Decreased Incidence of Hepatic Artery Thrombosis in Pediatric Liver Transplantation Using Technical Variant Grafts: Report of the Society of Pediatric Liver Transplantation Experience

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Objective To evaluate risk factors for hepatic artery thrombosis (HAT) and examine the long-term outcomes of graft and patient survival after HAT in pediatric recipients of liver transplantation.

Study design Using multicenter data from the Society of Pediatric Liver Transplantation, Kaplan-Meier and Cox regression analyses were performed on first-time pediatric (aged <18 years) liver transplant recipients (n = 3801) in the US and Canada between 1995 and 2016.

Results Of children undergoing their first liver transplantation, 7.4% developed HAT within the first 90 days of transplantation and, of those who were retransplanted, 20.7% developed recurrent HAT. Prolonged warm ischemia times increased the odds of developing HAT (OR, 1.11; $P = .02$). Adolescents aged 11-17 years (OR, 0.53; $P = .03$) and recipients with split, reduced, or living donor grafts had decreased odds of HAT (OR, 0.59; $P < .001$ compared with whole grafts). Fifty percent of children who developed HAT developed graft failure within the first 90 days of transplantation (adjusted hazard ratio, 11.87; 95% CI, 9.02-15.62) and had a significantly higher post-transplant mortality within the first 90 days after transplantation (adjusted hazard ratio, 6.18; 95% CI, 4.01-9.53).

Conclusions These data from an international registry demonstrate poorer long-term graft and patient survival in pediatric recipients whose post-transplant course is complicated by HAT. Notably, recipients of technical variant grafts had lower odds of HAT compared with whole liver grafts. *(J Pediatr 2020;226:195-201)*.

Although the incidence of hepatic artery thrombosis (HAT) seems to be decreasing by era, ongoing targets for quality improvement initiatives to prevent HAT remain paramount. HAT after liver transplantation leads to increased morbidity and risk of mortality in pediatric transplant recipients.[1] Although single-center studies outside of the US and Canada have examined outcomes after HAT, no multicenter registry studies have yet examined the long-term outcomes of both graft and patient survival in pediatric liver transplantation recipients whose postoperative course is complicated by HAT.

HAT has been reported in 1%-20% of children after liver transplantation and HAT accounts for 11.4% of late graft loss after the first year.[2-4] HAT also remains the most common indication for retransplantation (29%), with retransplantation graft and patient survival that is notably worse compared with children undergoing primary liver transplantation. Ng et al found that of those children in whom retransplantation is further complicated by a second HAT (21 recipients [9%]), 48% undergo a third liver transplantation.[5]

Previously reported risk factors for HAT include living donor and split grafts, excess blood product transfusions, large for size grafts, small recipient weight, aberrant donor or recipient arterial anatomy, and multiple arterial anastomoses.[2,3,6-11]

Recent quality improvement initiatives within the Society of Pediatric Liver Transplantation (SPLIT) focused on the dissemination of best practices from a high performing center with the lowest rate of HAT after liver transplantation.[2] These best practices defined specific surgical techniques for split and living donor transplant and anticoagulation protocols. With continuing quality improvement initiatives and advances in surgical techniques, we aim to examine long-term trends in graft and patient survival after HAT and hypothesize improving survival with advancing era.[12] In liver transplant recipients who survive without acute graft loss, we hypothesize poorer long-term graft survival secondary to biliary injury and late graft fibrosis.

HAT	Hepatic artery thrombosis
HR	Hazard ratio
SPLIT	Society of Pediatric Liver Transplantation
UNOS	United Network for Organ Sharing

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Supported in part by the Society of Pediatric Liver Transplantation Council Award, American Association for the Study of Liver Diseases Advanced/Transplant Hepatology Award, and NIDDK training grant to the Division of Gastroenterology at the University of Washington (T32 DK007742). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.06.053

Methods

Data Source and Study Population

We reviewed data from SPLIT on all patients who underwent liver transplantation in the US and Canada at 54 centers from 1995, the date of inception of the SPLIT database, to 2016. We limited our study to first-time transplant recipients (n = 5008) aged 0-18 years; pediatric recipients with recurrent HAT were analyzed separately (n = 25). Patients were excluded if they were missing HAT status (n = 76), if they completed an initial visit without any follow-up (n = 680), or if they underwent multiorgan transplantation (n = 451). A total of 3801 recipients were included in the final analysis. Institutional review board approval was required from each center before participation in the SPLIT database and this project was approved by the Seattle Children's Hospital Institutional Review Board.

