CLINICAL SCIENCE

CORRELATION OF PLASMA D-DIMERS WITH STAGES OF LIVER CIRRHOSIS AND ITS COMPLICATIONS

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Key words: liver cirrhosis, D-dimer, hyperfibrinolysis, Model for End-Stage Liver Disease, Child-Pugh-Turcotte

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Abstract

Aim of the study: To investigate plasma D-dimer levels in correlation with Child-Pugh-Turcotte (CTP) and Model for End-Stage Liver Disease (MELD) scores in patients with liver cirrhosis (LC) of different severity, as well as the correlation with LC-associated clinical, biochemical parameters and complications. Material and methods: Fifty patients with LC were divided in three groups according to LC severity using the CTP Score (CTP-A, CTP-B, CTP-C). The levels of D-dimer were measured in sodium-citrate plasma on Siemens, BCS XP Blood Coagulometer. Kruskal-Wallis test was used to compare D-dimer levels between the groups. Mann-Whitney U test was used to evaluate the difference of D-dimer levels in groups with different MELD score, and to evaluate the difference in D-dimer levels in patients with presence or absence of ascites and the difference of D-dimer levels in patients with or without spontaneous bacterial peritonitis (SBP). Pearson's coefficient of correlation was used to evaluate the correlation between D-dimer levels with MELD score and the correlation between D-dimer levels and the concentration of LC-associated biochemical, clinical parameters and complications. Results: D-dimer levels increased with severity of the disease as assessed with CTP and MELD scores, with a statistically significant difference between the groups (p=.0000 and ***p***=.0001, respectively). Group CTP-C demonstrated the highest D-dimer levels, followed by groups B and A. Patients with SBP had significantly higher levels of D-dimers than patients without SBP (p=.0006). A significant positive correlation between D-dimers and CTP and MELD score was detected (r= 0.74 and r=0.44, respectively; ***p***<.001). A correlation between D-dimer levels and several biochemical parameters characterizing progressive liver dysfunction was observed. From all investigated biochemical parameters, the highest significant correlation was detected between D-dimer levels and the concentration of serum albumin (r= -0.65, ***p***<.001). Conclusions: Plasma D-dimer levels are tightly correlated with the degree of liver dysfunction and LC-associated complications. Therefore, D-dimer levels could be utilized as a prognostic stratification marker and adjunctive diagnostic marker in LC-associated complications.

КЛИНИЧКИ ИСТРАЖУВАЊА

АСОЦИЈАЦИЈА НА ПЛАЗМА Д-ДИМЕРИТЕ СО СТАДИУМИТЕ НА ЦРНОДРОБНА ЦИРОЗА И НЕЈЗИНИТЕ КОМПЛИКАЦИИ

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Клучни зборови: цироза на црн дроб, Д-димери, хиперфибринолиза, Model for End-Stage Liver Disease, Child-Pugh-Turcotte

