Routine Postoperative Antithrombotic Therapy in Pediatric Liver Transplantation

Werner, Maureen J M; de Kleine, Ruben H J; de Boer, Marieke T; de Meijer, Vincent E; Scheenstra, René; Verkade, Henkjan J; Bodewes, Frank A J A; Bontemps, Sander T H; Reyntjens, Koen M E M; Dikkers, Riksta

Published in:
Thrombosis and Haemostasis

DOI:
10.1055/s-0039-1701010

Publication date:
2020

Routine Postoperative Antithrombotic Therapy in Pediatric Liver Transplantation: Impact on Bleeding and Thrombotic Complications

Maureen J. M. Werner[1,2] Ruben H. J. de Kleine[1] Marieke T. de Boer[1] Vincent E. de Meijer[1] René Scheenstra[3] Henkjan J. Verkade[3] Frank A. J. A. Bodewes[3] Sander T. H. Bontemps[4] Koen M. E. M. Reyntjens[5] Riksta Dikkers[6] Ton Lisman[1,2] Robert J. Porte[1,2]

[1] Section Hepato-Pancreatico-Biliary Surgery and Liver Transplantation, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[2] Surgical Research Laboratory, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[3] Department of Pediatric Gastroenterology and Hepatology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[4] Department of Pediatric Intensive Care, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[5] Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[6] Department of Pediatric Radiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Address for correspondence Robert J. Porte, MD, PhD, Section of HPB Surgery & Liver Transplantation, Department of Surgery, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands (e-mail: r.j.porte@umcg.nl).

Thromb Haemost

Abstract

Background Hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) are serious causes of morbidity and mortality after pediatric liver transplantation. To reduce thrombotic complications, routine antithrombotic therapy consisting of 1 week heparin followed by 3 months acetylsalicylic acid, was implemented in our pediatric liver transplant program in 2003. This study aimed to evaluate incidences of bleeding and thrombotic complications since the implementation of routine antithrombotic therapy and to identify risk factors for these complications.

Methods This retrospective cohort study includes 200 consecutive pediatric primary liver transplantations performed between 2003 and 2016. Uni- and multivariate logistic regression analysis, Kaplan–Meier method, and Cox regression analysis were used to evaluate recipient outcome.

Results HAT occurred in 15 (7.5%), PVT in 4 (2.0%), and venous outflow tract thrombosis in 2 (1.0%) recipients. Intraoperative vascular interventions (odds ratio [OR] 14.45 [95% confidence interval [CI] 3.75–55.67]), low recipient age (OR 0.81 [0.69–0.95]), and donor age (OR 0.96 [0.93–0.99]) were associated with posttransplant thrombosis. Clinically relevant bleeding occurred in 37%. Risk factors were high recipient age (OR 1.08 [1.02–1.15]), high Child–Pugh scores (OR 1.14 [1.02–1.28]), and intraoperative blood loss in mL/kg (OR 1.003 [1.001–1.006]). Both posttransplant

Keywords
- antithrombotic therapy
- pediatric liver transplantation
- bleeding
- thrombosis

received
June 25, 2019
accepted after revision
December 4, 2019

DOI https://doi.org/10.1055/s-0039-1701010.
ISSN 0340-6245.

thrombotic (hazard ratio [HR] 3.38 [1.36–8.45]; $p = 0.009$) and bleeding complications (HR 2.50 [1.19–5.24]; $p = 0.015$) significantly increased mortality.

Conclusion In 200 consecutive pediatric liver transplant recipients receiving routine postoperative antithrombotic therapy, we report low incidences of posttransplant vascular complications. Posttransplant antithrombotic therapy seems to be a valuable strategy in pediatric liver transplantation. Identified risk factors for bleeding and thrombotic complications might facilitate a more personalized approach in antithrombotic therapy.

Introduction

In both adult and pediatric patients with end-stage liver disease, the only curative treatment is liver transplantation. Over the past decades patient and graft survival rates have significantly improved, with 5-year patient and graft survival of 80 to 95% in contemporary series.[1–6] However, bleeding as well as thrombosis still complicate liver transplantation and contribute to significant morbidity and mortality.

The liver plays a central role in hemostasis, as it produces pro- and anticoagulant as well as pro- and antifibrinolytic factors and thrombopoietin. In patients with a liver disease, concurrent changes in both pro- and antihemostatic pathways occur, resulting in a new hemostatic balance.[7,8] This "rebalanced hemostasis," though, is fragile and can easily be tipped toward thrombosis or bleeding,[9,10] especially during liver transplantation when levels of pro- and antihemostatic factors decrease even further.[11,12]

In pediatric liver transplantation, the reported incidence of posttransplant hepatic artery thrombosis (HAT) varies between 5 and 18%, which is almost four times as frequent when compared with adults, and 5 to 10% of patients develop portal vein thrombosis (PVT).[13–16] We previously reported a high incidence (20%) of posttransplant vascular complications in a cohort study (1982–1999) in our pediatric liver transplant population.[17] The high incidence of thrombotic complications after pediatric liver transplantation is incompletely understood, but may be related to disease etiology, differences in plasma levels of hemostatic proteins children compared with adults, and discrepancy in vessel diameters between donor and recipient.[17–19]

Posttransplant bleeding complications occur in 5 to 20% of the pediatric recipients.[20,21] Improved surgical techniques, combined with anesthesiological strategies as restrictive transfusion, have reduced the bleeding risk significantly.[12,22] Despite this, excessive bleeding can still profoundly affect individual liver transplant recipients, warranting proactive hemostatic management.

To reduce the number of thrombotic complications, a routine posttransplant antithrombotic therapy protocol, consisting of 1 week continuous intravenous administration of unfractionated heparin, followed by 3 months oral acetylsalicylic acid, was implemented in our center in 2003. The aim of this study was to assess the incidence of posttransplant thrombotic and bleeding complications in pediatric recipients since the implementation of routine antithrombotic therapy and to identify risk factors for these complications.

Methods

Study Design and Setting

We performed a single-center retrospective cohort study of all pediatric patients ($\leq$ 16 years) who underwent a primary liver transplantation at the University Medical Center Groningen, the Netherlands, between January 2003 and December 2016. Electronical medical records were used to collect patient demographic data, including age, gender, indication for transplantation, and relevant medical history. Also, donor characteristics were identified. Transplant-specific details such as ischemia times and liver graft type and weight were obtained, as well as technical and clinical intraoperative details, such as implantation technique and type of anastomoses.

Postoperative outcome data including bleeding and thrombotic complications were collected up to 3 months after liver transplantation, along with perioperative administered blood products. Patient and graft survival were analyzed up to 10 years after transplantation. The study protocol was a priori approved by the Medical Ethical Research Board (2017.316) and adhered to the 1975 Declaration of Helsinki.

