Invasive Procedures in Patients with Cirrhosis

A Clinical Approach Based on Current Evidence

Annabel Blasi, MD, PhD[a,b], Andres Cardenas, MD, MMSc, PhD[b,c,d,*]

KEYWORDS

• Cirrhosis • Coagulopathy • Thromboelastography • Platelet transfusion
• Plasma transfusion • Endoscopic band ligation • Invasive procedures
• Portal hypertension

KEY POINTS

- Patients with advanced liver disease have both pro- and antihemostatic pathways.
- All available laboratory tests of hemostasis have major limitations in patients with cirrhosis and lack data, especially as preprocedure risk measures.
- Platelet count values less than 50,000/μL may be associated with higher risk of bleeding, and platelet transfusion should be considered before high-risk procedures.
- Fresh frozen plasma should not be administered in patients with cirrhosis before an invasive procedure.

Patients with cirrhosis have several hemostatic disturbances. These are mainly caused by an altered synthetic capacity of the liver that leads to decreased concentrations of coagulation factors, inhibitors of coagulation, and fibrinolytic factors.[1] In addition, platelets are low because of decreased thrombopoietin (TPO) synthesis (mainly synthesized in the liver), platelet sequestration in the spleen, and increased platelet destruction. **Box 1** describes the multiple hemostatic derangements that occur in patients with cirrhosis. Hemostatic pathways in cirrhosis are for the most part rebalanced in an unstable manner, and this balance can tip in both directions, bleeding and thrombosis.[1,2] Hemostatic changes that lead to bleeding and clotting can occur at the same time; this explains why patients with thrombocytopenia can

Funding: A. Cárdenas is funded by the Instituto de Salud Carlos III and Plan Estatal de Investigación Ciéntifica y Técnica y de Innovación - Grant No PI19/00752 and has received funding for this work by Fundación Marta Balust."
[a] Anesthesia Department, Hospital Clinic of Barcelona, Villarroel 170, Barcelona 08036, Spain; [b] Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS) and Ciber de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [c] GI/Liver Unit, Institut Clínic de Malalties Digestives i Metabòliques, Hospital Clínic, Barcelona, Spain; [d] Department of Medicine, University of Barcelona, Spain
* Corresponding author. Institut de Malalties Digestives i Metaboliques, University of Barcelona, Hospital Clinic, Villarroel 170, Esc 3-2, Barcelona 08036, Spain.
E-mail address: acardena@clinic.cat

Clin Liver Dis 25 (2021) 461–470
https://doi.org/10.1016/j.cld.2021.02.001
liver.theclinics.com

Box 1
Alterations in the hemostatic system of patients with cirrhosis

1. Defective hepatic synthetic capacity of coagulation factors, inhibitors of coagulation, and fibrinolytic factors
2. Low circulating platelets caused by a combination of decreased TPO synthesis, splenomegaly with sequestration, or accelerated platelet destruction
3. Elevated plasma levels of hemostatic proteins synthesized by endothelial cells
4. Increased consumption of hemostatic proteins
5. Acquired disorders in platelet function
6. Modification of hemostatic proteins (eg, fibrinogen) result in altered function

develop venous thrombosis. Patients with advanced liver disease have both pro- and antihemostatic pathways that are altered, but in balance, that is why it is so challenging to determine their real hemostatic status with currently available clinical tests. All available laboratory tests of hemostasis have major limitations in patients with cirrhosis and lack data, especially as preprocedure risk measures. Because of the multiple and intricate factors involved in hemostatic pathways, none of the commercially available blood tests are reliable for assessing the risk of bleeding this patient population.[3] In addition, the interpretation of many of these tests, mainly the platelet count and prothrombin time and international normalized ratio (INR), vary depending on different clinical situations (ie, infection, renal failure, volume status, and endothelial dysfunction). This article summarizes current concepts of coagulation in cirrhosis, available tests used to predict bleeding, procedures and risk of bleeding, and the rationale and expert-based recommendations of prophylactic measures for patients with cirrhosis who undergo invasive procedures.

