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Increased Risk of Graft Loss from Hepatic Artery Thrombosis After Liver Transplantation with Older Donors

Zoe A. Stewart, Jayme E. Locke, Dorry L. Segev, Nabil N. Dagher, Andrew L. Singer, Robert A. Montgomery, and Andrew M. Cameron
Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

Hepatic artery thrombosis (HAT) is the most common vascular complication after liver transplantation; it has been reported to occur in 2% to 5% of liver transplant recipients. Most reports of HAT in the literature describe single-center series with small numbers of patients and lack the power to definitively identify nontechnical risk factors. We used the United Network for Organ Sharing database of adult deceased donor liver transplants from 1987 to 2006 to identify 1246 patients with graft loss from HAT. Univariate and multivariate regression analyses were performed to identify donor and graft risk factors for HAT-induced graft loss. Although most donor predictors of HAT-induced graft loss were surrogates for vessel size, donor age $>$ 50 years was also a significant predictor of graft loss from HAT (relative risk = 1.45, $P < 0.001$). Furthermore, the risk of graft loss from HAT increased progressively with each decade of donor age $>$ 50 years, such that a 61% increased risk of HAT-related graft loss (relative risk = 1.61, $P < 0.001$) was associated with donor age $>$ 70 years. A separate analysis of risk factors for early HAT graft loss ($\leq$90 days) and late HAT graft loss ($>$ 90 days) found that older donor age was associated with increased late HAT graft loss. These findings are of interest in an era of ongoing organ shortages requiring maximum utilization of potential allografts and increasing allocation of older allografts. ***Liver Transpl 15:1688-1695, 2009.*** © **2009 AASLD.**

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Hepatic artery thrombosis (HAT) is the most common vascular complication after liver transplantation and is the most common technical indication for urgent retransplantation in the immediate postoperative period.[1-5] Early reviews reported HAT rates of 5% to 10%,[2,6,7] whereas more recent single-center reviews have described HAT rates of 2% to 4%.[5,8-11] Early HAT is defined as occurring in the first few months after transplantation and is most often due to the donor vessel caliber and other technical factors.[2] Late HAT is defined as occurring several months after transplantation and can be secondary to numerous factors, including rejection or sepsis.[12] HAT is associated with up to a 50% mortality rate overall, and over 30% of patients undergoing retransplantation fail to achieve long-term survival.[9] Furthermore, most patients who survive HAT develop significant biliary complications as the bile duct vasculature is dependent on the hepatic artery for its blood supply after liver transplantation.[12-14]

Researchers have mostly focused on technical risk factors for HAT related to small vessel size or back-table reconstruction due to anatomic arterial variants. Small caliber vessels have been definitively linked to increased HAT rates,[15] and smaller vessel size explains the much higher incidence of HAT in pediatric liver transplantation.[16] Numerous studies have demonstrated a significantly increased incidence of HAT in grafts requiring arterial reconstruction.[10,11,17,18] Fi-

Abbreviations: DRI, donor risk index; HAT, hepatic artery thrombosis; MELD, Model for End-Stage Liver Disease; RR, relative risk; UNOS, United Network for Organ Sharing.

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Address reprint requests to Andrew M. Cameron, M.D., Ph.D., Department of Surgery, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross Room 765, Baltimore, MD 21205. Telephone: 410-614-8297; FAX: 410-614-7649; E-mail: acamero5@jhmi.edu

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nally, a comparison of anastomoses performed with continuous running sutures versus interrupted sutures has shown that anastomoses performed with interrupted sutures have a significantly lower incidence of HAT.[14]

Nontechnical risk factors for HAT have also been reported. Recipient variables associated with an elevated risk of HAT include prior transplant,[8,10] cigarette smoking,[19] posttransplant diabetes mellitus,[20] and hypercoagulable states.[21-23] Donor factors linked to an increased risk of HAT include cytomegalovirus positivity[8,10,24,25] and death due to an intracerebral hemorrhage.[10] Graft characteristics that are independent risk factors for HAT include a cold ischemic time > 12 hours,[8] the use of a split graft,[26-28] ABO incompatibility,[29,30] and rejection.[30,31]

