ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2021; 26: e929145
DOI: 10.12659/AOT.929145

Received: 2020.10.12
Accepted: 2021.04.27
Available online: 2021.05.07
Published: 2021.05.28

Risk Factors Affecting Outcomes in Pediatric Liver Transplantation: A Real-World Single-Center Experience

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Source of support: Departmental sources

Background: Despite liver transplantation (LT) being the standard treatment for pediatric end-stage liver disease, complications often persist and can adversely affect the post-transplant outcomes. This study aimed to identify the risk factors affecting the outcomes in pediatric LT patients.

Material/Methods: Data from pediatric patients who underwent primary LT from March 1988 to December 2018 were retrospectively analyzed. Chronic liver disease was defined as an explanted liver showing fibrosis regardless of grade, cirrhosis, or any other underlying disease that may cause progressive liver injury leading to fibrosis or cirrhosis.

Results: A total of 255 pediatric patients underwent LT during the study period. Their 1-, 5-, and 10-year overall survival rates were 90.5%, 88.4%, and 87.8%, respectively. According to multivariate analysis, while liver disease without underlying chronic liver disease (P=0.024) and a pediatric end-stage liver disease (PELD) score ≥30 (P=0.036) were the only factors associated with worse survival, body weight <6 kg (P=0.050), whole-liver DDLT compared to LDLT (P=0.001), fulminant liver failure (P=0.008), and postoperative hepatic artery complications (P<0.001) were associated with worse graft survival. Liver disease without underlying chronic liver disease was the only factor independently associated with hepatic artery complications (P=0.003).

Conclusions: Greater caution is recommended in pediatric patients with liver disease unaccompanied by underlying chronic liver disease, high PELD score, or low body weight to improve survival after LT. Hepatic artery complication was the only surgical complication affecting the graft survival outcome, especially in patients having liver disease without underlying chronic liver disease.

Keywords: End Stage Liver Disease • Graft Survival • Hepatic Artery • Liver Transplantation

Abbreviations: **CI** – confidence interval; **DDLT** – deceased donor liver transplantation; **HAS** – hepatic artery stenosis; **HAT** – hepatic artery thrombosis; **HR** – hazard ratio; **LDLT** – living donor liver transplantation; **LT** – liver transplant; **PELD** – pediatric end-stage liver disease; **SD** – standard deviation

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Background

Since the first liver transplant (LT), which was performed by Starzl in 1963, the outcomes of LT have gradually improved due to development in surgical techniques, perioperative management, and immunosuppressive agents. LT is now considered the treatment of choice for acute liver failure and chronic end-stage liver disease in both adults and children [1].

In 1988, our center performed the first LT in Korea, for a 14-year-old girl suffering from Wilson disease; she survived for 30 years after LT [2]. Living donor liver transplantation (LDLT) was first performed in Korea in 1999, in a 1-year-old boy with biliary atresia who is still alive. Since the first LT in 1988, more than 250 pediatric LTs have been performed. Our pediatric LT program has developed into 3 stages [3]. The LT program, which includes adult and pediatric LTs, was set up in the early stage (1988-2007). The improvement in survival after LDLT and the prospective collection of donor data started in the middle stage (2008-2011). In the recent stage (2012-2018), recipient data were prospectively collected and a specialized LT program for children was created; furthermore, there was an increase in the number of split LTs. Under this program, we previously reported that the rate of hepatic artery complications was higher in pediatric recipients with metabolic liver disease than in those with biliary atresia [3]. However, the study had several limitations, including confinement to metabolic liver disease and biliary atresia as disease entities.

This study aimed to evaluate the outcomes of pediatric LT in Korea and identify the risk factors affecting the outcomes, including hepatic artery complications.

Material and Methods

The Institutional Review Board of Seoul National University Hospital (no. 2005-102-1123) approved this study and waived the requirement for informed consent. Furthermore, no organs of executed prisoners were used. The data of pediatric patients under 18 years old who underwent primary LT between March 1988 and December 2018 were retrospectively reviewed. Recipients who underwent simultaneous liver and kidney transplants were excluded.