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Извадок

Цел на студијата: Да се испита нивото на Д-димери во плазма во корелација со клиничките скорови: Child-Pugh-Turcotte (CTP) и Model for End-Stage Liver Disease (MELD) кај пациенти со црнодробна цироза со различна тежина, како и нивна корелација со клинички, биохемиски параметри и компликации поврзани со црнодробна цироза. Материјали и методи: Вкупно 50 пациенти со цироза на црн дроб беа поделени во три групи според тежината на цироза на црниот дроб врз основа на CTP Score (CTP-A, CTP-Б, CTP-C). Концентрацијата на Д-димерите беше одредена во плазма со натриум цитрат користејќи го Siemens, BCSXP крвниот коагулометар. Kruskal-Wallis тестот беше користен за да се спореда нивоата на Д-димери помеѓу CTP групите. Mann-Whitney U тестот беше направен за да се одреди разликата во нивоата на Д-димерите помеѓу групите со различен MELD скор, и за да се оцени разликата во нивоата на Д-димерите кај пациенти со присуство или отсуство на асцит и разликата во нивоата на Д-димерите кај пациенти со или без спонтан бактериски перитонитис (SBP). Pearson-овиот коефициент на корелација беше користен за да се оцени корелацијата помеѓу нивоата на Д-димери со MELD скорот и корелацијата помеѓу нивоата на Д-димери и концентрацијата на биохемиски, клинички параметри и компликации поврзани со црнодробна цироза. Резултати: Концентрацијата на Д-димерите се зголеми со тежината на болеста проценета со CTP и MELDскорот со статистички значајна разлика помеѓу групите (***p***=,0000 и ***p***=,0001, соодветно). Групата CTP-C покажа највисока концентрација на Д-димери, по што следуваа групите Б и А. Пациентите со SBP имаа значително повисока концентрација на Д-димери во споредба со пациентите без SBP (***p***= ,0006). Беше утврдена значителна позитивна корелација помеѓу Д-димерите и CTP и MELD скорот (коефициент на корелација r= 0,74 и r= 0,44, соодветно; ***p***< ,001). Дополнително, резултатите покажаа дека постои поврзаност меѓу плазма концентрацијата на Д-димерите со клиничките и биохемиски параметри кои карактеризираат прогресивна дисфункција на црниотдроб. Од сите испитувани биохемиски параметри, највисока статистички значителна корелација беше утврдена меѓу нивоата на Д-димерите и концентрацијата на серумските албумини (r = - 0,65, ***p***< 0,001). Заклучок: Плазматската концентрација на Д-димерите е тесно поврзана со степенот на дисфункција на црниотдроб и компликациите поврзани со цироза на црн дроб. Затоа, нивоата на Д-димерите може да се користат како прогностички маркер за стратификација и дополнителен дијагностички маркер во компликациите поврзани со цироза на црн дроб.

Introduction

Plasma D-dimers are the end products of fibrinolysis, the process which regulates fibrin degradation and prevents thrombosis or hemorrhage. In combination with clinical probability assessment, D-dimers are routinely used in clinical practice for ruling out pulmonary embolism[1,2], as well as for deciding on anticoagulant therapy in patients with risk of recurrent venous thromboembolism[3]. Liver cirrhosis (LC) is associated with changes in hemostasis[4], and accelerated hyperfibrinolysis may be one of the mechanisms that can contribute to serious coagulopathy which can occur in LC in different settings.

Incidence of hyperfibrinolysis and its association with clinical parameters of LC has not been extensively evaluated[5]. Plasma D-dimers give precise insight in the presence of fibrinolysis and elevated levels reflect overactive coagulation and fibrinolysis *in vivo*. Previous studies have shown elevated levels in association with liver dysfunction[6], presence of ascites[7], development of spontaneous bacterial peritonitis (SBP)[8], and in occurrence of portal vein thrombosis[9]. Consequently, it has been suggested that they may have a prognostic value for LC-associated outcomes[9,10].

In our study we aimed to evaluate plasma D-dimers in patients with LC with varying degree of liver dysfunction using the Child Turcotte Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. Additionally, we assessed the relationship between hyperfibrinolytic state with different biochemical and clinical parameters in LC at different stage of the disease.

Materials and methods

This was a cross-sectional study conducted at the University Clinic for Gastroenterohepatology in Skopje between June 2021 and December 2022. Patients consecutively admitted to the Clinic or evaluated at the outpatient level were enrolled. The inclusion criteria were as follows: 1) diagnosis of LC of different etiology (based on clinical presentation, routine laboratory tests and ultrasound examination of the abdomen); 2) patients at the age of 18 years and older; 3) a voluntary signed informed consent by patients or their family. Exclusion criteria were as follows: 1) presence of sepsis; 2) acute bleeding; 3) use of vitamin K antagonists, oral therapy with direct anticoagulants or antithrombotics; and 4) presence of malignant disease (hepatocellular carcinoma included). The present study was approved by the Ethics Committee at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

