Digestive and Liver Disease 56 (2024) 2111–2117

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Coagulation factor XI in cirrhosis does not predict thrombo-hemorrhagic complications and hepatic decompensation ☆

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ARTICLE INFO

Article history:
Received 11 April 2024
Accepted 19 May 2024
Available online 4 June 2024

Keywords:
Coagulation
Hemostasis
Bleeding
Thrombosis

ABSTRACT

Introduction: Factor XI (FXI) is associated with thrombosis in patients without liver disease, but it alterations and prognostic value in cirrhosis are uncertain.
Patients and methods: We studied a prospective cohort of cirrhosis patients determining FXI and its association with portal vein thrombosis (PVT), bleeding, and hepatic decompensation/ACLF during 1-year follow-up. Odds ratios (OR) and 95 % CIs were calculated using logistic regression.
Results: We included 183 patients (Child-Pugh [CP] A/B/C 57/59/57). FXI was reduced in cirrhosis, decreasing with CP stage (78 % [66–94] vs. 58 % [44–78] vs. 41 % [30–52] in CP A, B, and C, respectively; $p < 0.001$). FXI was correlated with MELD score (rho: -0.6, $p < 0.001$), INR (rho: -0.6, $p < 0.001$), and platelet count (rho: 0.4, $p < 0.001$). Sixteen patients (8.7 %) experienced PVT, which only predictor was baseline platelet count (OR: 0.94; CI95 %: 0.91–0.97, $p < 0.001$). Bleeding occurred in 7 patients (3.8 %). Cirrhosis severity, platelet count, fibrinogen, and FXI (60% vs. 78 %; $p = 0.2$) were comparable between bleeding and non-bleeding individuals. Finally, no association was found between FXI and hepatic decompensation/ACLF, which were predicted by lower albumin and platelet count, respectively.
Conclusion: FXI seems not to be responsible for thrombosis and cirrhosis progression. The lack of association between low FXI and bleeding events, however, indirectly opens to future studies evaluating FXI inhibitors in cirrhosis.

1. Introduction

Factor XI (FXI) is a homodimeric zymogen that is converted to a protease with 1 (1/2-fXIa) or 2 (FXIa) active subunits by factor XIIa or thrombin [1]. FXIa acts in the early phase of the intrinsic coagulation pathway (i.e., "contact phase"), contributing to hemostasis mainly through the activation of factor IX [2]. Current theory postulates that FXI has only a secondary role in initiating the coagulation cascade, whereas its contribution to coagulation propagation and thrombosis appears to be greater [3].

In patients without liver disease, high levels of FXI are associated with an increased risk of venous [4-6] and arterial [7] thrombosis. Moreover, in patients with atrial fibrillation and history of ischemic stroke, elevated FXI appears to predict, respectively, the risk of cardiovascular death [8] and all-cause mortality [9].

The role of FXI in patients with cirrhosis is not as clear. FXI is synthetized mostly by the hepatocytes [10] and its plasmatic level is reduced in chronic liver disease [11]. However, Turon et al. recently demonstrated that severity of portal hypertension, and not coagulopathy, predicted development of portal vein thrombosis (PVT) in cirrhosis [12]. Alterations of factor VIII/protein C ratio, which reflects cirrhosis severity and systemic inflammation, have been independently linked to hepatic decompensation and death [13], whereas a potential role of FXI in this setting has not been investigated yet.

Recently, there has been a growing interest towards the development of drugs targeting FXI or FXIa, which may be associated with a safer profile than low-molecular weight heparin and direct-acting anticoagulants (DOACs) [3]. This could be important in clin-

☆ Trial registration number: NA

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https://doi.org/10.1016/j.dld.2024.05.020

ical settings, such as cirrhosis, wherein administration of DOACs may be contraindicated due to severity of liver and/or kidney failure and bleeding tendency [14,15].

A better understanding of FXI in cirrhosis may therefore improve hemostatic management and eventually led to new therapeutic targets [16,17]. The goal of our study was to investigate alterations of FXI in cirrhosis and evaluate whether such alterations could predict development of thrombo-hemorrhagic complications and hepatic decompensation during 1-year follow-up.

2. Material and methods

2.1. Patients selection and study design

Between July 1, 2020, and September 30, 2021, patients with cirrhosis admitted to the Gastroenterology inpatient services or evaluated at our liver clinics in Padova University Hospital were recruited in 3 independent cohort studies evaluating coagulopathy of cirrhosis and its clinical implications (HIC protocol #0034435-08/06/20) [18-20]. These studies required baseline testing and 1-year prospective follow-up. All studies were conducted in compliance with the Declaration of Helsinki. All patients signed consent to participate.

Per original study protocols, diagnosis of cirrhosis was confirmed using available data including histology, radiology, laboratory, and clinical assessment. Compensated cirrhosis was defined by the absence of any present and past complications of cirrhosis. Decompensated cirrhosis was defined by the presence or history of clinically evident decompensating event: ascites grade≥2 at time of recruitment; history of variceal hemorrhage; hepatic encephalopathy (either at recruitment or in the past medical history).

