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ABOUT COVER

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AIM AND SCOPE

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INDEXING/ABSTRACTING

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EDITORS FOR THIS ISSUE

Retrospective Study

Predicting early outcomes of liver transplantation in young children: The EARLY study

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Abstract

AIM
To determine potentially modifiable predictors of early outcomes after liver transplantation in children of age < 3 years.

METHODS
This study was a retrospective chart review including all consecutive children of age less than 3-years-old having had a liver transplant done at the Western Canadian referral center from June 2005 to June 2015.

Pre-specified potential predictor variables and primary and secondary outcomes were recorded using standard definitions and a case report form. Associations between potential predictor variables and outcomes were determined using univariate and multiple logistic [odds ratio (OR); 95%CI] or linear (effect size, ES; 95%CI) regressions.

RESULTS
There were 65 children, of mean age 11.9 (SD 7.1) mo and weight 8.5 (2.1) kg, with biliary-atresia in 40 (62%), who had a living related donor [LRD; 29 (45%)], split/reduced [21 (32%)] or whole liver graft [15 (23%)]. Outcomes after liver transplant included: ventilator-days of 12.5 (14.1); pediatric intensive care unit mortality of 5 (8%); re-operation in 33 (51%), hepatic artery thrombosis (HAT) in 12 (19%), portal vein thrombosis (PVT) in 11 (17%), and any severe complication (HAT, PVT, bile leak, bowel perforation, intraabdominal infection, retransplant, or death) in 32 (49%) patients. Predictors of the prespecified primary outcomes on multiple regression were: (1) HAT: split/reduced (OR 0.06; 0.01, 0.76; *P* = 0.030) or LRD (OR 0.16; 0.03, 0.95; *P* = 0.044) *vs* whole liver graft; and (2) ventilator-days: surgeon (*P* < 0.05), lowest antithrombin (AT) postoperative day 2-5 (ES -0.24; -0.47, -0.02; *P* = 0.034), and split/reduced (ES -12.5; -21.8, -3.2; *P* = 0.009) *vs* whole-liver graft. Predictors of the pre-specified secondary outcomes on multiple regression were: (1) any thrombosis: LRD (OR 0.10; 0.01, 0.71; *P* = 0.021) or split/reduced (OR 0.10; 0.01, 0.85; *P* = 0.034) *vs* whole liver graft, and lowest AT postoperative day 2-5 (OR 0.93; 0.87, 0.99; *P* = 0.038); and (2) any severe complication: surgeon (*P* < 0.05), lowest AT postoperative day 2-5 (OR 0.92; 0.86-0.98; *P* = 0.016), and split/reduced (OR 0.06; 0.01, 0.78; *P* = 0.032) *vs* whole-liver graft.

CONCLUSION
In young children, whole liver graft and surgeon was associated with more complications, and higher AT postoperative day 2-5 was associated with fewer complications early after liver transplantation.

Key words: Liver transplantation; Pediatric; Complications; Thrombosis; Antithrombin

Core tip: In a retrospective review of 65 consecutive children having had liver transplant at age less than 3-year-old, done at a single referral institution, earlier post-operative complications were independently statistically associated with whole liver graft (compared to split/reduced or living related graft), surgeon, and lower antithrombin levels day 2-5 postoperatively. The finding that lower antithrombin levels were associated with any thrombosis, any severe complication, and ventilator days is a novel finding that should be confirmed by others.

INTRODUCTION
One-year graft and survival rates after pediatric liver transplantation (LT) approach 80%-90% and 90% respectively[1,2]. We found that long-term neurocognitive outcome in patients under 3-years-old at time of LT, assessed in 89% of survivors at 4.5 years of age, was shifted to the left of population norms [full scale intelligence quotient mean 93.9, standard deviation (SD) 17.1], with intelligence scores < 70 (below two SDs from the population mean, expected in 2.27% of the normative population) in 6%[3]. These patients often had significant postoperative complications in the intensive care unit, and these acute posttransplant illnesses (*e.g.*, use of inotropes, infection, higher creatinine) were associated with adverse neurocognitive outcomes[3]. These findings are important because "the early years" are increasingly recognized as the period of greatest vulnerability to, and greatest return on investment from, preventing adverse events[4-7]. Adverse long-term outcomes can have lasting and profound impacts on future quality of life, education, earning potential, and healthcare utilization[4-7]. In addition, these complications are life-threatening, involve repeat surgeries, prolong intensive care unit stay, and are stressful for patients, families, and the medical team.

There have been previous studies reporting the incidence of acute complications in the pediatric intensive care unit (PICU) postLT. The main complications include the following: hepatic artery thrombosis (HAT; < 10%)[8], portal vein thrombosis (PVT; < 10%)[9], biliary leak (< 15%)[10], bowel perforation (< 10%)[11], infection, and resulting retransplantation (in < 15%) and reoperations (in up to 50%)[12]. These postLT complications are predictors of 6-mo graft and patient survival[13]. Some risk factors for these complications have been suggested, including graft type, and transplant era (year of surgery); however, these are variable between studies[10,13-15]. Recipient age and weight are often not predictors[8,16-18].

