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Viscoelastic tests in liver disease: where do we stand now?

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Abstract

Hemostasis is a complex physiological process based on the balance between pro-coagulant and anticoagulant systems to avoid pathological bleeding or thrombosis. The changes in standard coagulation tests in liver disease were assumed to reflect an acquired bleeding disorder, and cirrhotic patients were considered naturally anticoagulated. In the light of the new evidence, the theory of rebalanced hemostasis replaced the old concept. According to this model, the hemostatic alteration leads to a unique balance between pro-coagulant, anticoagulant, and fibrinolytic systems. But the balance is fragile and may prone to bleeding or thrombosis depending on various risk factors. The standard coagulation tests [INR (international normalized ratio), platelet count and fibrinogen] only explore parts of the hemostasis, not offering an entire image of the process. Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) are both point of care viscoelastic tests (VET) that provide real-time and dynamic information about the entire hemostasis process, including clot initiation (thrombin generation), clot kinetics, clot strength, and clot stability (lysis). Despite prolonged PT/INR (international normalized ratio of prothrombin time) and low platelet counts, VET is within the normal range in many patients with both acute and chronic liver disease. However, bleeding remains the dominant clinical issue in patients with liver diseases, especially when invasive interventions are required. VET has been shown to assess more appropriately the risk of bleeding than conventional laboratory tests, leading to decrimal use of blood products transfusion. Inappropriate clotting is common but often subtle and may be challenging to predict even with the help of VET. Although VET has shown its benefit, more studies are needed to establish cut-off values for TEG and ROTEM in these populations and standardization of transfusion guidelines before invasive interventions in cirrhotic patients/orthotopic liver transplantation.

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Core Tip: Despite having specific alterations in all hemostasis phases and, thus, considered naturally anticoagulated, cirrhotic patients have, in fact, balanced hemostasis. However, this balance may be disturbed by different factors, and the result may vary from devastating bleeding to massive thrombosis. Conventional laboratory tests failed to predict these events. Viscoelastic tests appear to offer a better, global view of hemostasis in these patients. They have been used to assess bleeding risk before invasive interventions and for a precocious use of blood product transfusions.

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INTRODUCTION

Hemostasis in advanced liver disease

The hematological changes encountered in cirrhosis have shown a great interest in the last two decades. The misconception of the cirrhotic patient being naturally anticoagulated has changed with the new concept of balanced hemostasis.

The new cell-based model of hemostasis elaborated by Hoffman and Monroe[1] in 2001 led to a better understanding of hemostasis's complex process. In Hoffman's conception, three phases simultaneously cooperate for adequate hemostasis: primary hemostasis, which involves the activated platelets with the formation of platelet-plug; coagulation with the fibrin mesh construction and clot fortification, involving plasma procoagulant proteins and, finally, clot fibrinolysis by plasma anticoagulant proteins.

In liver cirrhosis, all these three phases are affected by hepatic synthetic dysfunction and portal hypertension[2].

In hemostasis, platelets have a dual role[3,4]. Through the adhesive protein von Willebrand factor (vWF), they adhere to the subendothelium and aggregate to initiate thrombus formation and, by assembling vitamin K dependent coagulation factors on their surface, they support thrombin generation. The most common abnormality in cirrhotic patients is the thrombocytopenia-numerical decrease of circulating platelet count[2-4]. The etiology of thrombocytopenia is multifactorial: platelet spleen sequestration, low thrombopoietin levels from impaired hepatic synthesis, immune destruction.

However, there is controversy over the qualitative changes in platelet function in chronic liver disease[2,3]. vWF, activated by cleavage into smaller subunits (high molecular weight multimers) by the endothelial-derived metalloproteinase ADAMTS13, mediates platelet adhesion and aggregation[3]. Lisman *et al*[5] have shown *in vitro* that cirrhotic patients' plasma may support the adhesion of normal or cirrhotic platelets. This is possible due to the increased level of vWF and, at the same time, a decrease in vWF collagen binding capacity, as well as a reduction in vWF and ADAMTS13 multimers. These results indicate that increased levels of VWF contribute to the induction of primary hemostasis by maintaining the platelets adherence despite the functional or numerical alteration of them. Tripodi *et al*[6] found in an *in vitro* study that thrombocytes from cirrhotic patients were qualitatively able to support thrombin generation if their range was over $50-60 \times 10^9/L$.

A reduction in the synthesis of procoagulant factors (FII, FV, FVII, FIX, FX, FXI) characterizes chronic liver disease[2,4]. The exception makes FVIII, whose level is elevated secondary to synthesis induced by cytokines, released from necrotic tissue, and reduced clearance[2,7]. Fibrinogen level is normal or increased in most patients with cirrhosis, and dysfibrinogenemia occurs in 50%-78% of patients with chronic liver disease[4]. Despite the reduction in hepatic synthesis of procoagulant factors, patients with liver cirrhosis do not experience spontaneous bleeding similarly to those with congenital deficiency of coagulation factors do (*e.g.*, haemarthrosis)[2]. The decreased

protein C synthesis, a potent anticoagulant, protein S, and antithrombin III, also contributes to the coagulations' normality[2-4,7].

