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Vascular thrombosis after pediatric liver transplantation: Is prevention achievable?

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Abstract

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Declaration of Competing Interest

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Supplementary materials

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Background: Vascular thromboses (VT) are life-threatening events after pediatric liver transplantation (LT). Single-center studies have identified risk factors for intra-abdominal VT, but large-scale pediatric studies are lacking.

Methods: This multicenter retrospective cohort study of isolated pediatric LT recipients assessed pre- and perioperative variables to determine VT risk factors and anticoagulation-associated bleeding complications.

Results: Within seven postoperative days, 31/331 (9.37%) patients developed intra-abdominal VT. Open fascia occurred more commonly in patients with VT (51.61 vs 23.33%) and remained the only independent risk factor in multivariable analysis (OR = 2.84, $p = 0.012$). Patients with VT received more blood products (83.87 vs 50.00%), had significantly higher rates of graft loss (22.58 vs 1.33%), infection (50.00 vs 20.60%), and unplanned return to the operating room (70.97 vs 16.44%) compared to those without VT. The risk of bleeding was similar ($p = 0.2$) between patients on and off anticoagulation.

Conclusions: Prophylactic anticoagulation did not increase bleeding complications in this cohort. The only independent factor associated with VT was open fascia, likely a graft/recipient size mismatch surrogate, supporting the need to improve surgical techniques to prevent VT that may not be modifiable with anticoagulation.

Keywords

Pediatric liver transplantation; Vascular complications; Hepatic artery thrombosis; Portal vein thrombosis

Introduction

Liver transplantation (LT) is lifesaving for patients with end-stage liver disease, selective metabolic disorders, and liver tumors. Refinements of anesthesia, surgical techniques and perioperative care have dramatically improved outcomes with prolonged survival and acceptable morbidity [1]. Acute hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) are reported in up to 25% of patients [2]. Though variable by centers, intra-abdominal vascular thrombosis (VT) represents the leading cause of graft loss in the immediate post-transplant period and affects patient survival [3]. Reduced production of anticoagulants due to liver dysfunction induces a prothrombotic stage [4]. Additional risk factors for vascular thrombosis inherent to LT in children include small donor and recipient size, partial variant grafts, complex vascular reconstructions [5], excessive use of blood products [6], and prolonged warm ischemia time [7].

Prophylactic anticoagulation is a routine practice to prevent life-threatening thromboembolic complications postoperatively. The utility of thromboprophylaxis after general surgery has been well-established in the literature [8]. However, it is not a standardized practice in LT, and there is marked variation in the type, dose, initiation, and duration of therapy across pediatric LT centers [9]. Additionally, most studies are from single institutions with significant variability in postoperative anticoagulation practices [10]. While there is a large-scale retrospective study on risk factors for HAT utilizing the Studies of Pediatric Transplantation (SPLIT) database, data on postoperative anticoagulation practices and

timing of thrombotic events were not included [7]. Furthermore, no rigorous studies have determined the optimal intervention to prevent vascular thrombosis post-LT.

The primary aim of this study is to identify risk factors for developing VT in pediatric LT recipients during the immediate postoperative period. Our secondary aim is to evaluate bleeding risks associated with anticoagulation use in the immediate post-transplant period.

Methods

This multicenter, retrospective cohort study includes children <18 years who underwent an isolated LT in twelve centers in the United States during a 2-year period. After a detailed review of medical records, data were abstracted and de-identified by collaborating investigators at the local study sites. Data were entered and managed using Redcap electronic data capture tools hosted at Indiana University [11]. A detailed description of the whole cohort has been previously reported [12]. The indication for and timing of LT, organ selection, anticoagulation practices, and selection of specific agents were based on local clinical practices and established guidelines.

