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Increased risk of venous thromboembolism in hospitalized patients with cirrhosis due to non-alcoholic steatohepatitis

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Abstract

Objective: Patients with cirrhosis are at increased risk for venous thromboembolism (VTE) and portal vein thrombosis (PVT). Cirrhosis due to non-alcoholic steatohepatitis (NASH) appears to be particularly prothrombotic. We investigated hospitalized patients with NASH cirrhosis to determine if they are at increased risk for VTE.

Methods: Data on adult hospitalized patients with cirrhosis and VTE (deep vein thrombosis and/or pulmonary embolism) between November 1, 2010 and December 31, 2015 were obtained. Cases with VTE were matched by age, gender, and model for end stage liver disease (MELD) score to corresponding controls without VTE.

Results: Two hundred and ninety subjects (145 matched pairs) with mean age of 58.4 ± 11.8 years and MELD score of 16.0 ± 7.2 were included. Baseline characteristics were similar between cases and controls. Independent adjusted risk factors for VTE included NASH (OR: 2.46, 95% CI: 1.07–5.65, $p = 0.034$), prior VTE (OR: 7.12, 95% CI: 1.99–25.5, $p = 0.003$), and presence of PVT (OR: 2.18, 95% CI: 1.03–4.58, $p = 0.041$). Thrombocytopenia was associated with decreased risk (OR: 0.49, 95% CI: 0.26–0.95, $p = 0.035$).

Conclusions: NASH is an independent risk factor for VTE among cirrhosis patients and provides further evidence that NASH is a hypercoagulable state. While all hospitalized patients with cirrhosis at risk for VTE should be considered for medical thromboprophylaxis, those with NASH cirrhosis are at particularly increased risk and therefore a high index of suspicion for VTE should be maintained even in the presence of thromboprophylaxis.

Introduction

Historically, patients with cirrhosis were thought to have an inherent "coagulopathy" that predisposed them to bleeding and, hence, protected against thrombosis. There is emerging evidence that shows a precariously rebalanced hemostatic system with simultaneous change in pro- and anti-hemostatic pathways[1]. This balance can be disrupted by hepatic decompensation, renal failure, active infection, or invasive procedures[1]. Hospitalized patients with cirrhosis are at increased risk for venous thromboembolism (VTE)[2–4]. Incidence rates of VTE in hospitalized patients with cirrhosis are between 0.5 and 8.2%[5–11]. Furthermore, a recent meta-analysis of eleven studies comprised of 695,012 subjects with cirrhosis documented a pooled adjusted odds ratio of 1.49 (95% CI: 1.22–1.76, $p < 0.0001$) when compared to subjects without cirrhosis[4]. While risk factors for VTE in hospitalized patients with cirrhosis are similar to other medical patients, disease-specific risk factors including hypoalbuminemia[5,6], age[8], male gender[4],

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severity of liver disease[9,10], and malnutrition[11] have all been described. Despite an increased risk of VTE, medical thromboprophylaxis is often withheld in hospitalized patients with cirrhosis[10] even with similar bleeding risks[12].

The etiology of underlying liver disease may play a role in thrombotic risk in patients with cirrhosis. In particular, non-alcoholic steatohepatitis (NASH) may predispose to prothrombotic events through longstanding chronic inflammation leading to activation of the coagulation system[13–20]. Others have argued that obesity is more strongly associated with a hypercoagulable environment than NAFLD[21]. Despite the lack of a definitive mechanism, it is clear that patients with NASH develop clinically relevant thrombotic events. Multiple reports have shown an association between NASH cirrhosis and portal vein thrombosis (PVT) prior to liver transplantation when adjusting for comorbid metabolic risk factors[22–24]. Hospitalized patients with non-alcoholic fatty liver disease (NAFLD) may also be at increased risk for VTE[25]. For these reasons, we investigated the relationship between NASH and thrombosis further and hypothesize that hospitalized patients with NASH cirrhosis are at increased risk for VTE when adjusting for comorbid metabolic risk factors.

