	*P* Value		
					CTP-A CTP-B	CTP-B CTP-C	CTP-A CTP-C
AGE (y)	A	12	52.73±16.316	4.920	0.815	0.351	0.358
	B	21	51.35±13.755	3.076			
	C	26	47.28±15.115	3.023			
Ascites	A	12	1.09±0.302	0.091	<0.001*	0.151	<0.001*
	B	21	2.20±0.894	0.200			
	C	26	2.56±0.712	0.142			
Total bilirubin (mg/dL)	A	12	1.0245±0.43304	0.13057	0.004*	0.035*	0.008*
	B	21	1.7760±0.88781	0.19852			
	C	26	4.4288±5.88616	1.17723			
Albumin (g/dL)	A	12	3.7855±0.54300	0.16372	0.008*	<0.001*	<0.001*
	B	21	3.1765±0.56123	0.12550			
	C	26	2.5132±0.52240	0.10448			
PT (s)	A	12	25.655±35.2939	10.6415	0.518	0.181	0.640
	B	21	18.485±5.2155	1.1662			
	C	26	20.500±4.5591	0.9118			
INR	A	12	1.1736±0.12816	0.03864	0.006*	0.275	<0.001*
	B	21	1.5865±0.58191	0.13012			
	C	26	1.7672±0.49135	0.09827			
a-PTT (s)	A	12	40.827±29.5040	8.8958	0.850	0.349	0.961
	B	21	39.075±7.5960	1.6985			
	C	26	41.276±7.9261	1.5852			
Fibrinogen (mg/dL)	A	12	268.00±77.051	24.366	0.202	0.719	0.173
	B	21	226.85±87.324	19.526			
	C	26	213.84±151.019	30.204			
D-dimer (ng/mL)	A	12	2.079±1.9551	0.6183	0.126	0.024*	<0.001*
	B	21	3.596±3.2863	0.7348			
	C	26	6.473±4.9155	0.9831			
Ammonia (mcg/dL)	A	12	47.230±33.99224	10.74929	0.508	0.435	0.094
	B	21	59.238±58.82186	14.26640			
	C	26	73.162±51.66675	10.33335			
ACTH (mg/mL)	A	12	21.860±10.2612	3.2449	0.297	0.540	0.657
	B	21	30.006±29.3423	6.9161			
	C	26	24.629±24.6792	5.2616			
Cortisol (mcg/dL)	A	12	12.373±2.8527	0.8601	0.923	0.765	0.795
	B	21	12.217±6.0168	1.3454			
	C	26	12.739±4.8970	1.0950			
GH (µU/mL)	A	12	3.4024±7.59993	2.29146	0.809	0.006*	0.016*
	B	21	3.9994±3.37022	0.75360			
	C	26	12.634±13.44439	2.80335			
IGF-1 (µU/mL)	A	12	65.78±12.465	5.574	0.002*	0.977	0.002*
	B	21	33.83±13.936	4.927			
	C	26	34.05±19.271	5.810			
DHEA-SO4 (mg/dL)	A	12	72.58±53.680	16.185	0.043*	0.428	0.098
	B	21	33.21±32.358	7.236			
	C	26	41.29±33.749	7.037			

	A	12	0.0153±0.009973	0.004460			
GH/IGF-1 ratio	B	21	0.1268±0.104235	0.036852	0.038*	0.2171	0.1680
	C	26	0.3841±0.556493	0.167789			
	A	12	0.0078±0.006612	0.002090			
D-dimer/fibrinogen ratio	B	21	0.0198±0.023836	0.005330	0.1349	0.0533	0.031*
	C	26	0.0441±0.050220	0.010044			
	A	12	0.296±0.2645	0.0797			
Progesterone (ng/dL)	B	21	1.052±1.6236	0.3725	0.061	0.533	0.057
	C	26	0.776±1.0932	0.2280			

CTP, Child-Turcotte-Pugh classification; PT, prothrombin time; INR, international normalized ratio; ACTH, adrenocorticotropic Hormone; aPTT, activated partial thromboplastin time; GH: growth hormone; IGF-1: insulin-like growth factor-1; DHEA-SO4: dehydroepiandrosterone sulfate; SD, standard deviation.

cirrhosis patients, increases in GH and reductions in serum IGF-1 and IGFBP-3 were identified. Serum IGF-1 and IGFBP-3 fell in cirrhosis patients and this reduction was shown to be correlated with the increase in CTP scores (17).