Patients with presence or history of PVT/venous thromboembolism, chronic kidney disease or other thrombophilic condition, those on anticoagulation or anti-platelet therapy, and patients who received recent transfusions of any blood product were not eligible for recruitment. Patients receiving anticoagulant prophylaxis were eligible for recruitment. For this retrospective analysis, only patients with availability of FXI were considered. Furthermore, since hepatocellular carcinoma (HCC) may influence coagulation and risk of PVT [21], those with HCC were excluded.

At recruitment, blood samples (see below) and clinical data were collected from all patients. Data collected from the medical records included patient demographics, etiology of cirrhosis, Model for End-Stage Liver Disease (MELD) score, Child-Pugh stage, and laboratory results.

Patients with cirrhosis were prospectively followed for 1-year for the following outcomes: development of PVT, bleeding unrelated to portal hypertension, hepatic decompensation (in compensated patients), further decompensation/acute-on-chronic liver failure (ACLF) (in decompensated patients) [22]. Bleeding unrelated to portal hypertension was further subclassified in procedure-related and spontaneous. Severity of bleeding was defined according to the International Society of Thrombosis and Hemostasis guidelines for non-surgical patients [23].

2.3. Blood sampling and coagulation assessment

At inclusion, peripheral blood was collected through venipuncture in citrate-containing vacutainer tubes with 0.109 M (3.2 %) sodium citrate (9:1 blood to anticoagulant ratio). The first few milliliters were discarded. Platelet-poor plasma was prepared within 1 hour by double centrifugation (2 × 10 min at 1500 g) at room temperature. Aliquots (1 mL) were immediately frozen and then stored at −80 °C until use.

The following procoagulant factors and inhibitors were determined: fibrinogen (n.v. 150–450 mg/dL), factor VIII (FVIII, n.v. 60 %−160 %), factor IX (FIX, n.v. 80 %−120 %), factor XI (FXI, n.v. 80 %−120 %), protein C coagulometric (PC coag, n.v. 80 %−120 %), and antithrombin (AT, n.v. 80 %−120 %), as previously described [20]. Thrombin-antithrombin complexes were included as marker for coagulation activation [24].

Since previous data show a correlation between FXI and thrombin-activatable fibrinolysis inhibitor (TAFI) in patients without liver disease [25], we included determination of TAFI a/ai (i.e., the total amount of TAFI that has been activated). TAFIa/ai was determined via an enzyme-linked immunosorbent assays (Asserachrom, Diagnostica Stago, Asnieres sur Seine, France; normal value: 8.5–22.1 ng/mL). All coagulation tests were performed at the Coagulation Lab of the Thrombotic and Hemorrhagic Diseases Unit of Padova University Hospital by expert personnel blinded to clinical characteristics.

Table 1
Baseline characteristics in patients with cirrhosis.

	Patients with cirrhosis (n = 183)
Age, years	62 (55–70)
Male sex,%	71
Etiology of cirrhosis,%	
Alcohol	48
HCV/HBV±HDV	29
Metabolic	13
Alcohol+metabolic	6
Alcohol+HCV	4
Child-Pugh class A/B/C,%	31/38/31
MELD score	13 (9–10)
Infection^,%	42
Acute kidney injury^,%	21
Hemoglobin, g/dL	11 (9–13)
Platelet count, 10^9/L	92 (64–129)
Thrombocytopenia, (%)	85
Total bilirubin, mg/dL	2 (1.1–4.9)
INR	1.4 (1.2–1.6)
Creatinine, mg/dL	0.8 (0.7–0.9)
Albumin, g/dL	31 (28–36)
Na, mmol/L	136 (133–138)

Median values reported with 25th and 75th percentile values in parenthesis.
Abbreviations: NASH: non-alcoholic steatohepatitis; MELD: Model for End-Stage Liver Disease.
^In-hospital patients.

2.4. Data analysis

Qualitative data are described using frequency and percentage. Quantitative data are described using median with 25 % and 75 % quartile ranges. Comparisons between independent groups were performed using the Mann Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. For comparison in three or more groups, Kruskal-Wallis test was computed. Logistic regression analyses were performed to evaluate parameters significantly associated with development of liver-related events. Odds ratios with 95 % confidence intervals were calculated. IBM SPSS version 26 (IBM, Armonk, NY) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA) were used for statistical analysis. Statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Baseline characteristics

We included 183 patients with cirrhosis (71 % male, median age 62 years) (Table 1). At baseline, 136 patients (74 %) had decompensated cirrhosis. Ascites was the most common reason for decompensation (79 %), followed by hepatic encephalopathy (13 %),

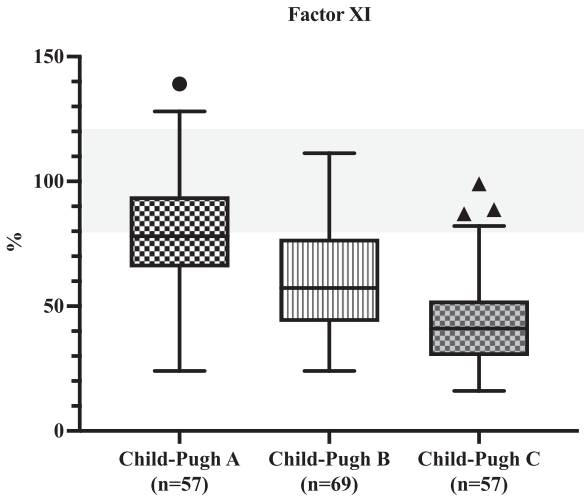

Fig. 1. Level of FXI in cirrhosis is lower than normal and decreases significantly with cirrhosis severity. Legend: the grey area refers to the reference range in healthy subjects. Median levels of FXI were 78 % [66–94] vs. 58 % [44–78] vs. 41 % [30–52] in Child-Pugh stage A, B, C, respectively.