Methods
Case and control selection

Data on all hospitalized adult patients with cirrhosis and VTE between 2010 and 2015 were obtained from the University of Virginia Clinical Data Repository using billing and administrative codes. Cirrhosis of the liver was confirmed by direct review of the medical record by study personnel including histology (if available) or by biochemical, imaging, and endoscopic findings, suggesting advanced liver disease with portal hypertension. Deep vein thrombosis (DVT) was diagnosed by imaging with Doppler ultrasound formally interpreted by radiology. Pulmonary embolus (PE) was diagnosed by either computerized tomography (CT) of the chest or ventilation–perfusion scan formally interpreted by radiology. NASH was defined by review of the medical record for liver histology showing features of steatohepatitis or cryptogenic cirrhosis in the presence of metabolic risk factors (e.g., diabetes, hypertension, and obesity), both in the absence of significant alcohol intake (<100 g of alcohol intake per week). Cases with VTE were matched 1:1 by age (within 5 years), gender and model for end stage liver disease (MELD) score (within 2 points) to the corresponding controls with cirrhosis but no VTE. Cases with VTE were time matched within 90 days of VTE diagnosis to the corresponding controls to ensure reproducibility in medical assessment for and treatment of VTE. Hospitalized controls were presumed not to have

Table 1 Padua Prediction Score predicts risk of venous thromboembolism in acutely ill hospitalized medical patients (including those with cirrhosis)[26]

Risk factor	Score
Active cancer ≤180 days	3
Previous VTE (excluding superficial thrombosis)	3
Reduced mobility	3
Inherited or acquired thrombophilic condition	3
Trauma/surgery ≤30 days	2
Age ≥70 years	1
CHF and/or respiratory failure	1
Acute MI or ischemic CVA	1
Acute infection and/or rheumatologic condition	1
Obesity (BMI >30 kg/m^2)	1
Hormonal treatment	1

A score ≥4 indicates increased risk of VTE
BMI body mass index, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *MI* myocardial infarction, *VTE* venous thromboembolic disease

VTE based on the absence of ICD codes for VTE. The diagnosis of VTE was confirmed by trained study personnel by review of available imaging and/or imaging reports that described a definitive thrombosis. Baseline patient characteristics were reviewed, including demographics (age, gender, and body mass index), etiology of liver disease, portal hypertensive complications (gastroesophageal varices, ascites, hepatic encephalopathy, portal vein thrombosis, and hepatocellular carcinoma), comorbidities (coronary artery disease, cardiomyopathy, diabetes, and hypertension), substance use (alcohol and tobacco smoking), medications, laboratory values, and imaging. VTE risk factors (prior admission within 90 days, presence of inherited or acquired thrombophilia, active cancer, respiratory failure, acute myocardial infarction or cerebrovascular accident, acute infection of any physiologic system, hormone therapy, recent trauma or surgery, prior VTE) were also collected. The Padua Prediction Score was calculated retrospectively and compared between groups (Table 1 shows a list of included variables)[26]. Immobility was defined according to the original definition put forth by Barbar et al.[26] as bed rest >3 days (with bathroom privileges) due to physician order or patient limitations in functional status as was active cancer (local or metastatic cancer that had been treated with chemotherapy or radiation the previous 6 months).

Statistical analysis

Univariate analysis was performed using paired *t*test and McNemar's test for continuous and categorical variables as appropriate. Conditional logistic regression models

