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General Medicine

COAGULOPATHY IN CHRONIC LIVER DISEASE. A DISTURBED COAGULATION HARMONY IN RELATION TO SEVERITY OF LIVER DISEASE.

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ABSTRACT Coagulation of blood is the most important vital function to obviate excessive bleeding. Many coagulation factors are involved in this process, among which most of them are synthesised in liver. Cirrhosis is defined as a final stage of chronic liver disease. It is associated with disturbances in the synthetic and metabolic function of liver and can leads to abnormalities in the coagulation process. The hemostatic system is a delicate balance between prothrombotic and antithrombotic processes. Liver acts as a key organ in the synthesis of various coagulation factors and hence participate in both primary and secondary haemostasis. Identification of specific biochemical markers that can predict the severity of liver cirrhosis and the probability of bleeding tendency can help the physician in early identification of complications. This study was done to analyse the efficacy of coagulation tests like PT, APTT, fibrinogen and platelets in predicting the severity of liver disease and its complications, to study the relevance and significance of coagulation tests in relation to bleeding complications in patients with CLD. We conducted a cross sectional observation study involving 100 patients diagnosed with CLD. **Results:** The mean levels of PT and APTT found to have positive association and a strong correlation with increasing grades of MELD and Child Pugh score, whereas the mean platelet count and serum fibrinogen levels showed a strong negative association. Significant correlations between PT, APTT, and declining fibrinogen and platelet levels and GI bleeding were observed. Coagulation parameters like PT, APTT, fibrinogen and platelet levels can be used for grading the severity of CLD and also predict the propensity of a patient with CLD to bleed.

KEYWORDS : Coagulopathy, Cirrhosis, MELD score, CP score.

INTRODUCTION

Cirrhosis is defined as a final stage of chronic liver disease and is described by advanced fibrosis and distortion of hepatic architecture[1]. Patients with cirrhosis are at increased risk of various complications such as jaundice, portal hypertension, ascites, hepatic encephalopathy, hepatorenal syndrome, and variceal hemorrhage[1]. Coagulopathy is a known complication in patients with cirrhosis and is associated with increased risk of bleeding in these patients[2].

The haemostatic system is an elegant balancing act between prothrombotic and antithrombotic processes, any kind of imbalance can lead to disturbances in the coagulation harmony. Liver acts as a key organ, since it is involved in the synthesis of various coagulation factors and hence participates in both primary and secondary haemostasis[3].

Bleeding is one of the common clinical presentation of patients with cirrhosis of liver, due to abnormal haemostasis. Coagulation abnormalities in chronic liver disease are identified based on assessment of routine coagulation parameters such as Prothrombin Time (PT), International normalized ratio (INR), the activated Partial Thromboplastin Time (aPTT), and platelet count[4]. Identification of specific biochemical markers that can predict the severity of liver cirrhosis and the probability of bleeding tendency can help the physician in early detection of complications.

However previous studies showed that bleeding and clotting tendency are not well measured by the conventional routine coagulation tests like Prothrombin Time and aPTT. Hence biomarkers which objectively measures abnormality in haemostatic system in relation with the severity of liver cirrhosis are still necessary to prognosticate and the management of condition. Fibrinogen is one of the clotting factors that can be used to identify the severity of liver cirrhosis along with PT and aPTT. MELD scoring is an excellent tool alternative to the Child- Pugh score and can be used in patients with liver cirrhosis to assess the spacious ranges of severity of disease. Currently, there is limited data to show the correlation between the level of plasma fibrinogen and MELD score in patients with liver cirrhosis. This study aimed to find the correlation between the levels of plasma fibrinogen and MELD score in patients with liver cirrhosis and to study the relevance and significance of coagulation tests in relation to bleeding complications in CLD.

MATERIALS AND METHODS.

Method: This was a cross-sectional study that included 100 patients with cirrhosis admitted at RajaRajeswari Medical College and Hospital. Patients with age group between 18-80 years, with clinical, biochemical or ultrasound findings suggestive of chronic liver disease were included from the medical out -patient department and medical wards.

Patients with CHF, chronic renal failure, diabetes mellitus, sepsis, malignancy, hypertension, patients on anticoagulants, antiplatelets, patients with H/O bleeding within one month, known coagulation disorders were excluded from study.

Coagulation screening tests: Prothrombin Time (PT) (using STA –NEOPLASTINE® CI Plus kit), activated partial thromboplastin time (aPTT) (using STA® C.K. CREST® 5) plasma fibrinogen (using STA-FIB 2 kit) levels were estimated.

About 5 mL of blood was drawn for the determination of fibrinogen and other biochemical tests.

INR was calculated using the raising prothrombin time ratio (PT INR) which is the ratio of plasma level of PT and the mean normal PT to the power of the international sensitivity index. The coagulation parameters were stratified according to the degree of alteration (elevation/reduction), and in relation to the severity of liver diseases. Institutional ethical committee clearance was obtained before the study.

