ORIGINAL ARTICLE

Liver transplant recipients with portal vein thrombosis receiving an organ from a high-risk donor are at an increased risk for graft loss due to hepatic artery thrombosis

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Meeting
This research was presented as a podium presentation at AASLD section of Digestive Diseases Week 2016, San Diego, CA.This research was also presented as a podium presentation at the Young Investigators Forum during the Controversies in Transplantation Conference, 2016, Breckenridge, CO.

SUMMARY

We hypothesize that recipients with pretransplant portal vein thrombosis (PVT) receiving organs from high-risk donors (HRD) are at an increased risk of HAT. Data on all liver transplants in the United States from February 2002 to March 2015 were analyzed. Recipients were sorted into two groups: those with PVT and those without. HRDs were defined by donor risk index (DRI) >1.7. Multivariable logistic regression models were constructed to assess the independent risk factors for HAT with the resultant graft loss ≤90 days from transplantation. A total of 60 404 candidates underwent liver transplantation; of those recipients, 623 (1.0%) had HAT, of which 66.0% (n = 411) received organs from HRDs compared with 49.3% (n = 29 473) in recipients without HAT ($P < 0.001$); 2250 (3.7%) recipients had pretransplantation PVT and received organs from HRDs. On adjusted multivariable analysis, PVT with a HRD organ was the most significant independent risk factor (OR 3.56, 95% CI 2.52–5.02, $P < 0.001$) for the development of HAT. Candidates with pretransplant PVT who receive an organ from a HRD are at the highest risk for postoperative HAT independent of other measurable factors. Recipients with pretransplant PVT would benefit from careful donor selection and possibly anticoagulation perioperatively.

Transplant International 2016; 29: 1286–1295

Key words
cirrhosis, coagulopathy, hepatology, outcomes, portal hypertension

Received: 21 March 2016; Revision requested: 23 May 2016; Accepted: 2 September 2016; EV Pub Online 6 October 2016

Introduction

Hepatic artery thrombosis (HAT) is an uncommon complication after liver transplantation with serious clinical implications including graft loss and increased recipient mortality [1–3]. Surgical risk factors including organ cold ischemia time (CIT), surgical technique, delay in reperfusion, and anatomic abnormalities all likely play a role in outcomes [4,5]. Less is understood about recipient-specific risk factors; however, prior liver transplantation, inherited thrombophilia, primary sclerosing cholangitis, acute intermittent porphyria, and onset of diabetes post-

doi:10.1111/tri.12855

transplantation may be associated with HAT [6–12]. We have previously shown that liver transplant recipients with pretransplantation portal vein thrombosis (PVT) are at increased odds of HAT and that donor risk index (DRI) is predictive of HAT [3]. PVT is commonly associated with increased hepatic decompensation and mortality complication in patients with cirrhosis [13–15]. Both PVT and increased DRI in liver transplantation recipients are associated with a higher rate of graft loss due to primary nonfunction, in many cases leading to re-transplantation [16]. While careful donor selection may be important in order to prevent postoperative HAT in recipients with pretransplantation PVT, a widely accepted cutoff has not yet been established. Originally proposed by Feng *et al.* in 2006 [17], DRI is the most widely used system to evaluate donor risk and assist the transplant team in decision-making regarding graft utilization [18]. A DRI cutoff of greater than 1.7 has been proposed to define "high risk" and validated by multiple studies showing that this value is predictive of poorer post-transplantation outcomes including recipient survival [19,20]. In this retrospective cross-sectional study of liver transplant recipients in the United States, we aimed to examine HAT risk factors in liver transplant recipients. Owing to their presumed hypercoagulable nature, we hypothesize that recipients with pretransplant PVT who receive organs from high-risk donors (HRD) are at an increased risk of HAT.