The following data were analyzed: age, gender, etiology of LC, presence of ascites, presence of SBP [defined as an elevated absolute fluid polymorphonuclear neutrophil (PMN) count in the ascites (>250/mm3) without an evident intra-abdominal surgically treatable source of infection], spleen diameter, portal vein diameter, red blood cell (RBC) count, hemoglobin (Hb) level, white

blood cell (WBC) count, platelet level (PLT), C-reactive protein (CRP), total bilirubin (TBIL), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), urea, prothrombin time (PT), international normalized ratio (INR), D-dimer levels, CTP and MELD scores. Blood samples for laboratory and hemostatic assessment were obtained before initiation of therapy for the hospitalized patients and at a regular follow-up. Patients were divided in 3 groups according to their LC severity and expected survival using the CTP score (CTP A - 5-6 points, CTP B – 7-9 points and CTP C – 10-15 points)[11,12]. Laboratory hemostatic assessment was according to already adopted protocols and standard practice using Siemens' fully automated coagulometer - Dade Behring BCS® XP System, hematological analyzer MEDONIC and Xprecia Stride analyzer which uses single-use test strips with reagents (Dade® Innovin®) at the Institute for Transfusion Medicine.

Categorical data are presented as mean ± standard deviation, and were compared using the Mann-Whitney U test. The comparison of D-dimer levels (reference range: 0-500 ng/ml) with the CTP score was evaluated using the Kruskal-Wallis test and Multiple Comparison test, while the comparison of D-dimer levels between patients according to MELD score, presence of ascites and SBP was made with Mann-Whitney U test. Boxplots were also constructed to demonstrate the difference in the D-dimer levels among various Child-Pugh classes (namely A-C) and MELD (namely scores >15 or <15). Scatterplots were constructed for displaying the correlation between evaluated variables and correlation was assessed with Pearson's coefficient of correlation. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using the IBM SPSS Statistics[20].

Results

Patients

In total, 50 patients with LC fulfilling the inclusion criteria were enrolled in the study. Patient characteristics are demonstrated in Table 1.The mean age in group CTP-A was 56.9±10.4 years with 38.9 % being men; in group CTP-B the mean age was 54.0±16.7 years with 50 % being men, and in group CTP-C the mean age was 51.6±14.4 years with 81.3% being men. The most common etiology of LC was alcoholic liver disease (13/50; 26%).

Table 1. Demographic and clinical characteristics of patients.

Variables	CTP-A	CTP-B	CTP-C	p
Number of patients (n)	18	16	16	
Age (mean±SD)	56.9±10.4	54.0±16.7	51.6±14.4	
Gender, %				
Male	7/38.9	8/50.0	13/81.3	
Female	11/61.1	8/50.0	3/18.7	
Etiology (n)				
Viral hepatitis	6	3	4	
Alcohol	2	5	8	
Autoimmune	6	3	/	
MAFLD*	3	2	/	
Others	1	3	4	
Albumin, g/L (mean±SD)	42.1±5.9	34.0±5.9	26.6±4.4	.0000
Bilirubin, mol/L (mean±SD)	15.5±8.6	43.3±28.8	143.2±139.5	.0000
Ascites, %	4/22.22	12 /75	16 /100	
SBP^, %	0	0	8/50	
Hepatic encephalopathy, %	0	2/12.5	10/62.5	
CRP‡, mg/L(mean±SD)	7.1±9.6	9.1±8.7	50.8±46.5	.0000
PT, s (mean±SD)	12.2±0.9	14.3±2.3	20.0±4.0	.0000
INR (mean±SD)	1.1±0.1	1.3±0.2	1.8±0.4	.0000
D-dimers, ng/ml (mean±SD)	670.2±419.1	2972.0±3815.7	6393.6±3086.1	.0000
MELD score† (mean±SD)	8.7±3.1	12.3±3.6	24.6±7.4	.0000
Patients with LC-associated complication that led to death, %	/	3/18.75	7/43.75	

**MAFLD: metabolic-associated fatty liver disease; ^SBP: spontaneous bacterial peritonitis; ‡CRP: C-reactive protein; †MELD score: Model for End-Stage Liver Disease score*

