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Serum and Ascitic D-Dimer in Cirrhotic Patients with Spontaneous Bacterial Peritonitis in Minia University Hospital

Eman Hussein Khalil, Fatma Mokhtar Shaaban
Department of Internal Medicine, Faculty of Medicine, Minia University, Egypt
***Corresponding author:** Eman Hussein Khalil, **Mobile:** (+20) 01142741126, **E-mail:** anjaz3036@gmail.com

ABSTRACT

Background: The D-dimer (DD) test can detect fibrinolysis with good specificity. Its irregularity is a result of the coagulation and fibrinolysis systems being overactive in vivo. Since disrupted hemostasis is linked to chronic liver illness, it's probable that clot lysis as well as coagulation problems are also present. Estimating DD might shed light on potential disruptions in the fibrinolytic process.

Objective: We aimed to determine the connection between ascites and the hyper fibrinolytic condition in hepatic cirrhosis. We evaluated serum DD in cirrhotic cases with and without ascites. We also examined how spontaneous bacterial peritonitis (SBP) affected the DD content in serum and ascitic fluid (AF).

Patients and methods: This prospective study was conducted on 60 patients from the Department of Internal Medicine in Minia University Hospital including patients hospitalized due to decompensated liver cirrhosis and ascites. First group included fifteen cases with hepatic cirrhosis and no ascites. Second group included fifteen cirrhotic cases with ascites. Third group included fifteen cirrhotic cases with ascites and SBP. Fourth group (Control group) included fifteen matched healthy individuals with no evidence of hepatic disorder.

Results: There was a diagnostic performance of serum DD in diagnosing of SBP in cutoff point of serum d dimer > 491.5 ng/ml, and ascitic DD in a cutoff point of ascitic d dimer > 380.5 ng/ml predicting cirrhotic ascitic cases with SBP.

Conclusions: Patients with SBP showed a substantial link between serum DD and AF DD, while patients with cirrhotic ascites without bacterial infection demonstrated no significant correlation. When used to diagnose SBP in cases with hepatic cirrhosis, DD performed well.

Keywords: D-dimer, Liver cirrhosis, AF, SBP.

INTRODUCTION

It is thought that there is a complex relationship between liver diseases and hemostasis; certain cases with advanced hepatic disorder may develop extensive blood loss, while others could even experience thrombotic adverse events due to reduced plasma values of clotting factors produced by the liver [1, 2]. A significant coagulopathy that can affect patients with liver cirrhosis might have many different causes, one of which is rapid hyperfibrinolysis. However, there is no sufficient precise data as regards the prevalence of hyperfibrinolysis in cirrhotic individuals, as well as the clinical indicators that may help diagnose and treat hyperfibrinolysis [3].

Since the AF is basically an ultrafiltrate of plasma, it includes proteins that are important for clotting. Ascites may be a contributing factor to the enhanced fibrinolysis and bleeding tendency commonly present in late hepatic disorder [4]. In individuals with cirrhosis, SBP is a dangerous adverse event. SBP occurs in roughly 20% of decompensated liver cirrhosis patients, and average mortality is 25% [5]. SBP is linked to high resource use and accounts for 2.5% of whole hospitalized cirrhotic cases [6].

Since up to 13% of patients might be without manifestations, a strong index of suspicion is required to avoid a delay in diagnosis and an escalation of the prognosis [7]. The D-dimer (DD) test can detect fibrinolysis with good specificity. Its irregularity is a result of the coagulation and fibrinolysis system being overactive in vivo. In certain conditions, which include deep vein thrombosis (DVT) and some malignant tumour-related thrombosis, D-dimer has been demonstrated to be a useful diagnostic and predictive test [8]. We aimed to determine the connection between ascites and the hyper fibrinolytic condition in hepatic cirrhosis, we evaluated serum DD in cirrhotic cases with and without ascites. We also examined how SBP affected the D-dimer content in serum and ascitic fluid.

PATIENTS AND METHODS

This prospective study was conducted on 60 patients hospitalized due to decompensated liver cirrhosis and ascites in the Department of Internal Medicine, Minia University Hospital. The patients were divided into 4 groups: First group included fifteen cirrhotic cases without ascites. The second group included fifteen cirrhotic cases with ascites. The third group included fifteen cirrhotic cases with both ascites and SBP. The fourth group (Control group) included fifteen age- and sex-matched healthy individuals with no evidence of hepatic diseases.

