Abstract

Aim of the study: The study aimed to investigate serum and ascitic fluid D-dimer level in patients with liver cirrhosis with and without ascites and to evaluate the impact of spontaneous bacterial peritonitis (SBP) on circulating serum and ascitic fluid D-dimer levels.

Material and methods: This study was conducted on 60 subjects who were further subdivided into group I comprising 15 patients with liver cirrhosis and no ascites, group II comprising 15 cirrhotic patients with ascites, group III comprising 15 cirrhotic patients with ascites and SBP, and group IV comprising 15 healthy controls. All patients were subjected to full history taking, physical examination, laboratory investigations, and measurement of serum D-dimer in all groups and ascitic fluid D-dimer in groups II and III. The diagnostic performance of serum D-dimer was tested to detect SBP.

Results: Serum D-dimer differed significantly between groups III and IV, whilst no significant differences were detected between the other groups and group IV. Moreover, group III showed a significantly higher level of serum D-dimer. Ascitic fluid D-dimer mean levels showed no statistically significant differences. A statistically significant positive correlation was found between serum D-dimer level and ascitic fluid D-dimer in group III, $r = 0.682$. Using a sensitivity and specificity level of 80%, a cut-off value (COV) of > 323.2 ng/ml could differentiate between patients with SBP and patients with ascites only.

Conclusions: Serum D-dimer significantly correlated with ascitic fluid D-dimer in patients with SBP, whereas no significant correlation was found in patients with cirrhotic ascites without bacterial infection. D-dimer showed good diagnostic performance for SBP among patients with liver cirrhosis.

Key words: D-dimer, liver cirrhosis, ascites, spontaneous bacterial peritonitis.

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Introduction

The relation between liver diseases and hemostasis is believed to be complex; some patients with advanced liver disease can experience severe bleeding whilst others may even suffer thrombotic complications because of reduced plasma levels of pro-coagulative and anticoagulative clotting factors synthesized by the liver [1, 2]. Patients with liver cirrhosis may develop a serious coagulopathy whose origin is multifactorial, and one of them is accelerated hyperfibrinolysis. However, the exact incidence of hyperfibrinolysis among patients with cirrhosis and the associated clinical parameters that may predict the diagnosis and clinical consequences of hyperfibrinolysis remain largely unknown [3]. The ascitic fluid is essentially an ultrafiltrate of plasma; thus it contains coagulation-relevant proteins. If the ascites compartment is a site at which fibrinolytic activity arises, then ascites may contribute to the exaggerated fibrinolysis and bleeding tendency typically found...
in advanced liver disease [4]. Spontaneous bacterial peritonitis (SBP) is a serious complication in patients with cirrhosis. The incidence of SBP in decompensated liver cirrhosis patients is about 20% with short-term mortality of about 15% to 40% [5]. SBP is associated with significant resource utilization and approximately 2.5% of all hospitalizations of patients with cirrhosis [6]. Up to 13% of cases may be asymptomatic; hence, a high index of suspicion is needed to prevent diagnostic delay and worsening of the prognosis [7]. D-dimer is a highly specific test for the presence of fibrinolysis. Its abnormality reflects the excessive activation of coagulation and fibrinolysis systems in vivo. D-dimer was found to be a valuable diagnostic and prognostic test in some diseases such as deep vein thrombosis and some cancer-related thrombosis [8]. We aimed to evaluate serum D-dimer in cirrhotic patients with and without ascites to assess the relationship between ascites and the hyperfibrinolytic state in liver cirrhosis. Additionally, we assessed the effect of SBP on serum and ascitic fluid concentration of D-dimer.

Material and methods

In the present study, all patients were recruited from the Hepatobiliary Unit, Department of Internal Medicine at Alexandria Main University Hospital. The study was conducted among 60 patients with liver cirrhosis classified into four groups: Group I comprised fifteen cirrhotic patients without ascites. Group II comprised fifteen cirrhotic patients with ascites. Group III comprised fifteen cirrhotic patients with ascites and SBP. Group IV comprised fifteen matched healthy subjects with no evidence of liver disease who were included in the study as a control group. The exclusion criteria were all other causes of ascites, pregnancy, history of deep venous thrombosis or portal vein thrombosis, current anticoagulation therapy, hepatorenal syndrome, and any known malignancy.

