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Hepatic artery thrombosis and use of anticoagulants and antiplatelet agents in pediatric liver transplantation

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Abstract

Background: Hepatic artery thrombosis (HAT) is a reported complication of 5%–10% of pediatric liver transplantations, rates 3–4 times that seen in adults. Early HAT (seen within 14 days after transplant) can lead to severe allograft damage and possible urgent re-transplantation. In this report, we present our analysis of HAT in pediatric liver transplant from a national clinical database and examine the association of HAT with anticoagulant or antiplatelet medication administered in the post-operative period.

Methods: Data were obtained from the Pediatric Health Information System database maintained by the Children's Hospital Association. For each liver transplant recipient identified in a 10-year period, diagnosis, demographic, and medication data were collected and analyzed.

Results: Our findings showed an average rate of HAT of 6.3% across 31 centers. Anticoagulant and antiplatelet medication strategies varied distinctly among and even within centers, likely due to the fact there are no consensus guidelines. Notably, in centers with similar medication usage, HAT rates continue to vary. At the patient level, use of aspirin within the first 72 h of transplantation was associated with a decreased risk of HAT, consistent with other reports in the literature.

Conclusion: We suggest that concerted efforts to standardize anticoagulation approaches in pediatric liver transplant may be of benefit in the prevention of HAT. A prospective multi-institutional study of regimen—possibly including aspirin—following transplantation could have significant value.

KEYWORDS
complication, liver allograft function/dysfunction, thrombosis and thromboembolism

1 | INTRODUCTION

Liver transplantation (LTx) is a life-saving measure for children with end-stage liver disease. Although long-term patient and allograft survival rates today exceed 80%,[1,2] significant post-operative complications continue to limit transplant success. In particular, the risk of thrombosis of the major hepatic vessels (hepatic artery, portal vein, hepatic veins) is concerning. These vascular thrombotic events can lead to severe allograft damage or the potential loss of the organ. Hepatic artery thrombosis (HAT) is the most common vascular event after liver transplant and can be particularly serious,[3] resulting in bile duct injury, sepsis, and/or loss of the allograft with need for re-transplantation if anti-thrombotic interventions are unsuccessful.

Abbreviations: ACD, anticoagulant citrate dextrose; ASA, aspirin; BA, biliary atresia; HAT, hepatic artery thrombosis; LTx, liver transplantation; PFIC, progressive familial cholestasis; PHIS, Pediatric Health Information Systems database; PSC, primary sclerosing cholangitis.

In children, HAT is a reported complication in approximately 5%–10% of all pediatric LTx recipients,[4–6] rates 3–4 times that observed in adults. Studies associate this increased incidence with whole allograft (versus split or living donor) transplants, longer warm ischemia time, and transplant program inexperience.[5,7] Yet, these factors alone do not fully account for the occurrence of HAT, suggesting additional uncontrolled differences in patients' clinical state and/or care patterns.

The use of antiplatelet and anticoagulant medications may impact the likelihood of HAT events.[8,9] Single-center reports have shown a reduced incidence of HAT with the use of aspirin (ASA)[10,11] and unfractionated and low-molecular-weight heparins,[12,13] among others. However, an international survey of post-operative LTx care spanning 98 centers noted a distinct lack of standardized protocols and thromboprophylactic medication variability.[14] This has created challenges in expanding the research needed to study preventive measures for HAT. Current literature suffers from reduced granularity by capturing only the general use of thromboprophylactic agents and from limited associations of programmatic HAT rates rather than patient events.

The work herein provides a patient- and drug-level description of HAT incidence related to antiplatelet and anticoagulant agent use in pediatric LTx recipients by analyzing a large, multicenter dataset of United States healthcare utilization. The manuscript begins with a review of patient-level factors and their relationship with HAT and expands to highlight differences by etiology. This is followed by a description of data regarding anticoagulant and antiplatelet exposure in the first 24, 48 and 72 h following LTx, and compared against the incidence of HAT. Our efforts are meant to highlight known variability among medication usage within programs and highlight the potential patient-specific associations with HAT.

2 | MATERIALS AND METHODS

2.1 | Data

Data utilized throughout this study were drawn from the Pediatric Health Information System® (PHIS) database maintained by the Children's Hospital Association. PHIS provides granular day-level clinical and resource utilization data for inpatient encounters for more than 49 children's hospitals across the United States. These data are augmented by the addition of a unique patient identifier allowing for longitudinal analysis of patient data. Data collected and utilized in this study fall into three broad categories:

1. *Diagnosis and procedure data*: All ICD-CM diagnosis and procedure codes were obtained from each encounter for a respective patient. While diagnoses were associated without timestamps to an encounter, specific dates for each coded procedure were obtained. For each diagnosis the "present on admission" flag was also recorded.
2. *Demographic and logistic data*: Age at admission, gender, and race/ethnicity data were extracted for each encounter. Logistic data included a unique hospital identifier and associated US Census region (North/South/East/West) for the center where a subject was treated. For confidentiality all hospital names were replaced with a random identifying integer used throughout this work.
3. *Medication data*: Day-level inpatient pharmacy data were obtained around drug class, therapeutic category, generic drug name, administration route, dosage form, strength, and unit. Although these data do not directly represent administrations, their presence in the billing to a patient strongly imply these orders have been completed. Medication brands and ingredients are standardized using the Clinical Transaction Classification™ to categorize hospital billing for pharmacy and other services.

2.2 | Study cohort

From this repository, our study cohort was created, focusing on pediatric transplants made during 10-year window between 01/01/2010 and 1/1/2020. Data post 2020 was not included given the possible variability in hospital transplantation patterns following the emergence of SARS-CoV-2. Due to variability in the "pediatric" age range treated by hospitals across the country this study considered patients up to 21 years of age (non-inclusive) at the time of transplant.

