Decreased Fibrinolytic Capacity in Cirrhosis and Liver Transplantation Outcomes

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Decreased Fibrinolytic Capacity in Cirrhosis and Liver Transplantation Outcomes

Patients with advanced liver disease develop multiple changes in their hemostatic system. The net result of these changes appears to be a hemostatic system that is in balance but has distinct hyper- and hypocoagulable features.¹ Studies over the last 15 years have characterized these changes in hemostasis and their consequences, leading to profound changes in the management of patients with liver disease. Importantly, we are shifting the emphasis from attempts to prevent bleeding to an increase in prophylactic antithrombotic interventions because we now appreciate that thrombotic events are common and potentially preventable.

Although major steps have been made in this field, there remains areas of controversy. One of these relates to the functionality of the fibrinolytic system.² Historically, accelerated fibrinolysis was considered a hallmark of cirrhosis and was implicated in bleeding. This concept, however, has been challenged with evidence that fibrinolysis in plasma remains in balance due to a concomitant decline in pro- and antifibrinolytic drivers.³

An article by Nicolau-Raducu et al. in this issue of Liver Transplantation reports on kaolin-induced thromboelastography (TEG) to assess fibrinolytic capacity in liver transplantation (LT) candidates.⁴ They report a hypofibrinolytic state in no less than 72% of patients on the basis of definitions derived from trauma-induced fibrinolysis (lysis at 30 minutes [LY30] of <0.8%).⁵ This pretransplant hypofibrinolysis is referred to by the authors as “fibrinolytic shutdown,” which I think is a misnomer in this context. Fibrinolytic shutdown occurs in response to surgery or trauma, presumably as a result of an acute release of fibrinolytic inhibitors, such as plasminogen activator inhibitor type 1. In patients who are about to undergo LT, an acute event leading to a hypofibrinolytic state is likely absent, and the hypofibrinolytic state is not an acute “shutdown” but rather an anomaly that has developed over time. It is somewhat surprising that almost three-quarters of their patients had developed this anomaly, and given the discrepancy with published literature, this finding deserves a closer look. It needs to be noted that thromboelastography is poorly validated for the detection of hypofibrinolysis. Importantly, because the proportion of hypofibrinolysis in a cohort of healthy individuals is not reported by the authors, it might be that the 72% reported is an overestimation. Indeed, reported reference values of LY30 in healthy individuals encompass all values of <0.8%,⁶ so what is defined as pathological by Nicolau-Raducu et al. is present in apparently healthy individuals. In addition, there is significant interlaboratory and intralaboratory variation in TEG readings,⁷ which appears to be a particular issue with the LY30 parameter. This indicates that thresholds such as a LY30 <0.8% may not even be reliable within a single laboratory but can certainly not be automatically transferred to another. Nevertheless, results are in line with a report of TEG results in a large cohort of stable patients with cirrhosis in which 60% had a LY30 <0.8%.⁸

Although there is a huge gap between the data in the present article and the 2 theories most prevalent in literature, which are that a substantial proportion

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**Abbreviations:** LT, liver transplantation; LY30, lysis at 30 minutes; NASH, nonalcoholic steatohepatitis; TEG, thromboelastography.

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of patients with cirrhosis have hyperfibrinolysis, or that the average patient with cirrhosis is normofibrinolytic, the concept of a hypofibrinolytic state in patients with liver disease does deserve attention. However, we need to better validate assays and come up with rational and validated definitions of normal fibrinolysis, hypofibrinolysis, and hyperfibrinolysis. Our group has used a plasma-based assay to assess fibrinolytic status in patients with liver disease, with definitions of “abnormal” based on reference values obtained in large groups of healthy individuals. Although this assay uses plasma and, therefore, ignores the important contribution of cellular components to fibrinolysis, it does have demonstrated clinical correlates. Specifically, a hypofibrinolytic state as defined by this test is associated with an elevated risk of both venous and arterial thrombotic events in the general population.\(^9\) Using this test, we have demonstrated normofibrinolysis in the majority of patients with compensated cirrhosis,\(^3\) hyperfibrinolysis in patients with acute decompensation of cirrhosis, and a hypofibrinolytic state in a proportion of patients with acute-on-chronic liver failure.\(^10\)

Also patients with renal failure\(^11\) and patients with obesity and/or nonalcoholic steatohepatitis (NASH)\(^12\) are hypofibrinolytic when tested with this assay. Thus, although the proportion of patients with cirrhosis and hypofibrinolysis may be much more modest than the 72% reported by Nicolau-Raducu et al., there are certainly patients, perhaps with unique clinical characteristics, who have a clear hypofibrinolytic state, which indeed may form a risk of thrombotic events. Studies designed to link the fibrinolytic status of patients with liver disease in relation to future thrombotic (and bleeding) events outside the context of liver transplantation are therefore warranted.

Despite the potential overestimation of the incidence of preoperative hyperfibrinolysis, a preoperative hypofibrinolytic status as defined as LY30 <0.8% appears predictive of postoperative thrombotic events, which in this study had an incidence of almost 5% with a 25% in-hospital mortality. It would be of interest to know whether this effect is dose-dependent (ie, higher thrombotic risks with lower LY30 values within the LY30 <0.8% cohort). Because platelet count and NASH as the underlying etiologies of disease were shown to be independent risk factors for preoperative hyperfibrinolysis, it is unclear whether the thrombotic events are directly linked to inadequate fibrinolysis, or whether the severity of disease (as reflected by a low platelet count) and/or a thrombogenic etiology of disease (ie, NASH) are related to thrombotic events. The fact that patients who developed a hyperfibrinolytic state during liver transplantation were mainly patients who had a preoperative hypofibrinolysis somewhat argues against preoperative hyperfibrinolysis being directly responsible for postoperative thrombotic events. Notably, those patients with hypofibrinolysis have longer K times and lower alpha angles, which are indicative of a (relative) hypocoagulable state that could, in part, compensate for the hypofibrinolytic state. This again argues against a causal role of hypofibrinolysis in the pathogenesis of posttransplant thrombotic complications.

Despite these concerns, the authors demonstrate a clear link between TEG-assessed preoperative fibrinolytic status and outcome. Whereas a preoperative hyperfibrinolytic state is clearly associated with a risk for postoperative thrombosis, a preoperative hyperfibrinolytic state predicts poor 1-year survival. Whether these associations are causally linked or whether the preoperative fibrinolytic status is simply a reflection of patient status remains to be investigated. It is evident that much remains to be learned, and the “fibrinolysis in cirrhosis controversy” is far from being solved.

**REFERENCES**


