Coagulopathy and hemostasis management in patients undergoing liver transplantation: Defining a dynamic spectrum across phases of care

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Abstract

Patients with acute and chronic liver disease present with a wide range of disease states and severity that may require liver transplantation (LT). Physiologic alterations occur that are dynamic throughout all phases of perioperative care, creating complex management scenarios that necessitate multidisciplinary clinical care. Specifically, alterations in hemostasis in liver disease can be pronounced and evolve with disease progression over time. Recent studies

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acutely decompensated; ADAMTS13, metalloproteinase with a thrombospondin type 1 motif member 13; ALF, acute liver failure; aPTT, activated partial thromboplastin time; AT3, antithrombin 3; DOAC, direct oral anticoagulant; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; LMWH, low molecular weight heparin; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; PCC, prothrombin complex concentrate; PELD, Pediatric End-Stage Liver Disease; PRBC, packet red blood cell; POD, postoperative day; Pt, prothrombin time; PVT, portal vein thrombosis; RBC, red blood cell; rFVIIa, recombinant Factor VIIa; ROTEM, rotational thromboelastometry; TAFI, thrombin activatable fibrinolysis inhibitor; TEG, thromboelastography; tPA, tissue plasminogen activator; TPO, thrombopoietin; VET, viscoelastic testing; VTE, venous thromboembolism; VKA, vitamin-K antagonist; vWF, von Willebrand factor.

Anjana A. Pillai and Michael Kriss contributed equally to this study and share co-first authorship.

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INTRODUCTION

Patients with acute and chronic liver disease may require liver transplantation (LT) during the course of their disease and present with a range of disease states. Dynamic alterations of hemostasis are common, and clinicians routinely face challenging scenarios when caring for this population. Recent studies and society guidance address this emerging paradigm and offer recommendations to assist with the management of bleeding and thrombosis in patients with liver disease. However, patients undergoing LT are diverse, often with unstable disease that requires specialized approaches.

Here we outline the hemostatic management of LT patients across various disease phenotypes to distinguish unique aspects of the three main phases of care (before LT, perioperative, and after LT) and to identify knowledge gaps for future research.

HEMOSTASIS IN LIVER DISEASE

Hemostasis is a dynamic process and occurs in three phases: primary hemostasis with primary platelet aggregation, secondary hemostasis with coagulation, and fibrinolysis. The balance between the prohemostatic and antihemostatic factors during the normal physiological state is altered in patients with cirrhosis. Because of alterations in both procoagulant and anticoagulant factors, the hemostatic system in patients with cirrhosis is rebalanced but can change toward thrombosis or bleeding under certain conditions.

Thrombocytopenia with platelet dysfunction, one of the earliest changes seen in patients with cirrhosis and portal hypertension, is attributed to splenic sequestration attributed to increasing portal hypertension and decreased synthesis of thrombopoietin (TPO). In addition, there are increased secretions of procoagulant proteins (von Willebrand factor [vWF] and Factor VIII) by endothelial cells. Most hepatocyte-derived coagulation and anticoagulation factors are low in cirrhosis and decrease as liver disease progresses. Elevated vWF and Factor VIII levels and low protein C levels contribute to a hypercoagulable state. In addition, low levels of α2-antiplasmin, Factor XII, and plasminogen and higher levels of tissue plasminogen activator affect fibrinolysis. Circulating fibrinogen is responsible for clot structure. Although most fibrinogen is synthesized by the liver, fibrinogen levels are well maintained in the early stages of cirrhosis, given that it is an acute-phase reactant, and fall in later stages of decompensated cirrhosis.

TRADITIONAL HEMOSTATIC ASSESSMENT TESTS

There is a poor correlation between traditional coagulation tests and thrombin-generating capacity in cirrhosis. Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) traditionally assess hemostasis; however, these tests measure only a discrete number of procoagulant and anticoagulant factors that can lead to an incomplete picture of hemostasis and have limitations in advanced liver disease and cirrhosis. PT/INR are usually prolonged in patients with decompensated cirrhosis as a result of reduced liver synthetic function; however, this does not account for all anticoagulant factors (including low levels of proteins C and S) and therefore does not correlate with bleeding risk and thus should not be corrected routinely with plasma transfusion. This is clearly demonstrated with studies using a modified thrombin generation assay, which adds thrombomodulin to activate protein C, thereby demonstrating a more accurate depiction of hemostasis in this population. Thrombocytopenia with platelet dysfunction, one of the earliest changes seen in patients with cirrhosis and portal hypertension, is attributed to splenic sequestration attributed to increasing portal hypertension and decreased synthesis of thrombopoietin (TPO). In addition, there are increased secretions of procoagulant proteins (von Willebrand factor [vWF] and Factor VIII) by endothelial cells. Most hepatocyte-derived coagulation and anticoagulation factors are low in cirrhosis and decrease as liver disease progresses. Elevated vWF and Factor VIII levels and low protein C levels contribute to a hypercoagulable state. In addition, low levels of α2-antiplasmin, Factor XII, and plasminogen and higher levels of tissue plasminogen activator affect fibrinolysis. Circulating fibrinogen is responsible for clot structure. Although most fibrinogen is synthesized by the liver, fibrinogen levels are well maintained in the early stages of cirrhosis, given that it is an acute-phase reactant, and fall in later stages of decompensated cirrhosis.
for platelet transfusions and demonstrates a reduction of platelet transfusion use.\textsuperscript{[26,27]} It remains unclear what level of thrombocytopenia represents an increased risk of bleeding in patients with cirrhosis.\textsuperscript{[9]}

Transfusion of blood products in patients with cirrhosis has risks, including exacerbation of portal hypertension from volume expansion, hemolysis, and infectious and immunologic complications. The risk of human leukocyte antigen or red cell antibody development from transfusion can impair the ability to receive further transfusions and impact subsequent transplantation.\textsuperscript{[28]} Transfusion-associated circulatory overload rates increase with the number of transfusions administered, and transfusion-related acute lung injury rates are higher when plasma-containing blood products, including platelets, are used.\textsuperscript{[29]} Blood products and transfusion thresholds are summarized in Table 1.