All profibrinolytic and antifibrinolytic factors are synthesized by hepatic cells, except tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI 1), which are produced by endothelial cells. Liver cirrhosis is associated with hyperfibrinolysis secondary to high levels of t-PA and low levels of plasma inhibitor and thrombin-activatable fibrinolysis inhibitor (TAFI), but also with hypofibrinolysis secondary to increased PAI and plasminogen levels[7]. Lisman *et al*[8] pointed out that a parallel decrease in antifibrinolytic factors counterbalances the low levels of profibrinolytic factors that occur in cirrhosis. However, Colucci *et al*[9] showed contradictory results, demonstrating that the reduction in TAFI level is associated with hyperfibrinolysis.

All of these changes (Figure 1) support the new theory of rebalanced hemostasis in patients with liver cirrhosis[2,4,7,10]. However, various circumstantial risk factors can quickly destabilize this balance, increasing the risk of bleeding or thrombosis[3,10].

HEMOSTASIS TESTING IN ADVANCED LIVER DISEASES

The problems appear when it comes to exploring hemostasis. The major inconvenience of conventional laboratory tests [platelet count, PT/INR (international normalized ratio of prothrombin time), procoagulant/anticoagulant factors, profibrinolytic/antifibrinolytic factors] is that they test parts of hemostasis, and they do not offer a global view of the process.

The INR appeared as a necessity in the standardization of anticoagulant therapy with vitamin K antagonists (VKA). Still, it is not calibrated to the specific changes of cirrhotic coagulation[2,3]. There were two attempts[11,12] to introduce a new liver dedicated INR (INR_{liver}) by recalibrating ISI (International Sensitivity Index). The method requires replacing plasma from the patients treated with VKA with cirrhotic patients' plasma. This technique has technological limits, so it remains more theoretical than a practical one[2]. Moreover, the usual lab tests are not useful for appreciating the hemorrhagic risk related to invasive maneuvers in cirrhotic patients[2].

There is no evidence that a prolonged PT/INR is an indicator of hemorrhagic risk during or following invasive procedures[13].

The platelet count seems to correlate better with the bleeding risk, but a cut-off value below which the risk is increased has not been demonstrated.

Some studies have associated values below 60.000-75.000 with increased hemorrhagic risk following invasive procedures[14].

The fibrinogen level is variable in hepatic diseases[15]. A correlation with bleeding risk has not been defined, except for evident disseminated intravascular coagulation syndrome, sepsis, and different liver transplant stages[16].

Thrombin generation tests measure the entire quantity of thrombin that is generated during hemostasis. Using this assay, several studies[17,18] have shown that compensated cirrhotic patient plasma can produce normal or increased quantities of thrombin, despite prolonged PT/INR.

Thromboelastography (TEG) and Rotational thromboelastometry (ROTEM) are tools based on Hartert's invention, which assesses overall hemostasis, reflecting the interaction between plasma, platelets, and blood cells[4].

ROTEM and TEG are both point of care viscoelastic tests (VET) of hemostasis in whole blood providing real-time, dynamic information about the entire coagulation process, including clot initiation (thrombin generation), clot kinetics, clot strength, and clot stability (lysis). The force exerted on a small metal pin suspended in whole blood during clot formation is measured while the cup (TEG) or the pin is rotated. Data are processed and analyzed with dedicated software and exposed as graphical and numerical values. Table 1 and Figure 2 represents the principal parameters from both VETs.

It should be highlighted that PT/INR correlates poorly with R/CT (reaction time/clotting time) VET parameters[19,20]. However, an excess of anticoagulants or low coagulation factors (less than 30%) would prolong the R/CT time. In contrast, a lot of tissue factor, high factor VIII, or low protein C would shorten these parameters[21]. An increase in maximum clot firmness (MCF) or amplitude could be explained by a combination of increased fibrinogen levels and platelet reactivity[22].

Since TEG/ROTEM are global hemostasis tests, they are more used to evaluate coagulopathy in chronic liver disease[23]. Consistent with the new vision of the rebalanced hemostasis, patients with compensated liver cirrhosis often have normal

Table 1 Parameters of viscoelastic tests numerical

	ROTEM	TEG	
Clotting initiation	CT (clotting time)	R (reaction time)	Enzymatic coagulation
Clot kinetics	CFT (clot formation time); α angle	K (K time); α angle	Speed to reach a certain level of clot strength; Rapidity of fibrin synthesis
Clot strength	MCF (maximum clot firmness)	MA (maximum amplitude)	Ultimate strength of the fibrin clot
Clot stability	CLI30 (clot lysis index at 30 min after MCF); CLI60 (clot lysis index at 60 min after MCF)	Ly30 (clot lysis at 30 min after MA); Ly60 (clot lysis at 60 min after MA)	Clot lysis

TEG: Thromboelastography; ROTEM: Rotational thromboelastometry; MCF: Maximum clot firmness; MA: Maximum amplitude; CT: Clotting time; CFT: Clot formation time.

