Research Article

The Role of Rotational Thromboelastometry in Early Prediction of Bleeding Esophageal Varices in Patient with Advanced Cirrhosis

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Abstract
Background: Bleeding Esophageal varices (EVs) is the most clinical complication of cirrhosis, Endoscopic surveillance of EVs in patients with cirrhosis is expensive and uncomfortable for many patients. Therefore, there is a particular need for noninvasive predictors for EVs. The aim of our study was to examine the Rotational Thromboelastometry (ROTEM) abnormalities in patients with acute variceal bleeding in relation to those without to explore if these ROTEM abnormalities have a role in the prediction of variceal hemorrhage. **Methods:** Our study included a group of HCV-related cirrhotic patients with acute variceal bleeding (20 patients). This group of patients was compared to a group of HCV-related cirrhotic patients without variceal bleeding (20 patients). **Results**: ROTEM tracing results in our study patients showed hypocoagulability. CFT(clot formation time) was more prolonged in patients with variceal bleeding than those without and values of A10(amplitude at 10miutes were lower in patients with bleeding varices group in INTEM and EXTEM assays, a significant reduction in MCF(maximum clot firmness) results in G I patients compared to those of G II. **Conclusion**: Majority of ROTEM tracing results in our study patients showed hypocoagulability which correlated to liver dysfunction. Platelets, fibrinogen level and coagulation factors are the most important factors which affect global hemostasis. Prolonged CFT/EXTEM and CFT/INTEM were independently associated with variceal bleeding in cirrhotic patients.
Key Words: Bleeding Esophageal varices-Hemostasis- Rotational thromboelastometry.
All authors have no conflict of interest.

Introduction
Bleeding EVs is the most clinically relevant complication of cirrhosis and still carries a mortality of up to 30% within 6 weeks of the bleeding episode. The liver plays a central role in the production of clotting and fibrinolytic factors, and coagulation abnormalities are one of the cardinal features of liver disease[1,2]. Endoscopic surveillance of EVs in patients with cirrhosis is expensive and uncomfortable for many patients. Therefore, there is a particular need for noninvasive predictors for EVs[3]. The altered coagulation parameters in patients with liver cirrhosis results in a state of "rebalanced hemostasis" and patients are just as likely to clot as they are to bleed. Commonly used coagulation tests do not always reflect this new state and can, therefore, be misleading. Point-of-care tests such as thromboelastometry more reliably predict the risk of bleeding in these patients and in addition may provide quicker turnaround times compared to routine tests[4].

ROTEM is a point-of-care analyser which uses a citrated whole blood sample and analyses the viscoelastic properties of the blood as it clots. A panel of up to 4 simultaneous tests can be performed to identify clot formation, propagation, and lysis as well as the nature of any coagulopathy in real time. The utility of ROTEM has been well established in the setting of liver transplantation[5], cardiopulmonary bypass[6], obstetrics[7] and trauma[8], while its role in other clinical scenarios is still matter of debate. Bleeding gastro-esophageal varices may be an ideal situation where ROTEM may be useful.

Material and Methods
1. Routin laboratory Investigations: Using the commertially available kits, all patients underwent full laboratory investigation including complete blood count, INR and aPTT, complete liver and renal function tests and viral markers

2. Rotational Thromboelastometry (ROTEM) tests: ROTEM was performed by ROTEM Delta (Tem International, Munich, Germany).

3. Imaging studies: Abdominal ultrasound with Doppler analysis was performed by the ultrasound machine, Toshiba Xario 100, Japan with 3-5MHz tranceducer and Plain chest-X ray (postero/anterior view) to exclude chest infection as a source of sepsis.

***4. Esophago-gastro-duodenosopy*:** EVs were examined and graded according to the criteria mentioned by Thakeb et al., (1988)

Statistical analysis: Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS software version 25).

Results

Table (1): Routine Laboratory Characteristics of Liver Cirrhotic Patients with Acute Variceal Bleeding Versus Those without.

