Research Article

Coagulation profile in patients with chronic liver disease

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ABSTRACT

Background: Chronic liver disease (CLD) is defined as a process of slow and continuous destruction and regeneration of the hepatic parenchyma giving rise to fibrosis and cirrhosis. When it has markedly progressed, it may present with clinical bleeding due to reduction in levels of procoagulant factors, barring some like factor VIII and von Willebrand factor, which are elevated. It is essential to observe that reduced levels of the procoagulants are accompanied by decrease in levels of anticoagulants such as antithrombin and protein C. Under normal conditions, the coagulation machinery is balanced, but the phenomenon of the simultaneous reduction of procoagulants as well as anticoagulants in patients with CLD has been an unsolved puzzle since long. **Objective:** This study was undertaken to study the relevance and significance of first-line coagulation tests (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) in relation to bleeding manifestations in patients with CLD, to classify the cases of CLD enrolled on the basis of etiology, to study the platelet count, PT, and aPTT values of the cases, and to calculate the Child–Pugh (CP) and model for end-stage liver disease (MELD) scores for all the patients and stratify them accordingly. **Materials and Methods:** It was a prospective observational study including 40 patients known to be diagnosed with CLD. CP score and MELD were calculated for all. Values of coagulation parameters were compared in patients with and without cirrhosis, in patients belonging to different CP classes, those with low and high MELD scores, and patients with or without upper gastrointestinal (UGI) bleed. **Results:** Means of PT and aPTT were compared in patients with and without cirrhosis where it was found that there was no statistically significant prolongation of PT or aPTT in patients with cirrhosis compared to those without. We also studied the values of PT and aPTT through increasing grades of CP score and found statistically significant difference between values of PT between those belonging to Class A versus Class C. It was observed that the difference of the mean of PT of the two groups (with MELD <15 and above 15) is statistically significant, whereas it is not true in case of aPTT. **Conclusions:** The study showed no significant alterations overall in patients with CLD except those in advanced CP classes and those with high MELD scores. They were not significant in patients presenting with UGI bleed, a common manifestation in cirrhotic patients, although those constituted a very small part of the study group. These indices alone are insufficient to include as part of their prognostic and clinical work up to predict bleeding.

KEY WORDS: Chronic Liver Disease; Coagulation; Bleeding

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INTRODUCTION

The liver has a pivotal role in the hemostatic system. It is the site of synthesis of proteins such as clotting factors and their inhibitors. Other than these, it also produces thrombopoietin, which is required for platelet production from the precursors.

Chronic liver disease (CLD) is a disease of the liver which lasts for over a period of 6 months. It is defined as a process of slow and continuous destruction and regeneration of the hepatic parenchyma giving rise to fibrosis and cirrhosis. They can arise as a result of several other liver pathologies such as inflammation (chronic hepatitis), liver cirrhosis, and hepatocellular carcinoma.

A common complication of CLD is portal hypertension, which leads to hemodynamic changes that may affect endothelial integrity and function. A sequela of portal hypertension, splenomegaly, in turn, causes increased platelet sequestration in the spleen.[1]

It is a common observation that CLD, especially cirrhosis, is a major health problem in tropical countries like India. The etiological basis of end-stage CLD has changed over the years in our part of the world. The hepatitis infection cases due to hepatitis C virus (HCV) have outnumbered hepatitis B virus (HBV) and are now the most common cause of both CLD and hepatocellular carcinoma. Due to lifestyle alterations, the alcohol-induced CLD has risen markedly and some cases of cirrhosis which were thought to be cryptogenic have now been seen to evolve from non-alcoholic fatty liver disease.[2]

When CLD has markedly progressed, it may present with clinical bleeding due to reduction in levels of procoagulant factors, barring some like factor VIII and von Willebrand factor, which are elevated. It is essential to observe that reduced levels of the procoagulants are accompanied by decrease in levels of anticoagulants such as antithrombin and protein C. Under normal conditions, the coagulation machinery is balanced, but the phenomenon of the simultaneous reduction of procoagulants as well as anticoagulants in patients with CLD has been an unsolved puzzle since long.[3]

Changes in clotting function associated with CLD are mostly assessed by the prolongation of first-line tests for clotting such as the prothrombin time (PT) and the activated partial thromboplastin time (aPTT).