All patients were subjected to full history taking, physical examination, laboratory investigations (complete blood count, liver test profile, viral markers, autoimmune markers, kidney function tests, metabolic diseases markers, serum α-fetoprotein, ascitic fluid analysis, and abdominal ultrasonography). Serum D-dimer level was measured in all patients; additionally it was measured in ascitic fluid in the second and third groups. D-dimer was measured using the ELISA kit, which is based on the principle of the double-antibody sandwich technique to detect human D-dimer (D2D). Liver cirrhosis was diagnosed according to clinical and ultrasonographic findings. Assessment of the severity of the condition was confirmed according to the modified Child-Pugh classification and model for end-stage liver disease (MELD) score. The presence of ascites was confirmed by ultrasonography and diagnostic paracentesis. SBP was confirmed by an elevated ascitic fluid absolute polymorphonuclear leukocyte (PMN) count ($≥$ 250 cells/mm$^3$) and ascitic fluid bacterial culture [9]. The study protocol was approved by the Research Review Committee of the Alexandria Faculty of Medicine and was confirmed to the principles of the Declaration of Helsinki. Informed consent was obtained from each subject included in the study.

Statistical analysis

IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, NY, USA) was used for data entry and analysis. All scores were presented as mean ± standard deviation. Analysis of quantitative variables was conducted by non-parametric tests: the Mann-Whitney U test was used for independent group comparison while the Wilcoxon signed-rank test was applied to assess dependent groups. They were described using range, mean, standard deviation, and median. Categorical data were expressed as numbers and percentages and compared using the χ$^2$ test. A p-value of less than 0.05 was considered statistically significant. The sensitivity and specificity of serum and ascitic D-dimer in patients and controls were assessed by plotting the receiver operating characteristic curve (ROC) to show the diagnostic performance in differentiating different groups of patients and determining its cut-off values.

Power analysis calculation

We conducted power analysis for the diagnostic performance of ascitic D-dimer to differentiate between SBP and control, which yielded a power of 73% using area under the curve. We performed calculations using the "pROC" package with R software [10].

Results

In the first group, 9 (60%) of patients were male. The proportion of males did not differ significantly between the four studied groups ($p = 0.266$). Also, there was no statistically significant difference in mean age ($p = 0.080$) or proportion of patients living in rural areas ($p = 0.070$) between all studied groups. Cirrhotic patients with ascites and SBP had a significantly higher mean MELD score than cirrhotic patients without ascites and cirrhotic patients with ascites ($p < 0.001$). Most patients in the second and third groups were classified in Child-Pugh class C compared to two-
thirds of patients with ascites classified in Child-Pugh class A ($p < 0.001$). Mean serum D-dimer was the highest among cirrhotic patients with ascites and SBP compared with mean values observed among cirrhotic patients without ascites, cirrhotic patients with ascites, and the control group ($p = 0.014$). However, no significant difference was found in mean D-dimer between the study groups ($p = 0.178$) (Table 1).

These findings are consistent with a detected significant positive strong linear relationship between serum D-dimer level and ascitic fluid D-dimer in group III ($r = 0.682, p < 0.05$). However, a significant linear relationship was not detected between serum D-dimer level and ascitic fluid D-dimer in group II ($p = 0.459$) (Fig. 1).

ROC curve analysis reveals the diagnostic performance of serum D-dimer to differentiate between patients with SBP and other different study groups. A cut-off $> 323.2$ ng/ml best differentiated between patients with SBP and patients with ascites only with a corresponding AUC of 0.778 (95% CI: 0.599 to 0.956, $p = 0.010$), sensitivity and specificity level of 80%. A cut-off $> 314.9$ ng/dl best discriminated between patients with SBP and patients with cirrhosis only with a corresponding AUC of 0.778 (95% CI: 0.597 to 0.958).
Assessment of D-dimer in cirrhotic patients

While a cut-off > 332.4 ng/ml best distinguished between SBP patients and normal controls with a corresponding AUC of 0.761 (95% CI: 0.564 to 0.958, \( p = 0.020 \)), a sensitivity of 80% and specificity of 83.3% (Fig. 2).

