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ORIGINAL RESEARCH

Study of Coagulation Profile in Liver Disease Patients at A Tertiary Care Hospital

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ABSTRACT

Background: The study of coagulation can be traced back to about 400 BC and to the father of Medicine, Hippocrates. The liver is the cornerstone of the coagulation system. The liver is the site of synthesis of fibrinogen and factors II, V, VII, IX, X, XI and XII. Von Willebrand factor (VWF) is synthetized by the endothelium. When both cellular and plasmatic coagulation are defective, represents a hallmark of advanced liver disease. There is substantial overlap in the hemostatic abnormalities observed in the patients with acute infectious or toxic hepatitis, chronic hepatitis, and cirrhosis, the severity of hepatocellular dysfunction is typically more informative than the etiology.

Aim & Objective:

1. To determine the coagulative abnormalities among liver disease patients admitted in medicine wards.
2. To study the association of coagulation abnormalities with the extent or severity of liver disease.

Methods: Study design: A Cross sectional study. Study setting: Department of pathology. Study duration: June 2019 to June 2020.

Study population: All patients of acute and chronic liver disease admitted to medicine wards in tertiary care hospital such cases included in the study.

Sample size: 200

Results: most common age group was between 31-40yrs of age, i.e., 32% of total patients. 174 (87%) were male population and 26 (13%) were female population.78(39%) cases of cirrhosis, 46(23%) cases of hepatitis, 44(22%) cases of Alcoholic liver disease, and 32(16%) cases of other liver diseases. patients showed coagulation abnormalities considering different parameters i.e., PT, APTT, Platelet count individually or in combinations, and 11(5.5%) patients showed normal test results. About 87% (174/200) had prolonged PT. Mean PT in present study was 28.33±22.29. P value was <0.05 i.e., 0.013 which was statistically significant

Conclusions: Cirrhosis was the most common pathology amongst the study subjects. The PT was most abnormal test among all tests performed. The platelet count and APTT were the least frequently abnormal test. Hence PT was most significant coagulation test among other tests. The proportion of raised PT was highest in alcoholic liver disease and lowest in case of

other liver diseases. Coagulation abnormalities were significantly associated with the extent of liver diseases.
Keywords: liver disease, coagulative abnormalities, PT, APTT, Platelet count, LFT

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INTRODUCTION

The study of coagulation can be traced back to about 400 BC and to the father of Medicine, Hippocrates [1]. The liver is the cornerstone of the coagulation system [2]. The liver is the site of synthesis of fibrinogen and factors II, V, VII, IX, X, XI and XII. Von Willebrand factor (VWF) is synthetized by the endothelium.[3]

When both cellular and plasmatic coagulation are defective, represents a hallmark of advanced liver disease.[4] There is substantial overlap in the hemostatic abnormalities observed in the patients with acute infectious or toxic hepatitis, chronic hepatitis, and cirrhosis, the severity of hepatocellular dysfunction is typically more informative than the etiology [5].

Prothrombin time (PT), correlates well with the severity of hepatocellular damage as well as with the occurrence of abnormal bleeding and the overall prognosis [6]. In chronic liver diseases, the levels of anticoagulant proteins like antithrombin III, protein S, protein C, and alpha2 macroglobulin are reduced.

Therefore, the coagulopathy pattern in liver disease is not limited to being anticoagulation. Rather, this group of disorders resulting from cirrhosis of liver encompasses procoagulant as well as anticoagulant tendencies.

In patients with liver cirrhosis, most coagulation factors and inhibitors of the coagulation and fibrinolytic systems are markedly reduced because of impaired protein synthesis, except for factor VIII and fibrinogen levels, which may be normal or increased [7,8].