The surgical technique and post-LT management at our center have been detailed in previous studies [3,4]. The piggy-back method was used, and a reduced graft was considered for small children with body weight <10 kg or children who had a graft-to-recipient weight ratio greater than 3-4% according to the existence of portal hypertension and the size of the recipient's abdominal cavity. The hepatic artery was reconstructed by one of 3 plastic surgeons who had more than 5 years of microscopy experience. Interrupted sutures were performed with 9-0 or 10-0 nylon strings. Aspirin (for 1 year or up to reaching 5 years of age), prostaglandin E1 (for 5 days), and antithrombin III (for 3 days) were used as postoperative anticoagulant agents.

Regarding the disease category, we defined liver disease with underlying chronic liver disease as an explanted liver showing fibrosis regardless of grade or cirrhosis, or as an underlying disease that caused a progressive liver injury which could eventually lead to fibrosis or cirrhosis. Among them, patients in end-stage liver disease status require life-saving LT, while others who have not yet reached the end stage may need LT to improve the quality of life by correcting ascites, variceal bleeding, hepatopulmonary syndrome, recurrent cholangitis, and growth retardation.

Since some congenital liver diseases initiate at the fetal stage and progressively injure the liver for several months, the term "chronic" seemed to be also appropriate for neonates as well.

Major complications defined as grade III or IV according to the Clavien-Dindo classification [5] were recorded. Hepatic artery complications included hepatic artery thrombosis (HAT) and hepatic artery stenosis (HAS). HAT was defined as the absence of intrahepatic flow due to an occluding thrombus and HAS as the absence of a Doppler signal or a tardus parvus waveform with a resistance index less than 0.5 and a systolic acceleration time greater than 0.08 s [3,6,7]. The management algorithm of hepatic artery complications at our center has previously been described in detail [3]. An episode of acute cellular rejection and post-transplant lymphoproliferative disorder was reported according to a biopsy-proven result. Acute cellular rejection was reported when the biopsy-proven rejection activity index was ≥4 [8]. Once acute cellular rejection was diagnosed, steroid pulse therapy and maintaining high levels of immunosuppressants were considered. If these therapies were not effective, use of antithymocyte globulin was considered, depending on the patient's condition.

Statistical Analysis

Results were expressed as mean and standard deviation (SD) for continuous data and as numbers with percentages for categorical data. Overall patient survival and graft survival rates were calculated using the Kaplan-Meier method and compared between groups (male vs female, age <1 vs ≥1 year, body weight <6 vs ≥6 kg, early vs middle vs recent period of LT, LDLT vs whole-liver DDLT vs split DDLT, BA vs others, fulminant vs others, chronic liver disease vs others, pediatric end-stage liver disease [PELD] score <30 vs ≥30, Child-Pugh score A vs B or C, hepatic artery complication yes vs no, portal vein complication yes vs no, hepatic vein complication yes vs no, bile duct complication yes vs no, acute cellular rejection yes vs no, post-transplant lymphoproliferative disorder yes vs no, donor sex male vs female, donor age <18 vs ≥18 years, and relationship to recipient mother vs other than mother) using a

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Table 1. Demographic and clinical characteristics of pediatric patients and their donors.