In this study, we aimed to determine potentially modifiable prespecified acute care variables that may be associated with prespecified primary and secondary acute intensive care postoperative outcomes in young LT recipients at our center over the past 10 years. In addition, we aimed to explore novel potential predictors of adverse outcomes, including: written comments made about abnormal liver vessels or biliary anatomy in the dictated operating report, measures of postoperative fluid balance (*i.e.,* highest hemoglobin, first day of negative fluid balance, first day of using furosemide, lowest central venous pressure); and

measures of postoperative coagulation status (*i.e.* time to start of heparin and achieving a therapeutic heparin level, lowest antithrombin levels, and use of other anticoagulants).

MATERIALS AND METHODS

Ethics statement
This study was approved by the University of Alberta Health Research Ethics Board (Pro00031805).

Study design
This was a retrospective observational cohort study. The charts of all patients meeting the eligibility criteria were reviewed. Inclusion criteria were having a LT done at age < 3 years at the Stollery Children's Hospital between June 2005 to June 2015. Patients having a multivisceral transplant were excluded. Potential predictor variables collected included descriptive pretransplant demographics, transplant surgery details, and early postoperative variables (see Tables E1 to E3 in Additional File 1). PICU outcomes recorded included length of stay, mortality, graft survival, retransplant, reoperations, and complications (HAT, PVT, bile leak, bowel perforation, and infection) (see Table E4 in Additional File 1). A severe complication was defined as any one of: HAT, PVT, bile leak, bowel perforation, intraabdominal infection, death, or retransplant.

Variables and outcomes were determined by review of the patient chart by one of the authors (RA), including: written notes, laboratory results, radiology reports, operating room surgical dictations, and anesthesia records. To verify accurate recording of severe complication outcomes, all patient charts with a severe complication were reviewed by a second author (ARJ) to ensure agreement, and severe complications were cross-checked in the independent LT database at our institution. A case report form, including strict conservative definitions of variables and outcomes, was agreed upon by all authors prior to chart review (Additional File 2).

Prior to any data analysis, we prespecified the primary and secondary outcomes. The primary outcomes were HAT and ventilator days; the secondary outcomes were any severe complication and any thrombosis (HAT or PVT). After local presentation of results, we were asked to add posthoc secondary outcomes of 6-mo graft survival, and to compare outcomes by year category and weight category; we include these results, acknowledging them to be posthoc, exploratory, and to be interpreted with caution.

Also prior to any data analysis, the following variables were prespecified to be used in the univariate analyses: preoperative (biliary atresia; growth failure - < 5th percentile for weight or height; albumin; graft type - whole liver, split/reduced, or living donor), operative (surgery duration; cold ischemia time; warm ischemia time; artery vascularity end-to-end anastomosis or

graft; fascia closed; comment about hepatic artery, portal vein, biliary, or any one of these anatomical concerns in the dictated operative report; packed red blood cell volume transfused), and postoperative (heparin started - hour; therapeutic heparin level by day 3; highest hemoglobin day 1 and day 2-5; lowest anti-thrombin day 1 and day 2-5; other anticoagulant used - dipyridamole, dextran, or aspirin; first day of negative fluid balance; first day of furosemide use; lowest central venous pressure day 1 and day 2-5) variables.

Statistical analysis
The statistical methods of this study were reviewed by Elham Khodayari Moez, MSc, PhD candidate, from School of Public Health, University of Alberta, Edmonton, Alberta, Canada. Data was entered into a REDCap database, and transferred to SPSS version 19 for analysis[19]. For binary outcomes, univariate followed by multiple logistic regression was used to identify potential predictors. For continuous outcomes, univariate followed by multiple linear regression was used to identify potential predictors. The possibility of presence of any correlation structure in the data caused by surgeon clusters was assessed using intraclass correlations (ICCs). For all the outcomes, ICCs were small and indicated no correlation structure among the observations within surgeon clusters. Therefore, the assumption of independent observations, required for regression modelling, was met.

In all multiple regressions, the following prespecified, as likely clinically significant, variables were included: Weight, pediatric end-stage liver disease (PELD) score, year of surgery, and surgeon. All three surgeons were Fellows of the Royal Society of Surgeons of Canada and performed all the adult and pediatric LTs during the entire 10-year period; transplant cases were done by whichever surgeon was on service at that time. Variables significant at $P < 0.10$ on univariate analysis were also used in the multiple regressions. In patients having a retransplant during their PICU stay, only variables from the first LT surgery, and the first 5 days' time after the first LT were used. Dummy variables were created for analysis of graft type (in three categories) and surgeon (in three categories). Multiple regressions were performed if missingness of a variable was < 5%, with those patients excluded from the analysis (*i.e.,* no imputation of missing variables). Results are presented as odds ratios (ORs) with 95%CIs for logistic regressions, and effect sizes (ESs) with 95%CIs for linear regressions. For the multiple regressions, a *P*-value ≤ 0.05 was accepted as statistically significant.