Subject variables and outcomes

Data collection included center demographics, patient demographics, clinical history, surgical details, type of graft, donor source, detailed critical care management, postoperative care strategies, and clinical outcomes. Critical care management and postoperative care data included type and length of anticoagulation, duration of mechanical ventilation, blood product usage, and sonographic evaluation while patients were receiving critical care management. The date of VT development was clinically determined by the physician or by the earliest detection of significant abnormal vascular flow on ultrasound. Outcome data points included thrombotic and bleeding complications. In addition, complications including unexpected reoperation, PICU readmission after transfer to the floor, delayed enteral nutrition, infection, neurological complications, graft loss, and mortality, were evaluated. Patients with incomplete data were excluded from those sections of the analysis.

Statistical analysis

We used the SAS software (Version 9.3, SAS Institute Inc., Cary, NC, USA) for statistical analyses. Student's *t*-test and chi-square tests were used for continuous and categorical variables, respectively. Univariate analyses were performed to assess for associations between anticoagulation therapy, vascular thrombosis, bleeding, unplanned return to the operating room, return to PICU, graft loss, and mortality. A regression model was built to identify independent risk factors for VT development, including patient demographic variables, comorbid conditions, and postoperative events with a p-value <0.2. Statistical significance was maintained at $p = 0.05$.

Ethical considerations

The institutional review board of each participating center approved all research work. The research was conducted following the principles of the Declaration of Helsinki and good clinical practice guidelines.

Results

Patient characteristics, critical care utilization and vascular complications

Among 331 patients who underwent liver transplantation, 31 (9.37%) developed an intra-abdominal VT. Two patients developed a deep vein thrombosis, including upper extremity nonocclusive thrombi, and were not included in the intra-abdominal VT cohort. The types of intra-abdominal VT included 11 HAT, 13 PVT, 5 with HAT and PVT and 2 with VT in the inferior vena cava. The median age at LT was 2 years; 169 (51.06%) were male. Most patients were Caucasian 182 (54.98%), and 105 (31.72%) were Hispanic. The main indications for LT were chronic liver disease with 157 patients (47.43%), metabolic/genetic disorders with 109 patients (32.93%), and acute liver failure with 36 patients (10.88%). The graft source was from a deceased donor in 281 patients (84.89%) and a whole liver was implanted in 169 patients (51.06%). (Table 1) In the whole cohort, 117 patients (35.35%) were hospitalized before the transplant, from whom 87 (74.36%) were in the PICU. Fascia was left open in 86 patients (25.98%). (Table 2) Twenty patients (6.04%) lost their grafts, including 11 re-transplanted and 9 patients who died (2.72%). (Table 3) Wide variation existed in anticoagulation regimens in both combination of anticoagulants as well as postoperative day administered (Supplemental Table 1, Supplemental Figure 1).

Risk factors for vascular complication

There were no significant differences between patients with or without VT regarding age, race, sex, transplant indications, and the location at the time of transplant (Table 1). Notably, patients' ages and sizes did not have a statistically significant impact on the VT observed in this cohort. Open fascia was the only pre-and perioperative variable significantly associated with an increased rate of development of VT (51.61 vs. 23.33%, $p = 0.001$) and remained the only independent risk factor in multivariable analysis with an odds ratio of 2.84 [(95% CI 1.27–6.34), $p = 0.012$]. Nearly all patients with fascia open had an open abdomen at the end of the primary surgery. (Table 2)

Most VT were detected early on with a median day of VT diagnosis of postoperative day (POD) 1 (IQR 0–4) as clinically determined by the physician or by the earliest significant vascular abnormalities noted on ultrasound. VT was detected on POD 0 in 29.03% (9/31) of the patients. Postoperative administration of blood products was higher in patients with VT overall (83.87 vs. 50.00%, $p<0.001$). Subsequent analysis demonstrated that 35.48% (11/31) with VT received blood products prior to the diagnosis of VT compared to 48.39% (15/31) who received blood products after VT diagnosis. A higher proportion of patients with VT received a heparin drip (77.42 vs 61.00%, $p = 0.072$) in the immediate postoperative period (POD 0–2) (Table 4). Among patients on heparin, VT risk was lower in patients with fixed doses of heparin in comparison to those receiving heparin with titrating levels based on assay levels (0% vs 14.59%, $p = 0.034$) with no difference in VT risk between the different assays of anti-Xa or PTT. Variability existed in heparin monitoring practices with fixed dosing versus titration of doses and in the types of assays used for titration. Goal ranges and protocols for titrating heparin levels were not available. (Table 5) Among VT patients who received heparin, 96.15% (25/26) received heparin on POD 0 or prior to VT formation,