D-dimer and CTP Score.The mean value of D-dimer was lowest in group CTP-A (670.2±419.1ng/ml), and progressively increased in group CTP-B (2972.0±3815.7ng/ml) and group CTP-C (6393.6±3086.1ng/ml) as shown in Fig.1. The difference in D-dimer levels among the groups was statistically significant (H(2) = 26.99, p = .0000) (Table 1). Furthermore, significant differences were observed between the different groups (A *vs.* B, *p*= .037; A *vs.* C, *p* = .0000; B *vs.* C, *p* = .026). The mean values of D-dimers in patients who died of LC-associated complication at least 2 weeks after being enrolled in the study were 4837.97±3480.124ng/ml. A significant strong positive correlation was demonstrated between D-dimer levels and CTP score (r= 0.74, *p*< .00001).

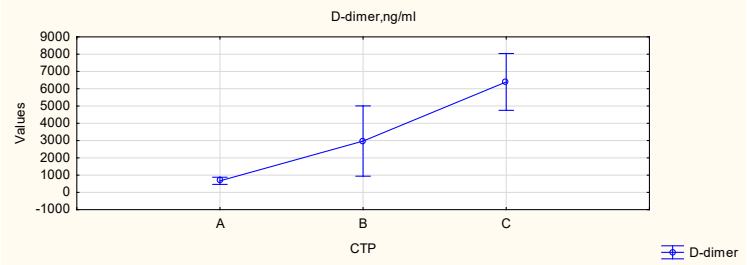


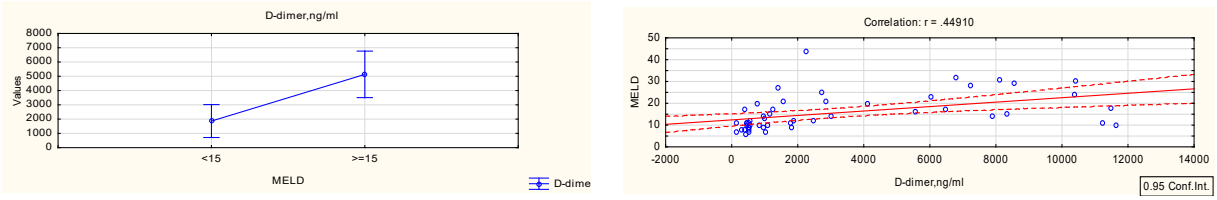
Figure 1. Average levels of D-dimers within different stage of LC according to CTP score

D-dimer and MELD score.

The mean value of D-dimer levels in MELD < 15 group was 1864.4±3027.781ng/ml, while in MELD group > 15 was significantly higher, 5135.6±3580.157ng/ml (Table 2). There was a statistically significant difference between the groups (z =-3.73, *p*=.0001). As shown in Fig. 2-b, D-dimer levels were positively correlated with the MELD score (r= 0.44; *p* =.001).

Table 2. D-dimer levels in patients according to MELD score

MELD score	Number of patients, n	D-dimer (mean±SD), ng, mL
< 15	29	1864.4±3027.781
> 15	21	5135.6±3580.157



a **b**

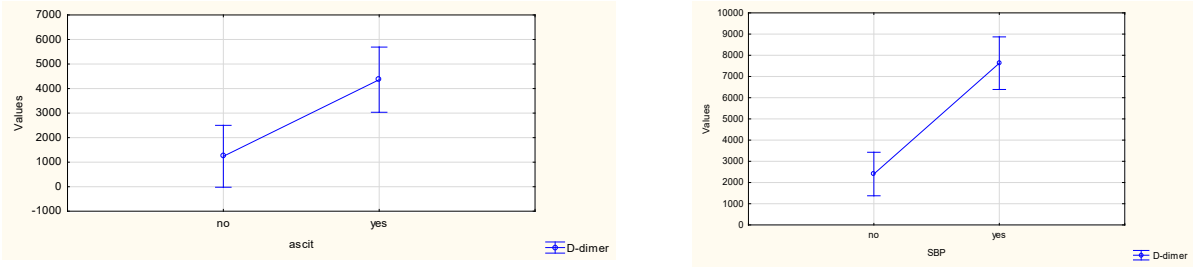
Figure 2. D-dimer levels and MELD score. a) average levels of D-dimers in patient with MELD score < 15 and > 15; b) correlation of D-dimer levels with MELD score

