

## ORIGINAL ARTICLE

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

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## Abstract

**Background:** A hypercoagulable state is not associated with development of portal vein thrombosis in cirrhosis, as we previously demonstrated. However, some groups demonstrated elevated levels of inflammatory markers and activation of hemostasis in the portal vein (PV) compared to posthepatic veins, but because the liver is involved in clearance of these markers, we hypothesize that interpretation of these data is not straightforward.

**Aim:** To determine whether the PV has particular proinflammatory/hypercoagulable characteristics by comparing plasma sampled in the PV, hepatic vein (HV), and the systemic circulation.

**Methods:** Plasma samples from 51 cirrhotic patients with portal hypertension undergoing transjugular intrahepatic portosystemic shunt placement, were taken from the PV, HV, and jugular vein (JV). Markers of inflammation (lipopolysaccharide, tumor necrosis factor- $\alpha$ , interleukin-6, thiobarbituric acid-reactive substances), neutrophil-extracellular-traps (cfDNA, MPO-DNA), endothelial damage (von Willebrand factor [VWF]), and hemostasis were determined and compared among the three vascular beds.

**Results:** Markers of inflammation were slightly, but significantly higher in the PV than in the HV and systemic circulation. VWF and markers of hemostasis were modestly elevated in the PV. Levels of multiple markers were lower in the HV compared with the PV and systemic circulation. Higher model for end-stage liver disease score was associated with a more prothrombotic state in all three sample sites.

Annabel Blasi, Juan-Carlos Garcia-Pagan and Ton Lisman are joint senior authors.

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**Conclusion:** In contrast to published studies, we did not detect a clear proinflammatory or prothrombotic environment in the PV of cirrhotic patients. Many markers are lowest in the HV, indicating that the low levels of these markers in the HV, at least in part, reflect clearance of those markers in the liver.

**KEYWORDS**

cirrhosis, coagulation, inflammation, portal vein thrombosis

## 1 | INTRODUCTION

Nontumoral portal vein thrombosis (PVT) is a common complication in patients with cirrhosis, with a prevalence varying from 5% to 26% in liver transplant candidates.<sup>1</sup> The exact pathogenesis of PVT is not fully understood. Although the three factors of Virchow's triad (reduced blood flow, endothelial damage, and hypercoagulability) are important contributors to the development of deep vein thrombosis (DVT), it remains unclear how these factors contribute to the development of PVT.<sup>2</sup> For example, although there is evidence for hypercoagulability in cirrhotic patients,<sup>3</sup> whether this hypercoagulable state contributes to development of PVT has been a matter of debate. Some studies showed a more profound hypercoagulable state in patients with PVT,<sup>4,5</sup> but if this relation is causal or whether enhanced hypercoagulability reflects more advanced disease is unclear. In addition, most published studies evaluating risk factors for PVT are retrospective, cross-sectional, and included a relatively small number of patients. In a recent large prospective study, we demonstrated that markers of portal hypertension, but not markers of inflammation or hypercoagulability were associated with the development of cirrhotic PVT.<sup>6</sup>

The portal venous system has some unique features compared with deep venous systems and may therefore also have a unique biochemical environment. For example, the portal vein receives drainage from the small and large intestines and may therefore have locally elevated levels of markers of endotoxemia, a well-known activator of thrombosis. This may be especially relevant in patients with cirrhosis, who have impaired intestinal barrier function, and in whom therefore bacterial translocation may be increased.<sup>7</sup> In addition, cirrhotic patients frequently have severe portal hypertension, possibly leading to endothelial damage and reduced portal flow velocity.<sup>8</sup> These features could contribute to a hypercoagulable environment in the portal venous system. Indeed, recent studies showed locally elevated levels of markers of endotoxemia, endothelial damage and activation of hemostasis in the portal vein (PV) compared with hepatic vein (HV) or peripheral veins.<sup>9-12</sup> It was hypothesized that these local prothrombotic factors contribute to PVT development. However, plasma from hepatic veins may not truly reflect the systemic circulation because the liver clears most of the proteins involved in coagulation.<sup>13</sup> Hepatic clearance of markers of inflammation and activation of coagulation may lead to lower plasma levels of those markers in the hepatic vein compared with the systemic circulation. Therefore, when comparing plasma samples taken from

