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Platelets in Chronic Liver Disease: Beyond Numbers

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Authors' contributions

This work was carried out in collaboration among all authors. Authors PP and ND conceptualized, designed, analyzed the data and drafted the manuscript. Authors VCG and SMAH wrote the protocol, collected, managed the clinical data and the patients. Author RR managed literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: Thrombocytopenia, a complication of Chronic Liver Disease (CLD), is considered to be a marker of advanced disease and an independent predictor of mortality. But this is disputable and hence is this study 1. To find out prevalence of thrombocytopenia in CLD; 2. To find out association with severity of liver disease and thrombocytopenia.
Materials And Methods: This was a descriptive study analyzing CLD patients diagnosed by clinical, biochemical, serological and radiological evaluation in our institution between March 2019 and December 2020.
Results: There were 48 patients; M: F 43:5; mean age 51.7±12.4 years; Thrombocytopenia: Mild (149999 – 75000/mm^3) in 45.8%, moderate (74999 – 50000/mm^3) in 12.5% and severe (< 49999/mm^3) in 8.3%. There was no association of thrombocytopenia with severity indices like Child-Pugh Class (C. P. C.) and Model for End-stage Liver Disease – Sodium (MELD-Na) Score.
Conclusion: The prevalence of thrombocytopenia in CLD is 66.6% in this study. Thrombocytopenia is not associated with severity of disease. This necessitates larger studies and analyzing the factors other than number of platelets. This includes 1. functional status of platelets (thrombocythemia) 2. In a stable CLD, haemostasis and coagulation pathways achieve a delicate

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"rebalance state" (new normal) which may be disturbed even by trivial insult. 3. Platelets also secrete platelet derived growth factor, transforming growth factor β, hepatocyte growth factor which can influence liver fibrosis and regeneration.

Keywords: Thrombocytopenia; chronic liver disease; portal hypertension; haemostasis; hypocoagulation-hypercoagulation.

1. INTRODUCTION

Chronic liver diseases (CLD) cause significant mortality, morbidity and health care expenditure. At least 3 million deaths occur globally every year due to CLD. Thrombocytopenia (< 150000 platelets/mm^3) is one of complications of CLD and it occurs at a frequency up to 76% [1,2]. The mechanisms of thrombocytopenia in CLD are multifactorial [1,3]. 1. Sequestration (trapping) of platelets occurring in the enlarged spleen for example hypersplenism, portal hypertension. 2. Direct splenic destruction. 3. Immune mediated destruction. 4. Hepatic dysfunction and subsequent reduction of hepatic synthesis of thrombopoietin which is a cytokine factor that regulate development and maturation of megakaryocytes - the precursor of platelets. 5. Can be due to suppression of thrombocytogenesis in bone marrow for example alcohol, hepatitis C, interferon therapy and folate deficiency. 6. Intra vascular volume expansion and subsequent dilution as happen in case of resuscitation with crystalloids, colloids, and massive blood transfusion [1,3]. 7. Pulmonary hypertension and pulmonary embolism which can occur in CLD also cause thrombocytopenia because of platelet consumption [4]. Pseudo-thrombocytopenia or false low platelet count is encountered when platelet clumping occurs when they are exposed to anticoagulant ethylene diamine tetra-acetic acid [4]. Thrombocytopenia is described as mild when the platelet count is in the range of 75000-150000/mm^3. It is reported up to 76% of CLD patients. Moderate thrombocytopenia (50,000 to 75,000 platelets/mm^3) occurs in about 13% and severe form (less than 50,000 platelets/mm^3) reported in 1% of CLD patients [1,2]. Platelet count can be used as a surrogate marker for advanced stage of liver disease especially fibrosis by means of calculating APRI (Aspartate Aminotransferase to Platelet Ratio Index), NAFLD (Non-Alcoholic Fatty Liver Disease) score, FIB – 4 (Fibrosis – 4). These are simple bedside reliable markers. Thrombocytopenia combined with splenomegaly can predict the presence of oesophageal varices as a non - invasive marker [5,6]. Giannini et.al. reported platelets count/spleen diameter ratio as an independent factor associated with the presence of large oesophageal varices [5]. Alam R. et al studied 84 children with CLD and found low platelet count and splenomegaly predicted presence of oesophageal varices and on this basis they suggested that screening endoscopy for varices can be focused on children with thrombocytopenia and splenomegaly that can reduce work load of endoscopic units [6]. Thrombocytopenia may pose problems with procedures done in a CLD patients especially liver biopsy, venous cannulation, liver transplantation. It may be necessary to correct platelet numbers by way of platelets transfusion before such procedures [1,3,7,8]. The treatment of hepatitis C with interferon is also affected. Dose modification or even discontinuation is reported in 19% and 2% of patients respectively in chronic hepatitis C patients [1]. Novel therapeutic thrombopoietin agonists like eltrombopag, avatrombopag and lusutrombopag are helpful in management of thrombocytopenic patients.

