



Original Article

Clinical Validation of Global Coagulation Tests to Guide Blood Component Transfusions in Cirrhosis and ACLF

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Abstract

Background and Aims: Patients with cirrhosis and acute-on-chronic liver failure (ACLF) may have bleeding complications and need for invasive procedures. Point-of-care (POC) coagulation tests like thromboelastography (TEG) and Sonoclot may be better for guiding patient management than the standard coagulation tests (SCTs), like prothrombin time, platelet count and international normalized ratio. **Methods:** We prospectively compared and validated the POC tests and SCTs in 70 persons with ACLF and 72 persons with decompensated cirrhosis who had clinical bleeding and checked for episodes of re-bleeding and transfusion requirements. We assessed pre-procedure requirement of blood components when correction was done based on an SCT or POC strategy. **Results:** Episodes of bleeding were seen in 45% and 28% of ACLF and cirrhosis patient, respectively ($p=0.036$), with the major site of bleeding being gastrointestinal (31% and 16%, respectively). Platelet counts correlated with TEG-maximum amplitude in cirrhosis ($p=0.045$) and prothrombin time correlated positively with TEG-reaction (R) time ($p=0.032$), TEG-Clot kinetics (K) time ($p=0.042$), Son-activated clotting time ($p=0.038$) and negatively with clot rate ($p=0.043$) in ACLF, making these correctable target variables in POC transfusion algorithms. Of 223 procedures, transfusion of fresh frozen plasma and platelet concentrate was reduced

by 25% ($p=0.035$) and 20.8% ($p=0.045$) by using a POC strategy in 76 patients. Correction of deranged Son-activated clotting time and TEG-reaction time was noted in 68% and 72% after 24 h of fresh frozen plasma transfusion in ACLF and 85% and 80% in cirrhosis, respectively. **Conclusions:** Our study clinically validates that POC tests can better detect coagulation defects and transfusion thresholds in ACLF and cirrhosis, whereas use of conventional tests appear to be less suitable in patients with clinical bleeding. **Trial Registration:** NCT04332484.

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Introduction

Standard coagulation tests (SCTs) like prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) and platelet count have been traditionally used to assess the hemostatic system in patients with cirrhosis of liver and acute-on-chronic liver failure (ACLF). However, these may not be accurate in cirrhosis, as there is deficiency of both pro-coagulants and anti-coagulants. Point-of-care (POC) viscoelastic coagulation devices, including those for thromboelastography (TEG) and the rotational thromboelastometer (ROTEM) and Sonoclot, are now being used increasingly for perioperative monitoring and for guiding blood component transfusion in patients with ACLF, variceal bleeding, or those undergoing liver transplantation. Fisher *et al.*¹ showed lower thrombin generation potential in ACLF compared to cirrhosis with acute decompensation. Studies in ACLF patients have also shown that viscoelastic tests may guide coagulation factor replacement effectively.^{2,3} We previously described the dynamic changes in specific coagulation factors, like Factor VIII, von-Willebrand factor (vWF), protein C and antithrombin III, in addition to standard coagulation tests (SCTs) and TEG in relation to presence of sepsis/ SIRS and bleeding events in ACLF.⁴ Algorithms for management of peri-transplant coagu-

Keywords: Coagulation; Cirrhosis; ACLF; Validation; Sonoclot; Thromboelastography.

Abbreviations: ACLF, acute-on-chronic liver failure; ACT, activated clotting time; aPTT, activated partial thromboplastin time; ATIII, antithrombin III; CI, confidence interval; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; CR, clot rate; CTP, Child-Turcotte-Pugh score; FFP, fresh frozen plasma; GCT, global coagulation tests; GI, gastrointestinal; HR, hazard ratio; INR, international normalized ratio; K, clot kinetics; Lys30 and Lys 60, lysis at 30 or 60 minutes, respectively; MA, maximum amplitude; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium; PAI, plasminogen activator inhibitor; R, reaction time; ROTEM, rotational thromboelastometry; SCT, standard coagulation test; SIRS, systemic inflammatory syndrome; TEG, thromboelastography; TPA, tissue plasminogen activator; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; vWF, von Willebrand factor.

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lopathy and blood component transfusion have been described.⁵ These instruments are based on similar principles and provide a graphical output depicting various facets of coagulation, like platelet function, clot initiation, stability, and lysis. However, it is still not clear whether TEG and Sonoclot provide identical information. In this study, we aimed to clinically validate and compare the results obtained from TEG and Sonoclot instruments, and whether these correlated with SCTs in ACLF and cirrhosis.

Methods

This was a prospective observational study conducted at the Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India between January 2018 and February 2020. Consecutive patients with ACLF (n=70) and cirrhosis (n=72) of any etiology, aged between 18 and 65 years of either sex were recruited. The exclusion criteria were blood or blood component transfusion in the last 2 weeks, human immunodeficiency virus infection, anti-platelet, anticoagulant or anti-fibrinolytic therapy, dialysis, pregnancy, active malignancy in the last 5 years, chronic heart failure, chronic pulmonary or end-stage renal disease. All patients were enrolled after providing written informed consent, and the protocol was performed in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the Postgraduate Institute of Medical Education and Research Institutional Ethics Committee (IEC/NK 5412/Study/586, dated 13/8/2019). The trial was registered at NCT04332484, available at <https://clinicaltrials.gov/ct2/show/NCT04332484>. All authors had access to study data and approved the final manuscript. The primary objective was to clinically validate the results of TEG and Sonoclot instruments in patients with cirrhosis and ACLF, and whether a POC- versus SCT-based strategy resulted in different transfusion volumes of platelet concentrate and fresh frozen plasma (FFP).

