

AN ASSESSMENT OF COAGULATION PARAMETERS IN LIVER CIRRHOSIS

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This study was carried out to assess the haemostatic defects in patients of liver cirrhosis by estimating prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen level, fibrinogen degradation products (D-dimer), and platelet count. It was carried out at the Department of Pathology, King Edward Medical College, Lahore. A total of 50 patients from all age groups of both gender with cirrhosis of liver were selected from Mayo Hospital, Lahore. All the investigations were carried out by standard procedures. Results were analyzed statistically with appropriate tests of significance. The mean values of PT and APTT were 14 second and 19 seconds longer than the control values respectively. These prolongations were highly significant statistically ($p < 0.0001$). Thirty-four out of fifty patients showed a serum fibrinogen level lower than normal with the mean value of 1.90 ± 1.30 g/L The difference from normal value was not significant statistically. All but one patient of cirrhosis, showed raised level of D-dimer i.e. >250 ng/ml. Mean platelet count in patients was significantly lower than normal value ($p < 0.05$). Prolongation of PT and APTT indicates plasma clotting factors deficiency due to impaired hepatic synthesis. Derangements of other coagulation parameters indicate that multiple factors like fibrinolysis, hypofibrinogenaemia, thrombocytopenia, and low grade DIC, all play a role in liver cirrhosis.

Liver cirrhosis is defined as necrosis of the liver followed by fibrosis and regeneration. Its clinical features are produced by hepatocellular dysfunction, portal hypertension and portosystemic shunting¹. Liver cirrhosis causes significant morbidity and mortality in our country, however early diagnosis prevents complications and carries good prognosis².

Coagulopathy in patients with liver disease results from impairments in the clotting and fibrinolytic systems, as well as from reduced number and function of platelets³. As liver parenchymal cells synthesize most factors of the clotting and the fibrinolytic systems, levels of these procoagulant and anticoagulant as well as fibrinolytic and antifibrinolytic factors will decrease in plasma. These changes may be minor in patients with mild liver disease but are severe in patients with cirrhosis. Thrombocytopenia and thrombocytopeny usually complicate the clinical picture⁴.

It is a common observation that chronic liver disease especially cirrhosis is a major health problem in tropical countries like Pakistan therefore this project was envisaged to study coagulopathy in patients with this disease. It will help the haematologists and the gastroenterologists to understand the severity of coagulation defects and their related complications e.g. bleeding / throm-

bosis in cirrhotic patients which will lead to better management and treatment of these patients^{5,6}.

SUBJECTS AND METHODS

A total number of 50 patients were included in this study. These subjects were selected from Mayo Hospital, Lahore. In each case a detailed history including age, sex, occupation, socio-economic status, personal and family history were taken. Thorough physical / clinical examination was performed.

Inclusion Criteria:

Primary criterion of inclusion was the presence of cirrhosis of liver, irrespective of aetiology. Diagnosis of cirrhosis of liver was based on a combination of (i) clinical features i.e. ascities and neurological disorder (ii) biochemical investigations i.e. raised serum bilirubin, reduced serum albumin (iii) abdominal ultrasound and (iv) liver biopsy in cases of compensated cirrhosis.

All patients of cirrhosis of liver irrespective of age, sex, and socioeconomic status were entertained.

Exclusion Criteria:

The patients of cirrhosis with a previous history of coagulation disorders and drug intake that causes changes in the coagulation parameters e.g. oral

contraceptive, aspirin, heparin, warfarin were excluded. Patients who had liver damage due to causes other than cirrhosis, and pregnant females were also excluded from this study.

Laboratory Investigations:

This Included:

- Plasma prothrombin time and controls.
- Activated partial thromboplastin time and controls.
- Plasma fibrinogen level.
- Fibrin degradation products (D-dimer).
- Platelet count.

All the laboratory investigations were performed in the Hematology Laboratory of King Edward Medical College, Lahore and the results were entered in the Performa. The reagents for PT, APTT and serum fibrinogen were provided by Human Biochemical and Diagnostic Ltd. Wiesbaden, Germany. The kit used for detection and semiquantitation of fibrin degradation products (D-dimer) was provided by Biopool, Sweden.

RESULTS

Age distribution of patients

The mean age of patients with cirrhosis was 52.54 ± 12.51 with range of 28-80 years.

Sex Distribution of patients

Sex distribution of the patients is shown in fig. 1.

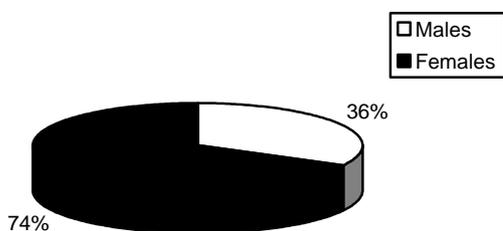


Fig. 1: Sex distribution of cirrhotic patients.

Clinical findings

The frequency of clinical findings in patients with cirrhosis is given in fig. 2.

Laboratory Investigations

i) Plasma Prothrombin Time and Plasma Activated Partial Thromboplastin time (Fig. 3).

Time:

Comparison of mean values of prothrombin time and activated partial thromboplastin time for patients and controls are shown in figure III. The difference of patients and control values in both patients and controls are statistically highly significant (P value < 0.0001).

ii) Plasma Fibrinogen Level and Fibrin D-Dimer:

Thirty-four out of fifty patients showed a serum fibrinogen level lower than normal with the mean value of 1.90 ± 1.30 g/L. All but one patient, showed raised level of FDP D-dimer i.e. > 250 ng/ml. The detailed quantitative findings of D-dimer are shown in table 1.

iii) Platelet Count:

The mean value in patients with cirrhosis was 119000 ± 63000 cells/al, which is significantly lower than the normal range of 150,000 - 400,000 cell/ ul (p=0.05).