Thrombocytopenia may be the first abnormality that give clue to presence of CLD [4]. Moore described thrombocytopenia as a marker of advanced disease and independent predictor of mortality. Thrombocytopenia is considered to represent an advanced stage of liver disease and poor prognosis [2,9,10]. Amir A. Qamar et al followed 213 patients with CLD over 9 years for development of abnormal haematological indices. Most of the patients had baseline thrombocytopenia. The outcome of death or transplant could be predicted by baseline thrombocytopenia. When combined with leukopenia, baseline thrombocytopenia predicted death or transplant, mortality and clinical decompensation [11]. Gotlieb et al., reported the decreasing trend of platelets over the years in the natural history of CLD may indicate advancing fibrosis and poor prognosis [12]. On the contrary Manoj et.al. found no correlation between spleen size, platelet count and MELD score in cirrhotic patients studied [13]. In the clinical setting patients with severe thrombocytopenia do not bleed always and few even undergo liver transplantation uneventfully.

In this conflicting situation we thought off analyzing platelet count in cirrhotic patients and hence this study.

2. AIMS OF STUDY

i. To find out the prevalence of thrombocytopenia in patients with chronic liver disease
ii. To evaluate the association of thrombocytopenia with stage of liver disease.

3. METHODOLOGY

This was a cross-sectional observational study. All the patients with CLD, attending both outpatient and inpatient departments from March 2019 to November 2020 were enrolled in the study. Inclusion criteria: Age more than 18, who have chronic liver disease at various stages. All the patients were evaluated clinically, biochemically, serologically, and radiologically. The basic demographic data were collected. Socio - Economic Status (S. E. S.) was classified according to modified Kuppuswamy's scale into upper class (I), upper middle class (II), lower middle class (III), upper lower class (IV), lower class (V). Anthropometric calculation: BMI was our main variable considered for nutritional status. The patients were classified as Underweight (BMI: < 18.5), Normal (BMI: 18.5 – 24.9), Overweight (BMI: 25 – 29.9) and Obese (BMI: > 30). A dry weight was calculated by subtracting 5% of total weight for mild ascites, 10% for moderate ascites, 15% for severe ascites, 20% for severe ascites and pedal edema. Disease severity grading: Severity of the disease is graded by Child - Pugh Class (C. P. C.) and Model for End-stage Liver Disease - Sodium (MELD-Na) Score. C. P. C. incorporates serum bilirubin, serum albumin, INR, ascites, hepatic encephalopathy. Grades of A (compensated cirrhosis), B and C (Decompensated cirrhosis) were given. MELD-Na score incorporates serum bilirubin, serum creatinine, INR, serum sodium level and whether patient is on dialysis or not.

3.1 Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences version 25. Data were analyzed using chi-square test for categorical variables. A p-value < 0.05 was taken as statistically significant. The required sample size was 121. The limitation of our study is small sample due inevitable reason. Hence we used simple charts in our study for interpretation and avoided advanced statistical applications since it may not be appropriate for small sample.

4. RESULTS

48 patients were included in this study. M:F 43:5; mean age 51.6 ±12.4 years. The basic demographic data and the study specific data were presented in Table.1.

The frequency wise distribution of various grades of thrombocytopenia was given in Fig. 1.

The aetiology wise distribution of CLD was given in Fig. 2.

The Fig. 3 depicts the negative association between thrombocytopenia and MELD – Na Score and Fig. 4 depicts the negative association between thrombocytopenia and C. P. Class.

Among 48 patients 3 patients had variceal bleed and six patients received 11 units of packed cells. In this study no one developed bleeding that can be attributed to thrombocytopenia.

