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***Retrospective Study***

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

Alobaidi R *et al.* The EARLY study

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**Abstract**

***AIM***

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

***METHODS***

This study was a retrospective chart review including all consecutive children ofage 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 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); PICU-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, intra-abdominal infection, re-transplant, or death) in 32 (49%) patients. Predictors of the pre-specified 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 anti-thrombin (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

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**Core tip:** In a retrospective review of 65 consecutive children having had liver transplant at age less than 3 years 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 post-operatively. 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.

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**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, SD 17.1), with intelligence scores < 70 (below two standard deviations from the population mean, expected in 2.27% of the normative population) in 6%[3]. These patients often had significant post-operative complications in the intensive care unit, and these acute post-transplant 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) post-LT. 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 re-transplantation (in < 15%) and re-operations (in up to 50%)[12]. These post-LT 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 pre-specified acute-care variables that may be associated with pre-specified primary and secondary acute intensive-care post-operative 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 post-operative fluid balance (*i.e.*, highest hemoglobin, first day of negative fluid balance, first day of using furosemide, lowest central venous pressure); and measures of post-operative coagulation status (*i.e*., time to start of heparin and achieving a therapeutic heparin level, lowest anti-thrombin 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 multi-visceral transplant were excluded. Potential predictor variables collected included descriptive pre-transplant demographics, transplant surgery details, and early post-operative variables (see Tables E1 to E3 in Additional File 1). Pediatric intensive care unit (PICU) outcomes recorded included length of stay, mortality, graft survival, re-transplant, re-operations, 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, intra-abdominal infection, death, or re-transplant. 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 pre-specified the primary and secondary outcomes. The primary outcomes were HAT, and ventilator days; and the secondary outcomes were any severe complication, and any thrombosis (HAT or PVT). After local presentation of results, we were asked to add post-hoc 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 post-hoc, exploratory, and to be interpreted with caution.

Also prior to any data analysis, the following variables were pre-specified to be used in the univariate analyses: Pre-operative (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 post-operative (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 ASA; 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 Intra-Class Correlations (ICC). 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 pre-specified, 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, performed all the adult and pediatric LTs during the entire 10 year period, and 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 re-transplant 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 (OR) with 95% confidence intervals (CI) for logistic regressions, and effect sizes (ES) with 95%CI 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) mo of age, of 8.5 (SD 2.1) kg weight (23% ≤ 7kg; 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. Pediatric ICU mortality was 5 (8%), and in survivors the ventilation days and PICU days were 12.5 (SD 14.1) and 21 (SD 21) days respectively. Complications were common, with HAT in 12 (19%), PVT in 11 (17%), biliary leak in 15 (23%), bowel perforation in 5 (8%), intra-abdominal infection in 18 (28%), re-transplant 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 pre-operative, operative, post-operative, 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 anti-thrombin day 2-5 was associated with ventilator days: The higher the anti-thrombin, 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 anti-thrombin day 2-5 was associated with severe complication risk: The higher the anti-thrombin, 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 anti-thrombin day 2-5 was associated with thrombosis: the higher the anti-thrombin, 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).

