# Hemostasis testing in patients with liver dysfunction: Advantages and caveats

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*MINIREVIEWS*

# Hemostasis testing in patients with liver dysfunction: Advantages and caveats

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## Abstract

Due to concomitant changes in pro- and anti-coagulant mechanisms, patients with liver dysfunction have a "rebalanced hemostasis", which can easily be tipped toward either a hypo- or a hypercoagulable phenotype. Clinicians are often faced with the question whether patients with chronic liver disease undergoing invasive procedures or surgery and those having active bleeding require correction of the hemostasis abnormalities. Conventional coagulation screening tests, such as the prothrombin time/international normalized ratio and the activated partial thromboplastin time have been demonstrated to have numerous limitations in these patients and do not predict the risk of bleeding prior to high-risk procedures. The introduction of global coagulation assays, such as viscoelastic testing (VET), has been an important step forward in the assessment of the overall hemostasis profile. A growing body of evidence now suggests that the use of VET might be of significant clinical utility to prevent unnecessary infusion of blood products and to improve outcomes in numerous settings. The present review discusses the advantages and caveats of both conventional and global coagulation assays to assess the risk of bleeding in patients with chronic liver disease as well as the current role of transfusion and hemostatic agents to prevent or manage bleeding.

**Key Words:** Hemostasis; Bleeding risk; Conventional tests; Thrombin generation; Viscoelastic tests; Hemostatic agents

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**Core Tip:** Patients with liver dysfunction have a "rebalanced hemostasis" which can easily be tipped toward either a hypo- or a hypercoagulable phenotype. Clinicians are often faced with the question whether patients with liver dysfunction undergoing invasive procedures or surgery and those having active bleeding require correction of hemostasis abnormalities. While conventional coagulation screening tests have numerous limitations and do not predict the risk of bleeding prior to high-risk procedures or during surgery, a growing body of evidence suggests that viscoelastic testing might be of significant clinical utility in this setting. The present review discusses the advantages and caveats of both conventional and global coagulation assays in patients with chronic liver disease and the current role of hemostatic agents to prevent and manage bleeding.

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## INTRODUCTION

The liver plays a crucial role in synthesizing numerous plasma proteins, including most of the clotting factors except factor VIII and von Willebrand factor (VWF)[1-3]. Liver cells also produce thrombopoietin (TPO), which is the primary regulator of megakaryopoiesis, accounting for approximately 90% of the overall platelet production[4]. Therefore, liver dysfunction results in decreased levels of circulating pro- and anticoagulant factors, decreased levels of circulating pro- and antifibrinolytic factors, and thrombocytopenia, which all worsen with disease severity. Alterations in platelet number and function are, however, partially compensated by elevated levels of VWF and decreased levels of ADAMTS13.

For many years, liver dysfunction has been considered as an acquired bleeding disorder, and patients with acute or chronic liver disease thought to be naturally "autoanticoagulated". Nevertheless, recent advances in the understanding of changes occurring in the hemostasis balance during liver dysfunction (summarized in Figure 1) support a paradigm shift from "liver disease-associated coagulopathy" to "rebalanced hemostasis"[1-3].

This overall "rebalanced hemostasis" is nevertheless fragile and can easily be tipped toward either a hypo- or a hypercoagulable phenotype, leading to either bleeding or thrombotic complications[5].

Clinicians are often faced with the question whether patients with liver dysfunction undergoing invasive procedures or surgery and those having active bleeding require correction of hemostasis abnormalities. While conventional coagulation tests do not accurately predict the risk of bleeding, a growing body of evidence now supports a role for viscoelastic testing (VET) to monitor hemostasis in this setting.

The present review will discuss: (1) the advantages and caveats of both conventional and global coagulation assays to assess the risk of bleeding in patients with chronic liver disease; and (2) the current role of transfusion and hemostatic agents to prevent and manage bleeding in patients with liver dysfunction.

## EVALUATION OF THE HEMOSTASIS PROFILE OF PATIENTS WITH LIVER DYSFUNCTION

### *Platelet count*

Thrombocytopenia, as defined by a platelet count < 150 × $10^9$/L, is common in patients with chronic liver disease (CLD), particularly in those with portal hypertension. Its prevalence varies widely according to the underlying disease and its severity[6-8]. However, data regarding the association between thrombocytopenia and the risk of

**Hemostasis changes that may favor thrombosis or bleeding in patients with liver dysfunction**

| | Favors thrombosis | Favors bleeding |
|---|---|---|
| Primary hemostasis | Increased levels of VWF<br>Decreased levels of ADAMTS-13 | Thrombocytopenia<br>Platelet dysfunction<br>Increased levels of NO and prostacyclin |
| Coagulation | Increased levels of factor VIII. Decreased levels of antithrombin, protein C and protein S | Dysfibrinogenemia<br>Decreased levels of fibrinogen. Decreased levels of factor II, V, VII, IX, X, XI XII, XIII |
| Fibrinolysis | Decreased levels of plasminogen<br>Increased levels of PAI-1 | Decreased levels of α2-antiplasmin & TAFI<br>Increased levels of t-PA |

