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.

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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,

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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

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models were constructed to assess statistical associations and risk factors for the development of HAT. Individual covariates were included in the multivariable model if they were statistically significant in the univariate analysis ($p < 0.20$) or have been shown in the literature to be clinically important.[3,19] Univariate comparisons were performed using the Fisher exact test, chi-square test, Wilcoxon sign rank test or Student-t test, as appropriate for categorical or continuous data. Multivariable models were constructed using logistic regression and analysis of the maximum likelihood estimates. Final variables included in the regression model included recipient age, gender, African American race, hepatocellular carcinoma, spontaneous bacterial peritonitis, hepatitis C, cholestatic liver disease, encephalopathy (which was dichotomized into those with severe encephalopathy with score >2), ascites (similarly dichotomized), PVT, final INR, final bilirubin, final creatinine, final albumin, final sodium, NASH, diabetes mellitus pre-transplant, DRI, BMI, heparin use intravenously at the time of cross clamp and DDAVP use in the donor. Interactions terms for diabetes and NASH and NASH and BMI were evaluated and were not included in the final model as this did not change the odds ratios significantly. 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. Because the OPTN data set is de-identified, institutional review board approval was not required for this study.

Results

63,182 recipients underwent liver transplantation during the MELD era through September 2014; of these, 662 (1.05%) had HAT leading to early graft loss within 90 days of LT. 62,520 recipients did not have HAT. On univariate analysis, background demographics, severity of liver disease including manifestations of portal hypertension and laboratory values, were in general statistically similar or within marginal clinically important differences for patients with and without HAT, with several exceptions. (Table 1 and Table 2) 91 (13.8%) recipients with HAT had pre-transplant PVT, versus 7.5% without HAT ($p < 0.0001$). Recipients with HAT were slightly younger (51.8 years, 95% CI 51.0–52.6) than those without HAT (53.9 years, 95% CI 53.8–54.0, $p < 0.001$) and were less likely to have diabetes (20.2% vs. 23.6%, $p = 0.046$).

Additionally, recipients experiencing graft loss due to early HAT were transplanted at lower MELD scores (19.9, 95% CI 19.2–20.6 vs. 21.3 95% CI 21.2–21.4, $p < 0.001$), and had lower INR values (1.74, 95% CI 1.69–1.80 vs. 1.87, 95% CI 1.86–1.88 $p = 0.006$). Serum creatinine at the time of transplantation was slightly lower for recipients with HAT (1.43 g/dL, 95% CI 1.32–1.54 vs. 1.54, 95% CI 1.53–1.55, $p = 0.034$).

In terms of donor characteristics and surgical considerations, recipients with HAT were less likely to receive organs from male donors (43.7% vs. 59.1%, $p < 0.001$) and less likely to receive organs from donors with an anoxic cause of death (12.4% vs. 18.2%, $p < 0.001$). Heparin use at the time of cross-clamp (75.7% vs. 91.9%, $p < 0.001$) was less common in recipients with HAT. DRI was greater for recipients with HAT (1.97, 95% CI 1.93–2.00 vs. 1.97, 95% CI 1.93–2.00, $p < 0.001$) as was cold ischemia time (7.31 h, 95% CI 6.96–7.65 vs. 6.87, 95% CI 6.84–6.89, $p = 0.002$).

In terms of PVT, 7.6% (n = 465) recipients had pre-transplant PVT, which is similar to the accepted prevalence of PVT.[17,27,32,45] 5669 did not have pre-transplant PVT (92.4%). Of the 465 recipients with pre-transplant PVT, 19.6% (n = 91) had post-transplant HAT; 10.1% (n = 571) of recipients without pre-transplant PVT had post-transplant HAT ($p < 0.001$).

In a multivariable analysis of risk factors for HAT, pre-transplant PVT was independently associated with a diagnosis of HAT with resultant graft loss within 90 days of LT (OR 2.17, 95% CI 1.71–2.76, $p < 0.001$) (Table 3). DRI (OR 2.02, 95% CI 1.65–2.48, $p < 0.001$) and BMI (1.02, 95% CI 1.00–1.03, $p = 0.042$) were also associated with increased risk of HAT. Other statistically significant factors included recipient age (OR 0.98, 95% CI 0.98–0.99), final INR (OR 0.84, 95% CI 0.74–0.96, $p < 0.001$), male donors (OR 0.59, 95% CI 0.49–0.71, $p < 0.001$) and heparin use at cross clamp (OR 0.67, 95% CI 0.52–0.87, $p = 0.002$). These covariates were all independently associated with a lower risk of HAT and early graft loss, several of which may be protective. Recipient age, diabetes, serum creatinine levels, anoxic cause of death, while significant on univariate analysis, were not found to be independently predictive in multivariable regression modeling.