RESULTS

Description of the cohort
There were 65 patients meeting the eligibility criteria over the 10 years. The patients were 11.9 (SD 7.1)

Table 1 Univariate and multiple logistic regressions for the primary outcome of hepatic artery thrombosis after liver transplantation

Variable	Univariate logistic regression, *n* = 65		Multiple logistic regression, *n* = 65	
	Odds ratio (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
Yr	1.10 (0.89, 1.35)	0.371		
Weight	0.65 (0.41, 1.04)	0.073		
PELD	0.98 (0.93, 1.04)	0.514		
Surgeon 2 *vs* 1	2.04 (0.41, 10.27)	0.388		
Surgeon 3 *vs* 1	4.33 (0.87, 21.60)	0.074		
Surgeon 2 *vs* 3	0.47 (0.10, 2.17)	0.334		
Fascia closed on admission	3.9 (1.1, 14.3)	0.04		
Hepatic artery any comment	3.9 (1.06, 14.31)	0.04		
Any operating note comment[1]	9.82 (1.18, 81.58)	0.034		
First day use of furosemide, *n* = 54[2]	1.21 (1.05, 1.41)	0.011		
Graft type R/SL *vs* WL	0.04 (0.01, 0.42)	0.006	0.06 (0.01, 0.76)	0.03
Graft type LR *vs* WL	0.10 (0.02, 0.48)	0.004	0.16 (0.03, 0.95)	0.044

[1]No meaningful difference if we use "any operating note comment" instead of "hepatic artery any comment" in the multiple regression; [2]If multiple regression is done with first day of furosemide (data available for *n* = 54), furosemide is significant with OR 1.67 (95%CI: 1.03, 2.73), *P* = 0.039, meaning the later furosemide is started the higher is the risk of HAT. CI: Confidence interval; HAT: Hepatic artery thrombosis; LR: Living related liver graft; PELD: Pediatric end-stage liver disease score; R/SL: Reduced or split liver graft; WL: Whole liver graft.

mo of age, of 8.5 (SD 2.1) kg weight (23% $\leqslant$ 7 kg; 52% with growth failure), with biliary atresia in 40 (62%), and with 34 (52%) having had a previous Kasai procedure. Graft type was whole liver in 15 (23%), reduced size/split graft in 21 (32%), and living related graft in 29 (45%) patients. A comment about concerning anatomy of the vessels or biliary tract was recorded for 39 (60%) patients. A therapeutic heparin level by day 3 was obtained for 20 (31%) patients. PICU mortality was 5 (8%), and in survivors the ventilation days and PICU days were 12.5 (SD 14.1) and 21 (SD 21) d respectively. Complications were common, with HAT in 12 (19%), PVT in 11 (17%), biliary leak in 15 (23%), bowel perforation in 5 (8%), intraabdominal infection in 18 (28%), retransplant in 9 (14%), and any severe complication in 32 (49%) patients. First graft survival was 52 (80%) in the PICU, and 51 (78%) at 6 mo. More details of the preoperative, operative, postoperative, and outcome variables are given in Tables S1-4 (Additional File 1).

Primary outcomes

The univariate and multiple logistic regression results for HAT are shown in Table 1. Reduced/split liver (OR 0.06; 95%CI: 1, 0.76; *P* = 0.03), and living donor liver (OR 0.16; 95%CI: 0.03, 0.95; *P* = 0.044) transplant had lower risk of HAT than whole liver transplant. The later the first use of furosemide (OR 1.67; 95%CI: 1.03, 2.73; *P* = 0.039) was also associated with higher risk of HAT.

The univariate and multiple linear regression results for ventilator days in the 60 survivors are shown in Table 2. Ventilator days were shorter for reduced/split liver (ES -12.5; 95%CI: -21.8, -3.2; *P* = 0.009) than for whole liver transplants. The lowest antithrombin day 2-5 was associated with ventilator days: The higher the antithrombin, the shorter the ventilator days (ES -0.23; 95%CI: -0.47, -0.02; *P* = 0.034). This

is shown graphically in Figure S1 (Additional File 1).

Secondary outcomes

The univariate and multiple logistic regression results for any severe complication are shown in Table 3. Reduced/split liver (OR 0.06; 95%CI: 0.01, 0.78; *P* = 0.032) transplant had a lower severe complication risk than whole liver transplant. The lowest antithrombin day 2-5 was associated with severe complication risk: the higher the antithrombin, the lower the risk (OR 0.92; 95%CI: 0.86, 0.98; *P* = 0.016). This is shown graphically in Figure S2 (Additional File 1).

The univariate and multiple logistic regression results for any thrombosis are shown in Table 4. Reduced/split liver (OR 0.10; 95%CI: 0.01, 0.85; *P* = 0.034) and living donor liver (OR 0.10; 95%CI: 0.01, 0.71; *P* = 0.021) transplants had a lower risk of thrombosis than whole liver transplants. The lowest antithrombin day 2-5 was associated with thrombosis: the higher the antithrombin, the lower the risk (OR 0.93; 95%CI: 0.87, 0.99; *P* = 0.038). This is shown graphically in Figure S3 (Additional File 1).