***Post-hoc 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 anti-thrombin 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* ≤ 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, 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 peri-operative 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 post-operative complications, including HAT (19%), PVT (17%), bile leak (23%), bowel perforation (8%), intra-abdominal bleeding (11%), abdominal compartment syndrome (12%), and intra-abdominal infection (28%). These complications necessitated re-operation of the abdomen for 51% (median 2 episodes, IQR 1-4), re-transplantation 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 pre-specified clinically important variables (weight, year, PELD score, and surgeon) and those variables significant at *P* ≤ 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 anti-thrombin level on day 2-5 post-operative, 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 regression**s**. 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 post-operative fluid status (*e.g.*, use of furosemide, lowest central venous pressure, and highest h**a**emoglobin), and measures of anti-coagulation (*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, re-transplant rates were 11%, and re-operation 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 day survival is 93%, again comparable to our findings[14]. A recent meta-analysis found that 1 year pediatric patient and graft survival for whole liver grafts is 91% and 84.9%, and for technical variant grafts 87.7% and 77.2% respectively, comparable to our 6 mo patient and graft survival 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 5%-10% (compared to our rate of 19%)[2,8,11,14,15,17,18,22-27], PVT in the range 5%-15% (compared to our rate of 17%)[2,11,15-18,24-26,28,29], and bile leak in the range 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 intra-abdominal 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 anti-thrombin levels post-LT with any thrombosis, any severe complication, graft loss, and ventilation days has not, to our knowledge, previously been examined or reported. Anti-thrombin 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, anti-thrombin has anti-inflammatory properties[34].Although anti-thrombin 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 re-balance, 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 re-exploration for intra-abdominal bleeding[42]. Treatment with anti-thrombin concentrate intravenously should be considered for low anti-thrombin 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 survival (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 OR 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 intra-abdominal 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 re-transplantation 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 anti-thrombin 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 anti-thrombin on day 2-5 post-operative, 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 post-hoc 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.*, anti-thrombin 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%) survival. These patients not infrequently experienced a combination of significant post-operative complications, including HAT, PVT, bile leak, bowel perforation, intra-abdominal bleeding, abdominal compartment syndrome, and intra-abdominal infection, sometimes necessitating re-operation of the abdomen, re-transplantation, and kidney dialysis. Whole liver graft was independently associated with a higher risk of complications. A novel predictor, the lower the anti-thrombin level on day 2-5 post-operative, was independently associated with a higher risk of complications. Other centers should determine whether anti-thrombin levels are associated with outcomes after LT in young children, and a prospective trial comparing anticoagulation strategies that incorporate anti-thrombin treatment should be considered.

**ARTICLE HIGHLIGHTS**

***Research background***

Post-operative 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***

Post-operative intensive care unit complications in young children can require re-operation, 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, intra-abdominal infection, or re-transplant), 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 pre-specified acute-care variables that may be associated with pre-specified primary and secondary acute intensive-care post-operative 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 post-operative 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. 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.

***Research results***

There were several important results from this study. First, although PICU patient (92%) and graft (80%) survival were high, patients experienced a combination of significant post-operative complications, including hepatic artery thrombosis (19%), portal vein thrombosis (17%), bile leak (23%), bowel perforation (8%), intra-abdominal bleeding (11%), abdominal compartment syndrome (12%), and intra-abdominal infection (28%). These complications necessitated re-operation of the abdomen for 51% (median 2 episodes, IQR 1-4), re-transplantation 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 pre-specified clinically important variables (weight, year, PELD score, and surgeon) and those variables significant at *P* ≤ 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 anti-thrombin 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 post-operative fluid status (*e.g*., use of furosemide, lowest central venous pressure, and highest haemoglobin), and measures of anti-coagulation (*e.g.*, achieving a therapeutic heparin level). Future study is required to confirm our findings. Treatment with anti-thrombin concentrate intravenously should be considered for low anti-thrombin 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 post-operative complications, including hepatic artery thrombosis, portal vein thrombosis, bile leak, bowel perforation, intra-abdominal bleeding, abdominal compartment syndrome, and intra-abdominal infection, sometimes necessitating re-operation of the abdomen, re-transplantation, 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 anti-thrombin level on day 2-5 post-operative, was independently associated with a higher risk of complications. Anti-thrombin 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, anti-thrombin has anti-inflammatory properties.Although anti-thrombin 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 anti-thrombin levels are associated with outcomes after liver transplant in young children, and a prospective trial comparing anticoagulation strategies that incorporate anti-thrombin 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 anti-thrombin post-operatively are risk factors for complications. If confirmed, future randomized controlled trials are needed of anticoagulation strategies after liver transplant in young children, and these should include monitoring and treatment of anti-thrombin levels.