Exclusion criteria: Other causes of ascites. Pregnancy. Cases with previous history of DVT or portal vein thrombosis (PVT). Cases on anticoagulation therapies. Hepatorenal syndrome. Hepatocellular carcinoma or any other associated malignancies.

Child-Pugh and MELD scores were measured.

All patients were subjected to:

- **Full clinical history:** Subject answered a questionnaire which comprised: Personal history, which include name, age, gender, residence, marital status, occupation and special habits as tobacco smoking and everyday alcohol intake in the last six months. History

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of viral infection or bilharziasis. History of Hepatic encephalopathy and ascites. History of any other chronic illness.

Current history of manifestations suggestive of SBP and risk factors for it as fever, altered mental condition, tender abdomen, gastrointestinal bleeding, chills, loss of appetite and diarrhea or emesis.

● **Carful physical examination:** Measurement of vital signs (temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)).
General examination on stigmata of hepatic cirrhosis, SBP, lower limb oedema, and degree of conscious level.
Cautious abdominal examination, which include hepatic and splenic conditions on terms of size, surface, edge, consistency and tenderness on examination and ascites.
Searching for sepsis manifestations. Besides, different body systems were assessed too.

● **Laboratory assessment:** Samples were withdrawn after eight hours of fasting by sterile venipuncture at 8 A.M. They were divided into 3 collecting tubes; the first one comprising EDTA was utilized for CBC, the second one comprising trisodium citrate and was utilized for detection of prothrombin time (PT) and concentration and for D dimer and the last one was a plane tube. The plane tube was left to clot after that was centrifuged. Separated serum was put into aliquot tube and utilized for traditional biochemistry tests [Liver function tests (LFT) and kidney function tests (KFT)].

Ascitic fluid sampling protocol: Sterilize skin at puncture site, 2 mL ascitic fluid was drawn and put in tube containing trisodium citrate.

➢ **Routine biochemical analyses:**
Complete blood count (C.B.C) was determined by automated cell counter (Sysmex Counter K-1000, TAO Medical Incorporation, Japan) based on the approach of **Simson and Groner** [9].
LFT tests included alanine transaminase (ALT) and aspartate aminotransferase (AST), serum bilirubin and serum albumin and Kidney function tests that included blood urea and serum creatinine (Ser Cr) by utilizing fully automated clinical chemistry auto-analyzer system (Finland). PT and concentration and international normalized ratio (INR) were performed by utilizing option 2 Biomerieux, Inc.595 (USA). Viral markers included HCV, HBV, HIV, and HAV it was taken from the patient sheet. Autoimmune markers included ANA. Serum α-fetoprotein to exclude HCC.

➢ **Specific laboratory Investigation:**
Ascitic fluid analysis: SBP was established by an increase in AF absolute PMN count ($\geq$ 250cells/mm^3) and AF bacterial culture. Serum DD level was evaluated in all cases, it was measured by the ELISA kit, (Double-antibody sandwich approach) to determine human D-dimer (D2D). D-dimer in AF in the 2nd and 3rd groups.

Imaging: They were done in the Radiology Department, El-Minia university hospital. They were carried out by an expert operator who was unaware of results of noninvasive markers of the patients. Abdominal ultrasound: To detect liver cirrhosis and the presence of ascites was established by ultrasonography.
Detection of severity of liver cirrhosis and in-hospital mortality by Child-Pugh classification: Chronic hepatic disease is classified into Child–Pugh class A to C, employing the added score from above [10].

MELD SCORE: MELD uses the patient's values for serum bilirubin, Ser Cr, and the INR for PT (INR) for prediction of survival. It is measured based on the next formula MELD = 3.78×ln [serum bilirubin (mg/dL)] + 11.2×ln [INR] + 9.57×ln [Ser Cr(mg/dL)] + 6.43 [11].

Ethical approval: Minia Medical Ethics Committee of the Minia Faculty of Medicine gave its approval to this study. All participants gave written consents following receiving all data. The Helsinki Declaration was followed throughout the study's conduction.