Technical Aspects

Liver grafts were derived from both deceased and living donors. Deceased donors included mainly donation after brain death, but full-size grafts from pediatric donors after circulatory death (DCD) were accepted as well. Adult full-size grafts were divided by split or reduction procedures.

Liver grafts were implanted by using classical implantation or piggyback technique. Portal vein reconstructions were performed using end-to-end portal anastomoses with running monofilament sutures. In case of vessel diameter discrepancy or a hypoplastic portal vein, venous interposition grafts were used. Arterial anastomoses were conducted end-to-end with interrupted monofilament sutures, mostly between recipients' common or proper hepatic artery and the donor common hepatic artery in case of full-size grafts and left hepatic artery in left partial liver grafts. All surgeons used magnifying loops during the entire procedure. Biliary reconstructions for partial grafts were conducted with a Roux-and-Y hepaticojejunostomy, for full-size grafts a duct-to-duct anastomosis was preferred. Immunosuppressive therapy consisted of triple

therapy including tacrolimus (Prograft), with basiliximab (Simulect), and prednisone as induction, supplemented with mycophenolate mofetil (Cellcept) in case of renal dysfunction.

All recipients, independent of type of primary disease or type of arterial reconstruction, were treated according to the routine antithrombotic therapy protocol, which was implemented in 2003. Before 2003, no standard thrombotic prophylaxis was administered in pediatric patients undergoing liver transplantation. The antithrombotic protocol consisted of 1 week continuous intravenous unfractionated heparin, followed by 3 months oral acetylsalicylic acid (►**Fig. 1**). Prophylactic vitamin K was administered as well. Heparin was started in the postreperfusion phase during liver transplantation or immediately afterwards, depending on intraoperative bleeding or thrombotic complications and coagulation state. If the prothrombin time (PT) and activated partial thromboplastin time (APTT) levels were below 20 and 50 seconds, respectively, and the platelet count was above 30×10^9/L, heparin was started at 10 U/kg/hour, with subsequent dose adjustments guided by APTT levels, targeting 50 to 65 seconds. When a patient received intravenous heparin, antithrombin III (AT-III) levels were routinely monitored and AT-III concentrate was administered when AT-III levels were $< 60\%$. The APTT goal for patients receiving intravenous heparin was independent from hemoglobin (Hb) levels. Hb levels were routinely monitored and red blood cells were routinely transfused when levels were < 4 mmol/L. Normotensive to supranormal (up to 20%) blood pressures were pursued. AT-III, Hb, and blood pressure targets did not change during the study period. Similar to our policy for adult patients,[10] we used a restricted transfusion policy for blood products and prohemostatic blood products were never administered based on the results of routine coagulation tests

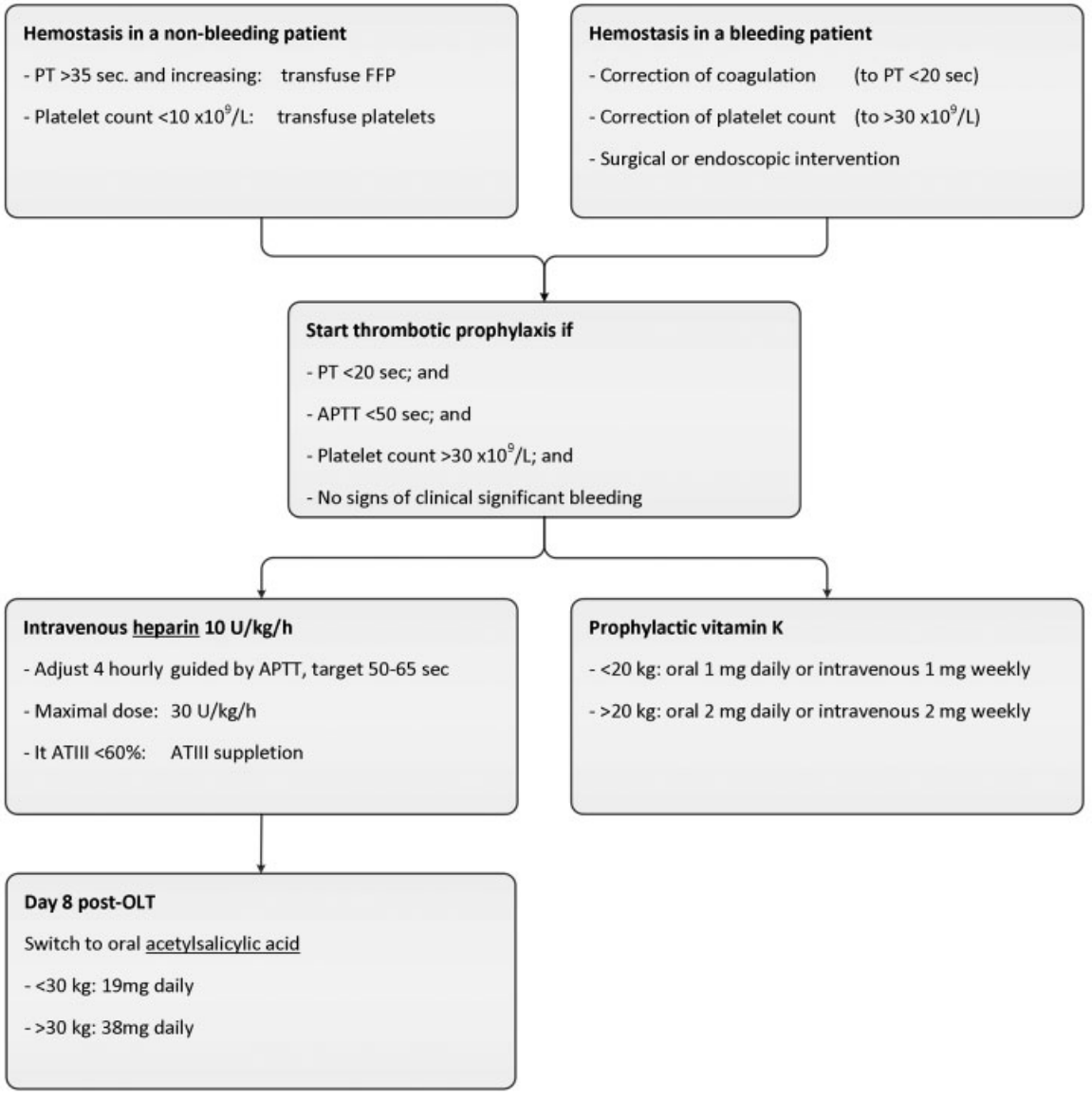

Fig. 1 Protocol posttransplant antithrombotic therapy in pediatric liver transplantation in the University Medical Center Groningen. Flowchart of the routine posttransplant antithrombotic therapy protocol in pediatric liver transplantation. APTT, activated partial thromboplastin time; ATIII, antithrombin III; FFP, fresh frozen plasma; PT, prothrombin time.