D-dimer and ascites

The mean values of D-dimers in patients with ascites were 4362.7±3687.4 ng/ml, which were significantly higher than those in patients without ascites, 1239.2±2537.6 ng/ml (Table 3 and Fig. 3-a). This difference was statistically significant (z =4.07, *p*=.00004). Additionally, the mean values of D-dimer levels were significantly higher in patients with large volume ascites (6196.9±3498.7 ng/ml), compared to patients with small amount ascites (1306±929.9 ng/ml) (Table 3). The difference between these groups of patients was statistically significant (z =6.41, *p*< .00001).

Table 3. D-dimer levels in presence or absence of ascites and the amount of ascites

Ascites	Number of patients (n)	D-dimers (mean±SD, ng/mL
< 15	29	1864.4±3027.781
> 15	21	5135.6±3580.157
Small amount ascites	12	1306±929.9
Large volume ascites	20	6196.9±3498.7



a b

Figure 3. D-dimer levels in: a) patients without and with ascites; b). patients with and without SBP

D-dimers and SBP

The mean value of D-dimers in patients with SBP was 7630.2±1483.5 ng/ml compared to patients without SBP (2401.7±3291.7 ng/ml), which was statistically significantly higher (z =-3.42, *p*=.0006) (Table 4 and Fig. 3-b). Likewise, the comparison of the mean value of D-dimers between patients with ascites but without SBP (3273.6±3564.4 ng/ml) and patients with ascites and SBP (7630.2±1483.5) showed a statistically significant difference (z = -2.85,*p* = .004).

Table 4. D-dimer levels in patients without and with SBP

	Number of patients (n)	D-dimers (mean±SD, ng/mL
Absence of SBP	42	2401.7±3291.7
Presence of SBP	8	7630.2±1483.5
Ascites without SBP	24	4362.7±3687.4
Ascites with SBP	8	7630.2±1483.5

D-dimers and other LC-associated clinical and biochemical parameters.

The evaluated LC-associated clinical and biochemical parameters (age, Hb, Hct, PLT, WBC, CRP, ALT, AST, albumin, bilirubin, blood urea nitrogen, serum creatinine, PT, INR, fibrinogen, etiology of disease, spleen diameter and portal vein diameter) showed a significant moderate positive correlation between D-dimer levels and WBC (r =0.55, *p* = .0000), CRP (r= 0.42, p = .0023), PT (r= 0.44, *p* = .001) and INR (r =0.44, *p* = .001) (Fig. 4). A significant moderate negative correlation of D-dimer levels was registered for albumin (r= -0.65, *p*< .00001) (Fig. 4).