Methods

Study design and recipient characteristics

Data on all liver transplantations between February 1, 2002, and March 31, 2015, in the United States were analyzed from the Organ and Transplantation Network (OPTN) with permission from the United Network for Organ Sharing (UNOS). This cross-sectional nationwide database has been previously validated to analyze HAT and PVT in recipients undergoing liver transplantation [3,13,21–23]. Only recipients who were transplanted at or above 18 years of age were included in our analysis. All living donor transplants, re-transplants, status one candidates, multivisceral transplants, acute liver failure transplants, and recipients with transjugular intrahepatic portosystemic shunts (TIPS) were excluded. Due to the higher rate of nonthrombotic complications, the analysis was performed both with and without donation after cardiac death (DCD) recipients and the fundamental conclusions of the statistical analysis were not changed; therefore, DCD organ recipients were also excluded. In the OPTN/UNOS dataset, there are ten values for the cause of graft loss variable: "recurrent disease, infection, chronic rejection, acute rejection, *de novo* hepatitis, recurrent hepatitis, primary nonfunction, biliary, vascular thrombosis and other (write-in field)." Based on previously validated methodology [3,24,25] utilizing the "vascular thrombosis" and "other" category with the search terms "hepatic artery thrombosis," HAT was defined by these two values provided that there was resultant graft loss within 90 days of liver transplantation. Recipients who experienced HAT >90 days post-transplantation were included in the non-HAT group ($n = 2$). Missing data were handled initially by comparing the patients with known HAT status to those with unknown status. This comparison yielded one major difference; an increased percentage of recipients with underlying chronic hepatitis C (HCV), which we have previously shown to not be associated with an increased or decreased risk of HAT [3] and thus not a clinically relevant difference. Given the similarities in the two cohorts, the decision was made to include all recipients with unknown HAT status and to consider them as having "no HAT" in order to prevent inducing allocation bias.

Baseline recipient, operative and donor characteristics were analyzed. Recipient characteristics included the etiology of liver disease [hepatitis B, HCV, NASH/cryptogenic, autoimmune, cholestatic, hepatocellular carcinoma (HCC), alcoholic, and other liver diseases, which included recipients receiving an organ for any other reason than those above], severity of liver disease based on laboratory model for end-stage liver disease (MELD) score at transplantation, and portal hypertensive complications including encephalopathy, ascites, and PVT. Operative factors reviewed included locoregional or national organ sharing, CIT, and parenteral heparin use at the time of cross-clamping. Donor variables included organ steatosis content, age, ethnicity, cause of death, desmopressin (DDAVP) use for bleeding complications, cytomegalovirus status (IgG), and DRI that was dichotomized into high-risk and normal-risk donor (NRD) based on a previously validated cutoff of >1.7 [19,20]. The OPTN/UNOS dataset does not contain sufficient information regarding anticoagulant use for pre-existing venous thromboembolic disease nor does it contain variables specifying the presence of an inherited thrombophilic state.

Statistics

Using univariate logistic regression modeling, recipients with pretransplantation PVT were compared statistically to those without PVT in an effort to compare recipient, operative, and donor characteristics. Similarly, candidates

receiving an organ from a HRD were compared with recipients transplanted with an organ from a standard risk donor (SRD). The primary outcome was graft loss secondary to HAT within the first 90 days of transplantation. Multivariable logistic regression models were then constructed to assess statistical associations and risk factors for the development of HAT utilizing maximum-likelihood estimates. Variables were included in the final model only if they have previously been shown to be clinically relevant to the development of post-transplantation HAT or were statistically significant by univariate analysis ($P < 0.20$) [26,27]. Final variables included in the logistic regression model included recipient age at transplantation, gender, BMI, African American race, diabetes, HCC, HCV, cholestatic liver disease, autoimmune hepatitis, encephalopathy (which was divided into those with encephalopathy score >2), ascites (similarly divided by score >2), laboratories at transplantation (INR, bilirubin, creatinine, albumin, sodium), PVT, operative (heparin use at cross-clamp, and donor factors (age, gender, HRD, DDAVP). Interaction terms for PVT and HRD, HCV and donor age, NASH and BMI, and NASH and diabetes were included in the final model. Possible covariates for the PVT–HRD interaction variable included PVT with HRD, no PVT with HRD, as well as PVT with SRD. These were compared with a reference of no PVT with SRD. A p-value of less than or equal to 0.05 was considered statistically significant, and all tests were two-sided. Data imputation was not performed. SAS (version 9.4, Cary, NC, USA) was utilized for all analyses and dataset manipulation. The OPTN/UNOS dataset is deidentified; thus, institutional review board approval was not required. No transplantations involving prisoners were included in our analysis.