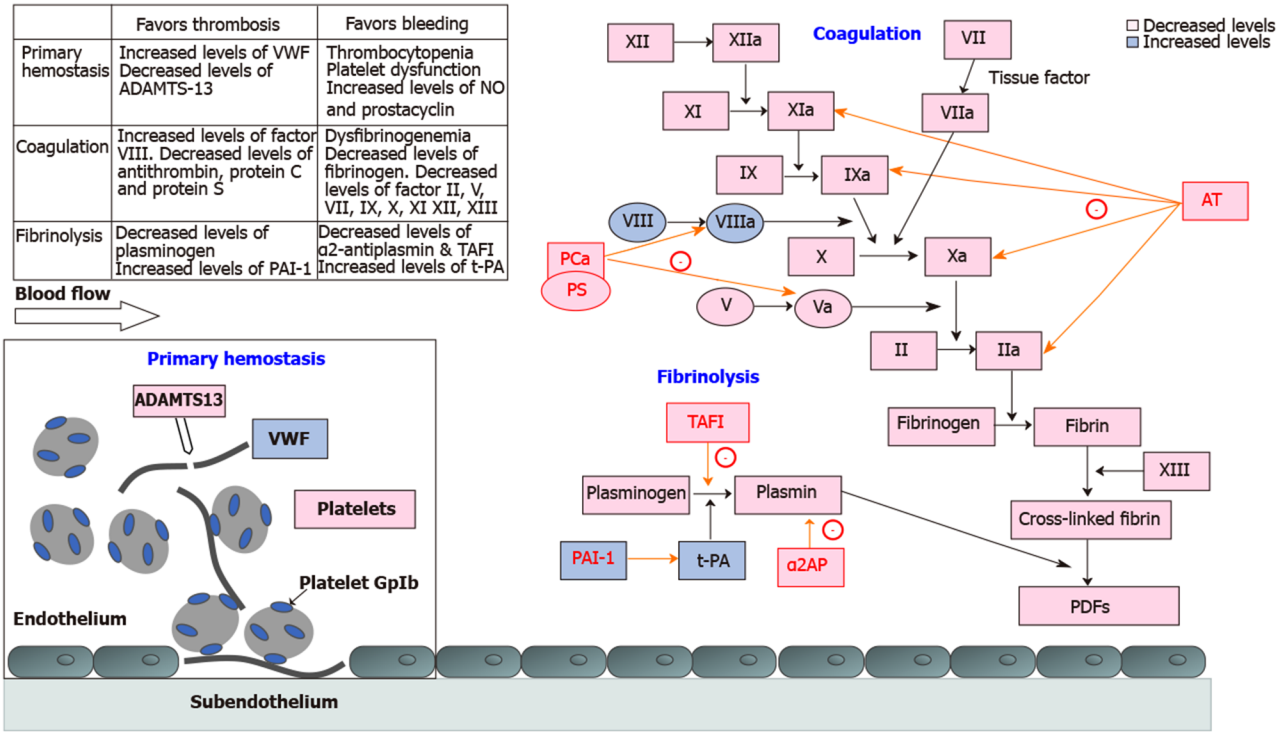


**Figure 1 "Rebalanced" Hemostasis in patients with liver dysfunction.** AT: Antithrombin; ADAMTS13: a disintegrin and metalloprotease with thrombospondin type I repeats-13; α2AP: α2-antiplasmin; PAI-1: Plasminogen activator inhibitor-1; PDFs: Fibrin degradation products; PC: Protein C; PS: Protein S; TAFI: Thrombin-activatable fibrinolysis inhibitor; t-PA: Tissue plasminogen activator; VWF: Von Willebrand factor.

bleeding in patients with liver dysfunction are conflicting.

In the PRO-LIVER study, 280 patients with cirrhosis were followed up for a median duration of 3 years. One hundred eighty-one (66%) patients had thrombocytopenia at inclusion while 23 (8%) of them had severe thrombocytopenia (defined as a platelet count < 50 × $10^9$/L). During the follow-up, bleeding occurred in 52 (18.6%) patients. However, platelet count did not predict the onset of unprovoked bleeding[9]. Similarly, platelet count did not predict the risk of bleeding in a case series of cirrhotic patients undergoing invasive procedure[10]. Conversely, severe thrombocytopenia was associated with a high risk of periprocedural bleeding in patients with advanced liver disease undergoing invasive procedure[11]. Severe thrombocytopenia also independently predicted the onset of major bleeding [odds ratio (OR) 6.476, 95%CI: 1.386-30.255, $P$ < 0.05] in a prospective study of 1493 critically ill patients with cirrhosis admitted to intensive care unit[12].

According to the 7th International Coagulation in Liver Disease Conference[13], platelet count alone is not sufficient to assess the risk of bleeding in patients with CLD. However, a platelet count < 50 × $10^9$/L may be associated with a high risk of bleeding.

### *Global platelet functional tests*

Global platelet functional tests are of low clinical utility in patients with liver dysfunction. Their use is limited by several factors including pre-analytical and analytical constraints, lack of standardization and their time-consuming nature. Moreover, none of them has been demonstrated to be clinically useful for stratifying the risk of bleeding in patients with liver dysfunction. The platelet function analyzer (PFA)-100® or PFA-200® closure time (CT) is the most widely used test to assess primary hemostasis. It measures the CT of an aperture within a membrane coated with either collagen/adenosine diphosphate or collagen/epinephrine under flow conditions. Importantly, this test is highly influenced by platelet count, VWF level and hematocrit, making the results challenging to interpret in many cases. Patients with stable cirrhosis or those with end-stage liver disease have been reported to have prolonged CT[14-16]. However, the prognostic value of CT in predicting bleeding complications in patients with liver dysfunction has yet never been investigated. Other functional platelet tests, such as light transmission aggregometry or whole blood aggregometry, have been extensively reviewed elsewhere[17-19].