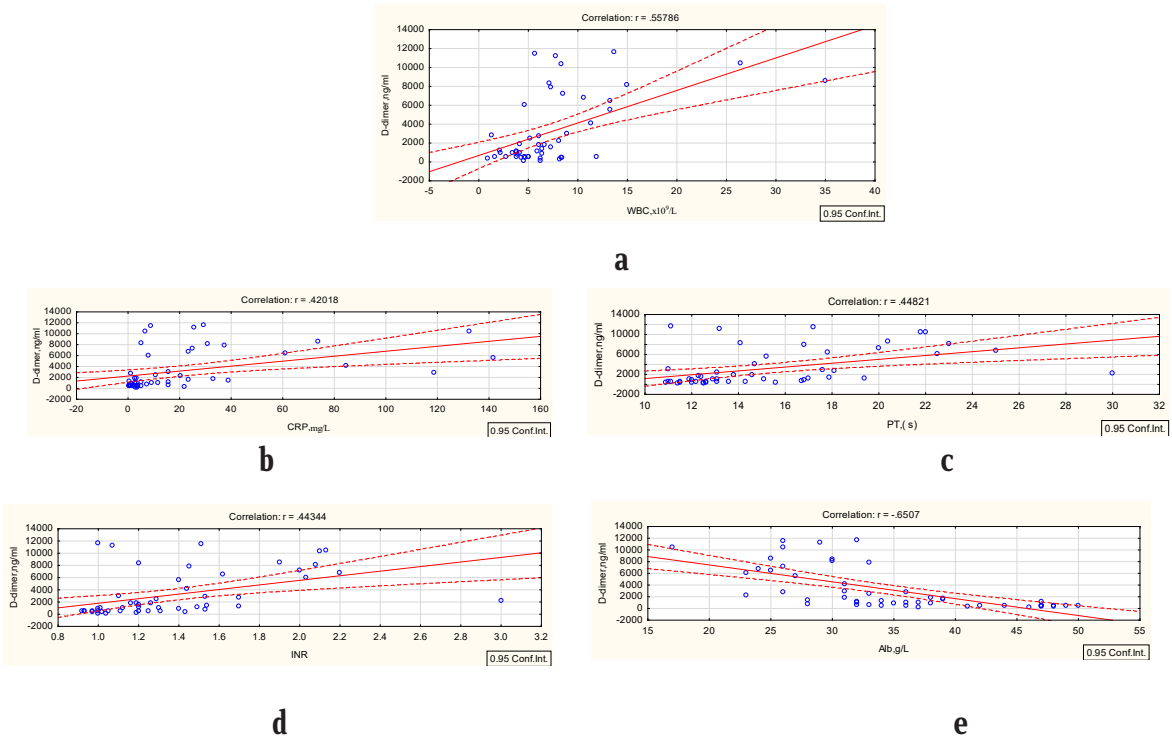


Figure 4. Significant moderate positive correlation of D-dimer levels with WBC, CRP, PT and INR (a-d) and significant moderate negative correlation with albumin (e).

Discussion

In our study we demonstrated that the increase of D-dimer levels throughout different stage of LC was in correlation with CTP and MELD scores. This finding was in line with previous studies. In our study, D-dimer levels in healthy subjects and subjects with non-cirrhotic chronic liver disease were not assessed, but in the study of El-Sayed *et al.*[13] a substantial difference in D-dimer levels between these groups of patients was demonstrated. The authors observed significantly higher D-dimer levels in patients with Child-Pugh class A and B compared to non-cirrhotic patients with chronic liver disease, and also compared to healthy controls. Similar results were demonstrated in two independent studies in which progressive increase of D-dimers among Child-Pugh class A, B and C was registered[14,15]. In a study evaluating the correlation of D-dimers with esophageal variceal bleeding in patients with LC, classified according to their

CTP and MELD scores, a significant increase was detected in patients in advanced stage of the disease, more specifically in Child-Pugh class C (with and without bleeding) and in those with MELD score > 17 with bleeding[16]. The results of our study correspond to the afore mentioned studies and has clearly demonstrated that as LC progresses, the levels of D-dimer progressively increase. Additionally, our study confirmed that between different stages of LC according to CTP score, there was a significant difference in D-dimer levels that was statistically significant (p = .0000, p < .05). The same result was obtained when evaluated with MELD score showing a positive correlation with D-dimer levels. Based on current guidelines, patients with LC and a MELD score of 15 or greater should be referredfor liver transplantation evaluation[17]. The group of patients with MELD score > 15 had significantly higher values of D-dimers compared to the group with MELD score < 15, with a statistically significant difference (p = .0001, p < .05). These findings support the tight correlation of accelerated fibrinolytic activity, i.e., hyperfibrinolysis with the degree of liver dysfunction as assessed by the CTP and MELD scores.

When comparing patients with LC without and with ascites in our study, we registered a significant difference between the two groups. D-dimer levels in patients with ascites were significantly higher than in those without (p = .00004, p < .05). Furthermore, there was a statistically significant difference (p <.00001) in D-dimer levels when evaluating the amount of ascites (Table 3). These results are also to be expected given that patients with ascites, especially those with higher amounts of ascites have more advanced LC, i.e., are common in the CTP-B and CTP-C class. But some studies suggest that the elevated D-dimer levels can also be the result of the ascitic fluid itself, as a fibrinolytic activity of the ascitic fluid has been demonstrated[18]. Still, this is controversial as not all studies have confirmed this finding[19,20]. Another finding that supports the role of developing ascites in the LC-associated hyperfibrinolysis, is the reduction of D-dimer level with treatment and resolution of ascites (medicamentous or with ascitic fluid paracentesis) [7,21,] though D-dimers are still higher than in patients with LC but without ascites [7,22].