### Essentials

- Systemic inflammation or hypercoagulability are not risk factors for cirrhotic portal vein thrombosis.
- Previous studies suggested an inflammatory and hypercoagulable state in the portal vein.
- Our data may explain against an inflammatory and hypercoagulable milieu in the portal vein.
- Hepatic clearance of inflammation and coagulation markers explains deviance from previous work.

the portal vein and the hepatic vein conclusions on an inflammatory and hypercoagulable state in the portal vein may not be justified. Instead, a comparison between the portal vein and the systemic circulation is required to truly assess whether the portal vein is clearly more inflammatory and hypercoagulable compared with other vascular beds of a given patient.

The aim of our study was to determine whether the PV in cirrhotic patients has particular proinflammatory or hypercoagulable characteristics by comparing blood sampled in the PV, in the HV, and in the systemic circulation. We compared markers of inflammation, endothelial damage, and hemostasis to reassess a local prothrombotic environment in the PV, and to include the effect of clearance by the liver of those markers.

## 2 | METHODS

Fifty-one consecutive patients with cirrhosis and clinically diagnosed with portal hypertension undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement were prospectively included between May 2016 and April 2021.

All patients gave written informed consent for participation in this study. Ethical approval was obtained from Hospital Clinic, Barcelona (HCB/2019/0391). Blood samples were taken from the systemic circulation (jugular vein) before the procedure of TIPS placement, and from the PV and HV during hemodynamic measurement and were collected into a citrate-containing tube (0.129 M, 3.8%; Vacutainer system, Becton Dickinson). After centrifugation at 3000g for 20 min at 4°C, plasma was aliquoted and stored at -80°C for subsequent analysis. Citrated plasma samples from 20 healthy

individuals were used to determine reference values in the systemic circulation.

Plasma levels of lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), thiobarbituric acid-reactive substances (TBARS), cell free DNA (cfDNA), complexes of myeloperoxidase with DNA (MPO-DNA), von Willebrand factor (VWF), factor VIII (FVIII), platelet factor 4 (PF4), thrombin-antithrombin (TAT) complexes, plasmin- $\alpha$ 2-antiplasmin (PAP) complexes, and D-dimers were determined as described before.<sup>14-17</sup> Quantification methods are summarized in Table S1. Data are presented as median with interquartile range (IQR) or numbers and percentage for continuous or categorical variables. Statistical analysis was performed with IBM SPSS 23.0 and GraphPad Prism 8 with a two-sided significance level of .05. The matched samples Wilcoxon test was used for comparison between the vascular beds and the Mann-Whitney *U* test was used for comparisons between subgroups of patients.

### 3 | RESULTS

This study included 51 adult ( $\geq 18$  years) cirrhotic patients who underwent TIPS placement. The median age was 58 (50–63) years and 16 (31.4%) were female. The majority of patients had moderate liver disease (Child A: 19 [37.3%]; Child B: 24 [47.1%]; Child C: 8 [15.7%]). Patient characteristics are summarized in Table 1.

To evaluate the biochemical status of the PV compared with the HV and systemic circulation, we first assessed plasma levels of inflammatory and oxidative stress markers in samples taken from these three vascular beds. Figure 1 shows levels of LPS, TNF- $\alpha$ , IL-6, TBARS, cfDNA, and MPO-DNA complexes in plasma collected at those sites. Levels of LPS, IL-6, and TBARS were slightly, but significantly, higher in portal plasma than in plasma from the HV and systemic circulation (Table 2). Plasma levels of cfDNA and MPO-DNA complexes were similar between the PV, HV, and systemic circulation (Table 2).