intraoperative anticoagulation use, including heparin use prior to portal vein anastomoses, was not included in data collection. Only 1 patient received heparin after VT diagnosis.

Vascular thrombosis and postoperative complications

Vascular complications had an impact on resource utilization and morbidity. Patients with VT had worse outcomes, reflected by a significantly higher rate of graft loss (22.58 vs. 1.33%, $p<0.001$) and infections (50.00 vs 20.61%, $p<0.001$). From those with graft loss, 7/11 (63.64%) had a hepatic artery thrombosis; resource utilization was higher in the VT cohort. These patients had a higher rate of an unplanned reoperation (70.97 vs 16.44%, $p<0.001$). (Table 6)

Among patients with VT, 22/31 (70.97%) returned to the OR, 12 of whom returned for thrombosis evaluation and/or vascular revisions and 7 for re-transplantation. Of 59 patients with bleeding complications, 25 (42.37%) returned to the OR, most commonly for hemoperitoneum. (Table 7) Anticoagulation use, however, did not increase the risk of bleeding (25.81 vs 17.12%, $p = 0.231$). (Table 8) Mortality was low in the overall cohort, with no significant difference between patients with and without VT (Table 6). Causes of death from transplantation until the last follow-up (comprising 90-day mortality) included sepsis, multiple organ dysfunction syndrome, intracranial hemorrhage, and post-transplant lymphoproliferative disorder (Table 3). There were no differences in the length of mechanical ventilation or hospital stay among the cohorts with and without VT.

Discussion

As the liver is a key synthesizer of both prothrombotic and anticoagulant clotting factors, bleeding and coagulopathy are critical issues complicating pediatric LT, contributing to morbidity and mortality ([13, 14]). Despite significant advancements in the surgical technique and perioperative care of pediatric liver transplant recipients, VT is a well-known complication after LT that is associated with significant morbidity, often leading to graft failure and, less frequently, death [15]. We report a multicenter cohort of children whose 9.37% developed VT during the primary admission after LT. Fascia left open was the only independent risk factor in multivariable analysis factor associated with intra-abdominal VT. Anticoagulation use did not significantly impact the incidence of VT but did not increase bleeding risk. VT was associated with unplanned return to OR, infections, and graft loss.

Data regarding VT incidence in children are sparse and heterogeneous. In this multicenter series of pediatric liver transplant recipients, 9.37% developed an intra-abdominal VT during their postoperative period in the PICU. This rate of VT is lower than the 20% reported by a single center from China [5], but similar to the 7.4% of HAT reported within the first 90 days of transplantation by Ebel et al. from the SPLIT registry [7]. The HAT rate decreased in the most recent SPLIT cohort which is more contemporaneous with our report. Our reports also focus on VT occurring during the index admission, with most VT occurring during the first three days post-transplant. Decreased incidence of VT in the most recent reports likely reflects improvements in surgical techniques ([10,16]), organ selection, anesthesia and critical care management.