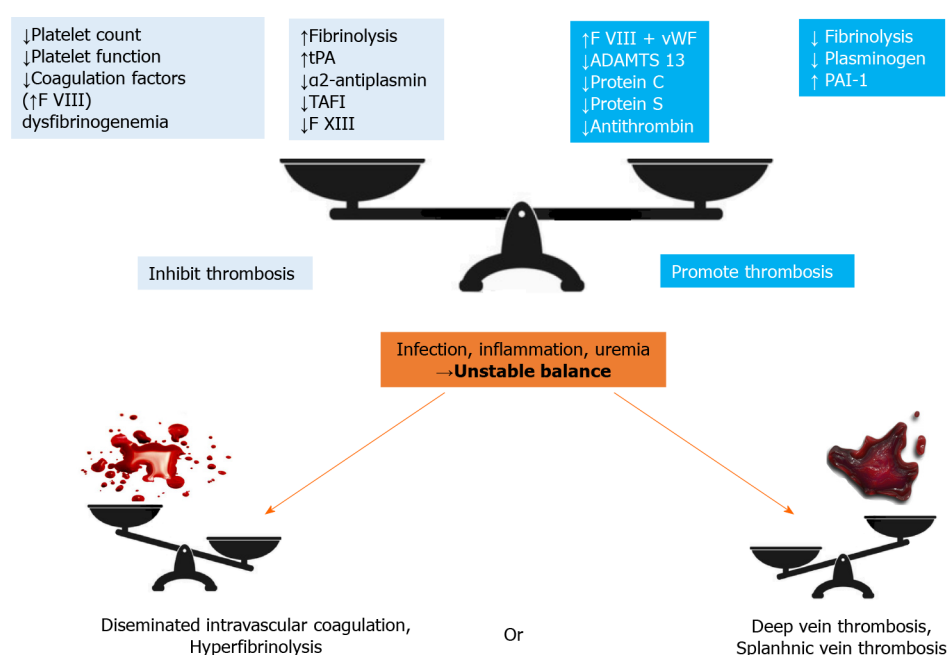


Figure 1 Rebalanced hemostasis in liver cirrhosis. In primary hemostasis, high levels of von Willebrand factor and low levels of disintegrin and metalloproteinase with a thrombospondin type 1 motif 13 counteract numerical or functional abnormalities of platelets. In the coagulation phase, low levels of procoagulant proteins are balanced by reduced synthesis of anticoagulant factors. In fibrinolysis, parallel changes are seen in profibrinolytic and antifibrinolytic proteins. The balance is though fragile, and various factors, as inflammation, infection, uremia may unstable it, leading to bleeding or thrombosis. tPA: Tissue plasminogen activator; TAFI: Thrombin-activatable fibrinolysis inhibitor; vWF: von Willebrand factor; ADAMTS13: Disintegrin and metalloproteinase with a thrombospondin type 1 motif 13; PAI-1: Plasminogen activator inhibitor-1.

TEG parameters[24].

We will discuss further the importance of VET in the most frequent settings from the hepatology field.

HYPERCOAGULABILITY, THROMBOSIS AND VET IN LIVER CIRRHOSIS

Despite the "natural anticoagulation" concept that marked the diagnosis of cirrhosis, portal vein thrombosis (PVT) is a relatively frequent complication of patients with cirrhosis (up to 25% of patients with decompensated cirrhosis)[25]. All the elements of Virchow's triad are present in patients with cirrhosis: decreased velocity (through the presence of portal hypertension), vessel-wall abnormalities (endothelial dysfunction, fibrotic mechanical distortion), and hypercoagulation[7]. However, using the conventional coagulation test, the hypercoagulation status is difficult to demonstrate.

Moreover, the hypercoagulation could vary among different etiologies of cirrhosis. Compared to only 5% of non-cholestatic cirrhosis, 28% of patients with primary biliary cholangitis (PBC) and 43% of patients with primary sclerosing cholangitis (PSC)