Definitions

ACLF was defined as a syndrome that defines a subgroup of cirrhotic patients who develop organ failure with or without an identifiable precipitating event and have increased mortality rates in concordance with criteria reported in the CANONIC study.⁶

Systemic inflammatory response syndrome and sepsis (life-threatening organ dysfunction caused by a dysregulated host response to infection) was defined as per the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).⁷ The presence of sepsis was assessed by various cultures, detection of C-reactive protein and procalcitonin, or findings of new infiltrates on chest radiographs. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis⁸ as fatal bleeding, symptomatic bleeding in a critical area/organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or intramuscular with compartment syndrome) and/or causing a fall in hemoglobin by ≥ 2 g/dL or requiring transfusion of ≥ 2 U of packed red cells. Assay validation was defined as documented control of the test performance according to predefined criteria relating to precision, linearity, accuracy, robustness, or measurement limits. Clinical validation of an assay requires the assessment of relevance of the test to clinical practice. Key considerations include comparability of results with previous results and evaluating effects of factors that may be encountered in clinical practice (e.g., variations in patient characteristics).^{9,10} Follow-up of enrolled patients for episodes of bleeding, sepsis events, procedures and transfusions were carried out until 28 days or death.

Procedure risk in cirrhosis and ACLF

Procedure-related bleeding is common in cirrhosis patients but estimates of incidence vary widely. Intagliata *et al.*¹¹ classified the risk of invasive procedures in liver disease with examples of high risk (cardiac, thoracic, intracranial surgery, etc.), intermediate risk (lumbar puncture, percutaneous or trans-jugular liver biopsy, trans-arterial embolization procedures, etc.) and low risk (paracentesis, thoracentesis, central line, etc.).

Transfusion strategy

Royston and von Kier developed the use of TEG in 60 patients undergoing complex cardiac surgery and compared the actual use of blood and blood components during cardiac surgery.¹² Spalding *et al.*¹³ and Görlinger *et al.*¹⁴ devised algorithms based on thromboelastometry according to the same principle. We have modified the concept for our patients with liver disease to predict the requirement of FFP and platelets using a TEG-based algorithm (Table 1).

Standard medical therapy

Standard medical therapy included nutritional intervention, antibiotics, albumin infusion, diuretics, and vitamin supplements. Administration of blood components was limited to patients with active bleeding, and prophylactic transfusions were not performed. Prognostic scores like the model for end-stage liver disease (MELD) and chronic liver failure-sequential organ failure assessment (CLIF-SOFA) were used for assessment of severity of ACLF.^{15,16}

Outcome measures

The main objective of the project was to evaluate the relationships of individual variables of the POC tests (activated clotting time (ACT), reaction time (R) and clot kinetics (K) time for clotting initiation) with the corresponding elements of serial SCTs (PT and aPTT). Platelet count and fibrinogen level was compared with clot rate (CR), maximum amplitude (MA), and a angle of the POC tests (Supplementary Table 1). We evaluated the ability of viscoelastic tests to predict spontaneous or procedure-related bleeding. We also studied the change in global coagulation tests (GCT) and SCT parameters over time and assessed correction with intervention. Since coagulation failure is associated with bleeding and sepsis, we also assessed the association of GCT variables, clinical events, and mortality in this large prospective cohort of patients. We also assessed the current practice of prophylactic FFP and platelet transfusion on the perceived risk of procedure-related bleeding and assessed transfusion requirements using an SCT correction or POC-based strategy. Lastly, we assessed whether any derangement in the SCT or GCT values at baseline could predict mortality in this large prospective cohort.

Sample size

Sample size was estimated using the G*Power program. Assuming incidence of coagulation defect in cirrhosis to be 10% and in ACLF to be increased by additional 20%,¹⁷ a total sample size of 60 patients would be required with an effect size of 0.5, alpha of 0.05, and power of 0.85. Therefore,

Table 1. Prophylactic transfusion thresholds for patients administered FFP or platelets based on perceived risk of interventions

Pre-procedure INR	Low risk procedures, n=167			High risk procedures, n=56			All procedures, n=223		
	FFP given, n (%)	Number of procedures	FFP given, n (%)	Number of procedures	FFP given, n (%)	Number of procedures	FFP given, n (%)	Number of procedures	
≤1.5	0 (0)	75	0 (0)	25	0 (0)	100	0 (0)	100	
1.6–1.7	2 (6.89)	29	4 (12.9)	20	6 (10)	49	6 (10)	49	
1.8–2.0	8 (27.58)	18	24 (77.4)	8	32 (53.33)	26	32 (53.33)	26	
>2.0	19 (65.51)	45	3 (9.67)	3	22 (36.67)	48	22 (36.67)	48	
Not checked	0	0	0	0	0	0	0	0	
Total	29	167	31	56	60	223	60	223	
Pre-procedure platelet count as x10 ⁹ /L	Platelets given, n (%)	Number of procedures	Platelets given, n (%)	Number of procedures	Platelets given, n (%)	Number of procedures	Platelets given, n (%)	Number of procedures	
<50	28 (96.55)	75	20 (80)	25	48 (90.5)	100	48 (90.5)	100	
50–69	1 (3.45)	29	3 (12)	20	4 (7.54)	49	4 (7.54)	49	
70–99	0 (0)	18	1 (4)	8	1 (1.88)	26	1 (1.88)	26	
≥100	0 (0)	45	1 (4)	3	0	48	0	48	
Not checked	0 (0)	0	0 (0)	0	0	0	0	0	
Total	29 (100)	167	25 (100)	56	53	223	53	223	

70 patients each with ACLF and cirrhosis were recruited to account for 10% attrition.