Coagulation tests and liver function tests are useful in the evaluation, management and assessment of prognosis. These tests provide a sensitive method of screening for the presence of liver dysfunction [9]. Normal range of prothrombin time (PT) is between 11 and 16 seconds, activated partial thromboplastin time (APTT) ranges between 2640 seconds [10]. Impaired hemostasis resulting from abnormal liver function in liver disease are usually measured by the prolongation of global screening tests such as the PT and the APTT [11]

PT is part of the ChildPugh score, which is the most commonly used prognostic score assessing the severity of liver disease [12]. Staging of chronic liver diseases is done by modified ChildPugh classification with a scoring system of 515 [13]

Studies have shown that significant prolongation of PT and activated partial thromboplastin time (APTT) in the absence of significant hypofibrinogenemia suggests their importance as a reliable marker of coagulopathies in chronic liver disease patients[14] Thrombocytopenia is defined as a reduction in the peripheral blood platelet count below the lower normal limit of 150x109/l[15].The common reason cited for thrombocytopenia in patients with cirrhosis is splenomegaly and portal hypertension with hypersplenism which results in thrombocytopenia [1].

This study was conducted to evaluate the coagulation profile of patients with liver disease admitted to a tertiary hospital unit using routine tests such as prothrombin time and aPTT along with platelet counts.

AIM AND OBJECTIVE

OBJECTIVES:

1. To determine the coagulative abnormalities among liver disease patients admitted in medicine wards by evaluating the following parameters of coagulation profile along with liver function test-

- Prothrombin time (PT)- Automated coagulation analyser
- Activated partial thromboplastin time (APTT)- Automated coagulation analyser
- Total platelet count – Automated hematology analyser

2. To study the association of coagulation abnormalities with the extent or severity of liver disease.

MATERIAL AND METHODS

Study design: A Cross sectional study.
Study setting: Department of pathology
Study duration: June 2019 to June 2020.
Study population: All patients of acute and chronic liver disease admitted to medicine wards in tertiary care hospital such cases included in the study.
Sample size: 200
Inclusion criteria: Patients of both sexes, age above 12 years with presence of liver disease (acute and chronic).
Exclusion criteria:

1. Patients with previous history of coagulation disorders or who were taking drugs which alter the coagulation profile.
2. Pregnant woman.

Ethical Clearance: The study protocol was approved by the Institutional Ethics Committee before the commencement of the study.
Informed Consent: Patients fulfilling the selection criteria were informed about the nature and purpose of the study and were enrolled after obtaining a written informed consent.. The consent was recorded in patient's own language.
Collection of samples: All these patients were tested for PT, APTT, Platelet count, along with liver function test on admission to the hospital. The tests were performed after taking consent for collection of samples. Blood (2ml) collected in vacutainer containing 3.2% sodium citrate and plasma separated after centrifugation at 37 ^{0}c for PT and APTT, in plain bulb for liver function test and in EDTA vacutainer for platelet count.
The tests were carried out using automated blood cell counter for PLT count and automated coagulometer for PT and, APTT. Liver function tests were carried out on automated biochemistry analyzer.Also, Renal function test done along with liver function test, as serum creatinine values were used to calculate MELD score.

METHODS:

1. PT and APTT

These tests were performed on blood collected in citrate vacutainer (up to given mark) using fully automated STA Compact Max analyser (Diagnostica STAGO)

2. Platelet count

By ERBA H-360 three part fully automated cell counter which uses coulters principle for automated hematology analyser. Since Wallace Coulter first described the hematology

analyser in 1956.A Coulter counter is an apparatus for counting and sizing particles suspended in electrolytes.

Statistical analysis: - The results were given as mean, standard deviation and frequency (number-percent). Chi square test (x^2-value) was used to correlate parameters with the disease. P<0.05 was accepted as significant and p value < 0.001 as statistically highly significant and p ≥0.05 as non-significant. Bar diagrams, pie chart and scatter diagrams were used for the graphical representation of the data.

RESULTS AND OBSERVATIONS

A total 200 patients of acute and chronic liver disease were enrolled for the present study.