(i.e., PT, APTT) alone. Only in the presence of excessive, nonsurgical bleeding problems, coagulation tests were used to direct transfusion of prohemostatic blood products (i.e., fresh frozen plasma, fibrinogen concentrate). Doppler-ultrasounds were conducted at three standardized moments during liver transplantation (before and after abdominal closure, and after arrival at the pediatric intensive care unit), daily in the first postoperative week and weekly afterwards until discharge.

Definitions and Variables

A posttransplant bleeding complication was defined as a bleeding requiring blood transfusion or reintervention, within 3 months after liver transplantation. A posttransplant thrombotic complication was defined as a clinically suspected thrombosis including HAT, PVT, and venous outflow tract obstruction, confirmed at diagnostic imaging or surgical exploration, within 3 months after liver transplantation.

Patient survival was defined as time from liver transplantation to death or end of follow-up (10 years after baseline or December 31, 2017). Graft survival was defined as time between date of transplantation and date of graft failure, death, or end of follow-up. Recipients with and without a posttransplant thrombotic complication were compared, as well as recipients with and without a posttransplant bleeding complication.

Statistical Analysis

Continuous data are presented as mean (standard deviation) or median (interquartile range [IQR]), where appropriate. Categorical variables are presented as number (percentage). To test for differences between recipients with and without posttransplant thrombotic/bleeding complications, two-sample independent *t*-tests or Mann–Whitney *U* test and Pearson's chi-square tests or Fisher's exact test were used for continuous and categorical variables, respectively. Patient and graft survival rates were determined by the Kaplan–Meier method and compared with log rank testing.

In addition, multivariable logistic regression and Cox regression analysis were performed using a backward stepwise selection strategy, including variables with p-values < 0.20 in the univariate analysis. The proportion of missing data was $< 5\%$ for all variables used in regression models. Data were presented as odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). All reported p-values are two-tailed and considered statistically significant if < 0.05. Statistical analyses were performed using IBM Statistics SPSS, version 23 (IBM Inc., Chicago, Illinois, United States).

Results

Baseline Characteristics

A total of 200 pediatric recipients underwent a primary liver transplantation in our center between 2003 and 2016 and were included in this study. Recipients had a median age of 2.6 (IQR 0.8–9.5) years and weight of 14.2 (9.1–30.4) kg at time of transplantation; 52% were male. Main indications for liver transplantation were biliary atresia (51%) and metabolic liver diseases (15%). Prior to transplantation, 6 (3.0%) recipients had a preexisting PVT and 56 (28%) experienced a bleeding event before transplantation, mainly due to esophageal varices (►**Table 1**).

Fifty-six (28%) full size and 144 (72%) partial grafts were derived from 161 (80%) deceased and 39 (20%) living donors. Five full-size DCD grafts were transplanted, derived from pediatric donors aged 1 to 13 years. Deceased donor grafts were divided via split ($n = 43$) or reduction ($n = 62$) procedures into left lateral lobe ($n = 69$), left lobe ($n = 29$), right lobe ($n = 5$), or right trisegmental grafts ($n = 2$). Living donor grafts concerned mainly left lateral lobes ($n = 38$) and one left lobe. Median graft/recipient weight ratio was 2.7% (2.0–3.3%). A piggyback implantation was used in 94% of the transplantations, whereas 6% of grafts were classically implanted. Median intraoperative blood loss was 71 (42–142) mL/kg. Median cold ischemia time (CIT) and warm ischemia time (WIT) were 456 (351–571) and 43 (36–51) minutes, respectively (►**Table 2**).

Posttransplant Thrombotic Complications

A posttransplant thrombotic complication occurred in 21 (11%) recipients, with 15 (7.5%) HATs, 4 (2.0%) PVTs, and 2 (1.0%) venous outflow tract obstructions. Thrombosis was diagnosed after a median time of 3.0 (1.0–5.5) days posttransplantation, and at the time of diagnosis 76% of the recipients had already started with routine antithrombotic therapy. In recipients without antithrombotic therapy at time of thrombosis, heparin was postponed because of coagulation disorders with inadequate APTT levels ($n = 3$) or intraoperative bleeding complications with hemodynamic instability ($n = 2$). All 21 recipients with a thrombotic complication underwent surgical reintervention, 12 recipients eventually had to undergo a retransplantation, concerning 9 recipients with HAT, 2 with venous outflow tract obstruction, and 1 with PVT.

An increase in posttransplant thrombosis over time was observed, with an incidence of 7.0, 9.5, and 15% in the consecutive eras 2003 to 2007 ($n = 71$), 2008 to 2012 ($n = 63$), and 2013 to 2016 ($n = 66$), respectively. When compared with recipients without a posttransplant thrombosis, recipients with a thrombosis more often had metabolic liver diseases (38 vs. 12%, $p = 0.003$) and more often received DCD liver grafts (14 vs. 1.1%, $p = 0.015$). In addition, patients with a posttransplant thrombosis more often had undergone intraoperative vascular interventions, during the transplant procedure (55 vs. 16%, $p < 0.001$), especially concerning the hepatic artery. These vascular interventions included surgical thrombectomy ($n = 20$), or a redo or reconstruction of the arterial or portal anastomosis ($n = 20$) during the liver transplantation, because of inadequate flow. Furthermore, recipients with a posttransplant thrombosis had a longer intensive care unit (ICU) stay (16.0 vs. 7.0 days, $p = 0.003$) and more recipients had to undergo a reintervention (100 vs. 49%, $p \leq 0.001$), compared with those without thrombotic complications (►**Table 2**).

After uni- and multivariable analysis, only intraoperative vascular interventions were identified as an independent risk factor for posttransplant thrombosis (OR 14.45 [3.75–55.67]). Furthermore, higher recipient age (OR 0.81 [0.69–0.95]),

Table 1 Basic characteristics of pediatric liver transplant recipients with and without posttransplant thrombosis