Variable	Cirrhotic Patients with Variceal Bleeding (GI) (no.=20)	Cirrhotic Patients without Variceal Bleeding (GII) (no.=20)	p value
Hemoglobin (gm/dl) Range: *Mean ± SD*:	(6.1-11.7) 9±1.4	(8.4-15) 12±2	***<0.001***
Hematocrit (%) Range: *Mean ± SD*:	(17.6-34) 27.5±4.8	(28.7-50) 40.9±6.5	***<0.001***
Platelets{(1x10^3/µl)} *Median IQR:*	72 (58.3-108.3)	115 (64.3-193)	***0.034***
Total Bilirubin(mg/dl) Range: *Mean ± SD:*	(1-4.9) 2.5±1.1	(0.4-1.5) 0.9±0.3	***<0.001***
ALT(IU/L) *Median IQR:*	79 (52.8-115)	22 (17.3-30)	***<0.001***
AST(IU/L) *Median IQR:*	93 (46.8-180)	37.5 (23.3-41.5)	***<0.001***
Albumin(gm/dl) Range: *Mean ± SD*:	(2.1-5) 2.9±0.7	(3.2-5.4) 4±0.6	***<0.001***
INR *Median IQR:*	1.3 (1.3-1.6)	1.2 (1-1.5)	***0.049***
aPTT(seconds) Range: *Mean ± SD*:	(28-88) 45±15	(28-63) 37.9±9.4	*0.081*
Serum creatinine(mg/dl) Range: *Mean ± SD*:	(0.6-1.9) 1.1±0.4	(0.5-1.2) 0.8±0.2	***0.008***

G: Group; no.: Number of patients; ALT: Alanine aminotransferase ; AST: Aspertate transaminase; INR: International normalization ratio; aPTT: Activated partial thromboplastin time; SD: Standard deviation; IQR: Interquartile range Bold values mean significant results

Table (2): ROTEM Parameters in Liver Cirrhotic Patients with Acute Variceal Bleeding Versus Those without.

Variable	Cirrhotic Patients with Variceal Bleeding (GI)	Cirrhotic Patients without Variceal Bleeding (GII)	P value
	no.=20	no.=20	
[1]**CT (secs.)**			
EXTEM			
Median (IQR)	56.5 (47.3-74.8)	53.5 (46.3-59.5)	*0.234*
INTEM			
Median (IQR)	181(137.5-225)	174.5 (162.5-205)	*0.989*
[1]**CFT (sec.)**			
EXTEM			
Median (IQR)	392 (200.5-796)	195 (123-309)	***0.008***
INTEM			
Median (IQR)	251 (170-402)	156 (100.5-207)	***0.009***
[2]**α –angle (degree)**			
EXTEM			
Range:	(18-83)	(41-79)	***0.007***
Mean ± SD:	52.7±17.4	65.5±9.9	
INTEM			
Range:	(31-89)	(32-82)	*0.067*
Mean ± SD:	57.6±14.3	65.8±13	
[2]**A10 (mm.)**			
EXTEM			
Range:	(8-50)	(11-68)	***0.001***
Mean ± SD:	25.1±11.5	39.1±12.7	
INTEM			
Range:	(15-67)	(9-74)	***0.012***
Mean ± SD:	31.7±11.9	43.1±15.3	
[1]**MCF (mm.)**			
EXTEM			
Median (IQR)	30 (22.5-43)	45 (40-58)	***0.002***
INTEM			
Median (IQR)	37.5 (31-46)	47 (40-59)	***0.014***
FIBTEM			
Median (IQR)	10 (9-13.8)	11.5 (7.3-15.5)	*0.447*
[1]**ML (%)**			
EXTEM			
Median (IQR)	0 (0-0)	0 (0-3.5)	*0.319*
INTEM			
Median (IQR)	0 (0-0)	0 (0-2)	*0.606*

G: Group; no.: Number of patients; CT: Clotting time; CFT: Clot formation time; α: Alpha; A10: Amplitude at 10 minutes; MCF: Maximum clot firminess; ML; Maximum lysis; IQR: Interquartile range; SD: Standard deviation

Reference values: CT/EXTEM= 38–79 seconds; CT/INTEM= 100–240 seconds; CFT/EXTEM= 34–159 seconds; CFT/INTEM= 30–110 seconds; α angle/EXTEM= 63–83°; α angle/INTEM= 70–83°; A10/EXTEM= 43-65millimeter; A10/INTEM= 44-66 millimeter; MCF/EXTEM= 50–72 millimeter; MCF/INTEM= 50–72 millimeter; MCF/FIBTEM= 9-25 millimeter; ML <15% (stable clot), ML>15% (clot breakdown by fibrinolysis).