Defining Early HAT

Within the SPLIT database there was a high degree of missing data regarding the exact date of HAT (76% missing). Therefore, we could not accurately differentiate if HAT developed within the first 14 days vs >14 days after transplantation. However, a history of HAT was reliably recorded at the first outpatient visits at 30, 60, and 90 days. We therefore defined early HAT as occurring within the first 90 days after liver transplantation. Patients who developed HAT at >90 days after transplantation were excluded (n = 18) and given the small number of recipients with late HAT, analyses comparing early vs late HAT could not be performed.

Defining Biliary Complications

The SPLIT database captures the following biliary complications: bile leak, biloma, nonanastomotic biliary stricture, and anastomotic stricture. Bile leaks are defined as occurring either from the liver cut surface or from the biliary tree and diagnostically as an extrahepatic fluid collection detected by imaging study and direct continuity of the fluid collection to the biliary tract. A biloma is defined as an extrahepatic fluid collection detected by imaging study that requires the placement of an indwelling percutaneous drain for treatment. A nonanastomotic biliary stricture is defined as typically multiple strictures, longer in length, and located in intrahepatic ducts and/or in the donor duct proximal to the site of biliary anastomosis. Anastomotic strictures required diagnosis by endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, or percutaneous transhepatic cholangiography. The SPLIT database captures cholangitis infection within the first 90 days after liver transplantation.

Limitations in Analyzing Graft Size Mismatch

Previous studies have noted small recipient weight and large-for-size grafts as risk factors for HAT. Evaluation of size mismatch used graft-to-recipient body weight ratio in living donor liver transplantation and body surface area index in deceased donor liver transplantation. Both calculations require donor height, which is not included in the SPLIT database; therefore, the potential contribution of graft size mismatch to HAT could not be analyzed as part of this study.

Treatment for HAT

Treatment for HAT was integrated into the SPLIT database starting in 2012 and included the following categories, which were not mutually exclusive: anticoagulation, interventional radiology procedure, observation, and reoperation. Type of treatment for HAT was a binary variable in the SPLIT database (yes/no) and further details regarding the type of anticoagulation or technique of a procedure or surgery were not available. The time from HAT intervention to retransplantation was not recorded as a variable in the SPLIT database.

Statistical Methods and Analytical Software

Descriptive statistics were calculated for all demographic and outcome variables. Predictors of HAT were evaluated using logistic regression models. Kaplan-Meier survival curves compared graft and patient survival between patients with and without HAT. Cox proportional hazards regression estimated hazard ratios (HR) and 95% CI for the association between patients with HAT and graft and patient survival at 5 years after transplantation. Recipient factors included in the model at the time of transplantation were sex, age, race and ethnicity, weight, indication for transplantation, year of transplantation, ABO blood group, Pediatric End-Stage Liver Disease/Model for End-Stage Liver Disease score, creatinine, dialysis (yes/no), serum sodium, total bilirubin, albumin, international normalized ratio, hospital status at transplant, and insurance type. Donor factors included in the model were: age, sex, race and ethnicity, weight, donor type (deceased [brain death], deceased [cardiac donor], living), and blood type. Transplant surgical factors included in the model were transplant type (whole vs reduced/split/living), warm ischemia time (defined as the number of minutes between the time of removal from cold storage to the time of reperfusion of warm blood), and cold ischemia time. Variables with a P values of ≤.3 were retained in the final model. All other significance testing was done at the $\alpha = 0.05$ level. SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

Results

Baseline Characteristics

Of the 3801 children who underwent first-time liver transplantation, 7.4% developed HAT within the first 90 days of transplantation. The incidence of HAT decreased by era: 8.3% developed HAT between 1995-2001 compared with 7.9% between 2002-2011 and 6.1% between 2012-2015 (Table I).