The use of global platelet functional tests to assess the risk of bleeding in patients with CLD is not recommended by current guidelines.

### Conventional coagulation tests

Conventional coagulation tests, such as the prothrombin time (PT)/international normalized ratio (INR) and the activated partial thromboplastin time (aPTT), are commonly used for screening of inherited bleeding disorders and for monitoring of anticoagulant therapy. However, they are of limited value in patients with liver dysfunction since they predict neither the risk of bleeding complications nor the efficacy of blood cell product transfusion or hemostatic agent infusion[1-3].

PT and aPTT are both performed on platelet-poor plasma by measuring the time for fibrin clot formation after addition of phospholipids, calcium, and a trigger agent (tissue factor for the extrinsic pathway and kaolin, celite or ellagic acid for the intrinsic pathway). These tests only evaluate the time to the start of fibrin polymerization, knowing that 90% to 95% of thrombin generation occurs after this step. Importantly, they are insensitive to coagulation inhibitors (*e.g.*, antithrombin, protein C and protein S), which are also decreased in patients with liver dysfunction who have a "rebalanced" hemostasis. Furthermore, they contain low amount of thrombomodulin which is required to activate protein C. Finally, they do not provide any insight on clot lysis.

PT and aPTT are influenced by the level of procoagulant factors [*e.g.* factors I (fibrinogen), II, V, VII and X for the PT and factors I (fibrinogen), II, V, VIII, IX, X, XI and XII for the aPTT]. With the exception of factor VIII, procoagulant factors are heterogeneously decreased in patients with liver dysfunction. Therefore, PT and aPTT are frequently prolonged in patients with acute or CLD. Nevertheless, thrombin generation has been demonstrated to be preserved in patients with liver dysfunction and prolonged PT/aPTT[20], due to a concomitant decrease in anticoagulant levels.

Although the INR is currently used as a prognostic factor when calculating the model for end stage liver disease (MELD) score (which includes serum bilirubin, INR, serum creatinine, dialysis, and serum sodium[21]), it is important to emphasize that it was exclusively designed to monitor vitamin K antagonist therapy. Several studies have shown that its use is not appropriate for patients with liver dysfunction since it may vary for a single sample according to the reagent used[22,23]. A prospective study of 29 consecutive patients listed for liver transplantation (LT) reported that the between-laboratory variability in INR determination had a significant impact on the calculated MELD score[24], further suggesting the need to establish a "modified INR" specific for liver diseases[25].

According to the 7$^{th}$ International Coagulation in Liver Disease Conference[13], the American Association for the study of liver diseases (AASLD)[26], and the American Gastroenterology Association (AGA)[27], the PT/INR and the aPTT should not be used for assessing the risk of bleeding or for guiding blood products transfusion in patients with CLD.

Fibrinogen levels (Clauss assay) are determined by measuring the time for fibrin clot formation in the presence of excess thrombin. The clotting time expressed in seconds is converted to mg/dL by using a calibration curve prepared by serial dilution of a reference plasma of known fibrinogen concentration. Fibrinogen levels may either be normal, increased or decreased in patients with liver dysfunction[3]. Dysfibrinogenemia has been observed in up to 76% of patients with cirrhosis, 78% of those with chronic active liver disease and 86% of those with acute liver failure[28]. In a prospective cohort study of 165 patients with cirrhosis, low fibrinogen levels were associated with decreased survival in univariate analysis[29]. Fibrinogen levels < 60 mg/dL were a strong independent predictor for major bleeding (OR 11.129, 95%CI: 1.189-104.173, $P < 0.05$) in critically ill patients admitted to intensive care unit[12]. In a series of 109 cirrhotic patients undergoing endoscopic variceal band ligation, patients who bled had significant lower median fibrinogen levels compared to those who did not bleed (146 mg *vs* 230 mg/dL, $P = 0.009$)[30]. A fibrinogen level cut-off of 179 mg/dL predicted bleeding with a sensitivity of 83.3% and a specificity of 73.0%[30]. Finally, in a retrospective study of 322 patients undergoing orthotopic LT, baseline fibrinogen levels were found to predict excessive transfusion[31]. Additional studies are warranted to determine the best fibrinogen level cut-off for predicting the risk of bleeding.

### Global coagulation assay

Compared to conventional coagulation tests, global coagulation assays such as thrombin generation assays (TGA) or VET, which take into account the interactions between procoagulants, anticoagulants, platelet function and the fibrinolytic system,

are expected to better reflect the overall hemostasis profile, especially in patients with liver dysfunction who have a "rebalanced" hemostasis.

### Thrombin generation assays

TGAs have been developed in the 1950s. The most widely used method is the calibrated automated thrombogram[32], which dynamically quantifies the total amount of thrombin generated in platelet-poor plasma or in platelet-rich plasma after initiating the coagulation by the addition of tissue factor, phospholipids and calcium. Tripodi *et al*[20] reported that the profile of thrombin generation measured without thrombomodulin was decreased in cirrhosis patients compared to healthy controls, while it was normal in the presence of thrombomodulin (which is required for protein C activation), demonstrating for the first time that patients with liver dysfunction have a "rebalanced hemostasis". Recent TGA studies (reviewed elsewhere by Lebreton *et al* [33]) further reported that patients with liver dysfunction may have an hypercoagulable phenotype which seems to correlate with the disease severity[33]. Studies assessing the ability of TGA in predicting bleeding or thrombotic complications in patients with liver dysfunction are yet lacking. For now, there is still a need for standardization and automation of TGA methods.

