CHAPTER 6

The Pediatric Retransplantation Risk Score: A prognostic model for survival after pediatric liver retransplantation

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ABSTRACT

Background: Although prognostic models for survival after pediatric liver transplantation (LT) have been developed, such models for liver retransplantation (reLT) are poorly defined. We aimed to develop a prognostic model for survival after pediatric reLT to optimize matching donor grafts with recipients.

Methods: Donor, graft and recipient data of pediatric reLT (<18 years) were collected from the European Liver Transplantation Registry (1995-2016). Prognostic factors for mortality after reLT were identified by multivariable Cox regression analyses. The Pediatric ReLT Risk Score was developed, followed by internal as well as external validation.

Results: A total of 1640 pediatric reLTs were included, with 1- and 15- year survival rates of 72% and 61%, respectively. Recipient age, primary liver disease, reLT indication, recipient medical condition, time between primary LT and reLT, and donor age were significant prognostic factors for mortality. Point scores were assigned for each prognostic factor according to its hazard ratio. Low-risk (4-7 points), medium-risk (8-9 points) and high-risk (10-13 points) groups were determined with significantly different 5-year survival rates of 75.1% (95%CI 69.1%-80.2%), 68.3% (95%CI 61.8%-74.0%) and 45.3% (95%CI 37.1%-53.2%), respectively ($P < 0.001$). The c-statistic was 0.689 (95%CI 0.641-0.728). External validation showed that the expected survival rates were closely aligned with the observed mortality probabilities.

Conclusions: A novel prognostic model for survival after pediatric reLT was designed and validated. The Pediatric ReLT Risk Score is an easy-to-use tool to balance donor and recipient factors, which may optimize matching donor grafts with recipients in clinical practice to improve outcome.

INTRODUCTION

Liver transplantation (LT) is the only curative treatment for pediatric patients with end-stage liver disease. Due to various developments in peritransplant care, outcomes after pediatric LT have significantly improved with current 5-year graft and patient survival rates of 70-85% and 80-95%, respectively.[1-3] Donor graft scarcity remains an important limiting factor in pediatric LT. To increase the number of available liver grafts for children, split liver grafts and living donor liver grafts are increasingly used for transplantation. With the increasing success of primary LT, more pediatric transplant recipients are in possible need for a second liver graft. At present, 11-15% of children develop graft failure and need to be retransplanted.[3-5] Outcomes after pediatric liver retransplantation (reLT) are inferior to primary LT with reported 5-year patient survival rates of 60-70%.[6,7]

Currently, about 10% of available donor livers are used for reLT.[8] Weighting between the prospect of success and urgency forms a serious challenge in clinical practice and careful selection of donor organs is crucial. For primary LT, models prognostic for post-transplant mortality have been developed.[9-11] However, high-risk combinations of recipient, donor, and transplant factors are poorly defined for pediatric reLT.

The aim of this study was to identify prognostic factors for mortality after pediatric reLT by using the European Liver Transplant Registry (ELTR) database. Based on the identified factors, we aimed to develop an easy-to-use risk assessment tool to provide prognostic information about patient survival after pediatric reLT to optimize matching donor grafts with recipients in clinical practice.

MATERIALS AND METHODS

Study population

In this study, we analyzed all pediatric patients who underwent reLT under the age of 18 years, between January 1995 to December 2016 and were included in ELTR database. The ELTR prospectively collects LT data from 174 centers over 33 countries. Quality of data from the ELTR is guaranteed by an internally developed control quality program and by regular audit monitoring of the contributing centers.[12,13] After a study request was reviewed and approved by the ELTR data committee, data were obtained as described previously.[13] All authors had access to the study data and reviewed and approved the final manuscript.

Study variables

Recipient, donor and transplant characteristics from all pediatric reLT patients were obtained, including data on their primary LT. Recipient variables analyzed included age, height and weight at transplant, sex, blood group (O, A, B, AB), primary liver disease, medical condition (at home, hospitalized or admitted to the intensive care unit), indication for reLT, date of inscription on the waitlist, high-urgency (yes/no) and Model for End-stage Liver Disease (MELD) score.

Pretransplant levels of serum albumin, bilirubin, creatinine, international normalized ratio, and sodium had high frequencies of missing data (>50%) and were therefore excluded from analysis.

Donor variables included age at donation/death, sex, height, weight, blood group, type of donor (donation after brain death, donation after circulatory death, domino, living) and cause of death. Transplant variables included date of transplant, country of graft procurement (same as transplant performing country, outside transplant performing country), type of liver graft (full-size, split, reduced, living) and total ischemia time.

