Thromboelastography versus Conventional Coagulation Tests in Pediatric Chronic Liver Disease

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Abstract:

Introduction: The liver is the major site for synthesizing and clearing activated haemostatic factors. Chronic liver disease (CLD) is a progressive deterioration of liver function. Consequently, in patients with liver dysfunction, a complicated disorder of the haemostatic system arises, causing both bleeding and thromboembolic complications. In the majority of patients, the etiology of CLD remains uncertain.

Aim of the Work: To compare thromboelastography test (TEG) and conventional coagulation tests (CCTs) in children with Chronic liver disease (CLD) who are admitted to Assiut University Children's Hospital and to detect the advantages of TEG in predicting the risk of bleeding and assessing haemostasis.

Methodology: This cross-sectional study was carried out at the Hepatology Unit, Assiut University Children's Hospital, and was conducted on 33 patients from the beginning of June 2023 to the end of May 2024.

Results: In CLD patients, the female predominance was noted (M:F ratio 0.94:1). The most common manifestation was abdominal pain and pallor (63.6%). ROTEM showed delayed clotting (↑CT), reduced firmness (↓MCF), and stable lysis (L30), with low FIBTEM MCF indicating fibrinogen deficiency. Metabolic liver disease was the leading cause (27.3%). Moderate positive correlations were observed between aPTT and CT/CFT, PT and CT/CFT/α angle/MCF, and INR and CT/CFT. FIBTEM MCF also correlated with platelet count.

Conclusion: There was a decline in coagulation function with increasing liver disease severity. ROTEM parameters were prolonged in severe cases, correlating with fibrinogen levels.

Keywords: Liver, thromboelastography, hemostasis, pediatric.

Introduction:

The liver is the major site of synthesis of haemostatic factors and clearance of activated haemostatic factors **[1].** Chronic liver disease (CLD) is a progressive deterioration of liver functions for more than six months. Consequently, in patients with liver dysfunction, a complicated disorder of the haemostatic system arises, causing both bleeding and thromboembolic complications **[2].** The spectrum of etiologies is broad for chronic liver disease **[3].**

Signs and symptoms of CLD can be nonspecific, such as fatigue, anorexia, weight loss, or depend on the complication that the patient has developed. The three significant complications are: portal hypertension (e.g., esophageal varices, caput medusa, rectal hemorrhoids, and ascites), hepatocellular insufficiency (e.g., jaundice, coagulopathy, hepatic encephalopathy, and spontaneous bacterial peritonitis [SBP]), and hepatocellular carcinoma (HCC) **[3]**.

Physiological haemostasis includes primary haemostasis, coagulation cascade, and fibrinolysis, which are involved with various haemostatic factors. Haemostatic tests mainly include conventional coagulation (CCTs) and thromboelastography (TEG). CCTs mainly include PLT count, prothrombin time (PT),

activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer, and fibrinogen degradation products (FDP) concentrations. The PLT count reflects primary haemostasis through a quantitative assessment of PLT. PT and APTT reflect the coagulation cascade by assessment of pro-coagulants involved in the extrinsic and intrinsic pathways, respectively. FIB concentration reflects the coagulation cascade through a quantitative assessment of FIB. D-dimer and FDP concentrations reflect fibrinolytic activity by quantitatively assessing D-dimer and FDP **[2].**

TEG, a whole blood viscoelastic test, detects the clotting time, kinetics, and stability to more comprehensively evaluate haemostatic status by several parameters **[4].**

Aim of the Work:

1. To compare the thromboelastography test (TEG) and conventional coagulation tests (CCTs) in children with Chronic liver disease (CLD) who are admitted to Assiut University Children's Hospital.
2. To detect the advantages of TEG in predicting the risk of bleeding and assessing haemostasis.

Methodology:

This cross-sectional study was conducted at the Hepatology Unit, Assiut University Children's Hospital. It was conducted on 33 patients from the beginning of June 2023 to the end of May 2024.

