Objective: The aim of the study was to investigate plasma D-dimer concentration in patients with liver cirrhosis with and without ascites and to evaluate the impact of ascites depletion on circulating plasma D-dimer levels. Methods: Sixty patients with liver cirrhosis were recruited and categorized into two groups: cirrhotic patients without ascites in group 1 (n=30) and patients with liver cirrhosis and ascites in group 2 (n=30). D-dimer levels were measured on day of admission, in patients with ascites D-dimer concentration levels were repeated measured after ascites resolution confirmed by ultrasonography. Results: Mean D-dimer levels showed significant increase in cirrhotic patients decompensated by ascites (626.0±231.08 μg/L) when compared with healthy controls (140.73±49.16 μg/L, p<0.001). There was also a statistically significant increase of mean D-dimer levels in patients with liver cirrhosis and no evidence of ascites (333.4±109.05 μg/L, p<0.001). In all patients after ascites resolution D-dimer levels showed significant reduction (437.66±130.47 μg/L, p<0.05). Values of D-dimer levels achieved after abdominal paracentesis (n=21) where still higher than those in patients without ascites (480.14±122.85 μg/L, p<0.001). In cirrhotic patients treated with diuretic therapy (n=9) circulating D-dimer levels were not significantly different from those in cirrhotic patients without ascites (338.56±90.55 μg/L, p=0.96). Conclusion: The presence of ascites in patients with liver cirrhosis is associated with increased plasmatic fibrinolytic activity. Less aggressive ascites resolution therapy has a greater impact on reducing plasmatic fibrinolytic activity than achieved by abdominal paracentesis. Key words: liver cirrhosis, ascites, D-dimer, hyperfibrinolysis, abdominal paracentesis

1. INTRODUCTION

Advanced liver disease is commonly associated with complex haemostatic defects that include impaired synthesis of clotting factors and coagulation inhibitors in association with thrombocytopenia and platelets defects. In addition, liver cirrhosis is often accompanied by hyperfibrinolysis (1). D-dimer, a breakdown product of cross-linked fibrin, is a marker of ongoing fibrin turnover and represent an accurate marker of fibrinolytic activity (2). Previous studies have suggested the possible role of ascites in the pathogenesis of increased fibrinolysis associated with liver failure (3, 4, 5). The present study was designed to determine whether a significant increase in circulating D-dimer levels may be observed in patients with liver cirrhosis complicated by ascites supporting the hypothesis that advanced liver failure is associated with a hyperfibrinolytic state and to evaluate the effect of ascites depletion on fibrinolytic activity.

2. MATERIAL AND METHODS

Study Patients

From july 2007 to may 2009, we studied sixty patients referred to the Department of Gastroenterology and Hepatology of the Clinical Center University of Sarajevo for liver cirrhosis. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethical Committee of the Clinical University Center of Sarajevo. Informed consent was taken from all patients who enrolled in the study.

All participants had screening abdominal ultrasonography at the time of recruitment into the study and proximal endoscopy was performed.

The patient group was divided into two groups. In the first group (n=30) patients with diagnosed liver cirrhosis and no signs of ascites were included. Group two (n=30) consisted of patients with liver cirrhosis complicated by ascites. The diagnosis of liver cirrhosis...
was established either histologically or by typical clinical picture together with sonographic features consistent with cirrhosis and evidence of portal hypertension. Patients with liver cirrhosis were further classified as stage A, B or C according to the modified Child-Pugh classification.

The aetiology of liver disease of the overall study group is summarized in Table 1.

D-dimer levels were obtained in all patients on day of admission to our department. Exclusion criteria were the following: history of deep venous thrombosis or portal vein thrombosis, current anticoagulation therapy, hepatocellular carcinoma or other known malignancy.

Control group
A control group consisted of 30 healthy individuals with normal results of physical examination and laboratory blood findings were selected from the general public.

Blood collection and testing
Blood samples were collected by venipuncture directly into vacuum tubes containing trisodium citrate. The blood samples tube were centrifuged at 1,500 x g for 10 min at room temperature, the supernant plasma was removed. Plasma D-dimer was measured by a latex-enhanced, immunoturbidimetric test using a commercially available kit (Dade Behring, Marburg, Germany). The D-dimer concentration was expressed in μg/L.

Statistical analysis
All data are presented as mean ± standard deviation. Statistical analysis was performed using the Student t-test to compare the means of independent groups. For one-way analysis of variance ANOVA test was used to evaluate difference between different groups. Correlations coefficient was evaluated by the Pearson’s test. A two tailed p-value below 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the statistical package SPSS 19.0.