Statistical analysis

A Cox proportional hazards regression was used to identify prognostic factors for patient mortality. Time to patient mortality was determined as the period between reLT and post-transplant all-cause mortality. Continuous variables were converted to categorical variables for the purposes of Cox regression. Categories were determined based on conventional thresholds (e.g. world health organization classification of BMI) or, if not applicable, to yield relatively equal numbers of patients in each category. Hazard ratios (HR) from regression analyses were expressed relative to the reference category (HR=1.00), which was defined as the category that was closest to physiological normal values or the largest group. Five key variables had a significant number of missing values, concerning MELD score (84%), recipient weight (52%), recipient height (45%), donor BMI (24%), and ischemia time (37%). Because of the substantial number of missing values, the MELD score was excluded from the multivariable analysis. For the other variables maximal case inclusion in the multivariable analysis was achieved by including the cases with missing values by assigning them to a separate 'missing' category. For each variable a 'missing' category is presented, but risk scores were created only for subjects without missing data on the variables included in the risk score.

Multivariable Cox regression analysis was performed by using a backward conditional selection methodology to determine the independent association between potential prognostic factors and the occurrence patient mortality. Variables with *P*-values < 0.10 in univariable Cox regression were included in the multivariable analysis and the variables significant at *P*-values < 0.05 were retained in the final multivariable model.

The Pediatric ReLT Risk Score

To design a clinically applicable prognostic assessment tool, a simple scoring system was derived based on dichotomized prognostic variables in the multivariable model. Dichotomization of continuous variables was established with receiver operating characteristics analysis and Youden's J Index to maximize sensitivity and specificity. Points were assigned for each prognostic factor by rounding the HRs of a Cox regression model using dichotomized values. The era of transplantation was not included in the prognostic risk score as it would not help to discriminate the prognosis of future patients undergoing LT.

Validation of the model

An internal bootstrap model validation was performed using 1000 bootstrap resamples. Internal validity of the risk score algorithm was evaluated for model discrimination by analyzing the bias-corrected area under the receiver operating characteristics curve (AUC) and model consistency and calibration by analyzing the Brier score and Somers' rank correlation. Brier scores closer to a value of 0 were considered as representing good calibration and Somers' rank correlation values > 0 with larger absolute value were considered as a stronger position association between the risk score and the probability of the outcome. Bootstrapping was performed on the cohort of subjects without missing data for the variables included in the risk score.

External validation of our model was performed by testing the performance of the risk score in the Organ Procurement and Transplantation Network / United Network for Organ Sharing (UNOS) database. Therefore, data on all pediatric reLTs between January 1996 and December 2016 were obtained from the UNOS database. External validation was performed on the cohort of patients with nonmissing data for the variables included in the risk score.

Differences were considered statistically significant when corresponding two-tailed *P*-values were < 0.05. Statistical analysis was performed using SPSS (version 23, BM Corp., Armonk, N.Y., USA) and Stata (Version 15.0, StataCorp LLC, College Station, T.X., USA). For further details regarding the methods used, please refer to the supplementary tables. Statistical review was performed by biostaticians SJS and DZ.

RESULTS

Baseline characteristics

During the study period, a total of 12075 pediatric patients underwent a primary LT, of whom 1361 (11%) underwent a reLT under the age of 18 years. Of 1361 pediatric reLTs, 246 (18%) patients underwent a second reLT, 31 (13%) a third and 2 a fourth reLT. Patient survival was comparable after first and second reLT with estimated 1-, 5- and 15-year survival rates of 72%, 66% and 61% after first reLT, and 69%, 66% and 61% after second reLT, respectively. After third reLT, 1-, 5- and 15-year survival rates decreased, to 61%, 57% and 49%, respectively (Figure 1A). For the aim of this study, only first reLTs were included for further analysis.

The main indications for primary LT were congenital biliary disease (44%) and metabolic liver disease (17%; Supplementary Table 1). The median time between primary LT and first reLT was 35 (7-688) days. Main indications for first reLT were vascular complications (35%), rejection (22%), primary non-function (PNF; 22%) or biliary complications (9%; Figure 1B). Median age at time of reLT was 5.1 years (1.5-11.5), 51% was female. Liver grafts were mainly derived from brain death donors (93%), with a median donor age of 32.2 (19.6-44.9) years, of whom 20% was < 18 years. The best survival rates were observed in patients after reLT for biliary complications compared to reLT for PNF, where patient survival was lowest (Figure 1C).

Median time on the waiting list was 6 (2-70) days. Patients who underwent a reLT because of vascular complications or PNF had shorter waiting list times (3 and 2 days, respectively) compared to patients retransplanted for rejection or biliary complications (46 and 84 days, respectively, $P < 0.001$; Figure 1D).