5. DISCUSSION

5.1 Prevalence

The prevalence of thrombocytopenia in our study was: mild - 34%, moderate 12.8% and severe 8.5%; It is almost in line with other studies; Trimukhe et.al., reported 20% prevalence of thrombocytopenia in liver cirrhosis in eastern Madhya Pradesh, India [14]. Vimal M. studied most diverse population of hospitalized patients for causes of thrombocytopenia and reported prevalence of thrombocytopenia in CLD as 16.7%, which was next to infective aetiology [15].

5.2 Association with Severity of Disease

We studied the correlation between platelet number and C.P.C. and MELD-Na Score. We found no association between thrombocytopenia and C.P.C. and MELD-Na Score. We also did not encounter major bleeding events that can be attributed to thrombocytopenia in this study. Manoj et al., in their study of 146 cirrhotics reported no association between thrombocytopenia and features of portal hypertension [13]. On the other hand thrombocytopenia is considered to represent an advanced stage of liver disease and poor prognosis [2,4,9,10].

Table 1. Demograhic and study specific data

No.	Parameter	Number (%) /Range	Mean ± S.D.
1	**Total number of patients**	48	
2	**Sex-wise distribution**		
	Males	43 (89.6)	
	Females	5 (10.4)	
3	**Age-wise distribution (years)**	24 – 80	51.7±12.4
	20 – 39	6 (12.5)	
	40 – 59	32 (66.7)	
	> 60	10 (20.8)	
4	**Socio-Economic Status (S.E.S.)**		
	Upper class	1 (2.1)	
	Upper middle class	---	
	Lower middle class	---	
	Upper lower class	27 (56.3)	
	Lower lower class	20 (41.7)	
5	**Aetiology-wise distribution**		
	Alcohol	32 (66.7)	
	Hepatitis B	5 (10.4)	
	Hepatitis C	1 (2.1)	
	NAFLD	4 (8.3)	
	Unknown cause	6 (12.5)	
6	**Duration of illness**		
	< 12 months	6 (12.5)	
	13 – 59 months	30 (62.5)	
	> 60 months	12 (25)	
7	**Body Mass Index (Kgs/M^2)**	13.1 – 36.8	21±15.0
	< 18.5 (Underweight)	17 (35.4)	
	18.5 – 24.9 (Normal)	20 (41.6)	
	25 – 29.9 (Overweight)	7 (14.5)	
	> 30 (Obese)	4 (8.3)	
8	**Haematological values**		
	Haemoglobin (gms/dl)	4.7 – 15.7	9.9 ± 2.3
	White blood cells (cell/mm^3)	1000 – 25900	7953.5 ± 4947
	MCV fl	71 – 112	95.2 ± 10.6
	MCHC %	27 – 37	33 ±12.1
	MCH pg	20 – 38	31.6 ±4.4
	Platelets (cells/$mm^{3)}$	32000 - 393000	127020 ± 6915
	Normal > 150000	16 (33.3)	
	Mild thrombocytopenia (149999 – 75000)	22 (45.8)	
	Mod. thrombocytopenia (74999 – 50000)	6 (12.5)	
	Severe thrombocytopenia (< 49999)	4 (8.3)	
9	**APRI**	0.1 – 5.6	1.8 ± .2
	< 0.69	6 (12.5)	
	> 0.7	42 (87.5)	
10	**MELD- Na**	8 – 34	18.7± 6.4
	< 15	20 (41.6%)	
	> 15.1	28 (58.3%)	
11	**C. P. Class**		
	A	6 (12.5)	
	B	15 (31.3)	
	C	27 (56.3)	
12	**I. N. R.**	1 - 3.8	1.55 ± 0.5
	Up to 1.5	31 (64.6)	
	> 1.51	17 (35.4)	

Abbreviations: APRI – Aspartate Aminotransferase to Platelet Ratio Index; BMI – Body Mass Index expressed as Kg/$M^{2.}$ C. P. C. – Child - Pugh Class. CLD – Chronic Liver Disease. I. N. R. – International Normalized Ratio. MCH – Mean Corpuscular Haemoglobin expressed as pg. MCHC – Mean Corpuscular Haemoglobin Concentration expressed as %. MCV – Mean Corpuscular Volume expressed as fl. MELD-Na Score – Model for End stage Liver Disease – Sodium Score. NAFLD – Non-Alcoholic Fatty Liver Disease. S.E.S. – Socio-Economic Status. We adopted modified Kuppuswamy's scale of S.E.S. < Less than. > More than. ± plus – minus sign