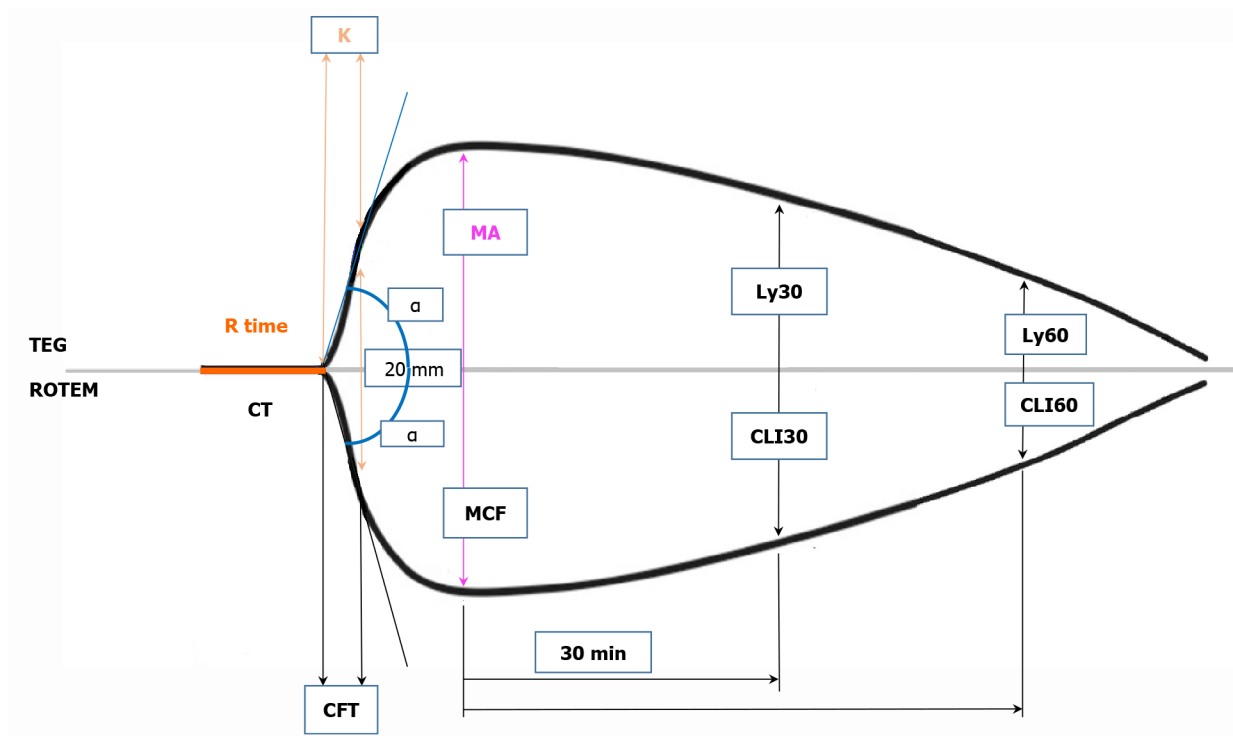


Figure 2 Parameters of viscoelastic tests graphical. TEG: Thromboelastography; ROTEM: Rotational thromboelastometry; CFT: Clot formation time; CT: Clotting time; R: Reaction time; K: K time; MA: Maximum amplitude; MCF: Maximum clot firmness; CLI30: Clot lysis index at 30 min after maximum clot firmness; Ly30: Clot lysis at 30 min after maximum amplitude; CLI60: Clot lysis index at 60 min after maximum clot firmness; Ly60: Clot lysis at 60 min after maximum amplitude.

demonstrated hypercoagulation status on TEG parameters[26]. Notably, the conventional coagulation tests did not identify this hypercoagulability. Pihusch *et al*[27] also found a hypercoagulable state in noncirrhotic patients with PBC/PSC.

Among various etiologies, non-alcoholic fatty liver disease (NAFLD) has a higher risk of thrombosis. Using TEG, patients with NAFLD had a significantly stronger clot development than healthy controls [maximum amplitude (MA) 58.3 ± 6.3 vs 52 ± 10 mm, $P = 0.01$][28]. The platelet contribution to overall clot strength was higher in NAFLD patients with a trend to reduced inducible clot lysis ($P = 0.03$). Based on shortened TEG's R and increased net clot strength, Krzanicki *et al*[29] found a high rate of hypercoagulation in patients with PBC (42.9%), patients with PSC (85.7%), patients with fulminate hepatic failure (50%), and patients with NAFLD (37.5%). Similar findings were also reported by Hugenholtz *et al*[30] in a large ($n = 270$) prospective study where 43% of patients with cholestatic liver disease had hypercoagulability MA values beyond the normal range. Contrary to what would be expected, 80% of patients with obstructive jaundice had hypercoagulable status on TEG analysis (increased MA), which was independent of prolonged PT[31]. However, three weeks after a biliary drainage procedure, all TEG parameters had returned to normal range.

It is still not clear whether a hypercoagulable status increases the risk of PVT[32]. It is tempting to assume that hypercoagulability in cirrhotic patients puts them at a higher risk of thrombosis. However, scarce data is supporting this hypothesis. Moreover, among the thrombotic risk factors, the lower portal velocity is the only independent factor of PVT [odds ratio of 44.9 (95% confidence interval (CI): 5.3-382)] [33]. The existing evidence is contradictory. Hugenholtz *et al*[30] found no difference in TEG parameters at baseline between patients who developed PVT (8 out of 270 patients followed almost three years). In another study[34], in patients with cirrhosis and gastroesophageal varices, TEG's R was significantly lower in the group with PVT (5.20 vs 6.00 , $P = 0.009$), a sign of enhanced coagulation activity.