Statistical analysis

Data analysis was performed by utilizing the IBM SPSS version 20.0. Normality of the data was evaluated by utilizing the Kolmogorov-Smirnov test. Data were expressed as median for non-parametric quantitative data, together with number and percentage for qualitative data. Kruskall Wallis test was done for non-parametric quantitative data between the three or four groups followed by Mann Whitney test between each 2 groups. The Chi-square test and Fisher‘s exact test were utilized for comparison of categorical variables. Spearman‘s rank correlation was conducted for non-parametric data. A ROC curve analysis was conducted to measure the AUC, optimum cut off point, sensitivity, specificity, PPV and NPV, and accuracy of serum DD in prediction of % of three months mortality based on MELD score. P $\leq$ 0.05 for statistical significance and <0.001 for high significance.

RESULTS

The study included 34 males and 26 females with age range from 18 to 85 years and mean age of 64.3 ± 10.9 in **Group I** (Cirrhotic with no ascites)**,** 58.5 ± 9.6 years in **Group II** (Cirrhotic with ascites), 61.1 ± 10.3 years in **Group III** (Cirrhotic with SBP) and 37.8 ± 13.6 years in **Group IV** (Control) which was statistically significant (P=<0.0001*). As regards gender, males in **Group I** were 7 (46.7%) versus 8 (53.3%) females, in **Group II** males were 8 (53.3%) versus 7 (46.7%) females, in **Group III** males were 8 (53.3%) versus 7 (46.7%) females, and in **Group IV** males were 11 (73.3%) versus 4 (26.7%) females (P=0.486) (Table 1).

Table (1): Comparison of demographic data between the four studied groups

Demographic data		Group I (Cirrhoticwith no ascites) n= 15	Group II (Cirrhotic with ascites)n= 15	Group III (Cirrhotic with SBP) n= 15	Group IV (Control) n= 15	p value
Age	**Mean ± SD (Range) Median (IQR)**	64.3 ± 10.9 (41.0 – 85.0) 65.0 (57.0 – 70.0)	58.5 ± 9.6 (40.0 – 75.0) 61.0 (50.0 – 65.0)	61.1 ± 10.3 (40.0 – 75.0) 63.0 (57.0 – 70.0)	37.8 ± 13.6 (18.0 – 62.0) 38.0 (26.0 – 50.0)	**<0.0001***
Gender: Males Females	**N (%)**	7 (46.7%) 8 (53.3%)	8 (53.3%) 7 (46.7%)	8 (53.3%) 7 (46.7%)	11 (73.3%) 4 (26.7%)	0.486
	I vs II	**I vs III**	**I vs IV**	**II vs III**	**II vs IV**	**III vs IV**
Age (p value)	0.124	0.493	**<0.0001***	0.467	**<0.0001***	**<0.0001***

-*: Significant level at p< 0.05

Concerning etiology of liver cirrhosis, hepatic encephalopathy and ascites between the three groups of cirrhotic cases, in group I the most common etiology was chronic viral infectious 10 (66.7%), fatty liver 3 (20.0%), and bilharziasis 2 (13.3%). While, in group II chronic viral infections 11 (73.3%), bilharziasis 2 (13.3%), fatty liver 1 (6.7%), and alcohol abuse 1 (6.7%). But, in group III chronic viral infections 12 (80%), fatty liver 2 (13.3%), and autoimmune hepatitis 1 (6.7%) with no significant differences between groups. As regards hepatic encephalopathy in group I, no encephalopathy were 8 (53.3%), grade 1-2 were 5 (33.4%) and grade 3-4 were 2 (13.3%). In group II, no encephalopathy was 8 (53.3%), grade 1-2 were 6 (40.0%) and Grade 3-4 were 1 (6.7%). In group III, no encephalopathy was 4 (26.7%), grade 1-2 were 4 (26.7%) and grade 3- 4 were 7 (46.6%), which was statistically significant (P=0.039*).

