ORIGINAL ARTICLE

Retrospective Cohort Study

Advanced non-alcoholic steatohepatitis cirrhosis: A high-risk population for pre-liver transplant portal vein thrombosis

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Abstract

AIM
To examine if liver transplant recipients with high-risk non-alcoholic steatohepatitis (NASH) are at increased risk for pre-transplant portal venous thrombosis.

METHODS
Data on all liver transplants in the United States from February 2002 through September 2014 were analyzed. Recipients were sorted into three distinct groups: High-risk (age > 60, body mass index > 30 kg/m^2, hypertension and diabetes), low-risk and non-NASH cirrhosis. Multivariable logistic regression models were constructed.

RESULTS
Thirty-five thousand and seventy-two candidates underwent liver transplantation and of those organ recipients, 465 were transplanted for high-risk and 2775 for low-risk NASH. Two thousand six hundred and twenty-six (7.5%) recipients had pre-transplant portal vein thrombosis; 66 (14.2%) of the high-risk NASH group had portal vein thrombosis *vs* 328 (11.8%) of the low-risk NASH group. In general, all NASH recipients were less likely to be male or African American and more likely to be obese. In adjusted multivariable regression analyses, high-risk recipients had the greatest risk of

pre-transplant portal vein thrombosis with OR = 2.11 (95%CI: 1.60-2.76, *P* < 0.001) when referenced to the non-NASH group.

CONCLUSION
Liver transplant candidates with high-risk NASH are at the greatest risk for portal vein thrombosis development prior to transplantation. These candidates may benefit from interventions to decrease their likelihood of clot formation and resultant downstream hepatic decompensating events. Prospective study is needed.

Key words: Liver transplantation; Non-alcoholic fatty liver disease; Portal hypertension; Hepatology; Coagulopathy

Core tip: Non-alcoholic steatohepatitis (NASH) is increasing in prevalence and is expected to be the leading indication for liver transplantation in the foreseeable future. There is a growing body of evidence supporting the clinical importance of a thrombophilic state in patients with NASH. In NASH patients, the most severe hypercoagulable environment is found in patients with NASH cirrhosis. High-risk NASH patients (concomitant age > 60 years, obesity, diabetes and hypertension) have inferior post transplantation outcomes, however, how this group's risk of clotting compares to other etiologies of liver disease is unknown. In a retrospective nationwide United States based cohort, we provide further evidence of coagulation derangement in NASH and identify a new high-risk subtype in the high-risk NASH population. Whether or not this high-risk group may benefit from preventative anticoagulation remains unknown.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of hepatic disorders ranging from simple steatosis with or without mild inflammation to non-alcoholic steatohepatitis (NASH) which is diagnosed by the presence of inflammation, cellular injury with hepatocyte ballooning and accumulation of Mallory-Denk bodies and in the most advanced cases, fibrosis[1]. NAFLD is increasing in prevalence in Western society[2] with rates approaching 20%-30%[3] and more importantly, NASH is projected to become the number one indication for liver transplantation in the foreseeable future[4], especially in light of the new all oral direct acting antiviral treatment regimens for

hepatitis C virus (HCV), and it is the most rapidly growing indication for simultaneous liver-kidney transplantation[5]. High-risk NASH (HR-NASH) is a subtype of NASH defined by the presence of the following: Age > 60 years, body mass index (BMI) > 30 kg/m^2, hypertension and diabetes[6,7]. In general, liver transplant recipients with NASH have similar liver graft and overall one-, three- and five-year survival rates when compared to other etiologies[4-6,8,9]. Outcomes for HR-NASH recipients are less promising with single center experiences showing significantly lower one-[7] and five-year survival rates[6]. While the exact explanation for this remains relatively unexplored, post-transplant cardiovascular events[8], some of which are attributable to macrovascular arterial thrombosis[7,9], and chronic renal dysfunction[10] are more common in NASH patients and these could contribute to lesser outcomes.