1= Data are expressed as median (IQR) and compared by Mann-Whitney U-test.

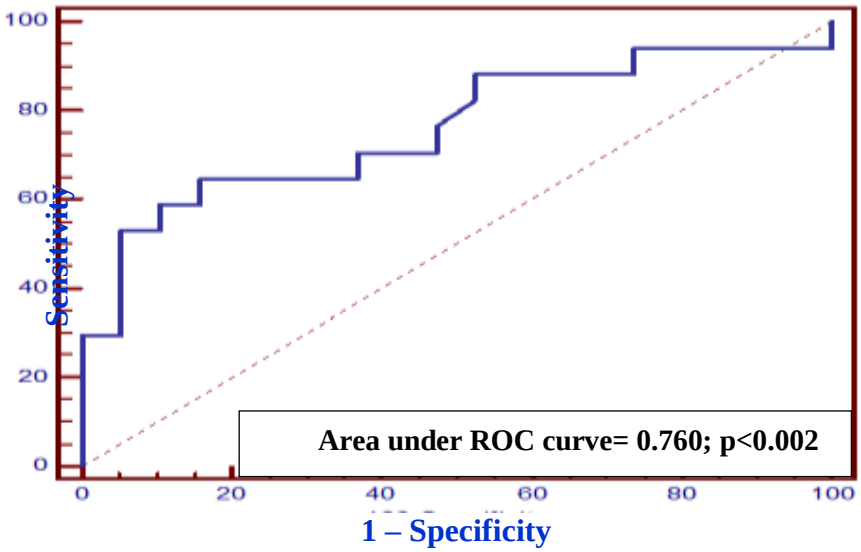
2= Data are expressed as mean ± SD and compared by Student's t-test.

Bold values mean significant results.

Cirrhotic patients with variceal bleeding had statistically significant lower levels of hemoglobin (p<0.001), hematocrit (p<0.001), platelet count (p=0.034), and serum albumin (p<0.001), while they had statistically significant higher levels of total bilirubin (p<0.001), ALT (p<0.001), AST (p<0.001), INR (p=0.049), and serum creatinine (p=0.008) when compared to cirrhotics without variceal bleeding. There was no significant difference between both groups as regard aPTT plasma levels, **Table 1.**

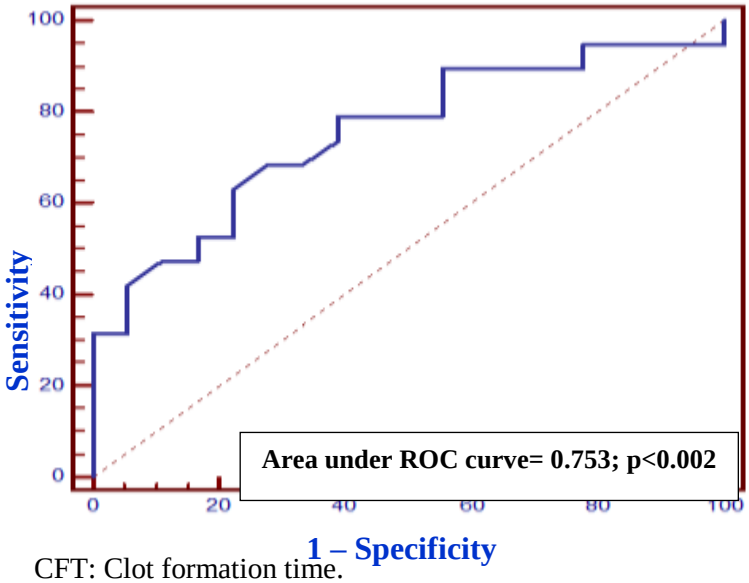
Regarding the ROTEM parameters, CFT was more prolonged in patients with variceal bleeding than those without (p=0.008) for CFT/EXTEM, and (p=0.009) for CFT/INTEM. The degree of α angle in EXTEM was lower in GI than GII (p<0.007); while there was no significant difference in INTEM assay. Values of A10 were lower in patients with bleeding varices than those without (p=0.001) for A10/EXTEM, and (p=0.012) for A10/INTEM. Both EXTEM and INTEM displayed a statistically significant reduction in MCF results of G I patients compared to those of G II (p=0.002), and p=0.014, respectively).

