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MINIREVIEWS

Approach to thromboelastography-based transfusion in cirrhosis: An alternative perspective on coagulation disorders

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Abstract

Viscoelastic tests, specifically thromboelastography and rotational thromboelastometry, are increasingly being used in the management of postoperative bleeding in surgical intensive care units (ICUs). However, life-threatening bleeds may complicate the clinical course of many patients admitted to medical ICUs, especially those with underlying liver dysfunction. Patients with cirrhosis have multiple coagulation abnormalities that can lead to bleeding or thrombotic complications. Compared to conventional coagulation tests, a comprehensive depiction of the coagulation process and point-of-care availability are advantages favoring these devices, which may aid physicians in making a rapid diagnosis and instituting early interventions. These tests may help predict bleeding and rationalize the use of blood products in these patients.

Key Words: Bleeding; Chronic liver disease; Cirrhosis; Thromboelastography; Viscoelastic tests

Core Tip: Viscoelastic hemostatic assays are increasingly used as "point-of-care" tests, providing real-time, dynamic insight into the complex coagulation aberrations seen in cirrhotic patients. In cirrhosis, all patients undergoing a high-risk invasive procedure or who are actively bleeding should undergo thromboelastography (TEG) on initial evaluation, if this testing is available. Any reasonable TEG-based strategy will likely represent an improvement over strategies using traditional coagulation tests. The best approach will be to use TEG supplemented by standard platelet count and fibrinogen testing. TEG is a promising diagnostic modality and may help in predicting bleeding and aid in the rationalization of the use of blood products in these patients.

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INTRODUCTION

The liver is essential in maintaining hemostasis[1]. Patients with cirrhosis may demonstrate altered coagulation and are often considered "auto-anticoagulated"[2]. However, the current understanding of coagulopathy is that patients with cirrhosis have a rebalanced coagulation status[3]. This balance is precarious due to alterations in the hepatic synthesis of pro- and anticoagulant factors. The resilience of the hemostatic system can be further decreased in cirrhotic patients by acute clinical conditions like systemic infection, altered volume status, and impaired renal function.

Given our current understanding of coagulation status in cirrhosis patients, there is considerable interest in tests of coagulation that could provide a truly global view of the coagulation system. Conventional coagulation tests (CCTs), like prothrombin time (PT) and activated partial thromboplastin time (aPTT), are indicators of general liver dysfunction. However, these tests fail to depict the totality of *in vivo* coagulation dysfunction, and lack insight into factors such as blood flow dynamics, endothelial tissue factor (TF), platelet function. They are also limited in their ability to aid in the decision of whether to administer plasma or whole blood[4,5]. Despite such concerns, these CCTs are commonly used to drive clinical decisions.

Thromboelastography (TEG) provides a more physiologically accurate assessment of the coagulation system. TEG has been used effectively as a rapid point-of-care test to assess hypercoagulable, hypocoagulable, and rebalanced coagulation states to evaluate blood transfusion requirements, suggest whether anticoagulation is required, and, if so, aid in the selection of anticoagulant therapy[6].

However, the ideal strategy for using TEG to guide the determination of blood product transfusion is unclear. Although the literature is replete with prospective data demonstrating the superiority of TEG over CCTs for non-surgical patients in terms of the requirement of blood transfusion, a mortality benefit has not been established[7-9]. The present article aims to review the current evidence supporting the use of TEG and the clinical significance of this testing modality in the guidance of blood transfusion in cirrhosis patients.

HEMOSTATIC SYSTEM IN LIVER DISEASE

Per the cell-based model of hemostasis, coagulation occurs not as a "cascade" but in 3 overlapping stages: (1) The initiation phase ensues on tissue factor (TF)-carrying cells. If the procoagulant stimulus is sufficiently strong, factors Xa, IXa, and thrombin are formed in adequate levels to initiate the coagulation process; (2) The amplification phase occurs as the activity moves from the TF-carrying cell to the platelet surface. The procoagulant stimulus is intensified causing platelets to attach, activate, and hoard activated cofactors on their surfaces; and (3) The propagation phase in which the "tenase" and "prothrombinase" complexes gather on the platelet surface and generate the large amounts of thrombin necessary to form a hemostatic fibrin clot[10].

In cirrhosis, all three phases are limited by hepatic synthetic dysfunction and portal hypertension, resulting in a delicate state of "new equilibrium" (Figure 1)[11]. However, this balance can be altered by concomitant conditions such as sepsis or acute kidney injury (AKI) as a result of the interaction between platelets and released inflammatory mediators (Figure 2). Thus, the coagulation profile in cirrhotic patients is dynamic, with possible resolution of global coagulation deficiencies once the acute critical illness resolves. The cell-based model of coagulation also explains why regional hemostatic changes at an injury site do not override the systemic hemostatic equilibrium. Accordingly, CCTs may remain unchanged in patients with liver dysfunction, even with clinically evident bleeding.

According to Hoffman's concept of the cell-based coagulation model, bleeding can arise from disorders of primary hemostasis (abnormal platelet plug formation) or secondary hemostasis (reduced thrombin generation and subsequent fibrin clot formation). The liver plays a critical role in maintaining both primary and secondary hemostasis[11]. In fact, the liver is the site of synthesis of most coagulation factors, with the exception of von Willebrand factor (vWF), factor VIII (only partly synthesized in the liver), and calcium[12].

Bleeding complications in cirrhotic patients may occur due to hemostatic failure or non-hemostatic causes. The term "spontaneous hemostasis-related bleeding" has recently been introduced to distinguish bleeding due to hemostatic anomalies from that related to portal hypertension, trauma, or peptic ulcers. It is defined as an unprovoked hemorrhage of unexplained cause. However, it should be emphasized that spontaneous bleeding is uncommon in patients with cirrhosis, and bleeding is typically

