The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (1), Page 3341-3346

Correlation between both Child Pugh Score and Spontaneous Bacterial Peritonitis with Plasma D-Dimer Level in Cirrhotic Patients

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ABSTRACT

Background: Cirrhosis is a chronic liver disease in which diffuse destruction and regeneration of hepatic parenchymal cells have occurred. D-dimer is regarded as a diagnostic marker for Portal vein thrombosis in liver cirrhosis.
Objective: To correlate plasma D-dimer levels as a hemostatic parameter with Child Turcotte Pugh (CTP) score of post hepatitis cirrhosis patients and occurrence of spontaneous bacterial peritonitis (SBP).
Patients and methods: This was a case-control study that included 84 patients with hepatitis C-related cirrhosis who were admitted to Al-Ahrar Teaching Hospital in the period from November 2020 to June 2021. 28 apparently healthy subjects were included as control group.
Results: There was a significantly higher level of D-dimer in each cirrhotic group; child A, child B and child C with median of 1.05 mg/l, 2 mg/l and 3 mg/l respectively compared to healthy control group with a median of 0.09 mg/l. The best cutoff of D dimer in prediction of Child C was ≥ 2.45 mg/l with area under curve of 0.986, sensitivity of 96.4%, specificity of 94%, positive predictive value (PPV) of 84.4%, negative predictive value of 98.8 % and accuracy of 94.6% ($p < 0.001$). There was a statistically significant association between SBP and D dimer, which was significantly higher among those with SBP.
Conclusion: D-dimer was correlated with esophageal varices grades and degree of ascites. D-dimer could be a marker for severity of liver disease in patients with post hepatitis c cirrhosis as indicated by Child' score.
Keywords: D-dimer, Child Pugh Score, Spontaneous bacterial peritonitis.

INTRODUCTION

Liver cirrhosis is the last frequent pathological route of liver damage caused by a range of chronic liver disorders [(1)]. Cirrhosis is caused by a variety of factors, including drinking, chronic hepatitis C virus infection, and nonalcoholic fatty liver disease (NAFLD) [(2)]. Egypt has the highest prevalence rate of hepatitis C virus infection in the world [(3)].

Though, the causes of liver cirrhosis are diverse, several clinical features are similar to all cases of liver cirrhosis, such as hepatocyte degradation and necrosis, liver parenchyma replacement by fibrotic tissues and regenerative nodules, and liver function loss. Fibrosis is a key pathogenic step in the progression of all chronic liver disorders to cirrhosis [(4)]. Liver cirrhosis is a serious hepatic parenchymal disease with life-threatening consequences. Synthetic functions are severely reduced in patients with decompensated liver cirrhosis. The liver produces many of the proteins involved in the coagulation process. As a result, many people think that decompensated liver cirrhosis is a precursor to hemorrhagic coagulopathy. Coagulation is now recognised as a complicated process including interactions between procoagulation, anticoagulation, and the fibrinolytic system [(5)].

Child-Torrcot-Pugh score (CTP score) involves total bilirubin, albumin, International Normalized Ratio (INR) or prothrombin time, hepatic encephalopathy and ascites. It is very frequently used scoring system for judging the prognosis of cirrhosis of liver. Every measure is scored 1-3 points and 3 indicates very intense imbalance [(6)].

The enzymatic breakdown of cross-linked fibrin produces a persistent and quantifiable characteristic known as D-Dimer. D-Dimer estimation has previously been used to diagnose diseases such as deep vein thrombosis and pulmonary embolism. Because chronic liver illness is linked to hemostasis problems, it's conceivable that it's linked to clot lysis problems as well. Estimation of D-Dimer might give some insight into potential fibrinolytic pathway derangements [(7)].

We aimed in this work to correlate plasma D-dimer levels as a hemostatic parameter with Child Turcotte Pugh (CTP) score of post hepatitis cirrhosis patients and occurrence of SBP.

PATIENTS AND METHODS

This is a case-control study that included 84 patients with hepatitis C-related cirrhosis with varying degrees of severity who were admitted to Al-Ahrar Teaching Hospital. 28 apparently healthy subjects were also included as control group. The studied hepatitis C patients were randomly categorized according to CTP score into: **Group (1)** that included 28 patients class A CTP score, **Group (2)** that included 28 patients class B CTP score and **Group (3)** that included 28 patients class C CTP score. **Group (4)** (Control group) included 28 apparently healthy subjects.