and history of variceal hemorrhage (8 %). Alcohol and chronic viral infections were the most common etiologies of cirrhosis (48 % and 29 %, respectively). Median MELD score was 13 [9-19]; 31 % of patients were Child-Pugh A, 38 % Child-Pugh B, and 31 % Child-Pugh C. Of 183 patients, 96 (52.5 %%) were recruited as inpatients. The most common reasons for hospitalization were ascites or oedema (28 %), abdominal pain or suspected infection (22 %), hepatic encephalopathy (18 %), and acute kidney injury (11 %). The median time from admission to patient recruitment was 1 day (range: 1–3).

3.2. Levels of FXI were significantly reduced in cirrhosis, decreasing with severity of liver dysfunction

FXI was significantly reduced in cirrhosis (59 % [41–79]), decreasing progressively with disease severity as assessed by Child-Pugh stage (Fig. 1). FXI was correlated with MELD score (rho: −0.6, $p < 0.001$), markers of liver synthetic function (rho: 0.4, $p < 0.001$ and rho: −0.6, $p < 0.001$ for albumin and INR, respectively) and portal hypertension (rho: 0.4, $p < 0.001$ for platelet count), whereas it was not correlated with C-reactive protein and thrombin-antithrombin complexes (Fig. 2). No difference was found between patients receiving thromboprophylaxis ($n = 20$, 11 %) and those who did not: 59 % [41–79] vs. 63 % [42–79], respectively ($p = 0.9$).

Fibrinogen plasmatic level was 235 mg/dL (152–323). Fibrinogen was mostly normal in Child-Pugh stage A cirrhosis (267 mg/dL [248–356]), whereas it was significantly reduced in Child-Pugh B and C patients (233 mg/dL [169–342] and 138 mg/dL [110–229], respectively). FVIII was higher (197 % [158–243]) and FIX (73 % [51–94]) - protein C/antithrombin were lower (41 % [23–68] and 54 % [33–78]), respectively, in cirrhosis than healthy subjects. FVIII increased (165 % [135–202] vs. 208 % [161–270] vs. 225 % [170–267]) and FIX (90 % [81–104] vs. 68 % [56–98] vs. 49 % [37–70])/protein C (82 % [55–110] vs. 38 % [27–55] vs. 19 % [12–30]) decreased, respectively, from Child-Pugh stage A to C.

Median level of TAFIa/ai was 22.8 ng/mL (17.3–31), increasing significantly from Child-Pugh A to C stage (19.6 [16.5–24.01] vs. 23 [17.9–30.0] vs. 26 [21–33], respectively; $p < 0.001$). FXI was not correlated with TAFIa/ai (rho: 0.1; $p = 0.5$) (Fig. 2).

Median ETP with and without TM were 941 nmol/L*min [796–1090] and 769 nmol/L*min [612–933], respectively. FXI was significantly correlated with the ETO without TM (rho: 0.3, $p < 0.001$), whereas it was not correlated with the ETP with TM (rho: −0.1, $p = 0.07$).

3.3. Baseline coagulopathy, including reduced level of FXI, did not predict development of PVT and bleeding events during 1-year follow-up

During a median follow-up of 179 days (rage: 92–263), 16 patients experienced PVT (8.7 %), which was complete in 11 patients, partial in 5 patients, and extended to the splenic or mesenteric veins in 4 patients. Table 2 shows the differences between patients who experienced PVT and those who did not. Patients with PVT were those with a more severe liver dysfunction/portal hypertension as reflected by a higher MELD score/Child-Pugh stage and lower platelet count/anticoagulant factors, respectively. Notably, FXI was significantly lower in patients who developed PVT (44% vs. 62 % in those who did not; $p = 0.01$). Level of FXI was comparable in patients with complete ($n = 7$) vs. partial ($n = 9$) PVT (44 % [35–54] vs. 38 % [25–73], respectively; $p = 0.7$).

Univariate analysis showed that MELD score, Child-Pugh stage, platelet count and FXI were associated with PVT. However, in two-variables at time models, only platelet count remained associated with development of thrombosis (Table 3).

Bleeding events unrelated to portal hypertension were observed in 7 (3.8 %) patients: 3 procedure-related (1 post-paracentesis hemoperitoneum after ultrasound-guided paracentesis; 2 hematomas after central line placement) and 4 spontaneous (1 subdural hematoma, 2 abdominal wall hematomas, 1 acute hemorrhagic gastritis). Bleeding was major in 6 patients and clinically relevant no major in 1 patient. Median time from blood drawn to development of bleeding was 78 days (range: 23–210). Severity of liver disease, platelet count, fibrinogen, and coagulation factors were comparable between patients who experienced bleeding and those who did not (Supporting Table 1). Levels of FXI and a platelet count $<50\times10^9$/L were not associated with development of bleeding (Fig. 3).