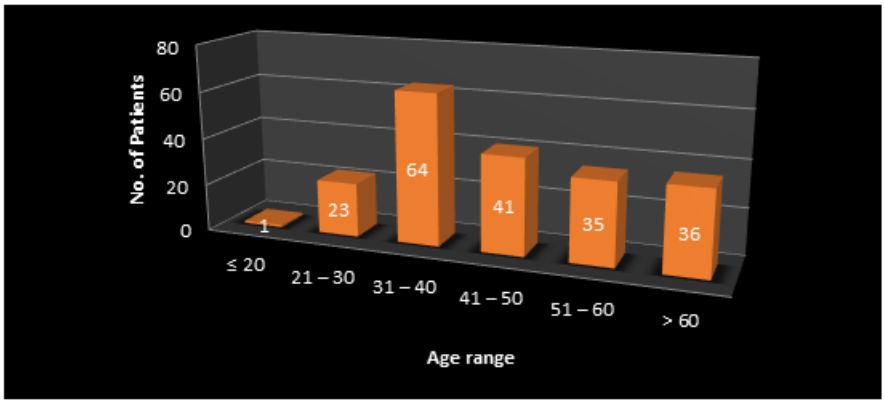

Figure 1: Age wise distribution of the patients

Age range involved in this study was 19 to 80 years of age, most common age group was between 31-40yrs of age, i.e., 32% of total patients. Mean ± SD of age is 46.17±13.60

Table 1: Sex wise distribution

Sex	Frequency	Percentage
Male	174	87%
Female	26	13%
Total	**200**	**100.0**

Out of 200 patients, 174 (87%) were male population and 26 (13%) were female population.

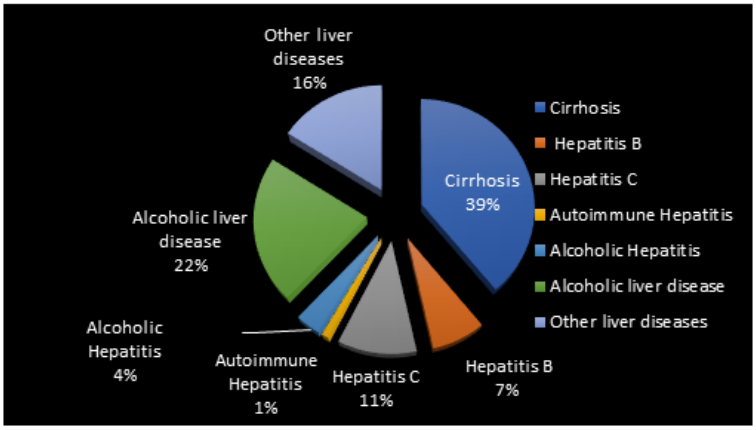

Figure 2: Disease wise distribution

Figure no: 2 shows disease wise distribution of cases which were divided into following four groups: 78(39%) cases of cirrhosis, 46(23%) cases of hepatitis, 44(22%) cases of Alcoholic

liver disease, and 32(16%) cases of other liver diseases.Out of 46 cases of hepatitis there were 22 cases (13%) of Hepatitis C, 15 cases (9%) of Hepatitis B, 7 cases (4%) of Alcoholic Hepatitis and 2 cases (1%) of Autoimmune Hepatitis.

Table 2: MELD score of patients in this study

MELD Score	Coagulation profile		Total	Percentage	p-value
	Abnormal	Normal			
< 9	24	5	29	14.5%	0.013
10 - 19	65	5	70	35%	
20 - 29	53	0	53	26.5%	
30 - 39	28	1	29	14.5%	
> 39	19	0	19	9.5%	
Total	**189**	**11**	**200**	**100.0**	

Number of patients with MELD score less than 9 was 29 cases (14.5%) and above 39 was 19 cases (9.5%). Maximum number of cases were between MELD score 10-19 i.e., 70 cases (35%). P Value is 0.013 which was statistically significant.