Next, we assessed levels of markers of activation of hemostasis. Figure 2 shows plasma levels of VWF, FVIII, PF4, TAT, PAP, and D-dimers that were measured in plasma collected from the PV, HV, and systemic circulation. The results are summarized in Table 2. VWF was slightly, but significantly, higher in the PV than in the systemic circulation. FVIII was slightly, but significantly, elevated in the systemic circulation compared with the HV. Plasma levels of PF4 were similar among all three sample sites. Levels of TAT, PAP, and D-dimers were higher in the PV than in the HV. TAT levels were also higher in the systemic circulation than in the HV. PAP levels were significantly higher in the PV than in the systemic circulation. TAT and D-dimer levels were also higher in the PV than in the systemic circulation, but this difference did not reach statistical significance.

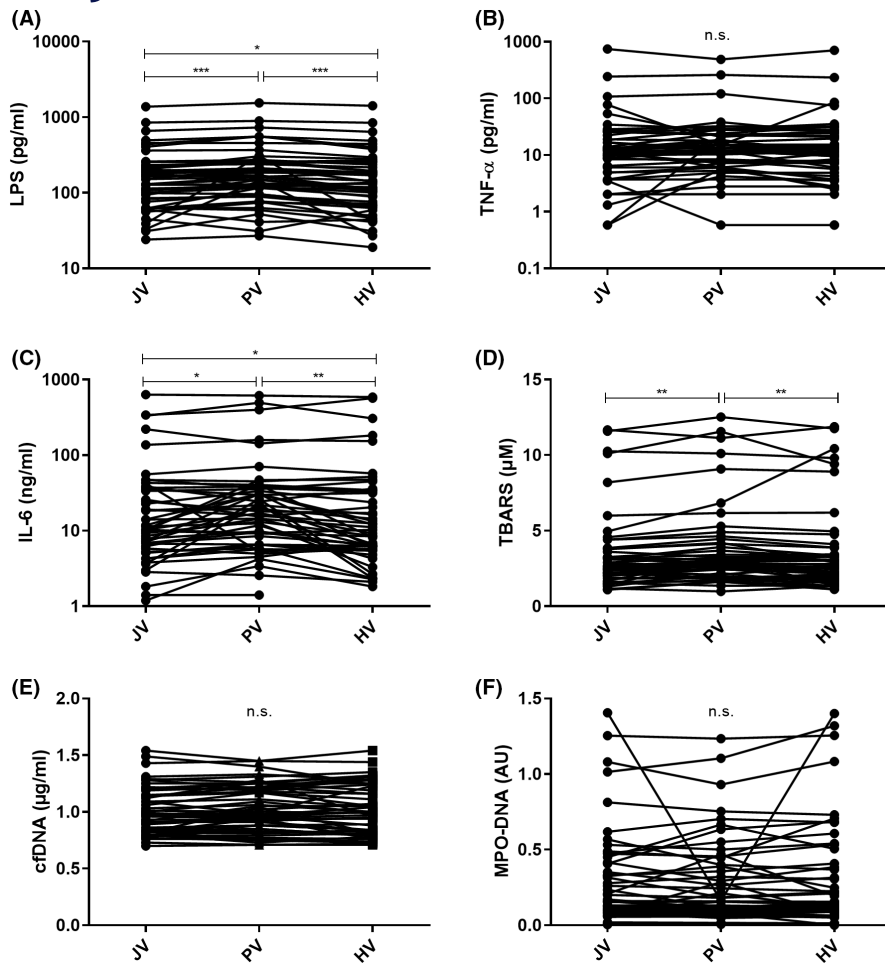
PVT was present in six of the 51 patients at the time of TIPS placement, of which five had occlusive PVT. Comparisons between the PV, HV, and systemic circulation were similar in the cohort of patients with PVT patients included compared with the cohort when PVT patients were excluded (Table S2). Relative differences