were constructed to assess risk factors for the development of new VTE utilizing the c-statistic as a standard measure of the predictive accuracy of the model. Patient characteristics were included as adjustment variables in the conditional logistic regression analysis if they had meaningful unadjusted levels of association in the paired univariate analysis (significant at $p < 0.20$), were clinically important, or had been shown to be significant in prior studies[27,28]. Categorical variables were analyzed as continuous variables where appropriate (albumin, BMI, and platelet count) prior to final model selection. Due to the inability to accurately capture grade of ascites based on data available for extraction in the medical record, we opted not to correct BMI for ascites. Covariates included in the final model were thrombocytopenia (platelet count <150 k/μL based on standard accepted definitions), hypoalbuminemia (serum albumin <2.8 g/dL as this has previously been shown to be the cutoff, where hypoalbuminemia is predictive of DVT risk[5]), proton pump inhibitor use, prior VTE, diabetes, coronary artery disease, PVT prior to VTE diagnosis, NASH, acute infection, and obesity (BMI >30 kg/m^2 based on standard accepted criteria). BMI, thrombocytopenia, and hypoalbuminemia were included as categorical variables rather than continuous variables to improve clinical decision-making based on the findings of the model. All statistical tests for significance were two sided and a significance level $p \leq 0.05$ was considered statistically significant. Data analysis and graph generation were performed using SAS Version 9.4 (Cary, NC, USA) and GraphPad Prism version 7.03 for Windows, GraphPad Software (La Jolla, CA, USA). Institutional review board approval was obtained from the University of Virginia Health Sciences Research Institutional Review Board. No data from prisoners or compromised individuals were included in this study.

Results

Two hundred and ninety subjects (145 matched pairs) with mean age of 58.4 ± 11.8 years and mean MELD score of 16.0 ± 7.2 (standard deviation) met inclusion criteria. Mean body mass index was 29.8 ± 0.6 kg/m^2 (standard deviation). Sixty-two percent of the cohort was male and 77% had advanced cirrhosis with Child-Turcotte-Pugh Class B or C disease. Sixty-nine percent had ascites, 52% gastroesophageal varices, and 49% hepatic encephalopathy. The most common etiologies of cirrhosis were NASH (38%), chronic hepatitis C (26%), and alcoholic liver disease (24%). One hundred two cases had isolated DVT while 25 had PE without evidence of DVT. Eighteen cases were diagnosed with both PE and DVT simultaneously. Thirty-one (21%) cases with VTE had been admitted to the hospital within 90 days preceding their diagnosis of PE or DVT.

When comparing cases with VTE to controls without VTE, the two groups were similar with several notable

exceptions (Table 2). While mean MELD scores were similar (15.7, 95% CI: 14.5–16.9 VTE vs. 16.3, 95% CI: 15.1–17.4, $p = 0.505$), cases with VTE had lower total bilirubin levels at the time of clot diagnosis (2.3 g/dL, 95% CI: 1.7–2.9 vs. 4.1 g/dL, 95% CI: 3.1–5.2, $p = 0.003$). Plasma creatinine and INR values were similar. Platelet counts were higher in the VTE group (154 k/μL, 95% CI: 136–171 VTE vs. 115 k/μL, 95% CI: 103–127 no VTE, $p < 0.001$) but albumin levels were similar. Rates of inherited or acquired hypercoaguability were similar between the two groups. Cases with VTE also had a greater incidence of acute infection (47 vs. 32%, $p = 0.007$). Prior VTE was also more prevalent in the VTE group (22 vs. 4%, $p < 0.001$) as was a diagnosis of PVT prior to VTE (23 vs. 14%, $p = 0.049$). There was a trend toward significance with higher rates of congestive heart failure (16 vs. 9%, $p = 0.075$) and respiratory failure (20 vs. 12%, $p = 0.080$) in the VTE group compared to the non-VTE group. Otherwise, other risk factors for clotting were similar between cases and controls, including hormone therapy, active cancer (including hepatocellular carcinoma), history of cerebrovascular accident, immobility and recent surgery or trauma. Metabolic risk factors coronary artery disease, diabetes mellitus, and hypertension were also similar between cases and controls. Body mass index was also similar (29.6 kg/m^2, 95% CI: 28.4–30.8 vs. 30.0 kg/m^2, 95% CI: 28.7–31.2, $p = 0.667$).