Conspicuously, open fascia, likely a graft/recipient size mismatch surrogate, was identified as the only independent risk factor for developing intra-abdominal thrombosis. Increased HAT has been found in smaller patients and those with a high donor-to-recipient weight ratio ([15,17]). Strategies to improve patient and graft sizes match practices may decrease the risk of thrombosis and help prevent graft loss. We did not find an impact of most of the factors previously reported to cause HAT or PVT. We did not see an increased frequency of VT based on graft type, which has been reported by others, though with conflicting results. Some have reported worse outcomes in patients receiving graft variants ([18,19]), while a more recent large cohort from the SPLIT data base reported decreased incidence of HAT in technical variant allografts. While it has been suggested that center volume may play an important role in VT development [20], we did not find a difference in VT development based on center size, which potentially may be due to the lack of low-volume centers included in the study [21]. These inconsistent findings suggest that the volume of the current practicing center may not accurately reflect the surgeons' skills. Surgeons may have developed excellent techniques and become familiar with pediatric-specific challenges during training or while practicing at a high-volume center prior to practicing at a lower volume center. Postoperative anticoagulation did not seem to protect against VT within our cohort. This could be due to perioperative events impacting VT risk, variable timing, and therapeutic goals of anticoagulation used, which could not be elucidated given the retrospective nature of this study and relatively limited sample size. A higher proportion of VT patients received a heparin drip in the immediate postoperative period, possibly reflective of institutional protocols or due to concerns about technical difficulties or complexity of the vascular anastomosis.

Thrombotic complications after LT cause significant morbidity, especially with the risk of causing graft loss. A recent SPLIT study reported that 50% of those with HAT developed graft failure within five years of follow up with 75% of patients with HAT requiring re-operation. Additionally, children with HAT had significantly higher post-transplant mortality within the first 90 days after transplantation [7]. Our cohort demonstrated similar graft failure rates, with almost half of all HAT patients experiencing graft failure.

The strengths of this study are the large sample size and granular data on preoperative, surgical, and critical care variables impacting the risk of developing thrombosis. It is a study comprised of 12 different pediatric transplant centers of different sizes from many regions in the United States, likely capturing different practice styles and patient populations. This study is limited by its focus on postoperative care in the PICU. Intraoperative events such as imaging performed to screen for thrombosis prior to abdominal closure, anticoagulation practices, and surgical practices such as graft reduction to lessen the need for open fascia or enlarging portal vein diameters if concern for diminutive vessels were not included. Certain factors that have been associated with increased risk of HAT and PVT were unable to be assessed, including graft-weight-body-weight-ratios, ischemia time, surgical time, artery size diameter, portal vein diameter, intraoperative administration of blood products, and dosing of anticoagulation agents. In addition, there is a lack of long-term follow-up to evaluate for biliary complications related to HAT or the development of portal hypertension related to PVT.

We demonstrate that current anticoagulation practices are variable and did not impact VT in this large cohort of 12 North American pediatric transplant centers. Pediatric transplantation is a unique field where numerous databases, including SPLIT and UNOS, prospectively collect detailed information on liver transplant recipients nationwide. Incorporating detailed intraoperative and postoperative anticoagulation practices including timing, dosage, and monitoring of anticoagulant agent as well as specific timing of the thrombotic event will be essential for developing standardized anticoagulation protocols. These observations support the need for a large, multicenter prospective pediatric study to evaluate the timing of optimal anticoagulation initiation, type of anticoagulation regimens, and therapeutic goals to identify optimal anticoagulation prophylaxis practices for pediatric liver transplant recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics of liver transplant recipients with and without thrombotic complication.

	Without thrombotic complication (*n* = 300)		With thrombotic complication (*n* = 31)		p-value
	n	%	n	%	
Age					0.265
0 – 6mo	28	9.33	2	6.45	
6mo <1	71	23.67	12	38.71	
1 to 5	89	29.67	6	19.35	
6 to 18	114	38.00	11	35.48	
Sex					0.286
Male	156	52.00	13	41.94	
Female	144	48.00	18	58.06	
Race					0.176
White	159	53.00	23	74.19	
African American	48	16.00	2	6.45	
Asian	15	5.00	1	3.23	
Other/not disclosed	78	26.00	5	16.13	
Underlying liver disease					0.844
Acute liver failure	33	11.00	3	9.68	
Chronic liver failure	139	46.33	18	58.06	
Liver tumor	21	7.00	1	3.23	
Metabolic/genetic	100	33.33	9	29.03	
Retransplant	7	2.33	0	0	
Weight <5kg	5	1.67	1	3.23	0.448

mo = months, kg = kilograms.