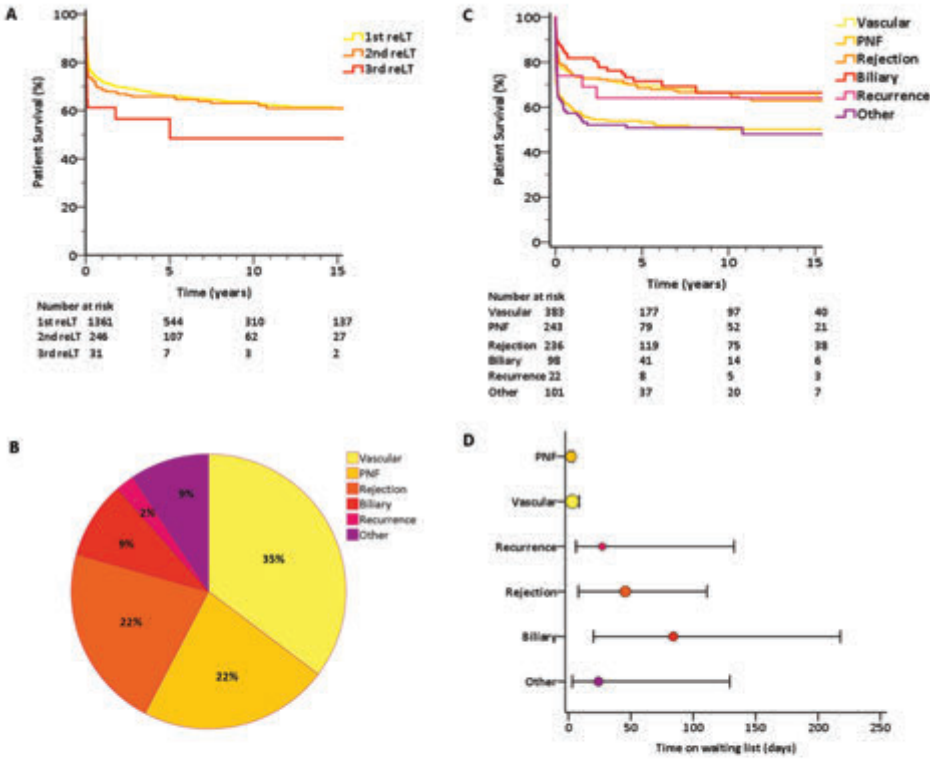

Figure 1 | Patient survival by number of pediatric retransplantations and indication for pediatric retransplantation. *Fifteen-year Kaplan-Meier survival curves are shown per (A) number of reLT (P = 0.185), and (B) indication for retransplantation (P < 0.001). Patient survival rates were compared between the groups using the log-rank test. (C) The proportions of indications for retransplantation and (D) their corresponding time on the waitlist presented as median and interquartile range. Abbreviations: reLT, retransplantation; PNF, primary non-function.*

Identification of prognostic factors for patient mortality

By using univariable Cox regression, the following recipient factors were associated with mortality after reLT: age, height, primary liver disease, indication for reLT, urgency status and medical condition (Supplementary Table 2). Donor factors associated with mortality were age, BMI, and cause of death. In addition, time between primary LT and reLT, allocation, type of graft, and era were significantly associated with patient mortality after reLT. A multivariable Cox regression analysis with backward conditional selection identified the following seven variables as significant prognostic factors for patient mortality: recipient age, primary liver

disease, indication for reLT, recipient medical condition, donor age, time between primary LT and reLT, and era (Supplementary Table 2).

Derivation of the Pediatric ReLT Risk Score

By using the prognostic factors from the multivariable Cox regression model, the Pediatric ReLT Risk Score was derived (Table 1). Point scores were assigned to each covariate in proportion to the HR for that factor to develop a 13-point score. The weighted scores were associated with a probability of mortality at any time following reLT ranging 15%-69% (Figure 2A).

Table 1 | Significant predictors of mortality after pediatric liver retransplantation (n = 1361; 1995–2016) and points according to the pediatric reLT risk score.