We also tested the correlation between serum D-dimer and different parameters stratified by study groups. No significant linear relationship was observed between serum D-dimer and age, hemoglobin, platelets, white blood cells (WBCs), MELD score and Child-Pugh classification among groups I, II and III (\( p > 0.05 \)) and ascitic fluid parameters for groups II and III (\( p > 0.05 \)). However, a large significant positive correlation was detected between hemoglobin as well as platelets and serum D-dimer in group III (\( p = 0.003, p = 0.038 \)) respectively. Moreover, a significant negative large correlation was discovered between serum D-dimer and splenic size (\( r = -0.714, p = 0.003 \)) and portal vein diameter (\( r = -0.538, p = 0.038 \)). Furthermore, ascitic D-dimer was significantly correlated with hemoglobin level (\( r = 0.630 \)) and platelets (\( r = 0.543 \)) among patients in group III (Table 2).

Table 3 compares the mean difference of ascitic fluid different parameters between groups II and III. Mean neutrophil and lymphocyte counts were significantly higher in cirrhotic patients with ascites and SBP than cirrhotic patients with ascites (\( p < 0.001, p = 0.004 \) respectively). However, the mean protein level was significantly lower in group II than group III (\( p = 0.044 \)). No significant difference was detected between groups for the other parameters.

**Discussion**

The current study confirmed that serum D-dimer among patients with SBP is significantly higher than that in normal and liver diseased participants whilst the higher ascitic fluid level of D-dimer among SBP patients did not significantly differ from other patients. Moreover, serum D-dimer showed a valuable diagnostic performance in differentiating patients with SBP from other patients with or without liver diseases and even patients with liver diseases suffering from ascites without bacterial infection.
SBP has usually subtle clinical presentation with considerable worsening of prognosis in patients with advanced liver cirrhosis [7]. Some studies linked the chronic liver disease to low-grade disseminated intravascular coagulation (DIC), ascribing the latter to accelerated fibrinolysis. However, the presence of DIC in liver cirrhosis is controversial. DIC-like laboratory abnormalities called “pseudo-DIC”) are observed in some autopsy studies in cirrhotics. More highly sensitive tests such as quantification of proteolytic cleavage products of the coagulation reaction demonstrated an abnormal profile called accelerated intravascular coagulation and fibrinolysis phenomenon (AICF) [1, 11]. Hyperfibrinolysis is correlated with the severity of liver dysfunction in cirrhosis as assessed by the Child-Pugh score [12]. The ascitic fluid has demonstrated increased fibrinolytic activity with up to 20 liters being reabsorbed daily and increased levels of D-dimers, prothrombin fragments, fibrin degradation products, and plasmin-α2-antiplasmin complexes being found [13]. However, there is some controversy regarding hyperfibrinolytic activity in cirrhotics as not all studies have confirmed this [14, 15]. Thus, the clinical research question for our study was whether cirrhotic patients when under “stress” such as SBP exhibit increased fibrinolysis.

In the present study, we observed a statistically significant difference between serum D-dimer levels of group IV and group III, whereas no statistically significant difference was found between serum D-dimer levels of group IV on one hand, and the groups I and II on the other hand. Plasma levels of fragment D-dimer represent an accurate marker of fibrinolytic activity. The finding of high D-dimer plasma concentration in

Table 2. Correlation between serum and ascitic D-dimer and different parameters in groups I, II and III