Basic characteristics	Total, $N = 200$		No thrombosis, $N = 179$		Thrombosis, $N = 21$		*p*-Value
Sex, male	103	(51.5)	90	(50.3)	13	(61.9)	0.313
Age, y	2.6	(0.81–9.5)	2.9	(0.84–9.8)	1.6	(0.62–6.8)	0.157
Weight, kg	14.2	(9.1–30.4)	14.6	(9.1–31.0)	11.0	(8.5–23.5)	0.201
Indication for LT							**0.003**
Biliary atresia	101	(50.5)	94	(52.5)	7	(33.3)	
Metabolic	30	(15.0)	22	(12.3)	8	(38.1)	
Acute liver failure	29	(14.5)	25	(14.0)	4	(19.0)	
Cholestatic	22	(11.0)	22	(12.3)	0	(0.0)	
Cirrhotic	13	(6.5)	13	(7.3)	0	(0.0)	
Other	5	(2.5)	3	(1.7)	2	(9.5)	
Child–Pugh score	9.0	(7.0–12.0)	9.0	(7.0–12.0)	7.0	(5.0–10.0)	0.062
PELD score[a]	28.0	(26.5–30.0)	28.0	(25.0–30.0)	28.0	(28.0–30.5)	0.792
Encephalopathy	44	(22.0)	38	(21.3)	6	(28.6)	0.418
Hepatopulmonary syndrome	14	(7.0)	13	(7.3)	1	(4.8)	0.663
Hepatorenal syndrome	43	(21.5)	39	(21.9)	4	(19.0)	0.794
Medical history of bleeding	56	(28.0)	52	(29.2)	4	(19.0)	0.327
Medical history of thrombosis	6	(3.0)	6	(3.4)	0	(0.0)	0.508
Prior abdominal surgery	117	(58.5)	110	(61.5)	7	(33.3)	**0.013**
High urgency state	49	(24.5)	44	(24.6)	5	(23.8)	0.938
Era							0.288
2003–2007	71	(35.5)	66	(93.0)	5	(7.0)	
2008–2012	63	(31.5)	57	(90.5)	6	(9.5)	
2013–2016	66	(33.0)	56	(84.8)	10	(15.2)	

Abbreviations: LT, liver transplantation; PELD, pediatric end-stage liver disease.
Note: Data presented as median (interquartile range [IQR]) or number (%) where appropriate. *p*-Value using two-sample independent *t*-tests or Mann–Whitney *U* test and Pearson's chi-square tests or Fisher's exact test as appropriate. *p*-Values < 0.05 are considered statistically significant and boldfaced.
[a]Eurotransplant PELD scores are given.

higher donor age (OR 0.96 [0.93–0.99]), higher Child–Pugh (CP) score (OR 0.81 [0.67–0.98]), and prior abdominal surgery (OR 0.04 [0.01–0.20]) all protected against posttransplant thrombotic complications (►**Table 3**).

Posttransplant Bleeding Complications

A posttransplant bleeding complication occurred in 73 (37%) recipients, at a median time of 2.0 (1.0–4.0) days after transplantation. In patients who received blood transfusion or reintervention for bleeding, these decisions were based on a combination of variables, including a low Hb value (55%), hemodynamic instability (37%), or clinical gastrointestinal bleeding (8%). At presentation of posttransplant bleeding, routine antithrombotic therapy had already been started in 75% of patients. More than half of the recipients with a bleeding complication (52%) could be stabilized with blood transfusion, while 35 (48%) needed surgical reintervention. During surgical reintervention, diffuse intra-abdominal oozing from tissues was seen in 48% of patients, 26% of patients had a bleeding from anastomosis or other vessels, and 26% an intra-abdominal hematoma without an identifiable bleeding point (►**Table 4**).

A significant decrease in posttransplant bleeding over the study period was observed, with an incidence of 49% in 2003 to 2007, 33% in 2008 to 2012, and 26% in 2013 to 2016 ($p = 0.014$). Recipients with a posttransplant bleeding complication had significant higher CP scores (10.0 vs. 8.0, $p = 0.003$), more often a medical history that included hepatorenal syndrome before transplantation (33 vs. 15%, $p = 0.003$) and longer CITs (506 vs. 441 minutes, $p = 0.012$) as compared with those without bleeding complications (►**Table 5**). In addition, recipients with a postoperative bleeding more often had experienced bleeding complications during transplantation (44 vs. 23%, $p = 0.002$) with a significantly higher intraoperative blood loss (85 vs. 62 mL/kg, $p = 0.040$). In multivariate analysis, independent risk factors for a postoperative bleeding complication were a higher recipient age (OR 1.08 [1.02–1.15]), higher CP scores (OR 1.14 [1.02–1.28]), and intraoperative blood loss in mL/kg (OR 1.003 [1.001–1.006]; ►**Table 3**).

Table 2 Univariate analysis of transplant characteristics and outcomes of recipients with and without posttransplant thrombosis

Transplant characteristics	Total, $N = 200$		No thrombosis, $N = 179$		Thrombosis, $N = 21$		*p*-Value
Donor age, y	39.0	(21.0–50.0)	39.0	(21.0–50.0)	30.0	(15.0–46.0)	0.192
Donor weight, kg	65.0	(58.0–76.0)	65.5	(85.8–76.0)	62.0	(41.0–80.0)	0.236
Donor type							**0.015**
Living donor	39	(19.5)	36	(20.1)	3	(14.3)	
DBD	156	(78.0)	141	(78.8)	15	(71.4)	
DCD	5	(2.5)	2	(1.1)	3	(14.3)	
Graft type							0.951
Partial	144	(72.0)	129	(72.1)	15	(71.4)	
Full size	56	(28.0)	50	(27.9)	6	(28.6)	
Graft weight, g	286	(250–423)	292	(250–430)	270	(245–324)	0.363
GRWR,%	2.7	(2.0–3.3)	2.6	(2.0–3.3)	2.9	(2.3–3.3)	0.503
Surgical technique							0.875
Piggyback	189	(94.5)	169	(94.4)	20	(95.2)	
Classical	11	(5.5)	10	(5.6)	1	(4.8)	
Biliary anastomosis							0.298
Duct-Roux Y	122	(63.5)	112	(64.7)	10	(52.6)	
Duct-duct	70	(36.5)	61	(35.3)	9	(47.4)	
Cold ischemia time, min	456	(351–571)	457	(342–574)	456	(408–550)	0.922
Warm ischemia time, min	43	(36–51)	43	(35–51)	45	(38–53)	0.976
Operation time, min	616	(551–717)	615	(546–713)	675	(585–746)	0.080
Intraoperative thrombosis							0.119
Portal vein	13	(6.5)	12	(6.7)	1	(4.8)	
Hepatic artery	5	(2.5)	3	(1.7)	2	(9.5)	
Vascular intervention[a]	40	(20.0)	29	(16.2)	11	(55.0)	**<0.001**
Portal vein	7	(3.5)	7	(3.9)	0	(0.0)	
Hepatic artery	23	(11.5)	15	(8.4)	8	(40.0)	
Both	10	(5.0)	7	(3.9)	3	(15.0)	
Blood loss, mL/kg	71	(42–142)	70	(41–142)	78	(49–144)	0.730
RBC, mL/kg	29	(12–57)	28	(11–57)	37	(18–82)	0.324
FFP, mL/kg	0.0	(0.0–18)	0.0	(0.0–16)	0.0	(0.0–30)	0.978
Intraoperative bleeding	61	(30.5)	55	(30.7)	6	(28.6)	0.839
Postoperative packing	27	(13.5)	22	(12.4)	5	(25.0)	0.162
Abdominal closure							**0.001**
Closure	151	(76.5)	142	(79.8)	9	(45.0)	
Partial closure	47	(23.5)	36	(20.2)	11	(55.0)	
Posttransplantation							
Reinterventions	109	(54.5)	88	(49.2)	21	(100)	**<0.001**
Bleeding complication	73	(36.5)	67	(37.4)	6	(28.6)	0.425
Biliary complication	25	(12.5)	22	(12.3)	3	(14.3)	0.732
ICU stay, d	7	(5–13)	7	(5–12)	16	(8–24)	**0.003**
Hospital stay, d	29	(21–44)	29	(20–43)	35	(29–51)	0.118
Readmission < 3 mo	37	(18.5)	34	(19.0)	3	(14.3)	0.771

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; FFP, fresh frozen plasma; GRWR, graft recipient weight ratio; ICU, intensive care unit; RBC, red blood cell count.