Whole-blood VET provides a comprehensive assessment of hemostatic balance, measuring the rate and strength of clot formation.\textsuperscript{[30]} These tests demonstrate intact pathways when conventional tests such as INR are prolonged; however, they lack well-defined thresholds for clinical interventions. These assays provide real-time information on the rate of clot formation, dissolution, and overall strength simultaneously with the ability to target clinical interventions based on the interplay of platelets, coagulation factors, and fibrinolysis factors. This allows a global and rapid assessment of hemostasis that more closely simulates in vivo clot formation. Interest in VET during LT and in patients with cirrhosis is increasing. VET is not available in all centers, and the interpretation of the results requires specialized training. As interpretation can be subjective, institutional VET algorithms are recommended and can reduce costs (Figure S1B,C).\textsuperscript{[31]} VET should be repeated following each hemostatic drug or blood product infused to allow for goal-directed hemostatic interventions. Hemostatic agents and factor concentrates currently in clinical use are summarized in Table 2. Importantly, there is limited evidence that the use of corrective agents mentioned in Table 2 are beneficial in the prevention or treatment of bleeding, and they should be used sparingly.

### Whole-Blood VET

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### HEMOSTATIC SPECTRUM IN PATIENTS PRIOR TO LT

Patients with well-compensated cirrhosis without significant portal hypertension but requiring LT, that is, unresectable hepatocellular carcinoma (HCC), have relatively preserved hemostatic systems.\textsuperscript{[32]} However, patients with acutely decompensated (AD) cirrhosis and
In vitro data suggest that plasma trans-

observation of increased bleeding risk in these co-

underlying mechanisms that may explain the clinical

injury, recent translational studies reveal potential

tients with AD and ACLF often develop acute kidney

Platelet transfusion should be considered at a
platelet count below 50,000/\mu l in the setting of active bleeding\cite{96,103,105}.

No recommendation is available on when to
transfuse whole blood in patients with cirrhosis or LT.

**TABLE 1** Review of blood products and transfusion thresholds

| Blood Product       | Characteristics                                                                 | Consideration                                                      |
|---------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------|
| RBCs                | PRBCs contain hemoglobin. Total volume infused is approximately 250–350 ml/unit| Consider an RBC transfusion when hemoglobin falls below 7 g/dl based on multiple studies and societal guidelines.\cite{96–99} In acute hemorrhage, higher thresholds can be considered |
| Plasma              | Plasma contains all factors, fibrinogen, and plasma proteins. One unit is approximately 250 ml | No recommendations are available on when to transfuse plasma in patients with cirrhosis, with societal guidelines cautioning against the prophylactic use of plasma\cite{100,101} |
| Cryoprecipitate     | Cryoprecipitate contains Factor VIII, Factor XIII, von Willebrand’s Factor, fibrinogen, and fibronectin. An average dose is 5–10 units, which is a volume of 50–200 ml | A fibrinogen level of 150–200 mg/dl is recognized by many societies as a threshold for transfusion of cryoprecipitate in the setting of acute blood loss\cite{96,101–104} |
| Platelets           | Platelets are pooled from 4 to 6 single donors or derived from apheresis of a single donor. A dose can be expected to increase the platelet count by 5000–10,000/\mu l. Total volume infused is approximately 250 ml | Platelet transfusion should be considered at a platelet count below 50,000/\mu l in the setting of active bleeding\cite{96,103,105} |
| Whole blood         | All components of blood                                                          | No recommendation is available on when to transfuse whole blood in patients with cirrhosis or LT |

Abbreviations: PRBC, packed red blood cells; RBC, red blood cell.

**COAGULOPATHY AND HEMOSTASIS MANAGEMENT IN LT**

In patients with acute liver failure (ALF), prolonged PT/INR defines the syndrome (along with hepatic encephalopathy) and may be significant, but does not predict bleeding complications although it is a marker of poor prognosis.\cite{44} In contrast, thrombocytopenia is associated with bleeding complications in addition to increased mortality or requirement for LT.\cite{45,46} In ALF, there is a state of rebalanced hemostasis.\cite{47} Local hypercoagulability in the liver microvasculature resulting from excessive vWF and deficient regulating protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), has recently been proposed to potentiate the primary liver injury of ALF.\cite{48} Hypofibrinogenemia, a consequence of decreased hepatic synthesis, may also contribute to deranged hemostasis in patients with ALF. A study of 200 patients with acute liver injury/ALF demonstrated that patients with abnormal ROTEM parameters were more likely to have severe systemic complications, that is, high-grade encephalopathy or kidney failure, but not increased bleeding tendencies.\cite{49} Despite the profound laboratory derangement seen in ALF, these patients seldom bleed.\cite{46} Bleeding is the proximate cause of death in patients with ALF in less than 5% of cases.