To begin, we identified a set of eligible transplant patients as defined by those encounters in which patients received a procedure code that included, ICD10: 0FY00Z0 (*Transplantation of Liver, Allogeneic, Open Approach*), or ICD9: 50.59 (*Liver Transplant/Other transplant of liver*). Given hospital varying adoption practices of the ICD10 coding standard, all analyses throughout this work utilized a combination of ICD9/10 codes to ensure the widest coverage of data. For patients identified to have received transplants in multiple encounters, only data from their first transplant encounter was included, as rates of HAT are known to differ based on previous transplant failures.

Critically, we recognize that in any observational cohort study, medical history exists for a given patient prior to the study window. To ensure we best captured true *initial* transplant events for patients, we extracted all procedure history and diagnoses for any patient after 1/1/2000, a full 10 years prior to the study period. Given changes in transplant techniques, medication usage, and variability in the quality of early PHIS data between multiple centers, those children with a prior transplant between 1/1/2000 and 1/1/2010 were excluded.

Next, each patient's transplant was labeled as having or not having a HAT event. Unlike venous events, HAT does not have a unique diagnostic code. To identify arterial thrombosis events, we utilized a combination of two ICD codes under the broad category of I74: Arterial embolism and thrombosis. Specifically, we utilized ICD10 I74.8: *Embolism and thrombosis of other arteries*, and I74.9: *Embolism and thrombosis of unspecified artery*, as well as their ICD9 counterparts 444.89, and 444.9 respectively.

We excluded those patients whose data indicated the thrombosis code was "present on admit" in the same encounter as their transplant. Moreover, patients with thrombotic events prior to our analysis window or prior to the transplant date were also excluded to ensure that we capture the post-transplant thrombosis events and not subsequent coding of existing conditions. Finally, we sought to capture only those patients with liver transplant-associated thrombosis, defined as a thrombosis diagnosis during the transplant encounter. As such, those patients with thromboses in an encounter following the transplant visit were excluded.

2.3 | Analysis

Utilizing this large nationally drawn cohort, our manuscript explores HAT in pediatric liver transplants in two ways. First, by describing the thrombosis rates in relation to the transplant etiology and overall patient demographics. Second, by presenting a comprehensive analysis of the medication profiles patterns across institutions and their potential associations to short-term thrombotic events. Details of each can be found in the respective subsections to follow.

All analyses and were performed using Python 3, Pandas, Numpy/Scipy and Statsmodels[15–19]; together with the glmer R package and bobyqa optimizer.[20]

2.3.1 | Demographics, etiology and thrombosis incidence

To begin, we provide descriptive statistics around the demographics of overall pediatric liver transplant cohort over the study period, stratifying those with and without short-term thrombotic events during the transplant encounter. In addition to distributions race, age, and sex, we include the prevalence of comorbid diagnosis known to drive transplant need were computed. A listing of diagnoses and respective codes used to determine prevalence across the cohort can be found in Table S1.

2.3.2 | Medication profiles

We next provide a series of analyses characterizing the exposure patterns of anticoagulant and antiplatelet agents over a 72-h window post-transplant and study their relationship to HAT rates across the aggregate, institutional-, and patient-level. Although we recognize that therapeutic antithrombotic protocols can extend beyond 72 h, in line with existing works this time threshold was set to limit the capture of additional medications that might be used as treatment for thrombosis, and not as prophylaxis.[21] As a specific timestamp of the transplant was not available on the date of service, the analysis was focused on the three absolute days following the procedure to aid in standardizing opportunity to receive medications. For reference the transplant day was defined as T_0, and the subsequent 72 h were denoted as $T_{24,}$ $T_{48,}$ and T_{72}, respectively. A complete list of therapeutics can be found in Table S2.

At the aggregate level, our analysis began with computing the proportion of both thrombosis and non-thrombosis cohorts with exposure to each agent over the 72-h window. As exposure is defined as medication use at or before a specific timepoint, percentages are expected to be monotonically increasing. We looked further to capture variability in usage by institution and assess how such usage might be related to center's HAT rates. To do so, we analyzed the percentage of patients within each center exposed to different medications across each day of the 72-h window study, allowing for objective data on medication usage post-transplant.

For both analyses, three areas warranted additional consideration in determining exposure:

1. *Flushes*: First, the use of low-dose anticoagulant agents for IV flushes (e.g., heparin flushes). To prevent biasing our data, we took extensive steps to remove these orders from the documented pharmacy data. At a high level, we were able to directly exclude listed flush agents in the *anticoagulant* category; these included: *Flush combination solutions* (*including Heparin and sodium chloride flush and kit and Heparin and vancomycin*, etc.) as well as *Vascular access device solutions* (*Hydrochloric acid flush*). However, it is recognized that heparin can be ordered and then diluted to perform the flush, thus potentially artificially inflating proportions of heparin exposure. To address this, we evaluated the captured dosing form of heparin and removed those below 100 units as discussed by Riley and colleagues.[22] Finally, all heparin without both a documented dosage unit and strength were also excluded.
2. *Multi-allograft patients*: Although we focus on the patients' initial transplant event, it was observed a proportion of patients ($n = 70$) received a second liver transplant in the same encounter, with a mean and median time to second transplant of 15 and 8 days respectively. A fractional subset of patients ($n = 14$) received a transplant within the 3-day window. Although these patients could not be excluded, as retransplantation is likely not independent from the incidence of early HAT, all analyses were adjusted to extract medications from T_0 up to, but not including or after, the date of their second transplant. Proportion denominators were adjusted for the change in $T_{48,}$ and $T_{72.}$
3. *Low-volume centers*: It was noted that across our study cohort, a small subset of patients received treatment at centers that do not routinely perform pediatric liver transplant. To remove potential bias protocol variability at institutions where transplants were not routinely performed and to better account for center-level variability, we removed "low-volume" centers, defined as those with the lowest 25% of transplants performed across our cohort. Ultimately representing those with >37 total transplants over the 10-year study period, or just under four transplants per year.