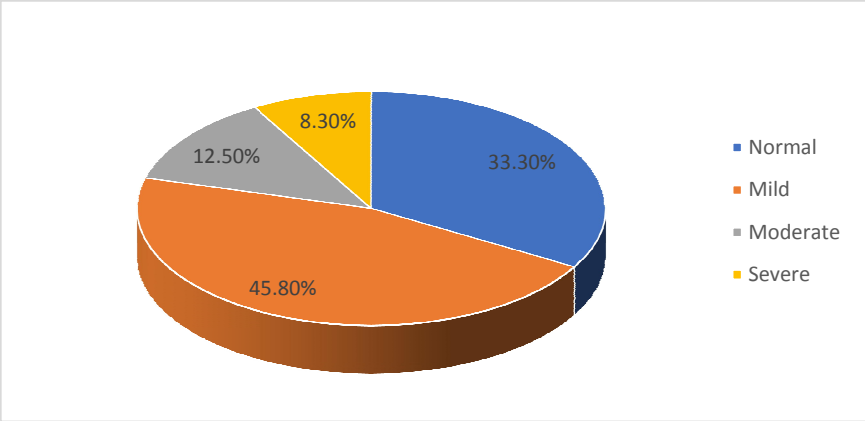


Fig. 1. Frequency of thrombocytopenia

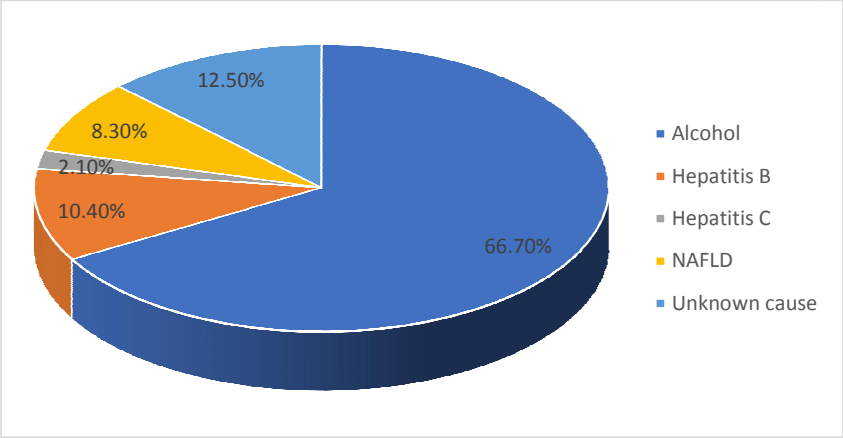
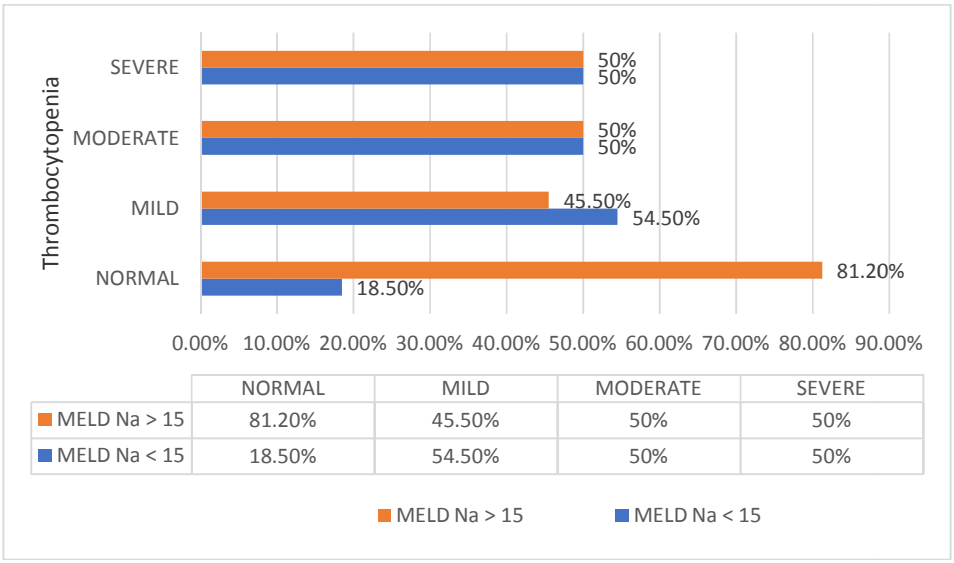