**PRETRANSPLANT COAGULOPATHY MANAGEMENT**

Consensus guidelines have risk stratified procedures (Table S1) based on technical, anatomic, and patient-related factors.\cite{1,2,50} Despite abnormal coagulation parameters in patients with varying phenotypes of liver disease, these parameters do not correlate with procedural bleeding risk. Current guidelines are therefore
best balanced and individualized according to each clinical scenario, and details of the specific management are beyond the scope of this review, although our general approach to coagulation management and supporting data to guide these decisions are summarized in Table 3.

**Use of anticoagulation in the listed patient**

In patients with compensated cirrhosis requiring anticoagulation, clinical studies demonstrate low rates of bleeding complications, including with low molecular weight heparin (LMWH) and vitamin-K antagonists (VKAs). Direct oral anticoagulants (DOACs) are emerging as a therapy for anticoagulation, and although data remain limited, clinical studies in patients with compensated cirrhosis support the safety of these agents.

Current societal guidelines suggest the use of anticoagulation in patients with cirrhosis with indications for therapy. Patients with cirrhosis demonstrate increased risks of thromboembolic disease, with portal vein thrombosis (PVT) occurring in up to 20% of patients. Improved outcomes in recanalization have been reported in those patients anticoagulated at 1 year, especially those patients with risk of evolution of thrombus or extensive mesenteric thrombosis, which may preclude LT if not addressed in a timely manner. The presence of nontumoral PVT can also be seen in patients with HCC, a rising indication for LT, and may portend worse survival and increased
### Table 3: Hemostasis patterns and management recommendations in pre-LT patients

| Scenario          | Laboratory coagulation testing patterns[^19,32,36,37,106,107] | Unique clinical features affecting hemostasis and thrombosis risk | VTE prophylaxis while hospitalized[^1] | Anticoagulation |
|-------------------|---------------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------|-----------------|
| Compensated cirrhosis | Traditional: preserved to slightly elevated INR and thrombocytopenia  
Global: VET similar to healthy controls | • Medical comorbidities common including cardiovascular disease, chronic kidney disease  
• Concurrent malignancy  
• Planned outpatient procedures | Recommended in all high-risk patients without contraindication | Traditional UFH, LMWH, VKA options  
**DOAC**  
Emerging evidence suggests safety and efficacy for VTE, PVT, and atrial fibrillation |
| Decompensated cirrhosis | Traditional: reduced factors, elevation in INR, worsening thrombocytopenia  
Global: preserved to increased thrombin production, variable VET profiles, variable fibrinolytic profiles | • More frequent hospitalizations  
• Multiple procedures  
• Infection common  
• Increased incidence of portal hypertension-related bleeding | Recommended in all high-risk patients without contraindication | Traditional UFH, LMWH, VKA options, caution advised  
**DOAC**  
Caution advised in patients with Child-Turcotte-Pugh Grades B and C cirrhosis |
| ACLF | Traditional: often severe derangements in fibrinogen, INR, platelets  
Global: variable and dynamic VET with hypocoagulable profiles and hypofibrinolysis may predominate; thrombin generation preserved | • Prolonged hospitalizations  
• Acute kidney injury  
• Frequent ICU admissions  
• Infection common | Recommended in all high-risk patients without contraindication | Traditional UFH, LMWH, VKA options, caution advised  
**DOAC**  
Not studied and caution advised |

[^1]: ACLF, acute-on-chronic liver failure; DOAC, direct oral anticoagulant; ICU, intensive care unit; INR, international normalized ratio; LMWH, low molecular weight heparin; LT, liver transplantation; UFH, unfractionated heparin; VKA, vitamin-K antagonist; VTE, venous thromboembolism.
risk of systemic venous thromboembolism (VTE).[55] In a meta-analysis of patients with cirrhosis and PVT, anticoagulation significantly increased the rate of re-canalization (71%) compared with untreated patients (42%).[51] There was no significant difference in the rate of any major or minor bleeding events between the groups. In addition, a single-center study of patients with Child-Turcotte-Pugh Grades B and C showed that a 12-month course of enoxaparin prevented PVT and delayed hepatic decompensation compared with controls.[56]

Patients listed for LT could be considered for portal vein reconstruction–transjugular intrahepatic portosystemic shunt while on the waiting list to decrease the risk of clot progression; these patients have chronic rather than acute thrombus, and routine anticoagulation is not indicated afterward unless there is a known underlying thrombotic disorder or high-risk feature such as complete portal vein obliteration or thrombus extending to the superior mesenteric vein.[57,58]

Reversal of anticoagulation

With the increasing use of DOACs in listed patients with VTE, the utility of reversal agents must be considered prior to LT. Data for the use of reversal agents in this setting appear to be safe and effective, albeit limited to case studies.[59] Reversal of LMWH and VKAs have historically been required prior to major surgery; however, a recent study of patients undergoing LT found no difference in bleeding in patients on VKAs who received prothrombin complex concentrate (PCC) compared with those who did not, implying reversal may not be necessary.[60]