2.4 | Mixed-model comparison

To provide a more direct comparison between exposure to various anticoagulants or antiplatelet agents and incidence of transplant encounter thrombosis, our final analysis moves to the patient level. To do so, a logistic mixed-effects model was fit, with binary flags were created for medication exposure at (T_{72}). All agents whose prevalence was found to be <5% across the cohort were rolled into an "Other" category for stability. The model was adjusted for age, sex, race, and census region of the treating institution with a random intercept added for institution. Additionally, given the observed differences in HAT rates by etiology, we adjusted for each comorbidities using a binary flag, rolling up rare conditions using the same 5% threshold.

3 | RESULTS

In total, 4999 patients had procedure codes matching the relevant transplant codes selected and evaluated for inclusion. Of these, 361 had multiple discrete transplant encounters, of which only the initial encounter was considered.

Of these, we excluded 1638 patients for transplants prior to the study start date of 1/1/2010. With respect to the remaining 3361 patients, 36 were excluded as a thrombosis diagnosis was listed as present on admit. An additional four were excluded for thrombosis events prior to the study window, and seven patients were removed for thrombosis events after the study window but prior to transplant. A final 55 patients were excluded as their records indicated a thrombosis event, but no transplant in the study window, and thus we excluded them to prevent bias of potentially including a long-term thrombosis event post-discharge from an earlier excluded transplant. A review of counts for each exclusion criteria can be found in Figure 1.

In total, our study cohort of 31 hospitals consisted of 3259 pediatric patients with transplants across 31 U.S. hospitals; 206 (6.3%) of whom had a documented HAT during their first transplant encounter.

3.1 | Demographics, etiology and thrombosis incidence

Table 1 presents the demographics and etiology for our population of patients who underwent initial pediatric liver transplant; data are provided separately for those with and without thrombosis events. While the gender proportions were well balanced, the mean age in years for patients developing HAT (μ: 3.55, σ: 4.71) was lower than those who did not (μ: 5.88, σ: 5.92). Caucasian patients were found to make up a slightly higher proportion of patients with HAT than those without (67% vs. 61.5%), while African American patients represented a slightly lower proportion of patients with HAT than those without (7.3% vs. 12.1%).

With respect to the transplant etiology, the diagnoses of primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), and biliary atresia (BA) were more prevalent in patients with HAT than in those without HAT (PSC: 12.1% vs. 7.3%, PFIC: 23.3% vs. 16.0%, BA: 38.8% vs. 34.2%). Notably, patients receiving a transplant due to metabolic disorders—maple syrup urine disease, methylmalonic acidemia and propionic acidemia—made up a larger proportion of HAT than non-HAT patients (6.3% vs. 3.9%), (5.3% vs. 3.3%) and (6.3% vs. 2.7%), respectively. Lower incidences of alpha-1 antitrypsin deficiency (0.5% vs. 2.7%), unspecified cirrhosis (18.5% vs. 24.8%), congenital hepatic fibrosis (10.7% vs. 16.6%), autoimmune hepatitis (2.9% vs. 5.2%), non-A/B/C viral hepatitis (0.5% vs. 1.1%), and Wilson disease (no cases reported vs. 1.2%) were seen in the HAT population compared to patients without HAT.

3.2 | Medication profiles

After removing the low-volume centers, 23 of the 31 centers were carried forward, representing 3152 patients, with 197 HAT events. It is worth noting that the low-volume centers had an increased mean incidence of HAT of 8.4%, but with only nine HAT events over 107 patients, their removal did not significantly impact the larger volume centers' 6.3% event rate. Looking first to the aggregate level, Figure 2 presents the overall rate of documented use for each agent at $T_{24,}$ $T_{48,}$ and $T_{72,}$ stratified by HAT outcome. In the first 24 h following surgery, heparin use was documented in 78% of patients, while dextran and the administration of ASA was documented in nearly 33% and 29% of patients, respectively. A diverse set of other anticoagulants were noted, including antithrombin III, dipyridamole, citrate, and enoxaparin. Within the first 72 h following surgery, heparin exposure was documented in 80% of patients, while dextran exposure remained at 34% and ASA exposure climbed to 47% of patients.

Breaking down the profiles by institution, we computed the percentage of patients exposed to each agent by center. Figure 3 presents the results at T_{72}, with T_{24} and T_{48} detailed in Figures S1 and S2 respectively. For reference, we ranked centers by their HAT rates from lowest (left) to highest (right) and indicate the 25th and 75th percentiles of HAT rates across all considered centers by those left of the blue and right of the red vertical lines respectively. It is clear, a diverse set of anticoagulant and antiplatelet agents are used nationally following pediatric liver transplant. The data are notable for a high prevalence of heparin and ASA use following liver transplant at multiple centers. Some agents (e.g., dipyridamole, enoxaparin), were used with relative frequency, but numbers were driven by a small subset of institutions. Others, such as anticoagulant citrate dextrose (ACD) solution A and antithrombin III, were less frequently used, but seen at most institutions.