Table 1: Values of D-dimer with corresponding number of patients.

D-dimer level (ng/ml)	No. of Patients
<250	1
250-500	6
500- 1000	10
1000-2000	15
> 2000	18

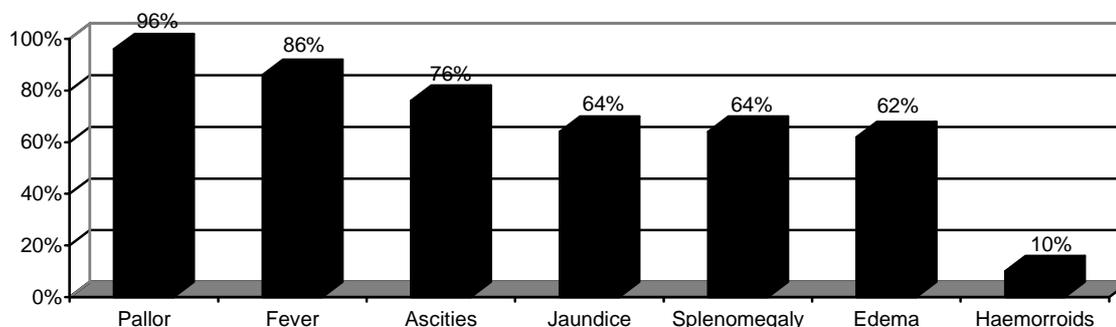


Fig. 2: Clinical findings in cirrhotic patients.

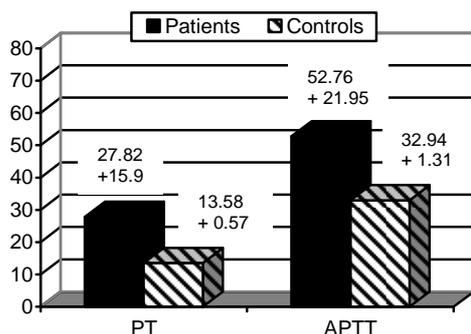


Fig. 3: Comparison of mean values of PT and APTT for patients and controls.

DISCUSSION

Haemostasis is intimately related to liver functions, because most coagulation factors are synthesized in liver parenchymal cells and the liver's reticuloendothelial system serves an important role in the clearance of activation products. The extent of coagulation abnormalities depends upon the degree of disturbed liver function⁷. Patients with cirrhosis suffer from a complex haemostatic disturbance, due to abnormalities in clotting and fibrinolytic system activation and in primary haemostasis⁸. Platelet abnormalities associated with hepatobiliary diseases include increased (thrombocytosis) and decreased (thrombocytopenia) number of platelets as well as abnormalities in function (thrombopathy or thrombasthenia)⁹.

In our study there was significant prolongation of prothrombin time and activated partial thromboplastin time in patient of liver cirrhosis. This finding is compatible with the previous studies^{10,11}. Prothrombin time is commonly increased in liver diseases because liver is unable to manufacture adequate amount of clotting factors including those involved in extrinsic pathway¹². Out of factors II, V, VII and X, factor VII is the rate limiting factor in this pathway and thus has the greatest influence on the prothrombin time. Fall of factor VII which has shortest half life (6 hours) has bad prognosis. As the liver function worsens, the APTT may become abnormal, the reason being that factors IX, XI and XII and fibrin stabilizing factors are also produced by the liver¹³. Prolongation of both PT and APTT may be noted while other biochemical tests of liver function in liver disease are still normal. Occasionally APTT may be abnormal when the PT is within the normal range¹⁴.

In thirty-four out of fifty patients plasma fibrinogen level was lower than normal, that is below 2 g/L. However this fall is not significant statistically. This finding is in accordance with the

previous reports^{2,12,15}. Fibrinogen is synthesized at the level of the hepatic microsomes and the existence of multiple coagulation defects, including a thrombin time prolongation with normal or high fibrinogen levels has been frequently observed in patient with severe liver disease^{16,17}. The normal fibrinogen level in our study may be due to compensation by the normal liver or dysfibrinogenaemia.

In this study 49 patients out of 50 had F.D.P levels above normal. Finding of this fibrinolytic activity is compatible with other studies^{18,19}. Increased fibrinolytic activity has frequently been associated with cirrhosis²⁰. The underlying mechanism for increased fibrinolysis is increased conversion of plasminogen to plasmin, increased tissue plasminogen activators and impaired clearance of circulating plasminogen activators. It may also be due to defect of the antiplasmin and other inhibitory factors. The major inhibitor of plasmin i.e α -2 antiplasmin is reduced in cirrhotic patients with resultant increased fibrinolysis. Fibrinolysis may also be secondary to disseminated intravascular coagulation²¹.

In the present study blood platelet count was significantly decreased in patients with hepatic cirrhosis. These finding are the same as reported in previous studies²²⁻²⁴. Thrombocytopenia is a common finding in patients with diagnosed liver disease²⁵. Severe thrombocytopenia < 30,000 associated with spontaneous bleeding is usually not seen in uncomplicated cirrhosis. The common reason cited for thrombocytopenia in patients with cirrhosis is splenomegaly and portal hypertension²⁶. Under normal conditions approximately 1/3rd of the circulative platelets are within the spleen. Splenomegaly and hypersplenism result in thrombocytopenia, although the total platelet mass may not be reduced²⁷.

We conclude that significant prolongation of PT, APTT in absence of significant hypofibrinogenaemia suggests their importance as a reliable marker of coagulopathies in cirrhotic patients and significant rise in D-dimers suggests an increased fibrinolytic activity in cirrhotic patients, which may be due to DIC.

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