Variable	Multivariable analysis HR [95% CI]	*P*-value	Points
Recipient age		0.066*	
<5 years	1.29 [0.98–1.70]		2
>5 years	1.00		0
Primary liver disease		0.074*	
Other	1.00		0
Acute liver failure	1.36 [0.79–1.91]		2
Indication of reLT		0.137*	
Other	1.00		0
Primary non function	1.26 [0.92–1.72]		2
Recipient medical condition		<0.001	
Home/hospital	1.00		0
Intensive care unit-bound	2.50 [1.64–3.81]		3
Time between primary LT and reLT		0.017	
<1 month	1.00		0
>1 month	1.52 [1.08–2.15]		2
Donor age		0.008	
<18 years	1.00		0
>18 years	1.71 [1.15–2.54]		2
Total points			0–13

CI: confidence interval, HR: hazard ratio, LT: liver transplantation, reLT: liver retransplantation. Predictor variables were determined using multivariable Cox regression analyses using a backward stepwise methodology. Variables with a *P*-value < 0.1 in the univariate analysis were included in the multivariable model. Points were assigned for each covariate by rounding the HRs. *Variables may not be significant in this model, but they were selected to be in the risk algorithm based on the previous multivariable Cox modeling adjusting for other variables.

Patients were stratified into the following three groups: low-risk (4-7), medium-risk (8-9), and high-risk (10-13), with cut-off values that resulted in maximum separation between groups. Estimated patient survival rates for each group are demonstrated in Figure 2B. Pediatric

patients in the low-risk group had 1-, 5- and 15-year survival rates of 80.5% (95%CI 74.9%-84.9%), 75.1% (95%CI 69.1%-80.2%) and 71.1% (95%CI 63.9%-77.2%) after reLT. Patients with medium-risk scores had 1-, 5- and 15-year post-transplant survivals of 74.2% (95%CI 68.2%-79.3%), 68.3% (95%CI 61.8%-74.0%) and 62.0% (95%CI 53.9%-69.1%), respectively. The high-risk group had patient survival rates of 52.1% (95%CI 43.8%-59.8%) at 1 year, 45.3% (95%CI 37.1%-53.2%) at 5 years and 40.3% (95%CI 31.7%-48.8%) at 15 years after reLT. To illustrate the impact of prognostic factors on the Pediatric ReLT Risk Score, Table 2 provides clinical examples. For example, matching a 12-year old recipient on the intensive care unit with a metabolic primary liver disease, in need of an early reLT due to vascular complications, with a liver graft from a 20-year old donor, results in a risk score of 5; a low risk of mortality after reLT.

Table 2 | Examples of recipient, donor, and transplant combinations with their corresponding reLT risk score, category, and patient survival rates.

Risk factor	**Example 1**	**Example 2**	**Example 3**
Recipient age	12 years	**4 years**	**2 years**
Primary liver disease	Metabolic	**ALF**	**ALF**
Indication of reLT	Vascular	Rejection	**PNF**
Recipient medical condition	**ICU-bound**	Hospitalized	**ICU-bound**
Time between primary LT and reLT	10 days	**3 years**	5 days
Donor age	**20**	**35**	**45**
ReLT risk score	**5** **Low-risk**	**8** **Medium-risk**	**12** **High-risk**
Survival after reLT			
1-year	80.5% (74.9% -84.9%)	74.2% (68.2% - 79.3%)	52.1% (43.8% - 59.8%)
5-year	75.1% (69.1% - 80.2%)	68.3% (61.8% - 74.0%)	45.3% (37.1% - 53.2%)
10-year	72.7% (66.2% - 78.2%)	65.2% (58.2% - 71.3%)	40.3% (31.7% - 48.8%)
15-year	71.1% (63.9% - 77.2%)	62.0% (53.9% - 69.1%)	40.3% (31.7% - 48.8%)

ALF: acute liver failure, LT: liver transplantation, PNF: primary non function, ICU: intensive care unit, reLT: retransplantation. Shown here are the Kaplan-Meier estimated survival rates (95% confidence interval).