According to the 7th International Coagulation in Liver Disease Conference[13], the use of TGA in patients with CLD should be restricted to clinical research studies.

### Viscoelastic tests

VETs, which are performed in whole blood, evaluate the *in vivo* dynamics of clot formation, clot stabilization and fibrinolysis. They are expected to provide a more accurate assessment of the overall hemostasis profile, and therefore to better predict the risk of bleeding and thrombosis. Nowadays, VETs are used as point-of-care testing and provide faster results than standard coagulation tests, which constitute an additional advantage.

Three methods are currently available, *i.e.*, thromboelastography (TEG, Hemonetics Corporation, Braintree, MA), thromboelastometry (ROTEM, TEM International GmbH, Munich, Germany) and sonorheometry (Quantra QPlus System, HemoSonics, LLC, Charlottesville, VA).

In patients with CLD, VET parameters correlate well with platelet count and fibrinogen levels (except in patients with fibrinogen levels < 100 mg/dL) but not with PT/INR and aPTT [34-42].

VETs have been mainly studied in patients with end-stage liver disease undergoing LT, but numerous studies have also been conducted in patients with less severe liver disease, including those well compensated.

### Viscoelastic tests in liver transplantation

Historically, the first orthotopic LT was performed by Starzl *et al*[43] in 1963. The recipient was a 3-year-old boy with congenital biliary atresia. Interestingly, coagulation was monitored by performing serial thromboelastograms[43]. Twenty years later, Kang *et al*[44] first suggested that VET-guided transfusion could substantially reduce blood products administration during LT. In their series of 66 patients undergoing LT, VET-monitoring was associated with a significant reduction in the administration of red blood cell units (17 ± 12.9 units *vs* 26.7 ± 23.8 units in the historical cohort, $P < 0.05$), fresh frozen plasma (FFP) units (18.3 ± 12.5 units *vs* 26.7 ± 24.1 units, $P < 0.05$) and total volume infused (20.2 ± 11.2 L *vs* 31.4 ± 19.2 L, $P < 0.05$). However, VET-guided transfusion led to a significant increase in the administration of platelets (20.8 ± 12.8 units *vs* 14.1 ± 13.7 units, $P < 0.05$) and cryoprecipitate units (17.2 ± 8.5 units *vs* 10.2 ± 4.5 units; $P < 0.05$). Numerous non-randomized studies further confirmed these findings[45-47].

Only two small randomized controlled trials (RCTs) compared VET-guided transfusion to the standard of care (SOC) during LT (Table 1)[48,49]. Importantly, they used different VET methodologies and various algorithms for VET-guided transfusion. Wang *et al*[48] randomized 28 adult patients with cirrhosis undergoing LT in either a TEG-guided transfusion arm or a SOC arm. Intraoperative administration of FFP was significantly reduced in the TEG-guided transfusion arm (12.8 ± 7.0 units *vs* 21.5 ± 12.7 units in the SOC arm, $P < 0.05$), without significant difference in the administration of other blood products between the two arms. In the TEG-guided transfusion arm, there was a trend towards reduction in blood loss (4775 ± 4264 mL *vs* 6348 ± 3704 mL in the SOC arm, $P$ = ns). More recently, Bonnet *et al*[49] randomized 82 adult patients with cirrhosis undergoing orthotopic LT in either a ROTEM-guided transfusion arm or a SOC arm. Median [interquartile range] intraoperative administration of blood

**Table 1 Randomized controlled trials assessing viscoelastic (tests) in patients with cirrhosis undergoing liver transplantation or invasive procedures and for the management of active bleeding**

