

The local ethics committee of the University of Bonn approved the study (029/13), and all patients signed an informed written consent in accordance with the Helsinki Declaration for the procedures they underwent.

Statistical analysis

Comparisons between vWF, LPS, and factor VIII in the portal and systemic circulation were carried out by Mann–Whitney test for unpaired samples, and data are expressed as median and interquartile ranges (IQR). The Spearman rank correlation coefficient (rS) was used for bivariate correlation.

RESULTS

The median age was 57 (IQR 41–74) years and 13 patients were men. Median model for end-stage liver disease was 14 (IQR 8–34); 4 patients were staged Child Turcotte Pugh (CTP) A, 14 were CTP B, and 2 were CTP C. Eleven patients had alcoholic etiology of liver cirrhosis. Indication for TIPS was variceal bleeding in 9 and refractory ascites in 11 patients. Although there was no significant correlation with the scores of liver disease severity (model for end-stage liver disease, CTP), we found a portal/systemic circulation gradient for all the 3 variables investigated: vWF (250.0 [IQR 214.0–267.0] vs 180.0 [IQR 161.0–204.0] U/dL, $P < 0.001$), factor VIII (164.0 [IQR 152.0–180.0] vs 112.0 [IQR 97.0–127.0] U/dL, $P < 0.001$), and LPS (56.5 [IQR 50.5–65.0] vs 43.0 [IQR 36.3–45.0] pg/mL, $P < 0.001$) were higher in the portal compared with systemic circulation (Figure 1a–c). Furthermore, LPS was significantly correlated with vWF ($rS:0.400$, $P = 0.01$) and factor VIII ($rS:0.360$, $P = 0.02$) (Figure 1d,e). Interestingly, we found a higher porto-systemic gradient of vWF in patients with ascites as indication for TIPS compared with variceal bleeding (hepatic–portal: 81.1 ± 38.4 vs -41.3 ± 48.5 U/dL, $P < 0.05$).

DISCUSSION

This study reports for the first time the existence of a portosystemic vWF gradient in cirrhotic patients, suggesting that the portal tree encompasses local factors predisposing to endothelial damage/perturbation are detectable in cirrhosis. We focused our attention on LPS because previous studies reported that LPS is elevated in the portal circulation of cirrhosis (5) and elicits endothelial perturbation with vWF secretion (8). The significant association between LPS and vWF is in favor of the hypothesis that LPS is one factor eliciting endothelial damage in the portal circulation of cirrhosis.

Another interesting finding of the study is the presence of a portosystemic factor VIII gradient in cirrhosis, which reinforces a previous study reporting an increased concentration of factor VIII in the portal circulation of cirrhotic patients compared with systemic circulation of healthy subjects (9). This finding supports and extends our previous report showing the existence of a hypercoagulation state in the portal circulation of cirrhosis (5) suggesting enhanced factor VIII as an important mechanism predisposing to the hypercoagulation state. LPS may also be relevant to this clotting change because it elicits endothelial secretion of factor VIII at concentrations commonly found in the venous circulation of cirrhosis (8). Thus, LPS could represent a unique mechanism which is implicated in enhancing either vWF or factor VIII in the portal circulation, thus favoring endothelial damage and hypercoagulation. However, we cannot exclude that other mechanisms such as increase of ADAMS 13 or microvesicles, both possessing procoagulant properties (10), may contribute to hypercoagulation in the portal circulation of cirrhosis (10,11). Changes in the gut permeability with consequent translocation of LPS into systemic circulation may be a factor accounting for the enhanced LPS concentration in the portal tree, but further study is necessary to explore this hypothesis. In conclusion, here, we provide evidence in