TABLE 1 Patient characteristics

	Cirrhotic patients (n = 51)
Age (years)	58 [50–63]
Female (%)	16 (31.4%)
BMI	25.7 [23.2–30.1]
Smoker (currently or stopped) (yes)	15 (29.4%)
Diabetes (yes)	15 (29.4%)
Etiology of liver disease	
ASH	32 (62.7%)
NASH	7 (13.7%)
Hepatitis C	7 (13.7%)
Hepatitis B	2 (3.9%)
Other	3 (5.9%)
Creatinine (mg/dl)	0.83 [0.64–1.12]
Bilirubin (mg/dl)	1.2 [0.8–2.5]
Albumin (mg/dl)	30 [28–35]
Platelets ( $\times 10^9/L$ )	106 [64–179]
INR	1.34 [1.2–1.5]
MELD score	12 [9–15]
MELD_Na score	14 [12–20]
Child Pugh score	8 [7–9]
Child Pugh A/B/C	19 (37.3%)/24 (47.1%)/8 (15.7%)
HVPG (mmHg)	19 [16–24]
Esophageal varices	
Small	5 (9.8%)
Large	46 (90.2%)
Variceal bleeding (yes)	34 (66.7%)
Ascites (yes)	39 (76.5%)
Ascites (mild, moderate, severe)	4 (7.8%)/12 (23.5%)/23 (45.1%)
Spontaneous bacterial peritonitis (yes)	5 (9.8%)
Hepatic encephalopathy (yes)	9 (17.6%)
PVT	
No	45 (88.2%)
Nonocclusive	1 (1.9%)
Occlusive	5 (9.8%)
Hepatocellular carcinoma (yes)	0
Reason for TIPS placement	
Hemorrhage	24 (47.1%)
Ascites	21 (41.2%)
PVT	2 (3.9%)
Other	4 (7.8%)
Use of beta-blockers (yes)	33 (64.7%)

Note: The results are presented as median [interquartile range] or *N* (%) for continuous and categorical variables of available data.

Abbreviations: ASH, alcoholic steatohepatitis; BMI, body mass index; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, model for end-stage liver disease; Na, sodium; NASH, nonalcoholic steatohepatitis; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.



**FIGURE 1** Levels of inflammatory and oxidative stress markers: LPS (A); TNF- $\alpha$  (B); IL-6 (C); TBARS (D); cfDNA (E), and MPO-DNA (F) in the systemic circulation (jugular vein; JV), the portal vein (PV), and hepatic vein (HV) of cirrhotic patients undergoing TIPS placement

in analyte concentrations between the three vascular beds were similar in subgroups with lower or higher model for end-stage liver disease (MELD) scores ( $\leq$  or  $>$  than the median MELD score of 12) or lower or higher hepatic venous pressure gradient (HVPG) ( $\leq$  or  $>$  than the median HVPG of 19) values (Tables S3 and S4).

Patients with higher MELD scores had numerically higher levels of VWF, MPO-DNA, and TBARS in all three sample sites compared with patients with lower MELD scores. Patients with higher MELD scores had lower levels of PF4 compared with patients with lower MELD scores (Table S3). Patients with higher HVPG values had higher levels of LPS in both the systemic circulation and the PV than patients who had lower HVPG, but levels of other analytes were similar in patients with high or low HVPG values (Table S4). There were no differences in plasma levels of the analytes between patients who used  $\beta$ -blockers and those who did not (data not shown).

## 4 | DISCUSSION

In contrast to previously published studies, where increased levels of inflammatory and activation of hemostasis markers in portal plasma were associated with local endothelial damage and a prothrombotic state,<sup>9-11</sup> here we show no particular inflammatory or hypercoagulable state in portal plasma compared with hepatic or peripheral

plasma in patients with cirrhosis. Differences between analyte concentration in the portal and systemic circulation were observed in individual patients but were overall absent or very modest. In line with published studies,<sup>18-20</sup> we do find increased levels of various prothrombotic markers in the systemic circulation, and increases in these markers are more pronounced in patients with higher MELD scores.