Venous thromboembolism (VTE) including portal vein thrombosis (PVT) is a common affliction in patients with cirrhosis[11]. Incidence rates of PVT are reported to be as high as 16%[12] and 30-d mortality is increased in patients with pulmonary embolism (PE) or deep vein thrombosis (DVT)[11]. In a matched retrospective case-control study of 414 patients, Di Minno *et al*[13] found that NAFLD was associated with VTE (PE or DVT) with an OR of 1.8 on adjusted multivariable analysis controlling for additional VTE and NAFLD risk factors. While the presence of PVT may mirror the degree of liver disease burden, it is nonetheless associated with adverse outcomes including increased pre- and post-liver transplant mortality and impaired quality of life, as well as technical challenges during the transplant procedure[14,15]. We have previously shown that liver transplant recipients with NASH are predisposed to pre-transplant PVT[16]. Patients with NASH and metabolic syndrome, which encompasses many of the features of the HR-NASH definition, are known to have increased degrees of fibrosis[17], and presumably increased thrombotic risk. To date, there is a lack of data investigating the relationship between pre-transplant PVT and HR-NASH. We aim to explore this potential association and hypothesize that liver transplant recipients with HR-NASH are at increased risk for PVT when compared directly to other NASH patients and all other etiologies of liver disease.

MATERIALS AND METHODS

Study design and recipient characteristics
Data on all transplants in the United States during the model for end-stage liver disease (MELD era) through September 2014 were reviewed from the Organ Procurement and Transplantation Network (OPTN) with permission from the United Network for Organ Sharing (UNOS). Status 1a, multi-organ, living donor, re-transplants, pediatric recipients, donation after cardiac death, recipients with pre-transplantation transjugular intrahepatic portosystemic shunts and malignancy (hepatocellular carcinoma, hepatoblastoma, cholangiocarcinoma) were excluded. Recipients with cryptogenic

cirrhosis were also excluded due to the potential for misclassification of NASH. The conclusions of the model were not significantly changed with the exclusion of the cryptogenic recipients. Recipients were sorted into two distinct groups: Those with NASH and those without NASH (all other etiologies except cryptogenic cirrhosis, which was excluded due to the potential for misclassification of NASH). The NASH group was then subdivided into HR and low-risk (LR) subgroups. HR-NASH was based on the standard definition used in previous large-scale single center experiences and was defined as the presence of all of the following: Age > 60 years, BMI > 30 kg/m^2, and pre-transplantation hypertension and diabetes[6,7]. Recipient characteristics (age at listing and at transplantation, ethnicity, gender, BMI, diabetes), severity of liver disease based on native laboratory MELD score at allocation, laboratory values [international normalized ratio (INR), bilirubin, creatinine, albumin], and clinically relevant manifestations of portal hypertension (ascites and hepatic encephalopathy) were reviewed in each of the three groups to compare baseline covariates.

Outcomes analysis

Separate analyses were performed comparing recipients with NASH to non-NASH controls and comparing HR-NASH to LR-NASH. In the UNOS data set, PVT is categorized as "Present", "Not present", or "Unknown" and the data are based upon direct surgical evaluation of the veins at the time of hepatectomy. The degree of clot burden is not specified in the dataset nor is the chronicity. Based on previously validated methodology and due to the potential for misclassification bias[16], 831 recipients with "Unknown" PVT status were excluded. In general, univariate comparisons of the excluded cases to the included cohort with known PVT status did not reveal any baseline differences with the exception that the included cohort had a greater percentage of patients with cholestatic liver disease (10.2% *vs* 5.5%, *P* < 0.001). It was felt by the study team that this was not a significant clinical factor in the analysis. The dataset also does not contain information on treatment of PVT or testing for thrombophilia.