Results

A total of 60 404 recipients underwent liver transplantation from February 27, 2002, through March 31, 2015, and met our inclusion criteria; of these, 623 (1.0%) had HAT leading to early graft loss within 90 days of LT, which is similar to the accepted incidence of post-transplantation HAT [3]. Overall PVT prevalence was 7.5%, similar to the previously published rates using the OPTN/UNOS dataset [3]. Of the recipients with post-transplantation HAT, 66.0% ($n = 411$) received organs from HRDs compared with 49.3% ($n = 29\,473$) in recipients without HAT ($P < 0.001$). Pretransplant PVT was found in 13.5% ($n = 84$) of recipients with post-transplantation HAT versus 7.5% ($n = 4471$) in those without HAT ($P < 0.001$); 2250 (3.7%) recipients had pretransplantation PVT and received organs from HRDs.

On univariate analysis, recipient characteristics including demographics, etiology of liver disease, and severity of liver disease (both portal hypertension and laboratory values) were statistically similar or within marginal clinically important differences for patients with and without pretransplantation PVT (Table 1) and when comparing HRD with NRD (Table 2), with several exceptions. Recipients with PVT were more likely to have pretransplantation diabetes mellitus (30.2% vs. 22.8%, $P < 0.001$), NASH (17.4% vs. 10.9%, $P < 0.001$), HCC (26.4% vs. 21.7%, $P < 0.001$), and grade 3–4 ascites (32.2% vs. 27.8%, $P < 0.001$). Recipients with PVT were less likely to have underlying chronic HCV (25.3% vs. 30.2%, $P < 0.001$). In terms of surgical factors, heparin use at aortic cross-clamp was more common in recipients with pretransplantation PVT (89.8% vs. 84.8%, $P < 0.001$) and CIT was slightly longer in the PVT group (6.95 ± 3.34 h vs. 6.81 ± 3.43 h, $P = 0.015$).

In comparing recipients receiving HRD versus SRD organs, several notable differences were observed in baseline characteristics. Candidates who received an organ from a HRD were less likely to be male (64.6% vs. 69.6%, $P < 0.001$), be on dialysis at the time of liver transplantation (8.3% vs. 12.6%, $P < 0.001$), have underlying chronic HCV (27.7% vs. 31.8%, $P < 0.001$), have lower mean BMI (27.0 ± 5.66 kg/m^2 vs. 28.4 ± 10.2 kg/m^2, $P < 0.001$), and have lower mean MELD scores (20.3 ± 10.0 vs. 22.1 ± 10.6, $P < 0.001$) at transplantation with the corresponding differences in the individual MELD covariates (serum bilirubin 7.33 ± 9.97 mg/dl vs. 8.57 ± 11.2 mg/dl, $P < 0.001$; INR 1.83 ± 1.23 vs. 1.92 ± 1.28, $P < 0.001$; creatinine 1.45 ± 1.24 g/dl vs. 1.64 ± 1.48 g/dl, $P < 0.001$). Interestingly, the HRD group had a lower rate of anoxic donor death (11.5% vs. 25.6%, $P < 0.001$). Heparin use at aortic cross-clamp was less likely as well (81.8% vs. 88.5%, $P < 0.001$) as was DDAVP use (18.5% vs. 24.0%, $P < 0.001$). HRD organ recipients were more likely to receive organs from older donors (mean age 52.5 ± 14.5 years vs. 30.9 ± 11.1 years, $P < 0.001$), female donors (53.0% vs. 29.4%, $P < 0.001$), donors with a cerebrovascular attack as the cause of death (57.2% vs. 23.0%, $P < 0.001$), organ sharing both regionally (25.9% vs. 16.0%, $P < 0.001$) and nationally (9.2% vs. 0.5%, $P < 0.001$), and longer CIT (7.18 ± 4.08 h vs. 6.48 ± 2.58 h, $P < 0.001$). CMV donor positivity was also more common in the HRD organ recipients (71.0% vs. 60.6%, $P < 0.001$).