Inclusion Criteria: Patients with hepatitis C-related cirrhosis with varying degrees of severity aged above 18 years from both sexes were included in the study.

Received: 8/8/2021
Accepted: 15/9/2021

Exclusion criteria: Patients with other causes of cirrhosis other than hepatitis C for example (other viral causes of cirrhosis, autoimmune cirrhosis, metabolic causes e.g Wilson disease, drug induced cirrhosis, hepatocellular carcinoma or other cancer, known hemostatic disorders other than cirrhosis, patients receiving blood transfusion, human albumin, anti-aggregates or anticoagulants, patients with diagnosis of portal vein thrombosis, recently esophageal variceal bleeding or injected varices and patients refused to participate in the study.

All studied patients and control group were subjected to the following:

1. Full history taking.
2. Complete physical examination.
3. Laboratory investigations: Complete blood picture, HCV antibodies, HCV RNA PCR and D-dimer levels. Plasma d-dimer was quantitatively estimated using immunoturbidimetric assay.
4. Radiological investigations:
   - A. **Abdominal ultrasonography:** Abdominal U/S was done for all patients and controls included in the study using TOSHIBA ECCOCEE machine with a convex-sector probe (PVF-375 MT-3.57 MHz).
   - B. **Upper gastrointestinal endoscopy:** This was done using disinfected upper gastrointestinal video scope for complete evaluation of the esophagus, stomach and down to the second part of the duodenum. Portal hypertensive gastropathy (PHG) was reported according to modified grading system proposed by the Baveno III meeting on portal hypertension. PHG was mild when a pink mosaic-like mucosal pattern with no red signs or black–brown spots is present. PHG was severe when the mosaic-like mucosal pattern is red and superimposed by any red sign (red point lesions and/or cherry-red spots) or black–brown spots [8].

Modified Child score:

Evaluation of the severity of liver cirrhosis was obtained in each cirrhotic patient with modified Child-Pugh score. This system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin and prothrombin time [9] as shown in table (1).

Table (1): Evaluation of severity of liver cirrhosis

Parameter	1	2	3
Ascites	None	Slight-moderate	Tense
Encephalopathy	0	Grade 1-2	Grade 3-4
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

Child A: 5-6, Child B: 7-9, hild C: 10-15

Ethical approval:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (IRB#:6769-21-2-2021). Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test and Fisher Exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare quantitative continuous data between more than two groups, one way ANOVA test was used when data was normally distributed and Kruskal Wallis test was used when data is not normally distributed. Spearman rank correlation coefficient was used to assess strength and direction of association between two continuous non-parametric variables respectively.

Linear stepwise regression analysis was performed to measure associated independent factors for dependent factor and to predict the value of a variable based on the value of another variable. ROC curve was used to determine cutoff of certain continuous variables for prediction of a health problem. The level of statistical significance was set at $P \leq 0.05$. $P \leq 0.001$ was considered as statistically highly significant.

RESULTS

There was a statistically non-significant difference between the studied groups regarding gender or age (Table 2).

There was a statistically significant difference between the studied groups regarding result of upper GIT endoscopy. About 39% with child A had normal upper endoscopy and 25% of them had hypertensive gastropathy, 17.9%, 7.1% and 10.7% had oesophageal varices (OV) grades I, II and gastric varices respectively. About 36%, 11%, 36% and 18% of patients with child B had PHG, OV grade I, II and gastric varices (GV) respectively. About 18%, 50%, 18% and 14% of those with child C had PHG, OV grade III, IV and GV respectively (Table 3).

There was statistically significant difference between the studied groups regarding D- dimer. On pairwise comparison the difference was significant between each two individual groups (Table 4).

There was a statistically significant association between result of upper endoscopy and D-dimer among the studied patients. On LSD comparison, the difference

was significant between levels of D-dimer among those with normal upper endoscopy and OV grade II, III, IV, gastric varices and portal hypertensive gastropathy. While levels did not differ significantly between normal and OV grade I. The difference was significant between levels of D-dimer among those with PHG and OV grade I, II, and III. The difference was significant between levels of D-dimer among those with OV I and each of PHG, GV, OV, II, III and IV. The difference was significant between levels of D-dimer among those with OV II and each of normal, OV1, III and IV. The difference was significant between levels of D-dimer among those with OV III and each of normal, PHG, GV, OVI, and II. The difference was significant between levels of D-dimer among those with OV IV and each of normal, PHG, OV I, and II. The difference was significant between levels of D-dimer among those with GV and each of normal, OV I, III and IV (Figure 1).