**REFERENCES**

1 **Kim WR**, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: liver. *Am J Transplant* 2015; **15** Suppl 2: 1-28 [PMID: 25626341 DOI: 10.1111/ajt.13197]

2 **Sundaram SS**, Alonso EM, Anand R; Study of Pediatric Liver Transplantation Research Group. Outcomes after liver transplantation in young infants. *J Pediatr Gastroenterol Nutr* 2008; **47**: 486-492 [PMID: 18852642 DOI: 10.1097/MPG.0b013e318175d7d2]

3 **Robertson CM**, Dinu IA, Joffe AR, Alton GY, Yap JY, Asthana S, Acton BV, Sauve RS, Martin SR, Kneteman NM, Gilmour SM; Western Canadian Therapies Follow-up Group. Neurocognitive outcomes at kindergarten entry after liver transplantation at &lt;3 yr of age. *Pediatr Transplant* 2013; **17**: 621-630 [PMID: 23961979 DOI: 10.1111/petr.12134]

4 **Johnson SB**, Riley AW, Granger DA, Riis J. The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics* 2013; **131**: 319-327 [PMID: 23339224 DOI: 10.1542/peds.2012-0469]

5 **Garner AS**, Shonkoff JP; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. *Pediatrics* 2012; **129**: e224-e231 [PMID: 22201148 DOI: 10.1542/peds.2011-2662]

6 **Campbell F**, Conti G, Heckman JJ, Moon SH, Pinto R, Pungello E, Pan Y. Early childhood investments substantially boost adult health. *Science* 2014; **343**: 1478-1485 [PMID: 24675955 DOI: 10.1126/science.1248429]

7 **Walhovd KB**, Krogsrud SK, Amlien IK, Bartsch H, Bjørnerud A, Due-Tønnessen P, Grydeland H, Hagler DJ Jr, Håberg AK, Kremen WS, Ferschmann L, Nyberg L, Panizzon MS, Rohani DA, Skranes J, Storsve AB, Sølsnes AE, Tamnes CK, Thompson WK, Reuter C, Dale AM, Fjell AM. Neurodevelopmental origins of lifespan changes in brain and cognition. *Proc Natl Acad Sci USA* 2016; **113**: 9357-9362 [PMID: 27432992 DOI: 10.1073/pnas.1524259113]

8 **Bekker J**, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant* 2009; **9**: 746-757 [PMID: 19298450 DOI: 10.1111/j.1600-6143.2008.02541.x]

9 **Hackl C**, Schlitt HJ, Melter M, Knoppke B, Loss M. Current developments in pediatric liver transplantation. *World J Hepatol* 2015; **7**: 1509-1520 [PMID: 26085910 DOI: 10.4254/wjh.v7.i11.1509]

10 **Feier FH**, da Fonseca EA, Seda-Neto J, Chapchap P. Biliary complications after pediatric liver transplantation: Risk factors, diagnosis and management. *World J Hepatol* 2015; **7**: 2162-2170 [PMID: 26328028 DOI: 10.4254/wjh.v7.i18.2162]

11 **Diem HV**, Evrard V, Vinh HT, Sokal EM, Janssen M, Otte JB, Reding R. Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. *Transplantation* 2003; **75**: 1692-1697 [PMID: 12777858 DOI: 10.1097/01.TP.0000062570.83203.A3]

12 **Utterson EC**, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R; Split Research Group. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005; **147**: 180-185 [PMID: 16126046 DOI: 10.1016/j.jpeds.2005.04.073]

13 **McDiarmid SV**, Anand R, Martz K, Millis MJ, Mazariegos G. A multivariate analysis of pre-, peri-, and post-transplant factors affecting outcome after pediatric liver transplantation. *Ann Surg* 2011; **254**: 145-154 [PMID: 21606838 DOI: 10.1097/SLA.0b013e31821ad86a]

14 **Diamond IR**, Fecteau A, Millis JM, Losanoff JE, Ng V, Anand R, Song C; SPLIT Research Group. Impact of graft type on outcome in pediatric liver transplantation: a report From Studies of Pediatric Liver Transplantation (SPLIT). *Ann Surg* 2007; **246**: 301-310 [PMID: 17667510 DOI: 10.1097/SLA.0b013e3180caa415]

15 **Ye H**, Zhao Q, Wang Y, Wang D, Zheng Z, Schroder PM, Lu Y, Kong Y, Liang W, Shang Y, Guo Z, He X. Outcomes of Technical Variant Liver Transplantation versus Whole Liver Transplantation for Pediatric Patients: A Meta-Analysis. *PLoS One* 2015; **10**: e0138202 [PMID: 26368552 DOI: 10.1371/journal.pone.0138202]