Patients were evaluated for bleeding symptoms. A detailed history and clinical examination were performed, blood was collected and plasma stored in deep freeze to assess full coagulation profile. Symptoms suggestive of bleeding was defined by history of hematemesis/ melena /haematochezia or positive faecal occult blood or bleed seen on upper gastrointestinal endoscopy (indicated by oozing of blood/active bleed/clots in oesophagus, stomach or duodenum). Patients assessed with demographic data (age, gender), routine biochemical (serum bilirubin, serum albumin, serum creatinine, coagulation profile and INR), and hematologic (platelet count) parameters in all patients. The severity of cirrhosis was defined based on the Child-Pugh and the Model for End-stage Liver Disease (MELD) scores. Severity of liver disease was classified on basis of Child Turcotte Pugh (CTP) class A (score 5 and 6), B (score 7-9) or C (score 10-15). Cirrhosis with a Child-Pugh score of ≥7 indicated decompensation. Mean values of PT,

aPTT, Fibrinogen and Platelet count and all other variables were calculated, were correlated with different categories of CP classes and MELD score [below 20 and above 20]. Mean PT, aPTT, Fibrinogen and Platelets were also compared with Upper GI scopy findings.

Statistical analysis

- Association between coagulation profile and several variables were tested using SPSS (Statistical Package for Social Sciences) version 20.
- The level of significance was set at 5%.

RESULTS

In our study on 100 patients with cirrhosis of liver, majority of patients were in age group between 51-60 years (44%), 34% patients between 41-50 years, 22% were in age group 31-40 years.

Distribution Of The Subjects Based On Age Groups [Table-1]

Age groups	Frequency	Percent
30 to 40 yrs	22	22.0
41 to 50 yrs	34	34.0
51 to 60 yrs	44	44.0
Total	100	100.0

Distribution Of The Subjects Based On Gender [Table-2]

Gender	Frequency	Percent
FEMALES	15	15.0
MALES	85	85.0
Total	100	100.0

In our study, 85% were males, 15%were females. Out of 100 patients, we found - 83% had jaundice and it was the most common symptom, ascites in 78% patients, oedema in 63%patients and abdominal pain in 43% , GI bleeding in 28% of patients. [Table-3]

Distribution Of The Subjects Based On Clinical Findings [Table-3]

		Frequency	Percent
Ascites	No	22	22.0
	Yes	78	78.0
Jaundice	No	17	17.0
	Yes	83	83.0
Odema	No	37	37.0
	Yes	63	63.0
Bleeding	No	72	72.0
	Yes	28	28.0
Pain	No	57	57.0
	Yes	43	43.0

Patients were categorised in to child pugh class based on clinical and laboratory parameters in to A(<7), B(7-9), C(>10) and also MELD score (<20 and >20) for grading of severity of the disease.The results of coagulation profle (Mean PT, aPTT, Fibrinogen and Platelets) were once again categorised and compared with severity scoring grades. (Table-4)

Cross Tabulation Of Coagulation Parameters With Child's Grading [Table-4]

Coagulation parameters	Child's Grade	N	Mean	p value
PT	Grade A	32	18.72	0.001*
	Grade B	42	24.47	
	Grade C	26	32.02	
APTT	Grade A	32	40.53	0.001*
	Grade B	42	49.00	
	Grade C	26	60.58	
Fibrinogen	Grade A	32	264.63	0.001*
	Grade B	42	208.36	
	Grade C	26	162.04	
Platelets	Grade A	32	176281.25	0.002*
	Grade B	42	129076.19	
	Grade C	26	98980.77	

In our study, out of 100 patients, 32 patients were categorised under child A, 42 patients under child B and, 26 patients in child C. Mean PT and aPTT was highest in child C grade (32 secs and 60secs) compared to other two grades (Table-4). With increase in child pugh score there was prolongation of mean PT and aPTT values. This observation was statistically significant (P value<0.001) and directly proportional. We found, plunging levels of mean fibrinogen and mean platelets with an increase in grades of child's scoring [Table-4]. These findings were statistically significant and indirectly proportional.

Cross Tabulation Of Coagulation Parameters With MELD Score (Table 5)

Coagulation parameters	MELD score	N	Mean	p value
PT	< 20	47	18.81	0.001*
	> 20	53	29.72	
APTT	< 20	47	40.13	0.001*
	> 20	53	57.43	
Fibrinogen	< 20	47	263.04	0.001*
	> 20	53	171.11	
Platelets	< 20	47	172319.15	0.001*
	> 20	53	104466.04	

MELD score was used to assess the severity of underlying liver disease. Patients were categorised with score of >20 [53 patients] and <20 [47 patients]. Mean PT was 29.72 secs in patients with MELD score of >20 compared to less than 20 and Mean aPTT was 57.43 secs in patients MELD score >20, the values were strikingly prolonged compared to patients MELD score<20. This observation was statistically significant and directly proportional. The Mean serum fibrinogen [171.11] and platelets levels [104466] in patients with MELD score >20 were low compared to MELD score<20 [Table-5]. These findings were Indirectly proportional and statistically significant.

