ORIGINAL ARTICLE

Pre-transplant portal vein thrombosis is an independent risk factor for graft loss due to hepatic artery thrombosis in liver transplant recipients

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Abstract

Background: Hepatic artery thrombosis is an uncommon but catastrophic complication following liver transplantation. We hypothesize that recipients with portal vein thrombosis are at increased risk.

Methods: Data on all liver transplants in the U.S. during the MELD era through September 2014 were obtained from UNOS. Status one, multivisceral, living donor, re-transplants, pediatric recipients and donation after cardiac death were excluded. Logistic regression models were constructed for hepatic artery thrombosis with resultant graft loss within 90 days of transplantation.

Results: 63,182 recipients underwent transplantation; 662 (1.1%) recipients had early hepatic artery thrombosis; of those, 91 (13.8%) had pre-transplant portal vein thrombosis, versus 7.5% with portal vein thrombosis but no hepatic artery thrombosis ($p < 0.0001$). Portal vein thrombosis was associated with an increased independent risk of hepatic artery thrombosis (OR 2.17, 95% CI 1.71–2.76, $p < 0.001$) as was donor risk index (OR 2.02, 95% CI 1.65–2.48, $p < 0.001$). Heparin use at cross clamp, INR, and male donors were all significantly associated with lower risk.

Discussion: Pre-transplant portal vein thrombosis is associated with post-transplant hepatic artery thrombosis independent of other factors. Recipients with portal vein thrombosis might benefit from aggressive coagulation management and careful donor selection. More research is needed to determine causal mechanism.

Received 5 October 2015; accepted 12 October 2015

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Introduction

Hepatic artery thrombosis (HAT) is an uncommon complication with incidence 2–4% following liver transplantation (LT), often leading to catastrophic complications of graft loss and patient death.[12,39,50] Several well-identified risk factors relating to surgical technique[16,20] and delay in reperfusion or abnormal arterial anatomy in the graft have been identified.[16] Advanced donor age remains controversial as a risk factor as it has been shown to be both associated[30,47] with increased HAT, in particular late graft loss from HAT,[23] but generally regarded as less important than surgical technique and cold ischemia times.[20] Other risk factors for HAT include donors who died of a cerebrovascular accident, and recipients of previous LT.[42,47] Other recipient-specific risk factors are less well defined, but HAT has been reported in the setting of pre-existing inherited thrombophilia,[34,36] acute intermittent porphyria,[28] primary sclerosing cholangitis,[43] and post-LT diabetes.[24] In general the data for these are less strongly supported than that describing surgical risk factors.

The fields of coagulation disorders, chronic liver disease and portal vein thrombosis (PVT) are ever evolving and continue to be controversial. PVT is common; prevalence rates range from 7 to 25%[17,27,32,45] and up to 36% of recipients have PVT on direct explant examination at the time of LT.[11] To date,

Abbreviations

BMI	body mass index
CMV	cytomegalovirus
DDAVP	desmopressin
DRI	donor risk index
HAT	hepatic artery thrombosis
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
INR	international normalized ratio
LT	liver transplant
MTHFR	methylenetetrahydrofolate reductase
NASH	non-alcoholic steatohepatitis
OPTN	organ procurement and transplantation network
PVT	portal vein thrombosis
SBP	spontaneous bacterial peritonitis
TEG	thromboelastrography
TIPS	transjugular intrahepatic portosystemic shunt
UNOS	united network for organ sharing

multiple studies have been published indicating adverse clinical outcomes in the setting of PVT with or without transplant including hepatic decompensation, increased post-transplant mortality and decreased quality of life.[8–10,15] While coagulation abnormalities in patients with chronic liver disease are well described,[6,7] several coagulation abnormalities have been specifically identified in patients with PVT including Factor V Leiden and prothrombin 20210A mutations,[5,44] and possibly low Factor VIII levels.[29] A single center, un-blinded randomized trial revealed that prophylactic dosing of low-molecular weight heparin can prevent the development of PVT, an effect that persists out five-years.[4] Regardless, others have argued that PVT does not lead to adverse outcomes.[26] In this retrospective nationwide United States cross-sectional study of liver transplant recipients, we aimed to examine the independent association between HAT and LT recipient and donor risk factors to investigate the hypothesis that recipients with pre-transplant PVT are at increased risk for early HAT resulting in graft loss within the first 90 days of LT.

Methods

Study design and recipient characteristics

Data on all LTs occurring in the United States between February 1, 2002 and September 30, 2014 were obtained from the Organ and Transplantation Network (OPTN) with permission from the United Network for Organ Sharing (UNOS). This nationwide database has been previously validated to analyze HAT in the liver transplant population.[14,23] Only recipients who were listed for transplantation at or above age 18 were included in the analysis. All transplantations for acute liver failure, status one candidates, multi-visceral transplants, re-transplants, and living donor transplants were excluded. The analysis was performed both with and without donation after cardiac death recipients and the fundamental conclusions of the statistical analysis was not changed. Thus, donation after cardiac death was excluded due to the higher rate of complications for reasons not related to thrombosis. Recipients were then sorted into two groups: those with HAT and those without. In the dataset, the cause of graft loss was reported as one of the following choices: "vascular thrombosis, biliary, primary nonfunction, recurrent hepatitis, de novo hepatitis, acute rejection, chronic rejection, infection or recurrent disease." There is also a write-in field labeled as "other". Based on the "vascular thrombosis" and "other" category searched for "hepatic artery thrombosis," HAT was further dichotomized into early HAT resulting in graft loss at or before 90 days post LT and late HAT based on previous studies.[22,46] Recipients with incomplete HAT data (unknown status or missing) were considered to not have HAT in order to avoid inducing selection and reporting bias. Recipients who developed HAT after 90 days post transplantation were excluded.

Baseline demographic characteristics were reviewed, including recipient characteristics, etiology of liver disease (hepatitis C, hepatitis B, alcoholic liver disease, NASH/cryptogenic, autoimmune, liver malignancy, cholestatic and other, which included any patients coded for any other reason for transplant besides the aforementioned categories), severity of liver disease based on MELD score at the time of allocation, other laboratory values, infection, hepatocellular carcinoma, transplant year and portal hypertension manifestations. Operative (organ sharing, cold ischemia time defined as the time from donor aorta clamping until the anastomosis of the organ to the vascular system of the recipient) and donor characteristics (age, race, cause of death, cytomegalovirus status, donor risk index (DRI), desmopressin (DDAVP) use given that it is known to marginate platelets and lead to a hypercoagulable state,[38] intravenous heparin use at the time of cross clamp) were also analyzed as were day of discharge laboratory values and length of stay.

Outcomes definition

Analyses were performed comparing recipients with HAT to the non-HAT group. Our primary outcome was graft loss secondary to HAT within the first 90 days of transplantation (early HAT). Data were incomplete to sufficiently review regarding the presence of concurrent inherited thrombophilic disorder and/or treatment of pre-existing clots with anticoagulation before or after transplantation.

Statistics

Recipients with HAT were compared to those without HAT statistically in multiple factors including demographics, waiting list characteristics, medical comorbidities, transplantation characteristics, outcomes and operative factors to identify statistically significant predictors of early HAT. Multivariable