There was a statistically significant association between SBP and D-dimer, which was significantly higher among those with SBP (Table 5).

The best cutoff of D-dimer in prediction of Child A was ≥ 0.35 mg/l to < 1.425 mg/l with are under curve of 0.999, sensitivity of 100%, specificity of 96.4%, positive predictive value (PPV) of 96.6%, negative predictive value (NPV) of 100% and accuracy of 98.2% ($p < 0.001$). The best cutoff of D-dimer in prediction of Child B was ≥ 1.425 mg/l to < 2.45 mg/l with are under curve of 0.987, sensitivity of 92.9%, specificity of 91.1%, PPV of 83.9%, NPV of 96.2% and accuracy 91.7% ($p<0.001$). The best cutoff of D-dimer in prediction of Child C was ≥ 2.45 mg/l with area under curve of 0.986, sensitivity of 96.4%, specificity of 94%, PPV of 84.4%, NPV of 98.8% and accuracy of 94.6% ($p < 0.001$) (Table 6).

The best cutoff of D-dimer in prediction of SBP among child C patients was ≥ 3.1 mg/l with area under curve of 0.96, sensitivity of 90.9%, specificity of 82.4%, PPV of 76.9%, NPV of 93.3% and accuracy of 85.7% ($p < 0.001$) (Figure 2).

Table (2): Comparison between the studied groups regarding demographic data**.**

Parameter	Groups				Test	
	Group 1	Group 2	Group 3	Group 4	F	p
	N=28(%)	N=28(%)	N=28(%)	N=28(%)		
Gender:						
Female	8 (28.6)	6 (21.4)	10 (35.7)	12 (42.9)	3.275	0.351
Male	20 (71.4)	22 (78.6)	18 (64.3)	16 (57.1)		
Age (years):						
Mean ± SD	55.25±3.41	53.25±4.15	54.14 ± 2.61	55.5±3.89	2.388	0.073
Range	50 – 60	48 – 62	50 – 61	45 – 63		

F One Way ANOVA

Table (3): Comparison between the studied groups regarding upper GIT endoscopy findings.

Parameter	Groups			Test	
	Group 1	Group 2	Group 3	χ^2	p
	N=28(%)	N=28(%)	N=28(%)		
Upper endoscopy:					
Normal	11 (39.3)	0 (0)	0 (0)	80.977	<0.001**
PHG	7 (25)	10 (35.7)	5 (17.9)		
OV grade I	5 (17.9)	3 (10.7)	0 (0)		
OV grade II	2 (7.1)	10 (35.7)	0 (0)		
OV grade III	0 (0)	0 (0)	14 (50)		
OV grade IV	0 (0)	0 (0)	5 (17.9)		
GV	3 (10.7)	5 (17.9)	4 (14.3)		

χ^2 : Chi square test **p ≤ 0.001 is statistically highly significant. PHG: portal hypertensive gastropathy
OV: oesophageal varices GV: gastric varices

Table (4): Comparison between the studied groups regarding D-dimer.

Parameter	Groups				Test	
	Group 1	Group 2	Group 3	Group 4	KW	p
	N=28(%)	N=28(%)	N=28(%)	N=28(%)		
D-dimer (mg/l)						
Median Range	1.05 0.4 – 1.7	2 1.3 – 3	3 2.4 – 4.2	0.09 0.01 – 0.4	101.33	<0.001**

**p ≤ 0.001 is statistically highly significant KW: Kruskal Wallis test ¥ the group responsible for significant difference