Table 2

Clinical and surgical variables of liver transplant recipients with and without thrombotic complication.

	Without thrombotic complication (*n* = 300)		With thrombotic complication (*n* = 31)		p-value
	n	%	n	%	
Liver transplant volume at center					0.955
Low (<10/year)	20	6.67	2	6.45	
Medium (10–20/year)	137	45.67	15	48.39	
High (>20/year)	143	47.67	14	45.16	
Any comorbidities	63	21.00	3	9.68	0.133
PICU stay prior to transplant					0.907
Yes	78	26.00	9	29.03	
No	216	72.00	22	70.97	
Unknown	6	2.00	0	0	
Technique					
Type of biliary anastomosis					0.214
Roux-en-Y	221	73.67	26	83.87	
Duct to duct	79	26.33	5	16.13	
Graft type					0.658
Whole	152	50.67	17	54.84	
Split	148	49.33	14	45.16	
Fascia left open	70	23.33	16	51.61	.001
Donor source					0.597
Deceased	253	84.33	28	90.32	
Living	47	15.67	3	9.68	
Liver type					0.868
Deceased, whole	150	50.00	17	54.84	
Deceased, split	103	34.33	11	35.48	
Live, whole	2	0.67	0	0	
Live, split	45	15.00	3	9.68	
List status					0.149
1A	37	12.33	1	3.23	
1B	25	8.33	2	6.45	
neither	183	61.00	28	90.32	
missing	55	18.33	0	0	
PELD (median, IQR)	25 (11, 35)		30 (17, 40)		0.200
MELD (median, IQR)	22.0. (12.96)		12 (7, 14)		0.120

PELD = Pediatric End-Stage Liver Disease, MELD = Model for End-Stage Liver Disease, std dev = standard deviation, PICU = pediatric intensive care unit, IQR = interquartile range.

Table 3

Vascular complications amongst liver transplant recipients with graft loss or death.

Event: Graft Loss				
ID	**HAT**	**PVT**	**Anticoagulation Initiation Day**	**Fixed or Titrated Anticoagulation**
1	yes	yes	POD 0	titrated
2	no	no	POD 0	titrated
3	yes	no	POD 1	titrated
4	yes	yes	POD 1	titrated
5	yes	no	POD 0	missing
6	no	no	POD 2	titrated
7	no	no	POD 0	fixed
8	no	no	POD 0	fixed
9	yes	no	POD 0	titrated
10	yes	no	POD 0	titrated
11	yes	yes	POD 0	titrated
Event: Death				
ID	HAT	PVT	IVC Thrombus	Cause of Death
12	no	no	no	Intracranial hemorrhage, sepsis
13	no	no	no	MODS
14	no	no	no	MODS, sepsis
15	no	no	yes	ITP and PTLD
16	no	no	no	Sepsis
17	no	no	no	MODS, adenovirus
18	no	no	no	MODS, sepsis
19	no	no	no	MODS
20	no	no	no	MODS

HAT = hepatic artery thrombosis, PVT = portal vein thrombosis, POD = postoperative day, IVC = inferior vena cava, MODS = multiple organ dysfunction syndrome, ITP = immune thrombocytopenia, PTLD = post-transplant lymphoproliferative disorder.

Table 4

Anticoagulation and blood product usage in liver transplant recipients with and without thrombotic complication.