Overall, cohort rate of chemical VTE prophylaxis was low at 42.4%. When comparing the two groups, rates of VTE prophylaxis were similar with 36.5% ($n = 53$) for cases with VTE vs. 42.8% ($n = 62$) for controls without VTE ($p = 0.285$). The type of medications prescribed for VTE prophylaxis were similar between the two groups as well: VTE-apixiban ($n = 1$), bivalirudin ($n = 1$), dalteparin ($n = 1$), heparin ($n = 40$), LMWH ($n = 10$), and no VTE-dalteparin ($n = 1$), heparin ($n = 43$), LMWH ($n = 18$), $p = 0.456$. Similar rates of therapeutic anticoagulation (9.5 vs. 6.5%, $p = 0.355$) and aspirin use (16.8 vs. 14.5%, $p = 0.600$) were seen when comparing cases and controls. Indications for anticoagulation were different, however, as the VTE group had eight subjects with previous VTE who were on therapeutic anticoagulation as the indication, three for atrial fibrillation, one for a mechanical heart valve, and one for coronary artery disease compared to the non-VTE group, where there were zero subjects with previous VTE, two with previous mesenteric vein thrombosis, three with atrial fibrillation, two with coronary artery disease, and one with an artificial heart valve ($p = 0.007$). The Padua Prediction Score was significantly higher in cases with VTE compared to controls without VTE (4.50, 95% CI: 4.02–4.98 vs. 3.01, 95% CI: 2.64–3.37, $p < 0.001$).

On adjusted multivariable analysis, independent risk factors for VTE included NASH (OR: 2.46, 95% CI:

Table 2 Unadjusted univariate analysis of baseline characteristics of 290 subjects with cirrhosis both in the presence and absence of venous thromboembolism

	VTE (n = 145)[a]	No VTE (n = 145)	pvalue
Age	58.6 (56.6–60.5)	58.2 (56.3–60.2)	0.820
Male gender	90 (62.1)	90 (62.1)	1.000
Body mass index (kg/m^2)	29.6 (28.4–30.8)	30.0 (28.7–31.2)	0.667
Disease etiology			
NASH/Crypto	62 (42.8)	49 (34.3)	0.175
Autoimmune	5 (3.5)	3 (2.1)	
Cholestatic	10 (7.0)	10 (7.0)	
Alcohol	30 (20.7)	39 (27.3)	
Hepatitis C	35 (24.4)	40 (28.0)	
Hepatitis B	2 (1.4)	1 (0.7)	
Hemochromatosis	2 (0.7)	17 (11.9)	
Alcohol use			
Active	25 (17.5)	28 (19.6)	0.231
Former	36 (25.2)	47 (32.9)	
Never	82 (57.3)	68 (47.6)	
Smoking history			
Active	36 (25.0)	38 (27.0)	0.394
Former	50 (34.7)	57 (40.4)	
Never	58 (40.3)	36 (32.6)	
Child-Turcotte-Pugh			
A	30 (22.9)	36 (35.5)	0.745
B	58 (44.3)	59 (41.8)	
C	43 (48.9)	45 (32.8)	
Laboratory values			
MELD	15.7 (14.5–16.9)	16.3 (15.1–17.4)	0.505
Total bilirubin (g/dL)	2.3 (1.7–2.9)	4.1 (3.1–5.2)	0.003
Creatinine (g/dL)	1.70 (1.35–2.05)	1.38 (1.19–1.58)	0.114
INR	1.50 (1.39–1.61)	1.57 (1.47–1.61)	0.340
Sodium (mEq/L)	135.5 (134.6–136.4)	134.7 (133.8–135.7)	0.248
Albumin (g/dL)	2.90 (2.79–3.01)	2.87 (2.77–2.98)	0.762
Platelet count	153.5 (135.7–171.3)	115.0 (103.1–126.9)	<0.001
Comorbidities			
Stroke history	20 (13.8)	19 (13.1)	0.863
Active cancer	18 (12.4)	20 (13.8)	0.729
Acute infection	68 (46.9)	45 (31.5)	0.007
Congestive heart failure	23 (15.9)	13 (9.0)	0.075
Respiratory failure	29 (20.0)	18 (12.4)	0.080
Coronary artery disease	27 (18.6)	19 (13.3)	0.217
Diabetes	73 (50.3)	60 (41.7)	0.139

