Coagulopathy Before and After Liver Transplantation

From the Hepatic to the Systemic Circulatory Systems

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KEYWORDS

• End-stage liver disease • Hypercoagulable state • Thromboembolic disease
• Coagulation • Hemostasis

KEY POINTS

- The hemostatic environment in patients with cirrhosis is a delicate balance between prohemostatic and antihemostatic factors.
- In general, there is a lack of effective laboratory measures of the coagulation cascade, platelet function, and thrombolysis in patients with cirrhosis.
- Contrary to prior widespread belief, patients with cirrhosis are predisposed to pulmonary embolus (PE), deep vein thrombosis (DVT), and portal vein thrombosis (PVT) in the pretransplantation setting.
- The pretransplantation hypercoagulable milieu seems to extend for at least several months post-transplantation and may result in venous thromboembolism (VTE) or intracardiac thrombosis, portal vein thrombosis, or hepatic artery thrombosis (HAT).
- The optimal anticoagulation regimen both for prevention of and therapy for pathologic thrombosis in cirrhosis has yet to be established but early reports suggest a potential role for low-molecular-weight heparins (LMWHs) and the direct-acting anticoagulants.

INTRODUCTION

The research field of hemostasis in chronic liver disease is ever-expanding yet poorly understood. Although the majority of clinical research focuses on PVT and relevant patient-centered outcomes, interpreting the delicate homeostasis between prohemostasis and antihemostasis in patients with cirrhosis is an issue that clinicians face on a

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daily basis in an attempt to assess for both bleeding and clotting risk. Despite this risk assessment being a well-established practice, conventional laboratory testing has proved unreliable, making this assessment one of the more challenging arenas of caring for patients with chronic liver disease. Historically, patients with cirrhosis were thought to have coagulopathy, as defined by elevations in conventional laboratory tests, such as the prothrombin time (PT) and PT–international normalized ratio (INR). This coagulopathy was thought to be protective from a hypercoagulable state and even predisposed patients with cirrhosis to spontaneous bleeding events. It is now known that conventional laboratory tests, such as PT and PT-INR, do not accurately predict thrombotic or bleeding risk in patients with cirrhosis[1,2]; specifically, PT-INR does not predict risk of VTE in hospitalized patients with cirrhosis.[3,4] Furthermore, measures of other components of the hemostatic system are not widely available, further limiting assessment of prohemostasis and antihemostasis in patients with cirrhosis.

Hemostasis can be broken down into primary, secondary, and tertiary components.[5] Primary hemostasis is defined by platelet activation and formation of a platelet plug. Secondary hemostasis involves the activation of the coagulation cascade by tissue factor and platelet factors, ultimately leading to thrombin activation and deposition of fibrin in an attempt to stabilize the platelet plug formed by primary hemostasis. Tertiary hemostasis occurs when the clot is dissolved through fibrinolysis mediated by tissue plasminogen activator and plasminogen.

Thrombosis and bleeding risk in patients with cirrhosis is due to a complex interaction of hypercoagulability, stasis in the form of reduced portal vein velocity, and vessel wall injury leading to endothelial dysfunction in the setting of circulating endotoxemia.[6,7] In terms of hypercoagulability, abnormalities in primary hemostasis, including elevated levels of von Willebrand factor and low levels of ADAMTS13,[8,9] reinforce a prohemostatic environment. Decreased levels of protein C and protein S, antithrombin III, and heparin cofactor II in addition to elevated levels of factor VIII also shift the equilibrium in favor of baseline thrombosis.[8,10] Interpretations of independent levels of anticoagulant protein C, protein S, and antithrombin III, however, are wrought with error in the setting of DVT or PVT due to activation of the coagulation system and artificially low circulating levels.[11] Low levels of plasminogen are found in patients with cirrhosis and affect the fibrinolytic system promoting an environment rich for clotting.[10,12] In addition, patients with chronic liver disease may have concurrent hypercoagulable disorders, including the presence of the antiphospholipid antibody syndrome, factor V Leiden mutation, prothrombin G20210A mutation, Janus kinase 2 (JAK2) mutation, or methylenetetrahydrofolate reductase C677T mutation.[13–15] These mutations are found more commonly in patients with PVT than in those without.[13] Several reports have suggested that bacterial lipopolysaccharide may predispose patients with cirrhosis to clotting because this gut-derived endotoxin translocation into the systemic circulation has been associated both with increased thrombin production through increased tissue factor activity[6,16,17] and increased release of von Willebrand factor from endothelial cells.[18] An endotoxin gradient has been described between the portosystemic and peripheral circulation systems, with the greatest values found in the portal circulation when directly measured in patients with cirrhosis.[6]

In summation, cirrhosis patients have a rebalanced hemostatic system with simultaneous changes in both their prohemostatic and antihemostatic pathways that is precarious at best and often tipped one way or another by infection, invasive procedures, hospitalization, and renal failure.[19] It is possible to have both bleeding and thrombosis in sequential fashion in a short time frame.