The evidence is more apparent in patients with hepatocellular carcinoma (HCC). In HCC patients, the fibrinogen and the MCF in the FIBTEM module were higher in patients who developed PVT during follow-up than those who did not (24 mm vs 16 mm, $P = 0.04$). An increased baseline MCF FIBTEM (0.25 mm) was linked to a higher risk of developing PVT in HCC patients [risk ratio: 4.8 (95%CI: 2-11.3), $P = 0.0001$][35]. These findings might be valid for cirrhosis patients and no HCC, which still needs to be proved.

Regarding the treatment of PVT, which is still a matter of debate, it would be ideal that the VET's parameters would predict which patients will recanalize with anticoagulation treatment and who will experience spontaneous recanalization. TEG use to guide antithrombotic therapy has been reported in Budd-Chiari syndrome (BCS)[36]. However, the problem is much more complicated as TEG's hemostasis proved to be heterogeneous in BCS. Contrary to the general belief that all patients with BCS have a hypercoagulable status, 20% of patients have a hypocoagulable status based on TEG [37]. However, large-scale prospective studies are mandatory to evaluate the impact of VET in managing PVT in cirrhotic patients.

Another real clinical dilemma is the ability to monitor the efficacy and safety of anticoagulant therapy in patients with liver diseases. First, patients with cirrhosis can develop vein thrombosis despite a prolonged INR[23]. Second, monitoring the efficacy of LMWH using anti-factor Xa is not readily available[38]. Third, TEG was shown to be a sensitive method for monitoring LMWH efficacy in non-cirrhotic patients[39]. And last, the use of LMWH in 70 patients with advanced cirrhosis completely abolished the risk of PVT compared to 17% in the control group[40]. Altogether, the use of point of care VET could be a solution for this scenario.

Coagulation in acute-on-chronic liver failure

When it comes to acute multisystem imbalances, such as acute-on-chronic liver failure (ACLF), available data is relatively scarce, and reliable reports are rare.

It is essential to recognize the distinctive features of ACLF, to understand better its impact on coagulation and why precise assessment is needed[41]. Along with the classic liver failure features, the clinics are dominated by a marked systemic inflammatory response syndrome, often associated with bacterial infections, sequentially leading to multiple organ failure and, ultimately, death[42]. The typical ACLF patient is either treated in a high-dependency or an intensive care unit, requiring multiple invasive procedures[41,42]. In this light, an adequate assessment of their coagulation status appears to be particularly important. Based on prior experience with compensated and decompensated liver disease, the validity of standard coagulation tests (SCTs) in accurately assessing coagulation and bleeding risk in this clinical setting may yet again stand on shaky grounds.

Most of the VETs' data is relatively recent. It comprises monocentric reports, typically including less than one hundred patients with ACLF, assessing coagulation *via* ROTEM or TEG.

To this point, three available published reports are assessing the role of TEG in ACLF, all on Asian populations. In 2018, Goyal *et al*[43], comparing the coagulation profile of 68 ACLF patients with non-ACLF acutely decompensated patients and healthy controls, revealed a stark increase in SCT alteration with liver disease severity. Yet, the dynamic assessment was mostly normal, except for the reduced MA in ACLF, entailing a minimally altered coagulation profile. These findings might suggest that SCTs better reflect liver failure, rather than *per se* coagulation failure, as the diagnostic criteria for ACLF would imply. However, conclusions drawn from this dataset are in relative discordance with the other two available reports.

The patients who developed sepsis had a worse coagulation profile, tilted towards hypocoagulation, expressed by a higher R time[44]. In addition, among the enrolled ACLF patients, those with a hypocoagulation TEG profile had a significantly higher risk of bleeding [hazard ratio (HR) 2.1; CI: 1.6-4.9; $P = 0.050$] and short-term mortality (HR 1.9; CI: 1.3-7.9; $P = 0.043$). A more recent Chinese report[45] compared 51 hepatitis B virus-related cases of ACLF with healthy controls and patients with fully compensated chronic hepatitis B. They found that the coagulation dynamics were significantly altered in ACLF, with higher R and K times and lower α angles and MAs, corresponding to a marked hypocoagulable state. However, in this case, the comparison groups may not be ideal because healthy subjects are at the opposite spectrum of the disease than ACLF patients. Here, SCTs and TEG variables appeared to follow a concordant trend line. Furthermore, 90-day mortality was significantly associated with hypocoagulation within the ACLF group, as patients with ACLF and low MA were prone to a worse outcome.

While the studies were significantly different in design, a fragile common ground seems to emerge. While not all patients appear to have a marked coagulation imbalance, those who do tend to be in a hypocoagulable state appear to have a worse outcome.