Table (2): Child Pugh and MELD scores comparison between the three groups of cirrhotic patients

	Group I n= 15	Group II n= 15	Group III n= 15	p value
Child-Pugh score: Child A Child B Child c	5 (33.3%) 10 (66.7%) 0	0 8 (53.3%) 7 (46.7%)	0 4 (26.7%) 11 (73.3%)	<0.0001*
MELD score: Mean ± SD (Range) Median (IQR)	10.9 ± 3.5 (8.0 – 21.0) 10.0 (8.0 – 12.0)	16.1 ± 6.5 (8.0 – 34.0) 16.0 (11.0 – 18.0)	22.2 ± 9.8 (7.0 – 36.0) 20.0 (14.0 – 35.0)	<0.001*
p value				
	I vs II	I vs III	II vs III	
Child-Pugh score	<0.001*	<0.0001*	0.143	
MELD score	0.005*	<0.001*	0.084	

*: Significant level at p value< 0.05

Table (3): Comparison of serum d dimer between all cirrhotic patients and the controls

		Cirrhotic Patients (N= 45)	Group IV (Control) N= 15	p value
Serum D dimer (ng/ml)	**(Range) Median (IQR)**	(170.0 – 875.0) 360.0 (296.5 – 561.5)	(221.0 – 301.0) 250.0 (235.0 – 266.0)	**<0.0001***

Range, median and IQR: nonparametric test. -*: Significant level at p value< 0.05

Table (4): Comparison of ascitic D dimer in cirrhotic ascitic patients non SBP and withSBP patients

		Group II (Cirrhotic with ascites) n= 15	Group III (Cirrhotic with SBP) n= 15	p value
Ascitic D dimer (ng/ml)	**(Range) Median (IQR)**	(186.0 – 445.0) 301.0 (234.0 – 418.0)	(252.0 – 615.0) 562.0 (385.0 – 583.0)	**<0.001***

Range, Median and IQR: nonparametric test. -*: Significant level at p value< 0.05

In Child A, mean serum D-dimer was 291.8 ± 17.4, in Child B, mean serum D-dimer was 342.7 ± 84.3 and in Child C, mean serum D-dimer was 562.2 ± 138.4, which was statistically significant (P=<0.0001*). Serum D dimer level was significantly increased in child C. There were no significant differences between Child A and Child B (P=0.17). Serum D-dimer in Child A vs Child C was statistically significant (P < 0.001*). Serum D-dimer in Child B vs Child C was statistically significant (P < 0.0001*) (Table 5).

Table (5): Serum D dimer level of the cirrhotic patients based on Child-Pugh scoreclassification

Cirrhotic patients n= 45					
		Child A n= 5	**Child B n= 22**	**Child C n=18**	**p-value**
Serum D dimer (ng/ml)	**Mean ± SD**	291.8 ± 17.4	342.7 ± 84.3	562.2 ± 18.4	**<0.0001***
p value					
		A vs B	**Avs C**	**B vs C**	
Serum D dimer (ng/ml)		0.17	**<0.001***	**<0.0001***	

-*: Significant level at p value< 0.05

We found correlation between serum D-dimer and MELD score, which was statistically significant (P < 0.0001*) (Table 6 and figure 1).

Table (6): Correlation of serum D dimer and MELD score

	Serum D dimer (ng/ml)	
	r	**P**
MELD score	0.863	**<0.0001***

-*: Correlation was significant at the level <0.05,

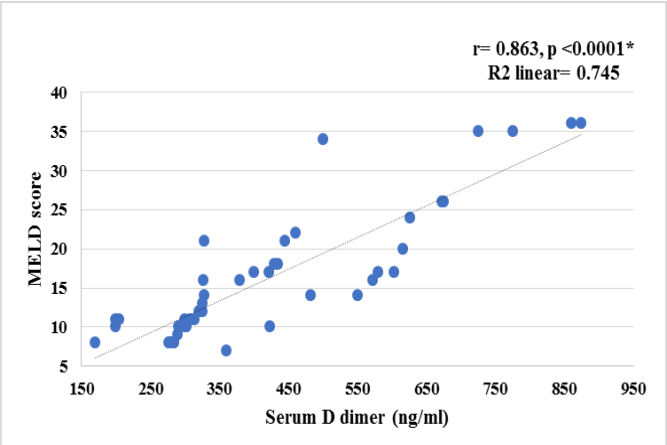

Figure (1): Correlation of serum D-dimer and MELD score

Finally, there were significant role of serum D-dimer in prediction of 3 months mortality based on MELD score in a cutoff point of serum d dimer > 674.0 ng/ml predicting >50% of 3 months mortality. When using the ROC curve for assessing the role of serum D-dimer in prediction of 3 months mortality based on MELD score, the AUC of serum D-dimer (0.96 , p value <0.001*), which was statistically significant (Figure 2 and table 7).