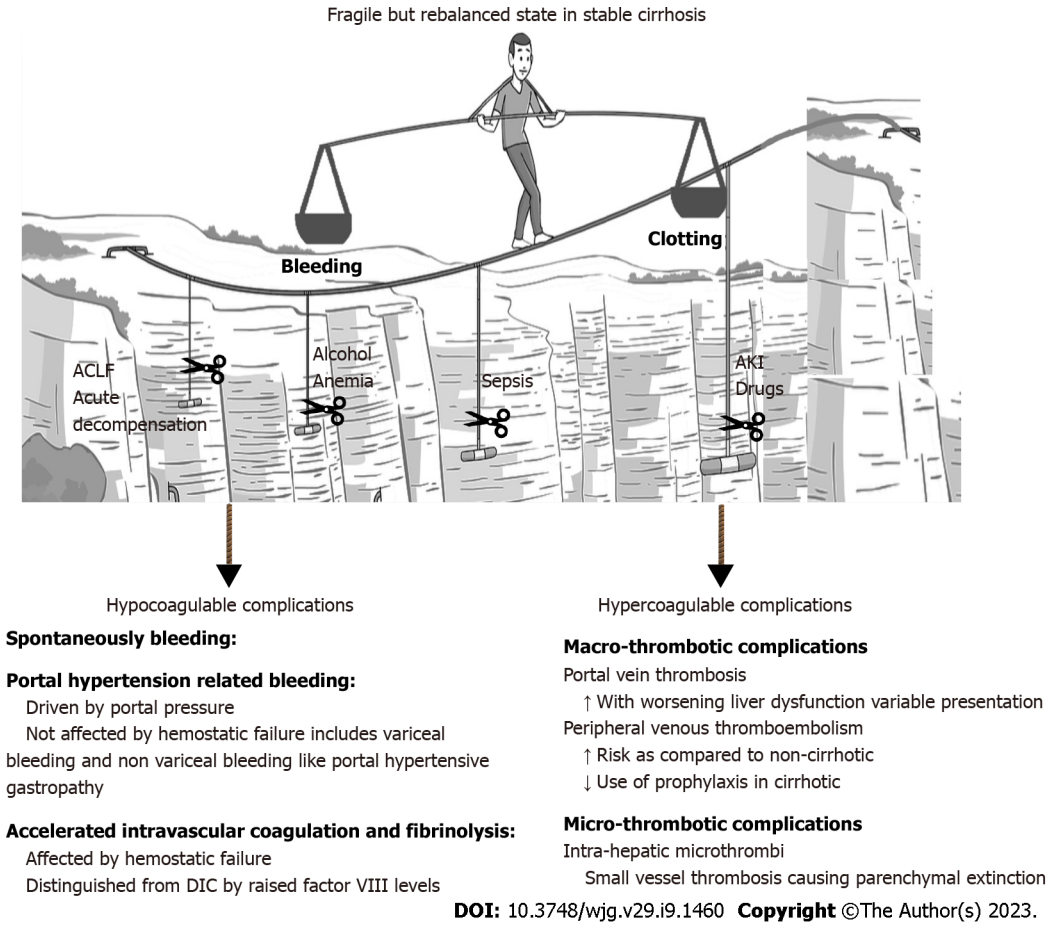

Figure 1 Rebalanced hemostasis in cirrhosis. ACLF: Acute-on-chronic liver failure; AKI: Acute kidney injury; DIC: Disseminated intravascular coagulation.

related to portal hypertension caused by increased portal pressure rather than hemostatic failure. This was conclusively demonstrated by the inability of recombinant factor VII to achieve better control of variceal rebleeding[13,14]. Notably, a bleed not primarily caused by hemostatic failure can evolve into a hemostatic bleed due to severe blood loss and consumptive coagulopathy. Bleeding (tertiary hemostasis disorder) can also be due to premature platelet or fibrin clot dissolution or excessive fibrinolysis, which in cirrhotic patients has been termed "accelerated intravascular coagulation and fibrinolysis" (AICF). AICF manifests as mucosal or puncture wound bleeding, and the pathophysiology of this disorder is not entirely understood. Hyperfibrinolysis parallels the severity of liver disease: mild systemic fibrinolysis is encountered in 30%-45% of cirrhotic patients, with clinically detectable fibrinolysis in only 5%-10%. AICF can be distinguished from disseminated intravascular coagulation by increased factor VIII levels (Figure 1)[15,16]. The 3 phases of coagulation in liver disease resulting in a "rebalancing" of hemostasis are summarized in Table 1[17,18].

For the past several decades, bleeding has been a major concern in the management of cirrhotic patients. However, thrombotic complications are being increasingly acknowledged and are attributed to shifts in hemostatic balance. In one case-control study, the relative risk of venous thromboembolism (VTE) in patients with cirrhosis was 1.74 (95%CI: 1.54-1.95)[19]. These conclusions were mirrored in a study by Wu *et al*[20], which showed an increased likelihood of VTE in cirrhosis [odds ratio (OR) 1.23 in compensated cirrhotic patients; OR 1.39 in decompensated cirrhotic patients]. Dysfibrinogenemia (*i.e.* altered fibrinogen) may result in decreased permeability of the formed clot, as well as other factors that contribute to coagulopathy. It may even confer hypercoagulable features, manifesting as macro- and micro-thrombotic complications. A hypercoagulable state also frequently occurs in cirrhosis patients due to concomitant primary biliary cholangitis, non-alcoholic fatty liver disease, or primary sclerosing cholangitis[21].

The most common macro-thrombotic presentation in liver disease is portal vein thrombosis (PVT), occurring in 8% to 18% of cirrhosis patients[18]. The incidence of PVT increases with deteriorating liver function and decreased portal flow. Deep venous thrombosis and pulmonary embolism (PE) are other macro-thrombotic complications, which have been reported in 5% of hospitalized patients with chronic liver disease (CLD)[17,22]. Micro-thrombotic complications include intrahepatic microthrombi ("parenchymal extinction"), resulting in nodules, porto-pulmonary hypertension, and cirrhosis arising as an ischemic/reinjury process. These complications often merit exigent consideration of anticoagulant

Table 1 Three phases of coagulation in liver disease

Hemostasis stage	Hypocoagulable state	Hypercoagulable state
Primary hemostasis: Platelet activation and interaction with injured endothelium	Thrombocytopenia: (1) Decreased amount: Splenic sequestration, decreased thrombopoietin levels, bone marrow suppression, autoantibody destruction; and (2) Poor function: Uremia, changes to the vessel wall phospholipid composition, anemia (Hgb < 7 g/dL), decreased margination	Low levels of ADAMTS-13; Increased levels of vWF; Increased number of activated platelets
Secondary hemostasis: Fibrin clot formation	Low levels of factors II, V, VII, IX, X, and XI; Low levels of fibrinogen; Vitamin K deficiency (malabsorption in cholestatic disorders)	Elevated levels of factor VIII; Decreased levels of proteins C and S; Decreased levels of antithrombin, and heparin cofactor II
Fibrinolysis	Accelerated intravascular coagulation and fibrinolysis: (1) Low levels of factor XIII and thrombin-activated fibrinolysis inhibitor; (2) Elevated levels of tPA; (3) Decreased level of α2-antiplasmin; and (4) Dysfibrinogenemia	Low plasminogen levels; Dysfibrinogenemia; High plasminogen activator inhibitor

Hgb: Hemoglobin; tPA: Tissue plasminogen activator; vWF: von Willebrand factor.