The impact of donor age on the risk of HAT remains unclear. In the majority of studies, older donor age has not been correlated with an increased incidence of HAT.[8,31-34] One exception is recent experience with grafts from very advanced age donors (> 60 years), with which there are reports of increased incidence of HAT.[5,10,35] However, even the largest of these latter studies had fewer than 200 donors over the age of 60 years, so they lacked sufficient sample size to generate stable multivariate models to determine the impact of very advanced donor age on the risk of HAT. In this study, we used the United Network for Organ Sharing (UNOS) database of 54,992 adult liver transplants from 1987 to 2006 to identify donor and graft risk factors for HAT-induced graft loss after liver transplantation.

PATIENTS AND METHODS

Study Design and Population

We retrospectively analyzed a prospective cohort study of liver transplant recipients included in the UNOS Standard Transplant Analysis and Research Files. Our study population initially included 78,124 recipients who underwent liver transplantation between January 1987 and June 2006. We then excluded pediatric donors (<18 years old; n = 9013), pediatric recipients (<18 years old; n = 9954), adult recipients who underwent living donor liver transplantation (n = 2058), and adult recipients who underwent multiorgan transplantation (n = 2107).

Determination of HAT-Induced Graft Loss

To report the cause of graft loss in the UNOS database, a box is checked to indicate one of the following choices: biliary, primary nonfunction, recurrent hepatitis, de novo hepatitis, acute rejection, chronic rejection, infection, recurrent disease, or vascular thrombosis. There is a separate field in which portal vein thrombosis can be checked, regardless of whether this contributed to the graft loss. Finally, there is a write-in field in which other causes can be indicated. We identified 58 patients for whom "hepatic artery thrombosis" or similar text was written in the other field and 1188 additional cases for whom vascular thrombosis was checked but portal vein thrombosis was not. This cohort should be representative of HAT cases because the majority of vascular thromboses after liver transplantation are HAT, as portal vein thrombosis and hepatic vein or caval thromboses (which we were unable to exclude) are very uncommon, with a combined incidence of <1% in large series.[1,36] As further validation of the HAT cohort, all statistical analyses were performed on the 58 patients with HAT specifically delineated in the graft loss field, and the statistical outcomes and conclusions were the same (data not shown). Furthermore, in order to rule out a confounding era effect, all analyses were performed by the division of the study population into 2 eras (1987-1996 and 1997-2006). However, as there were no differences in the results or inferences between these 2 eras (data not shown), the data are reported for the full cohort. Finally, the HAT cohort was stratified into "early" for graft loss in the first 90 days (n = 484) and "late" for graft loss beyond the first 90 days (n = 762).

Statistical Analyses

The primary outcome measured for this analysis was graft loss secondary to HAT or a vascular complication (not portal vein thrombosis). Postoperative patient death for any reason was considered a graft loss, even if the patient died with a functioning allograft. Exploratory data analysis was performed to identify UNOS donor, recipient, and graft covariates that were statistically significant ($P < 0.05$) predictors of the outcome measure on unadjusted logistic regression analysis and to determine the most functional form of each covariate (dichotomous or continuous). The covariates found to be statistically significant on univariate logistic regression analysis [donor age, gender, cause of death, and history of hypertension (defined as any reported history of hypertension in the donor); recipient age, gender, history of previous transplantation, and ventilator requirement at the time of transplantation; and split graft] were then used to build both a full multivariate logistic regression model and a Cox proportional hazards model. Of note, the Model for End-Stage Liver Disease (MELD) analysis was performed with the MELD score as a dichotomous or continuous variable for risk of HAT-mediated graft loss. For the dichotomous analysis, the MELD score was divided into quintiles to look for a break point, the score at which the odds of HAT became statistically significant on univariate analysis. The breakpoint occurred at a MELD score of 22, so this score was used as the break point for the dichotomization. For the analysis of the MELD score as a continuous variable such that the odds ratio reflected the increase in the odds of HAT for each 1-point increase in the MELD score, the odds ratio was 1.00 ($P = 0.88$, 95% confidence interval = 0.99-1.01). Furthermore, the MELD analyses reflected only the data available in the database after the institution of the MELD allocation system in February 2002 (n = 19,621).