Table I. Baseline characteristics for children with and without HAT (1995-2015)

Characteristics	With early HAT (n = 281)	Without HAT (n = 3520)
Recipients		
Age, y, mean (SD)		
<1	104 (37.0)	1054 (30.0)
1-5	101 (35.9)	1195 (34.0)
6-10	41 (14.6)	488 (13.9)
11-18	35 (12.5)	777 (22.1)
Missing	0	6
Female sex, n (%)	143 (50.9)	1832 (52.1)
Missing	0	0
Race and ethnicity, n (%)*		
Caucasian	183 (78.2)	2209 (74.5)
African American	31 (16.4)	526 (21.0)
Hispanic	40 (18.8)	612 (22.0)
Other	39 (13.9)	450 (12.8)
Weight, kg, mean (SD)	15.5 (14.4)	20.2 (19.2)
Blood group, n (%)		
A	108 (38.9)	1180 (33.8)
AB	10 (3.6)	158 (4.5)
B	37 (13.3)	451 (12.9)
O	123 (44.2)	1699 (48.7)
Missing	3	32
Serum sodium, mean (SD)	138.3 (6.7)	137.9 (4.5)
Serum albumin, g/dL, mean (SD)	3.2 (1.3)	3.3 (2.5)
Serum total bilirubin, mean (SD)	10.1 (11.3)	9.0 (10.5)
INR, mean (SD)	1.8 (1.2)	1.6 (0.9)
Serum creatinine, mg/dL, mean (SD)	0.4 (0.5)	0.4 (0.3)
Dialysis (yes/no)	74 (26.3)	969 (27.5)
Calculated PELD score at transplantation (no exceptions),† mean (SD)	11.2 (13.8)	12.7 (14.3)
Calculated MELD score at transplantation (no exceptions),† mean (SD)	16.8 (8.1)	18.1 (8.8)
PELD score at transplantation (exception granted), mean (SD)	15.9 (16.4)	16.9 (17.1)
MELD score at transplantation (exception granted), mean (SD)	17.3 (9.0)	19.1 (10)
Underlying liver disease		
Acute liver failure	23 (8.2)	483 (13.8)
Biliary atresia	126 (44.8)	1399 (39.9)
Other cholestatic liver disease	24 (8.5)	464 (13.2)
Metabolic	50 (17.8)	447 (12.8)
Malignancy	31 (11.0)	305 (8.7)
Other	27 (9.6)	406 (11.6)
Missing	3	107
Year of transplantation		
1995-2001	66 (23.7)	725 (21.2)
2002-2011	154 (55.4)	1794 (52.6)
2012-2015	58 (20.9)	894 (26.2)
Missing	3	107
Hospital status at transplantation		
ICU	50 (17.8)	832 (23.8)
Hospitalized, not ICU	46 (16.4)	659 (18.8)
Not hospitalized	185 (65.8)	2012 (57.4)
Missing	0	17
Medicaid and/or state-funded children's services, n (%)	106 (40.2)	1410 (43.0)
Missing	17	244
Donors		
Age, y, mean (SD)	12.8 (13.7)	16.9 (14.4)
Female sex, n (%)	110 (40.6)	1488 (44.4)
Missing	10	171
Race and ethnicity, n (%)*		
Caucasian	153 (89.0)	2168 (86.5)
African American	54 (54.0)	470 (36.5)
Hispanic	28 (38.9)	330 (34.0)
Other	10 (3.6)	128 (3.6)
Weight, kg, mean (SD)	32.3 (30.2)	42.4 (29.0)
ABO match, n (%)		
Identical	223 (82.6)	2818 (83.0)
Compatible	3 (1.1)	82 (2.4)
Incompatible	44 (16.3)	497 (14.6)
Missing	11	123
Warm ischemia time (mins), mean (SD)	49.7 (26.9)	46.0 (21.3)
Cold ischemia time (hours), mean (SD)	6.7 (3.1)	6.3 (3.2)
Donor type, n (%)		
Deceased, brain death	130 (46.8)	1603 (46.2)
Deceased, cardiac donor	6 (2.2)	57 (1.6)
Deceased, unknown	98 (35.3)	1222 (35.2)
Living	44 (15.8)	590 (17.0)
Missing	3	48
Liver type, n (%)		
Whole	174 (62.8)	1863 (53.5)
Partial/living	76 (27.4)	1043 (29.9)
Split	27 (9.8)	579 (16.6)
Missing	4	35

INR, international normalized ratio; *MELD*, Model for End-Stage Liver Disease; *PELD*, Pediatric End-Stage Liver Disease.
*Race/ethnicity categories were not mutually exclusive.
†For registrants that did not receive an exception score, the PELD/MELD score at listing was calculated by laboratory values only. Calculated MELD scores range between 6 and 40 and PELD scores range between −11 and ≥ 40.