PERIOPERATIVE AND INTRAOPERATIVE COAGULOPATHY MANAGEMENT

Perioperative management

Management of hemostasis in the perioperative period is dynamic (Figure 2) and requires multidisciplinary input from transplant surgeons, anesthesiologists, hepatologists, and intensivists. Preemptive transfusion to reverse hemostasis defects is not recommended in the absence of nonsurgical bleeding, although laboratory testing may predict intraoperative bleeding and inform intraoperative management.[61] Although limited by evidence, our expert panel recommends a preoperative hemoglobin of 7 or greater prior to surgery.[62] Preoperative hypofibrinogenemia (≤200 mg/dl) has been associated with increased red blood cell (RBC) transfusions, although a randomized controlled trial that transfused fibrinogen concentrate to >290 mg/dl preoperatively showed no benefit.[63] Increased central venous pressure and ascites have both been associated with increased intraoperative bleeding, so careful consideration of blood product transfusion is warranted to avoid unnecessary intravascular volume expansion.[64,65]

Preparations for LT should include prediction of the intraoperative transfusion requirement. Although preoperative VET variables can be helpful to predict massive transfusions and should be used to guide blood

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**Figure 2** Dynamic intraoperative factors impacting coagulation management. Perioperatively, multiple clinical factors impact dynamic changes in the coagulation cascade within hours, including donor and recipient factors as well as surgical and anesthesia management considerations that collectively require a multidisciplinary approach perioperatively.
Intraoperative management

In preparation for LT, the transplant team should communicate with the blood bank and laboratory staff to ensure an adequate supply of blood products and rapid responses during unforeseen bleeding events. The use of specialist anesthesia teams improves communication, reduces blood use, and improves postoperative outcomes. A laboratory-guided algorithm for diagnosing and treating intraoperative coagulopathy when clinically significant bleeding occurs should also be adopted because they have been shown to reduce intraoperative blood requirements. Examples based on TEG, ROTEM, and conventional coagulation tests can be found in Figure S2. Importantly, the output of specific VET differs, and the use of specific VET is dependent on center expertise and experience. Use of VET reduces blood product use and offers unique insights into intraoperative coagulopathy such as residual heparinization, dysfibrinogenemia, and fibrinolysis. Any algorithm should avoid plasma transfusion purely to correct an elevated PT/INR because this approach appears to worsen morbidity and mortality. The algorithm should also account for the three stages of the operation—preanhepatic, anhepatic, and neohepatic—as the goals of coagulopathy management and volume resuscitation differ with each stage. Specifically, during the preanhepatic phase, transfusion and intravenous fluids should be restricted to what is necessary to keep up with blood loss without worsening coagulopathy. During the anhepatic and neohepatic phases, focus should be on metabolic normalization and judicious, algorithm-guided transfusion to correct coagulopathy.

Antifibrinolytic lysine analogs such as tranexamic acid and epsilon aminocaproic acid prevent the conversion of plasminogen to plasmin. These drugs have been shown to decrease transfusion requirements during LT; however, their widespread adoption has been hindered by the concern of thrombotic complications. The thrombosis concern prompted contemporary studies to include such patient groups, and the benefits of tranexamic acid and epsilon aminocaproic acid were noted without the additional thrombotic risk.

POSTOPERATIVE COAGULOPATHY MANAGEMENT

When assessing the coagulation status in the immediate post-LT period, the impact of washout and ischemia/reperfusion injury need to be considered. Patients with cirrhosis have high levels of vWF with abnormally low levels of ADAMTS13, which peak after reperfusion, predisposing to microthrombi production and acute rejection. Thrombocytopenia is commonly observed because of platelet activation and consumption. An increase in platelet adhesion occurs in the subendothelial space, which can trigger worsening ischemia/reperfusion injury. However, platelet counts traditionally normalize as synthetic function returns with increases in TPO levels on Day 1, production of new circulating platelets within 5 days, and normalization of levels by 2 weeks (Figure 1).

As opposed to the normal return of coagulation indexes in functional liver grafts, the assessment of coagulation can be unclear in patients with delayed graft function or primary nonfunction (PNF). There can be gross abnormalities in standard coagulation indexes as well as VET. However, the need for correction is dependent on the degree of bleeding. In addition, the management of coagulopathy in these patients is complicated by multiorgan dysfunction, impacting how they receive blood products or blood product concentrates. There is no evidence that liver support systems improve the coagulopathy or graft dysfunction of PNF.

Pre-LT PVT has also been associated with increased early post-LT graft loss and mortality. The routine use of anticoagulation after LT has not been standardized in this setting and range from limited course of continuous dextran infusion followed by daily aspirin for 3 months to short courses of LMWH or warfarin. The decision to anticoagulate these patients should be carefully reviewed at the institutional level and made on an individual case-by-case basis.

INHERITED PROTHROMBOTIC DISORDERS AND THE ROLE OF LT

Factor V Leiden, PT gene G20210A mutation, proteins C and S, and antithrombin deficiency are the inherited risk factors of VTE. Of these, Factor V Leiden and PT gene mutation are the most common. LT is the curative treatment for all of these inherited prothrombotic disorders, although they are never the sole indications for LT in these patients. Although rare, there are cases of prothrombotic disorders that can be transmitted by LT and warrant attention if correlated with clinical presentation. Patients with preexisting thrombotic disorders requiring therapeutic anticoagulation prior to transplant should be able to discontinue anticoagulation. The timing and decision should be individualized with a careful discussion of risks and benefits.
**GRAFT-RELATED VENOUS AND ARTERIAL THROMBOSIS POSTTRANSPLANTATION**

Graft-related vascular complications after LT are rare and require prompt diagnosis and intervention. These include arterial complications such as acute or delayed hepatic artery thrombosis and venous complications including acute PVT and caval complications.