The AU-ROC curve for CFT/ EXTEM was 0.760 (95% CI= 0.589-0.886, P= 0.002). At a cut-off value of >316 sec., the sensitivity was 64.71% and the specificity was 61.11%. It showed PPV of 78.95 %, NPV of 72.7 % and an accuracy of 75 %. AU-ROC curve of CFT/ INTEM was 0.753 (95% CI= 0.584-0.879, P= 0.002). At a cut-off value of >167 sec., the sensitivity was 78.9% and the specificity was 61.1%. It showed PPV of 68.2 %, NPV of 73.3 % and an accuracy of 70.3 %**, Figures 1, 2**.



CFT: Clot formation time.

Figure (1): **Receiver Operator Characteristic (ROC) Curve for CFT/EXTEM in Cirrhotic Patients**



CFT: Clot formation time.

Figure (2): Receiver Operator Characteristic (ROC) Curve for CFT/INTEM in Cirrhotic Patients.

Discussion

In the current study, most of our patients had isolated decrease in platelet count with or without impairment in platelet function, cirrhotic patients with bleeding EVs who had higher frequency of grade III and IV EVs also had significantly lower median of platelet count compared to the other group. In accordance with our results (Nouh et al., (2018)[10] found that the severity of thrombocytopenia increases with higher grades of EVs. CFT in INTEM and EXTEM was prolonged,

In this study, MELD (Model for End stage Liver Disease) score exhibited a significant direct correlation with CFT in both EXTEM and INTEM and a significant inverse correlation with MCF/ FIBTEM. Our findings indicated that platelet disorder, but not fibrinogen was the rate-limiting factor to determine clot firmness, Tripodi et al., (2009)[11] found similar results.

In our study no patients were identified to have fibrinolysis, the idea of balanced fibrinolysis reflected by normal maximum lysis percentage in EXTEM and INTEM pathways. Similar results were noted in stable cirrhosis by Lisman et al., (2001) and Kleinegris et al., (2014)[12,13].

In contrast, Colluci et al., (2003)[14] and Rijkan et al., (2012)[15] observed a significant increase in fibrinolysis potential but they concluded that their finding remain in vitro observation without direct implication for clinical practice. ROTEM is specific but seldom sensitive for diagnosis of fibrinolysis as stated by Roullet et al., (2018)[16]. Furthermore we need more confirmation to our results by direct assessment for some pro- and anti-coagulants and/or thrombin generation assay.

Conclusions

ROTEM results revealed a hypocoagulable state in cirrhotic patients with and without bleeding EVs, however, it was more evident in cirrhosis bleeders. Platelet count and function are the most important factors which affect clot formation. CFT/EXTEM and CFT/INTEM might be useful as rapid and non-invasive tool to predict variceal bleeding in cirrhosis patients and also, might be helpful in assessment of disease severity and prognosis in cirrhosis patients.

Recommendations

Our results may offer clues for decrease morbidity and mortality rates of variceal hemorrhage via early detection and targeted correction of these ROTEM abnormalities in cirrhosis patients and further large prospective studies are needed to validate our results.

Limitations of the study:

There are potential limitations of our study which include relatively small sample size, lack

of vital informations such as plasma concentration of fibrinogen, non-availability of platelet mapping to evaluate platelet function and being the first study concerning this issue, ROTEM results have not been yet validated.

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