Posthoc outcomes

The univariate and multiple logistic regression results for 6-mo graft survival are shown in Table 5. Reduced/split liver (OR 15.4; 95%CI: 1.01, 234.9; *P* = 0.049) had better graft survival than whole liver transplant. The lowest antithrombin day 2-5 was associated with graft survival: the higher the anti-thrombin, the higher the graft survival (OR 1.08; 95%CI: 1.00, 1.16; *P* = 0/049). This is shown graphically in Figure S4 (Additional File 1).

Year (2005-2010 *vs* 2011-2015) and weight (> 7 kg *vs* $\leqslant$ 7 kg) were analyzed as categorical variables for their association with the primary and secondary outcomes and mortality. On univariate analysis (independent sample *t*-test or Fisher's exact test,

Table 2 Univariate and multiple linear regressions for the primary outcome of postoperative ventilator days after liver transplantation in *n* = 60 survivors

Variable	Univariate linear regression, *n* = 60		Multiple linear regression, *n* = 58	
	Effect size (95%CI)	*P*-value	Effect size (95%CI)	*P*-value
Yr	-0.34 (-1.51, 0.83)	0.568		
Weight	-1.36 (-3.06, 0.34)	0.114		
PELD	0.03 (-0.30, 0.35)	0.866		
Surgeon 2 *vs* 1	-0.77 (-8.69, 7.14)	0.845		
Surgeon 3 *vs* 1	12.09 (3.15, 21.03)	0.009	10.67 (1.34, 20.01)	0.026
Surgeon 2 *vs* 3	-12.86 (-22.45, -3.28)	0.009	-9.69 (-19.24, -0.15)	0.047
Surgery duration, *n* = 54[1]	-0.037 (-0.069, -0.005)	0.026		
Fascia closed on admission	8.10 (0.52, 15.68)	0.037		
Heparin started hour, *n* = 58[2]	0.31 (0.17, 0.45)	0.001		
Highest hemoglobin day 2-5	0.27 (0.001, 0.54)	0.049	0.22 (-0.04, 0.48)	0.096
Lowest anti-thrombin day 1, *n* = 44	-0.38 (-0.65, -0.11)	0.007		
Lowest anti-thrombin day 2-5, *n* = 58	-0.35 (-0.57, -0.13)	0.003	-0.24 (-0.47, -0.02)	0.034
First day furosemide used, *n* = 521	1.01 (0.31, 1.70)	0.005		
Graft type R/SL *vs* WL	-11.61 (-21.48, -1.74)	0.022	-12.53 (-21.82, -3.23)	0.009
Graft type LR *vs* WL	-9.27 (-18.73, 0.19)	0.055	-7.29 (-15.75, 1.17)	0.096

[1]If we add "surgery duration" and "first day furosemide used" (*n* = 49) neither variable is significant, and if add only "first day furosemide used" also not significant; [2]"Heparin started h" was not added to the multiple regression because it may be a marker of how worried the medical team are about bleeding *vs* thrombosis risk, and how long the INR is elevated [the correlation of "heparin started (h)" and "time for INR to be ⩽ 2" is *r* = 0.66] (*i.e.*, it may be an outcome, and not a determinant of outcome), and if added the effect size is 0.21 (0.07, 0.36); *P* = 0.005. INR: International normalized ratio; LR: Living related liver graft; PELD: Pediatric end-stage liver disease score; R/SL: Reduced or split liver graft; WL: Whole liver graft.

Table 3 Univariate and multiple logistic regression for the secondary outcome of any severe complication after liver transplantation

Variable	Univariate logistic regression, *n* = 65		Multiple logistic regression, *n* = 62	
	Odds ratio (95%CI)	*P*-value	Odds ratio (95%CI)	*P*-value
Yr	0.97 (0.83, 1.14)	0.721		
Weight	1.02 (0.81, 1.29)	0.857	1.44 (0.98, 2.12)	0.064
PELD	0.96 (0.92, 1.00)	0.067		
Surgeon 2 *vs* 1	2.96 (0.92, 9.53)	0.069	10.07 (1.49, 67.87)	0.018
Surgeon 3 *vs* 1	6.11 (1.52, 24.50)	0.011	17.29 (1.85, 161.4)	0.012
Surgeon 2 *vs* 3	0.49 (0.12, 2.03)	0.322		
Surgery duration, *n* = 59	0.995 (0.99, 1.00)	0.043		
Artery vascularity	8.96 (1.03, 77.66)	0.047		
Biliary anatomy comment	8.96 (1.03, 77.66)	0.047		
Highest hemoglobin day 2-5	1.04 (1.00, 1.09)	0.052		
Lowest anti-thrombin day 2-5, *n* = 62	0.95 (0.91, 0.99)	0.019	0.92 (0.86, 0.98)	0.016
First day of furosemide, *n* = 54[1]	1.23 (0.99, 1.54)	0.067		
Graft type LR *vs* WL	0.30 (0.08, 1.15)	0.079		
Graft type R/SL *vs* WL	0.22 (0.05, 0.95)	0.042	0.06 (0.01, 0.78)	0.032

[1]If multiple regression is done with first day of furosemide (*n* = 54), then furosemide is not significant. Surgery duration is collinear with surgeon, so only surgeon was used in the multiple regression. LR: Living related liver graft; PELD: Pediatric end-stage liver disease score; R/SL: Reduced or split liver graft; WL: Whole liver graft.

as appropriate), year category was not statistically significantly associated with any outcome, and this was confirmed when year was used as a categorical variable in the multiple logistic and linear regressions (Table S5, Additional File 1). On univariate analysis, weight category was associated with ventilator days (10.5, SD 13.2 *vs* 20.4, SD 15.2, *P* = 0.03), with a trend toward an association with graft survival (43/50, 86% *vs* 9/15, 60%; *P* = 0.06). However, these associations were not confirmed when weight was used as a categorical variable in the multiple logistic and linear regressions (Table S6, Additional File 1).