The difference in D-dimer levels was even more accentuated in patients with SBP compared to patients with LC without ascites or with ascites and no SBP. We demonstrated a significant difference (p = .0006) between D-dimer levels in patients with LC and without SBP and patients with SBP. This difference was also significant (p=.004) when comparing patients with LC and ascites but without SBP. These findings were confirmed in other studies[8,23]. Hence D-dimers can be an adjunctive diagnostic tool in identifying LC patients with SBP, and possibly differentiating patients with ascites, but without bacterial infection. This is of importance in the clinical management of these patients since

SBP has a subtle presentation and a high index of suspicion is needed for diagnosis and prevention of LC deterioration[24]. SBP is a serious LC-complication and leads to worsening of prognosis in patients with LC with short-term mortality of about 15-40%[25].

In our study we found a significant but moderate positive correlation of D-dimer levels with WBC, CRP, PT and INR, and a significant strong negative correlation with serum albumin. This correlation confirms once again that higher levels of D-dimers are present in advanced liver cirrhosis and reflect liver dysfunction.

Although our study did not evaluate the role of D-dimers as a predictor of mortality rate, we detected a marked increase of D-dimers in patients with LC-related death up to 2 weeks after inclusion in the study. The mean values of the D-dimers in this group of patients were4837.97±3480.12 ng/ml.D-dimers were evaluated as a possible predictive and prognostic marker in patients with LC. Primignaniet al. evaluated the association of D-dimers with the 6-week mortality rate in cirrhotic patients with esophageal variceal bleeding 16. Hyperfibrinolysis was present in 67% of non-survivors compared to 11% of survivors, and the odds ratio for D-dimer level for predicting 6-week mortality was 16[16]. Another study of 703 patients with LC showed that D-dimers can predict in-hospital mortality with sensitivity of 86.84% and a specificity of 49.17% for the cut off value of 0.28 μg/ml10.

The limitation of our study is the small sample and the fact that it was performed in a single institution. Additionally, this was a cross-sectional study and a follow-up of the patients would have added to the strength of D-dimers as diagnostic markers for liver dysfunction and diagnosis of SBP as well as a prognostic factor for LC-related mortality.

Conclusion

Hyperfibrinolysis and D-dimer levels are correlated with the degree of liver dysfunction. Furthermore, a significant increase in plasma D-dimers in the presence of ascitic fluid is highly correlated with SBP, thus it represents a promising marker for early detection of SBP. Our study suggests that higher D-dimer levels should further be investigated and validated as predictor of increased in-hospital mortality and thus, in the future can present a prognostication parameter for patients with advanced liver disease.

References

1. Rodger MA, Le Gal G, Wells P, et al. Clinical decision rules and D-Dimer in venous thromboembolism: current controversies and future research priorities. Thromb Res 2014;134(4):763-768.https://doi.org/10.1016/j.thromres.2014.07.031
2. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a