16 **Laurence JM**, Sapisochin G, DeAngelis M, Seal JB, Miserachs MM, Marquez M, Zair M, Fecteau A, Jones N, Hrycko A, Avitzur Y, Ling SC, Ng V, Cattral M, Grant D, Kamath BM, Ghanekar A. Biliary complications in pediatric liver transplantation: Incidence and management over a decade. *Liver Transpl* 2015; **21**: 1082-1090 [PMID: 25991054 DOI: 10.1002/lt.24180]

17 **Farmer DG**, Venick RS, McDiarmid SV, Ghobrial RM, Gordon SA, Yersiz H, Hong J, Candell L, Cholakians A, Wozniak L, Martin M, Vargas J, Ament M, Hiatt J, Busuttil RW. Predictors of outcomes after pediatric liver transplantation: an analysis of more than 800 cases performed at a single institution. *J Am Coll Surg* 2007; **204**: 904-14; discussion 914-6 [PMID: 17481508 DOI: 10.1016/j.jamcollsurg.2007.01.061]

18 **Evrard V**, Otte JB, Sokal E, Rochet JS, Haccourt F, Gennari F, Latinne D, Jamart J, Reding R. Impact of surgical and immunological parameters in pediatric liver transplantation: a multivariate analysis in 500 consecutive recipients of primary grafts. *Ann Surg* 2004; **239**: 272-280 [PMID: 14745337 DOI: 10.1097/01.sla.0000108681.24374.02]

19 **Harris PA**, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-381 [PMID: 18929686 DOI: 10.1016/j.jbi.2008.08.010]

20 **Emre S**, Umman V, Cimsit B, Rosencrantz R. Current concepts in pediatric liver transplantation. *Mt Sinai J Med* 2012; **79**: 199-213 [PMID: 22499491 DOI: 10.1002/msj.21305]

21 **Boudi FB**. Pediatric Liver Transplantation. In: Medscape. 2015. Available from: URL: http://emedicine.medscape.com/article/1012910-overview#showall

22 **Ooi CY**, Brandão LR, Zolpys L, De Angelis M, Drew W, Jones N, Ling SC, Fecteau A, Ng VL. Thrombotic events after pediatric liver transplantation. *Pediatr Transplant* 2010; **14**: 476-482 [PMID: 19849808 DOI: 10.1111/j.1399-3046.2009.01252.x]

23 **Uchida Y**, Sakamoto S, Egawa H, Ogawa K, Ogura Y, Taira K, Kasahara M, Uryuhara K, Takada Y, Kamiyama Y, Tanaka K, Uemoto S. The impact of meticulous management for hepatic artery thrombosis on long-term outcome after pediatric living donor liver transplantation. *Clin Transplant* 2009; **23**: 392-399 [PMID: 19191812 DOI: 10.1111/j.1399-0012.2008.00924.x]

24 **Tiao GM**, Alonso M, Bezerra J, Yazigi N, Heubi J, Balistreri W, Bucuvalas J, Ryckman F. Liver transplantation in children younger than 1 year--the Cincinnati experience. *J Pediatr Surg* 2005; **40**: 268-273 [PMID: 15868596 DOI: 10.1016/j.jpedsurg.2004.09.021]

25 **Venick RS**, Farmer DG, McDiarmid SV, Duffy JP, Gordon SA, Yersiz H, Hong JC, Vargas JH, Ament ME, Busuttil RW. Predictors of survival following liver transplantation in infants: a single-center analysis of more than 200 cases. *Transplantation* 2010; **89**: 600-605 [PMID: 19997060 DOI: 10.1097/TP.0b013e3181c5cdc1]

26 **Oh SH**, Kim KM, Kim DY, Lee YJ, Rhee KW, Jang JY, Chang SH, Lee SY, Kim JS, Choi BH, Park SJ, Yoon CH, Ko GY, Sung KB, Hwang GS, Choi KT, Yu E, Song GW, Ha TY, Moon DB, Ahn CS, Kim KH, Hwang S, Park KM, Lee YJ, Lee SG. Long-term outcomes of pediatric living donor liver transplantation at a single institution. *Pediatr Transplant* 2010; **14**: 870-878 [PMID: 20609169 DOI: 10.1111/j.1399-3046.2010.01357.x]