COAGULATION TESTS IN CIRRHOSIS

Table 1 describes the current coagulation tests in cirrhosis. The platelet count has traditionally been considered a parameter that can help guide the risk of bleeding and provide assessment of transfusion of platelets before procedures. That said, it is not a robust test that provides accurate information about primary hemostasis. Low platelet counts in patients with cirrhosis are mainly caused by decreased thrombopoietin production and splenic sequestration. Thrombocytopenia, defined as a platelet count below 150,000, is common in patients with cirrhosis, but levels below 50,000 occur in less than 2% of patients with cirrhosis.[3] However, elevated levels of Von Willebrand factor (vWF) protein, involved in platelet adhesion and platelet aggregation, offset this low platelet count.[4] Moreover, there is increased platelet activity in circulating platelets of patients with cirrhosis.[5]

Another commonly used test is the prothrombin time and the INR, which measures procoagulant factors I, II, V, VII, and X, but does not evaluate the status of anticoagulant factors such as protein C, S, or antithrombin; thus, it cannot assess the global hemostatic status in these patients. The INR is a calculation of the prothrombin time that was created to monitor oral anticoagulation with warfarin. It is normalized against warfarin-treated patients based on the activity of an added and commercially available thromboplastin reagent. This causes significant variation between different laboratories depending on which thromboplastin is used.[6,7]

The factor VIII/protein C ratio, as a balance of pro/anticoagulants, has been used to assess secondary hemostasis in patients with cirrhosis; however, the clinical

Table 1
Coagulation tests in cirrhosis

PT/INR	Designed for monitoring anticoagulation (warfarin) Does not help assess thrombin generation Does not help predict bleeding risk
Platelet count	Risk of spontaneous bleeding at very low levels (<15,000) Risk of bleeding after procedures <50,000
Fibrinogen levels	Not widely studied in cirrhosis, may help predict bleeding risk
Bleeding time	Does not predict the bleeding risk
Fibrinolysis	Not widely available
Global tests: thrombin generation Viscoelastic tests: thromboelastometry/ graphy	Ideal - clinical utility in cirrhosis is not well studied, mainly used in research Global viscoelastic tests (VETs) provide a more physiologic assessment of coagulation Thresholds have not been fully validated yet, do not predict bleeding risk

translation of this ratio is uncertain. Values in cirrhosis have a mean of 0.8, while in controls, it is of 0.66. Because the ratio correlates with the severity of liver disease, it allows differentiation between the presence of hepatic dysfunction from disseminated intravascular coagulation, which is associated with low levels of coagulation factors.[8]

Fibrinogen is a key step of the coagulation system, that can help predict the risk of bleeding. Target levels range from 100 to 200 mg/dL, but they are extrapolated from other settings.[9,10] Fibrinogen levels are typically low in patients with cirrhosis, because fibrinogen is synthesized by the liver. Additionally, the half-life of fibrinogen is shortened, and its function can be impaired in cirrhosis. Some patients with liver disease and prolonged thrombin times have a dysfibrinogenemia functionally characterized by an abnormality of fibrin monomer polymerization.[11,12] This deficiency is not reflected by the simple determination of fibrinogen plasma levels.

The whole blood tests, known as viscoelastic tests, include thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These tests depend on changes of a blood clot in a specific rotational machine and better simulate in vivo activity of the hemostatic pathways.[13] In most patients with compensated cirrhosis, clot formation, clot thickness, and clot lysis are preserved.[14] However, anticoagulant pathways are not considered in either of these tests, and normal range values were defined on healthy controls, without a specific cut off for patients with liver disease. ROTEM and TEG have been shown to be useful to guide transfusion in patients with cirrhosis who are actively bleeding during liver transplant and undergoing invasive procedures, but their ability to predict bleeding remains unknown.[15,16] From a clinical standpoint, the main input of ROTEM/TEG in patients with liver disease is the negative predictive value. A normal value means that despite abnormal conventional indices, the etiology of bleeding is not the coagulopathy.[17] This information can avoid unnecessary administration of procoagulants.

There are several concomitant situations that significantly impact on hemostasis. They are not assessed by the laboratory tests but need to be acknowledged, because they can tip the balance.

1. Volume status, portal-collateral pressure, and flow are important considerations. Volume administration/restriction interferes with coagulation factors and platelet concentration. Most bleeding in cirrhosis is related to portal hypertension, which should be lowered as the first hemostatic measure.[18,19]
2. For rheological reasons, once the hematocrit level drops below 25%, the erythrocyte concentration is insufficient to adequately push platelets toward vessel walls, reducing the platelet - endothelium interaction.[20]
3. Infections can lead to an additional increase in vWF levels (abnormally high in patients with cirrhosis), which elevates the risk for clotting. vWF levels may proportionally increase with the lipopolysaccharide blood concentration.[21,22]
4. Renal failure reduces the adhesive and aggregative properties of platelets.[23] Acute kidney injury has been associated with an increased risk of bleeding after low-risk procedures such as paracentesis in patients with decompensated cirrhosis[24]
5. Occult bleeding from gastrointestinal origin is common in patients with cirrhosis and can lead to iron deficiency that may increase the risk of clotting. Hypercoagulability in children with iron deficiency can be detected by thromboelastometry.[25]
6. Although controversial, bleeding can be attributed to hyperfibrinolysis. Current laboratory measures do not assess fibrinolysis, and thromboelastometry may not be sensitive enough to detect it. Hyperfibrinolysis can cause spontaneous mucocutaneous and other unusual bleeding manifestations and is more common in patients with decompensated cirrhosis and in those with acute liver failure.[26]