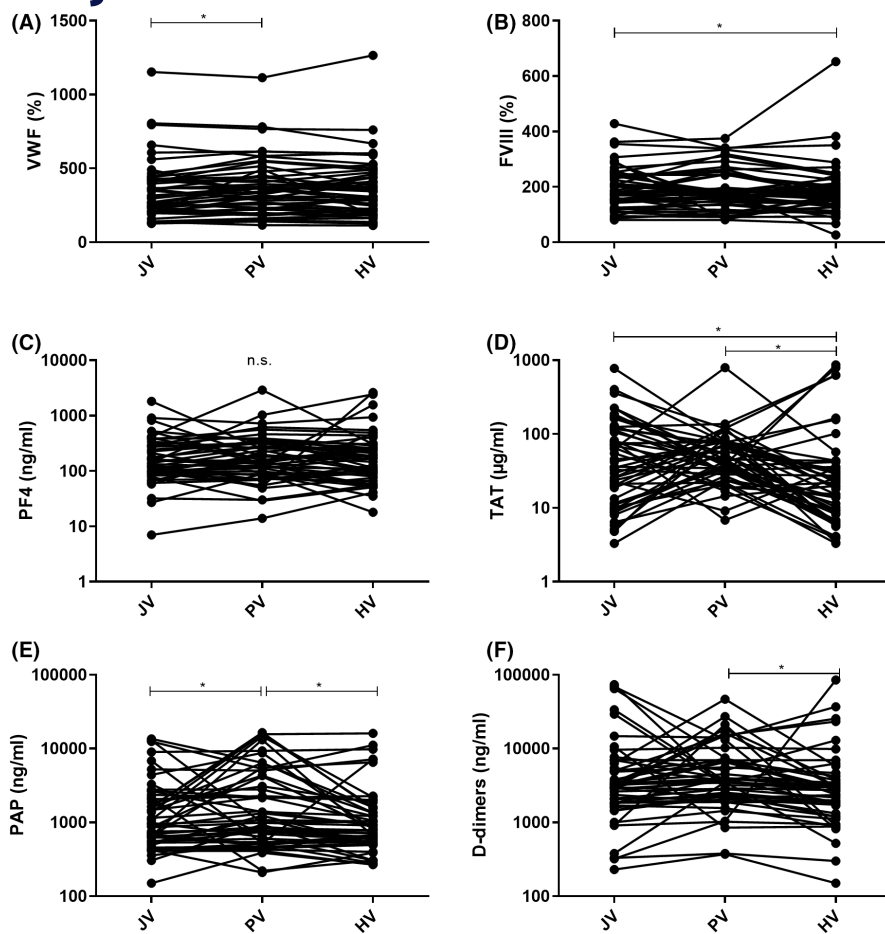
Cirrhosis is associated with an impaired intestinal barrier function, which facilitates bacterial translocation and endotoxemia, causing elevated production of markers of inflammation.<sup>21</sup> Elevated levels of LPS in the portal circulation compared with systemic circulation in patients with cirrhosis have been described before<sup>9-11</sup> and were associated with a prothrombotic state in the portal circulation. Of note, in those studies, LPS concentrations in the systemic circulation in cirrhotic patients was still higher than in healthy controls.<sup>10</sup> In our study, differences in LPS concentrations between portal, hepatic, and peripheral plasma from cirrhotic patients were small, and no marked increase in levels of other inflammatory markers were detected. It could be that, because of chronic endotoxemia, LPS concentrations are elevated throughout the entire circulation and are not limited to the portal circulation. We do not have a clear explanation for the differences between our results and those that were described in other studies, but differences in patient characteristics (including etiology of disease and clinical status, blood sampling

TABLE 2 Levels of markers of inflammation, endothelial damage, and hemostasis measured in plasma sampled from the systemic circulation, portal vein, and hepatic vein