Statistical analysis

Recipients were statistically evaluated in multiple factors including demographics, medical comorbidities, waiting list and transplantation characteristics. Univariate comparisons were performed using the Student-*t* test, Wilcoxon sign rank test, χ^2 test, or Fisher exact test as appropriate. Multivariable models were constructed using logistic regression and analysis of maximum likelihood estimates to test the primary hypothesis that patients with HR-NASH are at increased risk for the development of PVT and to assess statistical associations and risk factors for the development of PVT. Individual covariates were included in the multivariable model if they were statistically significant to *P* < 0.20 in univariate analysis, have been shown in the literature to be important or

were deemed to be clinically important by the study team[18,19]. In separate models, individual components of the HR-NASH definition (hypertension, age, BMI and diabetes) were entered into the model as individual variables to ensure one of these did not dominate. Final variables included in the regression model included HR-NASH, LR-NASH, individual laboratory values at transplant (creatinine, bilirubin, INR, albumin, sodium), HCV, cholestatic liver disease, male gender, African American race, Hispanic race, encephalopathy (which was dichotomized into those with severe encephalopathy with score > 2), ascites (similarly dichotomized), pre-transplant dialysis treatment and autoimmune liver disease. No data imputation was performed. All statistical tests for significance were two sided and a significance level *P* less than or equal to 0.05 was considered statistically significant. All data set manipulation and statistical analyses were performed using SAS (version 9.4, Cary, NC). No transplants involving prisoners were included in this analysis. Institutional review board approval was not required for this study as the UNOS/OPTN dataset is de-identified.

RESULTS

Thirty-five thousand and seventy-two candidates underwent liver transplantation and of those organ recipients, 3240 (9.2%) were transplanted for NASH of which 465 met criteria for HR-NASH (1.3%) and 2775 for LR-NASH (7.9%). Two thousand six hundred and twenty-six (7.5%) recipients had pre-transplant PVT, of which 394 (12.2%) were in the NASH group (Figure 1). The prevalence of PVT was not significantly different between HR-NASH and LR-NASH (*n* = 66, 14.2% *vs n* = 328, 11.8%, *P* = 0.145). In general, NASH recipients were older, more likely to be female, less likely to be African American or Hispanic, had higher BMI values and were more likely to have diabetes, hypertension and renal dysfunction (Table 1). Severity of liver disease, while statistically significantly different, was not deemed to be clinically significantly different (*e.g.,* MELD at listing of 20.0, 95%CI: 19.8-20.3 for NASH *vs* 19.6, 95%CI: 19.5-19.7 for non-NASH). The leading indication for transplantation in the non-NASH group was chronic HCV (46.6%) while alcoholic liver disease was the second leading indication (19.0%).

When comparing HR-NASH recipients to LR-NASH recipients, several differences were noted (Table 2). As expected by definition, HR-NASH recipients were older both at listing (64.0 years, 95%CI: 63.8-64.3 *vs* 56.7 years, 95%CI: 56.2-56.9, *P* < 0.001) and at transplantation (64.5 years, 95%CI: 64.2-64.7 *vs* 57.0 years, 95%CI: 56.8-57.4, *P* < 0.001). BMI values were greater for HR-NASH (35.1 kg/m^2, 95%CI: 34.7-35.5 *vs* 31.8 kg/m^2, 95%CI: 31.5-32.0, *P* < 0.001) as was renal dysfunction (mean creatinine 1.98 g/dL, 95%CI: 1.85-2.11 *vs* 1.78 g/dL, 95%CI: 1.73-1.85, *P* = 0.003).

Severity of liver disease based on MELD scores and portal hypertensive manifestations of ascites and

Table 1 Baseline characteristics comparing non-alcoholic steatohepatitis recipients to all other etiologies of liver disease *n* (%)