Fig. 2. Frequency of aetiology



	NORMAL	MILD	MODERATE	SEVERE
MELD Na > 15	81.20%	45.50%	50%	50%
MELD Na < 15	18.50%	54.50%	50%	50%

Fig. 3. Thrombocytopenia and MELD Na score

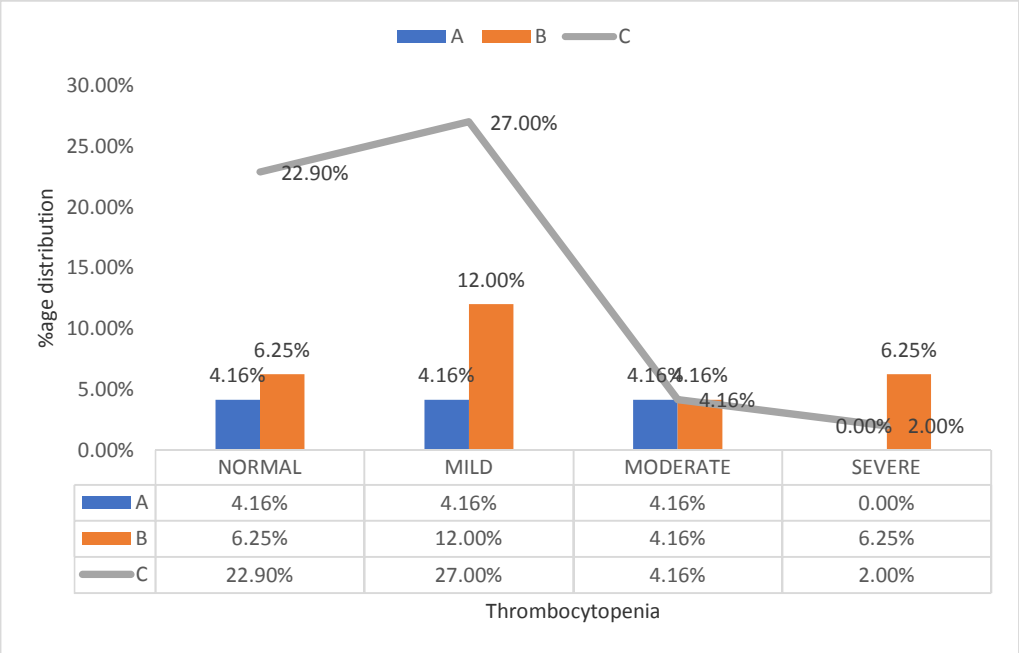


Fig. 4. Thrombocytopenia and C.P.class

The CLD is usually a hypo-coagulable state, yet thrombosis especially portal vein thrombosis is also equally seen. The platelets play a major role in the process of haemostasis and thrombosis [16]. Their main role is in 1. Primary haemostasis – the formation of loose platelet plug when platelets come in contact with injured vascular endothelium, the beginning of coagulation; 2. Secondary haemostasis or coagulation – the platelets provide a scaffold for various coagulative factors which by series of enzymatic reaction lead to the formation of fibrin from fibrinogen and stabilize the platelet plug. Previously this was described as "cascade" and now "cellular". Abnormal platelet number and function occur in CLD. The various mechanisms of thrombocytopenia are discussed earlier. Impairment of platelet function i.e. reduced adhesiveness and impaired aggregation can be due to intrinsic as well as extrinsic factors. The intrinsic factors include decreased thromboxane A2 synthesis, acquired storage pool defects, altered transmembrane signal transduction, quantitatively decreased glycoprotein 1b (Gly - 1b) and αIIβ3 receptors as a consequence of proteolysis. The extrinsic factors are abnormal high-density lipoproteins, reduced haemocrit and increased levels of endothelium derived nitic oxide and prostacyclin [16]. The reduction of platelet numbers and function may be compensated to some extent by an elevated Von Willebrand Factor (VWF). Thrombocytopenia in CLD is mostly mild to moderate degree and in general not associated with clinically significant severe bleeding. In CLD portal hypertension play a major role during bleeding and the role of haemostatic impairment is debatable. Tripodi A et al. investigated thrombin generation in the presence of coagulation inhibitors (thrombomodulin) in cirrhotic patients and found no significant difference from healthy controls [17]. The presently available diagnostic tests are of little use in identifying patients with high risk of bleeding. There is also lack of data in cases of prophylactic treatment with platelet concentrates before invasive procedures like liver biopsy or venous cannulation. The platelet count is not routinely corrected prior to liver transplantation. Giannini et al., expressed their optimism regarding the novel therapies for treating thrombocytopenia [18]. In their view "*the novel therapies are promising, although it remains to be established whether treating thrombocytopenia may help improve liver disease associated with coagulopathy*". Platelets also secrete many growth factors like PDGF (Platelet Derived Growth Factor), TGF - β (Transforming Growth Factor – beta). Their role in liver injury and fibrosis is unclear. The various haemostatic abnormalities that can occur in CLD are as follows [19,20].