27 **Seda-Neto J**, Antunes da Fonseca E, Pugliese R, Candido HL, Benavides MR, Carballo Afonso R, Neiva R, Porta G, Miura IK, Teng HW, Iwase FC, Rodrigues ML, Carneiro de Albuquerque LA, Kondo M, Chapchap P. Twenty Years of Experience in Pediatric Living Donor Liver Transplantation: Focus on Hepatic Artery Reconstruction, Complications, and Outcomes. *Transplantation* 2016; **100**: 1066-1072 [PMID: 27014791 DOI: 10.1097/TP.0000000000001135]

28 **Bourdeaux C**, Darwish A, Jamart J, Tri TT, Janssen M, Lerut J, Otte JB, Sokal E, de Ville de Goyet J, Reding R. Living-related versus deceased donor pediatric liver transplantation: a multivariate analysis of technical and immunological complications in 235 recipients. *Am J Transplant* 2007; **7**: 440-447 [PMID: 17173657 DOI: 10.1111/j.1600-6143.2006.01626.x]

29 **Yankol Y**, Fernandez LA, Kanmaz T, Leverson GE, Mezrich JD, Foley D, Mecit N, D'Alessandro AM, Acarli K, Kalayoglu M. Results of pediatric living donor compared to deceased donor liver transplantation in the PELD/MELD era: Experience from two centers on two different continents. *Pediatr Transplant* 2016; **20**: 72-82 [PMID: 26861217 DOI: 10.1111/petr.12641]

30 **Anderson CD**, Turmelle YP, Lowell JA, Nadler M, Millis M, Anand R, Martz K, Shepherd RW; SPLIT Research Group. The effect of recipient-specific surgical issues on outcome of liver transplantation in biliary atresia. *Am J Transplant* 2008; **8**: 1197-1204 [PMID: 18444930 DOI: 10.1111/j.1600-6143.2008.02223.x]

31 **Yang SC**, Huang CJ, Chen CL, Wang CH, Wu SC, Shih TH, Juang SE, Lee YE, Jawan B, Cheng YF, Cheng KW. Living donor liver transplantation with body-weight more or less than 10 kilograms. *World J Gastroenterol* 2015; **21**: 7248-7253 [PMID: 26109812 DOI: 10.3748/wjg.v21.i23.7248]

32 **Englesbe MJ**, Kelly B, Goss J, Fecteau A, Mitchell J, Andrews W, Krapohl G, Magee JC, Mazariegos G, Horslen S, Bucuvalas J. Reducing pediatric liver transplant complications: a potential roadmap for transplant quality improvement initiatives within North America. *Am J Transplant* 2012; **12**: 2301-2306 [PMID: 22883313 DOI: 10.1111/j.1600-6143.2012.04204.x]

33 **Cramm SL**, Waits SA, Englesbe MJ, Bucuvalas JC, Horslen SP, Mazariegos GV, Soltys KA, Anand R, Magee JC. Failure to Rescue as a Quality Improvement Approach in Transplantation: A First Effort to Evaluate This Tool in Pediatric Liver Transplantation. *Transplantation* 2016; **100**: 801-807 [PMID: 26910329 DOI: 10.1097/TP.0000000000001121]

34 **Allingstrup M**, Wetterslev J, Ravn FB, Møller AM, Afshari A. Antithrombin III for critically ill patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2016; **42**: 505-520 [PMID: 26862016 DOI: 10.1007/s00134-016-4225-7]

35 **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**: 18-26 [PMID: 25425338 DOI: 10.1111/petr.12407]

36 **Alvarez F**. Portal vein complications after pediatric liver transplantation. *Curr Gastroenterol Rep* 2012; **14**: 270-274 [PMID: 22434261 DOI: 10.1007/s11894-012-0257-5]

37 **Lisman T**, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010; **116**: 878-885 [PMID: 20400681 DOI: 10.1182/blood-2010-02-261891]

38 **Lisman T**, Stravitz RT. Rebalanced Hemostasis in Patients with Acute Liver Failure. *Semin Thromb Hemost* 2015; **41**: 468-473 [PMID: 26049071 DOI: 10.1055/s-0035-1550430]

