Correlation Study of Coagulation Profile in Spectrum of Liver Diseases

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ABSTRACT

BACKGROUND

Liver plays a central role in the maintenance of haemostasis. Impairment of liver parenchymal cell function disturbs haemostasis resulting in the development of multiple coagulation abnormalities. We wanted to study the coagulation profile and haemostatic dysfunction in liver disease patients so as to prevent bleeding related complications and evaluate the relationship between bleeding tendencies and coagulation profile abnormalities in such patients.

METHODS

This was a cross sectional study conducted in the Department of Pathology, JNMC, A.V.B.R.H, Sawangi, Wardha, from August, 2017 to July 2019 among 102 patients of liver diseases. PT, D-dimer, and platelet count were assessed in different liver diseases. Data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 102 patients were included in the study. Mean age of the patients was 40.07 ± 15.21 years. 69.61% patients were males. Fever with abdominal distension was the most common complaint. Mean with SD of Child Pugh score was 8.31±2.3 and Mean with SD of MELD score was 13.1±8.24. For predicting cirrhosis and other chronic liver disorders, out of all coagulation parameters, D-Dimer showed the best diagnostic accuracy.

CONCLUSIONS

Present study showed an overall good diagnostic power of coagulation parameters in assessing different liver diseases and also showed that D-dimer may be regarded as a stable and good predictor for chronic liver diseases.

KEY WORDS

D-Dimer, Child-Pugh Score, MELD Score, PT/INR.

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BACKGROUND

Liver plays a central role in the maintenance of haemostasis as it is the main site for synthesis of vast majority of proteins required for regulation of coagulation and fibrinolysis. Thus, impairment of liver parenchymal cell function disturbs haemostasis resulting in the development of multiple coagulation abnormalities that, depending on the degree of haemostatic impairment, can predispose the patient to bleeding or thrombus formation.^{1,2} Liver disease presents a major burden on healthcare systems in both North America,^{3,4} and Europe⁵ and can result in more than 70,000 annual visits to the emergency department (ED).⁶ Liver disease in the setting of acute liver failure (ALF) or trauma in a patient with cirrhosis are predictors of increased mortality and poor patient outcome.⁷ Chronic liver diseases (CLD) leading to end stage liver disease or liver cirrhosis and fibrosis is characterized by clinical bleeding and decreased coagulation factors. Liver disease arising out of infections like viral hepatitis, liver cirrhosis and fibrosis leading to deranged Child-Pugh's score, acute liver failure, liver trauma and sepsis. Hepatocellular carcinoma (HCC) results in decreased functional capacity of Liver and deranged coagulation factors.⁸

There are several tests which can assess the coagulopathy in Liver disease. Prothrombin time (PT), activated partial thromboplastin time (aPTT), Platelet count, bleeding time, platelet function analyser (PFA-100), thromboelastography, and platelet function assays are routine screening tests that can assess the coagulation status. PT determines vitamin K-dependent factors VII, X, II, IX as well as fibrinogen. The aPTT measures the activities of intrinsic and common pathways of coagulation cascade that are most sensitive to factor VIII, IX, XI, XII and those of the coagulation system.⁹ Coagulation followed by fibrinolytic activity leads to a fall in the levels of fibrinogen with a concomitant rise in the levels of fibrin degradation products [FDP's].¹⁰ Since chronic liver disease is associated with disordered haemostasis, it is possible that it could be associated not only with defects in coagulation but also of clot lysis. For assessing possible derangements in fibrinolytic pathway, estimating D-Dimer is significant. D-Dimer is a stable and measurable parameter formed by the enzymatic breakdown of the cross-linked fibrin. Estimation of D-Dimer has hitherto been used for the diagnosis of conditions such as deep vein thrombosis and pulmonary embolism.^{11,12}

Platelet count, bleeding time, platelet function analyser (PFA-100), thromboelastography, and platelet function assays are not clinically useful for stratifying bleeding risk in cirrhotic patients.¹³ Prolongation of the PT and aPTT in liver disease reflects the impaired synthesis of clotting factors by the diseased liver and is widely used in scoring systems (Child-Pugh, MELD and UKELD) in chronic liver disease and as a prognostic tool and for monitoring of liver function in acute liver failure. The PT-INR is widely used to assess the risk of bleeding in patients with liver disease, however, the evidence from clinical practice and the literature is that it does not correlate with bleeding after liver biopsy or other procedures.^{14,15} The limitations of PT-INR are that it is not possible to estimate the overall strength and stability of the clot because these tests are read at the initiation of fibrin polymerization which happens at very low levels of thrombin

generation of about 10 to 20 nM, which is less than 5% of the total thrombin that can be generated.¹⁶ Standard coagulation tests have been shown to be inadequate for the purposes of stratifying bleeding and thrombotic risk in patients with liver disease, and this mandates a search for combination of assessment tests – coagulation and fibrinolysis- which better reflect functional changes in haemostasis.