Table 2 continued

	VTE (n = 145)[a]	No VTE (n = 145)	pvalue
Hypertension	88 (61.0)	79 (54.9)	0.316
Medications			
VTE prophylaxis	53 (36.5)	62 (42.8)	0.285
Therapeutic AC	13 (9.5)	9 (6.5)	0.355
Hormone therapy	4 (2.8)	2 (1.4)	0.434
Aspirin	23 (16.8)	20 (14.5)	0.600
Nonselective BB	79 (57.6)	68 (48.9)	0.146
Diuretics	95 (69.3)	91 (65.5)	0.492
Lactulose	61 (44.5)	61 (45.3)	0.894
Proton pump inhibitor	94 (68.6)	80 (57.6)	0.057
Rifaximin	20 (14.6)	27 (19.6)	0.274
Hypercoagulability			
MTHFR homozygous	4 (57.1)	1 (12.5)	0.307
MTHFR heterozygous	2 (28.6)	0 (0.0)	0.710
ATIII deficiency	18 (66.6)	-	-
Anticardiolipan IgG	2 (12.0)	2 (28.6)	0.286
Anticardiolipan IgM	2 (8.7)	1 (14.3)	0.666
Factor V Leiden hetero	14 (93.3)	6 (85.7)	0.562
Lupus anticoagulant	0 (0.0)	1 (16.7)	0.057
Protein C deficiency	8 (57.1)	3 (60.0)	0.912
Protein S deficiency	2 (15.4)	1 (25.0)	0.659
Prothrombin mutation	1 (4.6)	1 (16.7)	0.307
VTE risk factors			
Prior VTE	32 (22.1)	5 (3.5)	<0.001
Immobility	31 (21.5)	21 (14.5)	0.119
Trauma/surgery	45 (31.0)	38 (26.2)	0.414
Prior admission <90 days	31 (21.4)	–	–
Padua Prediction Score	4.50 (4.02–4.98)	3.01 (2.64–3.37)	<0.001
Portal hypertension decompensations			
Ascites	100 (69.4)	100 (69.4)	0.923
Gastroesophageal varices	76 (52.8)	74 (51.0)	0.767
Hepatocellular carcinoma	16 (11.1)	18 (12.4)	0.731
Hepatic encephalopathy	73 (50.3)	70 (48.3)	0.725
Portal vein thrombosis	28 (23.0)	16 (13.8)	0.049
TIPS	13 (9.2)	16 (11.0)	0.597

In general, the cases with venous thromboembolism and the control group were similar with the exception of platelet count, active infection, prior venous thromboembolism, and the Padua Prediction Score

Subjects were matched on age ±5 years, MELD score ±2 and gender

AC anticoagulation, *AT* antithrombin, *BB* beta blocker, *MELD* model for end stage liver disease, *MTHFR* methyltetrahydrofolate reductase, *NASH* non-alcoholic steatohepatitis, *TIPS* transjugular intrahepatic portosystemic shunt, *VTE* venous thromboembolism
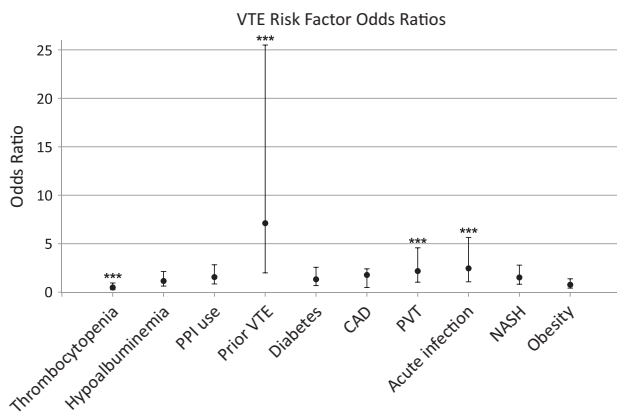
[a]DVT = 102, PE = 25, DVT + PE = 18