| Parameter | Serum D-dimer | Ascitic fluid D-dimer |
|-----------|---------------|-----------------------|
|           | Group I | Group II | Group III | Group II | Group III | Group II | Group III |
| Age (years) | 0.011 | 0.970 | 0.292 | 0.290 | 0.685 | 0.005 | 0.309 | 0.263 | 0.492 | 0.063 |
| Hb (g/dl) | −0.009 | 0.975 | 0.161 | 0.566 | 0.716* | 0.003* | 0.220 | 0.431 | 0.630* | 0.012* |
| PLT (×10³/µl) | −0.200 | 0.475 | 0.114 | 0.685 | 0.539* | 0.038* | 0.182 | 0.516 | 0.543* | 0.037* |
| WBCs (×10³/µl) | −0.264 | 0.341 | −0.200 | 0.475 | 0.229 | 0.413 | 0.168 | 0.550 | 0.096 | 0.732 |
| MELD score | −0.158 | 0.573 | −0.136 | 0.629 | −0.407 | 0.132 | −0.052 | 0.854 | −0.142 | 0.615 |
| Child-Pugh classification | 0.065 | 0.817 | 0.039 | 0.891 | −0.363 | 0.183 | −0.193 | 0.491 | −0.409 | 0.131 |
| Ultrasound | | | | | | | | | | |
| Size of the spleen | 0.088 | 0.774 | −0.714* | 0.003* | −0.301 | 0.275 | −0.170 | 0.545 | −0.515* | 0.050* |
| Size of the liver | −0.287 | 0.299 | −0.277 | 0.318 | 0.291 | 0.293 | 0.270 | 0.331 | 0.437 | 0.103 |
| Portal vein diameter | −0.229 | 0.412 | −0.538* | 0.038* | −0.097 | 0.731 | 0.290 | 0.295 | −0.240 | 0.388 |
| Ascitic fluid parameters | | | | | | | | | | |
| Protein | 0.102 | 0.718 | 0.190 | 0.497 | −0.077 | 0.785 | −0.057 | 0.839 | | |
| Glucose | −0.182 | 0.516 | 0.068 | 0.810 | −0.134 | 0.634 | 0.343 | 0.211 | | |
| LDH | 0.306 | 0.268 | −0.029 | 0.923 | −0.311 | 0.259 | −0.503 | 0.067 | | |
| Neutrophils | 0.216 | 0.439 | −0.021 | 0.940 | −0.256 | 0.358 | −0.050 | 0.860 | | |
| Lymphocytes | 0.197 | 0.482 | 0.295 | 0.286 | −0.109 | 0.699 | −0.043 | 0.879 | | |
| RBCs | 0.100 | 0.723 | −0.092 | 0.753 | −0.175 | 0.533 | 0.084 | 0.776 | | |

Table 3. Comparison between groups II and III according to different parameters of ascitic fluid analysis

| Parameter | Group II | Group III |
|-----------|---------|---------|
| Protein | 2.34 ± 1.54 | 1.40 ± 1.13 | 0.044* |
| Glucose | 142.87 ± 58.36 | 207.0 ± 228.53 | 0.983 |
| LDH | 188.33 ± 189.23 | 150.86 ± 117.08 | |
| Neutrophils | 83.40 ± 69.74 | 6094.60 ± 8784.31 | < 0.001* |
| Lymphocytes | 174.80 ± 341.61 | 322.60 ± 246.09 | 0.004* |
| RBCs | 8902.0 ± 25374.93 | 1086.67 ± 975.91 | 0.329 |

Group I – Cirrhosis group, group II – Cirrhosis + Ascites group, group III – Cirrhosis + Ascites + SBP group, group IV – Control group. * – Spearman coefficient. ** – statistically significant at p < 0.05.

Hb – hemoglobin, PLT – platelets, WBCs – white blood cells, MELD score – model for end-stage liver disease score, LDH – lactate dehydrogenase, RBCs – red blood cells.

Data are expressed as mean ±SD.
patients with liver cirrhosis, decompensated by ascites, suggested a major role of ascites in the pathogenesis of the hyperfibrinolytic state [4]. The current result was consistent with that of Zhu and Lu, who found that plasma of cirrhotic patients had fibrinolytic activity and suggested SBP among the possible causes of increased fibrinolysis in patients with liver cirrhosis [16]. Moreover, our result agrees with that of Wei yi et al., who demonstrated that SBP might play an active role in the pathogenesis of accelerated plasma fibrinolysis in patients with liver cirrhosis as indicated by the positive correlation between positivity for plasma D-dimer and the presence of SBP. As patients with SBP have higher levels of plasma D-dimer than those without SBP, these results indicate increased fibrinolytic activity in the ascitic fluid with superimposed infection [17]. Also, our result partially agrees with that of Hassan et al., who found that the D-dimer level was increased significantly as compared to the normal reference level and the value showed a significant increase from Child-Pugh class A to C and concluded that D-dimer concentration increased with the deterioration of the liver functions [18].

