Editorial Commentary

Bleeding risk and thrombosis in cirrhosis: a paradox with a need to address them

Anand V. Kulkarni[1]^, K. Rajender Reddy[2]^

[1]Department of Hepatology, Asian Institute of Gastroenterology, Hyderabad, India; [2]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, PA, USA

Correspondence to: Prof. K. Rajender Reddy, MD. Founders Professor of Medicine, University of Pennsylvania, 3400 Spruce Street, 2 Dulles, HUP, Philadelphia, PA 19104, USA. Email: reddyr@pennmedicine.upenn.edu.

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Patients with cirrhosis have a state of "rebalanced hemostasis" where there is a simultaneous reduction in both qualitative and quantitative properties of procoagulants and anticoagulants, i.e., platelets, fibrinogen, coagulation factors, protein C, S, and antithrombin and conversely, there is an increase in the levels of von Willebrand factor, endothelial factor VIII, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor type 1 (PAI-1) (1). Laboratory tests, such as INR, involving these coagulation proteins have been used for the prognostication of patients with cirrhosis/liver failure and have historically been part of several severity scores (2,3). Spontaneous bleeding due to clotting factor deficiencies is less frequent in the absence of mechanical trauma, while thrombosis is not uncommon and may merit anticoagulation therapy (4). However, the management of patients with cirrhosis with abnormalities in the hemostasis system is unclear. To meet this unmet need, the European Association for the Study of the Liver (EASL) developed new guidelines for the prevention and management of bleeding and thrombosis in patients with cirrhosis (5). The bleeding here is referred to mucocutaneous and visceral bleeding events.

This committee of well-known experts must be lauded for the painstaking efforts of reviewing the literature in depth and developing guidelines that are clinically relevant, simple to follow, and can be readily adopted in practice globally. The recommendations were made in accordance with the quality of evidence scored by the Oxford Centre for Evidence-based Medicine (OCEBM). Further, a Delphi panel provided opinions. Several of the recommendations have a bearing on day-to-day practice and are worthy of integration into clinical practice.

Laboratory tests of hemostasis [international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen] and, to some extent, viscoelastic tests are commonly used in the assessment of risk for spontaneous and post-procedural bleeding, while there is a lack of convincing evidence of their benefit and as such a tempered approach in using them widely in clinical decisions is warranted. These tests might provide an assessment of the severity of liver disease and provide a background to help manage post-procedural bleeding if it were to occur. Viscoelastic tests have often been used to predict bleeding risk during liver transplantation, and the information which, in turn, has been used to dictate treatment (6). Yet, there appears to be a lack of robust data to support it.

Spontaneous non-significant bleeding, especially epistaxis, hemorrhoidal bleeds, and ecchymoses, are common in patients with alcohol-related cirrhosis (7,8). The guidelines recommend not correcting the coagulation

^ ORCID: Anand V. Kulkarni, 0000-0002-1240-1675; Rajender K. Reddy, 0000-0002-4898-7778.

parameters if abnormal to prevent spontaneous hemostasis-related bleeding, defined as an unprovoked hemorrhagic event of an unexplained cause.

Sir William Osler aptly said, "*Medicine is a science of uncertainty and an art of probability*". Thus, the art of clinical medicine involves an appreciation that all is not "black" or "white" while there are many factors that dictate the risk of post-procedural bleeding and not necessarily due to abnormalities in hemostasis alone; type of procedure, severity of liver disease, duration of the procedure, operator expertise, and unanticipated complication such as traumatizing an abdominal wall vessel during paracentesis being some of the factors. To that end, the guideline appropriately stratifies the risk of a procedure leading to post-procedural bleeding as low risk (≤1.5%) and high risk (>1.5%), and this is nicely highlighted in the document. Most patients with liver disease require some form of intervention either for diagnosis [percutaneous or transjugular liver biopsy, hepatic venous pressure gradient (HVPG) measurement] or as a therapeutic measure [paracentesis, thoracentesis, dental extraction, endoscopic variceal ligation, endoscopic polypectomy, endoscopic retrograde cholangiopancreatography (ERCP)]. Tradition has it as a norm, in some centers and practices, to evaluate and correct coagulopathy, noted either with traditional tests (PT, aPTT, and platelets) or viscoelastic tests, prior to performing any intervention in patients with cirrhosis. An example of such concern comes around dental extraction, and the guideline is reassuring in that there is no evidence to support a correction of the coagulation abnormalities in this context. To be more specific, the guideline indicates that in patients with cirrhosis undergoing invasive procedures (both low and high risk), correction of a prolonged INR with fresh frozen plasma (FFP) is not recommended to decrease the rate of procedure-related clinically relevant bleeding. This is relevant given the well-known harms of FFP infusion, which is associated with an increased risk of lung injury and allergic reactions, and transfusion-associated circulatory overload (TACO) (9,10). Avoiding the use of blood products, in addition, can reduce the costs associated with laboratory testing and the unnecessary use of blood products. The guideline, in addition, also goes on to extensively discuss the role, if any, for the use of platelets, fibrinogen concentrate, prothrombin complex concentrates (PCCs), thrombopoietin receptor (TPO-R) agonists, cryoprecipitate, and antifibrinolytic (tranexamic acid) therapy, as prophylaxis in the prevention of post-procedural bleeding. Additionally, it rightly points out that imaging guidance for interventions such as liver biopsy (preferably done via transjugular route), central venous line placement, and jugular puncture for portosystemic stent placement would be preferred to minimize the risk of post-procedural bleeding.

The guideline also addresses the issue of risk and the occurrence of thrombosis in those with cirrhosis, an event that seems counterintuitive to the recognized risk of bleeding in this population. As such, there is a general reluctance to use anticoagulation for fear of bleeding when there is an indication for the use of anticoagulants such as venous thromboembolism (VTE) and portal vein thrombosis (PVT). Clinical prediction scores, including Padua prediction score and International Medical Prevention Registry on VTE (IMPROVE) have been recommended to aid in predicting VTE. Vitamin K antagonists (for Child A), low molecular weight heparin (Child A, B, C), unfractionated heparin (for those with renal failure), and direct-acting oral anti-coagulants (DOAC for CTP A) have been recommended for the treatment of VTE in patients with cirrhosis. These recommendations are invaluable and can guide clinicians in the prevention and management of these complications in those with cirrhosis.

While comprehensive, as highlighted by the guideline, the recommendations were mostly based on retrospective and observational studies that have been of suboptimal quality. In fairness though, randomized studies may not be pragmatic, in these patients with low risk of bleeding, for reasons of requiring a large number of patients in a study to demonstrate a benefit or of a lack of a benefit with the use of blood products in preventing post-procedural bleeding. Further, there may be reluctance on part of patients and health care providers to support such a study due to perceived fear of bleeding risk without use of blood products. This, however, should not detract from the fact that these are very relevant clinical issues and that there has been a need to provide guidance with the best available information as it is unlikely that large randomized trials will be done and become available in the near future. The guideline provides a framework on where the unmet needs are in generating robust data for several of the clinical scenarios and, as such, paves a path for future research in the area of bleeding and thrombosis. To quote the Late Sir Winston Churchill, "*To improve is to change*; *to be perfect is to change often*". Let us not continue to practice Medicine based on old dogmas and perceptions.

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Footnote

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