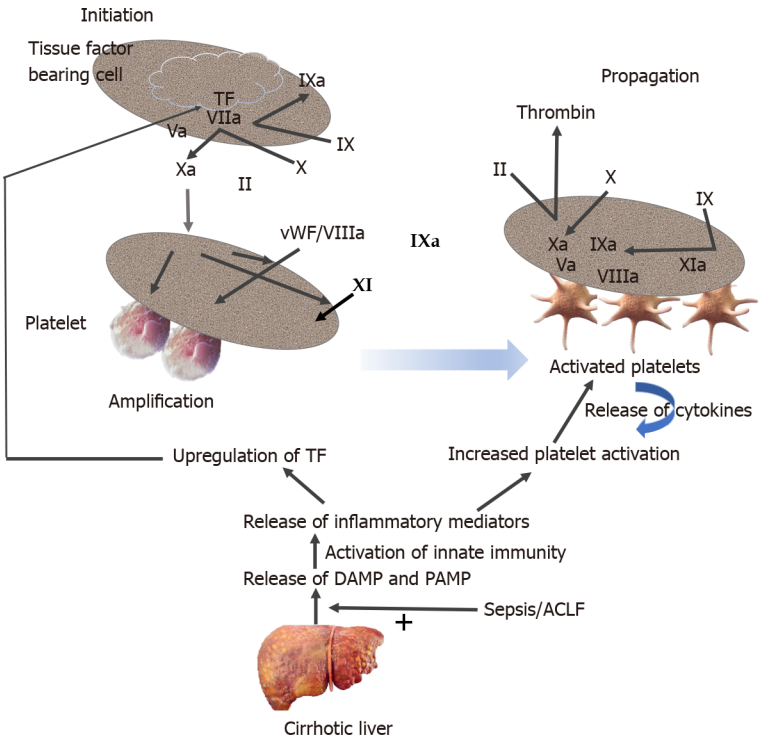

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Figure 2 Dynamic coagulation profile in cirrhosis. ACLF: Acute-on-chronic liver failure; DAMP: Damage-associated molecular patterns; PAMP: Pathogen-associated molecular patterns; TF: Tissue factor.

usage.

TESTS OF COAGULATION IN CIRRHOSIS

As of this article, all available laboratory hemostasis measures have significant limitations when applied to patients with liver disease. The paradigm of this phenomenon is the cirrhotic patient, for which PT and international normalized ratio (INR) were developed to monitor warfarin-treated patients by measuring the activity of an added commercially available thromboplastin reagent. PT and aPTT indicate the onset of thrombin generation; however, they do not reflect enzymatic coagulation. PT/INR has been validated as a prognostic marker for mortality in liver disease, but has never been validated to predict bleeding risk or guide transfusion of blood products, especially for pre-procedure risk mitigation[14]. Nonetheless, this measure has been used for decades as a surrogate for bleeding risk in cirrhosis despite the fact that the arbitrary cut-off points used as clinical targets for the prevention of bleeding are not supported by scientific evidence. Furthermore, using fresh frozen plasma (FFP) to

normalize a raised INR in cirrhosis does not alter thrombin (factor II) production, but exacerbates portal hypertension[23-25].

Thrombocytopenia is the most common hematological abnormality in patients with liver disease. Platelet count thresholds are often specified for invasive procedures in patients with severe cirrhosis-related thrombocytopenia. In vitro data suggest that a threshold of 50-55 × 10^9/L is necessary for adequate platelet activity, and levels below this range fail to promote thrombin generation[26]. However, the platelet function associated with primary hemostasis (*i.e.* adhesiveness and aggregation) has not been evaluated. Current guidelines and expert opinion recommend considering platelet-raising treatments before high-risk procedures, or in patients with active bleeding with platelet counts < 50 × 10^9/L. However, there is no firm evidence that prophylactic platelet transfusion to achieve this target enhances hemostasis[15,23].

As mentioned previously, platelet count alone does not account for other factors affecting platelet function in cirrhosis[27]. For example, uremic platelet dysfunction (*e.g.*, hepatorenal syndrome) can result in impaired platelet activity with decreased serotonin in alpha granules and dysregulated metabolism of thromboxane A2. Anemia can also affect platelet function. In patients with hematocrit < 25%, erythrocyte concentration is inadequate to facilitate platelet margination, impairing the clotting process. Sepsis and endotoxemia due to bacterial translocation also can affect platelet function.

Recently, fibrinogen levels have replaced INR to couple with platelet count in the evaluation of bleeding risk. The Clauss method for detecting fibrinogen is turbidimetric and relies on thrombin-induced fibrin formation. Nevertheless, fibrinogen levels do not account for the synthesis of abnormal fibrinogen in cirrhotic patients caused by hypersialylation of the fibrinogen, leading to impaired fibrinogen-to-fibrin conversion[28]. In trauma surgery patients without underlying liver disorder, administration of fibrinogen factor to accomplish levels of fibrinogen > 200 mg/dL is associated with improved hemostasis. However, in routine clinical practice, the most agreed-upon cut-off for fibrinogen in cirrhotic patients with active bleeding is > 120 mg/dL[29]. In cirrhotic patients, spontaneous or procedure-related bleeding is relatively common when plasma fibrinogen levels are less than 100 mg/dL. Whether this relationship is causal or reflects disease severity is unclear. As such, the available evidence suggests that tests measuring clot formation and strength (*i.e.* fibrinogen) may have better predictive value for bleeding events than coagulation initiation tests[29,30].

Primary hyperfibrinolysis is an increasingly vital pathophysiological process in CLD, resulting in an increased risk of variceal bleeding. D-dimer is a nonspecific marker of fibrin degradation. While evidence suggests that elevated D-dimer indicates hyperfibrinolysis and can predict gastrointestinal bleeding in this population, elevated D-dimer alone provides limited information regarding an individual's fibrinolytic state[31,32].