3.3 | Mixed-model comparison

We quantified the association of specific of anticoagulant or antiplatelet exposure agents within 72 h and the odds of HAT incidence during the transplant admission. Table 2 provides the results of our

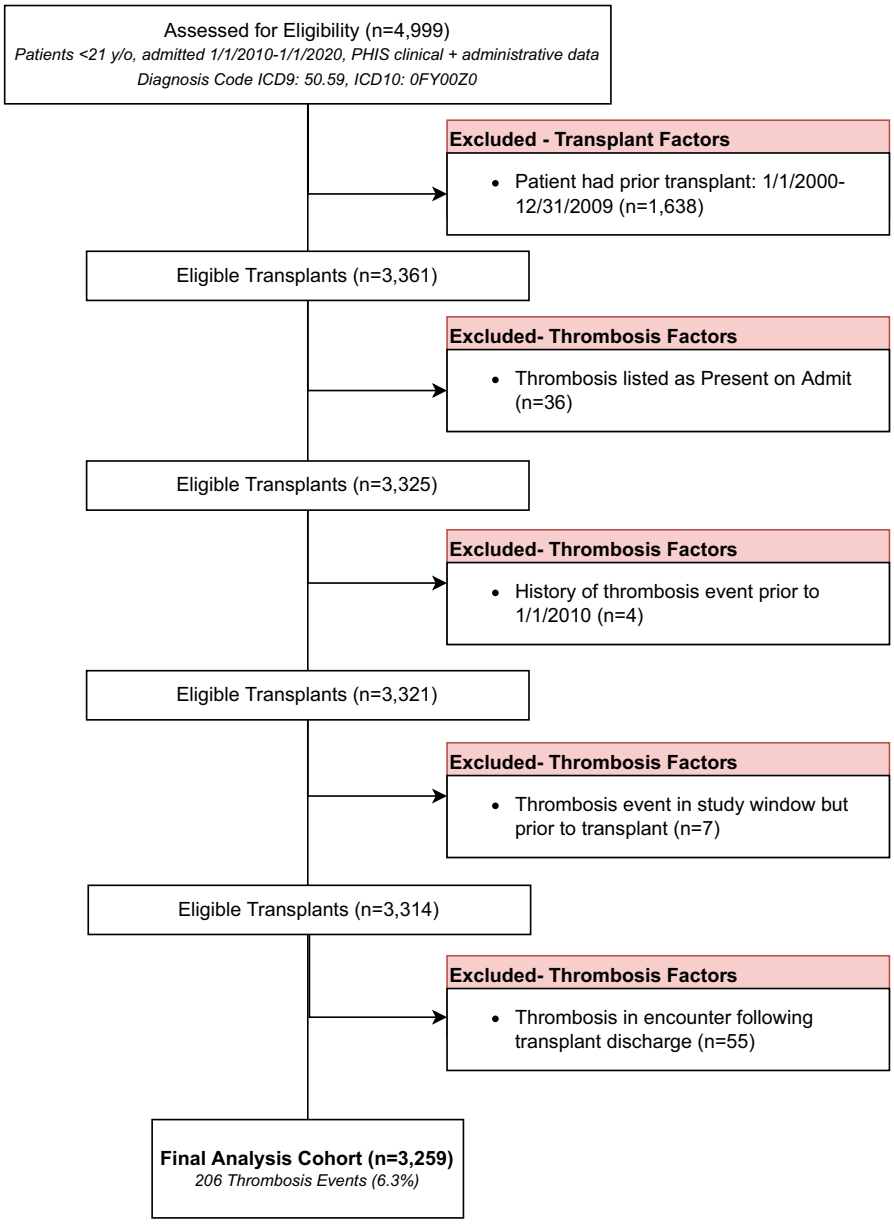

FIGURE 1 Study cohort CONSORT diagram.

mixed-model analysis. Adjusting for age, sex, race, census region, and fitting a random intercept to help adjust for institution-level variance, the use of ASA was associated with a significant reduction in the incidence of HAT ($p < .001$). We also note that antithrombin III was associated with an increased incidence of HAT, perhaps due to its use in conjunction with heparin for augmented anti-thrombotic activity in the face of possible HAT.

4 | DISCUSSION

Hepatic artery thrombosis is a serious complication of pediatric LTx, often resulting in ischemic injury to the biliary tree, graft loss and/or the possibility of urgent re-transplantation.[5,23] The reported incidence of HAT in pediatric patients can range from 1% to 26%,[14,15] but most studies in children (including our study) report an incidence between 5% and 10%.[3–5] Re-transplantation, arterial variants, operative time, and pediatric liver transplant in general have been associated with HAT.[24] Both early presentations of HAT (typically defined as within the first 7–30 days after transplant) and late HAT are problematic. Late HAT is often clinically silent—detected by screening imaging and/or suspicious laboratory work—and acute intervention may not be necessary if collateral arterial revascularization has developed naturally.[25] Early HAT, however, often requires urgent operative exploration, directed thrombolytic therapy (e.g., tissue plasminogen activator administration), revision of arterial anastomoses, and carries the possibility of additional surgical explorations or re-transplantation.

While thromboprophylactic therapy has been shown to affect HAT incidence in various reports, randomized investigations of therapies to prevent thrombosis in liver transplant patients are limited. A recent review by Surianarayanan and colleagues identified two

TABLE 1 Cohort demographics.

