LETTER TO THE EDITORS

Determinants of increased thrombotic tendency in NASH cirrhosis: not there yet!

Alberto Zanetto[1], Marco Senzolo[1], Elena Campello[2], Cristiana Bulato[2], Sabrina Gavasso[2], Graziella Saggiorato[2], Paolo Feltracco[3], Fabio Farinati[1], Francesco Paolo Russo[1], Patrizia Burra[1], Guadalupe Garcia-Tsao[4] & Paolo Simioni[2]

1 Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padova University Hospital, Padova, Italy

2 Thrombotic and Hemorrhagic Diseases Unit, General Internal Medicine, Padova University Hospital, Padova, Italy

3 Anesthesiology and Intensive Care, Department of Medicine, Padova University Hospital, Padova, Italy

4 Digestive Disease Section, Internal Medicine, Yale School of Medicine, and VA-Connecticut Healthcare System, New Haven/West Haven, CT, USA

E-mail: alberto.zanetto@phd.unipd.it

To the Editors

We read with great interest the article by Molinari et al, published in *Transplant International* [1]. By retrospectively analyzing the United Network for Organ Sharing (UNOS) registry from 2006 to 2016, they investigated the prevalence and trends of portal vein thrombosis (PVT) in liver transplant (LT) candidates with nonalcoholic steatohepatitis (NASH) versus alcohol-related cirrhosis. They found that patients with NASH had a greater prevalence of PVT than those with alcohol-related cirrhosis, and that it was independent of the presence of renal dysfunction (RD) [1].

Interestingly, the prevalence of PVT/RD was lower than that of PVT without RD and this is somewhat at odds with our recent prospective study that showed a prothrombotic tendency in patients with decompensated cirrhosis and acute kidney injury (AKI) [2]; however, this could be due to the nature of the UNOS registry that would not permit granularity regarding renal dysfunction.

More interestingly, the higher prevalence of PVT in NASH cirrhosis, as also described in another study [2], raises the possibility of NASH *per se* as a prothrombotic state. This was not demonstrated in a recent study that combined patients at all stages and etiologies of cirrhosis [3]. However, the majority (76%) of patients had compensated cirrhosis where hemostatic alterations are not as marked [4].

Taking advantage of data collected prospectively in two studies evaluating alterations of hemostasis in patients with cirrhosis of all etiologies, one including decompensated cirrhosis with AKI [2], and the other including patients with cirrhosis and hepatocellular carcinoma [5], we compared alterations of coagulation and fibrinolysis in decompensated patients with NASH versus two other common etiologies, alcohol-related and HCV-related cirrhosis. For this sub-analysis, patients with HCC were excluded. According to original studies' criteria, decompensation was defined by presence or history of clinically evident decompensating events (ascites, variceal hemorrhage, and hepatic encephalopathy) [6]. Coagulation assessment included pro and anticoagulant factors and thrombin generation assay with and without thrombomodulin. Fibrinolysis assessment included fibrinolytic factors and plasmin-antiplasmin complex.

As shown in the Table 1, patients with NASH cirrhosis were older while MELD score was higher in those with alcohol-related cirrhosis; however, Child-Pugh score was balanced among groups. There were no significant differences in coagulation or fibrinolysis tests among the three etiologies (NASH, alcohol, and HCV), consistent with findings observed in mostly compensated cirrhosis [3]. Therefore, alterations in coagulation and fibrinolysis do not explain the increased prevalence of PVT in NASH cirrhosis described by Molinari et al. [1].

Further studies are required to assess factors responsible for the purported increased thrombotic tendency in these patients (local factors? increased platelet function? higher levels of circulating microvesicles?) [7–9]. The characterization of such factors could potentially improve risk stratification and perhaps help identify patients at higher risk for PVT. This will eventually lead to most needed guidance regarding selection of

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Table 1. Clinical characteristics and alterations of hemostasis in patients with decompensated cirrhosis according to etiology

	NASH (n = 20)	Alcohol (n = 41)	HCV (n = 18)	P values**
Age, years	65 (56–72)	57 (52–64)	58 (52–68)	
Male gender, %	60	67	86	
MELD score	17 (11–25)	20 (13–26)	15 (10–25)	
Child-Pugh score*	10 (7–12)	10 (7–13)	9 (7–11)	
Ascites, %	82	85	70	
Acute kidney injury, %	33	38	27	
Infection, %	22	27	12	
Bilirubin, mg/dl	2.3 (1.1–4.6)	2.8 (1.6–5.4)	3.7 (1.2–4.7)	
Serum creatinine, mg/dl	0.8 (0.7–1.5)	0.9 (0.7–1.8)	0.9 (0.7–1.3)	
Platelet count, $\times 10^9$/l	75 (61–139)	85 (55–129)	50 (46–109)	
INR	1.3 (1.1–1.7)	1.6 (1.3–1.9)	1.5 (1.3–1.8)	
Coagulation (secondary hemostasis)				
Factor VIII, % (n.v.: 60–160)	235 (162–289)	203 (165–237)	176 (153–216)	0.2
Antithrombin, % (n.v.: 80–120)	53 (34–73)	36 (26–52)	39 (32–54)	0.1
Protein C chromogenic, % (n.v.: 70–130)	54 (24–68)	29 (22–48)	37 (25–56)	0.2
ETP without TM, nm/min	948 (832–1173)	949 (796–1158)	952 (864–1000)	0.9
ETP with TM, nm/min	887 (734–1005)	899 (745–1043)	821 (574–935)	0.4
ETP ratio	0.94 (0.86–0.98)	0.93 (0.87–0.96)	0.90 (0.68–0.94)	0.2
Fibrinolysis (tertiary hemostasis)				
Factor XIII, % (n.v.: 70–140)	55 (43–88)	54 (38–74)	54 (44–106)	0.6
Plasminogen, % (n.v.: 75–140)	42 (31–64)	35 (24–50)	50 (26–63)	0.2
Alfa-2 antiplasmin, % (n.v.: 80–120)	69 (59–88)	57 (50–76)	67 (47–85)	0.3
t-PA, ng/ml (n.v.:<10)	24 (18–44)	21 (17–32)	18 (10–25)	0.1
PAI-1, ng/ml (n.v.: 1–25)	19 (13–44)	24 (17–40)	34 (24–39)	0.3
TAFIa/ai, ng/ml (n.v.: 8.5–22.1 ng/ml)	22 (20–36)	20 (18–29)	24 (21–28)	0.5
PAP, ng/ml	44 (36–57)	41 (35–49)	45 (38–48)	0.6

Median values are reported with 25th and 75th percentile in parenthesis.

NASH, nonalcoholic steatohepatitis; HCV, hepatitis C virus; MELD, Model for End-Stage liver disease; ETP, endogenous thrombin potential by thrombin generation assay; TM, thrombomodulin (protein C activator); t-PA, tissue factor plasminogen activator; PAI-1, plasminogen activator inhibitor; TAFI, activated inactivated thrombin-activatable fibrinolysis inhibitor; PAP, plasmin-antiplasmin complex (marker for fibrinolysis activation).

*Median (range); **Kruskal–Wallis test.

candidates for thromboprophylaxis in patients with NASH cirrhosis awaiting LT [10].

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Conflict of interest

The authors have declared no conflicts of interest.

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