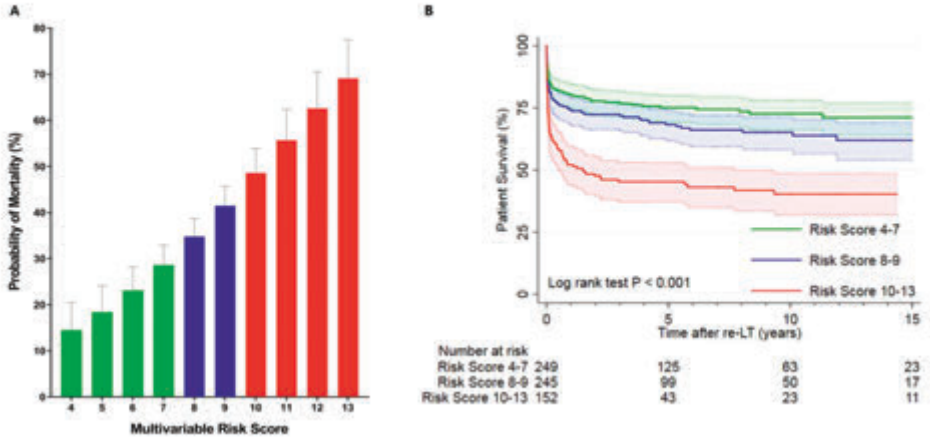

Figure 2 | Probability of all-time patient mortality after retransplantation per risk score points and patient survival according to the Pediatric ReLT Risk Score.
Point scores were assigned to each covariate in the multivariable model in proportion to the HR for that predictor to generate a 13-point score. Bars show probability of mortality at any time following retransplantation. Error bars represent 95% confidence intervals (A). Fifteen-year Kaplan-Meier survival plots were developed for patient survival according to the three risk groups of the Pediatric ReLT Risk Score (B). Comparisons between the groups were made using the log-rank test. Abbreviations: reLT, retransplantation.

Validation of the Pediatric ReLT Risk Score

Based on internal bootstrap validation, time-dependent AUC values were 0.689 (95%CI 0.641-0.728) at 1 year after reLT, 0.682 (95%CI 0.640-0.724) at 5 years after reLT, and 0.680 (95%CI 0.638-0.722) at 15 years after reLT. The corresponding Brier score and Somers' rank were 0.22 and 0.30, respectively.

External validation of the model was fulfilled in the UNOS database including 2366 pediatric reLT patients. The expected survival rates were closely aligned with the observed mortality probabilities with a time-dependent AUC value of 0.575 (95% CI 0.551-0.599; Table 3).

Table 3 | External validation of the reLT risk score using the OPTN/UNOS database.

		Observed	Expected
Score	**Number of cases**	**Number of mortalities, %**	**Model-based risk of mortality, %**
4	431	26	26
5	89	43	29
6	473	24	31
7	589	38	34
8	118	41	37
9	501	40	40
10	61	36	43
11	89	51	46
12	10	20	49
13	5	0	52

AUC = 0.575 (95% CI: 0.551-0.599). Abbreviations: AUC, area under the curve; reLT, liver retransplantation; UNOS, United Network for Organ Sharing.

DISCUSSION

With the current demand for donor grafts exceeding its supply, ethical questions arise around reLT concerning allocation of scarce donor organs to a group with assumed inferior outcomes compared with primary LT. Nevertheless, reLT remains the only chance for survival for pediatric patients with a failing primary liver graft. In this study, we developed the Pediatric ReLT Risk Score, which provides prognostic information about mortality after pediatric reLT based on six recipient, donor and transplant factors. In addition, this risk score determines three categories of low-risk (4-7 points), medium-risk (8-9 points), and high-risk (10-13 points) patients with significantly different survival rates. The results of this study suggest that with careful selection of donor and recipient factors, good long-term outcomes after pediatric reLT may be achieved.

Two studies in smaller cohorts previously analyzed risk factors for mortality after pediatric reLT.[3,5] The study by Ng et al. identified risk factors using data from the Studies of Pediatric Liver Transplantation Registry, including 246 children undergoing reLT in Northern America.[3] Donor age < 1 year, use of a technical variant, and international normalized ratio at the time of reLT were independent prognostic factors for mortality after reLT. Davis et al. developed a risk score based on the UNOS database including 1130 pediatric reLTs.[5] Risk factors for mortality included recipient life support at the time of reLT, receiving a split liver graft, and a primary liver disease with cholestasis, paucity of bile ducts, or congenital abnormalities. Protective factors were acute rejection of the primary liver graft and recipient age between 5-18 years. Even though the risk score presented by Davis et al. shows similar model performance in terms of the AUC, our model is based on a larger cohort, has a longer follow-up and was externally

validated. Moreover, we underline the importance of recipient/donor matching instead of looking at recipient factors only.

In line with the aforementioned studies, we identified recipient age < 5 years as a prognostic factor for mortality. Possible explanations are that younger recipients have inferior graft size matching, smaller metabolic reserves, and/or a more immature immune system.[14] Besides, technical difficulty is involved with fibrosis surrounding the graft and small blood vessels complicate the transplantation. Another contributing factor might be that these children are undergoing a second major surgery in their short lifespan and, hence, they have a lot less physical reserve. Related to this, being admitted to the intensive care unit at time of reLT and PNF of the primary liver graft were also identified as risk factors in the present study.