DISCUSSION

Liver transplant in young children is life-saving for end-stage liver disease, yet patients are known to have a high risk of post-operative complications[20,21]. We aimed to determine potentially modifiable perioperative variables that are independently associated with complications post LT. There are several important findings from this study of 65 young patients having LT over the past 10 years. First, although PICU patient (92%) and graft (80%) survival were high, patients experienced a combination of significant postoperative

Table 4 Univariate and multiple logistic regression for the secondary outcome of any thrombosis after liver transplantation

Variable	Univariate logistic regression, n = 65		Multiple logistic regression, n = 62	
	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Yr	0.96 (0.81, 1.14)	0.656		
Weight	0.74 (0.53, 1.03)	0.075		
PELD	0.97 (0.93, 1.02)	0.218		
Surgeon 2 vs 1	1.50 (0.37, 6.03)	0.568		
Surgeon 3 vs 1	7.20 (1.75, 29.57)	0.006	8.66 (0.99, 75.63)	0.051
Surgeon 2 vs 3	0.21 (0.05, 0.88)	0.033		
Surgery duration, n = 59[1]	0.99 (0.98, 1.00)	0.017		
Fascia closed on admission	2.55 (0.84, 7.78)	0.1		
Hepatic artery any comment[2]	2.55 (0.84, 7.78)	0.1		
Biliary anatomy comment[2]	5.12 (1.08, 24.20)	0.039		
Any operating note comment	3.44 (0.99, 11.94)	0.052		
Lowest anti-thrombin d2-5, n = 62	0.95 (0.91, 1.00)	0.03	0.93 (0.87, 0.99)	0.038
First day use of furosemide, n = 54[1]	1.24 (1.04, 1.47)	0.018		
Graft type R/SL vs WL	0.12 (0.03, 0.54)	0.006	0.10 (0.01, 0.85)	0.034
Graft type LR vs WL	0.10 (0.03, 0.44)	0.002	0.10 (0.01, 0.71)	0.021

[1]If multiple regression is done with first day furosemide (n = 54) a trend for first day of furosemide [OR 1.37 (0.99, 1.90), P = 0.062] is found, meaning the later the furosemide is started, the higher the risk of thrombosis; [2]"Any operating note comment" was used as it is collinear with "hepatic artery any comment" and "biliary anatomy comment". If instead, we remove "any operating note comment" and add "hepatic artery any comment" and "biliary anatomy comment", there is no meaningful change to the regression results. LR: Living related liver graft; OR: Odds ratio; PELD: Pediatric end-stage liver diseases score; R/SL: Reduced or split liver graft; WL: Whole liver graft.

Table 5 Univariate and multiple logistic regression for the posthoc secondary outcome of 6-mo first graft survival after liver transplantation

Variable	Univariate logistic regression, n = 65		Multiple logistic regression, n = 62	
	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value
Yr	1.08 (0.88, 1.32)	0.46		
Weight	1.65 (1.01, 2.68)	0.046		
PELD	1.02 (0.97, 1.07)	0.508		
Surgeon 2 vs 1	0.49 (0.10, 2.47)	0.388		
Surgeon 3 vs 1	0.17 (0.04, 0.84)	0.03		
Surgeon 2 vs 3	2.83 (0.63, 12.71)	0.174		
Fascia closed on admission	0.21 (0.06, 0.75)	0.016		
Biliary atresia	0.23 (0.05, 1.14)	0.072		
Surgery duration, n = 59[1]	1.01 (1.00, 1.01)	0.097		
Heparin started (h), n = 62[2]	0.97 (0.94, 0.99)	0.019		
Lowest anti-thrombin d2-5, n = 62	1.07 (1.01, 1.13)	0.018	1.08 (1.00, 1.16)	0.049
First day furosemide used, n = 54[1]	0.88 (0.78, 0.99)	0.035		
Graft type R/SL vs WL	8.31 (1.41, 49.06)	0.019	15.39 (1.01, 234.9)	0.049
Graft type LR vs WL	5.47 (1.27, 23.64)	0.023		

Surgery duration and surgeon are collinear, so we could not enter both in the regression. [1]If we added "first day furosemide used" (n = 54), furosemide is not significant; [2]If we added "heparin started h", it was not significant. LR: Living related liver graft; PELD: Pediatric end-stage liver disease score; R/SL: Reduced or split liver graft; WL: Whole liver graft.