Note: Data presented as median (interquartile range [IQR]) or number (%) where appropriate. *p*-Value using two-sample independent *t*-tests or Mann–Whitney *U* test and Pearson's chi-square tests or Fisher's exact test as appropriate. *p*-Values < 0.05 are considered statistically significant and boldfaced.

[a]Vascular interventions including surgical thrombectomy or a redo or reconstruction of the arterial or portal anastomosis during the liver transplantation, because of inadequate flow during liver transplantation.

Table 3 Multivariate analysis of risk factors for posttransplant thrombotic and bleeding complications

Factors associated with thrombosis	OR	95% CI	*p*-Value
Recipient age, y	0.809	0.687–0.954	0.012
Child–Pugh score	0.810	0.670–0.979	0.030
Prior abdominal surgery	0.041	0.008–0.204	<0.001
Donor age, y	0.962	0.932–0.992	0.013
Intraoperative vascular intervention	14.45	3.75–55.67	<0.001
Factors associated with bleeding			
Recipient age, y	1.082	1.017–1.151	0.013
Child–Pugh score	1.144	1.020–1.283	0.022
Intraoperative blood loss, mL/kg	1.003	1.001–1.006	0.027

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: Results of a multivariate logistic regression analysis performed by using backward stepwise selection strategy, including variables with *p*-values < 0.2 from univariate analysis. Data presented as odds ratios with 95% confidence intervals and *p*-values. *p*-Values < 0.05 are considered statistically significant and boldfaced. Factors associated with thrombosis including recipient age, indication, Child–Pugh score, thrombosis in past, prior abdominal surgery, donor age, donor type, operation time, intraoperative thrombosis, intraoperative vascular intervention, postoperative abdominal packing, and abdominal closure. Factors associated with bleeding including recipient age, Child–Pugh score, encephalopathy, hepatorenal syndrome, prior abdominal surgery, high urgency state, donor weight, donor type, cold ischemia time, intraoperative blood loss, and era.

Table 4 Basic characteristics of pediatric liver transplant recipients with and without posttransplant bleeding

Basic characteristics	Total, *N* = 200		No bleeding, *N* = 127		Bleeding, *N* = 73		*p*-Value
Sex, male	103	(51.5)	64	(50.4)	39	(53.4)	0.680
Age, y	2.6	(0.81–9.5)	2.1	(0.73–8.8)	3.5	(0.98–10.5)	0.117
Weight, kg	14.2	(9.1–30.4)	13.6	(9.0–28.0)	17.9	(9.5–35.0)	0.327
Indication for LT							0.483
Biliary atresia	101	(50.5)	70	(55.1)	31	(42.5)	
Metabolic	30	(15.0)	19	(15.0)	11	(15.1)	
Acute liver failure	29	(14.5)	17	(13.4)	12	(16.4)	
Cholestatic	22	(11.0)	12	(9.4)	10	(13.7)	
Cirrhotic	13	(6.5)	6	(4.7)	7	(9.6)	
Other	5	(2.5)	3	(2.4)	2	(2.7)	
Child–Pugh score	9.0	(7.0–12.0)	8.0	(7.0–11.0)	10.0	(7.5–12.5)	**0.003**
PELD score[a]	28.0	(26.5–30.0)	28.0	(28.0–30.0)	28.0	(24.3–30.0)	0.260
Encephalopathy	44	(22.0)	24	(18.9)	20	(27.4)	0.171
Hepatopulmonary syndrome	14	(7.0)	10	(7.9)	4	(5.5)	0.530
Hepatorenal syndrome	43	(21.5)	19	(15.0)	24	(32.9)	**0.003**
Bleeding in past	56	(28.0)	33	(25.9)	23	(31.5)	0.422
Gastrointestinal	32	(16.0)	20	(15.7)	12	(16.4)	0.547
Intracranial	11	(5.5)	7	(5.5)	4	(5.5)	
Perioperative	4	(2.0)	1	(0.8)	3	(4.1)	
Spontaneous	9	(4.5)	5	(3.9)	4	(5.5)	
Medical history of thrombosis	6	(3.0)	4	(3.2)	2	(2.7)	0.614
Prior abdominal surgery	117	(58.5)	79	(62.2)	38	(52.1)	0.161
High urgency state	49	(24.5)	27	(21.3)	22	(30.1)	0.160
Era							**0.014**
2003–2007	71	(35.5)	36	(50.7)	35	(49.3)	
2008–2012	63	(31.5)	42	(66.7)	21	(33.3)	
2013–2016	66	(33.0)	49	(74.2)	17	(25.8)	

Abbreviations: LT, liver transplantation; PELD, pediatric end-stage liver disease.
Note: Data presented as median (interquartile range [IQR]) or number (%) where appropriate. *p*-Value using two-sample independent *t*-tests or Mann–Whitney *U* test and Pearson's chi-square tests or Fisher's exact test as appropriate. *p*-Values < 0.05 are considered statistically significant and boldfaced.
[a]Eurotransplant PELD scores are given.