A study in Turkey identified that the IGF-1 and IGFBP-3 levels in 42 patients with liver cirrhosis were lower compared to a control group and found the reduction in IGF-1 and IFGBP-3 to be statistically significant in correlation with liver dysfunction degree. In the cirrhotic group, IGF-1 was positively correlated with serum albumin and negatively correlated with serum creatinine, serum sodium, and spleen size. IGFBP-3 was only positively correlated with serum albumin (18).

In our study, the GH and IGF-1 of non-alcoholic liver cirrhosis patients were investigated according to CTP points and GH was positively correlated with CTP points. As cirrhosis intensifies in the liver, there is an increase in GH level ($P<0.01$, r:0.464). As CTP points increased, there was a clear reduction in IGF-1 level ($P=0.002$, r: -0.589). According to these results, the increase in GH level linked to the fall in IGF-1 levels synthesized in the liver in our study, which is consistent with other similar studies.

In our cirrhosis patients, a positive correlation between serum IGF-1 level with albumin was found, while serum IGF-1 was negatively correlated with CTP score. Additionally, a positive correlation between serum IGF-1 level with albumin and negative correlation with CTP score was shown for cirrhosis patients (17). Serum IGFBP-3 levels reduced in liver cirrhosis patients, and there was a positive correlation with serum albumin and negative correlations with bilirubin level and prothrombin time (19).

In cirrhosis patients, there was a positive correlation between serum IGF-1 level with albumin level and a negative correlation between serum IGF-1 level and CTP score (19). In our study, IGF-1 had positive correlation with albumin and negative correlation with GH, which supports the study by Ronsoni et al (20). Albumin and IGF-1 are synthesized in the liver. As the CTP stage increases, albumin and IGF-1 synthesis decreases. However, an increase in the GH level and the amount of ascites is expected. There are inadequate studies related to the direct contribution of GH increase to ascites formation. There is a need for more studies to be performed on this topic.

The GH/IGF-1 ratio was calculated for our liver cirrhosis patients. This ratio was negatively correlated with age and positively correlated with CTP points ($P=0.013$, $P=0.004$, respectively). This ratio was found to be significant between encephalopathy groups ($P=0.004$). It is notable that this ratio was significant for encephalopathy, especially in cirrhosis patients. Between CTP groups, when the GH/IGF-1 ratio was compared, there was a statistically significant difference between CTP-A and CTP-B groups ($P=0.039$). The GH/IGF-1 ratio, which is a new parameter defined in the literature, may be used as an important parameter to assess encephalopathy patients. This correlation supports the direct effect of the GH-IGF system on encephalopathy. While ACTH secretion from the pituitary is stimulated by some stress factors, it is inhibited by glucocorticoids. ACTH regulates adrenal cortex functions. In humans, the main glucocorticoid is cortisol and synthesis is stimulated by ACTH. Quantitatively, dehydroepiandrosterone (DHEA) and DHEA-SO4 are major androgens secreted by the adrenal glands. Cortisol and sex steroids secreted by the adrenal glands circulate in blood linked to proteins synthesized in the liver. The liver is the major metabolism site where the ketone groups and unsaturated rings of all these steroid-structure hormones are reduced and later made water soluble with conjugation for excretion from the body (21). As a result, steroid hormone syndromes may be present in liver failure. Although there are many studies evaluating the correlation between liver disease and adrenal gland functions, most research has been performed on alcoholic patients (22, 23).

Due to complications like infection or hemorrhage occurring in cirrhotic patients, normal cortisol secretion from the adrenal glands gains importance. In our research, it was identified that glucocorticoid secretion functions were preserved even in CTP-C patients in the terminal period. Quantitatively, DHEA-SO4 is one of the major androgens secreted from the adrenal glands. In our study, in parallel with the severity of liver disease,

in spite of the reduction in DHEA-SO4 levels, there was no significant difference between CTP groups. Adrenal androgen secretion is stimulated by ACTH and there is a reduction in DHEA-SO4 levels with age. Although the increase in free cortisol fraction in liver disease can cause suppression in ACTH, there was a slight increase in ACTH levels in our study. This increase shows that it is effective in both protecting cortisol response and protecting androgen levels against low DHEA-SO4. However, as most of our patients were elderly, the DHEA-SO4 response was inadequate. Additionally, as the age in our study increased, the DHEA-SO4 levels fell ($P=0.014$, r: -0.325). This finding is similar to the results of some other studies. It was concluded that cortisol and DHEA-SO4 secretions are preserved in patients with non-alcoholic cirrhosis and it may contribute to hypogonadism in liver cirrhosis patients in spite of the reduction in DHEA-SO4 levels with age.