Predictors of HAT

Baseline characteristics in which there were notable differences included age, underlying liver disease, warm ischemia time, and liver type. The associated odds of developing HAT with these characteristics are listed in Table II. Adolescents age 11-18 years were less likely to develop HAT compared with younger children age 1-5 years (OR, 0.55; $P = .01$). Children transplanted for acute liver failure were less likely to develop HAT compared with children with biliary atresia (OR, 0.53; $P = .03$). Longer warm ischemia times were associated with an increased risk of developing HAT (OR, 1.11; $P = .02$) and split, reduced, or living donor grafts had a decreased risk of HAT compared with whole grafts (OR, 0.59; $P < .001$). Sex, albumin level at the time of transplantation, era of transplantation, cold ischemia time, and insurance payor status were not predictive of the development of HAT.

Complications after HAT

Biliary and infectious complications after liver transplantation by HAT status are included in Table III.

Association between HAT Status and Post-transplant Graft Survival

Of the 281 recipients who developed HAT within the first 90 days after transplantation, 50% (n = 140) developed graft failure within the first 5 years of follow-up. Recipients with HAT were significantly more likely to develop graft failure within the first 90 days after transplantation (adjusted HR, 11.87; 95% CI, 9.02-15.62) and at >90 days after transplantation (adjusted HR, 2.21; 95% CI, 1.34-3.65) compared with recipients without HAT (Table IV and Figure, A).

Table II. Predictors of early HAT, from logistic regression

Predictors	OR (95% CI)	*P* value
Age, y		
<1	1.20 (0.85-1.70)	.30
1-5	Reference	
6-10	1.03 (0.67-1.60)	.88
11-18	0.55 (0.35-0.88)	.01
Sex		
Male	0.88 (0.66-1.17)	.47
Female	Reference	
Diagnosis		
Acute liver failure	0.53 (0.29-0.94)	.03
Biliary atresia	Reference	
Other cholestatic liver disease	0.66 (0.39-1.17)	.12
Metabolic	1.47 (0.98-2.21)	.06
Malignancy	1.43 (0.89-2.29)	.14
Other	0.77 (0.45-1.30)	.32
Albumin	1.05 (0.97-1.13)	.25
Warm ischemia time (15-min time blocks)	1.11 (1.02-1.21)	.02
Cold ischemia time, h	1.02 (0.98-1.07)	.30
Liver type		
Split/reduced/living	0.59 (0.43-0.80)	<.001
Whole	Reference	
Payor		
Medicaid or equivalent and/or state-funded children's services	0.75 (0.57-1.01)	.05
Other insurance	Reference	

Association between HAT Status and Post-transplant Patient Survival

Of the 280 recipients who developed HAT within the first 90 days after transplantation, 20% (n = 55) died within the first 5 years of follow-up. Recipients with HAT had significantly higher post-transplant mortality within the first 90 days after transplantation (adjusted HR, 6.18; 95% CI, 4.01-9.53). Mortality at >90 days after transplantation was higher overall in recipients with HAT compared with those without HAT, although this finding was not statistically significant (Table V and Figure, B).

Recurrent HAT

Of the recipients who developed HAT after their first liver transplantation and were retransplanted (n = 121), 20.7% developed recurrent HAT at any time after their second transplant (n = 25). Demographics for recipients with recurrent HAT were similar to those with HAT after their first liver transplantation (Table VI; available at www.jpeds.com).

Table III. Complications after liver transplantation by HAT status

Complications	With early HAT (n = 281)	Without HAT (n = 3520)
Nonanastomotic biliary stricture	14 (5.0)	54 (1.5)
Anastomotic biliary stricture	43 (15.3)	207 (5.9)
Biliary leak	44 (15.7)	250 (7.1)
Biloma	5 (1.8)	20 (0.6)
Cholangitis within the first 90 d after transplantation	21 (7.5)	57 (1.6)

Values are number (%).