Inclusion Criteria

All patients aged from 6 months to 18 years with chronic liver disease of any aetiology.

Exclusion Criteria

1. Patients who received transfusions of blood products within 48 hours before the blood sample collection.
2. Patients who were on therapy with antiplatelet drugs or anticoagulants.
3. Patients with a history of primary disease with coagulation disturbance (paroxysmal nocturnal hemoglobinuria, polycythemia, idiopathic thrombocytopenia, or haemophilia).
4. Patients with concomitant chronic kidney disease.

All cases included in the study were subjected to:

Full history taking: Include name, age, sex, family history of liver disease, history of present illness, history of recent blood transfusion, and change in mental status.

Full clinical examination:

General Examination: for pallor, jaundice, lower limb oedema, clubbing of fingers, ecchymosis, telangiectasia, spider naevi, and palmar erythema.

Systemic Examination:

A. Abdominal Examination:

- **Inspection:** for abdominal contour, site and shape of umbilicus, movement of abdominal wall, visible dilated veins, and genitalia.
- **Palpation:**
  - Superficial palpation for hotness, tenderness, rigidity, or abdominal masses.
  - Deep palpation:
    - Liver (right and left lobes): Size, surface (smooth or irregular), border (rounded or sharp), Consistency (soft, firm, or hard), Tender/not, and Pulsating/not.
    - Spleen: Size (in cm) below the costal margin at left mid-clavicular line, Consistency, and Notch (preserved or not).
- **Percussion:**
  - For the upper border of the right lobe of the liver.
  - For detection of ascites (positive shifting dullness – positive transmitted thrill).
- **Auscultation**

Laboratory Investigations:

- 7 ml of blood was withdrawn from all patients and divided into: one EDTA tube, one gel separating tube, and sodium citrate tubes.
- The following investigations were done for all patients:

1. Complete blood count (CBC): using an EDTA-containing tube on the Advia 2120i.
2. [Prothrombin time (PT), prothrombin concentration (PC), and international normalized ratio (INR)], activated partial thromboplastine time (APTT), fibrinogen, and D-dimer were measured using tri-sodium citrate containing tubes using Thromborel S reagent, Pathromtin SL reagent, DADE thrombin reagent, and innovance, respectively, on Sysmex CA-2500.
3. Liver function tests were measured using a gel separating tube on Advia 1800.
4. Kidney function tests were measured using a gel separating tube on Advia 1800.
5. Rotational Thromboelastometry (ROTEM) is a whole citrated blood haemostasis system using thromboelastometry methodology.

- INTEM, EXTEM, and FIBTEM are among the ROTEM assays that help investigate haemostasis.
  1. INTEM: for rapid assessment of clot formation, fibrin polymerization, and fibrinolysis via the intrinsic pathway.
  2. EXTEM: for rapid assessment of clot formation, fibrin polymerization, and fibrinolysis via the extrinsic pathway.
  3. FIBTEM: for rapid qualitative assessment of fibrinogen status without platelet effect.
- Thromboelastography measures several key parameters, including:

CT (clotting time), CFT (clot formation time), Alpha Angle (α), MCF (maximum clot firmness), and LY30 (lysis 30). By measuring these parameters, the ROTEM system provides a comprehensive picture of a patient's coagulation status.