This study was conducted in which a battery of tests including Platelet count, PT and D-Dimer assays were done in patients of Liver diseases using Modified Child-Pugh score and MELD score to assess the bleeding tendencies and coagulopathy in such patients. It shall provide us with a deep insight into coagulation derangement in individual type of Liver disease.

METHODS

This is a cross sectional study conducted in the Departments of Pathology, Medicine and Paediatrics, of Jawaharlal Nehru Medical College and Central Clinical laboratory, A.V.B.R.H, Sawangi, Wardha. The study was approved by Ethics Committee. The study was conducted from August 2017 to July 2019.

Study Population

102 patients of liver diseases who were admitted in Medicine and Paediatric wards of A.V.B.R.H, Sawangi (Meghe), Wardha, were enrolled in the study.

Sample Size

The study of Shaila SN, et al observed that altered PT, and Plt was seen in 52% and 48% respectively. Taking this value as reference, the minimum required sample size with 10% margin of error and 5% level of significance is 96 patients. To reduce margin of error, total sample size taken is 102. Formula used is-

$$N \geq (p(1-p)) / (ME/Z_{\alpha})^2$$

Where Z_{α} is value of Z at two sided alpha error of 5%, ME is margin of error and p is proportion of patients with altered PT/Plt.

Calculations

1. Altered PT

$$n = ((.52 * (1-.52)) / (.011.96)^2) = 95.89 = 96 (\text{approx.})$$

2. Altered Plt

$$n = ((.48 * (1-.48)) / (.011.96)^2) = 95.89 = 96 (\text{approx.})$$

Inclusion Criteria

Patients having liver diseases like: cirrhosis, alcoholic, hepatitis, liver parenchymal diseases, hepatic encephalopathy, cholestasis, fatty liver, liver abscess, portal HTN, chronic liver disease.

Exclusion Criteria

Patients of cirrhosis with previous history of coagulation disorders and drug intake that causes changes in the coagulation parameters e.g. Oral contraceptives, Aspirin, Heparin, Warfarin. Pregnant females.

Methods

Platelet count- was done by automated haematology analyser from the EDTA sample by Horiba Pentra XLR. Liver function test (SGOT, SGPT, ALP, serum bilirubin, serum albumin, total protein): was done by automated biochemistry analyser by VITROS Integrated 5600. Coagulation tests (PT and aPTT) were done by reagent and diagnostic kit, (for PT: Thromborel reagent 200 μ L+ 100 μ L plasma, for aPTT: actin reagent 100 μ L + plasma 100 μ L + Calcium chloride 100 μ L). D – dimer: qualitative test was performed by adding 20 μ L plasma with 1 drop of latex reagent then rotated for 3 min, if agglutination was seen the test was labelled positive.

Statistical Analysis

Statistical tests were applied as follows-

1. Quantitative variables were compared using Mann-Whitney Test (as the data sets were not normally distributed) between the two groups. ANOVA/Kruskal Wallis test was used for comparison between more than two groups.
2. Qualitative variables were correlated using Chi-Square test.
3. Spearman rank correlation coefficient was used to assess the correlation of Child Pugh score and MELD score with age.

A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0, p value of <0.05 was considered statistically significant.

RESULTS

A total of 102 patients were included in the study. Mean age of the patients in our study was 40.07 ± 15.21 years. Majority of the patients (30.39%) belonged to the age group 31-40 years, followed by 21.57% of 41-50 years, and 13.73% in 21-30 years age group. Only 4 patients were ≤ 10 years. In our study, 69.61% (n = 71) patients were males and 30.39% (n = 31) were females. In this study, fever with abdominal distension was most common chief complaint in majority of the patients (23.53%), followed by abdominal distension in 22.55% patients, and pain in abdomen in 14.71% patients. In this study, 38.24% patients were chronic alcoholic, and no history of alcohol intake was noted in 61.76% patients. In this study, D-dimer was positive in 57.84% patients.