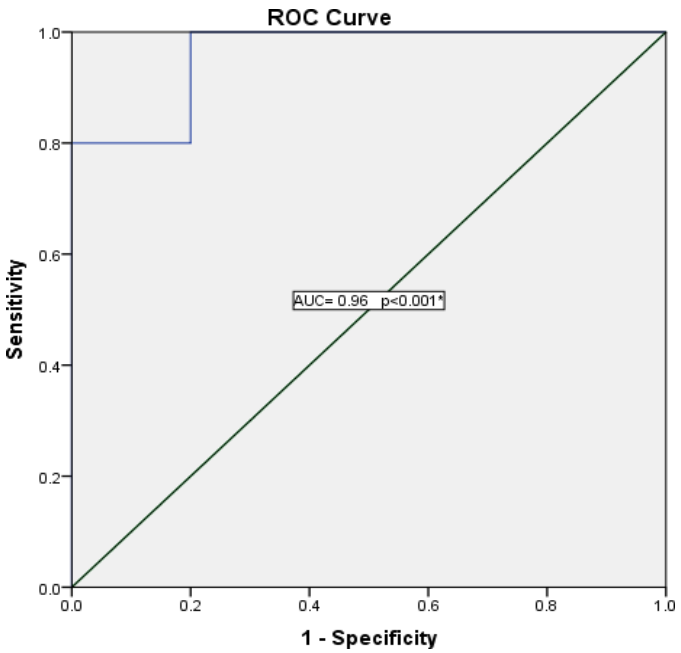

Figure (2): ROC curve analysis of serum D-dimer for predicting the 3 months mortality basedon MELD score.

A cutoff point of serum D-dimer > **674.0 ng/ml** predicting >50% of 3 months mortality **(AUC**= 0.96 - **p value <0.001*)** (Table 7)**.** When using the ROC curve for evaluating the diagnostic performance of serum D dimer in diagnosing of SBP, the AUC of serum DD (0.938, p value <0.0001*) which is statistically significant (Figure 3).

Figure (7): ROC curve analysis of serum D-dimer for predicting the 3 months mortality based on MELD score

Statistic	**Value**	**95% CI**
Sensitivity	80.00%	28.36% to 99.49%
Specificity	97.50%	86.84% to 99.94%
Positive Predictive Value	80.00%	35.48% to 96.68%
Negative Predictive Value	97.50%	87.10% to 99.56%
Accuracy	95.56%	84.85% to 99.46%

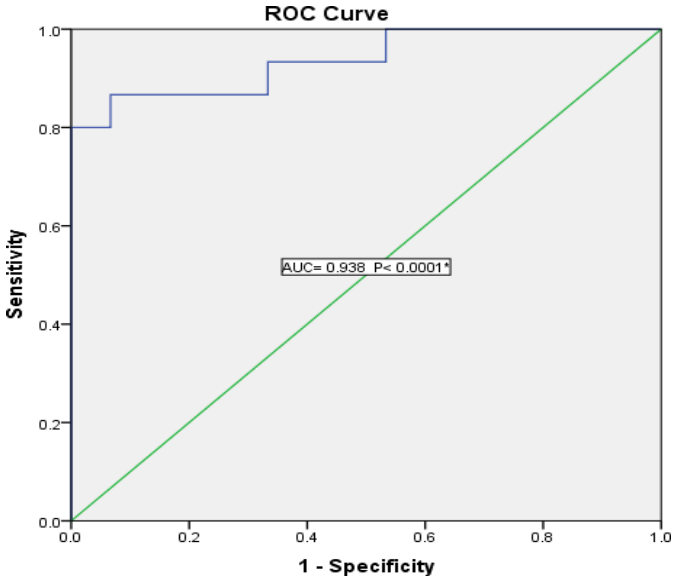

Figure (3): ROC curve analysis of serum D-dimer for predicting cirrhotic ascitic patients with or without SBP.