3. RESULTS
Basic epidemiological and clinical characteristics of healthy controls (n=30) and patients with liver cirrhosis (n=60) are presented in Table 2. The age at the time of the study was significantly higher among cirrhotic patients with ascites, whereas gender distribution was not significantly different across all groups. Mean platelet count were significantly lower among patients with cirrhosis and ascites. According to the Pugh-Child classification patients of group 2 had more advanced liver disease.

The mean D-dimer levels showed significant increase in patients with liver cirrhosis decompensated by ascites (626.0±231.08 μg/L) when compared with healthy controls (140.73±49.16 μg/L, p<0.001). There was also a statistically significant increase of mean D-dimer levels in patients with liver cirrhosis and no evidence of ascites (338.56±90.55 μg/L, 333.4±109.05 p=0.96) (Figure 1).

When comparing mean D-dimer levels in all different study groups, significant differences between all individual groups were observed (p<0.001). Plasma D-dimer levels were also evaluated with respect to the Child-Pugh class and no statistically significant correlation between D-dimer levels and Child-Pugh classification was found (Pearson's correlation coefficient was 0.100, p=0.613).

4. DISCUSSION
Elevated plasma values of D-dimer are frequently found in patients with liver cirrhosis with an higher incidence in decompensated disease [6]. The underlying pathogenesis is still unclear

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<th>Table 2. Epidemiological, biochemical and clinical characteristics of healthy controls and patients with liver cirrhosis. Quantitative values are expressed as mean (SD)</th>
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<td>Sex (M/F)</td>
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<th>Figure 1. Mean D-dimer levels in the overall study group. Numbers above the bar indicate mean D-dimer levels in μg/L</th>
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Association Between High D-dimer Plasma Levels and Ascites in Patients with Liver Cirrhosis

and controversy still exists whether it is a primary phenomenon or induced secondary to coagulation activation and delayed hepatic clearance (7, 8).

A higher incidence of hyperfibrinolysis was found in cirrhotic patients suffering from bleeding tendency and these patient group seemed to have a higher risk of fatal haemorrhagic episodes [9,10]. In a large prospective study hyperfibrinolysis was proven to be the main predictive marker of gastrointestinal bleeding in decompensated cirrhotic patients (11).

In this study we aimed to investigate the plasma D-dimer levels in cirrhotic patients with and without ascites as well as to evaluate the impact of ascites treatment either by paracentesis or conventional diuretic therapy on circulating D-dimer levels.

In the present study we found significantly increased D-dimer levels in patients with liver cirrhosis complicated by ascites when compared with healthy controls. These results are in agreement with that of Agarwal et al (5) who reported increased plasma D-dimer values in 93% of cirrhotic patients with ascites. Increased levels of D-dimer has been detected in ascitic fluid as well, suggesting that ascites reabsorption into systemic circulation contributes to hyperfibrinolytic state in patients with advanced liver disease [4,5]. This hypothesis is further underlined with our findings of significant decrease of circulating D-dimer after ascites depletion.

However, in our study in cirrhotics without ascites 71% showed D-dimer levels above the mean level of healthy controls. This percentage is higher than that reported of Agarwal et al [5] where elevated D-dimer levels were found only in 33% of cirrhotics without ascites. This could be contributed to the higher number of patients with more advanced degree of liver damage included in our study group 2 (57% with Child-Pugh score B).

According to our results 21(70%) of cirrhotic patients with ascites (patient group 2) were treated by abdominal paracentesis. Repeated D-dimer measurement after ascites resolution showed significant decrease in mean circulating D-dimer levels, but they were still higher than in patients who entered the study without ascites. This is in contrast to the findings of Spadaro et al (12) who reported of mean plasma D-dimer levels after ascites resolution returning to normal levels in half of the patients. We noted with much interest that in patients who were treated with conventional diuretic therapy to obtain ascites resolution D-dimer showed a significant decrease to mean levels not differing from those without ascites suggesting that the mode of ascites resolution has an impact on fibrinolytic activity.

Another study proposed that the association between high circulating D-dimer levels and ascites might be due only to advanced liver impairment with portal hypertension and bacterial translocation (13). However, we were not able to prove correlation between hyperfibrinolysis and severity of liver disease according to Child-Pugh classification.

5. CONCLUSION

On the basis of these findings we approve that in liver cirrhosis ascites counts to the main factors to be associated with increased fibrinolytic activity and the underlying mechanism for this observation remains to be clarified. Our data suggest that a less aggressive ascites resolution therapy has an greater impact on reducing plasmatic fibrinolytic activity than achieved by abdominal paracentesis and this may have an impact on prevention of bleeding complications.

REFERENCES