Studies using ROTEM for assessing the coagulation profile have reached similar conclusions to those using TEG. One report comparing 36 ACLF patients to 24 non-ACLF acutely decompensated patients estimated transfusion requirement, bleeding events, and short-term mortality[46]. On admission, patients with ACLF had a more

hypocoagulable state, and the parameters worsened at 72 h, contrasting to the control group, which had an improved coagulation profile. Hypocoagulation was associated with a marked pro-inflammatory status and led to increased 28-d mortality. However, there was no association with an increased risk of bleeding events or transfusion requirements despite a worse coagulation profile. Of note, while SCTs and ROTEM variables followed the same trend line, ROTEM was a better outcome predictor. A second study, published in 2020, compared 22 ACLF patients with a compensated control group[47]. In this small dataset, the agreement between SCTs and ROTEM was slightly better in the ACLF group, which had a more hypocoagulable state. Besides, bleeding events were more frequent among ACLF patients with a worse coagulation function.

VET in liver transplantation

Historically, orthotopic liver transplantation (OLT) was associated with significant blood loss and the need for massive blood product transfusions[48]. Recently, with the new concept of rebalanced hemostasis, a more conservative attitude towards transfusion of red blood cells (RBC), fresh frozen plasma (FFP), or platelets is proposed. VET-guided transfusion algorithms to treat coagulopathy in OLT were first proposed by Kang *et al*[16] in the 1980s. They evaluated the blood coagulation system of 66 consecutive patients undergoing liver transplantation using TEG or standard liver transplantation monitoring and assessed the first clinical use of TEG in OLT. The use of TEG contributed to a 33% reduction of RBC, FFP, and platelet transfusion, whereas blood loss was comparable in all patients.

Comparing the standard management with ROTEM-guided hemostatic control results in a significant reduction of transfused RBC, FFP, and platelets in the ROTEM group[49]. Moreover, the number of blood product-free transplantations increased from 5% to 24% ($P < 0.001$). Secondary endpoints like reintervention for bleeding, acute kidney failure, or hemodynamic instability were significantly lower in the ROTEM group.

During liver transplantation, enhanced physiological fibrinolysis can occur, especially during the anhepatic period due to lack of tPA clearance. Immediately after reperfusion, there is a substantial increase in tPA, which can lead to hazardous primary hyperfibrinolysis resulting in diffuse uncontrolled bleeding. Suppose the graft has a good function the hyperfibrinolysis after reperfusion is self-limiting and does not require treatment. Hyperfibrinolysis in OLT has been reported very frequently (range 5%-84%), mainly during the transplanted liver[50,51]. However, most fibrinolysis is self-limiting and shall only be treated when it occurs concomitantly with excessive bleeding[50].

In the context of OLT, VETs are particularly useful for detecting the presence of systemic fibrinolysis[52] and also to detect poor clot strength that is often the result of low fibrinogen levels[52,53]. Therefore, the VET parameters for fibrinogen (FIBTEM or TEG functional fibrinogen) are essential to avoid over transfusion of platelets to increase the MA or MCF[52], which is associated with higher mortality[54].

The risk-benefit balance of the routine use of prophylactic antifibrinolytic agents (*e.g.*, tranexamic acid 1-2 g) shifted to a more precocious use of antifibrinolytics, in high-risk patients or treatment only, since massive bleeding is less frequent. Because hyperfibrinolysis-induced bleeding may manifest in the postreperfusion stage of surgery and depends on the donor liver's quality, the assessment is more difficult[55]. Treatment with antifibrinolytics is recommended only when there is evidence of microvascular ooze or documented fibrinolysis (CLI > 15) on TEG/ROTEM[56].

Conventional coagulation tests give no information where the balance in the coagulation lies since they do not provide a composite picture of the interaction of plasma, blood cells, and platelets. Some data suggest that VET detected hypercoagulability increases individual patients' risk for both venous and arterial thrombotic events[57,58] and is associated with high morbidity and mortality rates[59].

In a systematic review[60] to predict postoperative thromboembolic events by TEG, the most relevant parameter was MA. However, there was significant inhomogeneity among the included studies regarding the definition of hypercoagulability, and the majority of them were underpowered. It seems that hypercoagulation is more common in alcoholic and viral cirrhosis, and most often during the anhepatic phase (28%)[61]. Moreover, there is an association between hypercoagulation TEG profile and intracardiac thrombi. Despite conventional tests proving hypocoagulation, more than 70% of cases demonstrated TEG parameters compatible with hypercoagulation[62].