	All ($n = 3259$)	HAT ($n = 206$)	No HAT ($n = 3053$)
Age (years, SD)	5.72 (5.87)	3.545 (4.71)	5.87 (5.92)
Sex: n = (%)			
Male	1626 (49.9)	104 (50.5)	1522 (49.9)
Female	1633 (50.1)	102 (49.5)	1531 (50.1)
Race: n = (%)			
Multi-racial	55 (1.7)	5 (2.4)	50 (1.6)
American Indian	56 (1.7)	2 (1.0)	54 (1.8)
Asian	179 (5.5)	13 (6.3)	166 (5.4)
Black	384 (11.8)	15 (7.3)	369 (12.1)
Other	438 (13.4)	24 (11.7)	414 (13.6)
Pacific Islander	28 (0.9)	3 (1.5)	25 (0.8)
White	2015 (61.8)	138 (67.0)	1877 (61.5)
Unknown	104 (3.2)	6 (2.9)	98 (3.2)
Etiology: n = (%)			
A1AT deficiency	84 (2.58)	1 (0.48)	83 (2.72)
Acute liver failure	269 (8.25)	18 (8.74)	251 (8.22)
Alagille	155 (4.76)	12 (5.82)	143 (4.68)
Autoimmune hepatitis	165 (5.06)	6 (2.91)	159 (5.21)
Biliary atresia	1125 (34.52)	80 (38.84)	1045 (34.23)
Cirrhosis	795 (24.39)	38 (18.45)	757 (24.8)
Congenital hepatic fibrosis	530 (16.26)	22 (10.68)	508 (16.64)
Glycogen storage disease	19 (0.58)	0 (0.0)	19 (0.62)
Hepatitis A	3 (0.09)	0 (0.0)	3 (0.1)
Hepatitis B	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis C	3 (0.09)	1 (0.48)	2 (0.07)
Hepatoblastoma	130 (3.99)	10 (4.85)	120 (3.93)
Hepatocellular carcinoma	19 (0.58)	2 (0.97)	17 (0.56)
Maple syrup urine disease	131 (4.02)	13 (6.31)	118 (3.86)
Methylmalonic acidemia	111 (3.41)	11 (5.34)	100 (3.28)
PFIC	537 (16.48)	48 (23.3)	489 (16.02)
Primary sclerosing cholangitis	248 (7.61)	25 (12.14)	223 (7.3)
Propionic acidemia	96 (2.95)	13 (6.31)	83 (2.72)
Urea cycle defect	357 (10.95)	25 (12.14)	332 (10.88)
Viral hepatitis	35 (1.07)	1 (0.48)	34 (1.11)
Wilson disease	35 (1.07)	0 (0.0)	35 (1.15)

Abbreviations: HAT, hepatic arterial thrombosis; PFIC, progressive familial intrahepatic cholestasis.

abstracts, but no full manuscripts.[26] Earlier studies by Heffron and colleagues in 2003 and Ziaziaris and colleagues in 2017 detailed non-randomized anticoagulation approaches to prevent HAT in children that resulted in low rates of HAT in their patient populations.[27,28] Heffron and colleagues attributed success to a combination of ASA and prostaglandin, while Ziaziaris and colleagues found that post-operative antithrombin III, fresh frozen plasma, and unfractionated heparin was successful in their patients. These variations in reported anticoagulation protocols and practices were reflected in the results of a survey of Studies of Pediatric Liver Transplant (SPLIT) Registry contributing members published in 2018. The study authors noted "marked variation in the type, dose, initiation, and duration of therapy across centers" and called for the systematic evaluation of anticoagulation strategies and the development of guidelines for the prevention and management of thrombotic complications following pediatric LTx.[29]

In our analysis, heparin, ASA, and dextran were the most common agents used in the first 72 h after transplant, given in 80%, 47% and 34% of patients, respectively. Interestingly, ASA administration documented within the first 72 h after surgery was the only medication

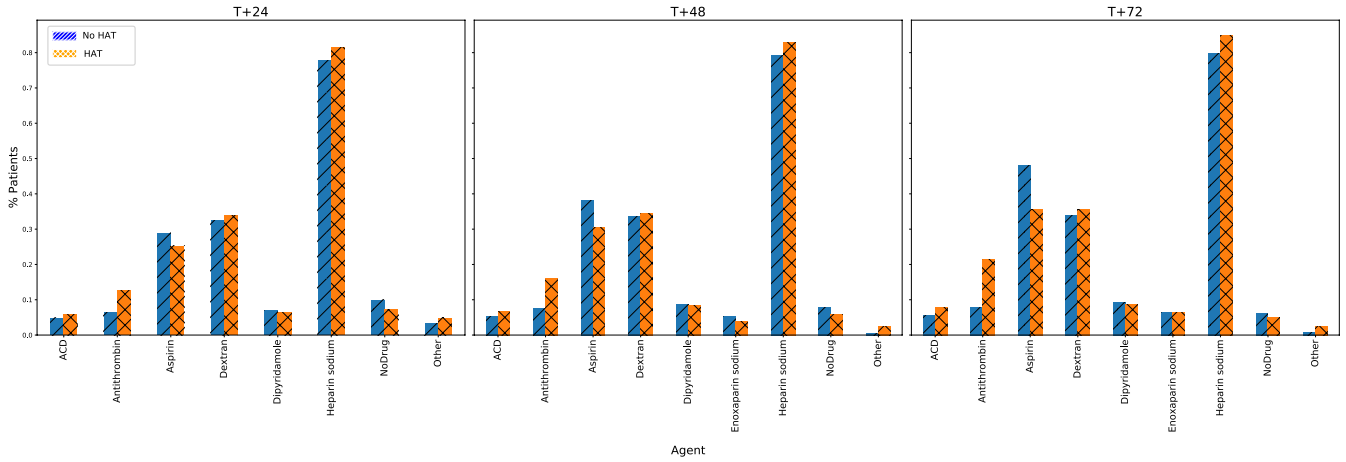

FIGURE 2 Percentage of medication exposure 24-, 48-, and 72-h post-transplant stratified by patient's HAT outcome. ACD, anticoagulant citrate dextrose.