Hepatic artery thrombosis is the most common vascular complication and can lead to graft loss, biliary issues, and increased mortality without early intervention. Although not universally accepted, prophylactic use of low-dose or full-strength aspirin has been used in transplant centers to prevent this complication. Treatment primarily involves endovascular intervention and, if unsuccessful, surgical revascularization or retransplantation.

Venous complications after LT are rare; acute PVT occurs at a rate of 1%–3%. Treatment options include anticoagulation, catheter-based thrombolytic therapy with or without stent placement, surgical revision, or rarely retransplantation. Finally, caval complications occur in less than 3% of grafts and are largely technical in nature and corrected by angioplasty or stent placement.

**RISK OF VENOUS THROMBOEMBOLISM IN THE POSTTRANSPLANT PATIENT**

The incidence of non–graft-related thrombosis after LT ranges from 2.8% to 8.6% in single-center studies and is comparable with patients undergoing other major surgeries. Potential risk factors for the development of non–graft-related thrombosis include intraoperative use of specific blood product concentrates, decreased mobility, peripherally inserted central access catheters, end-stage renal disease, and a prior history of venous thrombosis. However, given the single-center nature of these studies, with a relatively low incidence of thrombosis, the risk factors are not uniform.

The routine use of thromboprophylaxis in major surgeries has been established in recent guidelines; however, no recommendations for LT recipients specifically exist. Yip et al. showed the positive effect of routine thromboprophylaxis with subcutaneous heparin on non–graft-related thrombosis after LT without an associated bleeding risk. Although data are limited, programs have implemented thromboprophylaxis therapy to reduce the risk of graft-vessel thrombosis. Our expert panel recommends (1) thromboprophylaxis with subcutaneous heparin in the preoperative and postoperative periods while hospitalized; (2) use of sequential compression devices and thromboembolic-deterrent stockings in the operating room and postoperatively; and (3) encouragement of early ambulation, including in the intensive care unit (ICU) as able.

**CONCLUSION**

Patients with liver disease present with a wide spectrum of disorders, and alterations in hemostasis evolve with disease progression. The management of hemostasis and thrombosis in a patient undergoing LT is complex and requires a specialized, multidisciplinary approach. The increased availability of VET and recent societal guidelines have curtailed the unnecessary transfusion of blood products in this patient population; however, robust data and universal guidance on patient management are lacking. Although our review offers a comprehensive approach to the LT patient from waitlist management to intraoperative and posttransplant care, it is of critical importance to have a multidisciplinary approach to care for these patients given the complexity of medical decision making. Future research is likely to provide additional evidence to guide clinical decision making.

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**TABLE 4** Key points

| Advances in clinical practice |
|--------------------------------|
| • Management of coagulopathy and hemostasis in LT candidates and recipients requires a multidisciplinary team that emphasizes communication and adherence to center-specific protocols across phases of care |
| • Use of VET is essential to provide targeted correction of coagulopathy and hemostasis defects only when clinically indicated (eg, invasive procedures including complex surgery or active bleeding) and to minimize potential adverse consequences of excess transfusions |
| • Recognition of differences in coagulation and hemostasis disorders in pre-LT patients based on disease etiology and severity and in the perioperative setting dependent on donor and recipient characteristics is critical to guide appropriate management |
| • Our understanding of reversibility of coagulation and hemostatic abnormalities after LT continues to evolve and has potential implications on graft and patient outcomes that require ongoing consideration |

| Future research goals |
|-----------------------|
| • Provide standardization of VET output and interpretation to allow consistent comparison across institutions to facilitate prospective, multicenter research |
| • Determine the prognostic importance of individual VET metrics for pre-LT mortality prediction to determine if these may offer additive predictive power beyond traditional coagulation metrics (eg, INR) |
| • Determine the clinical impact of VET-directed transfusion protocols on patient outcomes both in pre-LT patients with bleeding complications and in patients undergoing LT |
| • Identify coagulation and hemostatic derangements that may persist after LT and the clinical importance of these persistent abnormalities particularly on post-LT complications |

Abbreviations: INR, international normalized ratio; LT, liver transplantation; VET, viscoelastic testing.
making in patients with liver disease undergoing LT with an even broader integration of VET into our clinical practice across phases of care.

CONFLICT OF INTEREST
Melissa M. Cushing consults for and advises Octapharma and advises Cerus Corporation and Haemonetics. Khashayar Farsad consults for and received grants from Gubert, LLC; consults for Cook Medical and Neuwave Medical; and advises Inquis Medical and Eisai. He received grants from W. L. Gore & Associates. Anjana A. Pillai advises Exelixis, Eisai, Genentech, AstraZeneca, and Replimune and is on the speakers’ bureau for Simply Speaking Hepatitis. Robert Lewandowski consults for and is on the speakers’ bureau for Boston Scientific Corporation and consults for Varian.

AUTHOR CONTRIBUTIONS
Anjana A. Pillai and Michael Kriss devised the concept of the manuscript, drafted portions of the manuscript, revised the manuscript, and provided critical revisions. Constantine J. Karvellas and Nicolas Intagliata revised the manuscript and provided critical revisions. All authors drafted portions of the manuscript and approved the final submitted manuscript.