3.4. Baseline level of FXI was not associated with development of hepatic decompensation, further decompensation, and ACLF

Among compensated patients ($n = 47/183$, 25.7 %), 4 (8.5 %) experienced the 1st event of decompensation (2 ascites, 1 hepatic encephalopathy, 1 variceal bleeding). Median time from recruitment to decompensation was 202 days (range: 141–298). MELD score (12 [10–16] vs. 8 [7–12]; $p = 0.08$) and platelet count (104×10^9/L [48–124] vs. 120×10^9/L [68–170]; $p = 0.3$) were both indicative of a relatively more advanced diseases in the 4 patients who experienced decompensation vs. the 43 who did not though the differences were not significant. Albumin levels was significantly reduced in patients who progressed towards decompensation: 32 g/dL [27-32] vs 38 g/dL [32-42], $p = 0.03$. Levels of FXI were comparable between groups (60 % [28–78] vs. 78 % [64–96], $p = 0.2$).

Among decompensated patients ($n = 136/183$, 74.3 %), 54 (39.7 %) experienced further decompensation/ACLF. These patients had higher MELD score, were more likely Child-Pugh C, and had lower fibrinogen and platelet count (Supporting Table 2). Level of FXI was comparable between groups. Univariate analysis showed that MELD score (OR: 2.2; CI95 % 1.08–4.36; $p = 0.03$), Child-Pugh C vs. A/B (OR: 2.1; CI95 % 1.03–4.19; $p = 0.04$), and platelet count (OR: 11.7; CI95 % 4.85–28.26; $p < 0.001$) – but not FXI – were associated with further decompensation and ACLF. A multivariate model including MELD score and platelet count showed that a platelet count $< 90\times10^9$/L was the only independent predictor of outcome (OR: 11.23, 95 %CI: 4.62–27.30; $p = 0.001$).

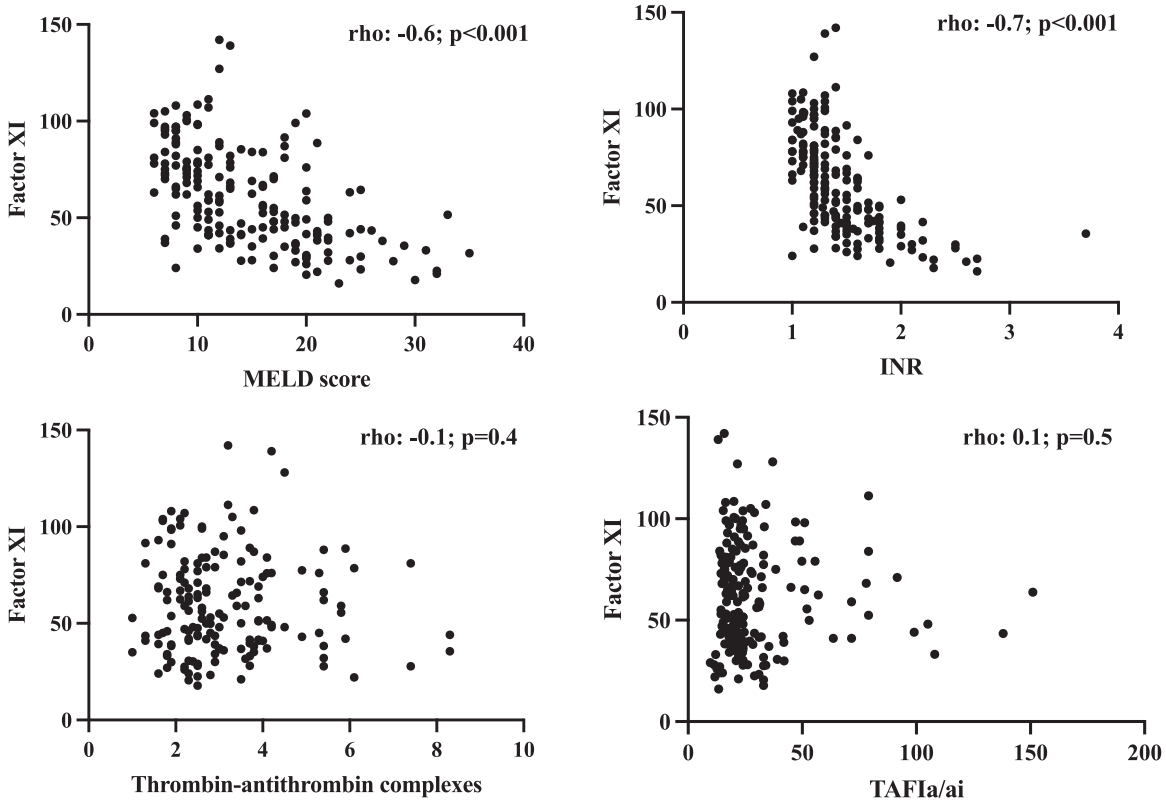

Fig. 2. Correlations between FXI and different markers of cirrhosis severity/coagulation.
Abbreviations: MELD: Model for End Stage Liver Disease; TAFI a/ai: activated inactivated thrombin-activatable fibrinolysis inhibitor.

Table 2
Comparison between baseline characteristics in patients experienced PVT during follow-up vs. those who did not.