Technical variant grafts (split, reduced or living donor) were significant predictors in both previously published studies on pediatric reLT, but not in our cohort. Possibly, experience in using split liver grafts has improved over time with improving outcomes, since the previous studies date back to 2006, whereas the present study includes reLTs up to 2016. Also, the introduction of living donor LT might have played a role, which seems to have favorable outcomes.[15,16]

Previous studies have analyzed outcomes after early versus late reLT without very uniform results.[3,6,17] We identified late reLT (> 30 days) as a risk factor for mortality. Late reLT might be associated with an additional immunologic risk because of prolonged exposure of the recipient to graft allogenic antigens. Furthermore, increased technical difficulty due to graft fibrosis complicates surgery in late reLT.[6] In support of this, Ng et al. found that operation time, amount of blood loss during surgery, and the number of transfusions needed appeared to be higher in late reLT versus early reLT.[3]

Although our study confirms that patient survival after pediatric reLT is inferior compared to primary LT, good outcomes after pediatric reLT may be achieved after careful recipient and donor matching. This study shows that a 5-year patient survival rate of 75.1% may be achieved for patients in the low-risk group. This emphasizes the fact that with careful balancing between the identified prognostic factors in our model, good outcomes after pediatric reLT can be pursued. Importantly, our risk score was not developed to decline grafts for patients who are considered high-risk as defined by the Pediatric ReLT Risk Score. When a child is waitlisted with a life-threatening liver disease, clinicians should obviously accept a high-risk graft, especially since children are expected to have a full lifetime ahead of them.

Strengths of the current study are its large patient cohort and both internal and external validation of the model. Besides that, recipient, donor, as well as transplant characteristics are taken into account. Therefore, the Pediatric ReLT Risk Score could be a relevant tool for physicians to balance donor and recipient factors before making a decision on organ acceptance. Moreover, the three risk groups are of significant prognostic relevance, which

makes it a clinically applicable tool to predict survival after reLT. Finally, we believe this can be a useful scoring system to provide prognostic guidance for the patient and/or its family about the risks after pediatric reLT. To simplify clinical use, an online calculator was made available on *www.evidencio.com*.

Our study also has some limitations. First of all, some variables which might have influenced survival after pediatric reLT were not included in the database. Besides, as with other large registry studies, some variables had a high frequency of missing data, and were therefore excluded from analysis. The Pediatric ReLT Risk score ranges from 4-13 as a result of missing values. If any of the variables needed to calculate the risk score were missing, the patient could not have a risk score assigned. Subsequently there were no patients with a score of 0-3 in the database for risk score assessment. Furthermore, the model performance is good based on internal bootstrap validation (AUC 0.689), but external validation in the UNOS database shows modest performance (AUC 0.575). However, these AUCs are comparable with previous designed prognostic models in the field of LT. The AUC of the widely used donor risk index has an AUC of 0.614, and the previously mentioned predictive score of Davis et al. has an AUC of 0.62.[5,9]

In conclusion, we developed and validated a novel prognostic model for survival after pediatric reLT. The Pediatric ReLT Risk Score is an easy-to-use, reliable tool to provide prognostic information about survival after pediatric reLT by combining donor and recipient factors. The results of this study may be used as a step towards better prediction of outcomes after pediatric liver reLT. In clinical practice, the Pediatric ReLT Risk Score may be useful for transplant teams and families as they consider re-listing, since it can provide personalized prognostic information about patient survival after reLT. Besides that, we believe that with the identified factors in the Pediatric ReLT Risk Score, matching donor grafts with recipients can be optimized, which my result in better outcomes after pediatric reLT.

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Supplementary Table 1 | Baseline characteristics of first liver retransplantations.

Recipient factors (n=1361)		
Sex		
Male	668	(49%)
Female	693	(51%)
Age		
<5 years	674	(50%)
>5 years	685	(50%)
Weight		
≤10	194	(14%)
11-20	170	(13%)
21-30	106	(8%)
31-40	70	(5%)
>40	112	(8%)
Missing	709	(52%)
Height (cm)		
≤75	185	(14%)
76-100	179	(13%)
101-125	137	(10%)
126-150	137	(10%)
>150	117	(9%)
Missing	606	(45%)
Blood group		
O	536	(39%)
A	551	(41%)
B	198	(15%)
AB	75	(6%)
MELD		
<15	83	(6%)
15-25	86	(6%)
25-35	29	(2%)
>35	18	(1%)
Missing	1145	(84%)
Primary liver disease		
Congenital biliary disease	598	(44%)
Metabolic liver disease	237	(17%)
Acute liver failure	192	(14%)
Cirrhosis eci	96	(7%)
Cholestatic liver disease	86	(6%)
Malignancy	51	(4%)
Other	71	(5%)
Missing	30	(2%)

Supplementary Table 1 | Continued.