Treatment for HAT

Of the 87 recipients who developed HAT after their first transplantation where treatment was recorded (from 2012 on): 5 were observed, 4 had an interventional radiology procedure (2 were also anticoagulated), 12 were anticoagulated only, and 66 underwent reoperation. Of the 66 recipients who developed HAT and underwent reoperation, 45 were also anticoagulated and 7 had interventional radiology procedures.

Discussion

This analysis of international registry data examines the incidence of HAT and long-term outcomes after HAT in children 0-18 years old undergoing first-time liver transplantation from 1995 to 2016. Notably, 7.4% of first-time pediatric liver transplantations were complicated by HAT within the first 90 days after transplantation, of which the highest incidence was in children <5 years old. The incidence of HAT after pediatric liver transplantation has previously been reported at rates between 1% and 20% from single-center studies. Prolonged warm ischemia time increased the odds of developing HAT and recipients of technical variant grafts (split, reduced, or living donor) had decreased odds of HAT compared with whole grafts. Among children who develop HAT, 50% developed graft failure within 5 years. Despite eligibility for status 1A priority or Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease score exception scores for recipients with HAT, 20% of recipients with HAT died within the first 5 years after transplantation.

Notably, although previous studies have reported a higher incidence of HAT in living donor and split transplants, we found that technical variant grafts (split, reduced, and living donor) had a decreased risk of HAT compared with whole grafts.[2,6,7] In support of this finding, previous single-center studies have reported a higher risk of HAT in the youngest recipients with whole compared with segmental grafts, potentially related to low flow states secondary to small artery diameter.[13-16] Alexopoulos et al also described that, in pediatric recipients transplanted for biliary atresia with whole livers, recipients weighing <7 kg had the highest risk of portal vein thrombosis and those >14 kg had the lowest risk of portal vein thrombosis compared with partial or living donor grafts; though this study did not examine the incidence of HAT directly.[15] Kasahara et al in a single-center experience of 12 infants <3 months old, reported no complications of HAT in children who underwent living donor liver transplantation.[17] We hypothesize that technical variant grafts typically come from larger donors with larger vessels, decreasing distal resistance in the hepatic artery and decreasing the risk of HAT. Donor height, however, is not captured in the SPLIT database; therefore, we could not

Table IV. Association between HAT status and post-transplant graft survival (Cox proportional hazards analysis)

HAT statuses	n	Patient-years	Failures	Failure rate (per 100 patient-years)	Unadjusted HR, HR (95% CI) ≤90 days	Unadjusted HR, HR (95% CI) >90 days	Adjusted* HR, HR (95% CI) ≤90 days	Adjusted* HR, HR (95% CI) >90 days
With early HAT	281	491.1	140	28.51	10.55 (8.31-13.39)	2.26 (1.51-3.38)	11.87 (9.02-15.62)	2.21 (1.34-3.65)
Without HAT	3514	10 039.0	398	3.96				

*Adjusted for the following recipient variables at the time of transplantation (Table I): age, sex, diagnosis, year of transplant, total bilirubin, hospital status at transplant, insurance type, and donor predictors of cold ischemia time (hours) donor type, and transplant type.

evaluate the important interaction between graft type and size mismatch, which likely plays a role particularly for segmental grafts in the smallest recipient. High-performing centers with the lowest incidence of HAT also tend to have high rates of living and split transplants, suggesting that surgical expertise may play a role in the decreased risk of HAT in select recipients with technical variant grafts.[2] Center-specific effects could not be analyzed owing to small numbers across multiple centers.