A goodness-of-fit test of the full model was performed. Specifically, the predicted probability for graft loss sec-

ondary to HAT generated by the model was compared with the observed rate of HAT graft loss with Pearson's chi-square test statistic. There were 43,096 observations and only 4208 covariate patterns. The goodness-of-fit test of the full multivariate logistic regression model was adequate ($P > 0.05$). The sensitivity of the model was also evaluated. Problematic observations were identified by the graphing of a 2-way scatter plot of predicted probabilities versus Pearson's residuals. Both the pseudo-R^2 values and the odds ratios from the full model before and after the problematic observations were dropped were compared. There were no significant changes, and the model was considered robust to sensitivity analysis. For the sensitivity analysis, the risk of graft loss from HAT was evaluated with both definitions of HAT used to generate the model: (1) the HAT cohort in which graft loss was delineated as HAT in the write-in field (n = 58) and (2) the HAT cohort including the write-in field as well as all graft losses from vascular complications excluding portal vein thrombosis (n = 1246). The trends were the same, and the results from these sensitivity analyses were robust and consistent with the findings from our initial model. Having demonstrated good model diagnostics with logistic regression, we refit the models with a generalized linear model with Poisson family, log link, and robust variance estimation to account for distribution misspecification according to the methods of Zou,[37] in which the resulting coefficients are interpreted as the more intuitive measure of relative risk (RR). These RR values were all numerically close to the odds ratios. All tests were 2-sided with statistical significance set at the $\alpha = 0.05$ level. All analyses were performed with STATA 10.0 for Linux (Stata Corp., College Station, TX).

RESULTS

We identified 1246 cases of HAT-induced graft loss reported to UNOS from 1987 to 2006. HAT graft loss was more common among grafts from donors who were > 50 years old, were female, succumbed to intracerebral hemorrhage, or had hypertension. Furthermore, HAT graft loss was more prevalent in recipients who had undergone a previous transplant, were ventilator-dependent, or received a split graft (Table 1). All these factors predicted significantly increased risk of graft loss from HAT by univariate logistic regression analysis (Table 2). The donor risk index (DRI), defined by Feng et al.[38] (of which donor age is a dominant feature), was also predictive of graft loss from HAT (RR = 1.58, $P < 0.001$). A MELD score > 22 was not associated with an increased risk of graft loss secondary to HAT (RR = 1.05, $P = 0.69$). Hepatocellular carcinoma was also not associated with an increased risk of graft loss but rather was associated with a lower risk of such (RR = 0.45, $P < 0.001$; Table 2).

Multivariate logistic regression and Cox proportional hazards analyses were then performed with adjustments for potentially confounding features of the donor, recipient, and graft (Table 3). A donor history of hypertension was not associated with a statistically increased risk of HAT on either analysis. Recipient age, though statistically significant ($P < 0.001$), had a minimal change from risk of 1.0 on either model. Both donor female gender (RR = 1.63, $P < 0.001$) and recipient female gender (RR = 0.81, $P = 0.004$) were significant on logistic regression analysis but not on Cox proportional hazards analysis. This finding reflects the difference between logistic regression evaluation as a binary event (the patient either has HAT or does not have HAT) versus Cox models, which incorporate time-to-event data and also censor for the follow-up time. Finally, recipient ventilator dependence was associated with an increased risk of HAT on Cox analysis only (hazard ratio = 1.46, $P < 0.001$), and this again was reflective of the time-dependent impact of this risk factor for HAT (Table 3).