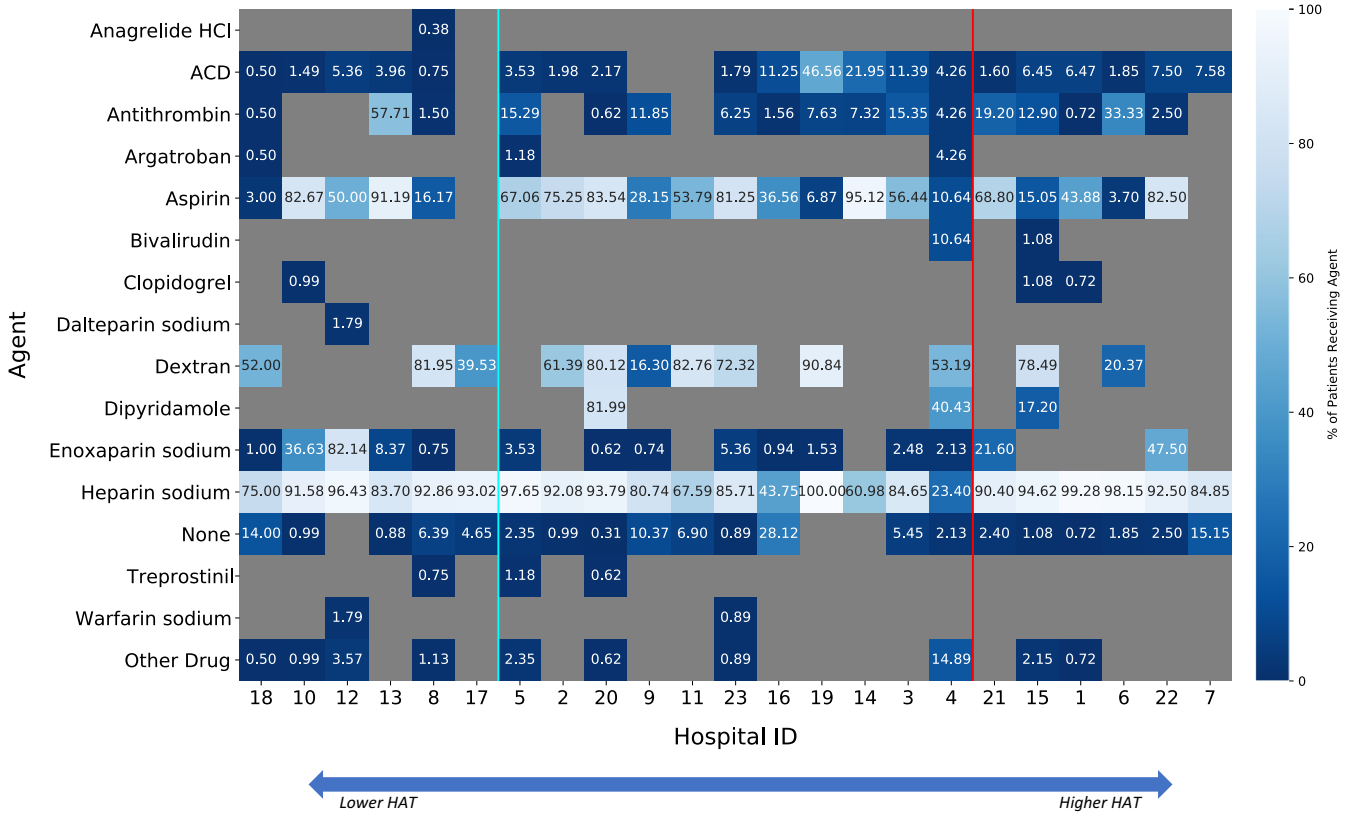

FIGURE 3 Heatmap of anticoagulant/antiplatelet medication within the first 72 h following liver transplant. Centers are ranked from the lowest incidence of HAT (left) to the highest (right). 25th and 75th percentiles are marked with green and red lines, respectively. ACD, anticoagulant citrate dextrose.

associated with a decreased incidence of HAT. Aspirin interferes with platelet aggregation and has been posited to be a helpful antithrombotic agent post-transplant by other groups. Vivarelli and colleagues demonstrated the benefit of ASA on *late* HAT in adults. They showed for "high-risk" patients (defined as those who received a graft from donors who died of a stroke and/or patients that received an interpositional iliac artery) HAT incidence >30 days after transplant was 0.6% in patients on ASA compared to 3.6% in those not on ASA with more than 1000 days of follow-up. An additional study by Shay and colleagues evaluated use of ASA after adult LTx and found decreased early HAT leading to graft loss and increased survival in patients given within their cohort of 469 patients (165 receiving ASA).[10] Few reports specifically evaluate ASA in pediatric patients. Aspirin was part of a regimen that prevented HAT (and other vascular complications) in a series of 69 pediatric and adult segmental allograft transplants.[30] In a separate study by Borst and colleagues,

TABLE 2 Mixed-model results: Association of anticoagulant and antiplatelet agents 72 h post-transplant and HAT.

		Coefficient	*p*-value	Bootstrapped 95% CI
Demographics	Log-age	0.743	<.001	(0.664–0.828)
	Gender			
	Male	1.047	.767	(0.778–1.446)
	Female	Reference		
Race	American Indian	0.715	.656	(0.062–1.86)
	Asian	1.007	.983	(0.467–1.759)
	Black	0.631	.111	(0.328–1.051)
	Pacific Islander	1.617	.46	(0.192–4.793)
	Multi-racial	1.221	.716	(0.265–3.069)
	Other	0.838	.507	(0.487–1.377)
	Unknown	0.737	.506	(0.214–1.563)
	Caucasian	Reference		
Census region	Northeast	0.458	.031	(0.219–0.947)
	South	0.67	.249	(0.317–1.359)
	West	0.606	.146	(0.299–1.223)
	Midwest	Reference		
Drug	ACD	1.309	.373	(0.65–2.31)
	Antithrombin	3.647	<.001	(2.327–5.891)
	Aspirin	0.522	<.001	(0.352–0.761)
	Dipyridamole	1.292	.524	(0.534–2.779)
	Dextran	1.353	.194	(0.874–2.114)
	Enoxaparin sodium	1.195	.609	(0.535–2.343)
	Heparin sodium	1.574	.081	(0.953–2.846)
	Other drug	5.392	.003	(1.367–15.391)
Etiology	Acute liver failure	1.059	.838	(0.535–1.712)
	Biliary atresia	0.87	.449	(0.614–1.3)
	Cirrhosis	0.89	.657	(0.526–1.394)
	Congenital hepatic fibrosis	0.692	.26	(0.363–1.224)
	PFIC	1.334	.121	(0.935–1.923)
	Primary sclerosing cholangitis	2.055	.004	(1.202–3.385)
	Urea cycle defect	0.767	.292	(0.42–1.166)
	Other diagnosis	1.14	.521	(0.749–1.716)

Abbreviations: ACD, anticoagulant citrate dextrose; PFIC, progressive familial intrahepatic cholestasis.