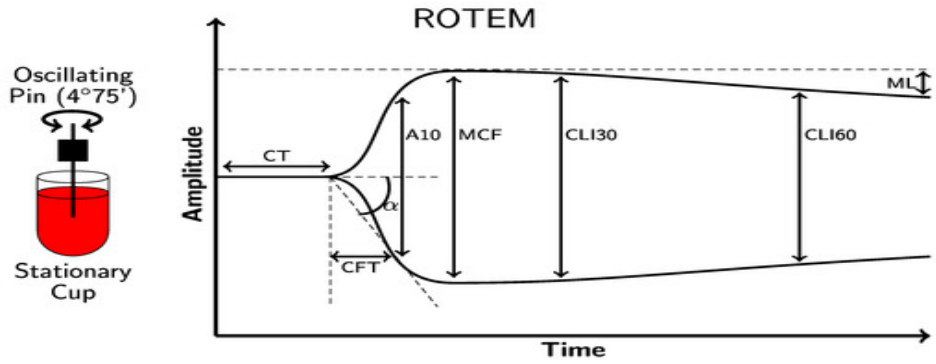


Figure [1] Depictions of the physiologic ROTEM® delta **[5]**

Ethical Considerations

The study was approved by the ethical committee of the Faculty of Medicine, Assiut University, Egypt (**Approval no. 04-2023-200155**), and written informed consent was taken from the participants' caregivers. The privacy of the patients during history taking and examination was assured. Confidentiality of all data was ensured.

Statistical Analysis:

Data were analyzed using SPSS v26. Categorical data were shown as frequencies and percentages, while numerical data were tested for normality (Shapiro-Wilk) and presented as mean ± SD or median (range).

T-test/Mann-Whitney and ANOVA/Kruskal-Wallis were used to compare two or more groups. Chi-square/Fisher's test compared proportions.

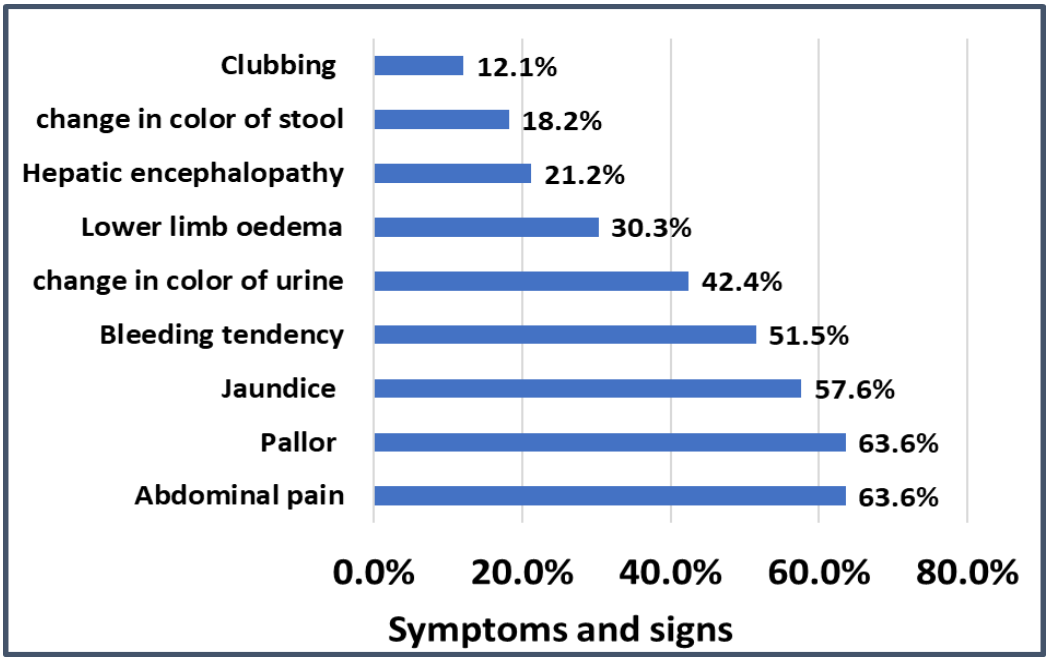
Pearson/Spearman correlations assessed relationships between continuous variables, with correlation classified from negligible (<0.2) to perfect (=1).

Significance was set at $P < 0.05$, and highly significant at $P < 0.001$.

Results:

A total of 33 patients with CLD, with a mean age of 8.0±4.09 years, ranging from 7 months to 15 years, 48.5% were males and 51.5% were females. 18.2 % of them have a positive family history of liver disease.