	NASH (*n* = 3240)	Other etiologies (*n* = 31832)	*P* value
Recipient characteristics			
Age at listing, mean years (95%CI)	57.6 (57.3-57.9)	52.2 (52.1-52.3)	< 0.001
Age at transplant, mean years (95%CI)	58.1 (57.8-58.4)	52.7 (52.6-52.8)	< 0.001
Male gender	1747 (52.9)	22099 (67.3)	< 0.001
African American race	65 (2.0)	3.559 (10.9)	< 0.001
Hispanic race	348 (10.5)	4009 (12.2)	0.005
BMI at transplant, kg/m², mean (95%CI)	32.3 (32.0-32.5)	27.8 (27.7-27.9)	< 0.001
Hypertension requiring medical treatment	160 (33.2)	2155 (19.2)	< 0.001
Diabetes	1698 (51.4)	6211 (18.9)	< 0.001
Portal vein thrombosis	394 (12.2)	2232 (7.1)	< 0.001
Etiology of liver disease			
Alcohol alone		6236 (19.0)	
Autoimmune disease		1.202 (3.7)	
Cholestatic disease		3638 (11.1)	
Hepatitis B		986 (3.0)	
Hepatitis C		15298 (46.6)	
Other		4472 (14.0)	
Severity of liver disease			
MELD score at listing, mean (95%CI)	20.0 (19.8-20.3)	19.6 (19.5-19.7)	0.014
MELD score at transplantation, mean (95%CI)	23.5 (23.2-23.8)	22.8 (22.7-22.9)	< 0.001
Laboratory values			
Serum bilirubin, mg/dL, mean (95%CI)	7.4 (7.1-7.8)	9.1 (9.0-9.2)	< 0.001
INR, mean (95%CI)	1.92 (1.90-1.95)	1.93 (1.92-1.94)	NS
Serum albumin, g/dL, mean (95%CI)	3.0 (3.0-3.1)	3.0 (2.9-3.0)	0.002
Creatinine, g/dL, mean (95%CI)	1.81 (1.76-1.86)	1.65 (1.63-1.67)	< 0.001
On dialysis at transplantation	488 (10.6)	4135 (12.2)	< 0.001
Portal hypertension manifestations			
Moderate-severe ascites at transplant	1210 (36.7)	10782 (32.9)	< 0.001
Moderate-severe hepatic encephalopathy at transplant	375 (11.7)	3708 (11.3)	NS

In general, NASH recipients were older, more likely to be female, less likely to be African American or Hispanic, had higher BMI values and were more likely to have diabetes, hypertension and renal dysfunction. BMI: Body mass index; NASH: Non-alcoholic steatohepatitis; NS: Not significant; INR: International normalized ratio; MELD: Model for end-stage liver disease.
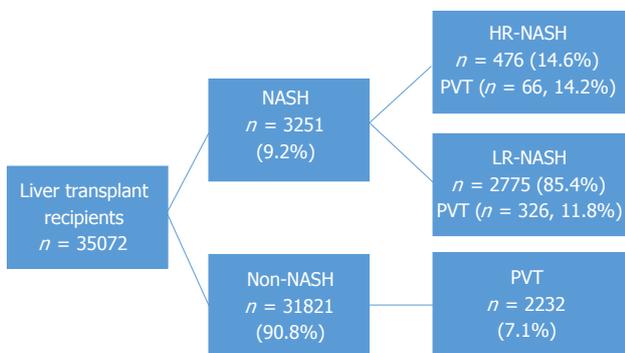

Figure 1 Study enrollment. HR: High-risk; LR: Low-risk; NASH: Non-alcoholic steatohepatitis; PVT: Portal vein thrombosis.

encephalopathy were similar between the two groups. Interestingly, non-NASH recipients with HR features were not at increased odds of PVT (*P* = 0.11), albeit only 58 patients met criteria for this subgroup.