Table 3: Disease wise derangement of PT in study subjects

PT	Diagnosis				Total	p-value
	Cirrhosis	Hepatitis	ALD	Others		
≤ 16	10	9	0	7	26	0.013
> 16	68	37	44	25	174	
Total	**78**	**46**	**44**	**32**	**200**	

Out of 78 patients of cirrhosis, a total of 68 (87.2%) had prolonged PT, out of 46 patients of viral hepatitis, a total of 37 (80.4%) had prolonged PT, out of 44 patients of alcoholic liver disease, all (100%) had shown prolonged PT and there were 32 cases of other liver diseases, out of which, 25 (78.1%) patients showed prolonged PT. P value was <0.05 i.e., 0.013 which was statistically significant.

Table 4: Disease wise derangement of APTT in study subjects

APTT	Diagnosis				Total	p-value
	Cirrhosis	Hepatitis	ALD	Others		
< 26	3	2	2	4	11	0.149
27 - 40	21	16	21	11	69	
> 40	54	28	21	17	120	
Total	**78**	**46**	**44**	**32**	**200**	

Out of 78 patients of cirrhosis, 54 (69.2%) patients had prolonged APTT, out of 46 patients of viral hepatitis, 28 (60.9%) patients showed prolonged APTT, out of 44 patients of alcoholic liver disease, 21(47.7%) patients showed prolonged APTT and there were 32 cases of other liver diseases, out of which 17 (53.1%) patients showed prolonged APTT.P value was 0.149 which was statistically not significant.

Table 5: Disease wise distribution of platelet count in the study subjects

Platelet	Diagnosis				Total	p-value 0.740
	Cirrhosis	Hepatitis	ALD	Others		
Normal	18	12	7	7	46	
Thrombocytopenia	60	32	37	25	154	
Total	**78**	**46**	**44**	**32**	**200**	

Out of 78 patients of cirrhosis, a total of 60 (76.9%) showed thrombocytopenia, out of 46 patients of viral hepatitis, 32 (69.6%) patients showed thrombocytopenia, and among 44 patients of alcoholic liver disease category, 37 patients showed thrombocytopenia. There were 32 cases of other liver diseases, out of which thrombocytopenia was seen in 25 (78.1%) patients. P value was 0.740 and it was not significant.

DISCUSSION

In the present study, we have studied 200 cases in detail those admitted under medicine department as diagnosed case of liver disease and sample were collected within 2 hours of admission for PT/INR, APTT, Platelets and Liver function test before starting the treatment. The findings for age and sex distribution are compatible with previous studies. The patients' age ranged from 19 to 80 years. The maximum patients were in the age group ranging from 31 to 40 years. The present study age group is similar to that of Shah and Jansari[1] in which maximum cases are above the age of 20 years. Mean age of present study subjects was 46.17±13.60 (Mean±SD) years which correlates with the study of Dr. Sheikh Sajjadieh[2].

This study included predominantly male population which was 87% of total population, this was in concordance with many other studies. such as by Devrajani et al[7] and Ahmad hameed et al[6] and Rajkumar Soloman T et al[102] where male preponderance is seen in cases of liver diseases. So, we can say Liver disease is more prevalent among male population. Male to female ratio is 6.6:1.

Liver disease patients were divided into following four groups: 78(39%) cases of cirrhosis, 46(23%) cases of hepatitis, 44(22%) cases of Alcoholic liver disease, and 32(16%) cases of other liver diseases. This study correlates with the study of Gautam Bhatia et al[14] in 2016 involving 300 study subjects, where most common were cirrhosis cases and second most common were hepatitis.

Out of 46 cases of hepatitis there were 22 cases (13%) of Hepatitis C, 15 cases (9%) of Hepatitis B, 7 cases (4%) of Alcoholic Hepatitis and 2 cases (1%) of Autoimmune Hepatitis. This distribution of cases of hepatitis in present study was similar to that of Siddiqui et al[16] where Hepatitis C cases were leading followed by Hepatitis B, and least cases were of Autoimmune Hepatitis.