Among the various diagnosis, three groups are comprised, acute viral hepatitis comprising 26 (25.49%) patients, cirrhosis of liver comprising 38 (37.25%) patients and other chronic liver diseases comprising 38 (37.26%) patients which include Alcoholic hepatitis, Alcoholic liver disease, Chronic liver disease, Chronic viral hepatitis and HCC. In this study,

mean value of Albumin was 3.26 g%; mean ALP was 361.8 IU/L; mean S. creatinine was 1.33 mg%; mean S. Protein was 6.54 g%; mean SGOT was 151.54 IU/L; mean SGPT was 134.88 IU/L; and mean T. Bilirubin was 6.04 mg%. In this study, mean value of INR was 1.44; mean PT was 17.91; and mean Platelet count was 157470.59.

Among clinical complications, hepatic encephalopathy, ascites, and bleeding tendency were present in 7.84%, 67.65%, and 13.73% patients, respectively. Grade III ascites was present in 56.52% patients, grade II in 31.88%, and grade I in 11.59% patients. In this study, mean Child Pugh score was 8.31; Child Pugh Stage B was present in majority (45.10%) of patients, Stage C in 28.43%, and Stage A in 26.47% patients. Mean MELD score was 13.1. In most of the patients (43.14%), MELD score was 10-19; ≤ 9 in 37.25%; and ≥ 20 in 19.61% patients.

Graph 1. Distribution of Deranged Coagulation Parameters

Graph 2. Association of Coagulation Parameters with Clinical Diagnosis

Coagulation Parameters		Child Pugh Score (Total)			Total	p
		Stage A (n=27)	Stage B (n=46)	Stage C F(n=29)		
PT	Mean $\pm$ SD	15.12 $\pm$ 1.81	18.18 $\pm$ 5.17	20.07 $\pm$ 5.56	17.91 $\pm$ 4.98	0.0003
	Median (IQR)	15.5 (14.250-16)	16.9 (15.200-20.100)	19.2 (15.575-23.200)	16.15 (15.200-19.700)	
Platelet	Mean $\pm$ SD	105814.82 $\pm$ 101444.2	171413.04 $\pm$ 162621.66	183448.28 $\pm$ 152907.91	157470.59 $\pm$ 148018.11	0.022
	Median (IQR)	72000 (46000-135500)	108000 (66000-200000)	118000 (87250-209250)	105000 (65000-176000)	
D-Dimer	Negative	19 (70.37%)	19 (41.30%)	5 (17.24%)	43 (42.16%)	0.0003
	Positive	8 (29.63%)	27 (58.70%)	24 (82.76%)	59 (57.84%)	

Table 1. Association of Coagulation Parameters with Child Pugh Score (All Liver Diseases)

Deranged PT was comparable in patients with or without bleeding ($p=0.530$). Bleeding was present in 13 out of 73 patients in which platelet count was deranged; deranged platelet count was comparable in patients with or without bleeding in terms of bleeding tendency ($p=0.064$). Bleeding was noted in 12 out of 59 patients in which D-Dimer was present; there was a significant association of D-Dimer and bleeding tendency. This is shown in Graph 3. To study association of coagulation abnormality with extent of disease by different scoring systems (Modified Child – Pugh score and MELD score). In the present study, number of patients with positive plasma D-Dimer levels were found to increase significantly with severity of liver disease (Child Pugh A vs B vs C, 29.63% vs 58.70% vs 82.76%, $P=0.0003$). Deranged PT were found to increase significantly with severity of liver disease (A vs B vs C, 15.12 $\pm$ 1.81 vs 18.18 $\pm$ 5.17 vs 20.07 $\pm$ 5.56, $P=0.0003$) and mean Platelet was found to become normal with increasing severity of liver disease (A vs B vs C, 105814.82 $\pm$ 101444.2 vs 171413.04 $\pm$ 162621.66 vs 183448.28 $\pm$ 152907.91, $P=0.022$). This is shown in Table 1.

Correlation Table		MELD Score (n=102)	Child Pugh Score (n=102)
PT	Correlation Coefficient	0.366	0.368
	p Value	0.0002	0.0001
	n	102	102
Platelet	Correlation Coefficient	0.305	0.231
	p Value	0.0018	0.0194
	n	102	102

Table 2a. Correlation between PT and Platelet with MELD score and Child Pugh Score

D-Dimer	Meld Score		p Value
	Mean $\pm$ SD	Median(IQR)	
Negative (n=43)	13.69 $\pm$ 7.66	12.76(7.443 - 19.662)	0.395
Positive (n=59)	12.67 $\pm$ 8.69	11.9(5.960 - 16.684)	

Table 2b. Association of D-Dimer and MELD Score

Present study shows significant correlation between PT and MELD score ($p=0.0002$). There was also a significant correlation between PT and Child Pugh score. ($p=0.0001$). There was also a significant correlation between platelet and MELD score ($p=0.0018$). A significant correlation was also noted between platelet and Child Pugh score ($p=0.0194$). This is shown in Table 2a. There was no significant association of D-Dimer with MELD score ($p=0.395$). This is shown in Table 2b. There was no significant association of bleeding tendency with mean Child Pugh score ($p=0.447$) as well as Child Pugh scores A to C ($p=0.429$). There was no significant association of bleeding tendency with mean MELD score ($p=0.082$).