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REFERENCES
1. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73:366–413.
2. Patel IJ, Rahim S, Davidson JC, Hanks SE, Tam AL, Walker TG, et al. Society of Interventional Radiology Consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions—Part II: recommendations: endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol. 2019;30:1168–84.e1161.
3. O’Shea RS, Davitkov P, Ko CW, Rajasekhar A, Su GL, Sultan S, et al. AGA clinical practice guideline on the management of arterial and venous disorders in patients with cirrhosis. Gastroenterology. 2021;161:1615–27.e1611.
4. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359:938–49.
5. Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. Semin Liver Dis. 2002;22:83–96.
6. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147–56.
7. Lisman T, Bongers TN, Adelmeijer J, Janssen HLA, de Maat MPM, de Groot PG, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology. 2006;44:53–61.
8. Arshad F, Adelmeijer J, Blokzijl H, van den Berg A, Porte R, Lisman T. Abnormal hemostatic function one year after orthotopic liver transplantation can be fully attributed to endothelial cell activation. F1000Research. 2014;3:103.
9. Gresele P, Binetti BM, Branca G, Clerici C, Asciutti S, Morelli A, et al. TAFI deficiency in liver cirrhosis: relation with plasma fibrinolysis and survival. Thromb Res. 2008;121:763–8.
10. Ichinomiya T, Murata H, Sekimo S, Sato S, Oshikiri Y, Matsumoto S, et al. Postoperative coagulation profiles of patients undergoing adult-to-adult living donor liver transplantation—a single-center experience. Transplant Rep. 2020;5:100037.
11. Ko S, Chisuwa H, Matsumoto M, Fujimura Y, Okano E, Nakajima Y. Relevance of ADAMTS13 to liver transplantation and surgery. World J Hepatol. 2015;7:1772–81.
12. Nedel WL, Rodrigo Filho EM, Pasqualotto AC. Thrombin-activatable fibrinolysis inhibitor (TAFI) as a novel prognostic factor after orthotopic liver transplantation: a pilot study. Transplant Proc. 2015;47:1912–4.
13. Nedel WL, Rodrigo Filho EM, Pasqualotto AC. Thrombin-activatable fibrinolysis inhibitor as a bleeding predictor in liver transplantation: a pilot observational study. Rev Bras Ter Intensiva. 2016;28:161–6.
14. Stahl RL, Duncan A, Hooks MA, Henderson JM, Millikan WJ, Warren WD. A hypercoagulable state follows orthotopic liver transplantation. Hepatology. 1990;12:553–8.
15. Velasco F, Villaflor RB, Fernandez M, de La mata M, Roman J, Rubio V, et al. Diminished anticoagulant and fibrinolytic activity following liver transplantation. Transplantation. 1992;53:1256–61.
16. Sinegre T, Duron C, Lecompte T, Pereira B, Massoulier S, Lablin G, et al. Increased factor VIII plays a significant role in plasma hypercoagulability phenotype of patients with cirrhosis. J Thromb Haemost. 2018;16:1132–40.
17. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. J Hepatol. 2013;59:265–70.
18. de Maat MP, Nieuwenhuizen W, Knot EA, van Buuren HR, Swart GR. Measuring plasma fibrinogen levels in patients with liver cirrhosis. The occurrence of proteolytic fibrin(ogen) degradation products and their influence on several fibrinogen assays. Thromb Res. 1995;78:353–62.
19. Tripodi A, Primignani M, Chantarangkul V, Dell’Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009;137:2105–11.
20. Deitcher SR. Interpretation of the international normalised ratio in patients with liver disease. Lancet. 2002;359:47–8.
21. Tripodi A, Chantarangkul V, Primignani M, Clerici M, Dell’Era A, Aghemo A, et al. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. Intern Emerg Med. 2012;7:139–44.
22. Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol. 2010;8:899–902; quiz e109.
23. Napolitano G, Iacobellis A, Merla A, Niro G, Valvano MR, Terracciano F, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med. 2017;38:79–82.

24. Terraut N, Chen Y-C, Izumi N, Kayali Z, Mitrub P, Tak WY, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology. 2018;155:705–18.

25. Peck-Radosavljevic M, Simon K, Iacobellis A, Hassanein T, Kayali Z, Tran A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology. 2019;70:1336–48.

26. Kumar M, Ahmad J, Maswall R, Choudhury A, Baijai M, Mitra LG, et al. Thrombelastography-guided blood component use in patients with cirrhosis with nonvariceal bleeding: a randomized controlled trial. Hepatology. 2020;71:235–46.

27. De Pietri L, Bianchini M, Montalli R, De Maria N, Di Maira T, Begliomini B, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. Hepatology. 2016;63:566–73.

28. O’Leary JG, Demetris AJ, Friedman LS, Gbel HM, Halloran PF, Kirk AD, et al. The role of donor-specific HLA alloantibodies in liver transplantation. Am J Transplant. 2014;14:779–87.

29. Rahimi RS, O’Leary JG. Transfusing common sense instead of blood products into coagulation testing in patients with cirrhosis: overtreatment not equal safety. Hepatology. 2016;63:368–70.

30. Davis JPE, Northup PG, Caldwell SH, Intagliata NM. Viscoelastic testing in liver disease. Ann Hepatol. 2018;17:205–13.

31. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19:1–228, v–vi.

32. Fisher C, Patel VC, Stoy SH, Singanayagam A, Adelmeijer J, Wendon J, et al. Balanced haemostasis with both hypo- and hyper-coagulable features in critically ill patients with acute-on-chronic liver failure. J Crit Care. 2018;43:54–60.

33. Stotts MJ, Lisman T, Intagliata NM. The spectrum of disease severity in cirrhosis and its implications for hemostasis. Semin Thromb Hemost. 2020;46:716–23.