Clinical data among studied patients with CLD **are shown in Figures (2,3):**



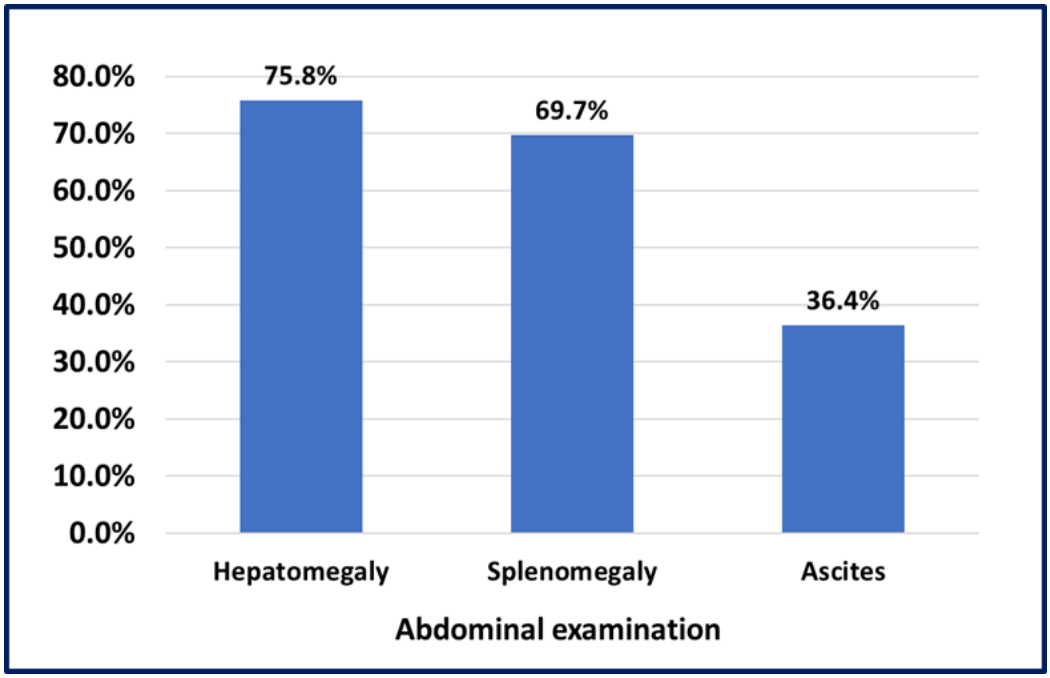


Figure [3] Abdominal examination among studied patients with CLD

Our patients' laboratory results revealed various measurements reflecting different physiological parameters, as shown in **Table [1].**

	Cases (N=33), Mean ± SD or SE /median (range)
CBC	
- WBCs	5.30 (0.98-21.70) $x10^3$/ul
- RBCs	3.92±0.92 (2.00-5.45) $x10^6$/ul
- HB	10.06±2.38 (4.5-13.9) g/dl
- HCT	30.80±6.23 (15.6-38.9) %
- PLT	97.00 (24-581) $x10^3$/ul
- MPV	8.35±1.11 (6.04-10.30) Fi
Coagulation profile	
- PT	16.10±6.19 (10.4-45.6) sec
- PC	69.37±26.38 (17.4-151.0) %
- INR	1.36±.55 (.82-4.02)
- aPTT	41.23±15.59 (21.2-108.3) sec
- D-dimer	1.48 (.19-35.20) mg/dl
- Fibrinogen	1.90±.71(.62-4.10) g/l
Liver functions	
- Total bilirubin	1.70 (0.20-42.00) mg/dl
- direct bilirubin	0.90 (0.08-28.00) mg/dl
- Albumin	3.25±0.80 (1.0-4.4) g/l
- ALT	70.00 (17-3442) u/l
- AST	77.00 (15-3756) u/l
- ALP	225.00 (55-912) u/l
Kidney functions	
- BUN	3.61±1.34 (1.2-6.9) mmol/l
- Creatinine	0.30 (0.1-1.0) mg/dl

The ROTEM results for patients with CLD demonstrate a complex coagulation profile in CLD patients, characterized by prolonged clot initiation (CT), reduced clot firmness (MCF), and preserved clot stability (L30), with significant variability among individuals. The particularly low FIBTEM MCF suggests a role for fibrinogen deficiency in clot instability.