Indication for reLT		
Vascular complication	385	(28%)
Rejection	237	(17%)
PNF	244	(18%)
Biliary complication	99	(7%)
Recurrence of disease	24	(2%)
Other	102	(8%)
Missing	270	(20%)
Urgency status		
No	495	(36%)
Yes	696	(51%)
Missing	170	(13%)
Medical condition		
At home	73	(5%)
Continuous medical care	125	(9%)
Hospitalization	137	(10%)
Intensive care unit	711	(52%)
Missing	313	(23%)
Donor factors		
Sex		
Male	723	(53%)
Female	610	(45%)
Missing	28	(2%)
Age (years)		
≤18	215	(16%)
>18	844	(63%)
Missing	302	(22%)
Body mass index		
<18.5	196	(49%)
18.5-25	660	(14%)
25-30	159	(12%)
>30	20	(2%)
Missing	326	(24%)
Blood group		
O	779	(57%)
A	435	(32%)
B	104	(8%)
AB	22	(2%)
Missing	21	(2%)
Type of donor		
DBD	1266	(93%)
DCD	4	(0.3%)
Domino	1	(0.1%)
Living	90	(7%)

Supplementary Table 1 | Continued.

Cause of death		
CVA/stroke	682	(50%)
Trauma	278	(6%)
Asphyxia	77	(5%)
Cardiovascular	63	(20%)
Other	37	(3%)
Living	90	(7%)
Missing	132	(10%)
Other factors		
Time between primary LT and reLT		
<1 month	668	(49%)
>1 month	691	(51%)
Total ischemia time (hrs)		
< 6	164	(12%)
6-12	577	(42%)
>12	117	(9%)
Missing	503	(37%)
Allocation		
Same as reLT performing country	1098	(81%)
Outside reLT performing country	209	(15%)
Missing	54	(5%)
Type of liver graft		
Full-size	596	(44%)
Split	499	(13%)
Reduced	176	(37%)
Living	90	(7%)
Era of reLT		
1995-2001	381	(28%)
2002-2008	472	(35%)
2009-2016	508	(37%)

Abbreviations: CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplantation; MELD, Model for End-stage Liver Disease; PNF, primary non function; reLT, retransplantation.

Supplementary Table 2 | Predictors of mortality after liver retransplantation by Cox proportional hazards regression.

Recipient factors	N	Univariate analysis HR [95% CI]	*P*-value	Multivariable analysis HR [95% CI]	*P*-value
Sex					
Male	668	1.00			
Female	693	0.900 [0.749-1.080]	0.257		
Age	1357	0.968 [0.951-0.985]	0.000	0.963 [0.943-0.982]	0.000
Weight					
≤10	194	1.000	0.056		
11-20	170	0.660 [0.461-0.944]	0.023		
21-30	106	0.666 [0.438-1.014]	0.058		
31-40	70	0.591 [0.350-0.998]	0.049		
>40	112	0.583 [0.385-0.884]	0.011		
Missing	709	0.757 [0.588-0.976]	0.032		
Height (cm)					
≤75	185	1.000	0.018		
76-100	179	0.813 [0.584-1.132]	0.221		
101-125	137	0.562 [0.375-0.841]	0.005		
126-150	137	0.690 [0.472-1.008]	0.055		
>150	117	0.531 [0.348-0.811]	0.003		
Missing	606	0.737 [0.567-0.958]	0.023		
Blood group					
O	536	1.000	0.104		
A	551	0.910 [0.740-1.119]	0.373		
B	198	1.001 [0.756-1.326]	0.993		
AB	75	1.452 [1.003-2.103]	0.048		
Primary liver disease			0.002		0.004
Congenital biliary disease	598	1.000		1.000	
Metabolic liver disease	237	1.007 [0.770-1.317]	0.959	1.112 [0.832-1.486]	0.475
Acute liver failure	192	1.578 [1.228-2.028]	0.000	1.626 [1.241-2.131]	0.000
Cirrhosis eci	96	1.150 [0.799-1.657]	0.452	1.351 [0.903-2.019]	0.143
Cholestatic liver disease	86	0.658 [0.411-1.055]	0.082	0.699 [0.421-1.160]	0.166
Malignancy	51	0.865 [0.551-1.464]	0.590	0.999 [0.573-1.738]	0.995
Other	71	1.241 [0.829-1.857]	0.294	1.445 [0.935-2.232]	0.097
Indication for reLT			0.000		0.000
Vascular complication	385	1.000		1.000	
Rejection	237	1.025 [0.771-1.362]	0.866	1.150 [0.818-1.615]	0.421
Primary non function	244	1.748 [1.351-2.260]	0.000	1.682 [1.281-2.208]	0.000
Biliary complication	99	0.873 [0.575-1.326]	0.542	1.035 [0.648-1.652]	0.887
Recurrence of disease	24	1.116 [0.546-2.284]	0.763	1.632 [0.724-3.675]	0.237
Other	102	1.772 [1.273-2.466]	0.001	1.965 [1.368-2.824]	0.000
Missing	270	0.759 [0.558-1.032]	0.079	0.884 [0.625-1.251]	0.487
Urgency status					
No	495	1.000			
Yes	696	1.547 [1.259-1.901]	0.000		
Missing	170	1.146 [0.836-1.570]	0.398		

Supplementary Table 2 | Continued.