34. Blasi A, Calvo A, Prado V, Reverter E, Reverter JC, Hernández-Tejero M, et al. Coagulation failure in patients with acute-on-chronic liver failure and decompensated cirrhosis: beyond the international normalized ratio. Hepatology. 2018;68:2325–37.

35. Seessle J, Lohr J, Kirchner M, Michalis J, Merle U. Rotational thrombelastometry (ROTEM) improves hemostasis assessment compared to conventional coagulation test in ACLF and Non-ACLF patients. BMC Gastroenterol. 2020;20:271.

36. Goyal S, Jadaun S, Kedia S, Acharya SK, Varma S, Nayak B, et al. Thromboelastography parameters in patients with acute-on-chronic liver disease. J Hepatol. 2018;67:1327–40.

37. Premkumar M, Saxena P, Rangegowda D, Baweja S, Mirza R, Jain P, et al. Coagulation failure is associated with bleeding events and clinical outcome during systemic inflammatory response and sepsis in acute-on-chronic liver failure: an observational cohort study. Liver Int. 2019;39:694–704.

38. Blasi A, Patel VC, Adelmeijer J, Azarian S, Hernandez Tejero M, Calvo A, et al. Mixed fibrinolytic phenotypes in decompensated cirrhosis and acute-on-chronic liver failure with hypoﬁbri nolysis in those with complications and poor survival. Hepatology. 2020;71:1381–90.

39. Hung A, Garcia-Tsao G. Acute kidney injury, but not sepsis, is associated with higher procedure-related bleeding in patients with decompensated cirrhosis. Liver Int. 2018;38:1437–41.

40. Intagliata NM, Davis JPE, Lafond J, Erdbreugger U, Greenberg CS, Northup PG, et al. Acute kidney injury is associated with low factor XIII in decompensated cirrhosis. Dig Liver Dis. 2019;51:1409–15.

41. Zanetto A, Rinder HM, Campello E, Saggiorato G, Deng Y, Cirleglio M, et al. Acute kidney injury in decompensated cirrhosis is associated with both hypo-coagulable and hyper-coagulable features. Hepatology. 2020;72:1327–40.

42. Lisman T, Kleiss S, Patel VC, Fisher C, Adelmeijer J, Bos S, et al. In vitro efficacy of pro- and anti-coagulant strategies in compensated and acutely ill patients with cirrhosis. Liver Int. 2018;38:1988–96.

43. Mort JF, Davis JPE, Mahoro G, Stotts MJ, Intagliata NM, Northup PG. Rates of bleeding and discontinuation of direct oral anticoagulants in patients with decompensated cirrhosis. Clin Gastroenterol Hepatol. 2021;19:1436–42.

44. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. Clin Gastroenterol Hepatol. 2018;16:1199–206.e1192.

45. Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lisman T, Lee WM. Acute Liver Failure Study Group. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol. 2016;14:613–20.e614.

46. Stravitz RT, Ellerbe C, Durkalski V, Schilsky M, Fontana RJ, Peterseim C, et al. Bleeding complications in acute liver failure. Hepatology. 2018;67:1931–42.

47. Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost. 2015;41:468–73.

48. Drievers EG, Stravitz RT, Zhang J, Aselmeijer J, Durkalski V, Lee WM, et al. VWF/ADAMTS13 imbalance, but not global coagulation or fibrinolysis, is associated with outcome and bleeding in acute liver failure. Hepatology. 2021;73:1882–91.

49. Stravitz RT, Fontana RJ, Meinerz C, Durkalski-Mauldin V, Hanje AJ, Olson J, et al. Coagulopathy, bleeding events and outcome according to rotational thrombelastometry in patients with acute liver injury/failure. Hepatology. 2021;74:937–49.

50. Hadi M, Walker C, Desborough M, Basile A, Tsetsis D, Hunt B, et al. CIRSE standards of practice on peri-operative anticoagulation management during interventional radiology procedures. Cardiovasc Intervent Radiol. 2021;44:523–36.

51. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology. 2017;153:480–7.e481.

52. Nisy SA, Mihm AE, Gillette C, Davis KA, Tillett J. Safety of direct oral anticoagulants in patients with mild to moderate cirrhosis: a systematic review and meta-analysis. J Thromb Thrombolysis. 2021;52:817–27.

53. Nanchal R, Subramanian R, Karvellas CJ, Hollenberg SM, Kayali Z, Tran A, et al. Incidence, risk factors and consequences of portal vein thrombosis: final analysis of a 61-patient cohort. J Vasc Interv Radiol. 2017;28:1714–21.e1712.

54. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol. 2012;57:203–12.

55. Connolly GC, Chen R, Hyrien O, Mantry P, Bozorgzadeh A, Abt P, et al. Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. Thromb Res. 2008;122:299–306.

56. Villa E, Cammà C, Marietta M, Luongo M, Cristelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143:1253–60.e1254.

57. Thornburg B, Desai K, Hickey R, Hohlostos E, Kulkil L, Ganger D, et al. Pretransplantation portal vein recanalization and transjugal intrahepatic portosystemic shunt creation for chronic portal vein thrombosis: final analysis of a 81-patient cohort. J Vasc Interv Radiol. 2017;28:1714–21.e1712.