In adjusted multivariable analysis (Table 3), recipients with HR-NASH had the greatest risk of pre-transplant PVT with OR = 2.11 (95%CI: 1.60-2.76, *P* < 0.001) when referenced to the non-NASH cohort and 30% increased odds when compared to LR-NASH recipients (OR = 1.71, 95%CI: 1.49-1.96, *P* < 0.001). Other significant associations with pre-transplant PVT included male gender (OR = 1.18, 95%CI: 1.07-1.29, *P*

< 0.001), Hispanic race (OR = 1.24, 95%CI: 1.10-1.39, *P* < 0.001) moderate-to-severe ascites (OR = 1.14, 95%CI: 1.04-1.25, *P* = 0.007) and autoimmune liver disease (OR = 1.43, 95%CI: 1.14-1.79, *P* = 0.002). African Americans were less likely to have pre-transplant PVT with OR = 0.75 (95%CI: 0.64-0.89, *P* < 0.001), similar to our previous findings[16].

While MELD was significantly different on univariate analysis, the individual factors (bilirubin, INR, creatinine) involved in the MELD regression equation were not clinically important statistically significant predictors in adjusted multivariable analysis nor was pre-transplantation dialysis.

DISCUSSION

Based on a large national liver transplant database and building on our previous work in transplant recipients with NASH[16], we have shown an independent cross-sectional association documenting an increased risk of pre-transplant PVT in recipients undergoing transplantation for HR-NASH. This association was significant despite adjustment for multiple established risk factors for pre-transplant PVT. Given the technical difficulties associated with pre-transplant PVT, careful recipient selection is paramount in preventing post-transplant vascular complications.

Table 2 Baseline characteristics comparing high-risk non-alcoholic steatohepatitis to low-risk non-alcoholic steatohepatitis recipients

	High-risk NASH (*n* = 465)	Low-risk NASH (*n* = 2775)	*P* value
Recipient characteristics			
Age at listing, mean years (95%CI)	64.0 (63.8-64.3)	56.7 (56.2-56.9)	< 0.001
Age at transplant, mean years (95%CI)	64.5 (64.2-64.7)	57.0 (56.8-57.4)	< 0.001
Male gender	247 (52.4)	1500 (53.0)	NS
African American race	7 (0.2)	58 (1.6)	NS
Hispanic race	43 (9.1)	305 (10.8)	NS
BMI at transplant, kg/m^2, mean (95%CI)	35.1 (34.7-35.5)	31.8 (31.5-32.0)	< 0.001
Portal vein thrombosis	66 (14.2)	326 (11.8)	NS
Severity of liver disease			
MELD score at listing, mean (95%CI)	19.5 (18.7-20.3)	20.1 (19.8-20.4)	NS
MELD score at transplantation, mean (95%CI)	22.8 (21.9-23.6)	23.7 (23.3-24.0)	NS
Laboratory values			
Serum bilirubin, mg/dL, mean (95%CI)	6.2 (5.4-7.0)	7.7 (7.3-8.0)	0.002
INR, mean (95%CI)	1.81 (1.75-1.86)	1.94 (1.91-1.97)	0.002
Serum albumin, g/dL, mean (95%CI)	3.1 (3.0-3.2)	3.0 (2.9-3.1)	0.006
Creatinine, g/dL, mean (95%CI)	1.98 (1.85-2.11)	1.78 (1.73-1.83)	0.003
On dialysis at transplantation	73 (15.5)	415 (14.7)	NS
Portal hypertension manifestations			
Moderate-severe ascites at transplant	178 (37.8)	1032 (36.5)	NS
Moderate-severe hepatic encephalopathy at transplant	51 (10.8)	324 (11.5)	NS

HR-NASH recipients were older, had higher BMI values and were more likely to have renal dysfunction. BMI: Body mass index; HR: High-risk; NASH: Non-alcoholic steatohepatitis; NS: Not significant; INR: International normalized ratio.