In the current study, 35 patients found to have bleeding symptoms and signs. These patients had prolonged mean PT and aPTT[29secs, 55secs respectively] and also low serum fibrinogen[181] and platelets [108885.71] compared to patients without bleeding symptoms [Table-6]. Increasing PT, aPTT levels along with low fibrinogen and platelets levels were consistent with greater tendency to bleed. These findings were statistically significant. (Table 6)

Comparison Of The Coagulation Parameters Based On Bleeding Manifestation (Table. 6)

Coagulation parameters	Bleeding	N	Mean	p value
PT	No	65	21.73	0.001*
	Yes	35	29.90	
APTT	No	65	45.75	0.001*
	Yes	35	55.89	
Fibrinogen	No	65	232.02	0.001*
	Yes	35	181.46	
Platelets	No	65	151149.23	0.002*
	Yes	35	108885.71	

Correlation Between Child Score And MELD Score With

Coagulation Parameters [table-7]

	Coagulation parameter	r value	p value
Child Score V/s	PT	0.643	0.001*
	APTT	0.578	0.001*
	Fibrinogen	-0.489	0.001*
	Platelets	-0.447	0.001*
MELD Score V/s	PT	0.749	0.001*
	APTT	0.687	0.001*
	Fibrinogen	-0.596	0.001*
	Platelets	-0.524	0.001*

Relation of proportionality of Child's grade / MELD score with PT, APTT shows a significant positive association and a strong correlation – statistically significant.

Relation of proportionality of Child's grade / MELD score with Fibrinogen, platelets shows a significant negative association and a strong correlation - statistically significant

DISCUSSION

In our study involving 100 patients diagnosed with chronic liver disease, we observed significant abnormalitites in the coagulation profile with an increase in the severity of liver disease. Abnormal coagulation indices like prolonged PT, aPTT were directly proportional to the severity of liver disease and statistically significant. In current study along with routine coagulation indices, specific markers like serum fibrinogen and platelets were also assessed. We found significant fall inserum fibrinogen and platelets levels with the progression of disease severity These findings were stastically significant. In study done by Pahwa et al., they calculated Mean PT and aPTT values and compared with CP score and MELD score. They also found mean PT and aPTT values increased from CP class A to C and aPTT between B and C, they also found worsening of mean PT and APTT with increase on MELD score the results of present study was similar to study by Pahwa et al.

In our study we found patients of age varying from 31 to 61 years. Majority of patients belong to age group of 51-60 years. In a study done by Pahwa et al., patient age group varied from 22 to 75 years and mean age was 42.78[5].

In our study males (85% males and 15% females) were predominant, since males were predominant in the study group, which explains alcoholism as a etiological factor attributing to cirrhosis of liver.

Gender distribution in our study was similar to study by Pahwa et al[5,6,7] Similar to other studies, we also observed majority of patients belonged to CTP B and C[8,9,10].

Sura O. AL-Dewachi et al., study on 50 patients with cirrhosis of liver found mean PT, INR, APTT significant prolongation and are statistically significant ($p < 0.001$). The mean level of platelet count and fibrinogen were significantly reduced in patients with chronic liver disease. They found a progressive prolongation in PT and APTT, and an increasing INR across Child-Pugh grades from A to C and they also observed, reduction in fibrinogen from Child-Pugh Grades A to C[11].

Niraj Bohania[12], in their study the mean age of study group was similar to our study group. Along with baseline coagulation profile they also evaluated relation of thrombin time (TT), factor VIII and D-Dimer level, protein S and factor VII, protein C, antithrombin III(AT) activity. In their study group, mean age of patients was 44.42 ± 10.26 years (100% males), 53% in Childs class C. Severity of liver dysfunction showed a significant association ($p<0.05$) with prolongation of prothrombin time (PT), activated partial thromboplastin time (aPTT) and Thrombin Time (TT), increasing factor VIII and D-Dimer level, low platelet counts, low protein S and factor VII activity, as well as decreasing fibrinogen levels, protein C and antithrombin (AT) III.

Out of 100 patients, we observed 35 patients with bleeding manifestations, found to have prolonged mean PT (29 secs) and mean aPTT (55secs), decreased mean Fibrinogen levels (181) and platelets (108885.71). Increasing PT, aPTT levels were consistent with greater tendency to bleed. This finding was similar to a study done by Niraj et al., they observed patients with GI bleed were found to have prolonged PT >20 sec (<0.05) and decreased plasma fibrinogen levels[12] , it was statistically significant.

From our study, we found the abnormal coagulopathy was striking and was statistically significant as well directly proportional to the increase in severity of liver disease.

CONCLUSION

Cirrhosis of liver is known to develop coagulation abnormalities, which will be more obvious in advanced stage. Routine assessment of tests for coagulation may not be sufficient to assess the bleeding risk.

- In our study we observed a significant elevation of mean PT, APTT and reduction in serum fibrinogen, platelets levels with greater degree of Child's grade and higher MELD score.
- GI bleeding was significantly associated with prolonged mean PT, APTT and low fibrinogen as well as platelet counts.
- Present study on patients with cirrhosis of liver revealed overall impact of abnormalities in coagulation factors and their relation with severity of disease which is known have definitive effect on outcome of patients.
- Hence the early diagnosis of coagulation abnormalities in decompensated liver disease patients would help treating physician to recognize the complications and also prevention of morbidity and mortality.

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