complications, including HAT (19%), PVT (17%), bile leak (23%), bowel perforation (8%), intraabdominal bleeding (11%), abdominal compartment syndrome (12%), and intraabdominal infection (28%). These complications necessitated reoperation of the abdomen for 51% (median 2 episodes, interquartile range 1-4), retransplantation for 14%, and renal replacement therapy for 14% of all patients. Second, there were few independent predictors of our primary and secondary outcomes. When adjusted for prespecified clinically important variables (weight, year, PELD score, and surgeon) and those variables significant at $P \leq 0.10$ on univariate analysis, whole liver graft had higher risk of complications (of HAT, ventilator days, any severe complication, any thrombosis, and graft loss), and a novel predictor, the lower the antithrombin level on day 2-5 postoperative, had higher risk of complications (ventilator days, any severe complication, any thrombosis, and graft loss). Third, we found no statistically significant change in outcomes over time on multiple regressions. Fourth, we found no statistically significant association of recipient weight with adverse outcomes on multiple regressions. Fifth, some of the novel predictors we examined were not associated with complication rates on multiple regressions. This included growth

failure (below 5th percentile on weight or height), surgical comments about concerning anatomy of the transplant vessels (hepatic artery or portal vein) or biliary tract, whether fascia was closed on admission to PICU, measures of postoperative fluid status (*e.g.*, use of furosemide, lowest central venous pressure, and highest hemoglobin), and measures of anticoagulation (*e.g.*, achieving a therapeutic heparin level).

This study cohort was similar to those reported in the literature, allowing cautious generalization of the findings to other centers. For example, the United States Scientific Registry of Transplant Recipients 2014 annual data report found 50.6% of recipients had previous abdominal surgery, and 4.8% had previous PVT, compatible with our rate of previous (Kasai procedure) surgery for 52%, and previous PVT in 9%[1]. The SPLIT database found that in LT for biliary atresia, retransplant rates were 11%, and reoperation was required in 48%, comparable to our rates of 14% and 51% respectively[12]. The SPLIT group also found that reoperation within 30 d was more common in split, reduced and living donor grafts (which accounted for 77% of our grafts)[14], and that 30-d survival was 93%, again comparable to our findings[14]. A recent meta-analysis found that 1-year pediatric patient and graft survival for whole liver grafts was 91% and 84.9%, and for technical variant grafts 87.7% and 77.2% respectively, comparable to our 6-mo patient and graft survivals of 89% and 78%[15].

Nevertheless, there are some differences from other reported cohorts that should be acknowledged. The rates of HAT, PVT, and bile leak were higher than in most reports. For example, HAT is often in the range of 5%-10% (compared to our rate of 19%)[2,8,11,14,15,17,18,22-27], PVT in the range of 5%-15% (compared to our rate of 17%)[2,11,15-18,24-26,28,29], and bile leak in the range of 2%-15% (compared to our rate of 23%)[10,15,16,26,29]. A report from the SPLIT database found high rates of vascular complications (25%), PVT (16%), and bile leak (21%) in the 6.7% of recipients with complex vascular anomalies[30]; however, we did not find an association of abnormal anatomy comments and thrombosis or severe complications. Although some reports have found complication rates to have improved over time, these are usually reports from the 1990s, with the improvements seen by the early-to-mid 2000s[10,11,14,17,18,24,28,31]. This is similar to reports that have found that young age and smaller weight is no longer a risk factor for complications[2,8,13,14,16-18,22,26,27,29,31]. Indeed, we did not find that year or weight was an independent predictor of complication rates. Finally, there are few reports of the incidence of bowel perforation or intraabdominal infection rates for comparison[11,13,21,26]. Quality improvement initiatives at all centers, including our own, may be needed to reduce these complication rates[32,33].

There are some novel findings from this study that warrant further investigation. First, the independent association of low antithrombin levels postLT with any thrombosis, any severe complication, graft loss, and ventilation days has not, to our knowledge, previously been examined or reported. Antithrombin is an anticoagulant produced by the liver, with its effect mediated by irreversibly inhibiting plasma serine proteases (including activated factors X and thrombin); this effect is greatly accelerated by heparin[34]. In addition, antithrombin has antiinflammatory properties[34]. Although antithrombin does not have beneficial effects in critically ill patients in general, it has not been studied in the setting of LT patients who are high risk for thrombosis[34]. Anticoagulation management after liver transplant is not standardized and often not reported in publications[35,36]. The hemostatic system during liver transplant is in a complex and precarious rebalance, with thrombotic complications often higher than bleeding complications, and is an area in need of extensive study[37-41]. The SPLIT research agenda specifically suggests a randomized trial of different anticoagulation profiles measuring the combined endpoints of PVT, HAT, and reexploration for intraabdominal bleeding[42]. Treatment with antithrombin concentrate intravenously should be considered for low antithrombin levels in such protocols.