Thrombin generation assays (TGAs) evaluate the time of thrombin generation and its decline when plasma is triggered by TF and phospholipids. Thus, TGA can reflect the activity of both pro- and anticoagulant factors[33,34]. Nevertheless, clinical trials are needed to test this conjecture. Similar to PT and aPTT, TGA is performed on plasma rather than whole blood. However, because of their method, TGAs approximate the *in vivo* coagulation balance better than CCTs.

TEG quantitatively assesses the capability of whole blood to form a clot, providing a comprehensive picture of coagulation status compared to standard laboratory tests, which are confined to developing the first fibrin strands. However, TEG is insensitive to the platelet adhesion and aggregation activity of vWF and the anticoagulant actions of protein C and protein S; therefore, it may lead to an underestimation of hemostatic capacity[17] (Table 2).

PRINCIPLES OF TEG

The principle of the *in vitro* TEG test is to detect and quantify dynamic changes in the viscoelastic properties of whole blood during clotting under low shear stress (Figure 3A). TEG results are depicted as 2-dimensional graphs, with time on the x-axis and amplitude (in millimeters) on the y-axis (Figure 3B). A normal TEG trace appears similar to a cognac glass lying on its side (Figure 4)[17]. An evident prolongation of R is associated with clotting factor levels of 30% or less[35]. Different activators can be added to the blood to better assess various aspects of the clotting cascade (Table 3). Conventional TEG involves clot initiation by adding kaolin, simulating the intrinsic coagulation pathway. In contrast, rapid TEG involves the addition of kaolin and TF, causing massive thrombin burst and providing initial results (K time) within 6 min and alpha angle/MA within 15 min[36,37]. Thus, the results of rapid TEG can be achieved approximately 10 min earlier than the kaolin TEG and about 30 min earlier than CCTs [37]. This could guide critical resuscitations more competently, enabling real-time monitoring and goal-directed therapy. Though the activators reduce the test turnaround time (*e.g.*, kaolin), the sensitivity of viscoelastic tests (VETs) could be blunted, and subtle changes in coagulation and clot lysis might not be detected[17] (Table 4).

Correlation of CCTs and VETs

A strong correlation between TEG measures of clot formation and clot strength and conventional

Table 2 Thromboelastography components and their clinical implications

Nomenclature	Definition	Function	Significance	Most closely related CCT
Reaction time or R-time	Time (min) to reach an amplitude of 2 mm	Clot initiation	Informs about enzymatic reaction leading to thrombin and fibrin generation. Increased R-time, factor deficiency or reduced function, resulting in hypocoagulability; Shortened R-time, factor hypercoagulability	PT and aPTT
K-time	Time (min) from 2-20 mm amplitude	Clot kinetics	Depicts rate of clot development–fibrin polymerization, cross-linking, and platelet interaction. Long K-time, hypocoagulability; Short K-time, hypercoagulability	Fibrinogen level and platelet count
Angle or α	Slope between R and K	Clot kinetics	Also depicts the kinetics of clot development. Low-angle, hypocoagulability; High-angle, hypercoagulability	
MA	Highest level of amplitude achieved by the clot	Clot strength	Provides assessment of overall clot strength	Platelet count and fibrinogen levels
Coagulation index	Composite indicator of coagulation profile		A linear combination of the above parameters serving as a global view of the patient's hemostatic profile. Increased in hypercoagulable states; Decreased in hypocoagulable states	
LY30	Degree of lysis (%) 30 min after MA is reached	Clot stability	Measure of fibrinolysis. Above normal LY30 suggests hyperfibrinolysis	No equivalent test

aPTT: Activated partial thromboplastin time; CCT: Conventional coagulation test; MA: Maximum amplitude; PT: Prothrombin time.

Table 3 Procedural bleeding risk in patients with cirrhosis

High-risk procedures	Intermediate-risk procedures	Lower-risk procedures
Intrabdominal/orthopedic/cardiac surgery	Percutaneous endoscopic gastrostomy	Paracentesis
Brain or spinal surgery	Percutaneous or transjugular liver biopsy	Thoracentesis
Intracranial catheter insertion	Transjugular intrahepatic portosystemic shunt	Central line placement
Endoscopic mucosal resection or endoscopic submucosal dissection	Endoscopy (*e.g.*, percutaneous gastrostomy placement, cystogastrostomy, biliary sphincterotomy)	Endoscopy (*e.g.*, diagnostic, variceal ligation, uncomplicated polypectomy)
Complicated polypectomy	Percutaneous biopsy of extra-hepatic organ or lesions	Cardiac catheterization
Natural orifice transluminal endoscopic surgery	Trans-arterial or percutaneous hepatocellular carcinoma therapies	Hepatic venous pressure gradient measurement
	Lumbar puncture	

Table 4 Various types of thromboelastography assays

TEG channel	Activator	Function
Native TEG	None	Theoretically most sensitive to subtle coagulopathic changes and hyperfibrinolysis
Conventional TEG	Kaolin	Activates clotting cascade to expedite results
Rapid TEG	Tissue factor + kaolin	Activates clotting cascade to expedite results
Functional fibrinogen TEG	Glycoprotein IIb/IIIa inhibitor	Inhibits platelets to isolate the contribution of fibrinogen
Heparinase TEG	Heparinase	Inhibits heparin; the presence of heparin (endogenous or exogenous) is suggested when this channel shows improved clotting compared to other channels

TEG: Thromboelastography.

fibrinogen level has been observed in CLD patients who are critically ill. Nevertheless, weak or unpredictable correlations exist between TEG and CCTs in measuring coagulation initiation (*i.e.* TEG R-time and PT/INR/aPTT), TEG and conventional platelet count, and measures of fibrinolysis (TEG LY30 and traditional D-dimer)[38-40]. The absence of a correlation between PT/INR and R may be explained by several elements, such as the use of different activators, the use of whole blood *vs* plasma, and the