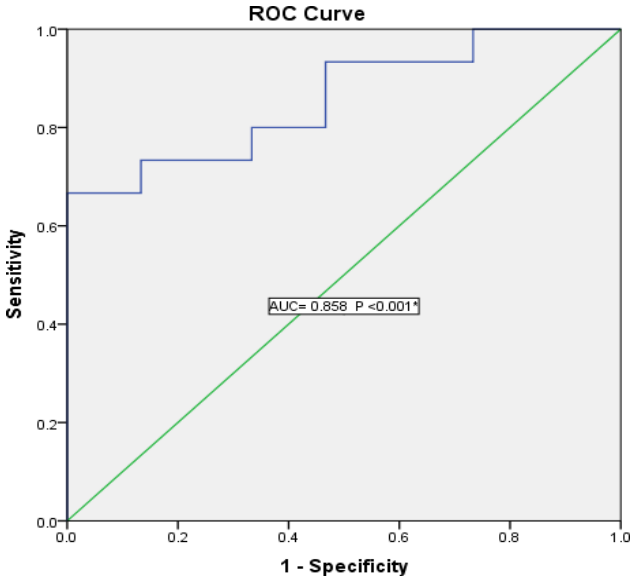

Figure (4): ROC curve analysis of ascitic D dimer for predicting cirrhotic ascitic patients with or without SBP.

A cutoff point of serum d dimer > **491.5 ng/ml** predicting cirrhotic ascitic patients with SBP **(AUC**= 0.938 - **p value <0.0001*)** (Table 8).

Table (8): ROC curve analysis of serum D dimer for predicting cirrhotic ascitic patients with or without SBP

Statistic	Value	95% CI
Sensitivity	80.00%	51.91% to 95.67%
Specificity	93.33%	68.05% to 99.83%
Positive Predictive Value	92.31%	63.98% to 98.78%
Negative Predictive Value	82.35%	62.70% to 92.83%
Accuracy	86.67%	69.28% to 96.24%

A cutoff point of ascitic d dimer > **380.5 ng/ml** predicting cirrhotic ascitic patients with SBP **(AUC**= 0.858 - **p value <0.001*).** When using the ROC curve for evaluating the diagnostic performance of ascitic D-dimer in diagnosing of SBP, the ROC of serum D-dimer (0.858, p<0.001*), which was statistically significant (Table 9 and figure 4).

Table (9): ROC curve analysis of ascitic D dimer for predicting cirrhotic ascitic patients with or without SBP

Statistic	Value	95% CI
Sensitivity	**70.59%**	**44.04% to 89.69%**
Specificity	**76.92%**	**46.19% to 94.96%**
Positive Predictive Value	**80.00%**	**58.60% to 91.87%**
Negative Predictive Value	**66.67%**	**47.47% to 81.57%**
Accuracy	**73.33%**	**54.11% to 87.72%**

DISCUSSION

In our prospective study, we plane to determine the connection between ascites and the hyper fibrinolytic condition in hepatic cirrhosis, we evaluated serum D-dimer in cirrhotic cases with and without ascites. We also examined how SBP affected the D-dimer content in serum and ascitic fluid.

It was conducted on 60 patients from the Department of Internal Medicine in Minia University Hospital including patients hospitalized due to decompensated liver cirrhosis and ascites. First, SBP, which shows as fever, shivering, discomfort on abdominal palpation, and feeling sick, is one of the consequences of ascites in cases with decompensated hepatic cirrhosis. However, up to 30% of patients may remain asymptomatic [12]. In order to avoid a delay in diagnosis and a deterioration of the prognosis, a high index of suspicion is needed [13].

A decrease in the likelihood that an infection would advance to sepsis, multi-organ failure (MOF), and/or mortality is made possible by early identification and effective management of infections, which remain a major clinical issue. There is still a significant demand for new laboratory tests that can distinguish between bacterial infections and other forms of illness [14].

A meta-analysis was recently conducted, and the results showed that D-dimer values are substantially correlated with the occurrence of PVT in hepatic cirrhosis and may be used for prediction of the development of PVT after splenectomy [12]. D-dimer could therefore be a prognostic marker that is unfavourably related to the outcomes of liver cirrhosis. After clot degeneration, the blood shows the presence of the fibrin breakdown product D-dimer. Currently, several healthcare practices use assays to determine the amount of D-dimer in the blood [8].