In our study, age, as a surrogate for weight, was also a predictor for HAT with children aged 0-5 years having the highest risk of HAT. Recipient weight likely also has a significant interaction with graft type in conferring risk of HAT, although we could not examine this factor directly. Other previously described risk factors for HAT include excess blood product transfusions and large-for-size grafts, which could not be examined because these data are not captured in the SPLIT database. We found that prolonged warm ischemia time was a risk factor for HAT, which has not previously been reported in pediatric studies and may be a proxy for surgical technique.[9,18] In adults, Warner et al also reported an increased risk of early HAT (in the first 4 weeks after liver transplantation) with prolonged reperfusion time.[19] Specifically, each additional 10-minute delay in reperfusion, defined as the interval between portal vein reperfusion and restoration of arterial flow after completion of the arterial anastomosis, was associated with a 27% increased risk of developing HAT.[19]

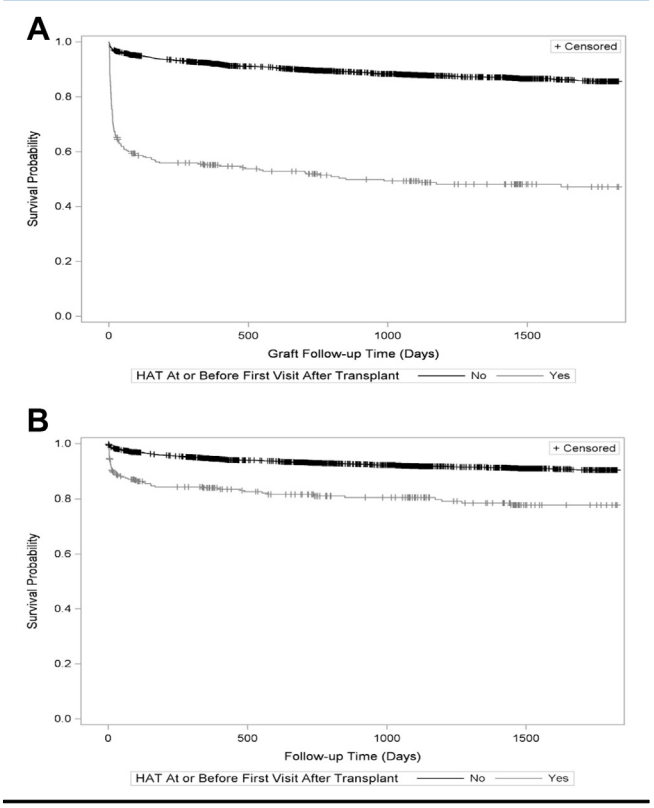

Figure. Kaplan-Meier curve of **A,** graft survival and **B,** patient survival in liver transplant recipients with and without HAT.

Long-term biliary complications represent a significant morbidity in recipients with HAT. HAT is associated with ischemic injury of the bile ducts leading to biliary necrosis, bile leak, and formation of nonanastomotic and anastomotic biliary strictures.[4,20,21] A greater proportion of recipients with HAT in our study developed bile leaks, biliary strictures, and cholangitis when compared with recipients without HAT. In children with biliary complications secondary to HAT, Ackermann et al described a median of 4 hospitalizations (median of 165 days of hospitalization) and a mean of 6 interventional radiology procedures for surgical or interventional radiology management.[4] The impact on the quality of life of children with biliary complications secondary to HAT is significant. Ongoing efforts to prevent HAT, allow for the earlier detection of HAT, and inform best practices for the treatment of HAT and timing to relist for liver transplantation are critical.

Not surprisingly, children with HAT were more likely to lose their graft at a significantly higher rate both within the first 90 days and at >90 days after transplantation compared with those without HAT. Recipients with HAT were significantly more likely to die in the first 90 days after transplantation compared with those without HAT. Current United Network for Organ Sharing (UNOS) policy grants 1A status for children <11 years old with HAT in the first 14 days after transplantation and 1A status for adolescents ≥12 years with HAT and severe graft dysfunction in the first 7 days after transplantation with consideration for a Model for End-Stage Liver Disease standard exception score of 40 for HAT occurring within 14 days without severe graft dysfunction. Our study could not reliably identify children who developed HAT within the first 14 days vs 90 days after transplantation owing to a high degree of missing data. However, given the high priority status for retransplantation allocated to these recipients, these findings may be partially explained by children with HAT either occurring or recognized beyond

Table V. Association between HAT status and post-transplant patient survival (Cox Proportional Hazards analysis)