TABLE 1. Demographics of Patients with Graft Loss from Hepatic Artery Thrombosis

	Hepatic Artery Thrombosis*		
Characteristics	No (n = 53,746)	Yes (n = 1246)	*P* Value
Donor			
Intracerebral hemorrhage (%)	48.6	56.8	<0.001
Age ≥ 50 (years) (%)	30.8	38.7	<0.001
Hypertension (%)	28.4	33.8	0.001
Gender (% female)	40.4	52.4	<0.001
Recipient			
Gender (% female)	35.9	33.7	0.113
Previous transplant (%)	10.7	25.8	<0.001
Ventilator-dependent (%)	3.9	5.4	0.01
Graft			
Split (%)	1.0	1.7	0.091

*Graft losses from vascular thrombosis, excluding portal vein thrombosis.

Characteristics independently associated with an increased risk of graft loss from HAT on both logistic regression and Cox analyses were donor death from an intracerebral hemorrhage, donor age ≥ 50 years, recipients with a history of a previous transplant, and patients receiving a split graft. Given that donor age ≥ 50 years was predictive of graft loss from HAT and given the association with DRI found on univariate logistic regression analysis, we examined other elements of the index. DRI variables that correlated with HAT graft loss were donor height (per 10-cm decrease), donor age ≥ 50 years, intracerebral hemorrhage as the cause of death, cold ischemic time, share type, and split graft (Table 4).

We also sought to determine if different variables correlated with early HAT graft loss (≤90 days) or late HAT graft loss (>90 days). Donor age ≥ 50 years was strongly associated with an increased risk of graft

TABLE 2. Univariate Analysis of Risk Factors for Graft Loss from Hepatic Artery Thrombosis

Characteristics	Relative Risk	95% Confidence Interval	*P* Value
Donor			
Intracerebral hemorrhage	1.39	1.24, 1.55	<0.001
Age ≥ 50 (years)	1.41	1.26, 1.58	<0.001
Hypertension	1.28	1.11, 1.46	0.001
Female	1.60	1.44, 1.79	<0.001
Donor risk index	1.57	1.46, 1.69	<0.001
Recipient			
Age ≤ 40 (years)	0.59	0.51, 0.67	<0.001
Female	0.91	0.81, 1.02	0.113
Hepatocellular carcinoma	0.45	0.31, 0.65	<0.001
MELD score > 22*	1.05	0.82, 1.36	0.69
Previous transplant	2.81	2.49, 3.18	<0.001
Ventilator-dependent	1.37	1.08, 1.75	0.01
Graft			
Split graft	1.69	1.12, 2.53	0.011

Abbreviation: MELD, Model for End-Stage Liver Disease.
*MELD scores were available only after February 2002 (n = 19,621).

TABLE 3. Multivariate Analysis of Risk Factors for Graft Loss from Hepatic Artery Thrombosis

	Logistic Regression			Cox Proportional Hazards		
Characteristics	Relative Risk	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval	*P* Value
Donor						
Intracerebral hemorrhage	1.17	1.00, 1.37	0.05	1.12	1.07, 1.17	<0.001
Age ≥ 50 (years)	1.45	1.25, 1.68	<0.001	1.26	1.21, 1.32	<0.001
Hypertension	1.03	0.88, 1.19	0.75	1.05	1.00, 1.10	0.06
Female	1.63	1.42, 1.87	<0.001	1.01	0.97, 1.06	0.522
Recipient						
Age	0.97	0.97, 0.98	<0.001	1.02	1.01, 1.02	<0.001
Female	0.81	0.70, 0.94	0.004	0.96	0.92, 1.00	0.082
Previous transplant	1.68	1.39, 2.02	<0.001	2.17	2.05, 2.31	<0.001
Ventilator-dependent	1.06	0.81, 1.38	0.67	1.46	1.36, 1.59	<0.001
Graft						
Split graft	2.24	1.45, 3.47	<0.001	1.20	1.00, 3.47	<0.001

NOTE: The analysis was adjusted for the following covariates: donor age, gender, cause of death, and history of hypertension; recipient age, gender, history of previous transplantation, and ventilator requirement at the time of transplantation; and split graft.

loss from late HAT (RR = 1.94, $P < 0.001$) but not early HAT (RR = 1.14, $P = 0.067$; Table 5). In contrast, a recipient history of a prior transplant (early HAT: RR = 1.30, $P = 0.001$; late HAT: RR 1.48, $P = 0.14$) and the use of a split graft (early HAT: RR = 1.63, $P = 0.03$; late HAT: RR = 1.51, $P = 0.57$) were specifically associated with an increased risk of graft loss from early HAT.