INTEM, EXTEM, and FIBTEM Findings are shown in Table [2].

Table (2) ROTEM results for patients with CLD

Thromboelastography	**Cases (N=33), Mean ± SD or SE /median (range)**
INTEM	
- CT	163.67±52.02 (31-287) sec
- CFT	114.00 (27-429) sec
- α angel	69.52±10.44 (40-90) °
- MCF	52.52±13.49 (25-88) mm
- L30	93.18±10.02 (70-100) %
EXTEM	
- CT	60.54±20.47 (20.00-120.00) sec
- CFT	162.00(29.00-511.00) sec
- α angel	65.81±11.09 (39.00-88.00) °
- MCF	50.75±13.73 (24.00-85.00) mm
- L30	92.36±9.89 (70.00-100.00) %
FIBTEM	
- MCF	7.00 (2-34) mm

The most common cause of CLD among studied patients was metabolic liver disease (27.3%) like Wilson's, Glycogen storage disease, Trosinemia, followed by autoimmune hepatitis (24.2%), idiopathic Liver cirrhosis (18.2%), budd-Chiari syndrome (9.1%), biliary atresia (6.1%), congenital hepatic fibrosis (6.1%) and one case (3.0%) with chronic hepatitis, intrahepatic biliary obstruction and progressive familial intrahepatic cholestasis **as showed in Figure [4]:**

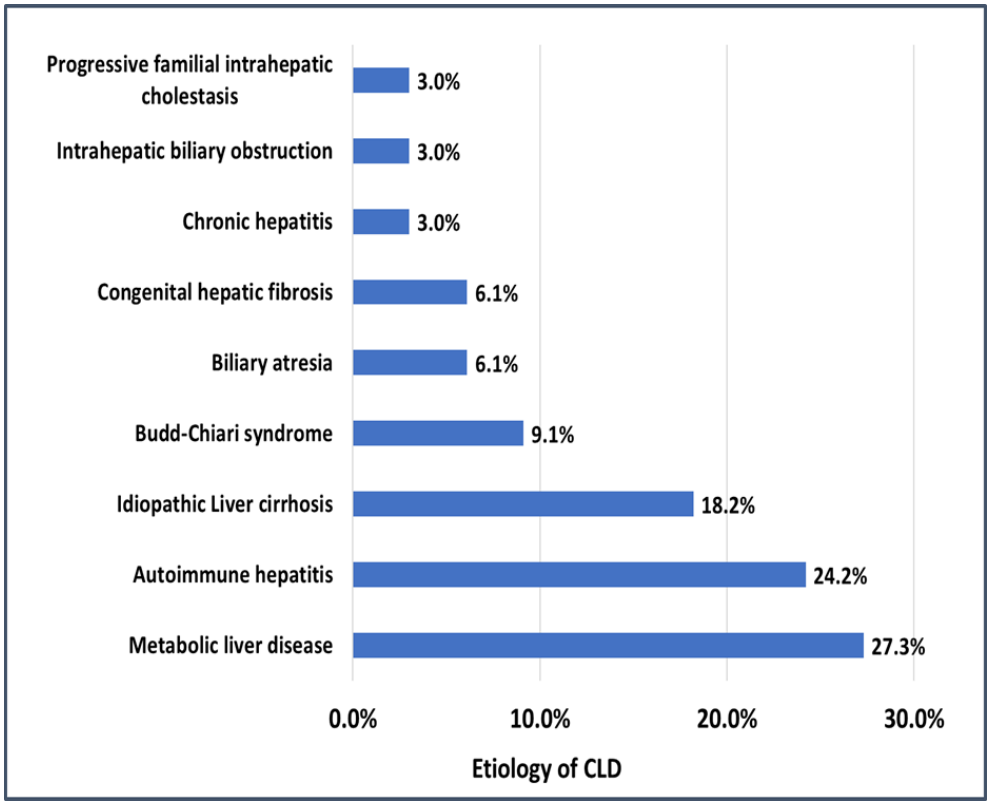


Figure (4): Etiology of CLD among studied patients

Correlation between aPTT and INTEM parameters:

There was statistically significant moderate positive correlation between aPTT with CT (r=0.514, p value=0.002), moderate positive correlation with CFT (r=0.559, p value=0.001), moderate negative correlation with α angle (r= -0.488, p value=0.004), and moderate negative correlation with MCF (r= -0.475, p value=0.005), however, there was no statistically significant correlation between aPTT with Lys 30 as showed in **Table (3):**

Table (3): Correlation between aptt and INTEM parameters (CT, CFT, alpha angle, MCF, Lys 30) among studied patients with CLD

	Aptt	
	R	**P-value**
INTEM		
- CT	0.514	0.002
- CFT	0.559	0.001
- α angle	-0.488	0.004
- MCF	-0.475	0.005

- Lys 30	0.006	0.972

Correlation between PT, PC, and INR with EXTEM parameters:

There was statistically significant moderate positive correlation between PT with CT (r=0.401, p value=0.021), moderate positive correlation with CFT (r=0.611, p value<0.001), moderate negative correlation with α angle (r= -0.536, p value=0.001), and moderate negative correlation with MCF (r= -0.585, p value<0.001), however, there was no statistically significant correlation between PT with Lys 30.

There was statistically significant mild negative correlation between PC with CT (r= -0.349, p value=0.049), moderate negative correlation with CFT (r= -0.437, p value=0.011), moderate positive correlation with α angle (r=0.512, p value=0.002), and moderate positive correlation with MCF (r=0.676, p value<0.001), however, there was no statistically significant correlation between PC with Lys 30

There was statistically significant moderate positive correlation between INR with CT (r=0.411, p value=0.017), moderate positive correlation with CFT (r=0.602, p value < 0.001), moderate negative correlation with α angle (r= -0.527, p value=0.002), and moderate negative correlation with MCF (r= -0.572, p value=0.001), however, there was no statistically significant correlation between INR with Lys 30 **as showed in Table (4):**

Table (4): Correlation between PT, PC, INR, and EXTEM parameters (CT, CFT, alpha angle, MCF, Lys 30) among patients with CLD

	PT		**PC**		**INR**	
	R	***P-value***	**R**	***P-value***	**r**	***P-value***
EXTEM						
- CT	0.401	0.021	-0.349	0.049	0.411	0.017
- CFT	0.611	<0.001	-0.437	0.011	0.602	<0.001
- Alpha angle	-0.536	0.001	0.512	0.002	-0.527	0.002
- MCF	-0.585	<0.001	0.676	<0.001	-0.572	0.001
- Lys 30	-0.046	0.801	0.107	0.552	-0.042	0.816

Correlation between FIBTEM and fibrinogen, D-dimer, PT, PC, INR, aPPT, and platelet count:

There was statistically significant moderate positive correlation between FIBTEM with fibrinogen (r=0.630, p value<0.001), mild negative correlation with D-dimer (r= -0.361, p value=0.039), moderate negative correlation with PT (r= -0.435, p value=0.011), moderate positive correlation with PC (r=0.448, p value=0.009), moderate negative correlation with INR (r= -0.418, p value=0.015), moderate negative correlation with aPPt (r= -0.456, p value=0.008).there was statistically significant moderate positive correlation between FIBTEM with platelets count **as showed in Table (5):**

Table (5): Correlation between FIBTEM (MCF) and fibrinogen, D-dimer, PT, PC, INR, aPPT, and platelet count among patients with CLD

	FIBTEM (MCF)	
	R	**P-value**
- Fibrinogen	0.630	<0.001
- D-dimer	-0.361	0.039
- PT	-0.435	0.011
- PC	0.448	0.009