Discussion

In our study, based on a large national transplant database, we document an independent cross-sectional association showing increased risk of early HAT with resultant graft loss in LT recipients with pre-transplant PVT. This difference was seen despite adjustment for known risk factors for HAT including donor, recipient and surgical factors such as cold ischemia time and organ sharing policies accounted for in the DRI. This argues for the consideration of recipient specific characteristics in determining and counseling patients regarding the risk of post-transplant HAT. Thoughtful donor selection by the liver transplant teams based on the DRI will be augmented by consideration of recipient factors when accepting an organ offer. This is especially important with the increasing use of high-risk donors[48] as the higher risk the donor the more likely early graft loss is to occur,[2] a finding we found to hold true as DRI was predictive of early graft loss from HAT. In other words, placement of a high-risk organ in a recipient at high-risk for HAT may deserve special consideration. Furthermore, we suggest that

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Table 1 Baseline characteristics of recipients with and without hepatic artery thrombosis within 90 days post-transplantation

	Hepatic artery thrombosis (n = 662)	No hepatic artery thrombosis (n = 62,520)	p-value
Recipient characteristics			
Age at transplant, mean years (95% CI)	51.8 (51.0–52.6)	53.9 (53.8–54.0)	<0.001
Male gender, n	436 (65.9%)	42,033 (67.2%)	0.455
African American race, n	63 (9.5%)	5779 (9.2%)	0.809
Diabetes, n	134 (20.2%)	14,723 (23.6%)	0.046
Transplant for liver malignancy (including HCC), n	122 (18.4%)	13,191 (20.1%)	0.094
TIPS, n	42 (7.5%)	5341 (8.6%)	0.081
On dialysis at transplantation, n	55 (8.3%)	6502 (10.4%)	0.079
BMI, mean kg/m^2 (95% CI)	28.4 (27.9–28.9)	28.2 (28.2–28.3)	0.051
Etiology of liver disease, n			
Alcohol alone	72 (10.9%)	7577 (12.1%)	0.329
Autoimmune disease	22 (3.3%)	1555 (2.5%)	0.170
Cholestatic disease	60 (9.1%)	4521 (7.2%)	0.071
Hepatitis B	15 (2.3%)	1326 (2.1%)	0.797
Hepatitis C	193 (29.2%)	19,153 (30.6%)	0.411
NASH	87 (13.1%)	7228 (11.6%)	0.206
Other	213 (32.2%)	21,160 (33.8%)	0.244
Severity of liver disease			
MELD score at transplantation, mean (95% CI)	19.9 (19.2–20.6)	21.3 (21.2–21.4)	<0.001
HCC, n	122 (18.4%)	13,191 (21.1%)	0.094
SBP, n	21 (3.2%)	1702 (2.7%)	0.480
PVT, n	91 (13.8%)	4696 (7.5%)	<0.001
Laboratory values			
Serum bilirubin, mg/dL, mean (95% CI)	7.3 (6.5–8.1)	7.8 (7.7–7.9)	0.182
INR, mean (95% CI)	1.74 (1.69–1.80)	1.87 (1.86–1.88)	0.006
Serum albumin, g/dL, mean (95% CI)	2.99 (2.93–3.04)	3.0 (2.99–3.00)	0.745
Creatinine, g/dL, mean (95% CI)	1.43 (1.32–1.54)	1.54 (1.53–1.55)	0.034
Sodium, mEq/L, mean (95% CI)	136.0 (135.5–136.4)	136.1 (136.0–136.3)	0.681
Portal hypertension manifestations			
Ascites grade > 2 at transplant, mean (95% CI)	172 (26.0%)	17,897 (28.7%)	0.134
Hepatic encephalopathy > 2 at transplant, mean (95% CI)	78 (11.8%)	6972 (11.2%)	0.608

patients at high risk for early graft loss from HAT may benefit from aggressive clotting risk management in the pre-and possibly post-transplantation phases. This would need to be validated with future prospective study.