Table 3 Adjusted multivariable analysis for predictors of portal vein thrombosis at the time of liver transplantation

	Odds ratio	95%CI	*P* value
African American race	0.75	0.64-0.89	< 0.001
AIH	1.43	1.14-1.79	0.002
Hispanic race	1.24	1.10-1.39	< 0.001
HR-NASH	2.11	1.60-2.76	< 0.001
LR-NASH	1.71	1.49-1.96	< 0.001
Male gender	1.18	1.07-1.29	< 0.001
Moderate-severe ascites	1.14	1.04-1.25	0.007

Recipients with HR-NASH had the greatest risk of pre-transplant PVT when referenced both to the non-NASH cohort and to LR-NASH recipients. Variables that were not significant in the model: Albumin levels, bilirubin levels, cholestatic liver disease, creatinine levels, hepatitis C, international normalized ratio (INR); moderate-severe encephalopathy, pre-transplant dialysis treatment, sodium levels. AIH: Autoimmune hepatitis; HR: High-risk; LR: Low-risk; NASH: Non-alcoholic steatohepatitis.

Patients with NASH and in particular NASH cirrhosis, have *in vivo* abnormalities in primary, secondary and tertiary hemostasis[20,21]. The role of platelet dysfunction *via* increased activation, adherence and aggregation is the best described abnormality in primary hemostasis[22-24], however multiple investigators have shown elevations in vonWillebrand factor as a surrogate for endothelial dysfunction as well[21,25]. Secondary hemostasis is impaired in NASH due to elevations in fibrinogen, factor VIII, IX, XI, XII, increased clotting activity of factor VII, and low levels of antithrombin III[20,21,25-27]. Protein C levels may be increased or decreased in patients with NASH[20]. Tertiary hemostasis is disrupted due to elevations in plasminogen activator inhibitor-1 and low levels in both thrombin activatable fibrinolysis inhibitor and tissue plasminogen activator[20,21,27]. The aggregate of these impaired mechanisms of coagulation leads to the hypercoagulable milieu responsible in part for the development of PVT.

Whether or not the presence of pre-transplant PVT plays a role in the decreased survival of HR-NASH[6,7] remains unknown as our study did not investigate patient centered outcomes such as graft and overall patient survival. We did not attempt to do this due to the limitations of the UNOS/OPTN dataset, which does not contain information on the use of anticoagulants and data on post-transplant vascular complications is hindered by a large degree of missing data. The lack of this information introduces significant heterogeneity into the dataset and concrete post-transplant outcomes based conclusions for patients with PVT are problematic. However, what is clear is that the high-risk subgroup of NASH is the most at risk for PVT both in comparison to other NASH recipients not meeting the HR definition and also to all other etiologies of liver disease. We have previously shown that the independent factors of diabetes and obesity do not predispose to PVT on an individual basis[16]. It is only in combination with advanced age > 60 years and hypertension that these factors interact in a way to produce clinically meaningful thrombotic disease, perhaps due to increased physiologic endothelial dysfunction with advancing age[28].

In general, treatment outcomes for patients with PVT are impaired by a lack of large-scale, randomized, placebo-controlled trials that are generalizable. Villa *et al*[29] demonstrated in an un-blinded, single center randomized controlled trial that daily prophylactic dosing of low molecular weight heparin (40 mg daily) for twelve months prevented the development of PVT in patients with compensated cirrhosis at 48 wk, an effect that persisted through the 5-year follow-up period when compared to standard of care[29]. This study also demonstrated significantly less hepatic decompensation in the low