Assessment of coagulation parameters

Blood samples for assessment of complete blood count, PT, INR, aPTT, D-dimer and fibrinogen (Supplementary materials) and the viscoelastic tests of TEG and Sonoclot were collected at presentation and 72 h later. The need for repeat testing was to assess correction of the coagulation defect after the first intervention. In case of clinically evident bleeding, POC tests were repeated to check for changes. No patient received drugs that could potentially alter coagulation results, such as anticoagulants or antiplatelet agents. The standard antibiotic started was ceftriaxone or piperacillin-tazobactam. All coagulation tests were performed by the same technician and all Sonoclot and TEG tracings were interpreted by a single investigator (MP). The operating principles of TEG and Sonoclot analyzer are described in the Supplementary Table 1, with nomenclature of different TEG/Sonoclot variables.

Statement of ethics

All patients were enrolled after providing written informed consent, and the protocol was performed in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the Postgraduate Institute of Medical Education and Research Institutional Ethics Committee (IEC/NK 5412/Study/586, dated 13/8/2019).

Statistical methods

Descriptive statistics were presented as mean ± standard deviation and median with inter-quartile range. Comparative analysis was done by Student's *t*-test/Mann-Whitney *U* test for continuous and Chi-square/Fisher's exact test for qualitative variables. Repeated measures analysis of variance (ANOVA) was used for analysis of changes in continuous variables by time. If necessary, logarithmic, or rank transformation was performed to obtain a good model fit. Linear correlations were evaluated by Pearson's coefficient of correlation. A *p*-value of <0.05 was considered statistically significant. Logistic-regression analysis was performed for predictors of 28-day mortality. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were computed to estimate the association of each predictor to clinical event/death. Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS Inc. Chicago, IL, USA).

Results

One hundred sixty-five eligible patients with liver disease were screened; of them, 23 were excluded (Fig. 1). Finally, 72 patients with decompensated cirrhosis and 70 with ACLF were enrolled. Patient demographics, clinical and laboratory data are presented in Table 2. Results of the POC tests at two time points are shown in Supplementary Table 2. Of the analyzed SCTs, repeated 72 h apart, only platelet count (*p*=0.042) and fibrinogen (*p*=0.037) values differed significantly with time and none correlated with clinical bleeding. There were significant changes for TEG variables R, K, alpha (clot rate) and MA (clot strength) at the two time points, indicating the dynamic nature of the coagulation milieu. For Sonoclot, only Son-ACT values differed significantly with time, especially in those with clinical bleeding.