	PVT (n = 16)	No PVT (n = 167)	P value
Age, years	62 (55–69)	63 (59–73)	0.3
MELD score	20 (14–26)	12 (9–18)	<0.001
Child-Pugh stage C vs. A/B,%	56	29	0.02
Creatinine, mg/dL	0.9 (0.7–1.8)	0.8 (0.7–0.9)	0.1
Albumin, g/dL	32 (28–34)	31 (28–36)	0.8
Bilirubin, mg/dL	2.7 (2.1–6.1)	2.1 (1.1–4.8)	0.1
Platelet count, x10^9/L	47 (32–64)	98 (67–134)	<0.001
INR	1.7 (1.3–2.1)	1.3 (1.2–1.6)	0.04
Fibrinogen, mg/dL	163 (110–259)	242 (163–326)	0.04
Factor XI,%	44 (32–57)	62 (42–81)	0.01
Factor VIII,%	192 (163–268)	197 (155–242)	0.6
Protein C,%	18 (0–36)	45 (24–69)	0.002
Antithrombin,%	30 (21–46)	55 (35–79)	0.008
Factor IX,%	60 (37–82)	74 (53–95)	0.01
Thrombin-antithrombin complex, ng/L	2.6 (2.3–5.4)	2.8 (2.2–3.8)	0.6

Median values reported with 25th and 75th percentile values in parenthesis. Legend: MELD: Model for End Stage Liver Disease.

Discussion

Factor XI is a serine protease produced by the hepatocytes, which contributes to hemostasis mainly through thrombin generation [2]. In patients without liver disease, elevated FXI has been associated with thrombosis and mortality [6], whereas its potential contributions to hemostasis and thrombosis in cirrhosis are poorly understood.

Considering the upcoming approval of a new class of antithrombotic drugs inhibiting FXI and FXIa [3], we analyzed alterations of FXI in a prospectively characterized cohort of patients with cirrhosis, evaluating associations with development of PVT, bleeding complications, and progression of chronic liver disease.

We found that patients with cirrhosis had a significant reduction in the circulating level of FXI. In the only previous study that looked at FXI in chronic liver disease, Walker et al. found a lower level of FXI in patients vs. healthy controls. However, only 39 unselected individuals were included, with no clear description of population characteristics nor analysis according to cirrhosis severity. In our cohort, we found that FXI significantly decreased in parallel with Child-Pugh stage (i.e., lower in decompensated vs. compensated patients), and was strongly correlated with multiple markers reflecting liver dysfunction/portal hypertension.

We [24,26] and others [13] previously showed that acute phase reaction and systemic inflammation lead to increased FVIII, reduced PC, and coagulation activation in cirrhosis. In patients without liver disease, endothelial injury/oxidative stress and higher lev-

Table 3
Parameters associated with PVT at univariate and multivariate analyses.

Univariate		
Variable	OR 95 % CI	P value
MELD score (median)		0.02
≤ 13	-	
>13	3.93 (1.21–12.69)	
Child-Pugh stage		0.03
A/B	-	
C	3.18 (1.12–9.04)	
Platelet count, x10^9/L^	0.94 (0.91–0.97)	<0.001
Factor XI,% (median)		0.02
≤ 59	-	
>59	0.21 (0.06–0.75)	
Fibrinogen, mg/dL (median)		0.1
≤ 235	-	
>236	0.42 (0.14–1.28)	
Multivariate		
MELD score (median)	2.42 (0.66–8.76)	0.2
Factor XI	0.32 (0.08–1.32)	0.1
Child-Pugh stage	1.93 (0.62–5.99)	0.2
Factor XI	0.27 (0.07–1.09)	0.7
Platelet count	0.94 (0.91–0.97)	<0.001
Factor XI	0.43 (0.10–1.76)	0.2

Legend: MELD: model for end-stage liver disease; OR: odds ratio; CI: confidence interval. ^As continuous variable (analysis with median could not be performed since all patients with PVT had a platelet count below median value).

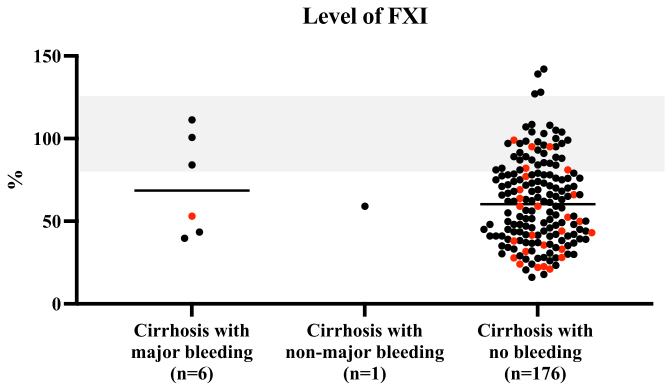

Fig. 3. Baseline level of FXI in patients who experienced bleeding complications during 1-year follow-up. Legend. In red are patients with a platelet count <50×10^9/L.

els of TAFI have been associated with increased level/activation of FXI [8,25,27]. In this cohort, however, FXI was not correlated with C-reactive protein, thrombin-antithrombin complexes, and TAFI a/ai, thus suggesting that liver synthetic dysfunction is the main determinant of FXI in cirrhosis.