THRESHOLDS AND BLEEDING RISK

INR was developed to monitor anticoagulation with warfarin. The administration of fresh frozen plasma before an invasive procedure can worsen portal hypertension and in addition does not change thrombin production.[27]

Platelets before an invasive procedure can be administered in certain patients. The idea behind platelet transfusion prior to an invasive procedure in cirrhosis stems from in vitro data that have shown that platelet levels over 50,000 μL promote thrombin generation.[28] The most accepted target for platelet prophylaxis is the cut off less than 50,000 μ/L platelets; however, there are no clinical studies that support this contention. Most experts and guidelines suggest that the thresholds vary depending on the risk of the procedure and concomitant clinical scenario (active bleeding, infection, renal failure).[24] This value has ranged between 30.000 and 75.000.[29–31]

The currently used target levels of fibrinogen are not well studied in cirrhosis. Nonetheless, in a series including 211 patients with cirrhosis admitted to the intensive care unit (ICU), fibrinogen and platelet count were identified as adequate routine coagulation parameters for prediction of new onset of major bleeding. Bleeding on admission, platelet count less than 30,000 u/L, fibrinogen level less than 60 mg/dL, and activated partial thromboplastin time values greater than 100 seconds were the strongest independent predictors for new onset of major bleeding in a multivariate regression analysis. Median plasma fibrinogen values within 24 hours prior to occurrence of bleeding were 110 (range 63–161) mg/dL.[9]

CLINICAL SCENARIOS

Bleeding after an invasive procedure in patients with cirrhosis may be the consequence of multiple factors including hemostatic dysfunction, portal hypertension, and type of procedure. Measures aimed at preventing and treating bleeding need to consider the etiology and the type of procedure. The most common procedures in patients with cirrhosis like paracentesis and endoscopy have a low risk of bleeding even

with a high INR and thrombocytopenia (<50,000 μ/L). That said, bleeding risk assessment of any procedure is the first step to decide if prophylaxis is needed. This depends on the type of procedure, stage of cirrhosis (ie, Child class or model for end-stage liver disease [MELD] score), and other factors such as concomitant infection, renal failure, or endothelial dysfunction. There is no uniform classification for the risk of procedures, but procedure risk stratification should be based on specific procedure type when data are available. For instance, endoscopic band ligation in patients with cirrhosis is associated with delayed bleeding in less than 3% to 5% of patients after an ulcer falls off, and this usually occurs between 5 and 10 days after the procedure; thus the administration of platelets or other blood products does not protect the patient in that timeframe.[30,31] In a study of 150 patients with cirrhosis undergoing band ligation, platelet count and INR were not predictive of bleeding, but advanced cirrhosis (Child- C) was the most important predictor of bleeding.[32] The authors have adapted previously published guidelines,[30,31,33] dividing procedures into low, moderate, and high risk of bleeding (**Table 2**). The consequences of bleeding and the opportunity to quickly detect and control the bleeding should be considered in the assessment. This classification does not apply to pharmacologically anticoagulated patients and patients with renal failure who may be at increased risk for bleeding.

PROPHYLACTIC TRANSFUSION

Prophylaxis of Bleeding Before Invasive Procedures

There are no data to support a specific INR or platelet cutoff in which procedural bleeding risk is elevated. Therefore, because no solid data support transfusion thresholds, decisions need to be individualized.