Variables	N=255
Sex, Male: Female	116:139
Age, mean±SD, months	59.8±61.9
Height, mean±SD, cm	97.7±37.0
Body weight, mean±SD, kg	19.2±16.0
Period of LT, n (%)	
Early (1988-2007)	124 (48.6)
Middle (2008-2011)	54 (21.2)
Recent (2012-2018)	77 (30.2)
Type of LT, n (%)	
LDLT	164 (64.3)
Whole-liver DDLT	53 (20.8)
Split DDLT	38 (14.9)
Underlying liver disease, n (%)	
Chronic liver disease	198 (77.6)
Biliary atresia	142 (55.7)
Wilson disease	12 (4.7)
Alagille syndrome	9 (3.5)
PBC or PSC	8 (3.1)
Byler disease	6 (2.4)
Congenital hepatic fibrosis	6 (2.4)
Caroli's disease	4 (1.6)
Cholestatic hepatitis	4 (1.6)
Langerhans cell histiocytosis	2 (0.8)
Hemochromatosis	2 (0.8)
Unknown origin liver cirrhosis	1 (0.4)
Autoimmune hepatitis	1 (0.4)
Cryptococcal infection related liver cirrhosis	1 (0.4)
Without chronic liver disease	57 (22.4)
Fulminant liver failure	29 (11.4)
Glycogen storage disease	10 (3.9)
Hepatoblastoma	6 (2.4)
Primary hyperoxaluria	5 (2.0)
Factor H deficiency	3 (1.2)
Tyrosinemia type 1	1 (0.4)
Urea cycle defect	1 (0.4)
Immature teratoma	1 (0.4)
Chemotherapy for osteosarcoma related liver damage	1 (0.4)
ABO-incompatible, n (%)	6 (2.4)
Child-Pugh score, mean±SD	8.2±2.1
PELD score, mean±SD	13.0±13.4
Donor sex, Male: Female	139:116
Donor age, mean±SD, years	28.9±12.2
Donor body weight, mean±SD, kg	60.8±16.9
Relationship to recipient	
Mother	79 (31.0)
Father	64 (25.1)
Other relatives	16 (6.3)
Non-relatives	96 (37.6)

SD – standard deviation; LT – liver transplantation; LDLT – living donor liver transplantation; DDLT – deceased donor liver transplantation; PBC – primary biliary cirrhosis; PSC – primary sclerosing cholangitis; PELD – pediatric end-stage liver disease.

log-rank test. Factors independently associated with recipient and graft survival ($P<0.05$) were then included in multivariate Cox proportional hazards regression models. Univariate analysis of factors associated with hepatic artery complications was also performed. Factors independently associated with hepatic artery complications ($P<0.05$) were included in a subsequent multivariate logistic regression model using backward selection. A P value <0.05 was considered statistically significant. SPSS (SPSS Inc., Chicago, IL) was used for the statistical analysis.

Results

Baseline Characteristics

The demographic and clinical characteristics of patients and their donors are summarized in **Table 1**. Of the 255 patients, 116 were male and 139 were female. The mean age was 59.8 months and the mean body weight was 19.2 kg. There was a significant majority of LDLTs (64.3%); biliary atresia (55.7%) was the most common underlying liver disease, followed by metabolic liver disease (13.3%). The proportion of liver disease with underlying chronic liver disease was 77.6%. The mean Child-Pugh and PELD scores were 8.2 and 13.0, respectively. Of the 255 donors, 139 were male and 116 were female. The mean donor age was 28.9 years and the mean body weight was 60.8 kg. Among the 164 patients who underwent LDLT, the mother (n=79) was the most common donor, followed by the father (n=64).

Survival Outcomes and Risk Factors

The 1-, 5-, and 10-year overall survival rates were 90.5%, 88.4%, and 87.8%, respectively (**Figure 1A**), while the 1-. 5-, and 10-year graft survival rates were 89.7%, 88.5%, and 87.2%, respectively