| Ref. | VET | Population | *n* | Exclusion criteria | Intervention in the VET arm | Intervention in the SOC arm | Blood product | Bleeding |
|---|---|---|---|---|---|---|---|---|
| Liver transplantation | | | | | | | | |
| Wang *et al*[48], 2010 | TEG | Adult patients with cirrhosis undergoing liver transplantation | 28 patients (14 in each arm) | Unspecified | FFP titrated to maintain R time < 10 min; 6-8 pooled platelet units if MA < 55 mm; 5 pooled units of cryoprecipitate if alpha angle < 45 degrees | FFP titrated to maintain PT and APTT at less than one and a half times control; Platelets to maintain a platelet count ≥ 50 × $10^9$ /L; Cryoprecipitate to maintain fibrinogen > 1 g/L | FFP use: 12.8 units in the TEG arm *vs* 21.5 units in the SOC arm ( $P < 0.05$); RBC: no difference; Platelets use: no difference; Cryoprecipitate use: no difference | Trend towards reduction in blood loss in the TEG arm (not statistically significant) |
| Bonnet *et al*[49], 2019 | ROTEM | Adult patients with cirrhosis undergoing orthotopic liver transplantation | 82 patients (41 in each arm) | Pregnancy; congenital coagulopathy; patients participating in another study | 2 FFP units if EXTEM CT < 110 s; 1 platelet unit if EXTEM MCF < 40 mm or A10 < 35 mm and FIBTEM A10 or MCF > 8 mm; Fibrinogen 3 g if FIBTEM A10 < 8 mm | 2 FFP units if PT < 40% at baseline or an hepatic phase or hemorrhage; PT < 30% at declamping or end of surgery and no hemorrhage; 1 platelet unit if platelet count < 50 × $10^9$/L at baseline or an hepatic phase or hemorrhageor if platelet count < 30 × $10^9$/L at declamping or end of surgery and no hemorrhage; Fibrinogen 3 g if fibrinogen ≤ 1 g/L | FFP use: 6 patients in the TEG arm *vs* 19 patients in the SOC arm ($P = 0.002$); RBC use: no difference; Platelets use: no difference; Cryoprecipitate use: 29 patients in the TEG arm *vs* 12 patients in the SOC arm ($P < 0.001$) | No difference in revision surgery or postoperative hemorrhage at 24 and 48 h |
| Invasive procedure | | | | | | | | |
| De Pietri *et al*[51], 2016 | TEG | Adult patients with cirrhosis undergoing invasive procedures with an INR > 1.8 and/or platelet count < 50 × $10^9$ /L | 60 patients (30 in each arm) | Ongoing bleeding; current thrombotic events; antiplatelets or anticoagulants use; infection or sepsis; hemodialysis | FFP 10 mL/kg if R > 40 min; Platelets if MA < 30 mm | FFP10 mL/kg if INR > 1.8; Platelets if platelet count < 50 × $10^9$/L | 16.7% in the TEG arm *vs* 100% in the SOC arm ($P < 0.0001$) | 1 post procedure bleeding after large volume paracentesis in the SOC arm |
| Vuyyuru *et al*[52], 2019 | TEG | Adult patients with cirrhosis undergoing invasive liver-related procedures with INR > 1.8 and/or < 50 × $10^9$/L | 58 patients(29 in each arm) | Cancer; hemophilia; DIC; antiplatelets use; pregnancy; renal failure; blood products in the previous 7 d | FFP if R > 14 min; 6-8 pooled platelet units; if MA < 30 mm | FFP if INR > 1.8; 6-8 pooled platelet units; if platelet count < 50 × $10^9$/L | 31% in the TEG arm *vs* 100% in the SOC arm ($P < 0.001$) | No bleeding in any group |
| Rocha *et al*[53], 2020 | ROTEM | Adult critically ill patients with cirrhosis undergoing CVC insertion | 57 patients (19 per arm) | Acute liver failure; vonWillebrand's disease; anticoagulants use; patients participating in another study | FFP10 mL/kg if CT EXTEM > 80 s; 1 apheresis platelets unit if A10 EXTEM < 40 mm and A10 FIBTEM ≥ 10 mm; 1 unit/kg of cryoprecipitate if A10 ESTEM < 40 mm and A10 EXTEM < 10 mm | SOC arm: FFP 10 mL/kg if INR > 1.5 or aPTT > 50 s 1 unit/kg of platelets if platelet count < 50 × $10^9$ /L; 1 unit/kg of cryoprecipitate if fibrinogen < 150 mg/dL; Restrictive arm: FFP 10 mL/kg if INR > 5; 1 unit/kg of platelets if | Significantly lower in the restrictive arm (15.8% *vs* 68.4% in the ROTEM arm; $P < 0.006$ and *vs* 73.7%; $P < 0.002$) in the SOC arm. No difference between ROTEM and SOC arms | No major bleeding in any group |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | platelet count < 25 × $10^9$/L | | |
| Active bleeding | | | | | | | |
| Kumar *et al*[55], 2020 | TEG | Adult patients with advanced liver cirrhosis presenting with nonvariceal upper gastrointestinal bleeding with INR > 1.8 and/or platelet count < 50 × $10^9$/L | 96 patients (49 in the TEG arm, 47 in the SOC arm) | Variceal bleed; postvariceal ligation; ulcer bleed, previous or current thrombotic events; anticoagulant therapy at the time of enrollment or that had been discontinued less than 7 d before evaluation for the study; hemodialysis in the previous 7 d; pregnancy; significant cardiopulmonary disease | FFP 10 mL/kg if R > 10 min; 6-8 pooled platelet units if MA < 55 mm; 5 pooled units of cryoprecipitate if α-angle < 45 degrees | FFP 10 mL/kg if INR > 1.8; 6-8 pooled platelet units if plateletcount < 50 × $10^9$/L 5 pooled units of cryoprecipitate if fibrinogen < 80 mg/dL | Patients transfused with all three blood components: 26.5% in TEG *vs* 87.2% SOC ($P$ < 0.001) | No difference in failure to control bleeding or rebleeding on day 5. No difference in mortality on day 5 and on day 42 |
| Rout *et al* [56],2020 | TEG | Adult patients with cirrhosis presenting with acute variceal bleeding with INR > 1.8 and/or plateletcount < 50 × $10^9$/L | 60 patients (30 in each arm) | Malignancy; hemophilia; DIC; antiplatelets use; pregnancy; blood products in the previous 7 d; shock; sepsis; acute-on-chronic liver failure, renal failure, encephalopathy | FFP 5mL/kg if R > 15 min; 3 pooled units of platelets if MA < 30 mm | FFP if INR > 1.8; Platelets if platelet count < 50 × $10^9$/L | 13.3% TEG *vs* 100% SOC ($P$ < 0.001) | No difference in control of bleeding or rebleeding on day 5 between the two groups.Rebleeding on day 42 less in TEG (10%) than SOC (36.7% ; $P$ = 0.012) |