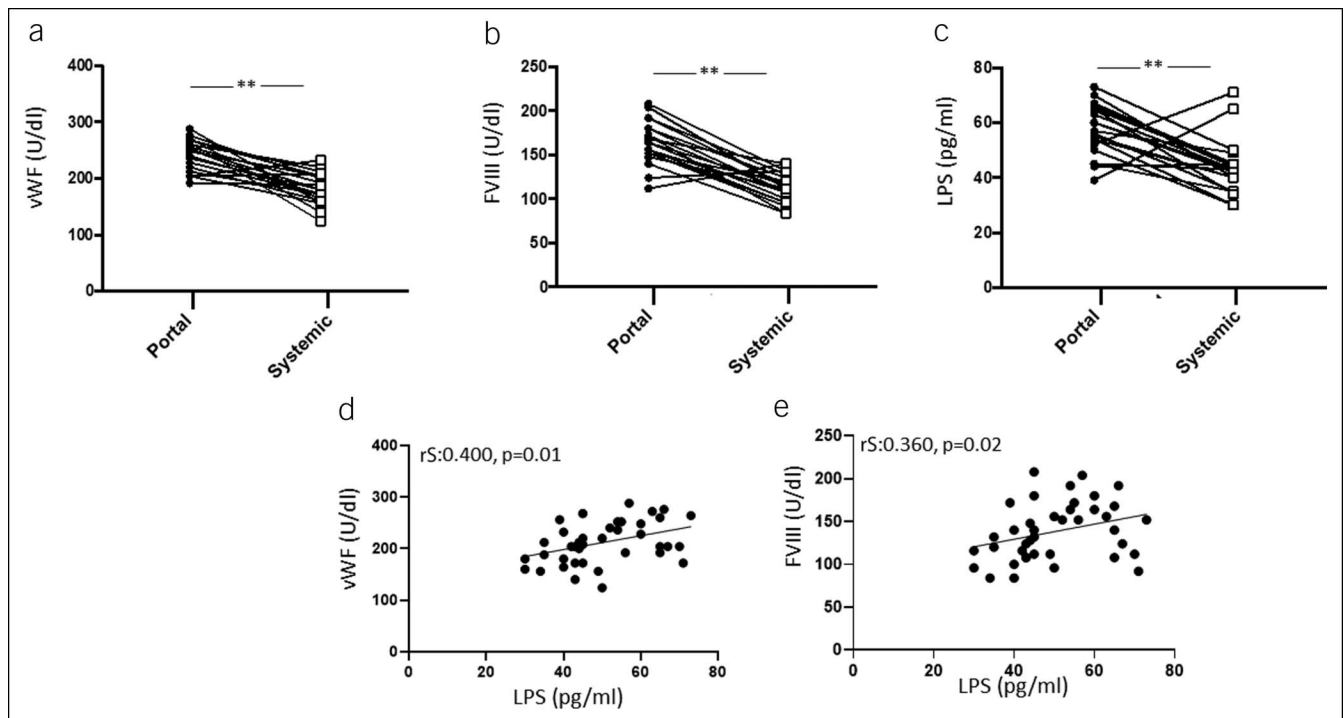


Figure 1. Differences in coagulation and inflammation biomarkers in the portal and systemic circulation. Levels of vWF (a), FVIII (b), and LPS (c) in the portal and systemic circulation of patients with cirrhosis ($n = 20$, $**P < 0.001$). LPS, lipopolysaccharides; vWF, von Willebrand factor.

support that endothelial damage is detectable in the portal circulation of cirrhosis and suggest LPS as a mechanism implicated in this phenomenon; modulation of LPS concentration may be a tool to reduce the thrombotic risk in cirrhosis (12).

CONFLICTS OF INTEREST

Guarantor of the article: Francesco Violi, MD.

Specific author contributions: Michael Praktiknjo, Jonel Trebicka, and Roberto Carnevale equally contributed to this work. M.P.: patients' recruitment, analysis and interpretation of data, and drafting of the manuscript. J.T.: patients' recruitment, analysis and interpretation of data, and critical revision of the manuscript. R.C.: acquisition of data, analysis and interpretation of data, and drafting of the manuscript. D.P.: statistical analysis. A.Q.: patients' recruitment and analysis and interpretation of data. E.E.: critical revision of the manuscript. F.V.: study conception, analysis and interpretation of data, and critical revision of the manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Cirrhosis is associated with portal vein thrombosis.
- ✓ A hypercoagulation status is detected in the portal circulation.

WHAT IS NEW HERE

- ✓ Endothelial damage, as assessed by vWF and factor VIII, is detectable in the portal circulation of cirrhosis.
- ✓ Serum lipopolysaccharides correlate with endothelial damage suggesting a cause-effect relationship.

TRANSLATIONAL IMPACT

- ✓ This finding provides further insight into the pathogenesis of portal vein thrombosis and reinforces the concept the hypercoagulation status does exist in cirrhosis.

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