To date, most HAT research has focused on surgical risk factors including cold ischemia time. A prolonged cold ischemia time greater than 12 h predisposes to HAT.[31] Arterial reconstruction, including the use of a cadaveric iliac jump graft, which is arguably the most technically difficult part of a liver transplant, has been shown repeatedly to predispose a recipient to HAT.[16,31,37,40,47] Suture type has also been associated with varying risk of HAT.[25] Additionally, small vessel size also predisposes to HAT, especially in the pediatric population.[13,21] Following development of acute PVT, hepatic blood flow is significantly reduced.[33] Vasodilation and increased flow in the hepatic artery is the first compensatory mechanism following this insult.[33,49] This "arterial rescue" leads to an increase in hepatic artery diameter in the setting of PVT which should theoretically make the arterial anastomosis less technically challenging, especially as this effect persists over time, and help overcome some of the difficulties with small vessel diameter. Moreover, the increased arterial flow in patients with preexisting PVT should lower the risk of HAT after transplantation as flow is an important component of the classical triad of Virchow in the

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Table 2 Baseline characteristics of donors and surgical considerations for recipients with and without hepatic artery thrombosis within 90 days post-transplantation

	Hepatic artery thrombosis (n = 662)	No hepatic artery thrombosis (n = 5472)	p-value
Age donor, mean years (95% CI)	42.7 (41.4–44.1)	41.6 (41.4–41.7)	0.074
Male donor, n	289 (43.7%)	36,934 (59.1%)	<0.001
African American donor, n	120 (18.1%)	10,182 (16.3%)	0.202
Anoxic cause of death, n	82 (12.4%)	11,376 (18.2%)	<0.001
Cerebrovascular attack as cause of death, n	296 (44.7%)	25,044 (40.0%)	0.322
Regional organ sharing, n	143 (21.6%)	12,714 (20.3%)	0.091
National organ sharing, n	43 (6.5%)	3043 (4.9%)	0.107
CMV donor positivity n	383 (65.0%)	39,316 (65.6%)	0.324
Heparin use at cross clamp, n	501 (75.7%)	53,105 (91.9%)	<0.001
Desmopressin use (DDAVP), n	127 (19.2%)	13,667 (21.9%)	0.097
Cold ischemia time, mean hours (95% CI)	7.31 (6.96–7.65)	6.87 (6.84–6.89)	0.002
Donor risk index, mean (95% CI)	1.97 (1.93–2.00)	1.78 (1.77–1.78)	<0.001
Macrovesicular fat content of donor liver (%)	8.2 (6.5–9.9%)	8.5 (8.3–8.6)	0.794

Table 3 Multivariable analysis for predictors of hepatic artery thrombosis (HAT) within 90 days of transplantation. An odds ratio greater than 1.0 indicates a relative risk for development of HAT while an odds ratio of less than 1.0 indicates protection from development of HAT

	Odds ratio	95% CI	p value
Recipient factors			
Age (years)	0.98	0.98–0.99	<0.001
Male	1.09	0.90–1.32	0.360
African American	1.14	0.84–1.53	0.410
HCC	0.92	0.70–1.21	0.546
SBP	1.43	0.80–2.56	0.229
HCV	0.98	0.76–1.25	0.837
Encephalopathy >2	1.28	0.96–1.72	0.094
Ascites >2	0.89	0.72–1.11	0.312
PVT	2.17	1.71–2.76	<0.001
Cholestatic disease	0.94	0.65–1.35	0.735
INR	0.84	0.74–0.96	<0.001
Bilirubin (mg/dL)	1.00	0.99–1.01	0.889
Creatinine (g/dL)	0.94	0.87–1.02	0.134
Albumin (g/dL)	1.00	0.88–1.14	0.947
BMI (m^2/kg)	1.02	1.00–1.03	0.042
NASH	1.24	0.92–1.67	0.154
Diabetes	0.88	0.70–1.10	0.250
Sodium (mEq/L)	0.99	0.98–1.01	0.445
Donor/Surgical factors			
Male donor	0.59	0.49–0.71	<0.001
Heparin use at cross clamp	0.67	0.52–0.87	0.002
Donor risk index	2.02	1.65–2.48	<0.001
Desmopressin (DDAVP) use	0.97	0.74–1.28	0.294

pathogenesis of intravascular thrombosis. However, we did not observe this in the current study; pre-transplant PVT was associated with increased risk of early graft loss from HAT indicating that while surgical technique factors are certainly well established, there are alternative covariates that must be considered beyond that of arterial reconstruction.