To further elucidate the impact of donor age on the risk of graft loss from HAT, we examined donor age by incremental decades. In the current study, a total of 7438 patients received allografts from donors ≥ 60 years (Table 6). The incidence of graft loss from HAT for donors < 50 years was 2.0% to 2.1%, with an increase for each decade of donor age > 50 years up to a 3.2% incidence of HAT graft loss with donors ≥ 70 years (Table 6). On multivariate analysis, donors between 40 and 49 years were not associated with an increased risk of HAT graft loss; however, we found a stepwise dose response for each decade of increasing donor age over 50 years (Table 7). Donors between 50 and 59 years were associated with a 35% increased risk of graft loss from HAT (RR = 1.35, $P < 0.001$). Similarly, donors between 60 and 69 years were associated with a 52% increased risk of graft loss from HAT (RR = 1.52, $P < 0.001$), whereas donors > 70 years were associated with a 61% increased risk of HAT-mediated graft loss (RR = 1.61, $P < 0.001$; Table 7).

TABLE 4. Donor Risk Index Variables and Risk of Graft Loss from Hepatic Artery Thrombosis

Characteristics	Relative Risk	95% Confidence Interval	*P* Value
Ethnicity: African American	0.90	0.76, 1.08	0.27
Height (per 10-cm decrease)	1.09	1.07, 1.11	<0.001
Donor age ≥ 50 (years)	1.41	1.26, 1.58	<0.001
Intracerebral hemorrhage	1.39	1.24, 1.55	<0.001
Donation after cardiac death	0.74	0.44, 1.25	0.26
Share type			
Regional	1.24	1.09, 1.41	0.001
National	1.58	1.35, 1.85	<0.001
Cold ischemic time (hours)			
≥4 < 8	0.96	0.70, 1.31	0.78
≥8 < 12	1.30	0.96, 1.77	0.095
≥12 < 16	1.94	1.41, 2.67	<0.001
≥16 < 20	2.06	1.40, 3.03	<0.001
≥20	1.58	0.99, 2.49	0.056
Split graft	1.69	1.12, 2.53	0.011

TABLE 5. Univariate Analysis of Risk Factors for Graft Loss from Early Hepatic Artery Thrombosis Versus Late Hepatic Artery Thrombosis

	Early Hepatic Artery Thrombosis*			Late Hepatic Artery Thrombosis†		
	Relative Risk	95% Confidence Interval	*P* Value	Relative Risk	95% Confidence Interval	*P* Value
Donor						
Intracerebral hemorrhage	1.21	1.05, 1.39	0.007	1.64	1.16, 2.32	0.005
Age ≥ 50 (years)	1.14	0.99, 1.31	0.067	1.94	1.38, 2.73	<0.001
Hypertension	1.03	0.87, 1.22	0.72	1.37	0.94, 2.00	0.10
Female	1.48	1.29, 1.70	<0.001	2.02	1.43, 2.86	<0.001
Donor risk index	1.28	1.15, 1.42	<0.001	1.60	1.31, 1.95	<0.001
Recipient						
Age ≤ 40 (years)	0.76	0.64, 0.90	0.002	0.78	0.50, 1.23	0.29
Female	0.89	0.77, 1.02	0.10	0.61	0.41, 0.91	0.014
Previous transplant	1.30	1.12, 1.52	0.001	1.48	0.88, 2.50	0.14
Ventilator-dependent	0.91	0.69, 1.18	0.46	1.51	0.67, 3.42	0.32
Graft						
Split	1.63	1.05, 2.52	0.03	1.51	0.37, 6.07	0.57

*Graft loss secondary to hepatic artery thrombosis within the first 90 days post-transplant (n = 484).
†Graft loss secondary to hepatic artery thrombosis after the first 90 days post-transplant (n = 762).