HAT statuses	n	Patient-years	Deaths	Mortality (per 100 patient-years)	Survival, n (%)			Unadjusted HR, HR (95% CI)		Adjusted* HR, HR (95% CI)	
					1 Year	2 Years	5 Years	≤ 90 days	> 90 days	≤ 90 days	> 90 days
With early HAT	280	748	55	7.35	195 (84)	162 (82)	156 (78)	4.63 (3.17-6.76)	1.61 (1.00-2.59)	6.18 (4.01-9.53)	1.71 (0.91-3.20)
Without HAT	3509	10 374	270	2.60	2725 (95)	2207 (93)	2159 (90)				

*Adjusted for the following recipient variables at the time of transplantation (Table I): sex, age, diagnosis, total bilirubin, patient hospital status, year of transplant, insurance type, and donor predictors of warm ischemia time, cold ischemia time, liver type, and donor type.

14 days who necessitate an equally high degree of attention and earlier petition for exception scores given their significant risk of mortality.

In children with HAT after first transplantation who underwent retransplantation, 21% went on to develop recurrent HAT. This incidence was significantly higher than the 7.4% of first-time liver transplant recipients whose course was complicated by HAT. Given the low number of recipients with recurrent HAT, additional analyses, particularly looking at center-specific effects, were not possible. Surgical expertise and center practice alone likely do not account for this increased incidence of recurrent HAT. A single-center case series of 4 adults found thrombophilic conditions in all, suggesting the need for expanded workup in recipients whose course is complicated by HAT.[22] Stine et al additionally found a higher incidence of HAT in adults with pretransplant portal vein thrombosis in an analysis of the UNOS database; comparable studies in pediatric recipients are needed to further delineate subsets of transplant recipients that may be at higher risk for HAT or recurrent HAT.[23] Additionally, although recommendations for anticoagulation of the pediatric recipient with first HAT to prevent recurrent HAT are not currently available, they may be extrapolated from pediatric anticoagulation protocols to prevent initial HAT and include consideration of postoperative dipyridamole, dextran 40, and aspirin, as well as intraoperative Doppler to ensure hepatic artery patency, ultrasound with Doppler on arrival to the intensive care unit and again on postoperative day 1 and avoiding overtransfusion with hematocrit target of 25-30.[2,16]

In 2012, SPLIT published a quality improvement initiative that disseminated best surgical practices from a high-performing center with a low incidence of HAT.[2] In our study, the incidence of HAT decreased from 7.9% between 2002 and 2011 to 6.1% between 2012 and 2015; although era of transplantation was not a predictor of HAT. Although a decreased incidence of HAT over time is likely multifactorial and cannot be directly correlated with this quality improvement initiative, the importance of ongoing discussion between pediatric hepatologists and transplant surgeons towards agreement of best practices must be underscored.

Since 2012, SPLIT began capturing treatments for HAT. The majority of recipients with HAT underwent reoperation (76%); 68% were also anticoagulated and a minority of recipients with HAT underwent an interventional radiology procedure, observation, or anticoagulation alone. Given the shorter time period and smaller volume of data related to HAT treatment, only descriptive statistics were possible. Ongoing data capture will allow for more complex analyses in the future to better delineate predictors of graft and patient survival after HAT intervention.

One limitation of our analyses is that some potential risk factors for HAT could not be assessed owing to limitations of the SPLIT database. Donor height, for example, is not included in the SPLIT database, which limits analyses of size mismatch. Future integration between UNOS and SPLIT data will allow capture of this important variable to inform future analyses. Certain intraoperative factors including number of blood transfusions or use of anticoagulation were not recorded. Moreover, certain analyses were limited owing to a high degree of missing data for existing variables including the timing of HAT from transplantation. Abnormal hepatic artery anatomy or need for hepatic artery reconstruction also is not captured. An additional 680 recipients were also excluded from analyses as they were missing any follow-up data. This limitation is a known factor in using a large international registry where missing data cannot be retrieved. This study also identified areas in which more granular data about the technical aspects of the transplant surgical procedure and graft characteristics are needed. These areas require more attention and could potentially be addressed by the coordinated efforts of a learning network environment.[24] These limitations, however, are balanced by the strengths of using a large transplant dataset, enhancing this studies power and the ability to detect meaningful differences while increasing the generalizability of its findings.