PT is measured as the time needed for the platelet-poor plasma to clot after the addition of tissue extracts (thromboplastin) and calcium chloride. It mainly is governed by the extrinsic pathway and it determines Vitamin K-dependent extrinsic factors VII, X, II, and V and fibrinogen. The extent of derangement in PT correlates with the severity of liver failure and is one of the constant parameter in widely used prognostic indices such as Child–Pugh (CP) score and model for end-stage liver disease (MELD) score.

The aPTT is the time taken for platelet-poor plasma to clot when mixed with an activator of the contact factors (factor XII, pre-kallikrein, and high-molecular-weight kininogen) and phospholipids.[4]

It is an indicator of intrinsic and common pathways of coagulation cascade, which depend on factor VIII, IX, XI, and XII and those of the contact system.[5]

However, the values of these screening tests are poorly correlated with onset and duration of bleeding after biopsy of liver or similar hemorrhagic procedures.[6]

These do not correlate with the occurrence of gastrointestinal bleeding also which is a common stigmata of end-stage liver disease.[7,8]

The aim of our study will be to classify the cases of CLD enrolled on the basis of etiology, to study the platelet count, PT, and aPTT values of the cases, to calculate the CP and MELD scores for all the patients and stratify them accordingly, to identify patients presenting clinically with bleeding or thrombotic manifestations, and to study their coagulation profile.

MATERIALS AND METHODS

In this hospital-based prospective study, we enrolled a total of 40 patients suffering from liver disease for more than 6 months. Cases included both outpatient department and admitted patients from gastroenterology and medicine departments.

The ethical clearance for this study was granted by the institutional ethical committee.

All patients with liver disease of more than 6 months duration of either sex, age >14 years were included in the study. We excluded pediatric population and patients on long-term treatment with drugs that cause changes in the coagulation parameters, for example, oral contraceptive, aspirin, heparin, warfarin, etc.

Informed consent was taken from all patients in a language they could comprehend.

A comprehensive history including chief presenting complaints, history, family history, and drug history was taken. An adequate history regarding hematemesis, melena, hemoptysis, and hematuria, the presence of petechial hemorrhages or bruises was taken. Examination was done for the presence of ascites (through shifting dullness and fluid thrill), presence of organomegaly, and the grade of hepatic encephalopathy.

CP's score and MELD were calculated for all the cases enrolled.[9]

MELD is an index formulated to predict survival in patients where transjugular intrahepatic portosystemic shunts were indicated.[10] Later, this model was also validated as a

predictor of survival in other groups of patients with different severity of hepatic dysfunction as well as patients from diverse backgrounds in terms of location and time.[11]

Formula used for calculating MELD score:

3.78 log (bilirubin in mg/dl) × 11.2 log (INR) × 9.57 log (creatinine in mg/dL) + 6.43 + 1.59 (135-S. Na^+) s.

Bilirubin and creatinine values below 1.0 mg/dL were rounded to 1.0 mg/dL to avoid a negative score.

Maximum creatinine level permissible for inclusion in formula was 4.0 mg/dL. MELD score calculated was rounded to the nearest integer.

Laboratory examination included parameters of serum bilirubin, total protein, albumin, PT international normalized ratio (INR), aPTT, serum creatinine, and serum Na+.

Venous blood in EDTA was used to estimate platelet count and complete blood count. These were performed in the automated analyzer Sysmex KX-21.

Citrate sample was used to measure PT and aPTT. PT and aPTT were performed in Transasia semi-automated analyzer CA-50.