In present study 94% cases shown deranged coagulation tests i.e., having at least one coagulation parameter deviated from the normality. About 87% (174/200) had prolonged PT. About 60% (120/200) had prolonged APTT. Thrombocytopenia was observed in 154 cases (77%) out of 200 total cases.

In the present study, 87% (174/200) patients had prolonged PT in liver diseases. The P value was 0.013 and it was significant. The present study findings agree with the study of with Sohail Ahmed Siddiqui et al study.[16]

There were 60% (120/200) patients of liver diseases having prolonged APTT .The present study findings agree with Shah and Jansari (62%)[1] and with Sohail Ahmed Siddiqui study (67%)[16]

Out of 78 patients of cirrhosis, a total of 68 (87.2%) had prolonged PT and 54 (69.2%) patients had prolonged APTT. Out of 46 patients of viral hepatitis, a total of 37 (80.4%) had prolonged PT and 28 (60.9%) patients showed prolonged APTT. There is significant prolonged PT and APTT in viral hepatitis.

Out of 44 patients of alcoholic liver disease, all (100%) had shown prolonged PT and 21(47.7%) patients showed prolonged APTT. There were 69 (23%) cases of other liver diseases. Out of which, 25 (78.1%) patients showed prolonged PT. The APTT was prolonged in 17 (53.1%) patients.

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[17]

In the present study, 154 (77%) patients out of 200 were having thrombocytopenia in liver diseases. Out of 46 patients of viral hepatitis, 32 (69.6%) patients showed thrombocytopenia. Thus, there is significant thrombocytopenia

Out of 78 patients of cirrhosis, a total of 60 (76.9%) showed thrombocytopenia. There were 69 (23%) cases of other liver diseases. Out of which thrombocytopenia was seen in 25 (78.1%) patients. P value was not significant.

In this study PT and Platelet count were most deranged tests than APTT. Class A (Well compensated disease) of Child Pugh Score consist 2(2.5%) cases out of 78 cases of cirrhosis, class B (Significant functional compromise) consists of 31(39.8%) cases out of 78 cases and class C (Decompensated disease) consist of 45(57.7%) cases out of 78 cases. P value is 0.011 which was significant.

In present study the coagulation profile was significantly correlated with the child-Pugh score[13] The findings were compatible with the previous study done by Sylvester chucks nwokediuko et al.[107]

Table 6: Comparison of coagulopathy with other studies

Other studies	**SS**	**Tests perform-ed**	**Prolong-ed PT**	**Prolong-ed APTT**	**Thrombo-cytopenia**	**Child pugh score Class**		
						A	B	C
Gautam Bhatia et al (2017)	300	PT, APTT, PC	62%	39.3%	46%	-	-	-
Patil Amita Yatish et al (2020)	120	PT, APTT, PC	63.33%	55.83%	17.5%	-	-	-
Archana Rautela et al (2019)	40	PT, APTT	27.5%	17.5%	-	33	3	4
Shah Shaila et al (2014)	100	PT, APTT, PC	52%	62%	48%	3	29	18
Sohail Ahmed Siddiqui et al (2011)	-	PT, APTT, PC	87.7%	71.3%	36.8%	-	-	-
Nwokediuko SC et al (2010)	-	PT, APTT, PC	36.6%	22.6%	42.7%	-	-	-
G. K. Tripathi et al (2016)	311	PT, APTT	100%	95.4%	-	-	-	-
Our Study	200	PT, APTT, PC	87%	60%	77%	2	31	45

(Abbreviations: SS- sample size, PC-platelet count)

CONCLUSIONS

Cirrhosis was the most common pathology amongst the study subjects. The PT was most abnormal test among all tests performed. The platelet count and APTT were the least frequently abnormal test. Hence PT was most significant coagulation test among other tests.The proportion of raised PT was highest in alcoholic liver disease and lowest in case of other liver diseases. Coagulation abnormalities were significantly associated with the extent of liver diseases.

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