THE HEMOSTASIS ASSESSMENT BEFORE INVASIVE PROCEDURES IN PATIENTS WITH CIRRHOSIS

Traditionally, due to the presence of thrombocytopenia and hypoprothrombinemia, it was considered that the patients with cirrhosis have an increased risk of bleeding after interventional procedures[14,63]. Consequently, guidelines have recommended the correction of INR and platelets deficits through FFP or platelet transfusion before invasive procedures to prevent bleeding complications[64]. Arguments against this fear were raised by liver transplantation, which can be easily performed without blood product replacement[63,65]. Moreover, recent studies show little evidence for a higher prevalence of post-procedural bleeding following invasive procedures[63]. In 6 trials studying the prevalence of severe bleeding after interventional procedures (of low, high, and intermediate-risk) was 0.69%, range 0%-2.75% (50 out of 7146)[63]. In one prospective Italian study, the incidence of bleeding among 380 cirrhotic with or without abnormal coagulation parameters (defined as an INR ≥ 1.5 and/or platelet count $\leq 50 \times 10^9/L$) was zero for low-risk procedures like paracentesis[66]. High-risk procedures like percutaneous liver biopsy and percutaneous ablation were associated with higher bleeding rates in the abnormal coagulation group than the normal coagulation group. When analyzing in detail, the presence of sepsis and Child-Pugh C cirrhosis was associated with a higher incidence of bleeding in the abnormal coagulation group[67]. One large retrospective single-center study from the United States analyzed bleeding complications from 3357 liver biopsies and found a bleeding rate of 0.6%[68]. The median pre-biopsy platelet count, PT, and APTT (activated partial thromboplastin time) did not differ between patients that experienced or not bleeding complications; however, multivariate logistic regression identified a combination of APTT > 35 s and platelet count $\leq 100 \times 10^9/L$, as independent predictors of bleeding risk[67]. Seeff *et al*[68] found a bleeding rate of 0.6% in 2740 cirrhotic patients undergoing liver biopsy. In this study, a platelet count of less than $60 \times 10^9/L$ was associated with a higher risk of bleeding meanwhile, an INR above 1.5 was not[68].

Therefore, the INR is not an accurate predictor of bleeding events in patients with cirrhosis. However, most of the studies have shown that severe thrombocytopenia was associated with a higher risk of bleeding, although the cut-off values were different in several studies ($50 \times 10^9/L$ - $75 \times 10^9/L$)[14,63]. Reflecting the recent findings showing that cirrhotic patients are more often on a procoagulant slope[14,63], conventional coagulation tests are limited in predicting bleeding risk in cirrhosis because they do not account for the true *in vivo* coagulation status[69,70]. A systematic review comparing cirrhotic patients with a prolonged INR to those with normal INR found no difference in bleeding between the groups[13].

Role of VET before invasive procedures in cirrhosis

Conventional SCTs (PT and aPTT) omit thrombomodulin, which activates protein C and, thus, downregulating *in vivo* the thrombin generation. Therefore, the SCTs are not suitable to investigate acquired deficiency of both pro- and anticoagulants as occurs in cirrhosis[64].

Four studies have assessed the role of TEG before invasive procedures in cirrhosis (Table 2). All four studies reported a statistically significant reduction in overall blood product use with TEG guided transfusion[64,71-73]. The trials reported different outcomes regarding the transfusion of specific blood products such as FFP, platelets, and cryoprecipitate. A statistically significant reduction in platelet transfusion was reported in all studies[64,65,71-73]. The most striking difference was in the study of Vuyyuru *et al*[71], where only 10.3% of patients with cirrhosis undergoing interventional procedures needed platelet transfusion when guided by TEG compared to 75.9% when guided by conventional methods. The number of platelets used for transfusion was significantly lower in 3 of 4 studies[64,72,73]. Interestingly the number of platelets transfused was significantly lower for high-risk procedures (6 units *vs* 78 units, $P < 0.001$) but not low risk[64].

Three out of four studies reported a statistically significant reduction in FFP use[64,72,73]. In the study of De Petri 0% required FFP in the TEG arm compared to 53.3% in the conventional arm ($P = 0.001$)[64]. The absolute volume of FFP transfused was also markedly reduced in the TEG arm, where 4400 mL of FFP was transfused compared with 17550 mL in the control arm[64]. The difference was also maintained in upper gastrointestinal bleeding (both variceal and non-variceal)[72,73]. The amount of cryoprecipitate transfused was also lower with TEG in non-variceal bleeding (4 units in the TEG group compared with 16 in the standard of care group)[73].