58. Wang Z, Jiang MS, Zhang HL, Weng N-N, Luo X-F, Li X, et al. Is post-TIPS anticoagulation therapy necessary in patients with LIVER TRANSPLANTATION
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cirrhosis and portal vein thrombosis? A randomized controlled trial. Radiology. 2016;279:943–51.
59. Intagliata NM, Maitland H, Pellitier S, Caldwell SH. Reversal of direct oral anticoagulants for liver transplantation in cirrhosis: a step forward. Liver Transpl. 2017;23:396–7.
60. Martinez S, Garcia I, Ruiz A, Tassies D, Reverter JC, Colmenero J, et al. Is antivitamin K reversal required in patients with cirrhosis undergoing liver transplantation? Transfusion. 2021;61:3008–16.
61. Pustavoitau A, Rizkalla NA, Perlstein B, Ariyo P, Latif A, Connor JP, Aufhauser D, Welch BM, Leverson G, Al-Adra D. Defining postoperative transfusion thresholds in liver transplant recipients: a novel retrospective approach. Transfusion. 2021;61:781–7.
62. Sabate A, Gutierrez R, Beltran J, Mallado P, Blasi A, Acosta F, et al. Impact of preemptive fibrinogen concentrate on transfusion requirements in liver transplantation: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Transplant. 2016;16:2421–9.
63. Badenoch A, Sharma A, Gower S, Selznier M, Srinivas C, Wąsowicz M, et al. Thrombocytopenia following liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2010;10:1276–83.
64. Dar WA, Sullivan E, Bynon JS, Eltzschig H, Ju C. Ischaemia reperfusion injury in liver transplantation: cellular and molecular mechanisms. Liver Int. 2019;39:788–801.
65. Richards EM, Alexander GJ, Calne RY, Baglin TP. Thrombocytopenia following liver transplantation is associated with platelet consumption and thrombin generation. Br J Haematol. 1997;98:315–21.
66. Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. Gastroenterology. 2000;118:183–91.
67. Faeh M, Hauser SP, Nydegger UE. Transient thrombopoietin peak after liver transplantation for end-stage liver disease. Br J Haematol. 2001;112:493–8.
68. Kok B, Dong V, Karvellas CJ. Graft dysfunction and management in liver transplantation. Crit Care Clin. 2019;35:117–33.
69. Conzen KD, Pommert EA. Liver transplant in patients with portal vein thrombosis: medical and surgical requirements. Liver Transpl. 2017;23:S59–63.
70. Molmenti EP, Reederhouse TW, Molmenti EJ, Aisikwal J, Jung G, Marubashi S, et al. Thrombendvenectomy for organized portal vein thrombosis at the time of liver transplantation. Ann Surg. 2002;235:292–6.
71. Goyal A, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood. 1998;92:2353–8.
72. Martinelli I, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood. 1998;92:2353–8.
73. Massicotte L, Beaulieu D, Thibeault L, Roy JD, Marleau D, Badenoch A, Sharma A, Gower S, Selznier M, Srinivas C, Wąsowicz M, et al. Thrombocytopenia following liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2010;10:1276–83.
74. Badenoch A, Sharma A, Gower S, Selznier M, Srinivas C, Wąsowicz M, et al. The effectiveness and safety of tranexamic acid in orthotopic liver transplantation clinical practice: a propensity score matched cohort study. Transplantation. 2017:101:1658–65.
75. Badenoch A, Sharma A, Gower S, Selznier M, Srinivas C, Wąsowicz M, et al. The effectiveness and safety of tranexamic acid in orthotopic liver transplantation clinical practice: a propensity score matched cohort study. Transplantation. 2017:101:1658–65.
76. Dar WA, Sullivan E, Bynon JS, Eltzschig H, Ju C. Ischaemia reperfusion injury in liver transplantation: cellular and molecular mechanisms. Liver Int. 2019;39:788–801.
77. Richards EM, Alexander GJ, Calne RY, Baglin TP. Thrombocytopenia following liver transplantation is associated with platelet consumption and thrombin generation. Br J Haematol. 1997;98:315–21.
94. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3:3898–944.

95. Roullet S, Freyburger G, Crucc M, Quinart A, Stecken L, Audy M, et al. Management of bleeding and transfusion during liver transplantation before and after the introduction of a rotational thromboelastometry-based algorithm. Liver Transpl. 2015;21:169–79.

96. O’Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. Gastroenterology. 2019;157:43–43.e31.

97. Garcia-Tsao G, Sanyal A, Grace N, Carey W. Practice parameters committee of the American College of Gastroenterology Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–38.

98. De Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.

99. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015;64:1680–704.

100. Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials (CME). Transfusion. 2012;52:1673–86.

101. Northup PG, Friedman LS, Kamath PS. AGA clinical practice update on surgical risk assessment and perioperative management in cirrhosis: expert review. Clin Gastroenterol Hepatol. 2019;17:595–606.

102. Drolz A, Horvattis T, Roedl K, Rutter K, Stauf K, Kneidinger N, et al. Coagulation parameters and major bleeding in critically ill patients with cirrhosis. Hepatology. 2016;64:556–68.

103. Beziover D, Dirkmann D, Findlay J, Guta C, Hartmann M, Nicolau-Raducu R, et al. Perioperative coagulation management in liver transplant recipients. Transplantation. 2018;102:578–92.

104. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol. 2017;34:332–95.

105. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. W J Gastroenterol. 2014;20:2595.

106. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology. 2005;41:553–8.

107. Lisman T, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. J Hepatol. 2010;52:355–61.