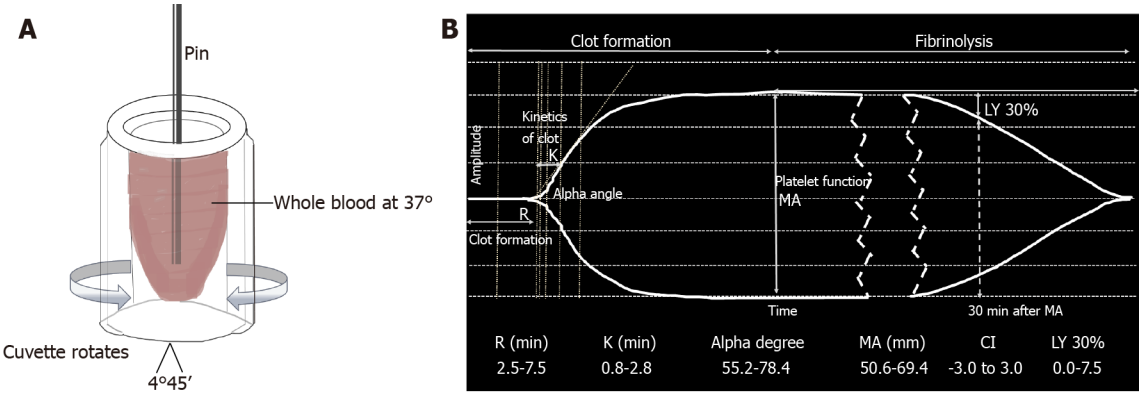

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Figure 3 Basis and results of the thromboelastography. A: Basis of the thromboelastography (TEG) test; B: TEG tracing and relevant parameters (kaolin-activated). MA: Maximum amplitude.

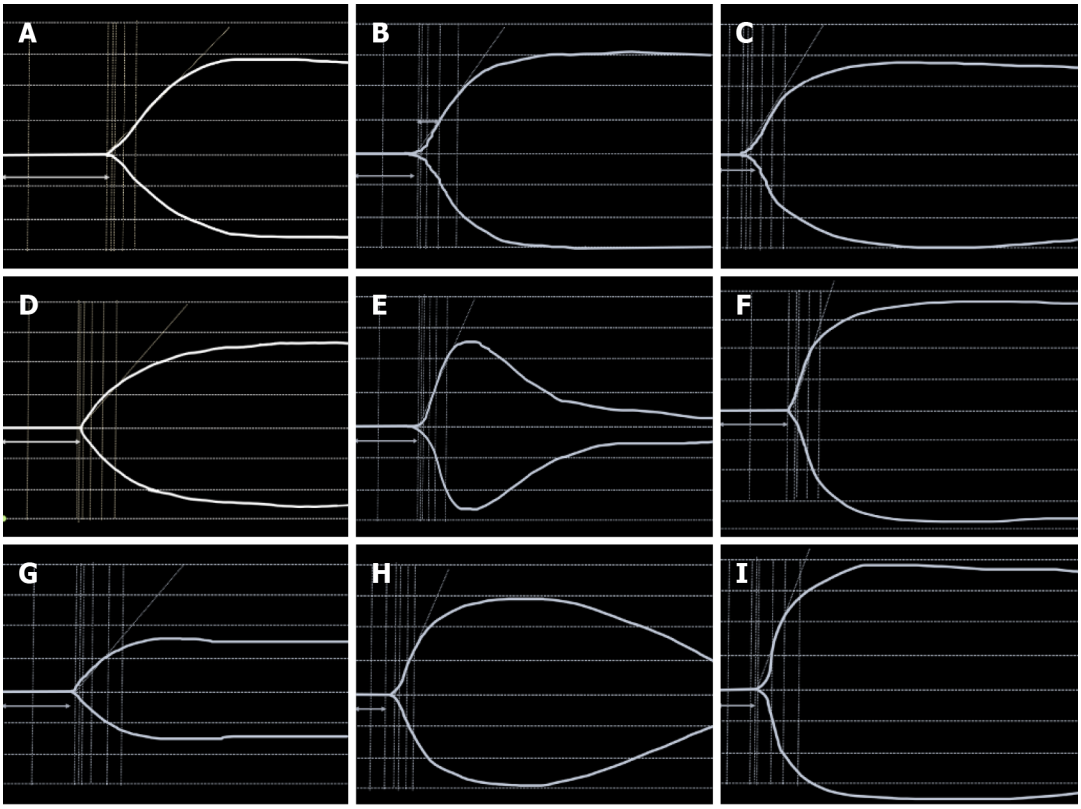

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Figure 4 Tracing of thromboelastography in various clinical conditions. A: Low clotting factors; B: Normal trace; C: Enzymatic hypercoagulability; D: Low fibrinogen levels; E: Primary fibrinolysis; F: Platelet hypercoagulability; G: Low platelet function; H: Secondary fibrinolysis; I: Enzymatic and platelet hypercoagulability.

fact that R-time, unlike INR, reflects the balance of both pro- and anticoagulant factors. This supports the evidence that clotting initiation and speed measures are challenging to interpret in this cohort, while TEG maximum amplitude (MA) and conventional fibrinogen may be more reliable. Nonetheless, the results of these tests should always be correlated with the clinical situation.

CLINICAL APPLICATIONS OF TEG IN LIVER DISEASE

TEG and invasive procedures in patients with cirrhosis

Bleeding complications after invasive procedures are always a concern in cirrhotic patients, though the incidence varies widely[41]. Although the risk of bleeding after the procedure is related to alterations in

clotting factors, the risk is also inherent to a given procedure (Table 3) and the given clinical situation [41]. In cirrhotic patients with acute illness or acute-on-chronic liver failure, the association between clotting tests and bleeding may not be as apparent or evident as in stable patients. Moreover, managing complications, such as sepsis or AKI, instead of correcting hemostatic abnormality, may result in improved outcomes. A retrospective study revealed that AKI was the only independent risk factor for post-paracentesis hemoperitoneum. In contrast, no significant difference was observed in CCTs (platelet count and INR levels) between patients with or without this complication[42].

Three recent randomized trials conducted in cirrhotic patients undergoing invasive procedures demonstrated a decreased requirement for prophylactic blood product transfusions using TEG-guided transfusions compared to standard test-based protocols[7-9]. However, they could not demonstrate any relationship between abnormal TEG tracing and bleeding, primarily due to the scarcity of documented bleeding events. Similarly, TEG did not help to predict the inability to control bleeding or prevent rebleeding. Also, no impact on other clinically relevant outcomes was observed. Moreover, each study used a different transfusion protocol, making it difficult to know whether the lower cutoff for transfusion would have been more beneficial. In another study of cirrhotic patients undergoing various invasive procedures without prophylactic administration of blood products, even with abnormal CCT and TEG R-time and MA, 1 patient experienced bleeding (0.7%)[43]. Also, a recent study in 90 patients with cirrhosis undergoing central venous cannulation demonstrated that a prolonged TEG K-time (≥ 3.05 min) could not predict bleeding complications (accuracy 69.4%, P = 0.047)[44]. These studies indicate that post-procedural bleeding events are rare, implying that uncorrected coagulopathy does not modify the post-procedural outcome. Nevertheless, coagulation tests can be utilized to evaluate the severity of liver disease or the patient's baseline hemostatic function and to provide a baseline to guide management in the case of post-procedural bleeding.