	Without thrombotic complication (*n* = 300)		With thrombotic complication (*n* = 31)		p-value
	n	%	n	%	
Any anticoagulant use PICU	269	89.67	31	100	0.096
Received heparin, POD 0–2	183	61.00	24	77.42	0.072
Received LMWH, POD 0–2	31	10.33	0	0	0.096
Received aspirin, POD 0–2	131	43.67	11	35.48	0.381
Received PGE, POD 0–2	82	27.33	5	16.13	0.177
Received blood products in PICU	150	50.00	26	83.87	<0.001
pRBC	142	47.33	24	77.42	0.001
FFP	22	7.33	6	19.35	0.035
Platelets	27	9.00	8	25.81	0.009
Cryoprecipitate	12	4.00	5	16.13	0.014
Ultrasound performed in PICU	299	99.67	31	100	0.748

PICU = Pediatric Intensive Care Unit, LMWH = low molecular weight heparin, PGE = Prostaglandin E, POD = postoperative day, pRBCs = packed red blood cells, FFP = fresh frozen plasma.

Table 5

Monitoring practices amongst heparin users.

	Without thrombotic complication (*n* = 185)		**With thrombotic complication (*n* = 27)**		**p-value**
	n	**%**	**n**	**%**	
Monitoring Type					0.034
Fixed dose	27	14.59	0	0.00	
Titrated dose	158	85.41	27	100.00	
	Without thrombotic complication (*n* = 158)		With thrombotic complication (*n* = 27)		p-value
	n	%	n	%	
Titrating Assay					0.235
anti-Xa	44	27.85	5	18.52	
PTT	113	71.52	21	77.78	
Missing	1	0.63	1	3.70	

*Patients with missing data were excluded from analysis of individual variables.

Table 6

Postoperative complications in liver transplant recipients with and without thrombotic complication.

	Without thrombotic complication (*n* = 300)		With thrombotic complication (*n* = 31)		p-value
	n	%	n	%	
Graft loss (%)	4	1.33	7	22.58	<0.001
Mortality (%)	8	2.67	1	3.23	0.592
Unplanned return to OR (%)	49	16.44	22	70.97	<0.001
Return to PICU (%)	33	11.00	7	25.00	0.062
Bleeding complication (%)	53	17.67	6	19.35	0.503
Delayed enteral nutrition (%)	37	12.33	6	19.35	0.272
Infection (%)	61	20.60	14	50.00	<0.001
Neurologic complication (%)	13	4.33	2	6.45	0.596
Length of MV (days), mean	3.86		4.70		0.705
median, (IQR)	0.80 (0–2.39)		1.66 (0.31–5.07)		
Hospital LOS (days), mean	26.96		30.30		0.786
median, (IQR)	14 (9–23)		23.5 (18–39)		

OR = operating room, PICU = pediatric intensive care unit, MV = mechanical ventilation, IQR = interquartile range, LOS = length of stay.

*Patients with missing data were excluded from analysis of individual variables.

Table 7

Indications for unplanned return to the operating room for liver transplant recipients with and without abdominal vascular thrombosis.

Indications for Return to Operating Room	Without thrombotic complication (*n* = 49)	With thrombotic complication (*n* = 22)
Biliary leak	6	1
Biliary stricture	2	0
Bowel perforation/obstruction	5	0
Compartment syndrome	4	0
Gastrointestinal bleeding	2	0
Hemoperitoneum	15	1
Peritonitis	4	0
Re-transplantation	4	7
Tracheostomy	2	0
Confirmed/Suspicion for Vascular Thrombosis	1	12
Other*	4	1

Other: splenic artery ligation, retained foreign body, paracentesis, or broviac placement.

Table 8

Bleeding Complications amongst Liver Transplant Recipients On and Off Anticoagulation.

	No bleeding complication		Bleeding complication		p-value
	n	%	n	%	
No anticoagulation (*n* = 31)	23	74.19	8	25.81	0.231
Any anticoagulation (*n* = 292)	242	82.88	50	17.12	

PICU = Pediatric Intensive Care Unit, LMWH = low molecular weight heparin, PGE = Prostaglandin E, POD = postoperative day, pRBCs = packed red blood cells, FFP = fresh frozen plasma.