- INR	-0.418	0.015
- aPPt	-0.456	0.008
- Platelets count	0.587	<0.001

Discussion

This study included 33 patients with CLD; their mean age was 8.0±4.09 and ranged from 7 months to 15 years, 16 (48.5%) were males, and 17(51.5%) were females. The male-to-female ratio is .094:1 with female predominance. 6 (18.2 %) of them have a positive family history for chronic liver disease. **Sokol et al.'s** study included 56 children [aged 1 mo-l0y, 38.9 ± 34.4 months (mean ± SD); 29 males, 27 females] **[6].**

Regarding clinical manifestations in our study, the most common clinical manifestations observed in the patients were abdominal pain and pallor, which were present in 63.6% of the cases, followed by jaundice in 57.6%. Bleeding tendency was noted in 51.5%. The most common presenting complaint in children, as noted by **Dhole et al.,** was jaundice, followed by hepatosplenomegaly and abdominal distension **[7].**

Our patients' laboratory results revealed various measurements reflecting different physiological parameters. For coagulation studies, the Prothrombin Time (PT) had a mean value of 16.10±6.19 sec, ranging between 10.4 and 45.6 sec. The prothrombin concentration had a mean of 69.37±26.38 %, ranging from 17.4 to 151.0 %. The International Normalized Ratio (INR) had a mean of 1.36±0.55, ranging from 0.82 to 4.02. The activated Partial Thromboplastin Time (aPTT) had a mean of 41.23±15.59 sec, with values ranging from 21.2 to 108.3 sec. The D-dimer had a median value of 1.48 mg/dl, ranging between 0.19 and 35.20 mg/dl. Fibrinogen levels had a mean of 1.90±0.71g/l, ranging from 0.62 to 4.10 g/l.

Regarding liver function tests, our study was consistent with findings by **Lisman et al.,** who emphasized the role of coagulation factor deficiencies in cirrhotic patients **[8].**

Our study reveals specific coagulation characteristics, as it reports a mean INTEM CT of 163.67 seconds, indicating a prolonged initiation phase of coagulation. A study by **Bedreli et al.** observed that patients with Acute-on-Chronic Liver Failure (ACLF) exhibited significant prolongation in CT over time, reflecting a hypocoagulable state. The mean EXTEM CT is 60.54 seconds, within the normal range, suggesting a relatively preserved extrinsic pathway. The study by **Bedreli et al.** noted that while ACLF patients showed prolonged CT in EXTEM assays, those with stable cirrhosis did not exhibit significant changes, aligning with the current findings **[9].**

Median INTEM CFT is 114 seconds, indicating delayed clot formation. **Kampelos et al.** reported that in patients with acute-on-chronic liver failure (ACLF), ROTEM parameters, including INTEM CFT, showed significant deterioration towards hypocoagulability at 24 and 48 hours post-admission compared to baseline. Specifically, the study reported a statistically significant prolongation of INTEM CFT ($P<0.001$) over these time points in the ACLF group, indicating a progressive delay in clot formation kinetics. While this study focuses on a specific patient population, it provides a clear example of how serial monitoring of INTEM CFT over 48 hours can reveal dynamic changes in coagulation status, with prolongation signifying delayed clot kinetics and a potential increase in bleeding risk. Such changes should be interpreted in conjunction with the overall clinical picture and other coagulation parameters. **[10].**

Median EXTEM CFT of 162 seconds, also suggesting delayed clot formation.

Mean of INTEM α-Angle is 69.52°, reflecting reduced fibrin polymerization.

The study by **Bedreli et al.** found that ACLF patients had a significant decrease in α-angle over time, indicating impaired fibrin formation **[9].**

Mean of EXTEM α-Angle 65.81°, suggesting similar impairment. Consistent with findings in ACLF patients, where a reduced α-angle was associated with a hypocoagulable profile **[9].**

Mean of INTEM MCF is 52.52 mm, indicating decreased clot strength.