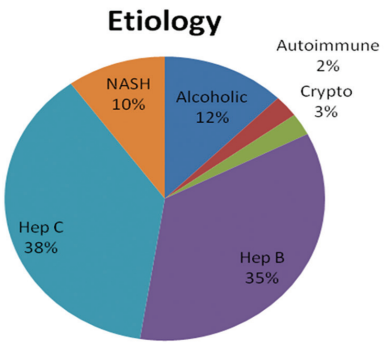
Mean values and standard deviations of PT, PTT, platelet count, and all other parameters that are serum bilirubin were calculated.

Values of coagulation parameters were compared in patients with and without cirrhosis, in patients belonging to different CP classes, those with low and high MELD scores, and patients with or without upper gastrointestinal (UGI) bleed using independent samples *t*-test and significance observed.

RESULTS

Of the total 40 patients, 32 were male and 8 were female. Patients age varied from 22 to 75 years. The mean of the age of all patients is 42.78.

Distribution of the 40 patients suffering from CLDs enrolled in the study according to etiology has been depicted in the pie chart below.



Number of patients with increased PT (more than reference range of 15 s) is 11 out of 40 (27.5%)

The number of patients with increased partial thromboplastin time is 7 of 40 (17.5%).

Patients in CP A=33, B=3, C=4

Number of patients with MELD score above 15=06

Number of patients with MELD score below 15=34

Clinical Manifestations

As evident from Table 1, above bleeding or coagulopathy was not a very frequent clinical manifestation in the patients.

Patients with radiologically or biopsy-proven cirrhosis=13

Patients without cirrhosis=27

As shown in Table 2, difference between mean values of PT and aPTT in both the groups is not significant (>0.05).

These parameters were also compared for patients with different CP scores categorized as A, B, and C and for patients with MELD above and below 15, Tables 3 and 4.

The statistical evaluation was done using independent sample *t*-test.

As shown in the table above, the difference of mean values of PT is not statistically significant between CP Classes A and B and B and C, whereas they are statistically significant between Classes A and C.

Similarly, the mean values of aPTT were computed and compared among the various classes. As shown in Table 3, difference between the mean values of aPTT among various classes is statistically significant between B and C and A and C but is not statistically significant between A and B classes.

The patients in the study were stratified based on the MELD scores as well into two broad groups, one with MELD score below 15 and the other above 15.

The PT and aPTT values of patients from both the groups [Table 4] were compared and the difference between the

Table 1: Clinical features of chronic liver disease patients enrolled in the present study

Clinical features	Number of patients
Jaundice	10/40
Ascites	5/40
Splenomegaly	6/40
Variceal/upper gastrointestinal bleeding	3/40
PV thrombosis	2/40

mean values of these parameters among the two groups was calculated.

The difference of the mean of PT of the two groups (with MELD <15 and above 15) is statistically significant.

The difference of the mean of aPTT of the two groups (with MELD <15 and above 15) is statistically not significant.

We also compared the parameters in patients with and without UGI bleed in Table 5.

As shown in Table 5, *P* value after applying *t*-test is > 0.05; hence, difference of the means is not significant for both coagulation parameters.

DISCUSSION

In the present study, a total of 40 patients were studied for basic first-line tests for clotting (PT and aPTT), platelet count, and various clinical and demographic features in CLD. Patients enrolled in the study ranged from 22 to 75 years of age, male-to-female ratio was 4:1.

Chronic hepatitis due to hepatitis C was found to be the most common cause of CLD among the study subjects.

The mean values of the serum bilirubin were slightly on the higher side, whereas values of total protein, serum creatinine, and platelet counts were within normal ranges. This is most likely due to the fact that most of the patients were in a compensated state.

Difference in mean values of PT and aPTT was statistically not significant in patients with or without cirrhosis.

Difference in mean values of PT and aPTT was observed along various CP classes, where it was significant for PT between A and C and for a PTT between B and C and A and C.