Multivariable regression analysis (Table 3) of risk factors for HAT with resultant graft loss within 90 days of liver transplantation demonstrated that in the presence of pretransplantation PVT, using an organ from a HRD was statistically significantly associated with an

Table 1. Recipient baseline characteristics comparing those with portal vein thrombosis (PVT) with those without PVT.

	Portal vein thrombosis (*n* = 4555)	No portal vein thrombosis (*n* = 55 849)	*P*-value
Recipient characteristics			
Age at transplant, mean years	55.7 ± 9.5	53.8 ± 10.2	<0.001
Male gender, *n* (%)	3191 (70.1)	37 350 (66.9)	<0.001
African American race, *n* (%)	285 (6.3)	5572 (10.0)	<0.001
Diabetes, *n* (%)	1376 (30.2)	12 740 (22.8)	<0.001
On dialysis at transplantation, *n* (%)	511 (11.2)	5821 (10.4)	NS
BMI, mean kg/m^2	28.7 ± 5.7	28.2 ± 5.7	<0.001
Etiology of liver disease, *n* (%)			
Alcoholic liver disease	500 (11.0)	6592 (11.8)	NS
Autoimmune disease	123 (2.7)	1384 (2.5)	NS
Cholestatic disease	275 (6.0)	4180 (7.5)	<0.001
Hepatitis B	75 (1.7)	1201 (2.2)	0.023
Hepatitis C	1151 (25.3)	16 847 (30.2)	<0.001
NASH	794 (17.4)	6058 (10.9)	<0.001
Other	1637 (35.9)	19 587 (35.0)	NS
Severity of liver disease			
MELD score at transplantation, mean	21.9 ± 9.8	21.2 ± 10.4	<0.001
HCC, *n* (%)	1204 (26.4)	12 136 (21.7)	<0.001
Ascites grade >2 at transplant, *n* (%)	1465 (32.2)	15 533 (27.8)	<0.001
HE >2 at transplant, *n* (%)	474 (10.4)	6124 (11.0)	NS
Laboratory values			
Serum bilirubin, mg/dl, mean	7.74 ± 10.72	7.79 ± 10.52	NS
INR, mean	1.89 ± 0.97	1.87 ± 1.28	NS
Serum albumin, g/dl, mean	3.03 ± 0.73	3.03 ± 0.73	NS
Creatinine, g/dl, mean	1.54 ± 1.16	1.55 ± 1.38	NS
Serum sodium, mEq/l, mean	135.7 ± 5.2	136.1 ± 5.2	<0.001
Donor characteristics			
Age donor, mean years	41.7 ± 16.9	41.5 ± 16.8	NS
Male donor, *n* (%)	2678 (58.8)	32 904 (58.9)	NS
African American donor, *n* (%)	803 (17.6)	9120 (16.3)	0.023
Anoxic cause of death, *n* (%)	969 (21.3)	10 289 (18.4)	<0.001
Cerebrovascular attack as cause of death, *n* (%)	1786 (39.3)	22 315 (40.0)	NS
Regional organ sharing, *n* (%)	924 (20.3)	11 704 (21.0)	NS
National organ sharing, *n* (%)	210 (4.6)	2683 (4.8)	NS
CMV donor positivity *n* (%)	2860 (65.5)	35 000 (65.5)	NS
DRI, mean	1.77 ± 0.40	1.78 ± 0.40	NS
High-risk donor (DRI >1.7), *n* (%)	2250 (49.4)	27 634 (49.5)	NS
Macrovesicular fat content of donor liver, mean percentage	8.3 ± 11.7	8.5 ± 12.1	NS
Surgical characteristics			
Heparin use at cross-clamp, *n* (%)	4091 (89.8)	47 372 (84.8)	<0.001
DDAVP use, *n* (%)	66 (1.5)	396 (0.7)	<0.001
CIT, mean hours	6.95 ± 3.34	6.81 ± 3.43	0.015

BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CMV, cytomegalovirus; DRI, donor risk index; DDAVP, desmopressin; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis; NS, not significant; PVT, portal vein thrombosis.

increased risk of post-transplantation HAT with OR 3.56, 95% CI 2.52–5.012, $P < 0.001$. Recipients with pretransplantation PVT who received an organ from a SRD still had an increased odds of post-transplantation HAT (OR 2.25, 95% CI 1.48–3.42, $P < 0.001$) as did recipients without pretransplantation PVT who received a HRD organ (OR 1.71, 95% CI 1.36–2.14, $P < 0.001$). Other factors protective against HAT included creatinine values at transplantation (OR 0.91, 95% CI 0.83–0.99, $P = 0.035$), heparin use at cross-clamp (OR

Table 2. Baseline characteristics of high-risk donors compared with low-risk donors.

	High-risk donor (n = 29 884)	Low-risk donor (n = 30 520)	P-value
Recipient characteristics			
Age at transplant, mean years	54.4 ± 10.1	53.4 ± 10.2	<0.001
Male gender, *n* (%)	19 291 (64.6)	21 250 (69.6)	<0.001
African American race, *n* (%)	2681 (9.0)	3176 (10.4)	<0.001
Diabetes, *n* (%)	7151 (23.9)	6965 (22.8)	0.001
On dialysis at transplantation, *n* (%)	2476 (8.3)	3856 (12.6)	<0.001
BMI, mean kg/m^2	27.0 ± 5.66	28.4 ± 5.66	<0.001
Etiology of liver disease, *n* (%)			
Alcoholic liver disease	3578 (12.0)	3514 (11.5)	NS
Autoimmune disease	726 (2.4)	781 (2.6)	NS
Cholestatic disease	2530 (8.5)	1925 (6.3)	<0.001
Hepatitis B	648 (2.2)	628 (2.1)	NS
Hepatitis C	8279 (27.7)	9719 (31.8)	<0.001
NASH	3584 (12.0)	3268 (10.7)	<0.001
Other	10 539 (35.3)	10 685 (35.0)	NS
Severity of liver disease			
MELD score at transplantation, mean	20.3 ± 10.0	22.1 ± 10.6	<0.001
HCC, *n* (%)	6688 (22.4)	6652 (21.8)	NS
PVT, *n* (%)	2250 (7.5)	2305 (7.6)	NS
Ascites grade >2 at transplant, *n* (%)	8041 (26.9)	6957 (29.4)	<0.001
HE >2 at transplant, *n* (%)	3065 (10.3)	3534 (11.6)	<0.001
Laboratory values			
Serum bilirubin, mg/dl, mean	7.33 ± 9.97	8.57 ± 11.20	<0.001
INR, mean	1.83 ± 1.23	1.92 ± 1.28	<0.001
Serum albumin, g/dl, mean	3.04 ± 0.72	3.01 ± 0.73	<0.001
Creatinine, g/dl, mean	1.45 ± 1.24	1.64 ± 1.48	<0.001
Serum sodium, mEq/l, mean	136.1 ± 5.20	136.1 ± 5.20	NS
Donor characteristics			
Age donor, mean years	52.5 ± 14.5	30.9 ± 11.1	<0.001
Male donor, *n* (%)	14 043 (47.0)	21 539 (70.6)	<0.001
African American donor, *n* (%)	5346 (17.9)	4577 (15.0)	<0.001
Anoxic cause of death, *n* (%)	3447 (11.5)	7811 (25.6)	<0.001
Cerebrovascular attack as cause of death, *n* (%)	17 078 (57.2)	7023 (23.0)	<0.001
Regional organ sharing, *n* (%)	7744 (25.9)	4884 (16.0)	<0.001
National organ sharing, *n* (%)	2756 (9.2)	137 (0.5)	<0.001
CMV donor positivity *n* (%)	19 507 (71.0)	18 353 (60.6)	<0.001
Macrovesicular fat content of donor liver, mean percentage	8.54 ± 11.88	8.41 ± 12.43	NS
Surgical characteristics			
Heparin use at cross-clamp, *n* (%)	24 453 (81.8)	27 010 (88.5)	<0.001
DDAVP use, *n* (%)	5526 (18.5)	7321 (24.0)	<0.001
CIT, mean hours	7.18 ± 4.08	6.48 ± 2.58	<0.001

BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CMV, cytomegalovirus; DRI, donor risk index; DDAVP, desmopressin; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis; NS, not significant; PVT, portal vein thrombosis.

0.61, 95% CI 0.47–0.79, $P < 0.001$), INR values at transplantation (OR 0.87, 95% CI 0.76–0.98, $P = 0.027$), and receiving an organ from a male donor (OR 0.53, 95% CI 0.44–0.64, $P < 0.001$). These recipient, surgical, and donor factors were all independently associated with a lower risk of HAT and early graft loss. While significant on univariate analysis, diabetes was not found to be independently predictive with multivariable regression modeling (OR 0.88, 95% CI 0.68–1.14, $P = 0.318$). Recipient age at transplantation was statistically significant on both univariate and multivariable analyses and for each year of age a recipient's risk of HAT decreased by 2% (OR 0.98, 95% CI 0.97–0.99, $P < 0.001$).

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Table 3. Univariate and multivariable analyses of risk factors for graft loss due to hepatic artery thrombosis within 90 days of liver transplantation.

	Univariate analysis (OR, 95% CI)	Multivariable analysis (OR, 95% CI)	*P*-values for multivariable model
Recipient characteristics			
Age at transplant, mean years	0.98 (0.98–0.99)	0.98 (0.97–0.99)	0.001
Male gender	0.94 (0.79–1.11)		
African American race	1.05 (0.81–1.36)		
Diabetes	0.78 (0.64–0.95)	0.88 (0.68–1.14)	0.318
On dialysis at transplantation	0.79 (0.60–1.04)		
BMI, mean kg/m^2	1.01 (0.99–1.02)		
Etiology of liver disease			
Alcoholic liver disease	0.91 (0.70–1.17)		
Autoimmune disease	1.37 (0.85–2.12)		
Cholestatic disease	1.24 (0.94–1.64)		
Hepatitis B	1.07 (0.63–1.82)		
Hepatitis C	0.97 (0.82–1.16)		
NASH	1.14 (0.90–1.44)		
Severity of liver disease			
HCC	0.82 (0.67–1.01)		
Ascites grade >2 at transplant	0.90 (0.85–1.07)		
HE >2 at transplant	1.08 (0.85–1.39)		
Laboratory values			
Serum bilirubin, mg/dl	0.99 (0.98–1.00)		
INR	0.88 (0.79–0.97)	0.87 (0.76–0.98)	0.027
Serum albumin, g/dl	0.97 (0.87–1.08)		
Creatinine, g/dl	0.92 (0.86–0.98)	0.91 (0.83–0.99)	0.035
Serum sodium, mEq/l	0.99 (0.98–1.01)		
Donor characteristics			
Male donor	0.52 (0.45–0.61)	0.53 (0.44–0.64)	<0.001
High DRI	1.99 (1.69–2.35)	—	
Macrovesicular fat content of donor liver	1.00 (0.96–1.01)		
Surgical characteristics			
Heparin use at cross-clamp	0.52 (0.43–0.63)	0.61 (0.47–0.79)	0.002
DDAVP use	0.90 (0.74–1.10)		
Thrombosis			
PVT and HRD*	3.84 (2.83–5.21)	3.56 (2.52–5.02)	<0.001
No PVT and HRD*	2.00 (1.67–2.39)	2.25 (1.49–3.42)	<0.001
PVT and SRD*	1.95 (1.32–2.89)	1.71 (1.36–2.15)	<0.001
PVT	1.93 (1.53–2.43)	—	