Table 5 Univariate analysis of transplant characteristics and outcomes of pediatric liver transplant recipients with and without posttransplant bleeding

Transplant characteristics	Total, $N = 200$		No bleeding, $N = 127$		Bleeding, $N = 73$		*p*-Value
Donor age, y	39.0	(21.0–50.0)	39.0	(21.0–48.0)	41.0	(21.0–50.0)	0.517
Donor weight, kg	65.0	(58.0–76.0)	67.0	(60.0–80.0)	65.0	(55.0–75.0)	0.132
Donor type							0.184
Living donor	39	(19.5)	29	(22.8)	10	(13.7)	
DBD	156	(78.0)	96	(75.6)	60	(82.2)	
DCD	5	(2.5)	2	(1.6)	3	(4.1)	
Graft type							0.244
Partial	144	(72.0)	95	(74.8)	49	(67.1)	
Full size	56	(28.0)	32	(25.2)	24	(32.9)	
Graft weight, g	286	(250–423)	280	(250–405)	300	(250–520)	0.571
GRWR, %	2.7	(2.0–3.3)	2.7	(2.0–3.1)	2.8	(1.9–3.9)	0.487
Surgical technique							0.214
Piggyback	189	(94.5)	122	(96.1)	67	(91.8)	
Classical	11	(5.5)	5	(3.9)	6	(8.2)	
Biliary anastomosis							0.261
Duct-Roux Y	122	(63.5)	83	(66.4)	39	(58.2)	
Duct-duct	70	(36.5)	42	(33.6)	28	(41.8)	
Cold ischemia time, min	456	(351–571)	441	(293–557)	506	(391–610)	**0.012**
Warm ischemia time, min	43	(36–51)	43	(35–51)	44	(38–52)	0.214
Operation time, min	616	(551–717)	614	(555–710)	633	(530–729)	0.703
Blood loss, mL/kg	71	(42–142)	62	(39–132)	85	(49–179)	**0.040**
RBC, mL/kg	29	(12–57)	25	(11–43)	44	(13–95)	0.059
FFP, mL/kg	0	(0–18)	0	(0–12)	0	(0–39)	**0.039**
Intraoperative bleeding	61	(30.5)	29	(22.8)	32	(43.8)	**0.002**
Spontaneous/oozing	42	(21.0)	19	(14.9)	23	(31.5)	**0.011**
Vascular	13	(6.5)	8	(6.2)	5	(6.8)	
Postoperative packing	27	(13.5)	12	(9.5)	15	(20.6)	**0.027**
Abdominal closure							0.355
Closure	151	(76.3)	98	(78.4)	53	(72.6)	
Partial closure	47	(27.3)	27	(21.6)	20	(27.4)	
Intraoperative thrombosis	18	(9.0)	11	(8.7)	7	(9.6)	0.852
Posttransplantation							
Reinterventions	109	(54.5)	56	(44.1)	53	(72.6)	<**0.001**
Thrombotic complications	21	(10.5)	15	(11.8)	8	(10.9)	0.425
Hepatic artery	15	(7.5)	10	(7.9)	5	(6.8)	0.552
Portal vein	4	(2.0)	4	(3.1)	0	(0.0)	
Venous outflow tract	2	(1.0)	1	(0.8)	1	(1.4)	
Biliary complication	25	(12.5)	16	(21.6)	9	(12.3)	0.956
ICU stay, d	7	(5–13)	7	(5–12)	7	(5–16)	0.546
Hospital stay, d	29	(21–44)	29	(21–42)	30	(21–52)	0.449
Readmission < 3 mo	37	(18.5)	24	(18.9)	13	(17.8)	0.849

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; FFP, fresh frozen plasma; GRWR, graft recipient weight ratio; ICU, intensive care unit; RBC, red blood cell count.

Note: Data presented as median (interquartile range [IQR]) or number (%) where appropriate. *p*-Value using two-sample independent *t*-tests or Mann–Whitney *U*-test and Pearson's chi-square tests or Fisher's exact test as appropriate. *p*-Values < 0.05 are considered statistically significant and boldfaced.

Patient and Graft Survival

Overall 1-year graft and patient survival rates were 78 and 87%, respectively. One- and 10-year graft survival in recipients with a posttransplant thrombosis (29 and 21%) were significantly lower when compared with recipients without a posttransplant thrombosis (83 and 71%; $p < 0.001$). One- and 10-year patient survival in recipients with a posttransplant thrombotic complication were 71 and 64%, which was significantly lower than 88 and 83% in recipients without a thrombotic complication ($p = 0.025$; ►**Fig. 2**, ►**Supplementary Fig. S1** [available in the online version]). One- and 10-year graft survival were also significantly lower in recipients with a bleeding complication (70 and 56%) compared with those without bleeding (82 and 73%; $p = 0.028$). This was similar for 1- and 10-year patient survival in those with bleeding complications (78 and 72%) and without bleeding complications (91 vs. 87%; $p = 0.006$).

In Cox regression analysis, posttransplant thrombotic and bleeding complications were significantly associated with mortality with a HR of 3.38 (1.36–8.45; $p = 0.009$) and 2.50 (1.19–5.24; $p = 0.015$), respectively, when adjusted for potential confounders including age, weight, diagnosis, CP score, urgency state, donor type, graft type, CIT, WIT, intraoperative blood loss, and era.

Discussion

In this study, we report an 11% incidence of posttransplant thrombotic complications in a cohort of 200 pediatric liver transplant recipients, including 7.5% HAT, 2.0% PVT, and 1.0% venous outflow tract obstruction. These incidences are relatively low, as incidences of 5 to 18% for HAT and 5 to 10% for PVT have been reported in literature.[13–16] When compared with our historical cohort, in which 20% posttransplant thrombosis was reported, an important reduction has been achieved in the past years.[17] The introduction of routine antithrombotic therapy might have played an important role in this, combined with other developments in peritransplant care. It was previously suggested that routine antithrombotic therapy is beneficial in pediatric liver transplant recipients, and it has been demonstrated that the combination of heparin and acetylsalicylic acid is the most commonly used antithrombotic therapy strategy.[15,23,24]

Low recipient and donor age, as well as DCD grafts and intraoperative vascular interventions, especially when