Second, the independent association of surgeon with outcomes has not, to our knowledge, previously been reported. The literature suggests that this is an expected finding, for several reasons. The outcomes among centers are highly variable, with most large centers reporting excellent outcomes[11,17,18,24-26,28], and some smaller centers reporting poor outcomes[43-47]. Some authors have reported a decrease in complication rates over time associated with what they call technical experience[10,17,18,27,29,48]. The SPLIT group has reported that the center where transplant is done is a predictor of patient and graft survivals (which in turn are predicted by complication rates), and that after adjusting for center there is no effect of age on transplant outcomes[13]. The Kid's Inpatient Database also found mortality varied by region[48]. The SPLIT Clinical Care and Quality Improvement Committee recently reported that they considered HAT and biliary complications as "essentially surgical complications"[32]. These data suggest that surgical technique is a potentially modifiable variable affecting outcome, and more study is needed to determine what accounts for these differences in outcomes among surgeons, something that is beyond the scope of our study.

Third, whole liver grafts were associated with higher complication rates in our study. This is contrary to the findings from a recent meta-analysis comparing outcomes between whole liver *vs* technical variant grafts in pediatrics, where the ORs for 1-year patient and graft survival were 1.62 and 1.78, and for PVT and biliary complications were 0.45 and 0.42 for whole liver grafts compared to technical variant grafts[15]. The SPLIT group also reported that whole liver grafts have lower rates of biliary complications, PVT, and reoperation compared to split, reduced or

living donor grafts[14]. Nevertheless, there is conflicting literature. Some groups have reported that graft type is not related to biliary complications[10,16,29]. Most groups have reported that graft type is not related to HAT[15], and UNOS data and some single center data suggests graft survival is better after living donor grafts than deceased donor grafts, particularly in younger patients[11,27,49,50]. It is possible that our findings of higher complication rates with whole liver grafts is due to the small patient size in which whole grafts contributed to intraabdominal hypertension and vascular compression[9,23]. In support of our findings, an analysis of the UNOS database examining liver transplants for biliary atresia from 2002-2014 found that in recipients ⩽ 7 kg the 1-, 5- and 10-year graft survival was lowest for whole liver grafts, and the vascular thrombosis and liver retransplantation rates highest for whole liver grafts, unlike in recipients weighing 7-14 kg and > 14 kg[51]. Future studies should determine whether graft type affects outcome differently in the youngest patients.

There are limitations to this study. First, this was a single-center, retrospective, observational study of 65 patients having had LT at age < 3 years over a time-period of 10 years. Some variables were missing from the medical records for several patients (*e.g.*, blood products given during the transplant surgery; size of hepatic artery, hepatic veins, or portal vein; and graft-to-recipient body size ratio). The subjective evaluations of the vessels and biliary anatomy in the surgical notes were not standardized, and thus difficult to interpret. As such, the findings cannot show cause and effect, and are only hypothesis generating; whether treatment to increase antithrombin levels can improve outcomes is unknown and requires prospective study, ideally in a randomized trial as suggested in the SPLIT research agenda[42]. In addition, other centers should confirm the findings to determine the generalizability of the results. Second, the "any severe complication" outcome was not based on the Clavien-Dindo classification of surgical complications; however, the definition we used would include only complications of Grade Ⅲ-Ⅴ, and mostly of Grade Ⅳ (life-threatening requiring ICU management)[52]. In addition, the main outcomes overlapped; for example, HAT was a component of "any thrombosis" and "any severe complication", and graft survival was often determined by thrombosis and other severe complications. Third, the novel predictor, lowest antithrombin on day 2-5 postoperative, could have been a finding during the development of the adverse outcome (*i.e.,* thrombosis), and thus may not be a modifiable predictor. Finally, the posthoc outcomes should be interpreted with caution given the multiple statistical testing and small cohort.

This study has several strengths. This was a modest sample size of young patients having a LT. Although retrospective, the outcomes and potential predictor variables collected were objective, and were all clearly defined prior to data collection. The predictors

and primary and secondary outcomes were pre-specified prior to analysis, to prevent "data dredging". Some novel variables were examined, and found not associated with outcomes (*e.g.*, central venous pressure, heparin therapeutic level by day 3, surgical comments about concerning anatomy of the transplant vessels or biliary tract). Some other novel predictors were associated with outcomes (*e.g.*, antithrombin level day 2-5 and surgeon) which generate novel hypotheses for future research.

Patients under 3-years-old having LT had high patient (92%) and graft (80%) survivals. These patients not infrequently experienced a combination of significant postoperative complications, including HAT, PVT, bile leak, bowel perforation, intraabdominal bleeding, abdominal compartment syndrome, and intraabdominal infection, sometimes necessitating reoperation of the abdomen, retransplantation, and kidney dialysis. Whole liver graft was independently associated with a higher risk of complications. A novel predictor, the lower the antithrombin level on days 2-5 postoperative, was independently associated with a higher risk of complications. Other centers should determine whether antithrombin levels are associated with outcomes after LT in young children, and a prospective trial comparing anticoagulation strategies that incorporate antithrombin treatment should be considered.

ARTICLE HIGHLIGHTS

Research background
Postoperative intensive care unit complications after liver transplantation in young children are common, and associated with significant morbidity and mortality. Risk factors for these early complications are poorly studied.

