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REVIEW ARTICLE

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; PNF, primary nonfunction; POD, postoperative day; PRBC, packet red blood cell; 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.

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and society guidance address this emerging paradigm and offer recommendations to assist with hemostatic management in patients with liver disease. However, patients undergoing LT are unique and diverse, often with unstable disease that requires specialized approaches. Our aim is to provide a focused review of hemostatic management of the LT patient, distinguish unique aspects of the three main phases of care (before LT, perioperative, and after LT), and identify knowledge gaps and critical areas of future research.

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.[1–3] 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 of the LT patient (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.[4] The balance between the prohemostatic and antihemostatic factors during the normal physiological state is altered in patients with cirrhosis.[5] 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.[6]

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.[7] Most hepatocyte-derived coagulation and anticoagulation factors are low in cirrhosis and decrease as liver disease progresses (Figure 1).[8–15] Elevated vWF and Factor VIII levels and low protein C levels contribute to a hypercoagulable state.[16,17] In addition, low levels of α2-antiplasmin, Factor XIII, 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.[18]

TRADITIONAL HEMOSTATIC ASSESSMENT TESTS

There is a poor correlation between traditional coagulation tests and thrombin-generating capacity in cirrhosis.[19] 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.[20] 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.[17,21] 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.[19]

Thrombocytopenia has historically been considered a risk factor for bleeding in patients with cirrhosis.[22] However, data are mixed, and the putative relationship between thrombocytopenia and bleeding risk is not well supported.[23] Changes in the hemostatic system may partially compensate for thrombocytopenia, including elevated vWF, which promotes platelet adhesion and forms a complex with Factor VIII (also elevated) to accelerate coagulation.[7] Large randomized controlled trials examining TPO use prior to procedures for patients with cirrhosis and thrombocytopenia were not designed to assess the effect on bleeding outcomes.[24,25] Viscoelastic testing (VET) has been used as a guide

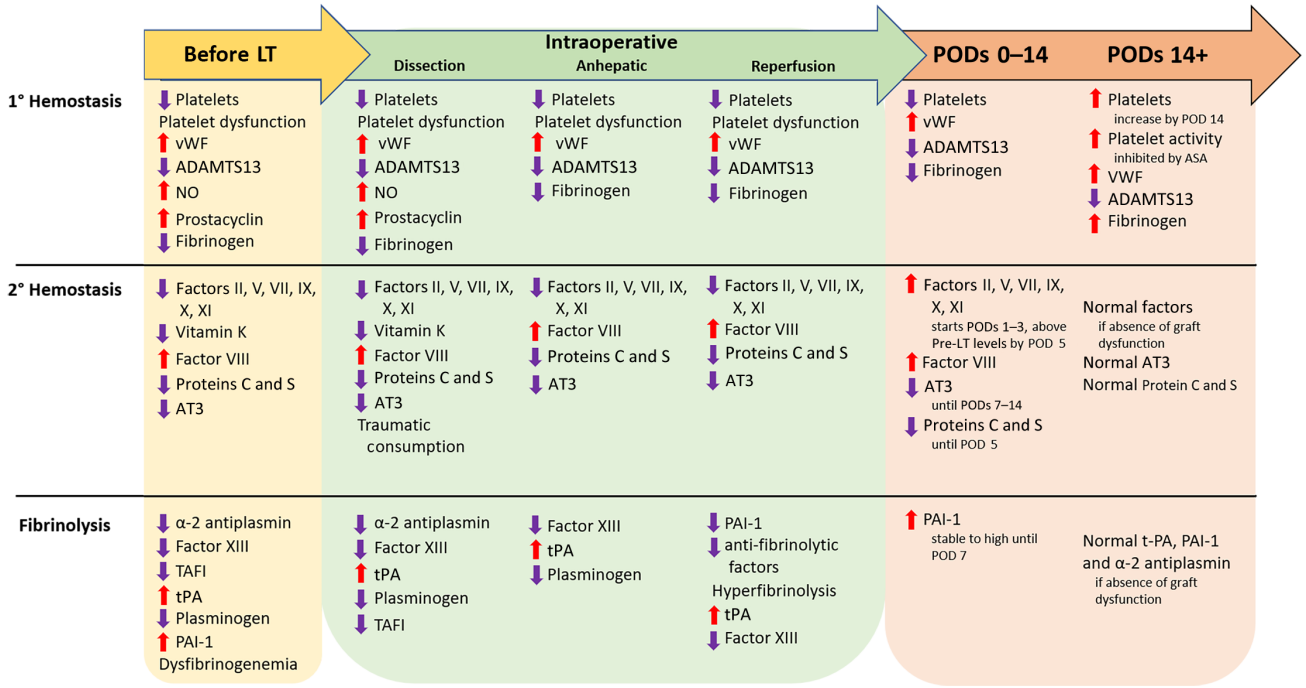

FIGURE 1 Dynamic changes in hemostasis across phases of care in patients with liver disease undergoing LT. Changes in primary and secondary hemostasis as well as fibrinolysis are outlined. Initial changes in patients with cirrhosis (yellow) are shown with subsequent dynamic changes associated with the perioperative period (green) and ultimately a return to normalcy in the posttransplant period (orange)[8–15]

for platelet transfusions and demonstrates a reduction of platelet transfusion use.[26,27] It remains unclear what level of thrombocytopenia represents an increased risk of bleeding in patients with cirrhosis.[1]

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, especially for simultaneous liver–kidney transplantation.[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.[29] Blood products and transfusion thresholds are summarized in Table 1.