Bedreli et al. observed a decline in MCF among ACLF patients, correlating with disease severity and higher mortality. Mean of EXTEM MCF is 50.75 mm, reinforcing the observation of weakened clot integrity. Similar reductions in EXTEM MCF were noted in ACLF patients, reflecting compromised hemostatic function **[9].**

Median of FIBTEM MCF is 7 mm, indicating significant fibrinogen deficiency or dysfunction. **Bedreli et al.** highlighted that decreased FIBTEM MCF is associated with severe coagulopathy in ACLF patients, necessitating careful management **[9].**

In our study, the most common cause of CLD among studied patients was metabolic liver disease (27.3%) like Wilson's, Glycogen storage disease, Trosinemia, followed by autoimmune hepatitis (24.2%), idiopathic Liver cirrhosis (18.2%), budd-Chiari syndrome (9.1%), biliary atresia (6.1%), congenital hepatic fibrosis (6.1%) and one case (3.0%) with chronic hepatitis, intrahepatic biliary obstruction and progressive familial intrahepatic cholestasis. **Khan et al.** reported that the causes of CLD were: Infections- Viral Hepatitis (B and C), parasitic (Chronic Schistosomiasis), Alcoholic& Non-Alcoholic Steatohepatitis (NASH), Cryptogenic, Metabolic(α1-antitrypsin deficiency, Wilson's Disease, Hemochromatosis), biliary obstruction (Primary biliary cirrhosis, sclerosing cholangitis), venous outflow obstruction (Budd Chiari Syndrome, veno occlusive disease), Drugs and Cardiac causes Congestive Heart Failure (CHF) and constrictive Pericarditis) **[11].**

Regarding the Correlation between aPTT and INTEM Parameters **in our study**, the observation of a moderate positive correlation between aPTT and INTEM clotting time (CT) (r=0.514, p=0.002) is consistent with findings by **De Pietri et al.** They reported that in patients with advanced liver disease, there was a significant correlation between aPTT and ROTEM parameters, suggesting that prolonged aPTT reflects changes in intrinsic coagulation pathways detectable by ROTEM **[12].**

In our study, there are also moderate positive correlations with CFT (r=0.559, p value=0.001), moderate negative correlation with α angle (r=-0.488, p value=0.004), and moderate negative correlation with MCF (r=-0.475, p value=0.005); however, there was no statistically significant correlation between aPTT and Lys 30. These findings align with **Theusinger et al.,** who investigated the relationship between standard coagulation tests and ROTEM parameters during major surgeries with hemorrhage. They reported that aPTT showed moderate to strong correlations with INTEM parameters, including CFT, α-angle, and MCF. Specifically, aPTT correlated significantly with INTEM CFT (r = 0.65), α-angle (r = -0.72), and MCF (r = -0.70), indicating that prolonged aPTT is associated with delayed clot formation and reduced clot strength **[13].**

Supporting evidence to **our findings** of moderate positive correlations between PT and EXTEM CT (r=0.401, p=0.021), as well as moderate negative correlations with the α-angle (r=-0.536, p=0.001) that align with the study by **Singh et al.** observed that early ROTEM parameters correlated well with conventional coagulation tests, suggesting

that ROTEM can reflect alterations in the extrinsic pathway as measured by PT and INR **[14].**

In our study, regarding Correlation between FIBTEM and Fibrinogen, D-dimer, PT, PC, INR, aPTT, and Platelet Count, the finding of a significant positive correlation between FIBTEM maximum clot firmness (MCF) and fibrinogen levels ($r=0.630$, $p < 0.001$) is supported by **Singh et al.,** who demonstrated early ROTEM parameters correlated well with fibrinogen concentrations in patients undergoing liver transplantation, suggesting FIBTEM as a reliable indicator of fibrinogen status **[14].**

Conclusion:

This study provides valuable insights into coagulation abnormalities in pediatric patients with chronic liver disease (CLD). It highlights a progressive decline in coagulation function with increasing disease severity. The study also showed that ROTEM parameters were significantly prolonged in severe CLD cases, with a positive correlation between clot firmness and fibrinogen levels.

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