Our study reported that serum D-dimer among cirrhotic cases was more elevated than that in non-cirrhotic patients, which was statistically significant

(P<0.0001*). The highest value of serum D-dimer was in group III (Cirrhotic with SBP), then in group II (Cirrhotic with ascites), then in group I (Cirrhotic without ascites), where the lowest level was in group IV (Control). Also we found that the ascitic d-dimer was more elevated in SBP group than non-SBP group. There was diagnostic performance of serum D-dimer in diagnosing of SBP in a cutoff point of serum d-dimer > 491.5 ng/ml, and ascitic D-dimer in a cutoff point of ascitic D-dimer > 380.5 ng/ml predicting cirrhotic ascitic patients with SBP. Also we approved that serum D-dimer level was significantly increased in Child C, but there were no significant differences between Child A and Child B (P=0.17). Also we found correlation of serum D-dimer and MELD score which was statistically significant (P<0.0001*). Finally, there were significant role of serum DD in prediction of 3 months mortality based on MELD score in a cutoff point of serum DD > 674.0 ng/ml predicting >50% of 3 months mortality.

In our study, we discovered that serum d-dimer levels were higher in cirrhotic cases compared to non-cirrhotic ones, and they were higher in cirrhotic cases with ascites than in cirrhotic patients without ascites. This result was generally in agreement with other earlier investigations. It is still unclear what causes cirrhotic individuals with ascites to have high D-dimer plasmatic levels. According to some publications, plasma and ascitic fluid may interchange certain coagulation and fibrinolytic proteins. Also, **Hu *et al.*** [15] discovered a significant elevation in mean DD values in cases with hepatic cirrhosis but no signs of ascites and more elevated mean DD values in cases decompensated by ascites, noting that despite a significant decrease in DD values following paracentesis of the abdomen, they were still greater than those in ascites free ones.

Additionally, our study revealed that the SBP group had higher ascitic and serum DD values than the non-SBP group. **Agarwal *et al.*** [16] in their study found a significant difference between the serum DD levels of the control group and the SBP group, but our study found no such difference between the control group's serum DD values and those of the cirrhotic without ascites group or the cirrhotic with ascites group.

The DD value of individuals with hepatic cirrhosis was shown to be substantially linked with the Child-Pugh and MELD scores in the current investigation. This result was generally in agreement with other earlier investigations. Our results are in the same line with **Lisman *et al.*** [17] who discovered that the DD level was significantly .higher than the normal level and that there was a significant elevation from Child-Pugh class A to class C. They also came to the conclusion that the DD concentration increased as the liver's functions declined. However, **Dhanunjaya *et al.*** [18] revealed that even cases with Child-Pugh class A had higher plasma DD levels relative to normal controls, and that these levels significantly rose with the degree of the hepatic disease.

The D-dimer levels in 30 healthy volunteers and 67 patients with chronic liver disorders, In comparison with non-cirrhotic cases and healthy controls, cirrhotic cases with Child-Pugh classes A and B had significantly higher DD levels (class B, 147.32 ± 114.16 ng/ml; class A, 115.3 ± 138.4 ng/ml; non-cirrhotic hepatic disease, 28.86 ± 40.03 ng/ml and healthy controls, 17.6 ± 11.7 ng/ml) [19]. The research aforementioned concurred that fibrinolysis should be activated depending on the degree of liver damage. Greater DD values could strongly predict the hospital mortality in cirrhotic cases, which was another conclusion of the current investigation. D-dimer tests can therefore be used to classify liver cirrhosis in terms of prognosis [20].

The limited sample size of this study, which was undertaken in a single institution was one of its weaknesses. A multicentric study level should be used in future research, and a sizable sample size should be used. Additionally, monitoring serum D-dimer levels following SBP therapy may strengthen the diagnostic utility of this straightforward marker.

CONCLUSIONS

The findings of this study pointed to a considerable and strong correlation between serum and AF D-dimers in those with SBP. Our research found no correlation between AF parameters and serum DD in either cirrhotic individuals with sterile ascites or SBP. Although the peritoneal tap remains the standard approach in these circumstances, serum D-dimer has the potential to be a valuable and straightforward marker for the early diagnosis of SBP.

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Competing interests: Nil.

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