

Editorial

Anticoagulant therapy among patients with cirrhosis: a challenging attempt to maintain a delicate balance

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Coagulopathy and thrombocytopenia are among the hemostatic abnormalities frequently observed in cirrhosis resulting in the traditional concerns for increased bleeding tendency.¹ However, growing evidence suggests that patients with cirrhosis are also at increased risk to develop thrombosis and may require treatment with anticoagulant therapy.^{1,2} Thus, to provide safe and effective anticoagulant therapy, a clear understanding of the complex hemostatic derangement occurring in chronic liver disease is essential.

Chronic liver disease causes parallel alterations in procoagulant and anticoagulant factors resulting in the rebalanced hemostasis.²⁻⁵ First, the markedly high levels of von Willebrand factor (VWF) and reduced levels of ADAMTS13, a plasma metalloproteinase synthesized by the liver that cleaves multimeric VWF into smaller less adhesive multimers counteract the primary hemostatic defects due to thrombocytopenia and platelet dysfunction in chronic liver disease.^{6,7} Secondly, reduced levels of natural anticoagulant proteins (antithrombin, protein C, and protein S), high levels of FVIII, which are synthesized by the endothelial cells^{3,8} and impaired function of tissue factor pathway inhibitor due to low protein S levels^{3,9} help balance the coagulopathy in end-stage liver disease due to decreased levels of procoagulant proteins synthesized by the liver parenchyma (fibrinogen, FII, FV, FVII, FIX, FX, and FXI) and dysfibrinogenemia.²⁻⁵

Lastly, the fibrinolytic system regains balance because of the parallel decline in both the profibrinolytic and antifibrinolytic proteins synthesized by the liver except for tissue plasminogen activator and plasminogen activator inhibitor-1, which are synthesized by the endothelial cells.^{3,10} Patients with cirrhosis have decreased levels of

plasminogen and elevated levels of plasminogen activator inhibitor-1 which offset the increase in fibrinolysis due to low levels of α 2-antiplasmin and thrombin-activatable fibrinolysis inhibitor, as well as high levels of tissue plasminogen activator.

Although several mechanisms restore the hemostatic balance in chronic liver disease, this rebalanced hemostasis is fragile as a result of the relative deficiency of procoagulant and anticoagulant factors, which may easily overturn to bleeding or thrombosis depending on the concomitant risk factors.²⁻⁵ Therefore, several concerns often arise when patients with cirrhosis, who have both thrombotic and bleeding potential, require anticoagulant therapy. In addition to primary hemostatic and coagulation defects, patients with chronic liver disease also have bleeding diathesis related to portal hypertension and other extrinsic factors including, bacterial infection or sepsis and acute renal failure, which may provoke hemorrhagic complications during anticoagulant treatment.¹¹⁻¹⁶

Furthermore, the monitoring of anticoagulant therapy among patients with cirrhosis is problematic. Because of the frequently prolonged baseline prothrombin time and activated partial thromboplastin time before the initiation of anticoagulant therapy, the usefulness of these conventional coagulation tests to guide the dose adjustment is limited.^{3,11}

Also, no established therapeutic range of anticoagulant therapy has been applied explicitly to patients with cirrhosis.^{4,11} For instance, an international normalized ratio (INR) of 2.0 to 3.0 is indicative of therapeutic anticoagulation with warfarin among patients without cirrhosis. However, the same therapeutic interval

might not be reliably protective against thrombosis in cirrhosis given that patients with cirrhosis already have pre-existing coagulopathy and probably require a lower warfarin dose than patients without cirrhosis to achieve the therapeutic INR.¹¹ Therefore, maintaining a delicate balance between the risks and benefits of anticoagulant therapy among patients with cirrhosis is a challenging endeavor.

In this issue of the Journal of Hematology and Transfusion Medicine, Nakornchai W. and Rojnuckarin P. conducted a retrospective study to address the unsettled matter regarding the bleeding and thromboembolic risk among Thai patients with cirrhosis treated with warfarin. The incidence of major bleeding, clinically relevant nonmajor bleeding and thromboembolic events among 32 patients with cirrhosis treated with warfarin were compared with that of 70 patients without cirrhosis. There was no statistically significant difference in baseline characteristics between the two groups except for between the two groups except for a higher number of alcohol consumers, lower number of patients with hypertension, lower levels of serum albumin and lower median platelet count among patients in the cirrhosis group. However, only two of 32 patients with cirrhosis and none in the control group had a platelet count lower than 100,000/ μ L. Approximately one fourth and 11.8% of patients with cirrhosis had prolonged INR, and thrombocytopenia, respectively. Most patients with cirrhosis were assigned Child-Pugh score A, and only 3.1% were assigned Child-Pugh score C. Atrial fibrillation was the most common indication for anticoagulant therapy, while the high-risk HAS-BLED score was similar between the two groups.

The current study revealed that patients with cirrhosis were four times more likely to develop major bleeding during warfarin therapy while no significant difference was observed in clinically relevant nonmajor bleeding and thromboembolic events between the two groups. Upper gastrointestinal hemorrhage due to variceal and

nonvariceal bleeding was the primary affected site among patients with cirrhosis, which significantly differed from that of the controls and may indicate the pro-hemorrhagic tendency mainly related to cirrhosis. Additionally, the number of patients with INR level greater than 3.0 at the time of bleeding was higher among patients with cirrhosis than that of the controls reflecting the greater difficulty to attain a usual safe therapeutic interval among patients with cirrhosis. Furthermore, only cirrhosis and alcohol consumption were the independent predictors of major bleeding among warfarin users.

The findings of this study were in agreement with related studies, showing increased bleeding risk among patients with cirrhosis receiving warfarin treatment.^{17,18} The study by Nakornchai W. and Rojnuckarin P. underscores the difficulty to concurrently provide safe and effective anticoagulant therapy among patients with cirrhosis. While the evidence-based guidance on the optimal care for patients with cirrhosis receiving anticoagulant therapy is not readily available, it would be best to exercise sound clinical judgment to maintain a good balance between the risks and benefits involved with anticoagulant therapy in this precarious situation of rebalanced hemostasis in cirrhosis.

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