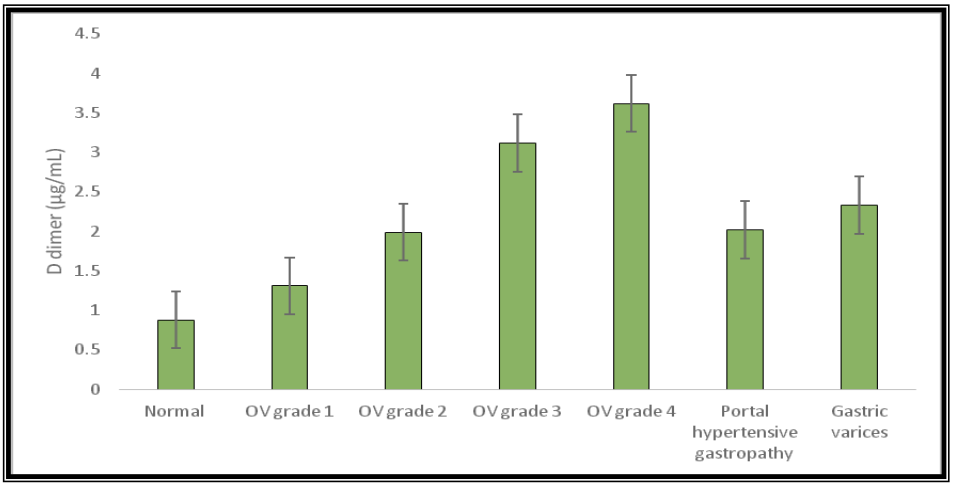

Figure (1): Simple bar chart showing D-dimer among patients with different upper endoscopy results.

Table (5): Relation between D-dimer and presence of SBP among the studied patients with child C.

	D dimer		Test	
	Mean ± SD	Range	t	p
SBP:				
Absent (17) Present (11)	2.86 ± 0.28 3.65 ± 0.34	2.4 – 3.6 3 – 4.2	-6.589	<0.001**

**p ≤ 0.001 is statistically highly significant Independent sample t test

Table (6): Analysis of D-dimer as a marker for severity of liver disease in patients with cirrhosis on Child score A, B, and C.

A							
Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
≥0.35	**0.999**	**100%**	**96.4%**	**96.6%**	**100%**	**98.2%**	**<0.001****
B							
Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
≥1.425	**0.987**	**92.9%**	**91.1%**	**83.9%**	**96.2%**	**91.7%**	**<0.001****
C							
Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
≥2.45	**0.986**	**96.4%**	**94%**	**84.4%**	**98.8%**	**94.6%**	**<0.001****

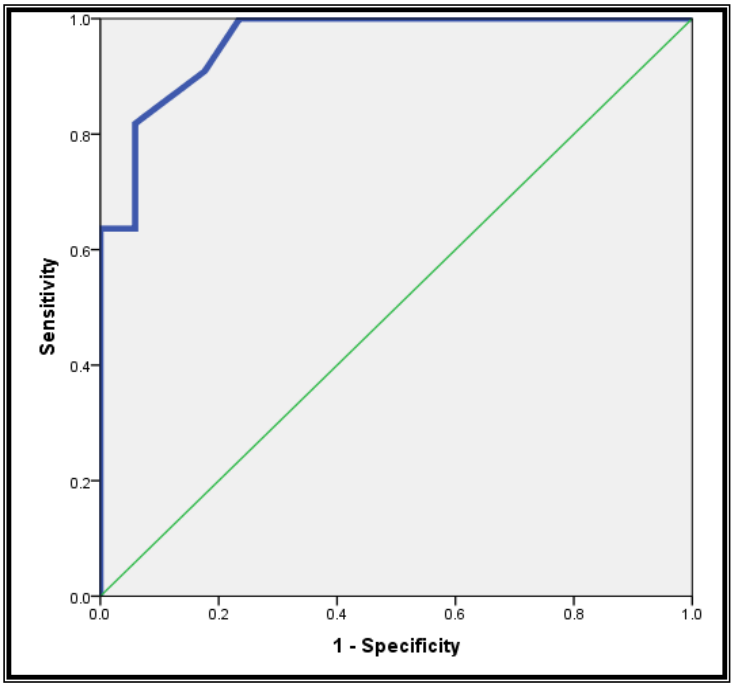

Figure (2): ROC curve showing performance of D dimer in prediction of SBP score among the studied patients.

DISCUSSION

One of the most common causes of liver cirrhosis, which is the ultimate stage of any chronic liver disease, is chronic hepatitis C. Variceal haemorrhage, ascites, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, Porto-pulmonary hypertension, and hepatocellular cancer are all many complications [(10)]. D-dimer is the smallest fibrinolysis-specific degradation product found in the circulation [(11)].