Patients with cirrhosis, particularly those who decompensated, are at risk of portal vein thrombosis [28]. In a prospective study investigating predictors of PVT in mostly compensated patients (i.e. those with less severe coagulopathy and lower risk of thrombosis), FXI levels were significantly lower in patients who experienced PVT during follow-up [12]. However, when the analysis was adjusted by clinical factors and portal blood flow velocity, lower FXI was not associated with PVT. We confirmed these results in a more diverse population including both compensated and decompensated patients. In fact, we found that platelet count, which reflects severity of portal hypertension, was the only independent predictor of PVT, indicating that FXI alterations are most likely a consequence of chronic liver dysfunction than a factor responsible for PVT.

It should be highlighted, however, that we assessed peripheral levels of FXI, whereas growing evidence indicates that portal blood milieu may have site-specific, prothrombotic alterations of endothelial cells [29] and coagulation [30,31]. Future studies comparing alterations of FXI and intrinsic coagulation pathway in portal vs. peripheral blood could further clarify whether FXI and intrinsic coagulation pathway may be implicated in development of PVT in cirrhosis with portal hypertension.

Recent international guidelines state that coagulation impairment, as assessed by conventional coagulation tests, does not accurately predict bleeding risk in cirrhosis and should not be used to guide pre-procedural prophylaxis [32-34]. Indeed, we found that baseline coagulopathy, low platelet count or severe thrombocytopenia, and increased INR were not predictive of bleeding complications during follow-up. This further confirms, in patients with cirrhosis, that thrombocytopenia alone does not predict bleeding risk and should not dictate whether a procedure can be safely performed or if blood product prophylaxis is indicated [35]. Moreover, it indirectly highlights the complexity of cirrhosis coagulopathy and the need for more comprehensive hemostatic tests, such as TEG or ROTEM, that should be combined with disease severity and associated complications for a more comprehensive and individualized prediction of bleeding risk [36].

There is strong need for a better risk stratification in cirrhosis. Blood microvesicles are nano-sized vesicles released by many cell types [37]. In cirrhosis, circulating microvesicles act as pro-inflammatory and pro-coagulant mediators [38], and have been proposed as prognostic biomarkers [39]. However, whether microvesicles are truly useful for thrombo-hemorrhagic risk stratification in cirrhosis remains unclear.

To our knowledge, this is the first study evaluating the association between FXI and bleeding unrelated to portal hypertension in a consecutive cohort of patients with cirrhosis. Notably, the lack of association between reduced FXI - with or without severe thrombocytopenia - and bleeding complications indirectly opens to future studies evaluating FXI inhibitors to prevent or treat thrombosis in high-risk patients with cirrhosis [3]. However, larger studies are required to confirm our preliminary results.

In patients without liver disease, oxidative stress and inflammatory responses driven by acute precipitants are associated with activation of coagulation [40] and elevated FXI [25]. In animal models, this may be responsible for micro-thrombosis, ischemic-reperfusion injury, and development of SIRS/multiorgan failures [40]. Villa et al. showed that anticoagulant therapy with low molecular wight heparin reduced the incidence of PVT and improved survival in Child-Pugh B/C patients [41]. More recently, a RCT showed that rivaroxaban (i.e., an anticoagulant drug that inhibits thrombin generation by blocking Xa activity and could prevent hepatic stellate cells activation) might improve portal hypertension complications free survival in Child-Pugh B7 cirrhosis [42]. Thus, understanding whether FXI is associated with progression of cirrhosis might not only improve prognostic stratification (i.e. identification of candidates for a quick evaluation for liver transplantation and/or disease-modifying therapies currently under investigation) [43], but also suggest new therapeutic hypotheses for the new FXI inhibitors. However, levels of FXI were comparable between patients who progressed towards hepatic decompensation and further decompensation/ACLF and those who did not, thus suggesting that alterations of intrinsic coagulation pathway (namely FXI activity) are not likely a major factor responsible for cirrhosis progression.

Our study has significant limitations. Firstly, we aimed to assess FXI alterations and did not include additional alterations of the intrinsic coagulation pathway. Secondly, it should be noted that the lack of association between coagulopathy and bleeding/thrombosis was with the baseline assessment, and not with the subsequent coagulation changes normally occurring with liver disease progression [44]. Further studies with serial assessment of coagulation

may improve definition of hemostatic risks in cirrhosis and clinical management of these challenging patients. Thirdly, the lack of interplay between blood components and vessel walls is unavoidable as in any study assessing hemostasis, perhaps especially in a study evaluating contact phase. Moreover, drugs and comorbidities might have somewhat interfered with FXI levels though many potential cofounders were excluded. Finally, as this is the first study to evaluate the association between FXI and clinical events in cirrhosis, additional studies are required to validate our results.

In conclusion, we found that plasmatic levels of FXI were significantly reduced in cirrhosis, decreasing progressively with severity of liver dysfunction. However, FXI was not associated with development of PVT, bleeding complications, and hepatic decompensation during follow-up. On the one hand, these results do not support the assessment of FXI to predict the risk of PVT and cirrhosis progression. On the other hand, they indirectly open to future studies evaluating FXI inhibitors as potential antithrombotic therapies in patients with cirrhosis.

Financial support

Research grant from the Italian Ministry of Education, University and Research to PS. The funders had no role in study design, data collection and analysis, or preparation of the manuscript.