WHOLE-BLOOD VET

Whole-blood VET provides a comprehensive assessment of hemostatic balance, measuring the rate and strength of clot formation.[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).[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.

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.[32] However, patients with acutely decompensated (AD) cirrhosis and

TABLE 1 Review of blood products and transfusion thresholds

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.[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[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[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/μl. Total volume infused is approximately 250 ml	Platelet transfusion should be considered at a platelet count below 50,000/μl in the setting of active bleeding[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.

acute-on-chronic liver failure (ACLF) develop clinically significant changes in the hemostatic system.[33] One in vitro study compared traditional coagulation profiles, thrombin generation, and fibrinolysis across the spectrum from stable cirrhosis to ACLF.[34] Although thrombin generation remained intact, a distinct hemostatic phenotype was identified in patients with ACLF with clear derangements in fibrinolytic potential. VET has emerged in these cases as an attractive tool. One study using rotational thromboelastometry (ROTEM) to compare patients with AD cirrhosis and ACLF demonstrated that patients with ACLF have delayed clot formation times and decreased clot firmness.[35] Goyal et al. compared patients with AD and ACLF using thromboelastography (TEG) and demonstrated preserved TEG parameters across the patient spectrum, but showed a higher propensity toward fibrinolysis in the group with ACLF.[36]

Hypocoagulable profiles on TEG have also been associated with bleeding in patients with ACLF.[37] Patients with AD and ACLF represent a heterogeneous group and are prone to concurrent sepsis and organ failure. A recent study examining the fibrinolytic system in this population showed a mixed fibrinolytic phenotype with both hyperfibrinolytic and hypofibrinolytic profiles.[38] Hypofibrinolysis was associated with sepsis in this study, and baseline hypofibrinolysis correlated strongly with 30-day mortality. As patients with AD and ACLF often develop acute kidney injury, recent translational studies reveal potential underlying mechanisms that may explain the clinical observation of increased bleeding risk in these cohorts.[39–41] In vitro data suggest that plasma transfusion does not significantly alter global hemostatic capacity, and anticoagulation should be used cautiously in this population.[42,43]

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.[44] In contrast, thrombocytopenia is associated with bleeding complications in addition to increased mortality or requirement for LT.[45,46] In ALF, there is a state of rebalanced hemostasis.[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.[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.[49] Despite the profound laboratory derangement seen in ALF, these patients seldom bleed.[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.[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

TABLE 2 Review of hemostatic agents and factor concentrates

Agent/concentrate[a]	Mechanism of action	Recommended dosage[b]
Tranexamic acid	A lysine analogue, tranexamic acid acts through interfering with the activation of plasminogen to plasmin and its binding to fibrin clots	Off-label use for perioperative bleeding: 10–30 mg/kg bolus with the addition of an infusion of 1–2 mg/kg/h
Epsilon-aminocaproic acid	A lysine analogue, epsilon-aminocaproic acid acts through interfering with the activation of plasminogen to plasmin and its binding to fibrin clots	Off-label use for perioperative bleeding: 5–10 g bolus with an infusion of 10–15 mg/kg/h
Desmopressin	Desmopressin causes the endothelial release of Factor VIII and vWF into the plasma. VWF directly promotes platelet adhesion and complexes with Factor VIII to increase density and promote fibrin plug formation at the site of bleeding	0.3 mg/kg intravenously as a single bolus
TPO agonists	These drugs are chemically synthesized, orally active human TPO receptor agonists that activate the signal transduction pathway in the same fashion as endogenous TPO and induce platelet production	Avatrombopag: Platelet count >40–40 mg oral once daily for 5 days, Platelet count <40–60 mg oral once daily for 5 days Lusutrombopag: 3 mg orally once daily for 7 days[96]
Prothrombin complex concentrate	Depending on the formation, the prothrombin complex concentrate may be three factors (II, IX, X) or four factors (II, VII, IX, X), and can contain proteins C and S	Off-label use for perioperative bleeding: a review of the literature revealed doses of 12.5–50 units/kg
Fibrinogen concentrate	Reconstituted, the concentration of fibrinogen is 20 mg/ml	Off-label use for perioperative bleeding: a review of the literature revealed doses of 25–50 mg/kg
rFVIIa	rFVIIa acts at the site of tissue injury by binding to exposed tissue factor, generating small amounts of thrombin that are sufficient to activate platelets. The activated platelet surface can then form a template on which rFVIIa directly or indirectly mediates further activation of coagulation, generating thrombin	Off-label use for perioperative bleeding: a review of the literature revealed doses of 20–600 mcg/kg
Factor XIII concentrate	Factor XIII is activated to Factor XIIIa, which promotes cross-linking of fibrin and protects clots against fibrinolysis	Off-label use for perioperative bleeding: 40 units/kg; however, dosing in the setting of bleeding should be based on Factor XIII levels

Abbreviations: rFVIIa, recombinant Factor VIIa; TPO, thrombopoietin; vWF, von Willebrand factor.