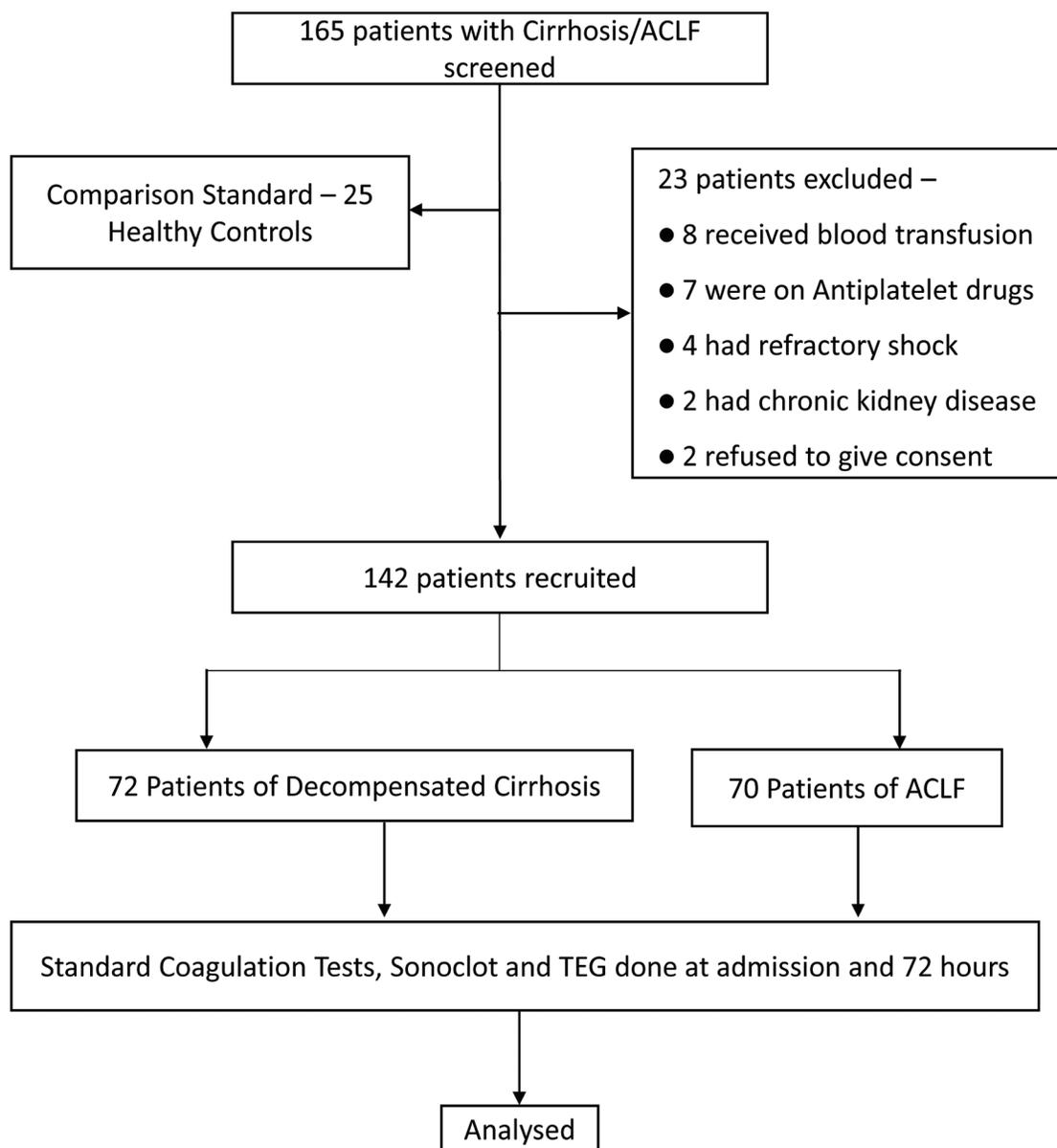


Fig. 1. Study participant enrollment flowchart.

Correlations of POC tests and SCTs

We performed multiple correlations between individual coagulation variables between POCs and SCTs to test plausibility based on the stage of coagulation (Table 3). Fig. 2A shows the TEG curve, with the stages of coagulation and the SCTs and TEG variables associated with defects at each step of clotting. Even though both TEG-alpha ($r=0.76$, $p=0.048$) and -K time ($r=-0.65$, $p=0.050$) were correlated to fibrinogen, in ACLF, only TEG-K was correlated to prediction of clinically evident bleeding ($r=0.73$, $p=0.040$). TEG-alpha and Sonoclot CR were the only variables that correlated with fibrinogen at all time points in ACLF.

Platelet counts correlated with TEG-MA in cirrhosis ($p=0.045$) but not in ACLF. PT correlated positively with TEG-R ($p=0.032$), TEG-K time ($p=0.042$) and Son-ACT ($p=0.038$), and negatively with CR ($p=0.043$) in ACLF but

not in cirrhosis, making it useful as a correctable target variable in POC transfusion algorithms. The only correlations with aPTT were with Son-ACT ($p=0.027$) and CR ($p=0.043$) in ACLF. Fig. 2B shows the Sonoclot signature and the corresponding SCTs used to detect the defect at each stage of coagulation. The TEG-R ($p=0.032$) and TEG-K ($p=0.040$) times correlated with Son-ACT in ACLF but, in cirrhosis, only the K time correlated with ACT ($p=0.052$). Overall, the TEG-MA, CR and platelet function did not show a direct correlation with each other, even when done simultaneously.

Clinical presentation of bleeding and thromboses in ACLF and cirrhosis

Bleeding episodes were seen in 45% and 28% of patients in ACLF and cirrhosis, respectively ($p=0.036$). The most com-

Table 2. Baseline characteristics of the ACLF patients and cirrhosis patients

Parameters	Cirrhosis, n=72, mean ± SD	ACLF, n=70, mean ± SD	P value
Age in years	46.7±12.2	41.5±12.5	0.053
Males, n (%)	65 (90.6%)	62 (89.7%)	0.870
Etiology	Ethanol-related (44, 61%) NASH (16, 22%) Chronic hepatitis C (10, 13.8%) AIH (2, 2.7%)	Ethanol-related (48, 68.5%) NASH (14.20%) Chronic hepatitis B (6, 8.5%) Chronic hepatitis C (2, 2.8%)	
Acute insult	-	Ethanol (48, 68.5%) Acute viral hepatitis (12, 17.4%) DILI (8, 11.4%)	
Duration of jaundice in days	20.5±6.5	16.1±8.3	0.041
Duration of ascites in days	10.4±4.7	8.2±2.5	0.045
Time between onset of disease to presentation to hospital in days	17.9±4.5	19.7±7.1	0.079
Total duration of stay in hospital in days	8.4±5.4	20.7±12.6	0.033
MELD-Na score	11.6±3.3	24.8±4.9	0.026
CLIF-SOFA score	-	8.6±2.1	-
APACHE II score	9.08±3.1	8.6±2.2	0.452
Age in years	46.7±12.2	41.5±12.5	0.053
Males, n (%)	65 (90.6%)	62 (89.7%)	0.870
BMI in kg/m ²	20.1±2.4	22.5±4.0	0.494
Hemoglobin in g/dL	10.9±2.1	10.5±0.31	0.177
Total leucocyte count as ×10 ⁹ /L	10.1±2.3	16.4±2.2	0.067
Platelet count as ×10 ⁹ /L*	130.3 (78.6–155.4)	153.6 (93.8–168.9)	0.034
Total bilirubin in mg/dL*	3.6 (2.5–7.8)	11.7 (5.6–18.5)	0.040
AST in IU/L*	36.0 (32–55)	120 (60–145)	0.050
ALT in IU/L*	30.5 (25–65)	95 (70–130)	0.024
Serum albumin in g/dL	2.9±0.5	2.6±0.7	0.319
S ferritin in ng/mL	237.3±94.5	514.5±167.3	0.036
Prothrombin time in s	18.5±7.5	23.5±7.5	
INR	1.56±0.8	2.32±0.5	0.039
S fibrinogen in mg/dL	145.8±45.9	144.2±25.9	0.180