molecular weight heparin arm and a survival benefit in the absence of a single bleeding event[29]. Building on this, Cui *et al*[30] recently published a controlled trial evaluating the efficacy and safety of anticoagulation therapy with different doses of enoxaparin (1 mg/kg twice a day *vs* 1.5 mg/kg daily) for PVT in patients with cirrhosis secondary to chronic hepatitis B in 65 patents, the majority of which had partial thrombosis. Importantly, 79% of patients achieved partial or complete response with anticoagulation based on follow-up imaging, however, non-variceal bleeding was significantly greater in the daily group (23.5% *vs* 6.4%) and the authors concluded that dosing at 1 mg/kg of enoxaparin subcutaneously twice a day was the preferred anticoagulation regimen. While the inclusion criteria were stringent limiting generalizability and the imaging guided definition of PVT open for criticism in these studies, the findings are nonetheless intriguing. A recent meta-analysis by Qi *et al*[31] of 16 studies (the authors did not include either of the aforementioned studies) and 960 patients found a pooled OR of 4.16 (95%CI: 1.88-9.20, $P < 0.001$) for complete portal vein recanalization with anticoagulation. Interestingly, the pooled rate of bleeding was only 3.3% (95%CI: 1.1%-6.7%). A recently published animal model found that 3 mo of dabigatran significantly reduced fibrin deposition, inflammation, hepatocellular injury, steatosis and weight gain[32] through mitigation of thrombin generation, the end-result of the coagulation abnormalities in NASH, suggesting a potential novel therapeutic approach. Newer data regarding the potential use of prothrombin complex concentrates in combination with antithrombin with or without concurrent fibrinogen administration to restore the delicate homeostasis of coagulation and normal thrombin and fibrinogen is emerging[33,34]. However, this combination of therapy has not been broadly studied in patients with chronic liver disease and concrete recommendations about the utility of this treatment cannot be made at this juncture.

In general, prospective, randomized, placebo-controlled studies are sorely needed in all patients with cirrhosis, however, targeting those most at risk including patients with HR-NASH, may provide the most substantial benefits including the potential to reduce disease burden from cerebrovascular accidents that this population is at risk for. If the reduction in inflammation and fibrosis with the direct thrombin inhibitors is validated in human subjects, these agents may provide an antifibrotic therapy which could alter the prognosis of liver disease.

Our study has several limitations. Despite containing a large number of transplant recipients in the MELD era, it is a retrospective study. Furthermore, missing data and correct diagnostic coding are potentially problematic with all large datasets. We attempted to control for missing data by excluding the small percentage of patients with unknown PVT status who were demographically similar to our included cohort to ensure bias towards or away from the null was not introduced. Although transplant centers are gaining increased experience transplanting recipients with PVT, it is possible that small volume centers may not have the same surgical technique or experience and pre-transplant PVT may in fact preclude transplantation in a subset of patients that would go on to be excluded from this study. The PVT variable in the dataset also has inherent heterogeneity as there is no differentiating between partial and complete thrombus or the chronicity of the clot. Our analysis also could not account for thrombophilia disorders and therapy in the pre-transplant phase. Additionally, our study excluded HCC patients in the event that PVT was associated with HCC as tumor thrombus, which may limit generalizability.

In conclusion, as the *in vivo* evidence of a thrombophilic state in patients with NASH continues to grow, epidemiologic evidence continues to lag behind. Building on our previous work, we have shown that liver transplant candidates with HR-NASH are at the highest risk for PVT development when compared to other NASH patients and also to all other etiologies of liver disease. Prospective study enrolling HR-NASH patients in anticoagulation trials seems warranted in order to determine a direct benefit in improving patient centered outcomes including the potential for overall and post-transplantation graft survival.

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COMMENTS

Background
Non-alcoholic steatohepatitis (NASH) is increasing in prevalence and will soon be the leading indication for liver transplantation in western nations. Patients with NASH are at increased risk for thrombosis. Patients with high-risk NASH have inferior liver transplantation outcomes. Whether or not this high-risk group has an increased risk of portal vein thrombosis (PVT) remains unknown.

Research frontiers
The field of coagulation disorders in chronic liver disease continues to grow. Much of the research focuses on PVT and/or venothromboembolic disease. Identifying high-risk groups for possible preventative intervention through clinical trials remains a goal of the liver and hematology fields alike.

Innovations and breakthroughs
In the present study, the authors investigated the association between high-risk NASH and PVT in liver transplant recipients with cirrhosis. This is the first report of PVT risk in patients with high-risk NASH.

Applications
The present report furthers understanding regarding the thrombophilic state of NASH and highlights a potential high-risk group who may benefit from further prospective study.

Peer-review
This is an excellent very large retrospective review that clearly shows that high risk NASH patients are more thrombophilic than low risk NASH patients and much more thrombophilic than non-NASH cirrhotic patients.

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