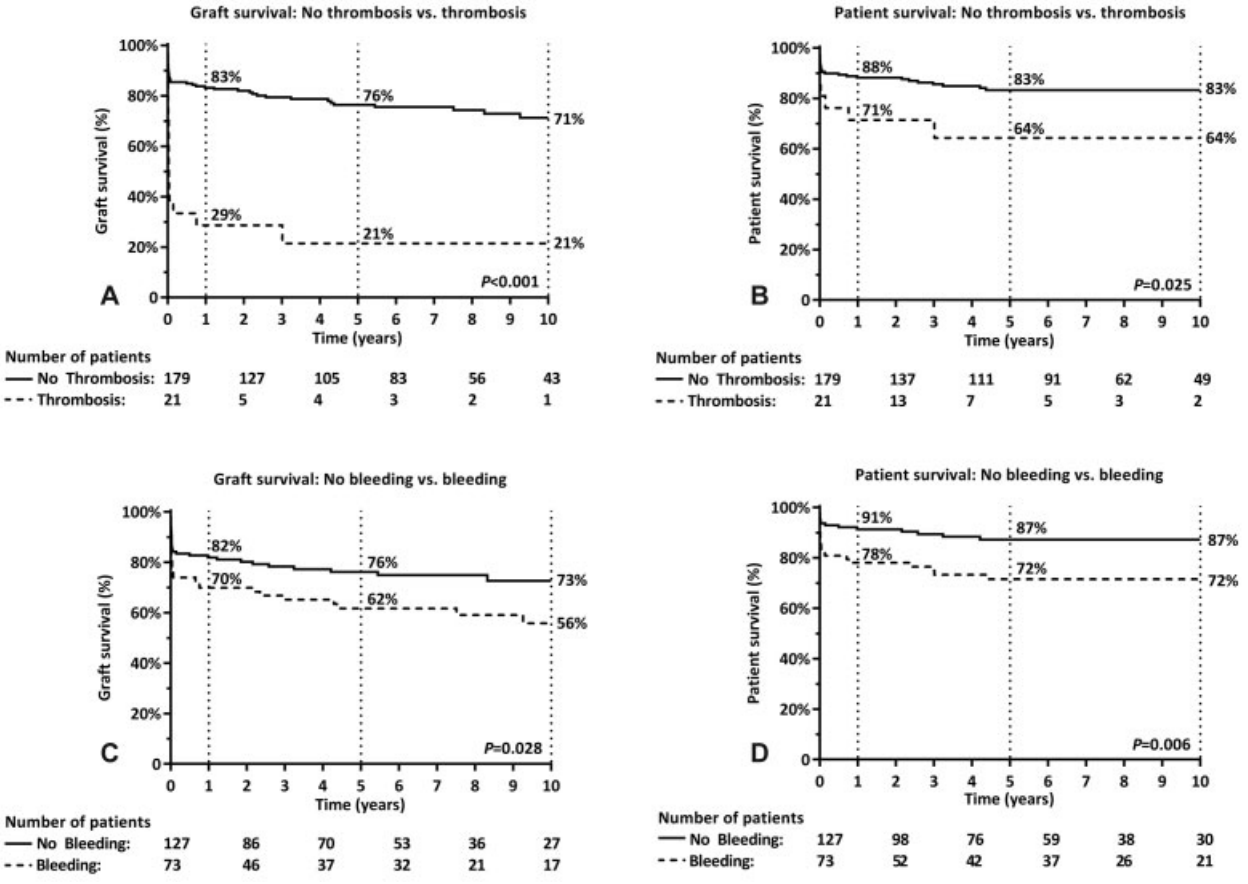

Fig. 2 Ten-year patient and graft survival of pediatric liver transplant recipients with and without posttransplant thrombotic or bleeding complications. Data presented as survival percentages, determined by the Kaplan–Meier method and compared with log rank testing. (**A**) Ten-year graft survival of pediatric liver transplant recipients with and without posttransplant thrombotic complications. (**B**) Ten-year patient survival of pediatric liver transplant recipients with and without posttransplant thrombotic complications. (**C**) Ten-year graft survival of pediatric liver transplant recipients with and without posttransplant bleeding complications. (**D**) Ten-year patient survival of pediatric liver transplant recipients with and without posttransplant bleeding complications.

concerning the hepatic artery, were identified risk factors for posttransplant thrombosis in this study, which is in line with previous studies.[15,20,25] Notably, 38% of the recipients with a posttransplant thrombotic complication had a metabolic liver disease. Thrombosis occurred in recipients with α-1-antitrypsine deficiency (38%), urea cycle defects (25%), primary hyperoxaluria (25%), and tyrosinemia (12%), but not in those with Wilson disease or glycogen storage diseases. Previous studies showed comparable results, and the risk of thrombotic complications in these patients have been attributed to their hemostatic status at baseline, which in these patients is unaltered compared with healthy children due to the absence of liver failure.[26–29]

Remarkably, prior abdominal surgery appeared to protect against postoperative thrombosis in our cohort. This might be explained by the fact that patients with previous abdominal surgery mainly concerned patients with biliary atresia who underwent a Kasai procedure. At present, recipients with biliary atresia are diagnosed early and subsequently transplanted in a better condition, which improved postoperative outcomes.

Posttransplant thrombosis had a major impact on clinical outcomes of recipients. More reinterventions and a longer ICU stay were seen in recipients with posttransplant thrombosis, and more importantly, both graft and patient survival were significantly decreased. This again emphasizes the demand for routine antithrombotic therapy in liver transplantation. On the other hand, caution is required with routine antithrombotic therapy in patients with an already fragile "rebalanced hemostatic" state, which easily can be disturbed. This is apparent from the high proportion of posttransplant bleeding complications, affecting 37% of the recipients.

The bleeding incidence in our study is substantially higher when compared with 5 to 20% as reported in literature.[20,21] Yet, it is difficult to compare bleeding incidences between studies because of a large variety of definitions for bleeding complications. Importantly, most patients with a bleeding complication could be stabilized with a blood transfusion. Although blood transfusions are not without risks, these risks are fairly minor compared with the risks of thrombosis, as is also reflected in the inferior graft and patient survival in those with thrombosis, as shown in ►**Fig. 2**.

Not all posttransplant bleeding complications are related to antithrombotic therapy. At the time of posttransplant bleedings, 25% of the recipients had not received intravenous heparin yet, due to the inadequate hemostatic state of the recipient. Independent risk factors for posttransplant bleeding were high recipient age, high CP scores, and intraoperative blood loss and recipients with posttransplant bleedings more than twice as often had a hepatorenal syndrome. Both high CP score and hepatorenal syndrome are manifestations of more severe, decompensated cirrhosis.[8,12]

An additional factor that could have played a role in the high proportion of bleeding complications, is the potentially overdosing of heparin in older pediatric patients. According to our clinical protocol, heparin is started at 10 U/kg/h and doses are guided by APTT levels, up to a maximum of 30 U/kg/h. Consequentially, in a 40-kg pediatric patient, doses of 1,200 U/hour could be reached, meaning 28,800 U/24 hours, whereas a therapeutic heparin dose for adult patients is only 20,000 U/24 hours. However, as the APTT is already prolonged prior to heparin infusion, target ranges are unclear. Importantly, the APTT appears to underestimate the anticoagulant effect of heparin in adult patients with cirrhosis.[30] Also, anti-Xa tests are unreliable to assess heparin dose in patients with cirrhosis. Therefore, it might be beneficial to explore other monitoring modalities such as thromboelastometry, and to establish a maximum heparin dose in pediatric patients.

Over the study period, the incidence of bleeding complications decreased. Improvements in surgical, anesthesiological, and posttransplant ICU care as well as donor organ quality and preservation may be an explanation for this. Furthermore, recipient age decreased substantially over time, and more experience with dosing of antithrombotic therapy, combined with the introduction of coagulation tests such as thromboelastography presumably played an important role in this reduction.

In contrast, we observed, though not significant, an increase in posttransplant thrombosis over time, which may be related to several factors. First, recipient age decreased substantially over time. Second, the proportion of patients transplanted for metabolic liver diseases and the proportion of DCD liver transplantations increased in the third era.