*Values of these parameters are in median (interquartile range).

Abbreviations: AIH, autoimmune hepatitis; AST, aspartate transaminase; ALT, alanine transaminase; APACHE, acute physiology and chronic health evaluation; BMI, body mass index; DILI, drug-induced liver injury; NASH, non-alcoholic steatohepatitis; S, serum; SD, standard deviation.

Table 3. Correlations between SCTs and POCs

Conventional tests		ACLF		Cirrhosis		
		r value	p value	r value	p value	
Platelet count	TEG-MA	0.64	0.073	0.76	0.045	
	Sonoclot platelet function	0.73	0.052	0.75	0.06	
PT	TEG-R time	0.81	0.032	0.66	0.083	
	TEG-K time	0.79	0.042	0.72	0.057	
	Son-ACT	0.8	0.038	0.67	0.076	
aPTT	CR	-0.65	0.043	-0.54	0.058	
	TEG-R time	0.76	0.078	0.72	0.057	
	Son-ACT	0.81	0.027	0.61	0.076	
Fibrinogen	CR	-0.7	0.043	-0.55	0.058	
	TEG-alpha	0.76	0.048	0.72	0.076	
	TEG-K time	-0.65	0.050	-0.70	0.037	
	TEG-MA	0.6	0.069	0.58	0.089	
Viscoelastic tests	CR	-0.65	0.043	-0.54	0.058	
	TEG-R time	Son-ACT	0.81	0.032	0.66	0.083
	TEG-K time	Son-ACT	0.76	0.04	0.72	0.052
	TEG-MA	Sonoclot platelet function	0.67	0.076	0.66	0.085
TEG-MA	CR	0.78	0.031	0.61	0.076	
TEG-alpha	CR	0.72	0.067	0.62	0.071	
TEG-MA	Platelet function	0.6	0.072	0.59	0.073	

mon sites of minor bleeding were cutaneous ecchymoses (45% and 18%) and epistaxis (7% and 2.3%). The most common site of major bleeding in ACLF and cirrhosis was gastrointestinal (GI), at 31% and 16%, respectively. The GI bleeding was variceal in 44.4% and 40.6% or diffuse portal hypertensive gastropathy related in 55.5% and 59.3% in ACLF and cirrhosis, respectively. Post-variceal ligation ulcer

bleeds (5.4%) were rare but severe, with a high re-bleeding rate and mortality. Spontaneous or iatrogenic hematomas (6.5%) and hemoperitoneum (3.4%) were the other bleeding sites. Thrombosis was observed in four patients with cirrhosis (one deep vein thrombosis, two portal vein, thrombosis, one superior mesenteric vein thrombosis). Clotting of central lines was noted in 14 subjects, but none was attrib-