DISCUSSION

We conducted this study to assess coagulation profile and haemostatic dysfunction in all groups of liver disease patients, so as future measures may be taken to prevent bleeding related complications and better the prognosis. The mean age of the patients in our study was 40.07 $\pm$ 15.21 years; 69.61% ($n=71$) patients were males. In a study by Li Y et al, mean age of patients was 56.42 $\pm$ 11.08 years; 68.7% patients were males.¹⁷ Deranged coagulation parameters were present in 92 (90.20%) patients in our study. Among these, PT was deranged in 4.90%, platelet count was deranged in 71.57% patients and D-Dimer was present 57.84% patients. In a study by Shah SN et al, PT was deranged in 52%, platelet count was deranged in 48% patients.¹⁸ In our study, bleeding tendency was present in 14 (13.73%) patients. Among these patients, there was no association of PT and platelet count with bleeding tendency. D-Dimer was present in significantly higher number of patients with bleeding as compared to patients without bleeding. This implies that there are higher chances of D-dimer presence in patients who had liver diseases with bleeding tendency. In our study, there was no association of bleeding tendency with Child Pugh score and MELD score.

In a study by Primignani et al,¹⁹ bleeding tendency was present in 50% patients. Significant association of bleeding tendency with MELD score was observed. Authors observed significant association of D-dimer levels with bleeding tendency. Li J et al,²⁰ observed bleeding tendency in 2.4% patients. No association of PT and platelet count with bleeding tendency was reported. Also, there was no association of bleeding tendency with Child Pugh score and MELD score. In our study, mean Child Pugh score was 8.31. Yun Li Y et al,¹⁷ reported that mean Child-Pugh score was 7.66. Drolz et al²¹ reported that median Child-Pugh score was 11. In this study, mean MELD score was 13.1. Yun Li et al,¹⁷ reported that mean MELD score was 8.63.

Coagulation Parameters and Severity Scores

Prothrombin Time- In present study, there was a significant increase in mean PT with increase in Child-Pugh score stages from A to C. Al-Dewachi et al,²² also reported that there was progressive prolongation in PT in Child-Pugh grades from A to C. According to Dhanunjaya Y et al,²³ reported PT increased significantly from A to C groups.

Platelet Count- Mean platelet count was significantly low in Child-Pugh score stage A and normal in stages B and C. Al-Dewachi et al,²² reported that mean platelet counts were progressively reduced from Child-Pugh grades A to B and then to C.

D-Dimer- Positive D-dimer was significantly high in Child-Pugh score stage C as compared to stages A and B. Al-Dewachi et al,²² reported that mean D-Dimer levels were found to increase significantly with severity of liver disease. Li Y et al,¹⁷ Primignani et al,¹⁹ and Violi et al²⁴ also identified that the median D-dimer levels gradually increased among Child-Pugh class A, B and C.

To sum up, determination of coagulation parameters in all spectrum of liver diseases is important to assess the bleeding tendency. The severity of the liver diseases must be measured independent of the bleeding risk. Deranged coagulation parameters can be present in most of the liver disease patients and thus a battery of coagulation tests like PT (INR), Platelet counts, D-Dimer; must be performed. Since the diagnostic power of each test varies in different liver disease; thus, cumulative testing and reporting may cover all causes of coagulation defects in liver disease patients.

In this study, deranged coagulation parameters were present in 90.20% patients; Platelet count and D-dimer were deranged in 71.57% and 57.84% patients, respectively. D-Dimer was significantly higher in patients with bleeding and therefore should mandatory be performed in patients with liver disease patients. PT, Platelet and D-Dimer showed a significant association with severity of Child Pugh stages A to C; however, MELD score showed significant positive correlation only with PT and platelet count and not with D-Dimer. Present study shows an overall good diagnostic power of coagulation parameters in assessing different liver diseases.

CONCLUSIONS

Present study showed an overall good diagnostic power of coagulation parameters in assessing different liver diseases and also showed that D-dimer may be regarded as a stable and good predictor for chronic liver diseases.

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