This study revealed that post-hepatitis c cirrhosis is more commonly among males (71.4%). These findings refer that cirrhosis occur more commonly in men than women as proved by **Davis *et al.*** [(12)] who explained this variation in the incidence rate by the fact that males are more likely to be infected with hepatitis C virus.

Our study revealed a significantly higher level of D-dimer in each cirrhotic group (Child A, Child B and Child C) with median of 1.05 mg/l, 2 mg/l and 3 mg/l respectively compared to healthy control group with median of 0.09 mg/l. These results are in agreement with **Dhanunjaya *et al.*** [(13)] and **Saray *et al.*** [(14)] who reported that D-dimer was high in cirrhotic patients, as liver cirrhosis is a state accompanied by an increase in D-dimer and progression of the disease. D-dimer is elevated due to hyperfibrinolysis, which has been described as a frequent clinical feature, which probably depends on primary clotting activation, impaired synthesis of inhibitors of fibrinolytic protein and delayed hepatic clearance of tissue plasminogen activator by the liver in cirrhotic patient [(15)]. The levels of D-dimer in the blood are significantly increased in patients with liver cirrhosis, and are gradually elevated further as the degree of liver dysfunction increases in severity [(14)].

The level of D-dimer was positively correlated with Child-Pugh score. D-dimer level was the highest in Child-Pugh class C group, followed by the Child-Pugh class B and then Child-Pugh class A groups. Cirrhotic patients with Child-Pugh class A and B had significantly higher D-dimer levels compared to the non-cirrhotic patients and healthy controls. This finding is largely consistent with several previous studies. For instance, an Egyptian study by **El-Sayed *et al.*** [(16)] investigated the D-dimer levels in 67 patients with chronic liver diseases and 30 healthy controls. The study observed that cirrhotic patients with Child-Pugh class A and B had significantly higher D-dimer levels compared to the non-cirrhotic patients and healthy controls. The D-dimer levels were demonstrated to gradually increase among Child-Pugh class A, B and C.

In our study, there was a statistically significant association between SBP and D-dimer, which was significantly higher among those with SBP. These results are in agreement with **Mikuła *et al.*** [(17)] who reported that D-dimers < 1500 ng/ml make the diagnosis of SBP unlikely. This association supports that infection may predispose to occurrence of intrahepatic micro thrombosis. The best cutoff of D-dimer in prediction of SBP among child C patients was ≥ 3.1 mg/l with area under curve of 0.96, sensitivity of 90.9%, specificity of 82.4%, PPV of 76.9%, NPV of 93.3% and accuracy of 85.7% ($p < 0.001$).

In the ROC analysis of D-dimer as a marker of liver disease in patients with cirrhosis according to Child classification, the best cutoff of D-dimer in prediction of Child A was ≥ 0.35 mg/l to < 1.425 mg/l with area under curve of 0.999, sensitivity of 100%, specificity of 96.4%, PPV of 96.6%, NPV of 100% and accuracy of 98.2% ($p < 0.001$). The best cutoff of D-dimer in prediction of Child B was ≥ 1.425 mg/l to < 2.45 mg/l with area under curve of 0.987, sensitivity of

92.9%, specificity of 91.1%, PPV of 83.9%, NPV of 96.2% and accuracy of 91.7% ($p < 0.001$). The best cutoff of D-dimer in prediction of Child C was ≥ 2.45 mg/l with area under curve of 0.986, sensitivity of 96.4%, specificity of 94%, PPV of 84.4%, NPV of 98.8% and accuracy of 94.6% ($p < 0.001$). However, **Li *et al.* [18]** suggested that the best cut-off D-dimer value was 0.28 mg/L, with a sensitivity of 86.84% and a specificity of 49.17%. Area under ROC of D-dimer level for this prediction was 0.729 (95% CI, 0.695–0.762; $P < 0.0001$). This difference between their cut off value and ours can be attributed to difference in the studied population and the number of patients included in both studies. The patients included in their studies were all cirrhotic patients whatever the cause like post-hepatitis B, alcoholic…. etc., while all the patients in this study were post-hepatitis c infection. Although we both found that D-dimer level was the highest in Child-Pugh class C group, followed by the Child-Pugh class B and then Child-Pugh class A groups compared to healthy control group.

CONCLUSION

D-dimer may be associated with development of ascites, esophageal varices and portal hypertensive gastropathy. D-dimer could be a marker for severity of liver disease in patients with post-hepatitis C cirrhosis as indicated by Child score.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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