Fig. 1 Risk factors for venous thromboembolism in hospitalized patients with cirrhosis (adjusted multivariable analysis). NASH cirrhosis patients were found to be at nearly 2.5-fold greater risk for VTE. CAD coronary artery disease; NASH non-alcoholic steatohepatitis; PPI proton pump inhibitor; PVT portal vein thrombosis; VTE venous thromboembolism. Adjusted for age, gender, and MELD. c-statistic 0.74. ***$P \leq 0.05$

1.07–5.65, $p = 0.034$), prior VTE (OR: 7.12, 95% CI: 1.99–25.5, $p = 0.003$), and the presence of PVT prior to the diagnosis of VTE (OR: 2.18, 95% CI: 1.03–4.58, $p = 0.041$) (Fig. 1). Thrombocytopenia was associated with decreased risk of VTE (OR: 0.49, 95% CI: 0.26–0.95, $p = 0.035$). While significant on unadjusted univariate analysis, acute infection was not predictive on adjusted multivariable analysis (OR: 1.52, 95% CI: 0.82–2.79, 95% CI: 0.182). Importantly, comorbid metabolic risk factors, such as diabetes, coronary artery disease, and obesity, were not significantly associated with VTE risk.

Discussion

This study confirms that NASH is a hypercoagulable state. NASH was found to be a strong independent risk factor for VTE in hospitalized patients with cirrhosis when adjusted for comorbid metabolic risk factors, including diabetes and obesity. This report highlights that the coagulation derangement is not just limited to local portal circulation with PVT risk[23,29], but rather extends systemically as well. NASH cirrhosis patients were 2.46 times more likely to be diagnosed with a PE and/or DVT compared to a composite of all other etiologies of liver disease. NASH patients with cirrhosis should be considered among the highest risk patients to develop future VTE while hospitalized and medical thromboprophylaxis should be administered in the absence of contraindications.

The mechanism leading to increased thrombotic risk in patients with NASH or NASH cirrhosis remains unknown. It has been postulated that repetitive injury from chronic inflammation from hepatic steatosis and lipid deposition over time leads to endothelial cell activation, oxidative injury, and necroapoptosis[13–16]. This proinflammatory process may lead to imbalance in hemostasis, thereby disrupting the delicate balance of hemostasis to favor hypercoagulability[17,18]. Abnormalities in elevated levels of vonWillebrand factor, mean platelet volume (surrogate of platelet activation), Factor VIII, fibrinogen and plasminogen activator inhibitor-1 have been reported in both NAFLD and NASH[17,18]. Levels of protein C and antithrombin are decreased in both NASH and NASH cirrhosis[17,18]. Plasminogen activator inhibitor-1 levels correlate with increasingly severe liver histopathology with greater levels of lobular inflammation, hepatocyte ballooning, steatosis, and fibrosis[20]. Figure 2 depicts a proposed mechanism for hypercoagulability in NASH.

Plasminogen activator inhibitor-1 inhibits breakdown of fibrin-based clots promoting thrombotic risk both in the macrovascular system as well as in local circulatory systems. Resultant intrahepatic thrombi induce tissue ischemia, which has the potential to accelerate liver disease progression through stellate cell activation and fibrogenesis[30]. A series by Papatheodoris et al.[31] found that the presence of at least one thrombotic risk factor was associated with a nearly two-fold fibrosis stage increase in NASH patients, confirming earlier observational reports correlating thrombotic risk factors to the extent of hepatic fibrosis[32].