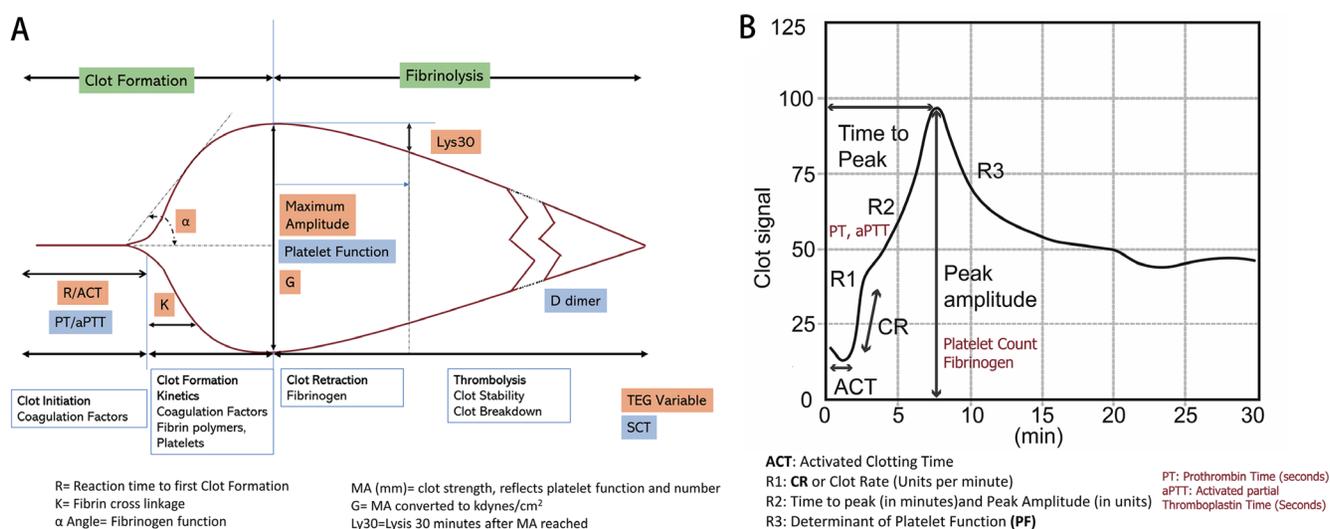


Fig. 2. Correlations of POC tests and SCTs. (A) TEG trace showing the stages of coagulation with corresponding standard coagulation tests. (B) Sonoclot signature showing the phases of clot formation and retraction, with corresponding standard coagulation tests.

Table 4. TEG-based transfusion algorithm at our center based on the method by Royston and von Kier¹²

TEG variable	Implication	Therapy
R>14 and <21 mm	↓ Clotting factors	Two FFPs
R>21 and <28 mm	↓↓ Clotting factors	Four FFPs
R>28 mm	↓↓↓ Clotting factors	Six to eight FFPs
MA <48 mm	↓↓ Platelet number/function	One SDP or four RDPCs
MA <40 mm	↓↓↓ Platelet number/function	Two SDPs or six to eight RDPCs
Lys30 >7.5%	Increased lysis	Tranexamic acid

Abbreviations: RDPC, random donor platelet concentrate; SDP, single-donor platelet.

unable to a hypercoagulable TEG/Sonoclot.

Bleeding, sepsis, and coagulation failure

Baseline SCTs were similar in patients with and without bleeding episodes. Also, the viscoelastic test values in cirrhosis did not differ much in patients who presented with a bleed and in those who did not. However, deranged TEG-R time at baseline was a predictor of bleeding [hazard ratio (HR) of 1.8; 95% confidence interval (CI) of 1.5–4.9, $p=0.040$] in ACLF. Overall, TEG-K time >9 m (HR of 1.3; 95% CI of 1.1–4.9, $p=0.039$), lysis >10% (HR of 1.9; 95% CI of 1.2–2.9, $p=0.040$) and MA<18mm (HR of 1.2; 95% CI of 1.1–3.5, $p=0.034$) predicted a major bleeding event. About 34% and 50% of patients with cirrhosis and ACLF respectively had sepsis at presentation. The sites of sepsis were spontaneous bacterial peritonitis (43%), pneumonia (24%), urinary tract infection (8%), and skin and soft tissue infection (3%). The presence of sepsis at baseline was associated with increased risk of a bleeding event in cirrhosis (HR of 1.2; 95% CI of 1.1–4.9, $p=0.052$) and ACLF (HR of 1.8; 95% CI of 1.5–9.1, $p=0.040$). Prolongation of the Son-ACT was observed in ACLF with sepsis at presentation (HR of 1.3; 95% CI of 1.1–7.6, $p=0.043$) when compared to ACLF without sepsis. There were no significant differences in CR, peak amplitude, or time to peak amplitude, with obvious trends related to sepsis. Supplementary Table 2 shows that in the absence of a new bleeding, thrombosis, or sepsis event, the GCT remained the same. Therefore, the GCT is a POC individualized test, should be compared in an individual patient for change with respect to baseline, and no absolute cut-offs can be given for the cirrhosis or ACLF population.

Transfusion thresholds for coagulation correction

Packed red cells were transfused when hemoglobin concentration was <7g/dL in a setting of clinical bleeding. We assessed the requirement for blood components pre-procedure when correction of a coagulation defect was done using a strategy based on SCTs versus POC. The correction was done based on SCTs, POCs or both, as per the discretion of the treating clinician. Table 4 shows the TEG-based transfusion algorithm followed at our center.^{12,14} A total of 223 procedures were included, which were divided into low-risk and high-risk (Table 1). Patients with major bleeding were transfused with red cell concentrates (median of 2.3; 2–6 U), platelet concentrates (2.4; 0–4 U) and FFP (3.5; 3–6 U) at the discretion of the clinician in consultation with surgical teams. An INR≤1.5 and platelet count≥70×10⁹/L did not merit prophylactic transfusion in low-risk procedures and INR≥1.8 and platelet count ≤50×10⁹/L were all transfused. However, compliance with the POC algorithm was erratic. Of the 223 procedures, only 76 were treated as per the POC strategy. Median transfu-

sion of FFP and platelet concentrate was reduced by 25% and 20.8% by using a POC strategy in cirrhosis. Only two patients developed transfusion-related acute lung injury (referred to as TRALI) after platelet transfusion in ACLF. Since the volume of products was minimized, we did not observe any transfusion related circulatory overload (referred to as TACO).

Eighteen patients received tranexamic acid post-endoscopy. Tranexamic acid was given when clot lysis was >5% in patients with bleeding. Correction of deranged Son-ACT and TEG-R time after 24 h was noted in 68% and 72% after 24 h of FFP transfusion in ACLF and 85% and 80% in cirrhosis, respectively.