On the other hand, Dhanunjaya et al. stated that even patients with Child-Pugh class A had an elevated plasma D-dimer level compared to normal controls, and plasma D-dimer levels were found to increase significantly with severity of the liver disease [19]. Also, Saray et al. found a significant increase of mean D-dimer levels in patients with liver cirrhosis and no evidence of ascites and more elevated mean D-dimer levels in patients decompensated by ascites, observing that a significant reduction of D-dimer levels was achieved after abdominal paracentesis but it was still higher than those in patients without ascites [20]. Wesam et al. reported a different result; plasma D-dimer levels were elevated in patients with liver cirrhosis without ascites and showed higher values in patients decompensated by ascites, but the D-dimer values after ascitic fluid paracentesis were not significantly different from those found in patients without ascites [21].

Our results showed a significant negative correlation between hemoglobin level and serum D-dimer and between platelet count and serum D-dimer, confirming that higher D-dimer levels are found in patients with complicated advanced liver disease where anemia and thrombocytopenia are common. This finding was consistent with that of Hassan et al., who found that plasma D-dimer correlated positively while platelet count correlated negatively with advanced liver disease according to the Child-Pugh score [18].

Because of the lack of normal levels of D-dimer in ascitic fluid, it is considered equal to that of blood as ascites is an ultrafiltrate of plasma. We found that D-dimer levels were much higher in ascitic fluid complicated with SBP (group III) than normal serum levels (group IV). Ascitic fluid D-dimer mean levels in group III were higher, but not significantly, in comparison to ascitic fluid D-dimer levels of group II. A significant positive correlation was found between ascitic fluid levels and serum levels in group III patients ($r = 0.682$).

Although there was no statistically significant correlation between serum and ascitic fluid D-dimer levels in group II, notably we found that 60% of ascitic fluid D-dimer values were higher than serum levels in the same group. The last finding was inconsistent to some extent with Romanelli et al., who found significantly elevated levels of ascitic fluid D-dimer compared to their levels in the plasma of the same patients, suggesting that the ascitic fluid compartment is in continuous exchange with the plasmatic compartment, possibly through lymphatic flux, and contributes to the coagulopathy of liver disease [4]. Takatori et al. stated that in ascitic fluid, the levels of D-dimer were significantly higher than those in plasma, concluding that the effect of ascites on the assessment of plasma coagulation and fibrinolytic parameters in decompensated liver cirrhosis cannot be ignored [22]. Similarly, Agarwal et al. found that elevated fragment D-dimer and fibrin split products were uniformly found in ascites fluid in concentrations that would be considered pathologically elevated if found in plasma, concluding that ascites fluid has fibrinolytic activity, which reenters the systemic circulation via the thoracic duct. Therefore, ascitic fluid warrants serious consideration as a pathological fluid that contributes to the systemic fibrinolytic state found in the majority of patients with ascites [13]. In contrast to our results, Mikula et al. found that D-dimer was not useful for confirming SBP due to low specificity (40.6%) and a low positive predictive value (61.2%), and the usefulness of D-dimers was limited by the fact that only 22.2% of the studied patients had D-dimer levels below 1500 ng/ml [23].

One of the limitations of this study is the small sample size, as it was conducted in a single institution. Further studies should be replicated at a multicentric study level with a large sample size. Also, follow-up of serum D-dimer levels after treatment of SBP could add to the strength of its diagnostic performance as a simple marker.

**Conclusions**

Taken together, the results of this study suggest that serum D-dimer and ascitic fluid D-dimer are significantly and highly correlated in patients with SBP. Our
study revealed no association between serum D-dimer and ascitic fluid parameters whether in cirrhotic patients with sterile ascites or SBP. Serum D-dimer could be a promising useful and simple marker for early detection of SBP even though the peritoneal tap is still the reference method in such situations.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Disclosure

The authors declare no conflict of interest.

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