Despite evidence suggesting a hypercoagulable state in patients with NASH and NASH cirrhosis, a recent report by Potze et al.[21] challenges this notion. The authors found that hemostatic profiles were similar when comparing non-cirrhotic biopsy-proven NAFLD to controls without NAFLD with several exceptions. NAFLD patients had increased PAI-1 levels, less fibrinolysis and a greater degree of prothrombotic structure to the fibrin clot. However, these prohemostatic features were also found in obese controls leading the authors to conclude that prothrombotic risk was perhaps related to the presence of obesity rather than NAFLD per se[21]. This distinction is important given multiple reports and a recent meta-analysis confirming that metabolic syndrome predisposes patients to VTE in the absence of cirrhosis[33–36]. In fact, when distilling the metabolic syndrome into individual components, abdominal obesity was the strongest independent predictor of VTE and may be a better predictor than BMI[33,34]. However, these studies did not examine comorbid NAFLD or NASH. To date, only one other study has investigated NAFLD specifically and shown an association between NAFLD and VTE risk[25]. While the study controlled for obesity by matching cases and controls on BMI, it excluded patients with cirrhosis. We did not match for obesity in our study design. Rather, we included obesity as a predictor in the multivariable logistic regression model and we did not find obesity predictive of VTE risk in patients with cirrhosis.
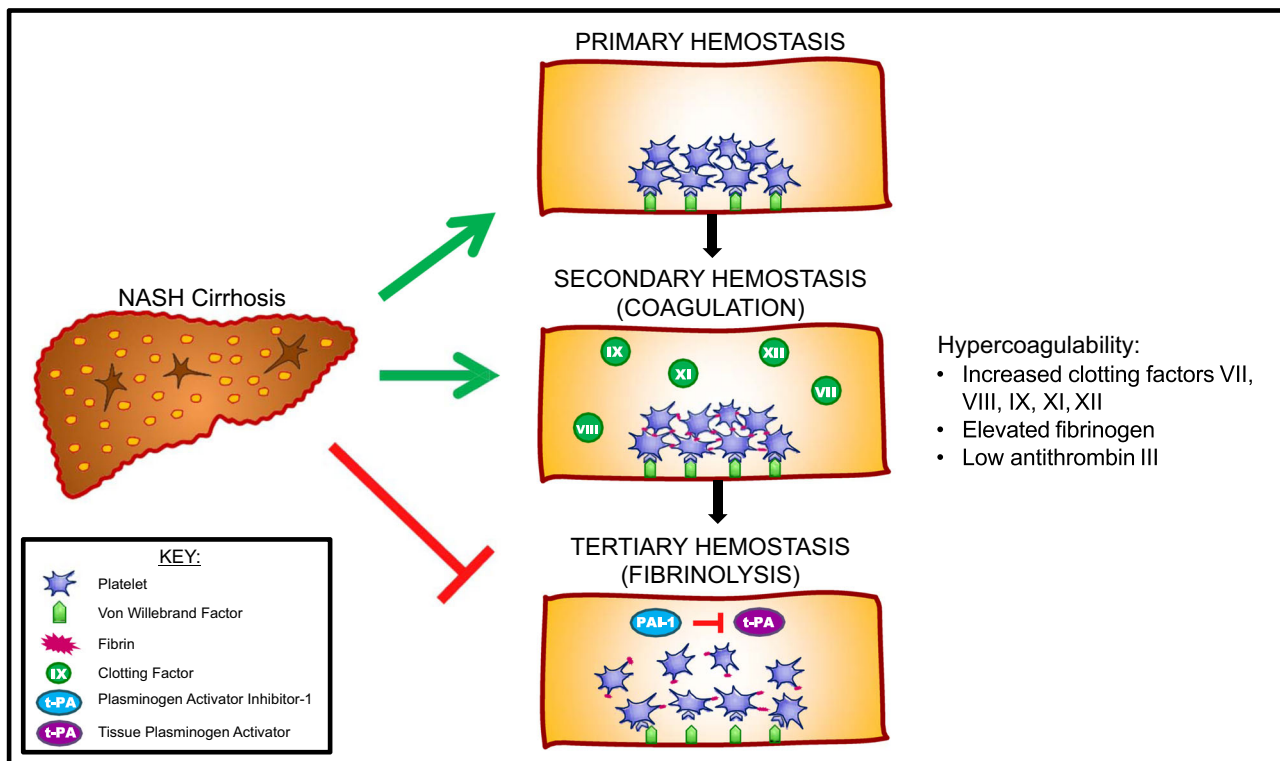
Fig. 2 Proposed mechanism for hypercoagulability in NASH cirrhosis. Prohemostatic changes are seen across all three phases of hemostasis in patients with NASH