	Normal value systemic circulation	Systemic circulation	Portal vein	Hepatic vein	p-value normal value SC vs SC/PV/HV	p-value SC vs PV	p-value PV vs HV/PV vs normal value	p-value SC vs HV/HV vs normal value
<b>Markers of inflammation</b>								
LPS (pg/ml)	79.5 [64.5–109.5]	151 [76–222]	163 [96–259]	131 [68–236]	0.0069/0.0002/0.014	<0.0001	<0.0001	0.038
TNF- $\alpha$ (pg/ml)	0 [0–16.4]	11.9 [5.0–19.0]	11.9 [6.0–22.0]	11.5 [4.9–22.0]	0.0006/0.001/0.0006	n.s.	n.s.	n.s.
IL-6 (ng/ml)	3.5 [2.7–11]	10.3 [5.8–35.1]	17.2 [6.6–35.6]	8.6 [5.6–32.8]	0.0015/<0.0001/0.0082	0.014	0.0004	0.0063
TBARS ( $\mu$ M)	2.7 [1.5–3.4]	2.6 [1.9–3.8]	2.9 [2.0–4.1]	2.6 [1.9–3.8]	<0.0001/<0.0001/<0.0001	0.0003	0.0007	n.s.
cfDNA ( $\mu$ g/ml)	1.0 [0.9–1.1]	1.0 [0.8–1.2]	1.0 [0.9–1.2]	1.0 [0.8–1.2]	n.s./n.s./n.s.	n.s.	n.s.	n.s.
MPO-DNA (AU)	0.1 [0–0.2]	0.2 [0.1–0.4]	0.2 [0.1–0.4]	0.1 [0.1–0.4]	0.0049/0.0096/0.01	n.s.	n.s.	n.s.
<b>Markers of hemostasis</b>								
VWF (%)	150 [102–204]	305 [211–426]	343 [227–452]	311 [218–461]	<0.0001/<0.0001/<0.0001	0.037	n.s.	n.s.
FVIII (%)	87 [70–103]	181 [147–244]	178 [143–244]	169 [136–211]	<0.0001/<0.0001/<0.0001	n.s.	n.s.	0.016
PF4 (ng/ml)	98 [75–143]	133 [92–283]	145 [89–281]	177 [88–289]	0.028/0.014/0.016	n.s.	n.s.	n.s.
TAT ( $\mu$ g/ml)	0.7 [0.4–1.2]	42 [12–118]	46 [29–79]	19 [7–35]	<0.0001/<0.0001/<0.0001	n.s.	0.005	0.0022
PAP (ng/ml)	191 [161–239]	876 [533–2173]	1075 [542–4296]	810 [533–1596]	<0.0001/<0.0001/<0.0001	0.044	0.0028	n.s.
D-dimers (ng/ml)	107 [64–176]	3050 [1820–5440]	3650 [2230–6920]	2750 [1690–3730]	<0.0001/<0.0001/<0.0001	n.s.	0.0003	n.s.

Note: The results are presented as median [interquartile range]. Comparisons between the vascular beds were made using the matched samples Wilcoxon test, and comparisons between patients and normal values were made using the Mann-Whitney U test. Healthy control values in the systemic circulation are presented as reference values.

Abbreviations: cfDNA, cell-free DNA; FVIII, factor VIII; HV, hepatic vein; IL-6, interleukin-6; LPS, lipopolysaccharide; MPO-DNA, myeloperoxidase-DNA; n.s., not significant; PAP, plasmin- $\alpha$ 2-antiplasmin; PF4, platelet factor 4; PV, portal vein; SC, systemic circulation; TAT, thrombin-antithrombin; TBARS, thiobarbituric acid-reactive substances; TNF- $\alpha$ , tumor necrosis factor alpha; VWF, von Willebrand factor.



**FIGURE 2** Levels of endothelial activation and activation of the hemostatic system: VWF (A); FVIII (B), PF4 (C); TAT (D); PAP (E); and D-dimers (F), in the systemic circulation (jugular vein; JV), the portal vein (PV), and hepatic vein (HV) of cirrhotic patients undergoing TIPS placement

techniques, or the timing of sampling during the TIPS procedure) may have contributed.<sup>9-11</sup> Our conclusions remain similar when analyzing patients with better or worse clinical status separately (Tables S2 and S3), and perhaps multicenter studies will be required to assess whether differences in local practices may influence the results of the analyses performed herein.