39 **Roberts LN**, Bernal W. Management of Bleeding and Thrombosis in Critically Ill Patients with Liver Disease. *Semin Thromb Hemost* 2015; **41**: 520-526 [PMID: 26080305 DOI: 10.1055/s-0035-1550431]

40 **Lisman T**, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, Tripodi A, Trotter JF, Valla DC, Porte RJ; Coagulation in Liver Disease Study Group. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol* 2010; **53**: 362-371 [PMID: 20546962 DOI: 10.1016/j.jhep.2010.01.042]

41 **Magnusson M**, Ignjatovic V, Hardikar W, Monagle P. A conceptual and practical approach to haemostasis in paediatric liver disease. *Arch Dis Child* 2016; **101**: 854-859 [PMID: 27013527 DOI: 10.1136/archdischild-2015-309535]

42 **Alonso EM**, Ng VL, Anand R, Anderson CD, Ekong UD, Fredericks EM, Furuya KN, Gupta NA, Lerret SM, Sundaram S, Tiao G; Studies of Pediatric Liver Transplantation (SPLIT) Research Group. The SPLIT research agenda 2013. *Pediatr Transplant* 2013; **17**: 412-422 [PMID: 23718800 DOI: 10.1111/petr.12090]

43 **Iglesias J**, López JA, Ortega J, Roqueta J, Asensio M, Margarit C. Liver transplantation in infants weighing under 7 kilograms: management and outcome of PICU. *Pediatr Transplant* 2004; **8**: 228-232 [PMID: 15176958 DOI: 10.1111/j.1399-3046.2004.00128.x]

44 **Ciria R**, Sánchez-Hidalgo JM, Briceño J, Naranjo A, Pleguezuelo M, Díaz-Nieto R, Luque A, Jiménez J, García-Menor E, Gilbert JJ, de la Mata M, Pérez-Navero JL, Solórzano G, Rufián S, Pera C, López-Cillero P. Establishment of a pediatric liver transplantation program: experience with 100 transplantation procedures. *Transplant Proc* 2009; **41**: 2444-2446 [PMID: 19715946 DOI: 10.1016/j.transproceed.2009.06.072]

45 **Mohamed El Moghazy W**, Ogura Y, Mutsuko M, Harada K, Koizumi A, Uemoto S. Pediatric living-donor liver transplantation for acute liver failure: analysis of 57 cases. *Transpl Int* 2010; **23**: 823-830 [PMID: 20158695 DOI: 10.1111/j.1432-2277.2010.01059.x]

46 **Gelas T**, McKiernan PJ, Kelly DA, Mayer DA, Mirza DF, Sharif K. ABO-incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. *Pediatr Transplant* 2011; **15**: 706-711 [PMID: 21762327 DOI: 10.1111/j.1399-3046.2011.01541.x]

47 **Mekeel KL**, Langham MR Jr, Gonzalez-Peralta RP, Hemming AW. Liver transplantation in very small infants. *Pediatr Transplant* 2007; **11**: 66-72 [PMID: 17239125 DOI: 10.1111/j.1399-3046.2006.00610.x]

48 **Wagenaar AE**, Tashiro J, Sola JE, Ekwenna O, Tekin A, Perez EA. Pediatric liver transplantation: predictors of survival and resource utilization. *Pediatr Surg Int* 2016; **32**: 439-449 [PMID: 27001031 DOI: 10.1007/s00383-016-3881-6]

49 **Roberts JP**, Hulbert-Shearon TE, Merion RM, Wolfe RA, Port FK. Influence of graft type on outcomes after pediatric liver transplantation. *Am J Transplant* 2004; **4**: 373-377 [PMID: 14961989]

50 **Berg CL**, Steffick DE, Edwards EB, Heimbach JK, Magee JC, Washburn WK, Mazariegos GV. Liver and intestine transplantation in the United States 1998-2007. *Am J Transplant* 2009; **9**: 907-931 [PMID: 19341415 DOI: 10.1111/j.1600-6143.2009.02567.x]

51 **Alexopoulos SP**, Nekrasov V, Cao S, Groshen S, Kaur N, Genyk YS, Matsuoka L. Effects of recipient size and allograft type on pediatric liver transplantation for biliary atresia. *Liver Transpl* 2017; **23**: 221-233 [PMID: 27862929 DOI: 10.1002/lt.24675]