Predictors of all-cause mortality in ACLF

None of the patients with cirrhosis died. Of the 14 (19.4%) deaths among the ACLF patients, causes of 28-day mortality included sepsis (57.1%), progressive liver failure (28.5%), and refractory variceal bleeding (14.3%). On univariate analysis, baseline model for end-stage liver disease-sodium (MELD-Na) >26 (HR of 6.7; 95% CI of 2.1–10.3, $p=0.027$), INR>2.6 (HR of 2.3; 95% CI of 1.8–8.5, $p=0.010$), CLIF-SOFA score >10.5 (HR 2.4; 95% CI of 1.4–6.1, $p=0.038$), clot lysis on TEG>10% (HR of 2.2; 95% CI of 1.9–3.4, $p=0.033$), and Sonoclot CR<15 (HR of 2.8; 95% CI of 1.1–4.5, $p=0.044$) predicted mortality in ACLF. However, on multivariate analysis, only MELD-Na (HR of 2.2; $p=0.041$), INR (HR of 1.9; $p=0.039$) and CLIF-SOFA score (HR of 1.2; $p=0.040$) predicted mortality (Table 5). Cox proportional HR for TEG and Sonoclot parameters served as predictors of mortality at 28 days in ACLF across two models with adjustment for age and baseline MELD. Derangement in four or five TEG parameters independently predicted mortality (Table 6).

Discussion

POC viscoelastic tests demonstrate specific functional coagulation defects that can direct blood component transfusion therapy in ACLF/cirrhosis, with clinical validation of individual parameters. This study clinically validates the use of two POC tests when done sequentially in cirrhosis and ACLF to estimate hypo- or hypercoagulability of any given patient. Secondly, our data suggest that the POC tests can be used to prevent unnecessary prophylactic transfusions if they demonstrate preserved global coagulation. Conventional practice of using target PT or platelet count correction for pre-procedure prophylaxis (i.e., correction of platelet counts or INR to an absolute value) has no evidence to support it. Our study demonstrates that the main utility of POCs is that they detect the defect in a stage of the coagulation and clot retraction process and, therefore, give a better actionable target for components like cryoprecipitate, platelets, FFP or antifibrinolytic drugs, like tranexamic

Table 5. Predictors of mortality in ACLF based on coagulation tests and severity scores

Variable	Cut-off at baseline	Univariate analysis			Multivariate analysis		
		HR	95% CI	p value	HR	95% CI	p value
MELD-Na	>26	6.7	2.1–10.3	0.027	2.2	1.2–7.1	0.041
INR	>2.6	2.3	1.8–8.5	0.010	1.9	1.2–4.3	0.039
CLIF-SOFA score	>10.5	2.4	1.4–6.1	0.038	1.2	1.1–5.5	0.040
Clot lysis, TEG	>10%	2.2	1.9–3.4	0.033			
CR	< 15	2.8	1.1–4.5	0.044			

acid. There was minimal comparability in the POC test and SCT variables, like INR or platelet count, suggesting that we need to re-evaluate the practice of pre-procedure correction of coagulation defects, and dose of blood components in patients with bleeding and ACLF.

Use of POCs for patients with bleeding

A POC test should be sensitive enough to indicate alterations in hemostasis in a timely fashion, with data at the time of bleeding being most relevant. We demonstrated correction of Son-ACT and TEG-R time in 68% and 72% after 24 h of FFP transfusion in ACLF and 85% and 80% in cirrhosis, respectively. Initial parameters like R and K times and alpha angle in TEG and ACT in Sonoclot can guide the use of FFP. These parameters are recorded in about 10–15 m and use of platelets (MA or platelet function) can be assessed in 30–40 m and data for use of fibrinolytics (lysis) is available in 30–60 m. These data suggest that the POC tests could better guide the transfusion protocol for bleeding patients and prophylactic transfusions and a corrected POC might be a better target than a corrected SCT, like INR or platelet count, which did not change much in serial tests.

Appraisal of POC tests: TEG and Sonoclot

Previous studies demonstrating interchangeability between TEG and thromboelastometry have been reported.^{18–20} We suggest comparing individual parameters of these tests is

futile even if they correspond to the same step in the coagulation cascade, as they are based on different estimation techniques (Tables 3 and 4). The same test, when used sequentially provides better information regarding adequacy of coagulation correction. Correction of ACT or R and K times after transfusion or resolution of sepsis is of greater significance than an individual parameter's numerical value. Structural differences in these POC tests, as highlighted in the supplementary materials, may explain divergent results obtained from the two instruments used in our study and in those by other authors.^{21–24} TEG and Sonoclot may be equally useful to quantify changes in fibrinogen, consistent with previous studies.^{18,25}

Comparison of POC tests and SCTs

Although we tried to find correlations between individual components of the POCs with corresponding SCTs in the coagulation cascade, we found little association. No correlations were found between INR and the TEG variable R or Sonoclot ACT, even though they all measure the time to the first fibrin formation. However, TEG-R time, TEG-K time and Son-ACT correlated with PT in ACLF. The reason for this discrepancy might be the different activators used, kaolin for TEG and tissue factor for INR. Sonoclot variables ACT and CR correlated significantly with aPTT. This is expected, as aPTT is usually prolonged in hypo-coagulable states, where a low CR can be found. Comparison of magnitude of the coagulation defect between two patients using numerical values of the component results is also fallacious. Rather, serial comparison of dynamic POC changes in the same patient makes clini-