cfDNA and MPO-DNA complexes are markers of neutrophil extracellular traps (NETs), which have been described as a link between inflammation and coagulation.<sup>22</sup> Increased levels of markers of NETs have been shown in acutely ill patients with cirrhosis.<sup>14</sup> In addition, NETs play a role in chronic inflammatory diseases<sup>23</sup> and have been implicated in arterial thrombosis, venous thrombosis, and cancer-associated thrombosis.<sup>24,25</sup> Of note, increased levels of cfDNA also indicate increased apoptotic or necrotic cell death, which may also be increased in patients with liver injury. In addition, the specificity of MPO-DNA complex assays has recently been questioned.<sup>26</sup> Animal studies have shown intrahepatic NET formation with resultant intrahepatic deposition of platelets and fibrin, which contributes to portal hypertension.<sup>27</sup> Thus, markers of NETs may be expected to be increased in the PV because of local inflammatory responses, but may also be expected to be higher in the HV because of intrahepatic NET formation or increased cell death. We detected no local increase in NET markers in portal nor in hepatic plasma, suggesting there is not (at least) a direct link between local inflammation and NETs in portal hypertension in cirrhotic patients.

TAT, PAP, and D-dimers, which are markers of activation of coagulation and fibrinolysis, have been shown to be elevated in patients with cirrhosis compared with healthy controls.<sup>28</sup> Although our results indicate elevated levels of these markers in portal plasma compared with hepatic and peripheral plasma, on careful inspection, levels of these markers are clearly the lowest in the HV. The notably lower levels of these markers in the HV signal clearance of these markers by the liver rather than a local elevation of these markers in the PV. Although TAT, PAP, and D-dimer levels are higher in the portal than in the systemic circulation, which suggests some degree of activation of coagulation in the portal venous system, the differences are modest, with the exception of TAT complexes, which seem clearly elevated in the PV.

The pathophysiology of PVT remains largely unknown. We recently showed that hypercoagulability and increased levels of inflammatory markers in the systemic circulation are not predictive of the development of PVT.<sup>6</sup> Factors that were associated with development of PVT were mainly related to the severity of portal hypertension.<sup>6</sup> Our recent findings that portal vein thrombi in patients with cirrhosis who underwent liver transplantation consist of intimal fibrosis in all patients, and contain fibrin in only one-third of the cases,<sup>29</sup> may also support the statement that PVT is a consequence of portal hypertension rather than hypercoagulability. Whether local inflammation, oxidative stress, and activation of hemostasis contribute to development of PVT, and whether the use of anticoagulants

would be beneficial for patients with locally increased levels of markers of inflammation and hemostasis should be subject to future research.

In conclusion, in contrast to published studies,<sup>9–11</sup> we failed to detect a clear inflammatory or prothrombotic environment in the PV in cirrhotic patients who underwent TIPS placement. We found no evidence for endothelial or platelet activation in the portal circulation, whereas activation of coagulation and fibrinolysis is, at best, modest. We do provide evidence that comparison of markers from the PV with that of the HV may erroneously lead to the conclusion that the portal circulation is hypercoagulable. Hepatic clearance may result in lower levels of markers of inflammation and activation of coagulation in blood from the posthepatic vein, which may explain why some markers are clearly lower in the HV than in both the systemic and portal circulation. It will be of interest to assess the clearance of those markers by the liver by, for instance, an isolated liver perfusion model.

### INFORMED CONSENT

All patients gave written informed consent for participation in this study. Ethical approval was obtained from Hospital Clinic, Barcelona (HCB/2019/0391).

### AUTHOR CONTRIBUTIONS

E.G.D. performed experiments, analyzed data, and wrote the manuscript. M.M. collected biomaterial, performed experiments, analyzed data, and revised the manuscript. J.A. performed experiments, analyzed data, and revised the manuscript. F.T. collected biomaterial, interpreted data, and revised the manuscript. A.B. collected biomaterial, interpreted data, and revised the manuscript. P.O. collected biomaterial, interpreted data, and revised the manuscript. V.P.C. collected biomaterial, interpreted data, and revised the manuscript. V.H.G. collected biomaterial, interpreted data, and revised the manuscript. A.B. conceived the project, collected biomaterial, interpreted data, and revised the manuscript. J.C.G.P. conceived the project, collected samples and supervised sample collection, interpreted data, and revised the manuscript. T.L. conceived the project, supervised experiments, interpreted data, and wrote the manuscript.

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### CONFLICT OF INTEREST

V.H.G. receives speaker fees from Gore. J.C.G.P. advises for GORE and Cook. The remaining authors declare no conflicts of interest that pertain to this work.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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