DISCUSSION

HAT remains a major cause of morbidity and graft loss after liver transplantation, but its overall low incidence makes it challenging to identify risk factors predictive of HAT. In the present study, we used data from the UNOS database to identify 1246 patients with graft loss secondary to HAT. To our knowledge, this study represents the largest cohort of HAT patients studied to date and has allowed the development of stable multivariate regression models to identify donor, recipient, and graft variables that are predictors of increased risk of HAT graft loss. In particular, the utilization of a national registry has allowed the analysis of the largest sample of donors ≥ 60 years (n = 7438) reported to date in the literature. Multivariate analysis found that donor death due to an intracerebral hemorrhage, donor age ≥ 50 years, donor female gender, a recipient history of a previous transplant, and split grafts were associated with an overall increased risk of HAT-mediated graft loss. Donor age ≥ 50 years was specifically associated with late HAT graft loss (>90 days post-transplant), whereas a recipient history of a previous transplant and split grafts were specifically associated with early HAT graft losses (<90 days post-transplant). Finally, there was a stepwise impact of age on the RR of graft loss from HAT, as the risk increased incrementally for each decade of donor age > 50 years.

A review of the literature for reports on the effect of donor age on HAT revealed a spectrum of results. Most reports have found no effect of donor age on HAT,[8,24,32-34] whereas others have detected an impact only with the use of very aged donors (>60 years).[5,10,35]

TABLE 6. Distribution of Donor Age by Decade and Incidence of Hepatic Artery Thrombosis

Donor Age (years)	Hepatic Artery Thrombosis		Hepatic Artery Thrombosis by Decade (%)
	No	Yes	
<40	26,012	523	2.0
40–49	11,177	241	2.1
50–59	9,308	255	2.7
60–69	5,136	159	3.0
≥70	2,075	68	3.2

TABLE 7. Impact of Donor Age on the Risk of Graft Loss from Hepatic Artery Thrombosis

Donor Age (years)	Relative Risk	95% Confidence Interval	*P* Value
<40	Reference		
40-49	1.07	0.92, 1.25	0.37
50-59	1.35	1.17, 1.57	<0.001
60-69	1.52	1.28, 1.82	<0.001
≥70	1.61	1.26, 2.06	<0.001

NOTE: The multivariate analysis was adjusted for the following covariates: donor age, gender, cause of death, and history of hypertension; recipient age, gender, history of previous transplantation, and ventilator requirement at the time of transplantation; and split graft.

However, these latter studies are limited by the fact that only a small number of patients with HAT had donors > 60 years (4 patients,[35] 19 patients,[5] and 26 patients[10]). The small sample sizes of these prior studies make it difficult to interpret the significance of the results, given the inability to effectively control for potential confounding variables. Our multivariate analysis of a large, pooled national experience and the finding of increased risk of HAT graft loss with each decade of donor age may help to reconcile reported differences in the literature.

The finding that donor age ≥ 50 years is associated with late HAT suggests that the increased risk could be secondary to factors intrinsic to the graft vasculature, as one would expect most etiologies of early HAT to be related to technical factors and vessel caliber. Previous studies examining the impact of donor age on early HAT versus late HAT found that donor age > 60 years was not a risk factor for late HAT.[10] However, this latter study had only 13 cases of late HAT and thus lacked the power to detect an age-specific impact on late HAT. Furthermore, in support of age-related factors affecting the graft vasculature, we found that donor age ≥ 50 years did not correlate with an increased risk of graft loss from primary graft nonfunction or the overall recipient risk of death from any cause post-transplant (data not shown).

Our confirmation with this large national registry analysis that advanced donor age predisposes patients to graft loss from HAT comes at a time when there is a national trend toward utilization of older donors. In 1990, only 13% of donors used for liver transplants were over 50 years. In contrast, by 2005, over 40% of liver allografts were from donors over 50 years. Interestingly, an examination of the elements that compose the DRI for extended criteria donors[38] found that in addition to donor age > 50 years, split grafts and decreasing donor height (surrogates for smaller vessel size) and donor death due to intracerebral hemorrhage (possibly a marker for donor vasculopathy) were variables correlating with an increased risk of HAT graft loss.

