



Cirrhotic patients with venous thromboembolism: how to deal with an unstable balance?

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Chronic liver disease may predispose patients to thrombotic events for local risk factors, such as portal hypertension and consequent venous stasis, which can lead to portal vein thrombosis (1). Moreover, the delicate haemostatic balance between reduced production of procoagulant factors and decreased levels of anticoagulants (such as protein C and antithrombin) (2) may determine a systemic prothrombotic state with an increased risk of venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), in combination with an increased bleeding risk. This bleeding risk is at least partially explained by thrombocytopenia and esophageal varices. For this reason, it is relevant to investigate the complex link between cirrhosis and thrombosis genesis, the clinical characteristics and the natural history of VTE in cirrhotic patients, as well as novel treatment options for VTE: treating physicians urgently need useful tools to face the delicate balance between the risk of VTE and the very high risk of bleeding.

In the current issue of the Journal, Xintong Zhang and co-authors describe clinical features and outcomes of VTE patients with and without cirrhosis in retrospective case-control study (3). In a 4 years' time, they enrolled 16 cases with cirrhosis and 160 controls matched for age, sex and Charlson Comorbidity Index score. In their study, patients VTE with cirrhosis received less frequently anticoagulant therapy and have a significantly increased risk of major bleeding and in-hospital mortality compared to VTE patients without cirrhosis. The rate of major bleeding

among cirrhotic patients treated with anticoagulants in this study was very high (25%): data from a recent large prospective study (4) and a meta-analysis of observational studies (5) on anticoagulation for portal vein thrombosis in patients with cirrhosis, mainly with low molecular weight heparin, reported a bleeding rate less than 4%. Moreover, the authors report that the incidence of major bleeding and in-hospital mortality seem not to be influenced by withholding anticoagulant therapy and, interestingly, in-hospital mortality was more associated with arterial and venous thrombosis than with major bleeding. However, it should be emphasized that these are observational data and analyses are clear underpowered (only sixteen patients included), which makes it impossible to draw any conclusion. In addition, quality of anticoagulation with vitamin K antagonist and dosage of low-molecular weight heparin were not reported in the study and could have affected results.

The findings of this study confirm that physicians correctly recognized cirrhosis as a condition at very high bleeding risk and, consequently, VTE is frequently treated differently than the current recommended standard of care. Unfortunately, no relevant information is available in this paper. Many physicians do not start anticoagulation in patients with DVT and cirrhosis, in particular those at low risk of embolization, as long as esophageal varices are not safely treated. Moreover, a transient condition, such as an acute infection, may cause both VTE and temporary reduced platelet count: in those cases, physicians may

temporary interrupt or postpone start of anticoagulation.

This study highlights how challenging it is to treat VTE in patients with liver cirrhosis. It confirms that the best approach to VTE in end-stage liver disease remains unclear, and that cirrhosis is a prognostic marker of unfavorable VTE outcome: VTE patients with cirrhosis are more vulnerable patients than most VTE patients without cirrhosis. Besides a low platelet count and gastrointestinal sources of possible bleeding, the choice of the best drug and best dosage is more difficult in comparison to other VTE patients: (I) ascites may incorrectly influence the measure of body weight; (II) hepatorenal syndrome may modify drug clearance; (III) prolonged INR makes difficult to manage vitamin K antagonists.

Data on efficacy and safety of anticoagulation in cirrhotic patients are mainly limited to their use for portal vein thrombosis. Available evidence suggests that patients experience more frequently partial or complete recanalization of the portal venous axis when they are treated with anticoagulants, in particular with low molecular weight heparin (6), and have a better clinical outcome (7).

In summary, no solid evidence is available how to deal with this unstable balance between thrombosis and bleeding. Prospective clinical studies on the treatment of VTE in patients with cirrhosis are urgently needed. To the best of our knowledge, there is only an ongoing randomized controlled trial ongoing focused on prevention of thrombotic events in hospitalized cirrhotic patients and not on VTE treatment (NCT02802605) (8). As physicians are still lacking of effective tools to treat patients with VTE and cirrhosis, we may suggest some practical advices: first, it is necessary to admit patient in a dedicated unit to start or not adequate treatment both for VTE and for cirrhosis-related complications; second, it is necessary, at least initially, a daily clinical and laboratory assessment to decrease both thrombotic and bleeding risk; third, a multidisciplinary team should take care of these patients, both in the hospital admission phase and, most importantly, in the follow-up phase, when it is necessary to implement adequate strategies to reduce VTE recurrence and bleeding events.

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References

1. Galli L, Gerdes VE, Guasti L, et al. Thrombosis associated with viral hepatitis. *J Clin Transl Hepatol* 2014;2:234-9.
2. Tufano A, Di Capua M, Coppola A, et al. The infectious burden in atherothrombosis. *Semin Thromb Hemost* 2012;38:515-23.
3. Zhang X, Qi X, De Stefano V, et al. Impact of liver cirrhosis on the outcomes of patients with venous thromboembolism: a case-control study. *AME Med J* 2017;2:26.
4. Ageno W, Riva N, Schulman S, et al. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. *JAMA Intern Med* 2015;175:1474-80.
5. Qi X, De Stefano V, Li H, et al. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. *Eur J Intern Med* 2015;26:23-9.
6. Amitrano L, Guardascione MA, Menchise A, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. *J Clin Gastroenterol* 2010;44:448-51.
7. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of

anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol* 2012;10:776-83.

8. Safety and efficacy of bemiparin in the prevention of

thrombotic events in hospitalized cirrhotic patients (BEMI-2015). Available online: <https://clinicaltrials.gov/ct2/show/NCT02802605>

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