Table 2
Procedural risk of bleeding in cirrhosis

Low-Moderate (<1.5–2%)	High (≥2%)
Polypectomy <1 cm	Mucosectomy/polypectomy ≥1 cm
Central line placement	Therapeutic bronchoscopy
Cardiac catheterization	Enteral or biliary dilatation, biliary sphincterotomy
Hepatic catheterization	Lumbar puncture/central nervous system procedures
Paracentesis	Balloon enteroscopy
Esophageal band ligation	Radiofrequency, transarterial chemoembolization of HCC
Endoscopy and colonoscopy	Percutaneous liver biopsy
Diagnostic endoscopic ultrasound	Therapeutic coronary angiography
Pacemaker/defibrillator placement	Endoscopic ultrasound- fine needle aspiration/ FNB
Diagnostic bronchoscopy without biopsy	Percutaneous gastrostomy
Diagnostic thoracentesis	Percutaneous biopsy of extrahepatic organ
Transesophageal echocardiogram	All major surgery (cardiac, intra-abdominal, orthopedic) and dental extractions
Skin biopsy	Transjugular intrahepatic portosystemic shunt, transjugular liver biopsy
Other	Intraocular therapy

Data from Refs.[30,31,33]

Thrombocytopenia

As mentioned before, in vitro studies suggest that platelet levels greater than 50,000/μL are required for thrombin generation in cirrhosis, but these data did not consider hemostatic compensation by vWF and other endothelial-based components.[28] In addition, this cutoff has not been validated as a predictor of bleeding in cirrhosis. Platelet transfusions are commonly used in patients with less than 50,000/μL before invasive procedures, but their half-life is short, and transfusions carry a potential for infections and transfusion-related lung injury syndromes. Studies have shown that the platelet count before the procedure does not accurately predict procedural bleeding complications.[29] Current guidelines suggest that an individualized approach is needed for patients with thrombocytopenia before procedures because of the lack of data in regards for safety and efficacy of transfusions platelet counts in patients with cirrhosis.[33] Based on published data, the authors administer prophylactic platelet transfusions in patients with severe thrombocytopenia (<30,000 μ/L) in low-risk procedures and use a cutoff of 50,000 μ/L platelets in those undergoing a high-risk procedure.

Two medications, avatrombopag and lusutrombopag, were recently approved by the US Food and Drug Administration (FDA) and European Medication Agency (EMEA). Both increase platelet counts in patients with cirrhosis by acting as TPO receptor agonists that promote the bone marrow to produce platelets.[34,35] Experience with these agonists is limited outside clinical trials. The indication is for elevating the platelet count in patients with cirrhosis who are scheduled for an outpatient procedure. These drugs are given 5 days before the procedure in those individuals with a platelet count less than 50,000. Both are comparable and achieve platelet counts greater than 50,000/μL prior to the procedure, and the elevation in platelet counts lasts for up to 2 weeks, which may be desirable in patients who develop delayed bleeding after a procedure. Both drugs showed no statistical differences in thrombotic complications compared with placebo.[34,35] Despite increasing the platelet count, neither medication was evaluated for postprocedural bleeding events.

There are no data on platelet cut-offs prior to procedures, and general interventions to increase platelet counts to specifically prevent bleeding are not well studied and should be individualized.

Factor deficiencies

As discussed previously, the INR only assesses quantitative problems with procoagulant clotting factors and thus is not a reliable test of hemostatic balance and does not predict procedural bleeding risk. The INR should not be used to assess procedural bleeding risk in patients who are not taking warfarin. Fresh frozen plasma (FFP) transfusion prior to procedures is associated with risks and no proven benefits. Large volumes of fresh frozen plasma (15–20 mL x Kg) are required to reach an arbitrary INR target, with minimal effect on thrombin generation (because FFP contains both pro and anticoagulants).[36] This volume can worsen portal pressure, and FFP transfusions carry a risk of transfusion-related lung injury syndrome.[27,37]

Recombinant factor VIIa can normalize the INR in patients with cirrhosis. However, a randomized clinical trial showed no role in the setting of acute variceal bleeding, and because it may carry a risk of thrombosis, it is not recommended.[38] The authors do not administer vitamin K unless the patient has malnutrition or prolonged cholestasis, because vitamin K replacement has minimal effect on the INR in patients with cirrhosis.

INR is no longer considered relevant as a hemostatic parameter, and as such there is no place for FFP administration before an invasive procedure.[30–33] The authors

consider is use deleterious and advice against is use as a prophylactic measure prior to invasive procedures in patients with cirrhosis.

Low fibrinogen

As mentioned before, low fibrinogen levels (<100 mg/dL) can be associated with spontaneous and procedure-related bleeding in critically ill patients with cirrhosis.[9] That said, it is believed that the low levels are mostly caused by critical illness and not liver dysfunction per se.[33] Hyperfibrinolysis is also uncommon in patients with cirrhosis, but there are no commercially available tests to evaluate hyperfibrinolysis in clinical practice.