A10: Amplitude at 10 min; ACLF: Acute-on-chronic liver failure; aPTT: activated partial thromboplastin time; CCT: Conventional coagulation test; CT: Clotting time; CVC: Central venous catheter; DIC: Disseminated intravascular coagulation; INR: International normalized ratio; FFP: Fresh frozen plasma; MA: Maximum amplitude; R: Reaction time; ROTEM: Rotational thromboelastometry; SOC: Standard of care; TEG: Thromboelastography; VET: Viscoelastic test.

products was significantly decreased in the ROTEM-guided transfusion arm [3 (2–4) *vs* 7 (4–10) units in the SOC arm, $P$ = 0.005]. FFP was administered less frequently in the ROTEM-guided transfusion arm (15% *vs* 46.3% in the SOC arm, $P$ = 0.002). However, fibrinogen concentrates were administered more frequently (72.5% *vs* 29.3% in the SOC arm, $P$ < 0.001). There was no difference in revision surgery or postoperative bleeding at 24 and 48 h.

Overall, the body of evidence supporting the use of VET to guide transfusion during LT remains poor. Nevertheless, VETs have been widely adopted in most large-volume academic transplant centers, as reported in a recent survey[50].

### *Viscoelastic tests during invasive procedures*

Three small RCTs assessed the benefit of VET-guided prophylactic transfusion during invasive procedures (Table 1)[51-53]. De Pietri *et al*[51] randomized 60 adult cirrhosis patients with an INR > 1.8 and/or a platelet count < 50 × $10^9$/L undergoing invasive procedures in either a TEG-guided prophylaxis transfusion arm or a SOC arm. Nearly half of patients (47%) underwent low-risk procedures such as paracentesis or thoracentesis. FFP alone (0% *vs* 53.3%, $P$ < 0.001), platelets alone (6.7% *vs* 33.3%, $P$ = 0.021) and overall blood products (16.7% *vs* 100%, $P$ < 0.0001) were administered less frequently in the TEG-guided arm compared to the SOC arm. Post-procedure bleeding occurred in only 1 patient in the SOC arm after large-volume paracentesis.

A second RCT[52] randomized 58 adult cirrhosis patients with an INR > 1.8 and/or a platelet count < 50 × $10^9$/L undergoing high-risk invasive procedures (83% of liver biopsy) in either a TEG-guided prophylaxis transfusion arm or a SOC arm. Transfusions of any blood products (31% *vs* 100%, $P$ < 0.0001), and platelet transfusions (6.9% *vs* 42.4%, $P$ < 0.001) were administered less frequently in the TEG-guided arm. There was no difference in the rate of patients who received FFP. No procedure-related bleeding was observed.

Finally, Rocha *et al*[53] randomized 57 adult critically ill patients with cirrhosis undergoing central venous catheterization in three arms, *i.e.*, a restrictive strategy arm,

a SOC arm, or a ROTEM-guided arm. The restrictive strategy decreased the rates of any blood component administration compared to the SOC (OR 0.07, 95%CI: 0.01-0.45, $P$ = 0.002) and to the ROTEM-guided strategy (OR 0.09, 95%CI: 0.01-0.56, $P$ = 0.006). There was no difference in bleeding, length of stay, mortality, and transfusion□related adverse events between the three arms.

Overall, the current evidence suggests that the use of VET-guided transfusion during invasive procedures might significantly decrease the prophylactic infusion of blood products. However, the benefit of VTE monitoring during low bleeding risk procedures remains debated.

### *Viscoelastic tests in patients with liver dysfunction and active bleeding*

In a prospective study of 20 cirrhotic patients with active variceal bleeding, serial TEGs were performed daily for 7 d to assess the association between changes occurring in TEG profile and early rebleeding[54]. Patients who presented early rebleeding had longer median R (42 mm *vs* 24 mm, $P$ < 0.001) and median K (48 mm *vs* 13 mm, $P$ < 0.001) and smaller median alpha (12 *vs* 38, $P$ < 0.001) on the day of rebleeding compared with the mean of all daily results in patients who did not rebleed[54].

Two small RCTs evaluated the benefit of using VETs to monitor transfusion in cirrhotic patients with active upper gastrointestinal bleeding (Table 1)[55,56]. The first one randomized 96 adult patients with advanced liver cirrhosis, coagulopathy (as defined by an INR > 1.8 and/or platelet count < 50 × $10^9$/L) and active non-variceal upper gastrointestinal bleeding in either a TEG-guided transfusion arm or a SOC arm. The volume of FFP infused per patient was significantly lower in the TEG-guided arm (440 mL *vs* 800 mL in the SOC arm, $P$ < 0.001). Moreover, the rate of patients who received blood products was significantly lower in the TEG-guided arm (26.5% *vs* 87.2% in the SOC arm, $P$ < 0.001). The rates of control of bleeding, rebleeding, and mortality did not differ between the two arms[55]. The second RCT[56] randomized 60 adult patients with cirrhosis, coagulopathy (as defined by an INR > 1.8 and/or platelet count < 50 × $10^9$/L) and active variceal upper gastrointestinal bleeding in either a TEG-guided transfusion arm or a SOC arm. A significant reduction in the rate of blood product infusion was observed in the TEG-guided arm (13.3% *vs* 100% in the SOC arm, $P$ < 0.001). The rate of initial control of bleeding at the primary endoscopy and the rate of rebleeding at 5 d did not differ between the two arms.