Although the incidence of HAT seems to be decreasing by era, ongoing targets for quality improvement initiatives to prevent HAT remain paramount. Currently, center-specific techniques to decrease the incidence of HAT remain variable. Expansion of the SPLIT registry to include the use of intraoperative and/or postoperative anticoagulation prophylaxis would allow for better study of these interventions. In a time of organ scarcity with greater use of technical variant grafts, we describe the important finding of a lower risk of HAT in split, reduced, and living donor grafts compared with whole liver grafts, whereas previously technical variant grafts had been described as a risk factor for HAT in single-center studies. This finding, that the odds of developing HAT is lower in technical variant grafts, may be intrinsic to the graft itself, coming from a larger donor with larger vessels. Additionally, because higher volume centers have a higher use of technical variant grafts, surgical expertise may also play a role in decreasing the rate of HAT. Rana et al described

higher waitlist and post-transplantation mortality at low-volume transplant centers, defined as those performing <5 cases per year, with similar findings across all solid organs.[25] At a time of expansion of low-volume centers, ongoing discussion is required to determine where pediatric recipients may be best served and help to mitigate the risk of potentially avoidable morbidity and mortality. In this international registry study, we also demonstrate poorer short- and long-term graft and patient survivals in pediatric recipients whose post-transplant course is complicated by HAT. Specifically, we call attention to the still high rate of mortality in pediatric recipients with HAT despite allocation priority to facilitate urgent retransplantation. In a population of often very young children in whom survival benefit is significant, future SPLIT studies with linkage to the UNOS database and Social Security Death Master file are necessary to further elucidate the cause of death, status, and priority of listing for retransplantation at the time of death to improve outcomes in this vulnerable population. Ongoing collaboration and conversation between pediatric transplant surgeons and hepatologists at different centers, particularly with the dissemination of best practices from high-volume, high-performing centers, is needed to allow for real-time changes that will decrease the incidence of HAT and improve short and long-term outcomes for children with HAT after liver transplantation. ■

We acknowledge all SPLIT centers in the registry with special recognition of the coordinators who collect and submit data and allow these studies to be possible.

Submitted for publication Mar 21, 2020; last revision received May 26, 2020; accepted Jun 17, 2020.

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Table VI. Baseline characteristics for children with recurrent HAT after second transplantation (1995-2015)

Recipient and donor characteristics	HAT status	
	With HAT after first transplant (n = 281)	With HAT after second transplant (n = 25)
Age, y, mean (SD)		
<1	104 (37.0)	10 (45.5)
1-5	101 (35.9)	6 (27.3)
6-10	41 (14.6)	4 (18.2)
11-18	35 (12.5)	2 (9.1)
Missing	0	
Female sex	143 (50.9)	9 (40.9)
Missing	0	
ABO match		
Identical	223 (82.6)	19 (86.4)
Incompatible	44 (16.3)	3 (13.6)
Indication for first liver transplantation		
Acute liver failure	23 (8.2)	3 (13.6)
Biliary atresia	126 (44.8)	12 (54.6)
Other cholestatic liver disease	24 (8.5)	1 (4.6)
Metabolic	50 (17.8)	3 (13.6)
Malignancy	31 (11.0)	1 (4.6)
Other	27 (9.6)	2 (9.1)
Year of transplantation		
1995-2001	66 (23.7)	10 (45.5)
2002-2011	154 (55.4)	9 (40.9)
2012-2015	58 (20.9)	3 (13.6)
Hospital status at transplantation		
ICU	50 (17.8)	3 (13.6)
Hospitalized, not ICU	46 (16.4)	3 (13.6)
Not hospitalized	185 (65.8)	16 (72.7)
Medicaid and/or state-funded children's services	106 (40.2)	9 (47.4)
Missing	17	
Donor type		
Deceased, brain death	130 (46.8)	6 (27.3)
Deceased, cardiac donor	6 (2.2)	0
Deceased, unknown	98 (35.3)	9 (40.9)
Living	44 (15.8)	7 (31.8)
Missing	3	
Liver type (%)		
Whole	174 (62.8)	14 (63.6)
Split, reduced, or living	103 (37.2)	8 (36.4)
Missing	4	

Values are number (%) unless otherwise indicated.