Most of the latest guidelines recommend against using CCTs and correction of coagulopathy before undergoing common gastrointestinal procedures in patients with stable cirrhosis. Also, there are no recommendations for or against using TEG in such patient populations (Table 5)[15,23,45,46]. However, in patients with severely abnormal coagulation parameters or thrombocytopenia undergoing a moderate- to high-risk procedure, clinical judgment regarding prophylactic blood transfusion should consider the possible benefits and risks (Figure 5)[7,15].

Use of TEG in cirrhosis with active bleeding

Bleeding related to portal hypertension, variceal and non-variceal, is primarily managed with local measures such as endoscopic band ligation, laser or injection therapy, and by lowering portal pressure using vasoactive drugs than pro-hemostatic therapy. The observation that variceal bleeding in patients on anticoagulants was not severe or associated with worse outcomes compared to patients who are not on anticoagulants confirms that the role of the hemostatic system in variceal bleeding, if present, is minor[47]. Randomized controlled studies have shown that in cirrhotic patients with variceal and non-variceal bleeding, using VETs to guide blood product transfusion did not result in superior control of bleeding nor any morbidity or mortality benefit compared to CCTs[48-50]. However, the transfusion requirement was significantly lower in the VET group. Although the study by Kumar *et al*[51] demonstrated significantly shorter ICU stays using TEG-guided resuscitation, there was no difference in other outcomes. Nevertheless, it is questionable whether in active variceal bleeding, VETs-guided pro-hemostatic therapy is beneficial or contributes to the control of bleeding when the standard treatment with vasoactive drugs and endoscopic therapy is provided.

If local measures and portal pressure-lowering drugs cannot contain bleeding, the decision to correct coagulopathy by transfusing blood products should be considered on a case-by-case basis[13]. Since VETs are quicker and more accurate than CCTs and provide a more practical understanding of fibrinolysis, which may indicate the need to start antifibrinolytic therapy, they have a theoretical advantage over CCTs in guiding the management of active bleeding.

Unlike pressure-driven bleeding, AICF arises due to disturbed hemostatic mechanisms[15]. Antifibrinolytic therapy, such as epsilon aminocaproic acid or tranexamic acid, is potentially effective, inhibiting the fibrin clot's dissolution. Neither agent is thought to have inherent hypercoagulable risk, except in the case of a preexisting pathological thrombus such as PVT. The "native TEG" can detect this condition in liver disease patients by the presence of an increase in LY30[17].

TEG-based algorithms may allow targeted and specific blood product transfusions in patients with severe bleeding (*e.g.*, FFP or cryoprecipitates)[17]. However, the threshold values of various VETs to trigger transfusion are yet to be validated in appropriate clinical studies.

Heparin-like effect in cirrhosis

A stressful condition such as surgery or sepsis can trigger the release of endogenous glycosaminoglycans (GAGs) (*e.g.*, heparin sulfate and dermatan sulfate) from the endothelium glycocalyx layer or mast cell, which, when shed, retain their anticoagulant activity[52,53]. This is thought to be an adaptive reaction to maintain the patency of progressively procoagulant microvasculature through endogenous heparinization, thus preventing spontaneous thrombosis.

Table 5 Thresholds for coagulation parameters prior to high-risk procedures in patients with cirrhosis

Parameters	EASL 2022	ISTH 2021	AASLD 2021	AGA 2021
PT/INR	Against routine evaluation and correction	Against correction	Against correction	Against routine evaluation and correction[a]
Platelet count	Against correction[b]	Against correction[b]	Against correction	Against routine evaluation and correction[a]
Fibrinogen	Against routine correction	Against routine evaluation	Against correction	No specific recommendation
TEG	Against routine evaluation[c]	Do not use routinely	Do not use routinely	No specific recommendation

[a]In case of severe coagulopathy, prophylactic blood transfusions should be considered on case-to-case basis by evaluating potential benefits and risks in consultation with a hematologist.
[b]If the bleeding cannot be controlled by the local hemostasis method, administration of platelet concentrate or thrombopoietin receptor agonist can be considered if the platelet count is < 50000 × 10^6/L.
[c]May provide a baseline coagulation status and guide in the case of bleeding events.
AASLD: American Association for the Study of Liver Diseases; AGA: American Gastroenterological Association; EASL: European Association for the Study of the Liver; INR: International normalized ratio; ISTH: International Society on Thrombosis and Hemostasis; PT: Prothrombin time; TEG: Thromboelastography.