Similarly, comparison between two groups based on MELD was done and only difference in mean PT values was significant.

The mean age of patients in this study was similar to those of the previous studies.[9,12,13]

The gender distribution of patients of this study (80% of males and 20% of females) was also in agreement with findings of the previous studies with males being predominantly affected.[14-16]

Etiological distribution of cases in the present study was similar to that of Siddiqui *et al.* where HCV was the leading

Table 2: Parameters of coagulation in patients with and without cirrhosis

Cirrhosis=*n*	Mean prothrombin time±SD	*t*-test (significant)	Mean activated partial thromboplastin time±SD	*t*-test (significant)
Present=13	16.215±3.230	0.117	36.184±5.998	0.066
Absent=27	14.444±3.202		32.703±2.879	

SD: Standard deviation

Table 3: Comparison of mean PT and activated partial thromboplastin time scores in various Child–Pugh class patients

Child–Pugh class	Mean PT±SD	*t*-test (significant)	Mean PTT±SD	*t*-test (significant)
A=33	14.054±1.67	A and B –0.200	32.739±2.188	A and B –0.344
B=3	15.666±1.52	B and C –0.059	32±1	B and C –0.0266
C=4	22.50±4.79	A and C –0.037	44.25±6.184	A and C –0.0321

PT: Prothrombin time, SD: Standard deviation

Table 4: Comparison of mean scores of PT and activated partial thromboplastin time in patients with MELD below and above 15

MELD group=n	Mean PT±SD	*t*-test (significant)	Mean PTT±SD	*t*-test (significant)
MELD<15=34	14.023±1.605	0.0171	32.717±2.159	0.0704
MELD>15=6	20.666±4.676		40.166±7.9603	

MELD: Model for end-stage liver disease, PT: Prothrombin time, SD: Standard deviation

Table 5: Comparison of coagulation parameters in patients with UGI bleed

UGI bleed	Mean prothrombin time±SD	*t*-test (significant)	Mean activated partial thromboplastin time±SD	*t*-test (significant)
Present=3	16.26±2.19	0.405	35.13±1.85	0.3387
Absent=37	14.91±3.35		32.70±4.53	

UGI: Upper gastrointestinal, SD: Standard deviation

cause of CLD (56%) followed by HBV (34%).[9] These were followed by alcoholic liver disease and non-alcoholic steatohepatitis. There were single cases of autoimmune hepatitis and cryptogenic cirrhosis each as well. The observation regarding the PT and partial thromboplastin time was different from those of the previous studies. Only 27.5% of patients had prolonged PT and the mean values also are not significantly prolonged (15.0200 ± 3.27940) when compared to normal values (11–15 s).

The mean values of PT and aPTT are also not significantly prolonged as opposed to that seen in other studies, as shown in Table 6.

Many of the patients in our study who were suffering from chronic hepatitis were otherwise asymptomatic with no recent history of jaundice or liver dysfunction and were admitted only for medical recategorization.

These findings in conjunction with other parameters suggest that most of the patients in this study are in a stable condition and are not in liver failure.

Lack of significant prolongation of PT may be explained by the fact that in CLD, significantly increased PT is not seen in early stages until that of cirrhosis and the liver fibrosis.[17]

Over the course of CLD worsening, both PT and aPTT levels are prolonged; however, in cases, where compensatory mechanisms are intact, increase in factor VIII may suppress the increase in aPTT.

There are not many studies comparing these values among subgroups of CLD, but Waghmare *et al*. compared PT among subgroups of liver disease patients and observed that the increase in PT in acute liver disease was more than that in CLD and both values as compared to the controls were statistically significant ($P = 0.04$ and $P < 0.001$).[16]

Al-Dewachi *et al.* also subdivided the patients of CLD into groups of chronic hepatitis and cirrhosis and the mean PT values of these two groups were quite similar although prolonged to a greater extent on comparing with our study as shown in Table 6.