In all liver diseases, a variety of levels of hemostatic disorders and resulting thrombosis, petechiae, ecchymosis, epistaxis, hemorrhage after liver biopsy, varicose hemorrhage, and disseminated intravascular coagulation (DIC) may be observed. Generally, hemostatic problems are encountered in nearly 75% of liver diseases. This situation is generally linked to reductions in clotting factors, dysfibrinogenemia, thrombocytopenia, thrombocytopathy, and DIC. Many scoring methods involving clinical and laboratory tests were investigated to determine patients with poor prognosis in cirrhotic diseases. A scoring system based on laboratory parameters, which shows liver damage very precisely in patients with liver failure, seems to be important both for the progression of the disease and for its follow-up and treatment. Among these laboratory parameters, hematological tests have a significant value. In liver diseases, disruption develops in many laboratory parameters as a result of liver cell function failure, and hemostatic disorders may occur. Generally, as the degree of liver disease increases, laboratory and hemostatic disorders become more severe (24).

Prothrombin time is a valuable indicator showing the severity of liver failure (25). Coagulation factors, especially plasma fibrinogen level, reflect liver functions. However, a clear reduction in plasma fibrinogen level occurs, especially in end-stage liver failure. Hence, it has limited predictive value in the early periods of cirrhosis (26). Plasma albumin concentration is an important criterion for CTP score and is an important parameter for follow-up of patients with liver cirrhosis (27). When albumin synthesis and fibrinogen synthesis were compared in cirrhosis patients, CTP score showed significant correlation with albumin synthesis; however, there was no correlation identified for fibrinogen synthesis (28). In our study, as CTP points increased, a reduction was identified in fibrinogen amounts ($P=0.035$). in addition, as CTP points increased, there was an increase in D-dimer levels ($P=0.004$). There was no significant correlation between CTP groups for fibrinogen level ($P>0.05$). As the CTP of the groups increased, there was a significant increase in D-dimer levels between CTP-A and CTP-B and between CTP-B and CTP-C groups ($P<0.001$, $P=0.024$, respectively). Although there was no significant correlation with fibrinogen as liver cirrhosis became more severe, there was a significant increase in D-dimer amount. These findings support the results of studies by Manzano et al and Ballmer (26, 28). The increase in D-dimer level, a fibrinogen destruction product, in cirrhosis patients is due to preservation of fibrinogen level even in end-stage patients. Another study compared D-dimer levels in patients with liver cirrhosis and patients with hepatocellular carcinoma (HCC). They found a significant correlation between D-dimer with ascites and HCC. Ascites patients had high D-dimer, while patients with high D-dimer without ascites had high rates of HCC (28, 29). The results obtained in our study support the results of previous studies.

In our study, we calculated the D-dimer/fibrinogen ratio. We thought that if the D-dimer / fibrinogen ratio increases, the increased d-dimer level against insufficient fibrinogen production may be a decompensation parameter in liver failure. The D-dimer/fibrinogen ratio was statistically significant for CTP points ($P<0.001$, $P=0.006$, respectively). As liver cirrhosis worsened, this ratio increased. In the literature, there was no study conducted on the D-dimer/fibrinogen ratio in liver cirrhosis cases. In spite of the significant correlation for this ratio in pulmonary embolism cases, there is no similar study of liver cirrhosis patients. This ratio was correlated with INR, ascites amount, encephalopathy severity, and total bilirubin used in CTP staging, indicating that it is a very important parameter to be used for staging of chronic liver disease and determining the degree of liver injury.

Conclusion

Serious hemostatic and endocrine complications develop in patients with non-alcoholic liver cirrhosis. Additionally, it seems that using D-dimer and D-dimer/fibrinogen ratio, along with fibrinogen level, can be beneficial in showing liver damage in these patients. However, more comprehensive studies with longer-term patient follow-up are needed to confirm our results.

Conflict of Interest Disclosures

None.

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Ethical Statement

In this study, all ethical considerations were considered by the authors. The research protocol was approved by the Research Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine on

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Authors' Contributions

All authors have contributed equally to all stages of the study.

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Informed Consent

An informed consent was obtained from all participants.

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