Our cohort of patients was largely comprised of decompensated liver disease. In total, 77.3% had CTP Class B or C disease. By controlling for disease severity with matching by MELD score, we postulate that the coagulation balance in patients with NASH cirrhosis tips toward thrombosis as the patient becomes more decompensated. This could explain why we did not find NASH cirrhosis patients to be predisposed to DVT in our previous work as our prior cohort of patients was a much healthier population with significantly lower MELD scores and near-normal platelet counts[5]. Additionally, we did not analyze portal hypertensive complications in our previous work[5]. Future study confirming this from a mechanistic and translational standpoint would be interesting to undertake and may validate our findings.

Our study has several limitations. Namely, data on patient-centered long-term outcomes could not be captured due to a significant amount of missing longitudinal data. Because the study was retrospective, we also were unable to capture previously described abnormal biomarkers of coagulation. Thrombophilia testing was also not performed in the majority of patients. A matched case–control study design was chosen to provide greater statistical precision given the relatively low even rate of VTE and to allow for direct matching on confounding variables.

Other findings in this study beyond the primary objective deserve attention. Pre-existing PVT was significantly associated with future development of VTE, adding to the speculation that cirrhosis can be a hypercoagulable state. We have previously described pre-transplantation PVT to be predictive of post-transplantation hepatic artery thrombosis[37,38]. Whether or not the post-transplantation hypercoagulable milieu extends to post-operative PE or DVT has yet to be explored. Thrombocytopenia was associated with a lower risk of VTE, which is intriguing in that multiple reports have found thrombocytopenia was not predictive of bleeding risk. Whether or not thrombocytopenia is protective against clotting remains to be determined and should be validated with further prospective study. Recent reports have surfaced that reactive thrombocytosis following treatment of chronic hepatitis C with direct acting antiviral medications may be implicated in the development of PVT further implicating the role of the platelet in prohemostatic risk[39]. While hypoalbuminemia has previously been shown to be predictive of DVT development, our analysis did not confirm this finding[5]. As both thrombocytopenia and hypoalbuminemia can be considered markers of advanced liver disease, our matching by MELD score controlled for liver disease severity in order to avoid confounding with the primary outcome and may offer an explanation to the lack of

confirmation of these previous findings. Similar to previous findings[26,40], the Padua Prediction Score was predictive of VTE risk in patients with cirrhosis.

In conclusion, we have shown that NASH is an independent risk factor for VTE among cirrhosis patients, providing further evidence that NASH is a hypercoagulable state. While all hospitalized patients with cirrhosis should be considered for medical thromboprophylaxis, those with NASH cirrhosis are at particularly increased risk and a high index of suspicion for VTE should be reserved in these patients.

Study Highlights

What is current knowledge

- Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease worldwide.
- NAFLD is associated with derangements in all three phases of hemostasis.
- Patients with NASH cirrhosis are at increased risk for portal vein thrombosis independent of other comorbid metabolic conditions.

What is new here

- The prothombotic state of NASH cirrhosis extends beyond the portal venous system and into the systemic circulatory system.
- NASH is an independent risk factor for venous thromboembolism (VTE) among cirrhosis patients with nearly 2.5-fold greater risk when compared to all other etiologies of cirrhosis.
- While all hospitalized patients with cirrhosis should be considered for medical thromboprophylaxis, those with NASH cirrhosis are at particularly increased risk and a high index of suspicion for VTE should be reserved in these patients.

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