[a]Limited evidence agents are beneficial in the prevention or treatment of bleeding.

[b]Dosage is off label in the United States and based on a review of the literature.

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).[51] 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.[52]

Current societal guidelines suggest the use of anticoagulation in patients with cirrhosis with indications for therapy.[1,53] Patients with cirrhosis demonstrate increased risks of thromboembolic disease, with portal vein thrombosis (PVT) occurring in up to 20% of patients.[51,54] 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

Abbreviations: 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 recanalization (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

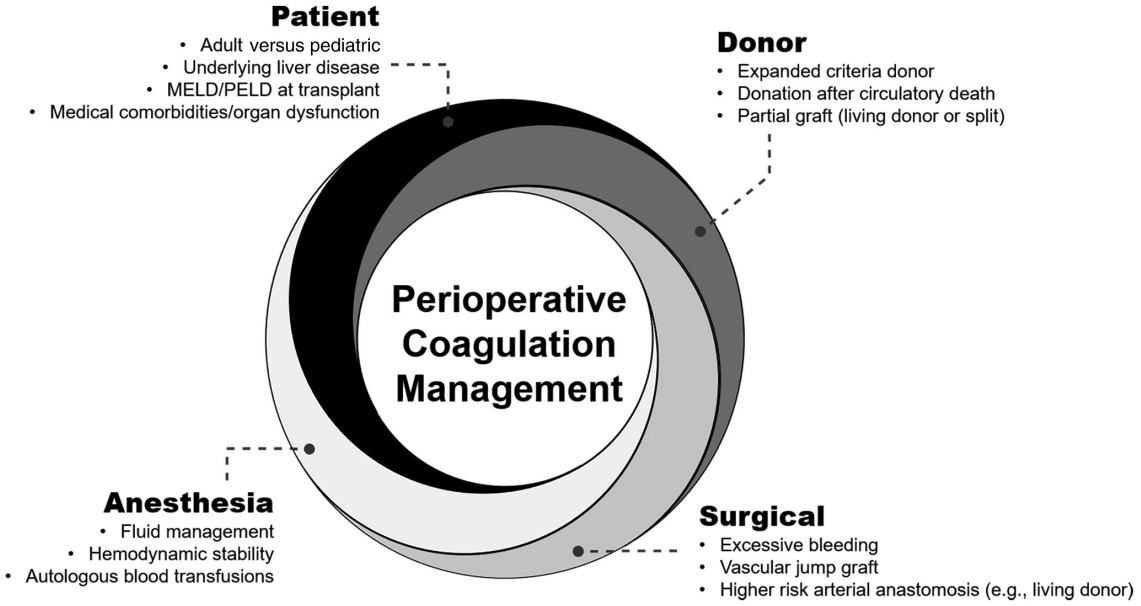

FIGURE 2 Dynamic intraoperative factors impacting coagulation management. Perioperatively, multiple clinical factors impact dynamic changes in the coagulation cascade within hours, including donor and recipient factors as well as surgical and anesthesia management considerations that collectively require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

bank resource use, there are no data to support using VET to initiate preemptive transfusion therapies.[61,66]

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 anesthesiology teams improves communication, reduces blood use, and improves postoperative outcomes.[67] 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.[68] 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.[69] Any algorithm should avoid plasma transfusion purely to correct an elevated PT/INR because this approach appears to worsen morbidity and mortality.[70] 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.[71] 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.[71,72]

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.[73] 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.[11] Thrombocytopenia is commonly observed because of platelet activation and consumption.[74] An increase in platelet adhesion occurs in the subendothelial space, which can trigger worsening ischemia/reperfusion injury.[75] 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).[76]

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).[77] 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.[78,79] 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.[80] Of these, Factor V Leiden and PT gene mutation are the most common.[80] 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.[81] 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.[82,83] These include arterial complications such as acute or delayed hepatic artery thrombosis and venous complications including acute PVT and caval complications.[83]

Hepatic artery thrombosis is the most common vascular complication and can lead to graft loss, biliary issues, and increased mortality without early intervention.[82,84] Although not universally accepted, prophylactic use of low-dose or full-strength aspirin has been used in transplant centers to prevent this complication.[85] Treatment primarily involves endovascular intervention and, if unsuccessful, surgical revascularization or retransplantation.[86]

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.[87] Finally, caval complications occur in less than 3% of grafts and are largely technical in nature[88] and corrected by angioplasty or stent placement.[89]

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.[90–93] 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.[90–93] 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.[94] 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.[93] 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.

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.

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 (Table 4). 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 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 Gurbet, 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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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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