ASA was associated with reduced risk of post-operative thrombosis in their cohort of 92 pediatric liver transplants in 82 patients.[11]

Of note, we found that centers with similar thromboprophylactic profiles (including those utilizing high rates of ASA) may have disparate rates of HAT (Figure 3). While our model adjusted for transplant etiology and other patient-specific characteristics, this suggests that consideration of a broader set of conditions is warranted. Data including the exact dosage and timing of medications would be necessary. Moreover, the ability to expand patient representation with operative data will be valuable. Re-transplantation, arterial variants, operative time, and pediatric liver transplant in general have been associated with HAT.[24] Illustrative of this, Ebel and colleagues evaluated the records of 3801 pediatric recipients from 54 centers in the SPLIT registry. These data showed an incidence of HAT of 7.5% from 1995 to 2016, and the authors found that prolonged warm ischemia time was associated with an increased risk of developing HAT, while receiving a variant allograft (reduced, split, or living donor grafts) was associated with a decreased risk of HAT.[5] Patient selection and operative techniques may also play a large role in HAT. A graft-to-weight ratio of 1.1% or less and intraoperative HAT were independently associated with post-operative HAT in a study by Seda-Neto and colleagues.[31]

Finally, a small subset (~6.2%) of patients was identified across institutions for whom none of the selected anticoagulants or antiplatelet agents were given after LTx. This could be due to missing data or center-based variations in practice. For instance, in a patient with perceived risk of increased post-operative bleeding, prophylaxis may have been withheld by the transplant team.[10] Similarly, certain centers may not routinely administer post-LTx anticoagulant. Other considerations could include the use of vasodilators (e.g., prostaglandins) as part of a center's strategy to manage HAT risk, factors that we did not evaluate.

4.1 | Limitations

Given the descriptive nature of the described study, this work has several notable limitations. First, while the accessibility and large size of health care utilization databases are valuable in examining limited events like HAT, they lack of detailed clinical information, particularly around the timing of HAT events. This in turn raises the possibility that drug exposures within 72 h of transplant may be reactive and not part of a preventive strategy. While we cannot definitively say that medications from the database were used in the post-operative period and not in the operating room, we think it highly likely that most anticoagulant and antiplatelet agents were administered after the surgery. In general, anticoagulants are held prior to the surgery or patients receive a reversal agent at or near the time of the operation. Furthermore, we are unable to gauge the effectiveness of medications that are rarely used and/or newly developed for anticoagulation measures, like bivalirudin.[32]

Second, our data rely on proper documentation and coding for each event and medication. Errors or missing information create inaccuracy. Even within the diagnostic codes chosen, there is room for overlap with other conditions. For instance, the ICD-9-CM code for HAT (444.89), also covers thrombosis for "specified site NEC (not elsewhere classified)." While the majority of arterial thromboses (e.g., coronary, pulmonary, cerebral, etc.) have their own ICD-9-CM codes, coding vagaries such as this could mean that a non-HAT event was coded similarly. Similarly, without access to anti-factor Xa levels, heparin exposure that would not be considered therapeutic (e.g., central venous catheter or arterial line monitoring), may not have been identified and excluded. Additionally, while antithrombin III administration was observed across most centers, the inability to evaluate antithrombin III activity levels limited the ability to assess therapeutic efficacy. Antithrombin III activity levels are generally incorporated into heparin therapy protocols and are essential to ensure the therapeutic efficacy of heparin.[29,33]

Finally, this work did not specifically account for the impact of multi-organ transplants (heart-liver, kidney-liver, etc.). For descriptive studies such as this, excluding these patients may have introduced a latent selection bias from institutions who are more or less likely to perform such operations, and themselves have differing rates of HAT. However, we note that separation of these data will be critical in strategies for prospective studies.

5 | CONCLUSION

HAT is a significant complication of LTx that can limit both allograft and patient survival. We have presented retrospective data on the incidence of HAT and anticoagulation strategies associated with HAT based on the multicenter PHIS comparative pediatric database. Altogether, we believe these data provide a thought-provoking overview of the use of anticoagulants and antiplatelet agents in pediatric LTx. While the PHIS database includes clinical diagnosis and medication data from inpatient hospital stays, these data are limited. However, our work—along with others—strongly suggests the need for prospective, multicenter studies evaluating standardized thromboprophylactic regimens. Based on our findings, a regimen that incorporates an antiplatelet agent (e.g., ASA) early in the post-operative course may be a prudent option. Transplant centers and leaders should create standardized approaches to better understand the role of anticoagulants and antiplatelet agents in pediatric LTx.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Keith Feldman, Ryan T. Fischer; data collection: Keith Feldman; analysis and interpretation of results: Keith Feldman, Daniel E. Heble, Richard J. Hendrickson, Ryan T. Fischer; draft manuscript preparation: Keith Feldman, Daniel E. Heble, Richard J. Hendrickson, Ryan T. Fischer. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

No relevant conflicts of interest are noted by the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Rawal N, Yazigi N. Pediatric liver transplantation. *Pediatr Clin North Am*. 2017;64:677-684.
2. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: liver. *Am J Transplant*. 2021;21(suppl 2):208-315.
3. Yang Y, Zhao JC, Yan LN, et al. Risk factors associated with early and late HAT after adult liver transplantation. *World J Gastroenterol*. 2014;20:10545-10552.
4. Yazigi NA. Long term outcomes after pediatric liver transplantation. *Pediatr Gastroenterol Hepatol Nutr*. 2013;16:207-218.
5. Ebel NH, Hsu EK, Dick AAS, Shaffer ML, Carlin K, Horslen SP. Decreased incidence of hepatic artery thrombosis in pediatric liver transplantation using technical variant grafts: report of the