There are scarce data on the use of fibrinogen-rich products in cirrhosis. These include cryoprecipitates and fibrinogen concentrate. Both increase fibrinogen levels in patients with cirrhosis, but there are no data to indicate that they prevent bleeding. Fibrinogen concentrate contains 1 g per vial, and the doses are based on baseline fibrinogen level (usually <100 mg/dL) and range from 2 to 4 g with a half-life of 2 to 3 days. The data on fibrinogen replacement are derived from experience in active bleeding during major surgery and liver transplantation but not in prophylactic bleeding for bleeding in patients with cirrhosis. That said, the authors and other experts do consider fibrinogen replacement in patients with cirrhosis and low levels of fibrinogen (<100 mg/dL) who will undergo a high risk procedure.

Prophylaxis and Active Bleeding

It should be considered that in most cases active bleeding in cirrhosis patients is related to portal hypertension. The authors use transfusion thresholds similar to those for high-risk procedures and during an acute bleed, the authors aim for a platelet count greater than 50,000 and fibrinogen levels above 100 mg/dL. Hemoglobin of 7 to 8 g/dL is the recommended target transfusion for red blood cells. Fluid administration and hemodynamic monitoring should be considered as a part of hemostatic treatment. It is now well documented that a restrictive fluid management strategy during bleeding is likely beneficial..[39] If fluids are needed (ie, hypotension/shock), the authors favor the use of crystalloids. Vasoactive drugs (somastostatin, terlipressin) are recommended to maintain mean arterial pressure greater than 65 mm Hg.

CURRENT RECOMMENDATIONS BASED ON AVAILABLE EVIDENCE

Most available data on testing for bleeding risk in cirrhosis are not validated. The standard tests used for the evaluation of hemostasis are the platelet count and fibrinogen. The INR level is not recommended as a test that predicts bleeding risk. Global tests of clot formation, such as ROTEM and TEG, are promising but need to be validated, and they need to evaluate the risk of bleeding, not only thresholds for transfusion. The authors do not routinely correct thrombocytopenia and coagulopathy before common low-risk procedures such as diagnostic paracentesis and routine upper endoscopy. The transfusion of platelets or fibrinogen carries a risk of transfusion-related acute lung injury and/or transfusion reactions. The authors advise against using FFP as it does not improve hemostasis and can cause circulatory overload. The authors do consider transfusion of platelets and/or fibrinogen for management of active bleeding and/or low- to high-risk procedures. They aim for a hemoglobin level greater than 7 g/L, platelet count greater than 30,000 to 50,000 μ/L, and fibrinogen greater than 100 mg/dL. Thrombopoietin agonists are promising and an adequate replacement of platelet transfusion in scheduled procedures. **Table 3** summarizes the authors' current practice, which is only based on their interpretation of the current data, expertise, and consensus among different specialties.

Table 3
Prophylaxis transfusion in cirrhosis

Low-Risk Procedure	High-Risk Procedure	Active Bleeding

• INR – not relevant
• Platelets ≤30.000
• Slant
  ○ Platelets or TPO agonist
	• INR – not relevant
	• Fibrinogen <100 mg/dL
	• Platelets ≤50.000
	• Slant
	  ○ Fibrinogen 50 mg/kg
	  ○ Platelets or TPO agonist
		• INR – not relevant
		• Fibrinogen <100 mg/dL
		• Platelets ≤50.000
		• Slant
		  ○ Fibrinogen 50 mg/kg
		  ○ Platelets or TPO agonist

CLINICS CARE POINTS

- INR and prothrombin time do not measure bleeding risk in cirrhosis. Fresh frozen plasma should not be administered.
- Platelet count values less than 50,000/μL may be associated with higher risk of bleeding, and platelet transfusion should be considered before high-risk procedures, but this practice lacks supportive data.
- Viscoelastic tests are not standardized/do not appear to fully predict bleeding or thrombosis.
- Thrombopoietin agonists in patients with thrombocytopenia (<50,000 μ/L) may have a role in pre-planned procedural prophylaxis.

DISCLOSURE

A. Cárdenas is a consultant for Mallinckrodt Pharmaceuticals, Boston Scientific Corp, Shionogi Inc., Sobi Pharmaceuticals and has participated on Advisory Boards for Mallinckrodt Pharmaceuticals and has received grant support from Mallinckrodt and Boston Scientific Corp.

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