We found a statistically significant difference between mean values of PT between those belonging to CP Class A versus Class C. This is similar to the observations in the study by Al-Dewachi *et al*., as shown in Table 7.

Although the values in the present study are lower than the previous studies, it is observed that the difference in aPTT values is not significant among Classes A and B in both the studies. Similarly, it was observed that the difference of the mean of PT of the two groups (with MELD <15 and above 15) is statistically significant, whereas it is not true in case of aPTT.

This is because CP scores and MELD scores include INR that is derived from PT as one of its criteria and does not take into account aPTT values.

Comparison of PT and aPTT values in patients presenting with UGI bleed with those without it was also done and no significant prolongation of these parameters was noted in these patients. The reason behind this finding may be the small sample size, of which only three patients had UGI bleed. Furthermore, it is more closely related to the development of portal hypertension following cirrhosis. It is noted that all three patients with this presentation had cirrhosis.

PV thrombosis is another feature found in two patients in our study. These patients were also worked up for other thrombophilic conditions such as hyperhomocysteinemia, protein C and S deficiency, and factor V deficiency but were negative. It is a commonly observed in patients of advanced cirrhosis and is now detected more often due to better availability of ultrasound screening in cirrhosis. Literature search revealed scarcity of data available on the pathogenesis of portal vein thrombosis in cirrhosis. It has been seen to accompany other complications such as deteriorating portal hypertension and mesenteric infarction. It is also considered a criteria for excluding a patient from

Table 6: Mean PT and aPTT levels in chronic hepatitis and cirrhosis observed in the present study compared to other studies

PT	Chronic hepatitis	Cirrhosis
Present study	14.444±3.202	16.215±3.23054
Al-Dewachi *et al*.	23.4±10.69	23.0±7.77
aPTT		
Present study	32.703±2.879	36.184±5.998
Al-Dewachi *et al*.	55.5±14.23	50.5±23.96

PT: Prothrombin time, aPTT: Activated partial thromboplastin time

Table 7: Coagulation parameters in patients of various Child–Pugh grades, compared with other studies

Parameter	Child–Pugh A	Child–Pugh B	Child–Pugh C
PT (present study)	14.054±1.676	15.666±1.527	22.5±4.795
PT (Al-Dewachi)	17.75±2.35	20.89±5.62	26.39±8.95
aPTT (present study)	32.739±2.188	32±1	44.25±6.184
aPTT (Al-Dewachi)	43.17±3.49	43.29±10.04	58.56±32.23

PT: Prothrombin time, aPTT: Activated partial thromboplastin time

transplant listing and may negatively impact the survival post-transplantation.[18]

Strengths

This study was able to challenge the ability of the first-line coagulation parameters to predict or correlate them with bleeding tendency in patients of CLD.

Limitations

The sample size was restricted to 40. Many studies have also included levels of plasma fibrinogen and antithrombin in the coagulation parameters and have shown a significant reduction in their levels in cirrhotic patients. However, due to lack of availability, we could not include these investigations in our study.

CONCLUSIONS

Over the years and in literature, CLD has been thought to be associated with a complex hemostatic deficiency that involves primary hemostasis, fibrinolysis, and coagulation. Our study, however, shows no significant alteration of PT and aPTT in patients with bleeding. Researchers in recent past have elucidated the fact that PT and aPTT may not be sufficient to reflect the balance as it occurs *in vivo* in cirrhosis, where naturally occurring anticoagulants such as protein C, antithrombin, and tissue factor pathway inhibitor are decreased simultaneously with procoagulants. Other factors which need to be corrected are severe thrombocytopenia, hemodynamic changes associated with portal hypertension, endothelial injury, bacterial infections, and kidney dysfunction.[19]

Studies with larger patient size and including tests which represent the balance operating *in vivo* such as thrombin generation tests need to be done to understand the rebalanced hemostasis in these patients.

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