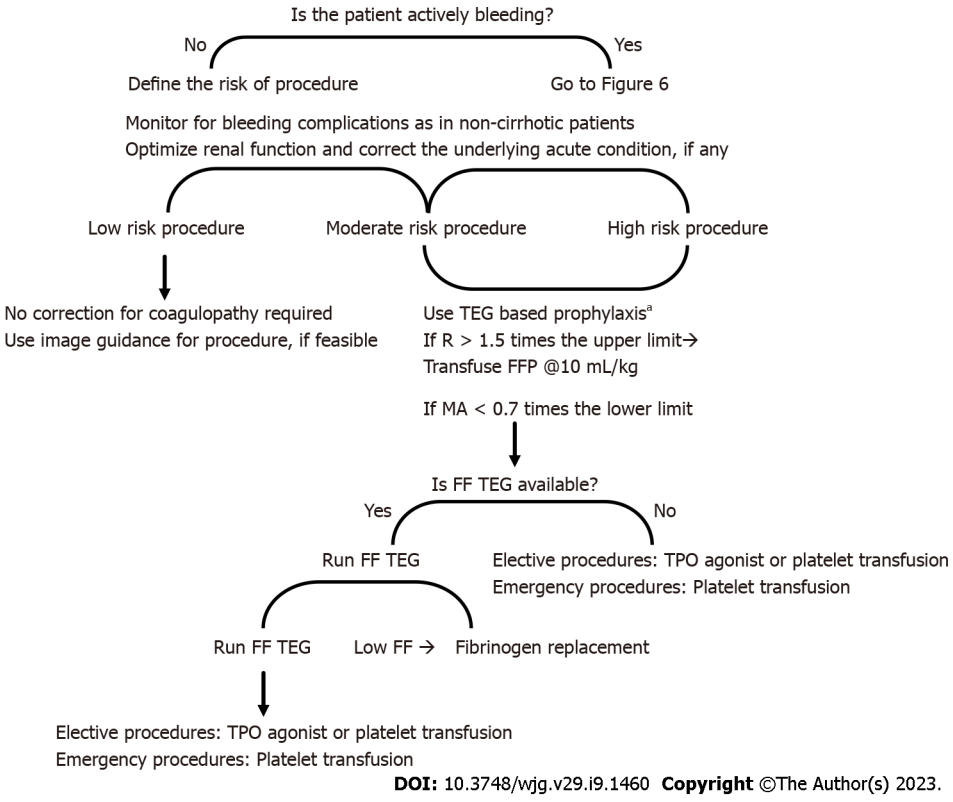

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Figure 5 Algorithm for coagulation factor administration in the cirrhotic patient with coagulopathy undergoing an invasive procedure. FF: Functional fibrinogen; FFP: Fresh frozen plasma; MA: Maximum amplitude; TEG: Thromboelastography; TPO: Thrombopoietin.

Endogenous GAGs may increase the bleeding risk in some patients. This was illustrated by Senzolo *et al*[54], where GAGs affected hemostasis in cirrhotic patients with sepsis. Another prospective analysis further confirmed the presence of an endogenous heparinoid in patients with cirrhosis and acute variceal bleeding and was found to be associated with bleeding-related mortality[55]. After appropriate therapy, endogenous heparinoids are cleared with normalization of the coagulation profile, emphasizing the association between the coagulation cascade and inflammatory pathways.

Although CCTs are insensitive to this effect, the native TEG is extremely sensitive to the presence of heparin and heparin-like substances, which is detectable by an increased R-time on TEG analysis[56]. Adding heparinase I, which cleaves heparin-like compounds, can demonstrate a heparin-like effect due to elevated GAGs, correlating with an anti-Xa activity[57]. Therefore, heparinase TEG will normalize the prolongation of the R-value observed with native TEG. Thus, TEG helps differentiate between a coagulation factor deficiency and heparin-produced coagulopathy by using heparinase-modified TEG

and the native TEG (Table 4).

TEG in orthotopic liver transplant

Kang *et al*[58] at the University of Pittsburgh introduced TEG-based algorithms to guide blood product transfusion for correcting coagulopathy in orthotopic liver transplantation in the early 1980s (Figure 6). It was shown that TEG reduced transfusion requirements by 33% compared with a historical cohort. Secondary endpoints like re-intervention for bleeding, AKI, or hemodynamic instability were significantly lower in the VET group. Although numerous studies have described the usefulness of VET in lowering transfusion requirements in liver transplant (LT), most of these studies commonly compared the results with historical cohorts having a relatively high baseline transfusion rate[59,60]. A recent study of 60 LT patients showed no significant differences with and without VET monitoring though overall transfusion was low, with many patients receiving no transfusion[61]. As bleeding and transfusion management continues to evolve, the results of these earlier studies cannot be easily employed in the present era. Also, the thresholds described for VET for initiating transfusion are still to be established, and values may be substantially above the normal ranges before an intervention is advised.

A significant proportion of patients undergoing LT will inevitably have enormous blood loss, and VET can be helpful in such occasions to enable goal-targeted treatment and assess the effectiveness of any therapeutic intervention. The short turnaround times of VET (10-20 min) are vital for directing therapy and averting inappropriate transfusion during surgery and in the ICU. Monitoring coagulation with functional fibrinogen TEG (Table 4) for goal-directed fibrinogen substitution seems more appropriate and avoids unnecessary platelet transfusions. This is particularly important in LT, as platelet administration is associated with a substantial decline in 1-year survival[62].

Fibrinolysis and orthotopic liver transplant

It is well known that increased fibrinolytic activity can occur at any juncture during LT. However, it is significantly enhanced during the anhepatic period due to a lack of tissue plasminogen activator (tPA) clearance[63]. Also, it may become most pronounced in the post-reperfusion stage by an erratic upsurge in tPA, leading to diffuse uncontrolled bleeding due to primary hyperfibrinolysis[64]. If the graft function is good, hyperfibrinolysis after reperfusion is usually self-limiting and does not require treatment. However, in the presence of an inadequately functioning graft, it may persist[65]. During LT, prophylactic antifibrinolytic agents were often used in earlier years because of the high mortality associated with tremendous blood loss, and the potential peril associated with antifibrinolytics was minor. As massive bleeding is currently less frequent, there is a preference towards the selective use of antifibrinolytics only in high-risk patients. Systemic fibrinolysis can be efficiently detected using VETs (demonstrated by increased or worsening LY30 and LY60), which may not be possible with CCTs. Thus, the transfusion requirement may be decreased with VET use in liver transplantation, where hyperfibrinolysis commonly occurs.

TEG and hypercoagulability

The risk of developing VTE is similar in cirrhotic and non-cirrhotic patients[15,23]. Hypercoagulability detected on TEG can either be due to shortened R or K, enhanced clot strength (MA), or a combination of both. Huang *et al*[66] observed a significantly shorter R in cirrhosis with non-malignancy PVT. Zanetto *et al*[67] found that elevated MA was associated with PVT in cirrhotic patients with hepatocellular carcinoma. Given that malignancy itself could also cause hypercoagulation, the clinical use of TEG in this setting may be questionable. In another study, hypercoagulability was defined as the presence of at least 2 of the following criteria: reduced R, reduced K, raised α, or increased MA. Hypercoagulability was not associated with PVT in cirrhosis[68].

In cirrhotic patients with elevated CCTs, we tend to avoid prophylactic anticoagulation in hospitalized patients. Presently, the European Association for the Study of the Liver Clinical Practice Guidelines in cirrhosis does not recommend using VETs to identify the risk of VTE[23]. Further prospective studies may explore the utility of TEG in predicting the risk of VTE during hospitalization.

Acute intracardiac thrombi and PEs are rare, although a well-recognized, potentially fatal complication of LT, associated with high mortality. Krzanicki *et al*[69] demonstrated that a hypercoagulable state is quite common during liver transplantation. A review of 27 case reports of TE in orthotopic LT showed that TEG indicated hypercoagulability in greater than 70% of cases[70]. Also, hypercoagulable TEG patterns correlated well with the formation of intracardiac thrombi. Indeed, a quick inspection of the rapid TEG after 5 or 10 min of clotting time might predict thrombosis, demonstrated by the increase in the MA. The clinical importance of hypercoagulability on TEG during LT is yet to be recognized. However, it would appear unreasonable to transfuse blood products or avoid anticoagulants based on raised CCTs when a hypercoagulable state is seen on TEG.