1. Low platelet count: (thrombocytopaenia) the various possible mechanisms are already discussed.
2. Impaired platelet functions: (thrombocythaemia/thrombocytopathy) this is also discussed earlier.
3. Impaired coagulation: impaired synthesis of coagulation factors, vitamin K deficiency, dysfibrinogenaemia
4. Hypercoagulable state: increased factor VIII and VWF, low levels of protein C, S and antithrombin.
5. Excessive fibrinolysis: impaired clearance of t-PA (tissue Plasminogen Activator) and fibrinolytic enzymes, reduced synthesis of alpha 2 antiplasmin and TAFI (Thrombin Activatable Fibrinolysis Inhibitor).
6. Disseminated intravascular coagulation: This mechanism is debatable. This can be due to increased consumption of coagulative proteins and platelets, reduced clearance of activated clotting and reduced synthesis of coagulative factors, release of procoagulants from damaged hepatocytes.

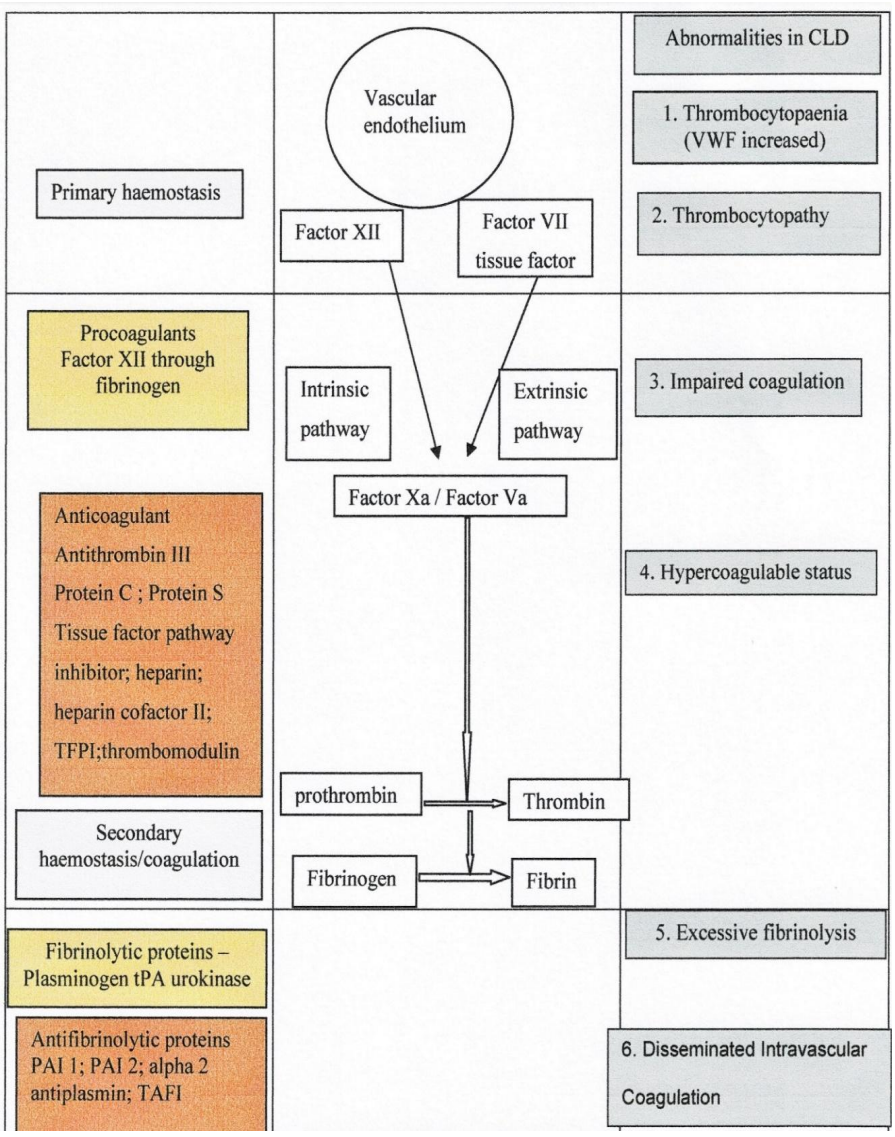


Fig. 5. Coagulation - concised

Abbreviations - PAI – 1 – Plasminogen Activator Inhibitor – 1; PAI – 2 - Plasminogen Activator Inhibitor – 2; TAFI – Thrombin Activatable Fibrinolysis Inhibitor; t PA – tissue Plasminogen Activator; TFPI – Tissue Factor Pathway Inhibitor

Traditionally CLD is considered to be a disease of hypo-coagulable state based on conventional tests of coagulation which are abnormal. The conventional tests measure mainly procoagulants factors. In CLD decreased levels of procoagulant factors are accompanied by "commensurate decrease" in levels of anticoagulants like antithrombin III and protein C. The exact haemostatic balance in vivo in CLD cannot be estimated accurately. Shah. A. et al., in their study reported that only 3 out of 128 CLD patients with abnormal coagulation parameters developed clinically significant bleeding [21]. Yet that was not statistically significant. ($p = 0.061$). In the comparative group of 180 CLD patients with normal coagulation profile who underwent low and high risk procedures, none developed bleeding complications. None of their patients received periprocedural corrections with plasma/platelets concentrates. They concluded that deranged conventional parameters did not predict clinically significant bleeding in CLD and invasive procedures could be safely carried out in CLD patients without prior correction of coagulation abnormalities. The periprocedural correction with transfusion also is a subject of debate [19]. Segal et al., also expressed the lack of evidence that abnormal coagulation tests predict the bleeding occurrence [22]. There can be pathogenetic mechanisms other than coagulation parameters such are 1. sequelae of portal hypertension. 