Table 6. Cox proportional HR models for TEG and Sonoclot parameters as predictors of mortality at 28 days in ACLF across two models with different levels of adjustment

	Multivariate HR (95% CI)			
	Model 1 [†]	P value	Model 2 [‡]	P value
Number of TEG parameters deranged				
*None/1 parameter	1.0 (reference)		1.0 (reference)	
2	1.2 (0.9–3.98)	0.096	–	–
3	2.1 (2.2–4.3)	0.043	–	–
4	2.7 (1.9–6.3)	0.031	1.26 (1.38–2.17)	0.044
5	2.2 (1.8–7.4)	0.018	1.22 (1.32–1.54)	0.040
Number of Sonoclot parameters deranged				
*None/1 parameter	1.0 (reference)		1.0 (reference)	
2	1.1 (0.6–1.98)	0.080	–	–
3	1.3 (1.2–4.3)	0.070	–	–

[†]Model 1 adjusted for age.

[‡]Model 2, adjusted as Model 1, and baseline MELD.

cal sense. Although viscoelastic tests are not perfect, they are the best currently available tests for determination of coagulation status. They certainly perform better objectively in patients with clinical bleeding than the SCTs like aPTT, PT, fibrinogen, platelet count, and INR. Since we have demonstrated a reduction in transfusions and reduced the number of additional coagulation tests, replacing it with a POC strategy, our costs have reduced, and transfusion-related adverse events like TRALI and TACO have been minimized. No POC tests showed correlations with platelet counts at the same time points. Thus, the use of MA/platelet function in POC tests is more clinically relevant than platelet count.

Our study was not designed to investigate clinical outcomes in relation to POC tests, which would require a much larger patient population with more frequent measurement of variables. The main limitation was difficulty performing the POC tests at the exact time of bleeding. The way to overcome this limitation will be to adopt use of GCTs in our Intensive Care Units in the same way that it is currently being used in the transplantation operating rooms. At our center, we have adopted a viscoelastic test as the standard algorithm, gradually replacing the use of platelet count or INR to guide blood transfusion for pre-procedure prophylaxis for invasive procedures or for coagulopathy-related GI re-bleeding. Our results are consistent with previous studies that separately evaluated TEG and Sonoclot in cardiac surgery.^{26,27} Although transfusion of FFP and platelet concentrate in our Intensive Care Unit was reduced by 25% and 20.8% by using a POC strategy in cirrhosis, the agreement for the raised transfusion threshold for primary prophylaxis prior to invasive procedures was difficult, as interventional radiologists and surgeons remained skeptical. Ideally, GCTs should be repeatedly only when a new bleeding or clotting event occurs, or correction of coagulopathy is required (as is clear from the results of our study). Secondly, since individual baseline TEG and Sonoclot parameters did not correlate with survival, there is no need to repeat a TEG or Sonoclot assessment, unless an elective procedure is contemplated or there is a bleeding diathesis or thrombosis event. A GCT is a useful indicator of the coagulation defect in a patient who is bleeding and will indicate the appropriate correction. It should not be used as a predictor of bleeding in an individual case but should be done as a reliable test to define the need for blood products in a patient with bleeding or new thrombosis.

MELD-Na, INR, CLIF-SOFA score, and derangement of four or five TEG variables predicted mortality. Though a greater number of abnormal parameters on a GCT may predict increased likelihood of mortality, these are dynamic tests, and a single cut-off does not carry any relevance as a predictor of mortality.²⁸

Until better standardization in liver disease is possible and knowledge about factors affecting POCs is increased, SCTs and POCs will remain complimentary for assessment of hemostasis.²⁹ Our study supports the use of POC tests to guide clinicians in the choice of blood products, contributing to better transfusion management in ACLF and cirrhosis. However, more studies are needed for safe POC algorithms in patients with bleeding for correction of the coagulation defect. If these GCTs replace use of ancillary tests like fibrinogen, D-dimer and aPTT and remain complementary to platelet count and INR, then TEG and Sonoclot are more cost effective than a SCT strategy. This is because a single POC test gives the ACT or R and K times (indicating coagulation factor deficiency, and guising FFP), the CR or MA which guide use of platelets or cryoprecipitate and the fibrinolysis is guiding the use of tranexamic acid.

Conclusions

In conclusion, TEG and Sonoclot can be used to detect he-

mostatic defects and correction targets in ACLF and cirrhosis, whereas use of conventional tests like INR appears to be less suitable, at least in patients with clinical bleeding. It is not possible to match SCTs and variables from POC tests, even though they apparently match the same stage of coagulation. POC tests vary with time and can be normalized after correction of sepsis or use of blood components, unlike SCTs. Variables from TEG and Sonoclot provide more actionable targets at the bedside than SCTs, including correction of platelet function and clot lysis. By reducing additional tests, and reducing transfusion of blood components, the POC strategy is safer and more cost effective than an SCT transfusion strategy. Further studies are necessary to establish adequate reference values for patients with active bleeding and to standardize these assays in ACLF to achieve reliable results.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Design of the study (RM, MP, KK), diagnostic procedures and data collection (MP, RD, AD), TEG performance (KK), Sonoclot performance (Harpreet K, Harman K), statistical analysis and manuscript preparation (SD, AVK, MP). All the authors have read and approved the manuscript and had access to the study data.

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