Authors' contribution

AZ: research idea and design, performance of the research (patients' enrollment and follow-up), statistical analysis, interpretation of the data, writing of the manuscript.

EC: laboratory work, interpretation of the data, critical revision of the manuscript.

LC: interpretation of the data, critical revision of the manuscript.

SG: laboratory work.

CB: laboratory work.

PB: acquisition of the data.

FPR: acquisition of the data.

MS: acquisition of the data, critical revision of the manuscript.

PS: research idea and design, funding of the research, organization of lab facilities and testing, interpretation of the data, critical revision, and final approval of the manuscript.

Declaration of competing interest

We don't have any conflict of interest to declare.

Data availability

Data are available from the first author (Dr. Alberto Zanetto: alberto.zanetto@unipd.it) upon reasonable request.

Acknowledgments

the authors wish to thank the nurses of Gastroenterology and Thrombotic and Hemorrhagic Diseases Unit of Padova University Hospital for their assistance with collection of blood samples.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.05.020.

References

[1] Geng Y, Verhamme IM, Smith SB, Sun MF, Matafonov A, Cheng Q, et al. The dimeric structure of factor XI and zymogen activation. Blood 2013;121(19):3962–9.
[2] Kravtsov DV, Matafonov A, Tucker EI, Sun MF, Walsh PN, Gruber A, et al. Factor XI contributes to thrombin generation in the absence of factor XII. Blood 2009;114(2):452–8.
[3] Campello E, Simioni P, Prandoni P, Ferri N. Clinical pharmacology of factor XI inhibitors: new therapeutic approaches for prevention of venous and arterial thrombotic disorders. J Clin Med 2022;11(21).
[4] Cushman M, O'Meara ES, Folsom AR, Heckbert SR. Coagulation factors IX through XIII and the risk of future venous thrombosis: the Longitudinal Investigation of Thromboembolism Etiology. Blood 2009;114(14):2878–83.
[5] Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. N Engl J Med 2000;342(10):696–701.
[6] Spiezia L, Forestan C, Campello E, Simion C, Simioni P. Persistently high levels of coagulation factor XI as a risk factor for venous thrombosis. J Clin Med 2023;12(15).
[7] Doggen CJ, Rosendaal FR, Meijers JC. Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: opposite and synergistic effects of factors XI and XII. Blood 2006;108(13):4045–51.
[8] Zabczyk MT, Hanarz M, Malinowski KP, Pociask E, Butenas S, Gajos G, et al. Active FXI can independently predict ischemic stroke in anticoagulated atrial fibrillation patients: a cohort study. Thromb Haemost 2022;122(8):1397–406.
[9] Yang DT, Flanders MM, Kim H, Rodgers GM. Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. Am J Clin Pathol 2006;126(3):411–15.
[10] Cheng Q, Kantz J, Poffenberger G, Powers AC, Gailani D. Factor XI protein in human pancreas and kidney. Thromb Haemost 2008;100(1):158–60.
[11] Walker IR, Milner RA, Johnston MA, Rand CA, Neame PB, Hirsh J. Factors XI and XII are low in subjects with liver disease. Dig Dis Sci 1983;28(11):967–70.
[12] Turon F, Driever EG, Baiges A, Cerda E, Garcia-Criado A, Gilabert R, et al. Predicting portal thrombosis in cirrhosis: a prospective study of clinical, ultrasonographic and hemostatic factors. J Hepatol 2021;75(6):1367–76.
[13] Scheiner B, Balcar L, Nussbaumer RJ, Weinzierl J, Paternostro R, Simbrunner B, et al. Factor VIII/protein C ratio independently predicts liver-related events but does not indicate a hypercoagulable state in ACLD. J Hepatol 2022;76(5):1090–9.
[14] Zanetto A, Northup P, Roberts L, Senzolo M. Haemostasis in cirrhosis: understanding destabilising factors during acute decompensation. J Hepatol 2023;78(5):1037–47.
[15] Zanetto A, Senzolo M, Blasi A. Perioperative management of antithrombotic treatment. Best Pract Res Clin Anaesthesiol 2020;34(1):35–50.
[16] Zanetto A, Campello E, Bulato C, Willems R, Konings J, Roest M, et al. Whole blood thrombin generation shows a significant hypocoagulable state in patients with decompensated cirrhosis. J Thromb Haemost 2023.
[17] Zanetto A, Campello E, Senzolo M, Simioni P. The evolving knowledge on primary hemostasis in patients with cirrhosis: a comprehensive review. Hepatology 2024;79(2):460–81.
[18] Zanetto A, Campello E, Bulato C, Gavasso S, Farinati F, Russo FP, et al. Increased platelet aggregation in patients with decompensated cirrhosis indicates higher risk of further decompensation and death. J Hepatol 2022;77(3):660–9.
[19] Zanetto A, Campello E, Bulato C, Gavasso S, Saggiorato G, Shalaby S, et al. Global hemostatic profiling in patients with decompensated cirrhosis and bacterial infections. JHEP Rep 2022;4(7):100493.
[20] Zanetto A, Campello E, Bulato C, Gavasso S, Saggiorato G, Shalaby S, et al. More pronounced hypercoagulable state and hypofibrinolysis in patients with cirrhosis with versus without HCC. Hepatol Commun 2021;5(12):1987–2000.
[21] Zanetto A, Campello E, Pelizzaro F, Farinati F, Burra P, Simioni P, et al. Haemostatic alterations in patients with cirrhosis and hepatocellular carcinoma: laboratory evidence and clinical implications. Liver Int 2022;42(6):1229–40.
[22] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–74.
[23] Schulman S, Kearon C. Subcommittee on control of anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692–4.
[24] Zanetto A, Rinder HM, Campello E, Saggiorato G, Deng Y, Ciarleglio M, et al. Acute kidney injury in decompensated cirrhosis is associated with both hypo-coagulable and hyper-coagulable features. Hepatology 2020;72(4):1327–1340.
[25] Paszek E, Polak M, Bryk-Wiazania AH, Konieczynska M, Undas A. Elevated plasma factor XI predicts cardiovascular events in patients with type 2 diabetes: a long-term observational study. Cardiovasc Diabetol 2023;22(1):182.
[26] Zanetto A, Pelizzaro F, Campello E, Bulato C, Balcar L, Gu W, et al. Severity of systemic inflammation is the main predictor of ACLF and bleeding in individuals with acutely decompensated cirrhosis. J Hepatol 2023;78(2):301–11.
[27] Von dem Borne PA, Bajzar L, Meijers JC, Nesheim ME, Bouma BN. Thrombin-mediated activation of factor XI results in a thrombin-activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. J Clin Invest 1997;99(10):2323–7.
[28] Russo FP, Zanetto A, Campello E, Bulato C, Shalaby S, Spiezia L, et al. Reversal of hypercoagulability in patients with HCV-related cirrhosis after treatment with direct-acting antivirals. Liver Int 2018;38(12):2210–18.
[29] Shalaby S, Simioni P, Campello E, Spiezia L, Gavasso S, Bizzaro D, et al. Endothelial damage of the portal vein is associated with heparin-like effect in advanced stages of cirrhosis. Thromb Haemost 2020;120(8):1173–81.