2. endothelial dysfunction, 3. development of endogenous heparin like substances owing to bacterial infection or renal failure. Premkumar and Sarin reviewing the current concepts in coagulation profile described the dynamic nature of coagulation and the role of neutrophil activation with release of interleukins 1, 6 and tumour necrosis factor alpha (TNFα) [23]. In a stable CLD, haemostasis and coagulation pathways achieve a delicate "rebalance state" (new normal) which may be altered even by trivial insult.

This study has limitations. This study consisted of only 48 patients and as a hospital at a rural locality, the cases seen by us might not match with liver transplant units which handle cases in a very advanced stage with variety of complications. Even though many studies proved the positive correlation between platelets and advanced stage of CLD, only handful of studies reported negative correlation. This need not be due to selection bias only. The calculation of C.P.C. and MELD-Na Score do not incorporate platelet number where as APRI includes platelet number which can be correlated with stage of disease. The level of coagulative factors is determined by synthetic function of liver where as the number of platelets is determined by liver function (thrombopoitic factor) and also by effect of splenomegaly and portal hypertension. Platelets and other coagulative factors are intertwined and cannot be considered in isolation in the pathogenesis of coagulation in CLD. The dynamic nature of the disease which is already in a delicate rebalanced state has also to be considered. The Fig. 5. depicts the process of coagulation in a concise way.

6. CONCLUSION

Though this study is limited by small size, the negative observation we made can be scientifically explained. The coagulopathy of CLD is a challenging field. The potential area of research can be the evaluation measures and unfolding the dynamic nature of coagulation process.

CONSENT AND ETHICAL APPROVAL

Ethical clearance was granted by the institutional ethical committee (Study Reference Number: 97/Gastroenterology Faculty/IEC/2021). The guidelines issued by Indian Council of Medical Research were followed throughout the study. All the participants were explained the procedure of the study and informed written consent was taken.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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