Final variables included in the logistic regression model included recipient age at transplantation, gender, BMI, African American race, diabetes, HCC, HCV, cholestatic liver disease, autoimmune hepatitis, encephalopathy (which was divided into those with encephalopathy score >2), ascites (similarly divided by score >2), laboratories at transplantation (INR, bilirubin, creatinine, albumin, sodium), PVT, operative (heparin use at cross-clamp, and donor factors (age, gender, HRD, DDAVP). Interaction terms for PVT and HRD, HCV and donor age, NASH and BMI, and NASH and diabetes were included in the final model. Possible covariates for the PVT–HRD interaction variable included PVT with HRD, no PVT with HRD, as well as PVT with SRD.

BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CMV, cytomegalovirus; DRI, donor risk index; DDAVP, desmopressin; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; HRD, high-risk donor (DRI >1.7); INR, international normalized ratio; NASH, nonalcoholic steatohepatitis; NS, not significant; PVT, portal vein thrombosis; SRD, standard risk donor (DRI ≤1.7).

*Compared with reference group of no PVT and NRD.

Discussion

Based on a large U.S.-based national liver transplantation database and after adjusting for known donor, recipient, and surgical risk factors, we have found that liver transplant recipients with pretransplant PVT who receive an organ from a HRD (DRI >1.7) are at

increased odds of post-transplantation HAT. These findings lend credence to the consideration of more than just surgical technique and CIT in determining a recipient's risk for HAT, especially in the setting of pretransplantation coagulation abnormalities, including PVT, which by itself is associated with higher rates of primary graft nonfunction and re-transplantation [16]. With the increasing utilization of HRDs to meet the organ supply and demand issue [28], it appears we can expect more issues with early graft loss from post-transplantation thrombosis and we would suggest this patient population as a potential target recipient for more aggressive postoperative care and prevention, certainly in the presence of pretransplantation venothromboembolic disease.

Our findings also raise the question "What is the most appropriate pre-, peri-, and postoperative management strategy for anticoagulation?" Efficacy data on routine administration of antiplatelet agents (namely aspirin) for the prevention of postoperative HAT are mixed and complicated by retrospective study limitations including varying time definitions of early and late HAT; however, aspirin does appear safe as bleeding events are generally infrequent [29–31]. We are unaware of any studies looking at dual antiplatelet therapy as prophylaxis. Our Coagulation in Liver Disease Study Group recently published a series of 39 patients with cirrhosis comparing the safety of utilizing direct oral anticoagulants (DOAC) (factor Xa inhibitors apixaban and rivaroxaban) with traditional anticoagulants warfarin and low molecular weight heparin (LMWH) and found the similar safety profiles in terms of bleeding and no episodes of drug-induced liver injury [32]. The bleeding rate of 5% with DOAC and the absence of fatal bleeding were similar to the pooled incidence from a recent meta-analysis of 16 studies by Qi *et al.* [33] who found a pooled rate of 3.3% for LMWH or warfarin use, 95% CI 1.1–6.7%. The widespread use of DOACs may be limited by the lack of currently available reversal agents, although a recent randomized placebo-controlled study of 101 healthy older adults, none of whom had liver disease, by Siegal *et al.* [34] utilizing intravenous andexanet alpha holds promise. While the exact role of DOACs in the management of perioperative coagulopathy unique to liver transplantation recipients has yet to be firmly established, these data are nonetheless promising and provide a starting point for future prospective study. Given that there are significant hemostatic abnormalities in the peri- and postoperative periods that may interact to create a hypercoagulable milieu [35], it seems that DOAC use in recipients at high risk for post-transplantation thrombotic complications could be considered at least until the coagulability equilibrium shifts away from a prothrombotic state, the timing of which could be aided by the routine use of post-transplantation thromboelastography (TEG), a method for determining the real-time viscous and elastic properties of blood and blood clot.