In our study population, 76% of the recipients with posttransplant thrombosis had actually started with antithrombotic therapy at time of diagnosing thrombosis, indicating 24% ($n = 5$) had not. Would thrombotic events in these latter recipients have been preventable? Intraoperative bleeding seems to be an adequate reason to postpone antithrombotic therapy. Inadequate APTT levels though, could be questioned as reason to postpone antithrombotic therapy, since APTT tests only measures the procoagulant pathway, which is probably rebalanced by the anticoagulant pathway in these patients. This again indicates the vulnerable rebalanced hemostatic state in these patients, which can be easily turned from a hypo- to a hypercoagulable state and vice versa, and requires further research.

The current study has its limitations. First, this is a single-center retrospective cohort study, which is susceptible to confounding and selection bias. Second, to study the effects of routine antithrombotic therapy, recipients are ideally compared before and after its introduction. However, to identify a significant reduction, large groups are needed over a long period, which will lead to results confounded by the various other developments in peritransplant management that took place over time.

In conclusion, in 200 consecutive pediatric transplants receiving routine postoperative antithrombotic therapy, including 1 week unfractionated heparin followed by 3 months acetylsalicylic acid, we report a low incidence of posttransplant vascular complications. Posttransplant antithrombotic therapy seems valuable for pediatric liver transplant care. A more personalized approach in antithrombotic therapy to optimize the risk/benefit ratio, with a more proactive use of antithrombotic therapy in young recipients with metabolic liver failure, especially in case of intraoperative vascular

interventions, and a more careful approach in older recipients with high CP scores or significant intraoperative blood loss may have merit, but this requires clinical confirmation.

What is known about this topic?

- Bleeding and thrombotic complications are serious causes of morbidity and mortality after pediatric liver transplantation.
- Postoperative antithrombotic therapy is increasingly applied strategy to reduce thrombotic complications in pediatric liver transplantation.

What does this paper add?

- We report low incidences of posttransplant thrombosis in 200 pediatric liver transplant recipients receiving routine postoperative antithrombotic therapy.
- Posttransplant antithrombotic therapy might be a valuable strategy in pediatric liver transplantation, despite the increased bleeding risk.
- Identified risk factors might facilitate a more personalized approach in antithrombotic therapy.

Funding
None.

Conflict of interest
None declared.

References

1 Bartlett A, Rela M. Progress in surgical techniques in pediatric liver transplantation. Pediatr Transplant 2010;14(01):33–40
2 Gurevich M, Guy-Viterbo V, Janssen M, et al. Living donor liver transplantation in children: surgical and immunological results in 250 recipients at universite catholique de louvain. Ann Surg 2015;262(06):1141–1149
3 Hackl C, Schlitt HJ, Melter M, Knoppke B, Loss M. Current developments in pediatric liver transplantation. World J Hepatol 2015;7 (11):1509–1520
4 Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. World J Gastroenterol 2009;15(06):648–674
5 Patient survival in 2–18 years. European Liver Transplant Registry Website. Available at: http://www.eltr.org/Pediatric-transplantation.html. Accessed August 2018
6 Werner MJM, de Kleine RHJ, Bodewes FAJA, et al. Liver transplantation in paediatric patients in the Netherlands; evolution over the past two decades. Ned Tijdschr Geneeskd 2017;161(00):D2136
7 Lisman T, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. J Hepatol 2010;52(03):355–361
8 Lisman T, Porte RJ. Pathogenesis, prevention, and management of bleeding and thrombosis in patients with liver diseases. Res Pract Thromb Haemost 2017;1(02):150–161
9 Lisman T, Platto M, Meijers JC, Haagsma EB, Colledan M, Porte RJ. The hemostatic status of pediatric recipients of adult liver grafts suggests that plasma levels of hemostatic proteins are not regulated by the liver. Blood 2011;117(06):2070–2072
10 Weeder PD, Porte RJ, Lisman T. Hemostasis in liver disease: implications of new concepts for perioperative management. Transfus Med Rev 2014;28(03):107–113
11 Arshad F, Lisman T, Porte RJ. Hypercoagulability as a contributor to thrombotic complications in the liver transplant recipient. Liver Int 2013;33(06):820–827
12 de Boer MT, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. Dig Surg 2005;22(04):265–275
13 Kamran Hejazi Kenari S, Mirzakhani H, Eslami M, Saidi RF. Current state of the art in management of vascular complications after pediatric liver transplantation. Pediatr Transplant 2015;19(01):18–26
14 Nacoti M, Corbella D, Fazzi F, Rapido F, Bonanomi E. Coagulopathy and transfusion therapy in pediatric liver transplantation. World J Gastroenterol 2016;22(06):2005–2023
15 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(04):. Doi: 10.1111/petr.12917
16 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(04):746–757
17 Sieders E, Peeters PM, TenVergert EM, et al. Early vascular complications after pediatric liver transplantation. Liver Transpl 2000;6(03):326–332
18 Ignjatovic V, Mertyn E, Monagle P. The coagulation system in children: developmental and pathophysiological considerations. Semin Thromb Hemost 2011;37(07):723–729
19 Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987;70(01): 165–172
20 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(05):e26955
21 Kaneko J, Sugawara Y, Tamura S, et al. Coagulation and fibrinolytic profiles and appropriate use of heparin after living-donor liver transplantation. Clin Transplant 2005;19(06):804–809
22 Bos S, Bernal W, Porte RJ, Lisman T. Hemostatic complications in hepatobiliary surgery. Semin Thromb Hemost 2017;43(07):732–741
23 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(01):e13317
24 Heffron TG, Pillen T, Welch D, Smallwood GA, Redd D, Romero R. Hepatic artery thrombosis in pediatric liver transplantation. Transplant Proc 2003;35(04):1447–1448
25 Voulgarelis S, Vitola B, Lerret SM, Hong JC, Scott JP. Perioperative anticoagulation practices for pediatric liver transplantation. Pediatr Transplant 2018;22(04):e13193
26 Arnon R, Kerkar N, Davis MK, Anand R, Yin W, González-Peralta RP; SPLIT Research Group. Liver transplantation in children with metabolic diseases: the studies of pediatric liver transplantation experience. Pediatr Transplant 2010;14(06):796–805
27 Dowman JK, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, Newsome PN; UK Liver Selection and Allocation Working Party. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transpl 2012;18(02):195–200
28 Mazariegos G, Shneider B, Burton B, et al. Liver transplantation for pediatric metabolic disease. Mol Genet Metab 2014;111(04):418–427
29 Lisman T, Porte RJ. Hepatic artery thrombosis after liver transplantation: more than just a surgical complication? Transpl Int 2009;22(02):162–164
30 Potze W, Arshad F, Adelmeijer J, et al. Routine coagulation assays underestimate levels of antithrombin-dependent drugs but not of direct anticoagulant drugs in plasma from patients with cirrhosis. Br J Haematol 2013;163(05):666–673