Society of Pediatric Liver Transplantation Experience. *J Pediatr*. 2020;226:195-201.e1.
6. Kutluturk K, Sahin TT, Karakas S, et al. Early hepatic artery thrombosis after pediatric living donor liver transplantation. *Transplant Proc*. 2019;51:1162-1168.
7. Channaoui A, Tambucci R, Pire A, et al. Management and outcome of hepatic artery thrombosis after pediatric liver transplantation. *Pediatr Transplant*. 2021;25:e13938.
8. Algarni AA, Mourad MM, Bramhall SR. Anticoagulation and antiplatelets as prophylaxis for hepatic artery thrombosis after liver transplantation. *World J Hepatol*. 2015;7:1238-1243.
9. Flynn E, Huang JY, Hardikar W, Herd L, Hodgson A, Monagle P. Antithrombotic management and thrombosis rates in children post-liver transplantation: a case series and literature review. *Pediatr Transplant*. 2019;23:e13420.
10. Shay R, Taber D, Pilch N, et al. Early aspirin therapy may reduce hepatic artery thrombosis in liver transplantation. *Transplant Proc*. 2013;45:330-334.
11. Borst AJ, Sudan DL, Wang LA, Neuss MJ, Rothman JA, Ortel TL. Bleeding and thrombotic complications of pediatric liver transplant. *Pediatr Blood Cancer*. 2018;65:e26955.
12. Hashikura Y, Kawasaki S, Okumura N, et al. Prevention of hepatic artery thrombosis in pediatric liver transplantation. *Transplantation*. 1995;60:1109-1112.
13. Sugawara Y, Kaneko J, Akamatsu N, Imamura H, Kokudo N, Makuuchi M. Anticoagulant therapy against hepatic artery thrombosis in living donor liver transplantation. *Transplant Proc*. 2002;34:3325-3326.
14. Calinescu AM, Karam O, Wilde JCH, Ansari M, McLin VA, Wildhaber BE. International survey on anticoagulation and antiplatelet strategies after pediatric liver transplantation. *Pediatr Transplant*. 2019;23:e13317.
15. McKinney W. *Data Structures for Statistical Computing in Python*. Proceedings of the 9th Python in Science Conference; 2010.
16. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B. Scikit-learn: machine learning in python. *J Mach Learn Res*. 2011;12:2825-2830.
17. Harris CR, Millman KJ, van der Walt SJ, et al. Array programming with NumPy. *Nature*. 2020;585:357-362.
18. Virtanen P, Gommers R, Oliphant TE, et al. SciPy 1.0: fundamental algorithms for scientific computing in python. *Nat Methods*. 2020;17:261-272.
19. Seabold S, Perktold J. Statsmodels: econometric and statistical modeling with python. *Proceedings of the 9th Python in Science Conference*. 2010;57:61.
20. Bates DM, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *arXiv*. 2014.
21. Kim BR, Oh J, Yu KS, Ryu HG. Pharmacokinetics of human antithrombin III concentrate in the immediate postoperative period after liver transplantation. *Br J Clin Pharmacol*. 2020;86:923-932.
22. Riley M, Meyers R; Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Position Statement on heparin safety concerns. *J Pediatr Pharmacol Ther*. 2016;21:530-532.
23. Mourad MM, Liossis C, Gunson BK, et al. Etiology and management of hepatic artery thrombosis after adult liver transplantation. *Liver Transpl*. 2014;20:713-723.
24. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant*. 2009;9:746-757.
25. Kivela JM, Kosola S, Kalajoki-Helmio T, et al. Late hepatic artery thrombosis after pediatric liver transplantation: a cross-sectional study of 34 patients. *Liver Transpl*. 2014;20:591-600.
26. Surianarayanan V, Hoather TJ, Tingle SJ, Thompson ER, Hanley J, Wilson CH. Interventions for preventing thrombosis in solid organ transplant recipients. *Cochrane Database Syst Rev*. 2021;3:CD011557.
27. Heffron TG, Pillen T, Welch D, Smallwood GA, Redd D, Romero R. Hepatic artery thrombosis in pediatric liver transplantation. *Transplant Proc*. 2003;35:1447-1448.
28. Ziaziaris WA, Darani A, Holland AJA, et al. Reducing the incidence of hepatic artery thrombosis in pediatric liver transplantation: effect of microvascular techniques and a customized anticoagulation protocol. *Pediatr Transplant*. 2017;21:12917.
29. Voulgarelis S, Vitola B, Lerret SM, Hong JC, Scott JP. Perioperative anticoagulation practices for pediatric liver transplantation. *Pediatr Transplant*. 2018;22:e13193.
30. Rodriguez-Davalos MI, Arvelakis A, Umman V, et al. Segmental grafts in adult and pediatric liver transplantation: improving outcomes by minimizing vascular complications. *JAMA Surg*. 2014;149:63-70.
31. Seda-Neto J, Antunes da Fonseca E, Pugliese R, et al. Twenty years of experience in pediatric living donor liver transplantation: focus on hepatic artery reconstruction, complications, and outcomes. *Transplantation*. 2016;100:1066-1072.
32. Craig-Schapiro R, Banc-Husu AM, Taylor SA, Bercovitz RS, Lemoine CP, Superina RA. Bivalirudin for the prevention of hepatic artery thrombosis in pediatric liver transplantation. *Pediatr Transplant*. 2021;25:e14068.
33. Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1995;108:258S-275S.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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