While PVT is a common complication in patients with cirrhosis [13,14] and is associated with both increased hepatic decompensation and mortality [15], prospective studies with a direct comparator group examining both pharmacologic prevention and treatment for PVT are lacking and consensus guidelines on preoperative management of PVT have yet to be disseminated. Nonetheless, several unblinded single-center studies have found the regression of liver disease with the mitigation of portal hypertensive complications as well as a long-term survival benefit with either daily prophylactic (the equivalent of 40 mg/day) [36] or therapeutic dosing (1 mg/kg every 12 h or 1.5 mg/kg daily) [37] of low molecular weight heparin. Following these studies, multicenter investigation of the safety and efficacy of prevention of PVT with pharmacologic anticoagulation is currently underway with the anticipated results within the next 5 years.

A recent multicenter Canadian experience with 118 liver transplant recipients published by Seal *et al.* [38] found that intraoperative use of tissue plasminogen activator (tPA) directly into the donor hepatic artery either before hepatic artery anastomosis or before portal vein anastomosis (5–10 min before portal reperfusion) reduced the complications from ischemic biliary strictures and led to superior one- and three-year overall and graft survival rates in recipients receiving DCD organs and significantly lower re-transplantation rates in the absence of increased bleeding. While the authors did not look specifically at HAT and others have argued that the inherent profound activation of fibrinolysis with withdrawal of life support is enough to prevent the significant downstream ischemic thrombotic biliary complications [39], these findings are, nonetheless, thought provoking given that no deaths or graft loss was attributable to HAT in the tPA group. These findings combined with our findings that intraoperative administration of heparin at the time of aortic cross-clamping is associated with a lower risk of HAT lend importance to further consideration of perioperative anticoagulation when using organs from HRDs.

Our study has several weaknesses worth noting. Despite the aggressive verification by auditors and data technicians, large datasets are dependent on diagnostic coding accuracy to preclude the induction of information

bias and also suffer from bias due to missing data, and the OPTN/UNOS database is no exception to this rule [40]. Our method of handling the missing data provided similar incidence rates of HAT when compared with those published by other study groups who utilized the UNOS database to investigate HAT. The OPTN/UNOS database also does not contain information on preoperative anticoagulant use nor does it provide information on inherited thrombophilia testing. However, previous study has found the incidence of inherited thrombophilia to be similar when comparing recipients who experience post-transplantation HAT with those who do not [1]. The database also does not contain a description of the extent of pretransplantation PVT, including which specific vessels are involved and whether the clot is partial or complete, nor does it contain information regarding the method of surgical reconstruction including arterial reconstruction, which is arguably the most technically challenging aspect of liver transplant surgery and has been implicated in post-transplantation complications including HAT [5,6,41–44]. Information on the extent of hepatic hilar manipulation during portal vein reconstruction is also lacking. This may predispose to hepatic artery injury or rethrombosis of the portomesenteric veins [45]. Interestingly, a recent single-center experience of 10 patients with grade 4 PVT suggests that intraoperative renoportal bypass combined with the direct measurements of portal vein and hepatic artery flow may be used successfully to mitigate post-transplantation complications including primary graft nonfunction and mortality associated with pretransplantation PVT [46]. Creating renoportal or cavoportal anastomoses in transplant recipients with pretransplantation PVT may also decrease the risk of post-transplantation vascular complications [47].

Conclusions

Liver transplant candidates with pretransplant PVT who receive an organ from a HRD are at the highest risk for postoperative HAT independent of other measurable recipient, surgical, and donor factors. Utilizing a DRI cutoff of 1.7 in order to prevent postoperative vascular thrombotic complications may be useful. Recipients with pretransplant PVT would benefit from careful donor selection and the consideration of aggressive perioperative anticoagulation to improve the patient-centered outcomes.

Authorship

JS and PN: involved in planning/conducting the study, collecting and/or interpreting the data, drafting the manuscript, and final approval. SP, CA and DM: involved in drafting the manuscript and final approval. PGN: guarantor of the article.

Funding

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK007769.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

Acknowledgements

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was supported in part by Health Resources and Services Administration Contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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