Patients with cirrhosis and VTE should be treated with anticoagulation, similar to other non-cirrhotic patients. In patients at increased risk of bleeding, unfractionated heparin (UFH) is the preferred anticoagulant, owing to its shorter half-life (45 min) and the availability of an effective antidote (protamine sulfate). aPTT is the most commonly used test to monitor UFH therapy. Although the anti-Xa activity

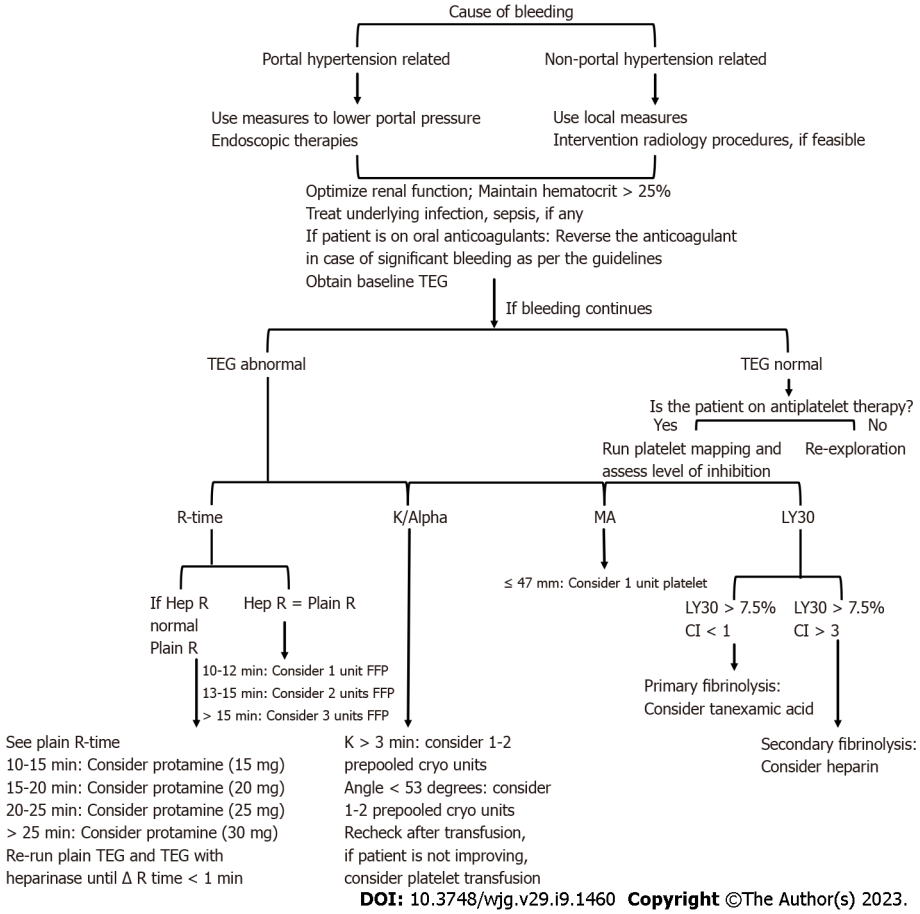

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Figure 6 Algorithm for guiding blood product transfusion by thromboelastography. Cryo: Cryoprecipitate; FFP: Fresh frozen plasma; Hep R: Heparinase R-Time; MA: Maximum amplitude; TEG: Thromboelastography.

assay is used explicitly for monitoring low molecular weight heparins, as they primarily inhibit factor Xa, it may also be superior to aPTT for titrating UFH[71].

Given that heparin activity mainly depends on the liver-derived activity of the heparin cofactor antithrombin III, monitoring heparin therapy with CCT in patients with cirrhosis is challenging. TEG may provide a better representation of the *in vivo* heparin effect than aPTT[72,73]. A higher concentration of heparin tends to be associated with larger R-values with dose-dependence. Levels of anti-factor Xa activity correlate with the R-value of TEG. In addition, TEG can help diagnose and treat heparin-induced coagulopathy. Thus, platelet and enzymatic hypercoagulability demonstrated with TEG mandates aggressive treatment with a direct thrombin inhibitor.

LIMITATIONS OF TEG

Like any other test, TEG is associated with certain limitations. It measures blood coagulation *in vitro* instead of during flow within the vasculature, and as such does not reflect the endothelium's function in coagulation. Inherently, the test is less sensitive to platelet adhesion and interactions between vWF and protein C and S system. TEG results do not correlate with the effects of hypothermia, as TEG is performed at 37 °C. Kaolin cannot effectively detect alterations in the extrinsic coagulation pathway, as it only activates the intrinsic coagulation pathway. Thus, INR is still the gold standard for monitoring warfarin therapy, and TEG may overlook a clinically significant coagulopathy. TEG detects fibrinolysis only when tPA levels are 5 times normal. Studies have shown that using plasmin-α2-antiplasmin as a biomarker for fibrinolysis can detect fibrinolytic activation in over 80% of severely injured patients, whereas TEG detected hyperfibrinolysis in only 5%-18%. Each TEG run generally takes 30 min to an hour, and only a few tests can run simultaneously, unlike CCT. The optimization of TEG is essential in providing appropriate patient laboratory testing. Additionally, testing should be performed by trained personnel and is susceptible to technical variations.

CONCLUSION

VETs are increasingly used as "point-of-care" tests, providing a real-time, dynamic picture of complex coagulation aberrations (*e.g.*, hypocoagulability, hypercoagulability and hyperfibrinolysis) in cirrhotic patients. In cirrhosis, all patients undergoing a high-risk invasive procedure or who are actively bleeding should undergo TEG at initial evaluation, if this testing is available. Any reasonable TEG-based strategy will likely represent an improvement over strategies using traditional coagulation tests. The best approach will be to use TEG supplemented by platelet count and fibrinogen measures. TEG is a promising diagnostic modality, but given the limited clinical trials, there are no consensus guidelines for its use. Further prospective studies are required to validate TEG algorithms for use in the context of patients with cirrhosis.

FOOTNOTES

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