Similarly, donor female gender as a risk for HAT graft loss may be a function of vessel size. The finding that recipient female gender reduces the risk of HAT graft loss suggests that other factors, such as the gender-specific differences in the etiology of end-stage liver disease (ie, males are more likely to have hepatitis C cirrhosis and alcoholic cirrhosis and females are more likely to have autoimmune cirrhosis, cryptogenic cirrhosis, or primary biliary cirrhosis), contribute to HAT development.

The finding that donor age ≥ 50 years increases the risk of HAT-induced graft loss may also have implications for the postoperative care of these graft recipients. A recent study by Vivarelli et al.[39] found that low-dose aspirin therapy was effective at reducing the incidence of HAT in all patients from 2.2% to 0.4%. An analysis of patients at an increased risk for HAT due to donor death from an intracerebral hemorrhage or the use of an iliac conduit found that in these high-risk patients, the incidence of HAT decreased from 3.6% in the control group to 1.0% in the aspirin treatment group with negligible bleeding complications.[39] These results suggest that recipients of older donor allografts may benefit from the institution of antiplatelet therapy in the early postoperative period.

It is important to acknowledge that there are several limitations to our study. As with all studies using the UNOS database, our conclusions are limited by the assumption that there is no systematic bias generated by reporting error or nonreporting. Furthermore, there are many potential variables that could be predictors of HAT-induced graft loss (eg, aberrant hepatic arterial anatomy) that are not captured in the UNOS data set, so our conclusions are limited only to those variables reported. Additionally, the variable donor hypertension is defined in the UNOS data set as any history of donor hypertension, and this is an important caveat to consider when one is interpreting the significance of this variable and risk of HAT graft loss. Most significantly, our analysis addresses HAT only in the context of graft loss. Clearly, there is a subset of patients who develop HAT and do not suffer graft loss but nonetheless suffer significant morbidity; the UNOS data set does not accurately capture this patient population.

It is also important to note that there are specific limitations to the graft loss data in the UNOS database. For those cases for which an etiology has been identi-

fied, that does not exclude other causative factors, as graft losses are often multifactorial. For example, HAT that led to biliary complications and subsequent graft loss could be captured in the UNOS database as HAT, biliary complication, both, or neither. However, there is no reason to suspect that a misclassification bias affects the inferences of the study, as presumably the factors affecting HAT identified as a vascular complication would not be different than factors affecting HAT identified as a biliary complication. Furthermore, it would not be anticipated that there would be a specific donor age–related reporting bias with respect to how centers categorized graft losses or failed to indicate a cause. Finally, it is important to note that we do not attempt to make any statements about the incidence of HAT-induced graft loss, given the inability to adjust for missing data, so any incidence calculated from the current study population would be underestimating the true incidence.

As previously noted in the Patients and Methods section, we cannot exclude hepatic vein or caval thromboses as potentially contributing to the vascular complications causing graft loss. However, this factor is unlikely to significantly alter the results, given the very rare occurrence of hepatic vein complications ($< 1\%$) in large series of either whole organ or split grafts.[1,36] Furthermore, the majority of the rare instances of hepatic vein thrombosis with split grafts occur in pediatric recipients, who were excluded from our study population.[26,27]

In conclusion, we have shown that for each decade of donor age ≥ 50 years, the RR of HAT-induced graft loss increases. Furthermore, advanced donor age was found to most significantly influence the development of late HAT. These findings are of interest in an era of ongoing organ shortages requiring maximum utilization of potential allografts and increasing allocation of older allografts. Given the continuum of risk for any given recipient with any particular graft, clearly the risk of graft loss from HAT as a function of any single variable such as donor age is going to be outweighed by the risk of death faced by the majority of patients on the waiting list. Additional studies are required to determine if patients receiving allografts from donors ≥ 50 years may benefit from the institution of postoperative antiplatelet therapy to help reduce the risk of graft loss from HAT.

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