"The portal vein in patients with cirrhosis is not an excessively inflammatory or hypercoagulable vascular bed, a prospective cohort study"

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LETTER TO THE EDITOR

"The portal vein in patients with cirrhosis is not an excessively inflammatory or hypercoagulable vascular bed, a prospective cohort study": reply

Dear Editor,

We are grateful to Violi et al. for their interest in our recent publication in the Journal of Thrombosis and Hemostasis [1]. Violi et al. raised concerns about the high levels of lipopolysaccharide (LPS) in our study due to methodological or clinical issues. They propose that we do not have sufficient elements to exclude endotoxemia as a factor favoring hypercoagulability and eventually portal vein thrombosis (PVT) in cirrhosis. We agree with Violi et al. that endotoxemia and inflammation in cirrhosis may cause activation of coagulation and contribute to the development of thrombotic complications. However, in our opinion, it does not seem to play an important role in the development of cirrhotic PVT. We would like to, at least in part, refute the concerns on our study and would like to offer alternative views on the pathophysiology of PVT based on recent observations by our group.

In their letter, Violi et al. suggested that LPS levels in our study are high compared with other studies because of methodological (contamination of samples or laboratory supplies) or clinical (inclusion of patients with active infection) issues. LPS is a small bacterial-derived endotoxin present in the outer cell membrane of gram-negative bacteria. Contamination of laboratory ware is common due to the hydrophobicity of endotoxins and their strong affinity for other hydrophobic materials such as plastics used in the laboratory. As indicated by Violi et al., contamination can be avoided, for example, by working in a laminar air flow cabinet, sterilizing consumables, and using ultrapure water. Indeed, we neither processed blood samples to plasma under sterile conditions, nor did we perform our LPS level measurements in a laminar air flow cabinet. Even with proper aseptic techniques, contamination may occur, which is especially a problem in cell culture experiments. However, potential contamination would evenly affect the samples taken from the portal and hepatic veins. Thus, even if contamination explains the elevated levels of LPS in our study compared with other studies, we still do not find a portosystemic gradient of other inflammatory markers, suggesting that the portal vein is not a proinflammatory environment in our study. Indeed, other markers of inflammation such as IL-6 and TNF-alpha also did not show a portosystemic gradient in our study. The second concern was regarding active infection in our cohort of patients, which may explain the elevated levels of LPS in our results compared with other studies. However, in Hospital Clinic in Barcelona where patients were included, active infection is an absolute contraindication for transjugular intrahepatic portosystemic shunt placement and thus was not present in the patients included in our study. However, we cannot exclude that differences in results between our study and other studies may be due to other differences in patient characteristics.

Violi et al. proposed that endotoxemia contributes to the 3 factors of Virchow's triad (venous stasis, endothelial dysfunction, and hypercoagulation) and thereby to the development of cirrhotic PVT, as also described in their recent literature review published in Blood Reviews [2]. In our recent, prospective study on clinical, ultrasonographic, and hemostatic factors to predict PVT in patients with cirrhosis, we found that although the levels of many markers of activation of coagulation, levels of coagulation proteins, hereditary hypercoagulability, levels of inflammatory markers and neutrophil extracellular traps, and functional tests of hemostasis are altered in patients with cirrhosis, none of them predicted PVT development during the follow-up of up to 48 months [3]. On the basis of these findings, we concluded that the pathophysiology of cirrhotic PVT does not directly involve a systemic hypercoagulable or inflammatory profile. Factors that did predict the development of PVT were mainly those related to portal hypertension. Portal hypertension may be a result of hepatic vascular resistance leading to reduced portal venous flow velocity and may cause endothelial damage due to hypertension-related shear stress. Therefore, the other factors of Virchow's triad—venous stasis and endothelial damage—may contribute to the development of PVT. We recently described the composition and structure of portal vein thrombi in patients with cirrhosis and found that these thrombi consist of a thickened, fibrotic tunica intima of the portal vein vessel wall, with a fibrin-rich thrombus in only one-third of the cases [4]. These findings again argue against a primary role of coagulation activation in the development of PVT but support the role of portal hypertension and endothelial damage.

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Finally, a portosystemic gradient in patients with cirrhosis of markers of inflammation and activation of coagulation was not found in our study [1], in contrast to previously published studies [5–7]. Additionally, these data argue against the concept of the portal vein as a particularly hypercoagulable vascular bed. Nevertheless, we do acknowledge that differences between our study and studies performed by others are incompletely understood, although our study compared the hemostatic status of the portal, posthepatic, and systemic circulation. We propose that multicenter studies should be performed to assess whether the differences in the results are influenced by the differences in sampling techniques or patient characteristics. In addition, none of the studies have evaluated the levels in portal plasma from patients with PVT; therefore, the contribution of a possible portosystemic gradient in the development of PVT remains unclear. We do agree with Violi et al. that prevention and treatment of inflammation may be beneficial in the prevention of other thrombotic complications in patients with cirrhosis. In addition, it could help prevent the progression of liver disease because systemic inflammation has been described as an important factor in the development of disease complications and may lead to acute decompensation of cirrhosis or acute-on-chronic liver failure [8].

In summary, our collective data [1,3,4] argue against the concept that hypercoagulability along with portal activation of coagulation is a key mechanism underlying the development of PVT. Interventions aimed at nonhemostatic mechanisms underlying PVT development require clinical evaluation in prevention and treatment of this common complication in patients with cirrhosis.

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DECLARATION OF COMPETING INTEREST

The authors declare no competing interests.

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