Overall, a growing body of evidence indicates that VETs may be useful to guide transfusion, particularly in patients with active bleeding. Further studies to establish standardized algorithms and cut-off values to guide transfusion are warranted.

Nevertheless, some limitations of VTE leading to underestimate the true hemostatic potential should be acknowledged[57]. First, some VET parameters such as the maximum amplitude are frequently hypocoagulable in patients with liver dysfunction. This is mainly due to thrombocytopenia. However, it is important to notice that VETs are insensitive to VWF levels which are increased in patients with liver dysfunction, promoting platelet adhesion and partly compensating thrombocytopenia. Second, VETs are insensitive to the protein C system which requires the transmembrane protein thrombomodulin expressed on the luminal surface of endothelial cells to be activated. Third, VETs do not capture clot quality. Finally, most VETs parameters are obtained after the addition of an activator of the intrinsic pathway, which might not be relevant to study the physiological initiation of coagulation.

According to the 7$^{th}$ International Coagulation in Liver Disease Conference[13], the use of VETs in patients with CLD should be restricted to clinical research studies.

## CURRENT ROLE OF HEMOSTATIC AGENTS IN PATIENTS WITH LIVER DYSFUNCTION

### *Platelet transfusion and thrombopoietin agonists*

Platelet transfusion is the standard of care to transiently increase platelet count in patients undergoing invasive procedures or in those with active bleeding. A conventional threshold of 50 × $10^9$/L, which is exclusively based on expert opinion, is recommended by the AASLD[26]and the AGA[27]. However, *in vitro* studies have suggested that platelet-dependent thrombin generation should be preserved in patients with cirrhosis having a platelet count above 56 × $10^9$/L[58].

Due to platelet transfusion detrimental side effects, treatments stimulating endogenous production of functional platelets are increasingly used in CLD patients undergoing invasive procedures. Two second generation TPO receptor agonists

(avatrombopag and lusutrombopag) were recently approved by the Food and Drug Administration for the treatment of severe thrombocytopenia in this setting.

The ADAPT-1 and ADAPT-2 trials randomized a total of 435 CLD patients with severe thrombocytopenia (platelet count < 50 × $10^9$/L) undergoing a diagnostic or therapeutic invasive procedure to receive either avatrombopag ($n$ = 277) or placebo ($n$ = 158) daily for 5 d[59]. The primary endpoint was the rate of patients not requiring platelet transfusions or rescue therapy for bleeding within 7 d following procedure. In ADAPT-1, the rate of patients who met the primary endpoint was significantly higher in patients receiving avatrombopag (66% in patients receiving 60 mg avatrombopag *vs* 23% in the placebo arm, and 88% in patients receiving 40 mg avatrombopag *vs* 38% in the placebo arm). Similarly, in ADAPT-2, the rate of patients who met the primary endpoint was significantly higher in patients receiving avatrombopag (69% in patients receiving 60 mg avatrombopag *vs* 35% in the placebo arm, and 88% in patients receiving 40 mg avatrombopag *vs* 33% in the placebo arm). There was no difference in serious adverse events between the two arms.

The L-PLUS 1 trial randomized 96 CLD patients with severe thrombocytopenia (platelet count < 50 × $10^9$/L) undergoing an invasive procedure to receive either lusutrombopag ($n$ = 48) or placebo ($n$ = 48) daily for up to 7 d[60]. The primary efficacy endpoint was the rate of patients not requiring platelet transfusion before the invasive procedure. Seventy-nine percent of patients met the primary endpoint in the lusutrombopag arm *vs* 12% in the placebo arm ($P$ < 0.001). Lusutrombopag was well tolerated. The L-PLUS 2 trial randomized 215 CLD patients with severe thrombocytopenia (platelet count < 50 × $10^9$/L) undergoing an invasive procedure to receive either lusutrombopag ($n$ = 108) or placebo ($n$ = 107) daily for up to 7 d[61]. The procedure was scheduled 2 to 7 d after the last dose of lusutrombopag or placebo. The primary efficacy endpoint was the rate of patients not requiring platelet transfusion before the invasive procedure or rescue therapy for bleeding. Sixty-five percent of patients met the primary endpoint in the lusutrombopag arm *vs* 29 % in the placebo arm ($P$ < 0.001). There was no difference in serious adverse events between the two arms.

Importantly, TPO receptor agonists have a slow onset of action (5 d or more) and are indicated only in stable CLD patients having severe thrombocytopenia t without active bleeding who undergo planned elective procedures. Performing platelet count on the day of the procedure is warranted.

### FFP

FFP is commonly used to correct coagulation factor deficiencies in patients with active bleeding when coagulation tests are abnormal. However, there is currently insufficient evidence to support the prophylactic use of FFP in patients with CLD.

In an *in vitro* study of 58 patients with advanced cirrhosis (Child–Pugh B and C), addition of normal pooled plasma to plasmas from cirrhotic patients shortened both PT and aPTT ($P$ < 0.0001), without significant change in endogenous thrombin potential (ETP) in presence of thrombomodulin ($P$ = ns)[62]. In line with these results, a small sample study ($n$ = 53) found that infusion of FFP increased the ETP by only 5.7%[63]. Two out of 53 (3.8%) patients had baseline ETP below normal values and infusion of FFP corrected thrombin generation in only one out of two patients.

The only large multicenter, RCT aiming to assess the efficacy and safety of prophylactic FFP infusion in CLD patients undergoing invasive procedures[64] was unfortunately interrupted due to inadequate enrollment.

