



## Coagulopathy in Acute Liver Failure

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In this issue of the *Journal of Clinical and Translational Hepatology*, Seetharam describes the complex disease entity that is acute liver failure (ALF), which often manifests in multiorgan dysfunction and requires management in the intensive care unit.<sup>1</sup> ALF is defined as the presence of acute liver injury of fewer than 26 weeks in duration, any degree of encephalopathy, and international normalized ratio (INR)  $\geq 1.5$ .<sup>2</sup> The INR value of 1.5 is well accepted in the medical community as a reflection of the loss of synthetic function in ALF and is sometimes used to manage coagulopathy. However, as clinicians, we need to understand the implications of relying on INR as the dominant measure of coagulopathy in ALF.

The INR value itself does not accurately or directly reflect the true bleeding risk in ALF because coagulopathy in ALF is much more complex than what a single laboratory value can measure. Despite the typically prolonged INR in ALF, prior literature suggests that the true bleeding risk is lower than expected because hemostasis in ALF is a rebalanced normal state.<sup>3</sup> ALF leads to a reduction of clotting factors that are normally synthesized by hepatocytes, which subsequently results in prolonged INR values. However, conventional tests such as activated partial thromboplastin time (aPTT), prothrombin time, and INR measure only the reduced circulating procoagulant proteins. These tests often fail to capture the rebalanced hemostasis in ALF, including impaired anticoagulants like antithrombin III and plasminogen, fibrinolytic systems, and platelet function/activation.<sup>4</sup>

Current guidelines recommend against prophylactic transfusion of blood products based on prolonged INR alone. European Association for the Study of the Liver (EASL) recommends limiting transfusions, unless patients with ALF are actively bleeding.<sup>5</sup> American Association for the Study of Liver Diseases (AASLD) also recommends

transfusions for thrombocytopenia or prolonged prothrombin time only in the setting of bleeding or invasive procedures.<sup>2</sup> There are several arguments to consider for this particular recommendation made by both societies. Prophylactic transfusion of fresh frozen plasma (FFP) limits the evaluation of recovering or worsening liver function as measured by INR, which is an important prognosticating marker in ALF. FFP transfusion is associated with increased risks of transfusion-related lung injury, volume overload, thrombosis, and immunologic complications.<sup>2,5</sup> Unnecessary transfusions of FFP can also increase venous pressure, leading to increased surgical bleeding and intracranial hypertension without necessarily affecting the thrombin (factor II) production.<sup>3</sup>

The real challenge of managing coagulopathy in patients with ALF arises when these patients develop active bleeding. Clinically significant bleeding in ALF is uncommon at around 5% of patients, and bleeding complications in ALF are more typically capillary-type in the setting of mucosal injury rather than from portal hypertension.<sup>4</sup> Hemorrhage from esophageal varices is rare unless Budd-Chiari syndrome is the underlying etiology of ALF.<sup>4</sup> Regardless of the type of bleeding, there are currently no specific guidelines for the management of acute hemorrhage in patients with ALF, especially regarding the target INR level. EASL suggests transfusion of blood products to goal fibrinogen 150–200 mg/dL and platelets  $>60,000/\text{mm}^3$  in patients with significant bleeding.<sup>5</sup> It is worth noting that EASL does not suggest a specific INR target. AASLD states that FFP alone does not correct severely elevated INR, and recombinant activated factor VII (rFVIIa) or plasmapheresis may be considered.<sup>2</sup> Transfusion to the platelet count of  $50,000/\text{mm}^3$  is reasonable in patients with significant bleeding, but this statement comes with the disclaimer that the transfusion threshold for platelet count has not been studied in patients with ALF.<sup>2</sup> AASLD does not define an optimal INR cutoff in bleeding ALF patients.

The most recent American Gastroenterological Association (AGA) clinical practice update on coagulopathy in cirrhosis perhaps gives us some insights into the management of coagulopathy in ALF. The AGA guidelines outline the suggested thresholds for transfusions in actively bleeding patients with cirrhosis: hematocrit  $\geq 25\%$ , platelet count  $>50,000/\text{mm}^3$ , and fibrinogen  $>120 \text{ mg/dL}$ .<sup>6</sup> Once again, there are no recommendations toward transfusion to a target INR given the paucity of literature support. More importantly, the AGA guidelines suggest the use of global assessments of clotting, such as rotational thromboelastometry (ROTEM), thromboelastography (TEG), and sonorrheometry, in patients with cirrhosis.<sup>6</sup> While EASL recommends possibly using thromboviscous

**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ALF, acute liver failure; aPTT, activated partial thromboplastin time; EASL, European Association for the Study of the Liver; FFP, fresh frozen plasma; INR, international normalized ratio; PT, prothrombin time; rFVIIa, recombinant activated factor VII; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

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technologies to assess coagulopathy in patients with ALF,<sup>5</sup> more studies are needed to define these tests' diagnostic accuracies in the acute setting.

Viscoelastic blood tests including ROTEM and TEG are not yet routinely adopted to supplement the assessment of coagulopathy in cirrhosis and ALF. However, they may prove to be powerful tools in evaluating coagulopathy by simulating a more physiologic *in vivo* hemostasis pathway. While the conventional tests of platelet count and INR provide static snapshots of the dynamic coagulation process, both ROTEM and TEG evaluate the ever-changing mechanics of clot formation, clot strength, and fibrinolysis in real-time.<sup>7</sup> They allow for a more comprehensive depiction of the ongoing coagulopathy, which can be invaluable for the care of high risk bleeding patients. More recently, studies in cirrhotic patients have compared the utility of TEG-guided transfusions to the standard of care (i.e., transfusions guided by platelet count and INR). These studies offered that TEG-guided transfusion protocols can reduce the number of transfused blood products without worsening the bleeding complication in high bleeding risk procedures, for both variceal and nonvariceal bleeding situations.<sup>8-10</sup> Unfortunately, there are no analogous studies to date that evaluate viscoelastic blood tests in patients with ALF.

Coagulopathy in ALF can be multifaceted, and the current standard diagnostic measures are suboptimal in providing a comprehensive assessment. To date, gastroenterology and hepatology professional societies have not yet provided guidance on INR thresholds for transfusion in bleeding ALF. Perhaps, aside from its position in the standard definition of ALF, the INR value should not be considered when evaluating coagulopathy in ALF. Instead, a more global assessment using viscoelastic testing may yield better diagnostic value. We need more primary studies on the implementation of viscoelastic blood testing for gauging the severity of coagulopathy in ALF and for guiding transfusion decisions.

## Conflict of interest

The authors have no conflict of interests related to this publication.

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