Research motivation
Postoperative intensive care unit complications in young children can require reoperation, threaten liver graft viability, and prolong length of stay. These complications include thrombosis of vessels necessary for blood flow to the liver graft (*i.e.* hepatic artery thrombosis and portal vein thrombosis), other life-threatening events requiring intensive care management (*i.e.* bile leak, bowel perforation, intraabdominal infection, or retransplant), or death. Identifying risk factors for these complications can generate hypotheses for future research testing, leading to improved outcomes after liver transplantation.

Research objectives
The authors aimed to determine potentially modifiable prespecified acute care variables that may be associated with prespecified primary and secondary acute intensive care postoperative outcomes in young liver transplant recipients at our center over the past 10 years. In addition, the authors aimed to explore novel potential predictors of adverse outcomes, including written comments made about abnormal liver vessels or biliary anatomy in the dictated operating report, measures of postoperative fluid balance, and measures of post-operative coagulation status. The authors identified risk factors that are potentially modifiable and that should be confirmed by future research.

Research methods
This study was a retrospective chart review including all consecutive children of age less than 3-years-old having had a liver transplant done at the Western Canadian referral center from June 2005 to June 2015. Prespecified potential predictor variables and primary and secondary outcomes were recorded using

standard definitions and a case report form. Associations between potential predictor variables and outcomes were determined using univariate and multiple logistic (odds ratio, OR; 95% confidence interval, CI) or linear (effect size, ES; 95%CI) regressions.

Research results

There were several important results from this study. First, although pediatric intensive care unit (PICU) patient (92%) and graft (80%) survivals were high, patients experienced a combination of significant postoperative complications, including hepatic artery thrombosis (19%), portal vein thrombosis (17%), bile leak (23%), bowel perforation (8%), intraabdominal bleeding (11%), abdominal compartment syndrome (12%), and intraabdominal infection (28%). These complications necessitated reoperation of the abdomen for 51% (median 2 episodes, interquartile range 1-4), retransplantation for 14%, and renal replacement therapy for 14% of all patients. Second, there were few independent predictors of our primary and secondary outcomes. When adjusted for prespecified clinically important variables (weight, year, pediatric end-stage liver disease score, and surgeon) and those variables significant at $P \leq 0.10$ on univariate analysis, whole liver graft had higher risk of complications (of hepatic artery thrombosis, ventilator days, any severe complication, any thrombosis, and graft loss). A novel predictor, the lower the antithrombin level on day 2-5 post-operative, had higher risk of complications (ventilator days, any severe complication, any thrombosis, and graft loss). The independent association of surgeon with outcomes (of any thrombosis, any severe complication, and ventilator days) has not, to our knowledge, previously been reported. Third, the authors found no statistically significant change in outcomes over time on multiple regressions. Fourth, the authors found no statistically significant association of recipient weight with adverse outcomes on multiple regressions. Fifth, some of the novel predictors the authors examined were not associated with complication rates on multiple regressions. This included: growth failure (below 5th percentile on weight or height), surgical comments about concerning anatomy of the transplant vessels (hepatic artery or portal vein) or biliary tract, whether fascia was closed on admission to PICU, measures of postoperative fluid status (*e.g.*, use of furosemide, lowest central venous pressure, and highest hemoglobin), and measures of anticoagulation (*e.g.*, achieving a therapeutic heparin level). Future study is required to confirm our findings. Treatment with antithrombin concentrate intravenously should be considered for low antithrombin levels in studies of anticoagulation protocols.

Research conclusions

Patients under 3-years-old having liver transplant had high patient (92%) and graft (80%) survival. These patients not infrequently experienced a combination of significant postoperative complications, including hepatic artery thrombosis, portal vein thrombosis, bile leak, bowel perforation, intraabdominal bleeding, abdominal compartment syndrome, and intraabdominal infection, sometimes necessitating reoperation of the abdomen, retransplantation, and kidney dialysis. Whole liver graft was independently associated with a higher risk of complications. Surgeon was independently associated with a higher risk of complications. A novel predictor, the lower the antithrombin level on day 2-5 postoperative, was independently associated with a higher risk of complications. Antithrombin is an anticoagulant produced by the liver, with its effect mediated by irreversibly inhibiting plasma serine proteases (including activated factors X and thrombin); this effect is greatly accelerated by heparin. In addition, antithrombin has antiinflammatory properties. Although antithrombin does not have beneficial effects in critically ill patients in general, it has not been studied in the setting of liver transplant patients who are high risk for thrombosis. Other centers should determine whether antithrombin levels are associated with outcomes after liver transplant in young children, and a prospective trial comparing anticoagulation strategies that incorporate antithrombin treatment should be considered. In addition, more study is needed to determine what accounts for differences in outcomes among surgeons.

Research perspectives

The findings are hypothesis generating and require confirmation by other centers, ideally in prospective studies. Future prospective observational research is needed to confirm the findings that whole liver graft, surgeon, and low antithrombin postoperatively are risk factors for complications. If confirmed, future randomized controlled trials of anticoagulation strategies after liver transplant in young children are needed, and these should include monitoring

and treatment of antithrombin levels.

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