Table 2 Role of thromboelastography prior invasive procedures in cirrhosis

Ref.	Type of invasive procedure	Threshold for intervention	Transfusion	Blood products transfused (%) / total amount of FFP (mL) and PLT (units)	Bleeding complications (%)	No. of death
De Pietri <i>et al</i> [64] (2016)	All invasive procedures (low and high risk)	TEG: FFP R > 40 min; PLT MA < 30 mm. SOC: FFP INR > 1.8; PLT transfusion PLT < 50000/mm ³	TEG guided (<i>n</i> = 30); SOC (<i>n</i> = 30)	TEG guided/SOC: All % 16/100; FFP % 0/53.3; PLT % 6.7/33.3; FP + PLT % 3/13.3. Low risk procedures: FFP (mL) 4000/11050; PLT (unit) 22/28. High risk procedures: FFP (mL) 0/6500; PLT (unit) 6/78	TEG 0; SOC 3.3	TEG 8; SOC 7; 90 d
Vuyyuru <i>et al</i> [71] (2020)	All invasive procedures (low and high risk)	TEG: FFP R > 14 min; PLT MA < 33 mm. SOC: FFP INR > 1.8; PLT transfusion PLT < 50000/mm ³	TEG guided (<i>n</i> = 29); SOC (<i>n</i> = 29)	TEG guided/SOC: All % 27.6/96.6; FFP % 24/27; PLT % 10.3/75.9; FFP + PLT % 3.4/3.4	TEG 0; SOC 0	TEG 0; SOC 1; 28 d
Rout <i>et al</i> [72] (2020)	Procedures for treating variceal bleeding	TEG: FFP R > 15 min; PLT MA < 30 mm, SOC: FFP INR > 1.8; PLT transfusion PLT < 50000/mm ³	TEG guided (<i>n</i> = 30); SOC (<i>n</i> = 30)	TEG guided/SOC: All % 13.3/100; FFP % 13.3/46.7; PLT % 10/70; FFP + PLT % 10/16.7; FFP (mL) 4000/11050; PLT (mL) 450/3450	Rebleeding 5 d; TEG 3.3; SOC 13.3. Rebleeding 42 d; TEG 10; SOC 36.7	TEG 13; SOC 26
Kumar <i>et al</i> [73] (2020)	Procedures for treating nonvariceal bleeding	TEG: FFP R > 10 min; PLT MA < 55 mm; CryoP angle < 45. SOC: FFP INR > 1.8; PLT transfusion PLT < 50000/mm ³ . CryoP Fibrinogen < 80 mg%	TEG guided (<i>n</i> = 49); SOC (<i>n</i> = 47)	TEG guided/SOC: All % 26.5/87.2; FFP 4.1/0; PLT % 4.1/0; FFP + PLT % 14.3/0; Cryo % 12.2/0; Cryo + PLT % 8.2/4.3; CryoP + FFP % 16.3/8.5; None % 14.3/0; FFP (mL) 440/880; PLT (unit) 1/2; CryoP (unit) 4/16	Failure to control bleeding at 5 d. TEG 22.4; SOC 29.8. Failure to prevent bleeding after 5 d. TEG 50; SOC 57	TEG 22.4; SOC 29.8; 5 d. TEG 55; SOC 66; 42 d

TEG: Thromboelastography; INR: International normalized ratio; SOC: Standard of care; FFP: Fresh frozen plasma; PLT: Platelets; CryoP: Cryoprecipitate.

There was no statistically significant difference in blood loss and bleeding events in the two trials, which examined the use of TEG before an invasive procedure [64,71]. It is important to emphasize that the bleeding rates were low in both arms [64,71].

There was no difference in the control of initial bleeding between the TEG and conventional hemostasis assessment in the two trials in cirrhotic patients with upper gastrointestinal bleeding [72,73]. In those with variceal bleeding, the re-bleeding rate at 42 d was lower in the TEG guided transfusion group (10% *vs* 26.7%, *P* = 0.012) [72]. This advantage is not surprising since the over transfusion was associated with worse bleeding control and prognostic in cirrhosis patients [74].

Still, when considering overall mortality [64,71-73], length of stay in the intensive care unit [73], and the number of days in the hospital, there is no difference between the two guiding modalities [73].

One of the main advantages of using TEG for hemostasis assessment may be reducing transfusion-related adverse effects, 30.6% in the TEG group *vs* 74.5% in the control arm [73].

CONCLUSION

Recently, VETs of hemostasis are increasingly used for “point-of-care” assessment of complex hemostatic abnormalities. These tests' advantages lie in providing real-time, dynamic information about the whole coagulation process, including clot initiation (thrombin generation), clot kinetics, clot strength, and clot stability (lysis). In cirrhosis, SCTs are reliable tools in assessing liver function, but they fail to evaluate the hemostasis correctly. VET based assessment of bleeding risk and VET-guided transfusion strategies have been shown to reduce blood product use in cirrhotic patients who require invasive procedures and those presenting with variceal and non-variceal gastrointestinal bleeding. The reduction in blood product use was not associated with an increased risk of bleeding, the difference in controlling bleeding, morbidity, or mortality compared to standard care. The main disadvantage is related to the lack of extended validation in cirrhosis using more robust endpoints. By now, in the majority of the interventional randomized validation studies, the primary endpoint was the transfusion reduction, with eventual benefit extended to clinical endpoints as bleeding or survival. Therefore, all these studies were underpowered for reliable validation of some robust endpoints, and, thus, the VETs use is not widely available.

However, the standardization of TEG cut-off is mandatory to ensure a more reproducible evaluation of bleeding risk in cirrhosis patients.

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