52 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542]

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

|  |  |
| --- | --- |
| Univariate logistic regression (*n* = 65) | Multiple logistic regression (*n* = 65) |
| **Variable** | **Odds ratio (95%CI)** | ***P* value**  | **Odds ratio (95%CI)** | ***P* value**  |
| Year | 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) | 0.040 |  |  |
| Hepatic artery any comment | 3.9 (1.06, 14.31) | 0.040 |  |  |
| Any operating note comment1 | 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) | 0.030 |
| Graft type LR *vs* WL | 0.10 (0.02, 0.48) | 0.004 | 0.16 (0.03, 0.95) | 0.044 |

1No meaningful difference if we use “any operating note comment” instead of “hepatic artery any comment” in the multiple regression; 2If 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. PELD: Pediatric end-stage liver disease score; LR: Living related liver graft; R/SL: Reduced or split liver graft; WL: Whole liver graft; HAT: Hepatic artery thrombosis.

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

|  |  |
| --- | --- |
| Univariate linear regression (*n* = 60) | Multiple linear regression (*n* = 58) |
| **Variable** | **Effect size (95%CI)** | ***P* value** | **Effect size (95%CI)** | ***P* value** |
| Year | -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 hr (*n* = 58)2 | 0.31 (0.17, 0.45) | 0.001 |  |  |
| Highest hemoglobin d2-5 | 0.27 (0.001, 0.54) | 0.049 | 0.22 (-0.04, 0.48) | 0.096 |
| Lowest anti-thrombin d1 (*n* = 44) | -0.38 (-0.65, -0.11) | 0.007 |  |  |
| Lowest anti-thrombin d2-5 (*n* = 58) | -0.35 (-0.57, -0.13) | 0.003 | -0.24 (-0.47, -0.02) | 0.034 |
| First day furosemide used (*n* = 52)1 | 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 |

1If we add “surgery duration”, and “first day furosemide used” (*n* = 49): Neither variable is significant; if add only “first day furosemide used”, also not significant; 2”Heparin started hr” 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 (hr)” and “time for INR to be ≤ 2” is *r* = 0.66] (*i.e.*, it may be an outcome, and not a determinant of outcome); if added, the effect size is 0.21 (0.07, 0.36); *P* = 0.005. PELD: Pediatric end-stage liver disease score; LR: Living related liver graft; 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**

|  |  |
| --- | --- |
| Univariate logistic regression (*n* = 65) | Multiple logistic regression (*n* = 62) |
| **Variable** | **Odds ratio (95%CI)** | ***P* value** | **Odds ratio (95%CI)** | ***P* value** |
| Year | 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 d2-5 (*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 |

1If 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. PELD: Pediatric end-stage liver disease score; LR: Living related liver graft; R/SL: Reduced or split liver graft; WL: Whole liver graft.

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

|  |  |
| --- | --- |
| Univariate logistic regression (*n* = 65) | Multiple logistic regression (*n* = 62) |
| **Variable** | **Odds ratio (95%CI)** | ***P* value**  | **Odds ratio (95%CI)** | ***P* value**  |
| Year | 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) | 0.100 |  |  |
| Hepatic artery any comment2 | 2.55 (0.84, 7.78) | 0.100 |  |  |
| Biliary anatomy comment2 | 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) | 0.030 | 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 |

1If 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; 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. PELD: Pediatric end-stage liver diseases score; LR: Living related liver graft; R/SL: Reduced or split liver graft; WL: Whole liver graft.

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

|  |  |
| --- | --- |
| Univariate logistic regression (*n* = 65) | Multiple logistic regression (*n* = 62) |
| **Variable** | **Odds ratio (95%CI)** | ***P* value**  | **Odds ratio (95%CI)** | ***P* value**  |
| Year | 1.08 (0.88, 1.32) | 0.460 |  |  |
| 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) | 0.030 |  |  |
| 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 (hr) (*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. 1If add “first day furosemide used” (*n* = 54): Furosemide is not significant; 2If add “heparin started hr”: Not significant. PELD: Pediatric end-stage liver disease score; LR: Living related liver graft; R/SL: Reduced or split liver graft; WL: Whole liver graft.