The exact mechanism of HAT in recipients with pre-transplant PVT is unknown. We do know that in the post LT period, high levels of von Willebrand factor, increased thrombin generation, hyperfibrinolysis and low levels of ADAMTS13 all create a hypercoagulable milieu.[35] Furthermore, low levels of antithrombin III and high levels of factor VIII are found in recipients with HAT.[12] Many of these imbalances are also found in patients with PVT in the pre-transplant setting,[12] however they are also found in patients with NASH or NASH cirrhosis without PVT and thus are non-specific markers of thrombosis. They may be a part of the causal pathway as a mediator rather than a marker.[41] We speculate that early HAT could be due to ongoing endothelial dysfunction, continued mileu of hypercoagulability and resultant thrombus generation and that it takes some time to shift back towards equilibrium post-transplant.[41] This, combined with surgical technique and cold ischemia time makes donor selection even more paramount as a high-risk donor in the setting of this proposed hypercoagulability would seemingly predispose a recipient to HAT on a greater scale. Unfortunately, this study is not designed to determine this nor has the timing of coagulation equilibrium post LT been well established. On the other hand, our findings of heparin use at the time of cross clamp being associated with a lower risk of HAT further supports the ongoing hypercoagulable state post-transplant. Intraoperative use of thromboelastrography (TEG), a method for determining the real-time viscous and elastic properties of blood and blood clots, is helpful in determining the pro or anticoagulant environment facing the transplant surgeon[1,18] and utilizing this along with other markers of coagulation imbalance in the ninety days post LT when patients are at highest risk for HAT may prove useful. Prospective study with this diagnostic tool may validate this

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further; we would suggest a prospective cohort with serial measures of coagulation both pre-transplantation, intra-operatively and post-transplantation.

Our study has several weaknesses. While we reviewed a large national dataset spanning over a decade of LT, it is nonetheless retrospective and as in all large datasets, suffers from issues due to missing data. Large datasets are also dependent on the accuracy of diagnostic coding which can induce information bias. While this data is verified aggressively by auditors and data technicians, errors do occur. However, our incidence of HAT was similar to that published in previous studies not involving the UNOS database. Additionally, the UNOS database does not contain information about donor or recipient inherited thrombophilic conditions. Regardless, the prevalence of inherited thrombophilia in all liver transplant recipients with HAT is relatively low: 2.4% for Factor V Leiden heterozygote mutation, 4.5% for prothrombin gene mutation heterozygote G20210A and 14.1% for Methylenetetrahydrofolate reductase (MTHFR) C677T homozygote. The importance of inherited thrombophilia predisposing to HAT remains controversial. Ayala *et al.*[12] found similar rates of inherited thrombophilia in recipients with HAT when compared to recipients without HAT, however Pereboom *et al.*[51] found that the risk of HAT was increased three-to-seven fold in association with recipient MTHFR C677T or donor factor V Leiden or factor XIII G100T. Prospective study of larger, multicenter registries is needed. The database also does not contain information on anticoagulant use post-operatively, nor does it contain information on detailed coagulation profiles including intra-operative TEG/ROTEM, the need for clotting factor replacement and/or surgical re-exploration for bleeding. This is important given our findings that heparin infusions at cross clamp were associated with a decreased risk of HAT on univariate and multivariable analysis.

Conclusions

We have provided the first large-scale observational data that PVT is associated with HAT and resultant graft loss through an undetermined mechanism independent of other variables, including surgical factors. Careful donor selection is imperative in preventing the development of HAT. More research is needed to determine a causal mechanism between PVT and HAT, which cannot be provided in our cross sectional epidemiologic study. Identification of this mechanism is impaired by a lack of effective laboratory measures of the coagulation cascade and platelet function. Further exploration in the therapeutic and prophylactic treatment of PVT may help alleviate the problem of post-LT HAT with the goal of improving post-LT outcomes and ultimately recipient survival.

Guarantor of the article

Patrick G. Northup MD MHS.

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Authorship statement

All authors participated in the listed roles below.

JS- planning/conducting study, collecting and/or interpreting data, drafting manuscript, final approval.

SP- drafting manuscript, final approval.

TS- drafting manuscript, final approval.

RP- drafting manuscript, final approval.

PN- planning/conducting study, collecting and/or interpreting data, drafting manuscript, final approval.

Conflicts of interest/disclosures

None to declare.

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