Potential detrimental side effects of FFP, such as transfusion-related acute lung injury or volume expansion leading to portal hypertension exacerbation, should be considered.

Based on available evidence, the AASLD[26] and the AGA[27] do not recommend using prophylactic infusion of FFP in CLD patients undergoing invasive procedures or surgery.

### Fibrinogen

Cryoprecipitates or fibrinogen concentrates are generally preferred over FFP to correct hypofibrinogenemia due to lower volume to infuse and best standardized fibrinogen content. Cryoprecipitates contain fibrinogen, von Willebrand factor and factor VIII. One unit of cryoprecipitate per 10 kg of body weight increases fibrinogen levels by approximately 50 mg/dL. In a randomized, multicenter, double-blind, controlled trial comparing preemptive fibrinogen administration to placebo during LT, preemptive fibrinogen infusion did not reduce blood products transfusion (RR 0.80, 95%CI: 0.57-1.13)[65]. In cirrhosis patients with active bleeding, maintaining fibrinogen levels above 120 mg/dL is generally required.

### Recombinant activated factor VII

The use of activated recombinant factor VII (rFVIIa) is restricted to patients presenting massive bleeding.

Two RCTs aiming to assess the efficacy and safety of rFVIIa on upper gastrointestinal or variceal bleeding in cirrhosis patients reported no difference between the rFVIIa and the placebo arms in the composite primary endpoint of failure to control acute bleeding, rebleeding within the first 5 d, and death within the first 5 d [66,67]. However, patients with variceal bleeding receiving rFVIIa had a significantly lower rate of 42-d mortality compared to those receiving placebo (15% *vs* 29%, OR 0.31, 95%CI: 0.13-0.74)[67].

Consensus guidelines on the use of rFVIIa as an adjuvant treatment for massive bleeding do not recommend using rFVIIa in patients with Child-Pugh A cirrhosis (grade B evidence)[68]. Furthermore, they consider its benefit as uncertain in patients with more advanced liver disease (grade C evidence)[68].

### Prothrombin complex concentrates

Data on the benefit of prothrombin complex concentrates (PCC) in patients with cirrhosis are limited to retrospective studies and case reports[69,70]. PCC infusion was reported to significantly reduce INR in critically ill cirrhosis patients, with lower amount of blood transfusion requirements compared to FFP. The ongoing double-blind, multicenter, placebo-controlled randomized PROTON trial comparing infusion of PCC *vs* placebo prior to surgery to reduce transfusion requirements in cirrhotic patients undergoing LT is expected to provide more data on the benefit of PCC in the near future[71].

### Desmopressin

The 1-deamino-8-D-arginine vasopressin (DDAVP) is commonly used to prevent blood loss in a variety of bleeding disorders. It has also been demonstrated to improve platelet function in patients with severe renal failure. An early study reported that intranasal DDAVP was effective and safe in cirrhotic patients undergoing dental extraction and having thrombocytopenia < 50 × $10^9$/L. However, later RCTs found no benefit of DDAVP administration in controlling acute variceal bleeding[72] or in preventing blood loss in CLD patients undergoing LT[73]. In line with these results, DDAVP administration did not improve VWF-dependent platelet adhesion in patients with cirrhosis in a flow-based model[74]. According to the AGA clinical practice guidelines, the use of DDVP in CLD patients should be restricted to those with concomitant end-stage renal disease[27].

### Antifibrinolytic agents

Data regarding the benefits and risks of antifibrinolytic agents to prevent or manage bleeding in patients with CLD are conflicting. A metanalysis pooled the results of several RCTs assessing their efficacy and safety to prevent blood loss in patients undergoing LT[75]. In the pooled analysis, aprotinin or tranexamic acid (TXA) reduced red blood cell and FFP transfusion requirements compared with placebo, without increasing the rates of hepatic artery and venous thromboembolism[75]. The recent international, randomized, double-blind, placebo-controlled hemorrhage alleviation with tranexamic acid-intestinal system (HALT-IT) trial randomized 12009 patients with gastrointestinal bleeding to receive either TXA or matching placebo[76]. TXA did not decrease death from gastrointestinal bleeding [risk ratio (RR) 0.99, 95%CI: 0.82–1.18] but it increased the risk of venous thromboembolism (RR 1.85; 95%CI: 1.15-2.98)[76]. Conversely a recent pooled analysis of 11 RCT including the HALT-IT trial found that TXA significantly decreased the risk of mortality compared to control (RR 0.75, 95%CI: 0.57-0.96)[77].

Based on available evidence, the AGA suggests using antifibrinolytic agents for a short duration to control periprocedural bleeding in case of hyperfibrinolysis[27].

## CONCLUSION

In patients with liver dysfunction, hemostasis is rebalanced due to concomitant changes in pro- and anti-coagulant mechanisms. In these patients, current conventional coagulation screening tests, such as the PT/INR and the aPTT, have numerous limitations and should not be used to predict the risk of bleeding prior to high-risk procedures. The introduction of global coagulation tests has been an important step

forward in the assessment of the overall hemostasis profile. There is nowadays a growing body of evidence suggesting that they might be of significant clinical utility to prevent unnecessary infusion of blood products and to improve outcomes in numerous settings. Further studies are, however, required to develop standardized algorithms and establish clinical practice guidelines for VET-guided transfusion in patients with liver dysfunction.

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