[30] Queck A, Carnevale R, Uschner FE, Schierwagen R, Klein S, Jansen C, et al. Role of portal venous platelet activation in patients with decompensated cirrhosis and TIPS. Gut 2020;69(8):1535–6.
[31] Shalaby S, Zanetto A, Campello E, Gavasso S, Barbiero G, Battistel M, et al. Reply to "Peripheral versus central venous blood sampling does not influence the assessment of platelet activation in cirrhosis". Platelets 2022;33(7):1104–6.
[32] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol 2022;76(5):1151–84.
[33] Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the study of liver diseases. Hepatology 2021;73(1):366–413.
[34] Roberts LN, Lisman T, Stanworth S, Hernandez-Gea V, Magnusson M, Tripodi A, et al. Periprocedural management of abnormal coagulation parameters and thrombocytopenia in patients with cirrhosis: guidance from the SSC of the ISTH. J Thromb Haemost 2022;20(1):39–47.
[35] Zanetto A, Toffanin S, Campello E, Radu CM, Gavasso S, Burra P, et al. Reticulated platelets are increased and hyper-activated in patients with cirrhosis, especially those with poor outcome. Dig Liver Dis March 2024. doi:10.1016/j.dld.2024.03.00736.
[36] Zanetto A, Rinder HM, Senzolo M, Simioni P, Garcia-Tsao G. Reduced clot stability by thromboelastography as a potential indicator of procedure-related bleeding in decompensated cirrhosis. Hepatol Commun 2021;5(2):272–82.
[37] Campello E, Zanetto A, Radu CM, Toffanin S, Shalaby S, Gavasso S, et al. Profiling plasma alterations of extracellular vesicles in patients with acutely decompensated cirrhosis and bacterial infection. Liver Int 2024.
[38] Campello E, Zanetto A, Radu CM, Bulato C, Truma A, Spiezia L, et al. Acute kidney injury is associated with increased levels of circulating microvesicles in patients with decompensated cirrhosis. Dig Liver Dis 2021;53(7):879–888.
[39] Zanetto A, Pelizzaro F, Mion MM, Bucci M, Ferrarese A, Simioni P, et al. Toward a more precise prognostic stratification in acute decompensation of cirrhosis: the Padua model 2.0. United. European Gastroenterol J 2023;11(9):815–24.
[40] Lisman T, Luyendyk JP. Systemic inflammation and disorders of hemostasis in the AD-ACLF syndrome. J Hepatol 2021;74(5):1264–5.
[41] Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143(5) 1253-60 e4.
[42] Puente Sanchez A, Turon F, Martinez J, Fortea JI, Hernandez-Guerra M, Alvarado-Tapias E, et al. Rivaroxaban improves survival and decompensation in cirrhotic patients with moderate liver dysfunction. Double-blind, placebo-controlled trial. J Hepatol 2023;78:S2–3.
[43] Deltenre P, Zanetto A, Saltini D, Moreno C, Schepis F. The role of transjugular intrahepatic portosystemic shunt in patients with cirrhosis and ascites: recent evolution and open questions. Hepatology 2023;77(2):640–58.
[44] Sinegre T, Duron C, Lecompte T, Lamblin G, Talon L, Muti L, et al. Intraindividual variability over time of thrombin generation in patients with cirrhosis. J Thromb Haemost 2023;21(6):1441–52.