Recipient factors	N	Univariate analysis HR [95% CI]	*P*-value	Multivariable analysis HR [95% CI]	*P*-value
Medical condition					0.009
At home	73	1.000	0.000	1.000	
Continuous medical care	125	1.098 [0.556-2.169]	0.787	0.934 [0.451-1.933	0.853
Hospitalization	137	2.119 [1.139-3.941]	0.018	1.740 [0.907-3.338]	0.095
Intensive care unit	711	2.707 [1.552-4.721]	0.000	1.969 [1.067-3.635]	0.030
Missing	313	2.009 [1.178-3.724]	0.012	1.415 [0.764-2.622]	0.270
Donor factors					
Sex					
Male	723				
Female	610	1.00			
Missing	28	1.005 [0.835-1.210]	0.956		
Age (years)					0.000
≤18	215	1.000	0.000	1.000	
18-30	283	1.622 [1.139-2.310]	0.193	1.573 [1.085-2.280]	0.017
30-45	310	1.950 [1.388-2.738]	0.000	1.932 [1.347-2.770]	0.000
46-60	212	2.548 [1.790-3.628]	0.000	2.590 [1.774-3.781]	0.000
>60	39	3.655[2.202-6.066]	0.000	3.414 [1.994-5.848]	0.000
Missing	302	1.563 [1.103-2.217]	0.012	1.429 [0.988-1.632]	0.062
Body mass index					
<18.5	196	0.992 [0.746-1.318]	0.014		
18.5-25	660	1.000	0.954		
25-30	159	1.594 [1.209-2.102]	0.001		
>30	20	1.382 [0.682-2.801]	0.370		
Missing	326	1.149 [0.916-1.441]	0.231		
Blood group					
O	779				
A	435	1.000	0.226		
B	104	0.838 [0.681-1.029]	0.092		
AB	22	0.860 [0.596-1.240]	0.419		
Missing	21	1.362 [0.701-2.645]	0.362		
Type of donor		1.000			
DBD	1266	1.657 [0.413-6.649]	0.537		
DCD	4	3.318 [0.466-	0.476		
Domino	1	23.630]	0.231		
Living	90	1.049 [0.724-1.519]	0.802		
Cause of death					
CVA/stroke	682	1.000	0.042		
Trauma	278	1.010 [0.791-1.289]	0.935		
Asphyxia	77	0.860 [0.555-1.333]	0.500		
Cardiovascular	63	1.425 [0.942-2.156]	0.093		
Other	37	0.932 [0.521-1.668]	0.814		
Living	90	1.137 [0.780-1.656]	0.505		
Missing	132	1.553 [1.165-2.071]	0.003		

Supplementary Table 2 | Continued.

Recipient factors	N	Univariate analysis HR [95% CI]	*P*-value	Multivariable analysis HR [95% CI]	*P*-value
Other factors					
Time between primary LT and reLT					0.026
<1 month	668	1.000		1.000	
>1 month	691	0.773 [0.644-0.929]	0.006	1.384 [1.039-1.842]	
Total ischemia time (hrs)					
< 6	164	1.000	0.213		
6-12	577	1.063 [0.779-1.452]	0.669		
>12	117	1.014 [0.667-1.542]	0.949		
Missing	503	1.274 [0.931-1.743]	0.130		
Allocation					
Same as reLT performing country					
Outside reLT performing country	1098 / 209	1.000 / 1.351 [1.058-1.725]	0.016		
Type of liver graft			0.009		
Full-size	596	1.000			
Split	499	1.385 [1.125-1.705]	0.002		
Reduced	176	1.423 [1.081-1.874]	0.012		
Living	90	1.258 [0.854-1.854]	0.246		
Era of reLT			0.000		0.004
1995-2001	381	1.000		1.000	
2002-2008	472	0.701 [0.563-0.873]	0.001	0.758 [0.601-0.956]	0.019
2009-2016	508	0.629 [0.499-0.873]	0.000	0.655 [0.506-0.846]	0.001

Predictor variables were determined using multivariable Cox regression analyses using a backward stepwise methodology. Variables with a *P*-value < 0.1 in the univariate analysis were included in the multivariable model. Abbreviations: CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplantation; PNF, primary non function; reLT, retransplantation.