diagnostic meta-analysis. BMJ. 2009;339:b2990. https://doi.org/10.1136/bmj.b2990

3. Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. Blood 2014;124(2):196-203.https://doi.org/10.1182/blood-2014-01-548065
4. Tripodi A. Hemostasis in Acute and Chronic Liver Disease. Semin Liver Dis 2017;37(1):28-32.https://doi.org/10.1055/s-0036-1597770
5. Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. Clin Gastroenterol Hepatol. 2013;11(9):1064-1074.https://doi.org/10.1016/j.cgh.2013.02.026
6. Cioni G, Cristani A, Mussini C, et al. Incidence and clinical significance of elevated fibrin(ogen) degradation product and/or D-dimer levels in liver cirrhosis patients. Ital J Gastroenterol. 1990;22(2):70-74.
7. Saray A, Mesihovic R, Gornjakovic S, et al. Association between high D-dimer plasma levels and ascites in patients with liver cirrhosis. Med Arch 2012; 66(6):372-4. https://doi.org/10.5455/medarh.2012.66.372-374
8. El Gohary AM, Elyamany AS, Mikhael NL, Mahmoud MG, Tawfik MMR. Serum and ascitic D-dimer in cirrhotic patients with spontaneous bacterial peritonitis. Clin Exp Hepatol. 2021;7(2):134-140.https://doi.org/10.5114/ceh.2021.105915
9. Dai J, Qi X, Li H, Guo X. Role of D-dimer in the development of portal vein thrombosis in liver cirrhosis: A Meta-analysis. Saudi J Gastroenterol. 2015;21(3):165-174. https://doi.org/10.4103/1319-3767.157567
10. Li Y, Qi X, Li H, et al. D-dimer level for predicting the in-hospital mortality in liver cirrhosis: A retrospective study. Exp Ther Med. 2017;13(1):285-289.https://doi.org/10.3892/etm.2016.3930
11. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1-85. https://pubmed.ncbi.nlm.nih.gov/4950264/
12. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124(1):91-96.https://doi.org/10.1053/gast.2003.50016
13. El-Sayed R, El-Karaksy H, El-Raziky M, et al. Assessment of coagulation and fibrinolysis in children with chronic liver disease. Blood Coagul Fibrinolysis 2013; 24(2):113-117.https://doi.org/10.1097/MBC.0b013e3283569297
14. Cong YL, Wei YX, Zhang LW, Yin ZJ, Bai J. The relationship between hemostatic changes in liver cirrhosis patients with different degrees of liver lesions in reference to Child-Pugh scores. Zhonghua Gan Zang Bing Za Zhi. 2005;13(1):31-34. Chinese. https://pubmed.ncbi.nlm.nih.gov/15670488/

15. Violi F, Ferro D, Basili S, et al. Association between low-grade disseminated intravascular coagulation and endotoxemia in patients with liver cirrhosis. Gastroenterology 1995;109(2):531-539. https://doi.org/10.1016/0016-5085(95)90342-9

16. Primignani M, Dell'Era A, Bucciarelli P, et al. High-D-dimer plasma levels predict poor outcome in esophageal variceal bleeding. Dig Liver Dis 2008; 40(11):874-881.https://doi.org/10.1016/j.dld.2008.01.010

17. Kalra A, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. Curr Opin Organ Transplant 2016; 21(2):120-126. https://doi.org/10.1097/MOT.0000000000000281

18. Agarwal S, Joyner KA Jr, Swaim MW. Ascites fluid as a possible origin for hyperfibrinolysis in advanced liver disease. Am J Gastroenterol. 2000;95(11):3218-3224. https://doi.org/10.1111/j.1572-0241.2000.03299.x

19. Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. Gastroenterology. 2001; 121(1):131-139.https://doi.org/10.1053/gast.2001.25481

20. Colucci M, Binetti BM, Branca MG, et al. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. Hepatology 2003; 38(1):230-237.https://doi.org/10.1053/jhep.2003.50277

21. Romanelli R, Cellai A, Lami D, et al. D-dimer and fibrinolytic activity in patients with decompensated liver cirrhosis. Digest Liver Dis 2015; 47: e33. https://doi.org/10.5114/ceh.2021.105915

22. Wesam AI, Abdelhakam S, Helmy A, et al. Evaluation of plasma D-dimer level in patients with chronic liver disease. Researcher 2011; 3: 13-18.

23. Weiyi X, Baode C, Qing X. The application of plasma D-dimer in the diagnosis of spontaneous peritonitis in cirrhotic patients with ascites. Int J Lab Med 2014; 21: 2883-2884.

24. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010; 53: 397-417.https://doi.org/10.1016/j.jhep.2010.05.004

25. Komolafe O, Roberts D, Freeman SC, et al. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database Syst Rev 2020;1(1):CD013125.https://doi.org/10.1002/14651858.CD013125.pub2