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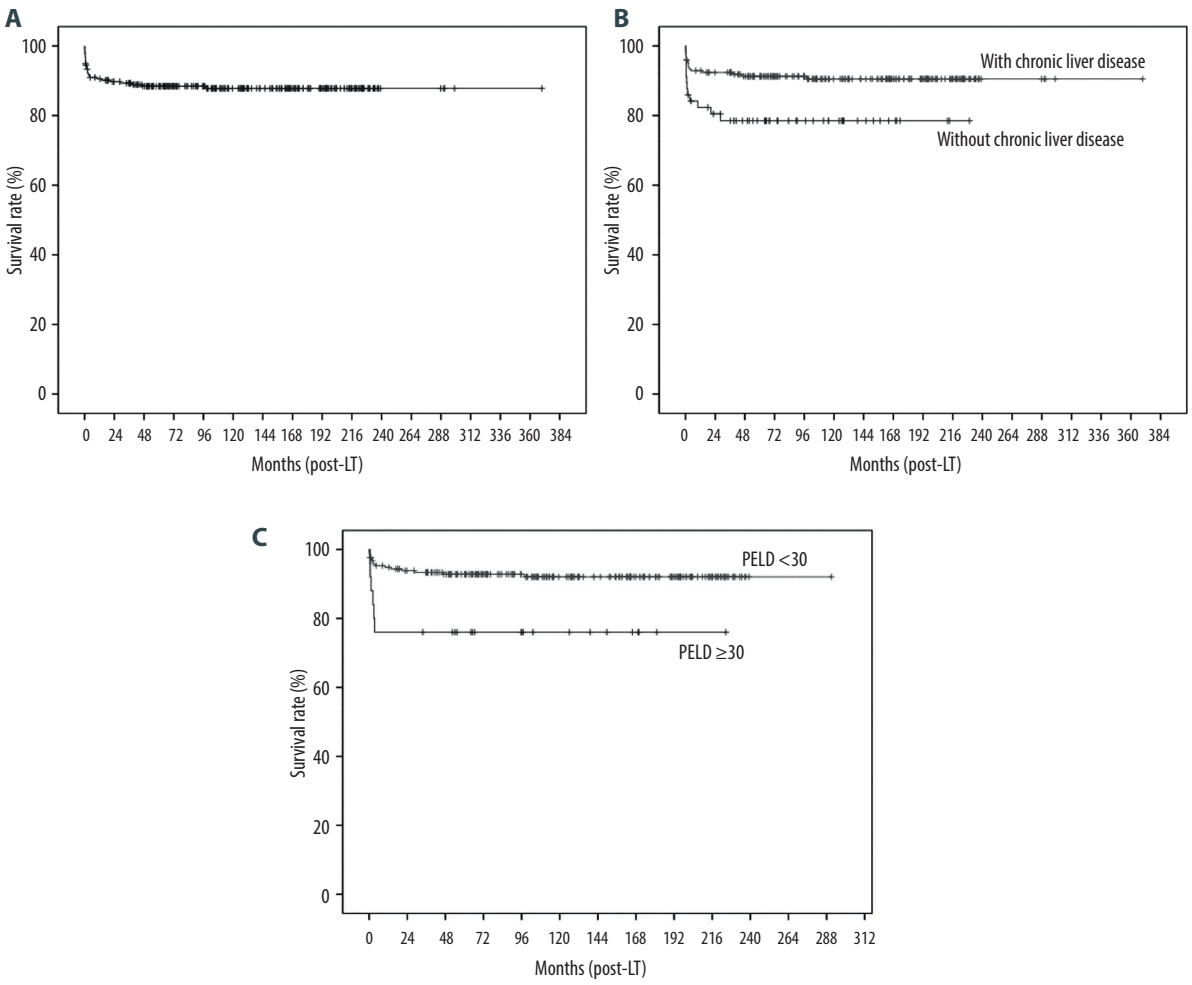

Figure 1. Kaplan-Meier analysis of overall survival: (**A**) all patients, (**B**) according to liver disease (with vs without chronic liver disease), and (**C**) according to pediatric end-stage liver disease (PELD) score.

(**Figure 2A**). Graft failure was recorded when the patient underwent retransplantation or when the graft was no longer functioning at the time of death. The most common cause of graft failure was primary nonfunction, followed by hepatic artery complications and acute cellular rejection (**Table 2**). Univariate analysis showed that factors that were significantly associated with patient survival were body weight (<6 vs ≥6 kg), type of LT (LDLT vs whole-liver DDLT vs split DDLT), underlying liver disease (fulminant vs others, with vs without chronic liver disease), PELD score (<30 vs ≥30) and postoperative hepatic artery complications (**Table 3**). Multivariate analysis showed that liver disease without underlying chronic liver disease (hazard ratio [HR]: 2.69, confidence interval [CI]: 1.14-6.38, *P*=0.024) (**Figure 1B**) and PELD score (HR: 2.81, CI: 1.07-7.37, *P*=0.036) (**Figure 1C**) were the only factors that were independently associated with overall survival.

Factors affecting graft survival were body weight <6 kg (*P*=0.035), type of LT (LDLT vs whole-liver DDLT vs split DDLT) (*P*=0.043), liver disease other than biliary atresia (*P*=0.015), fulminant liver failure (*P*=0.001), liver disease without underlying chronic liver disease (*P*=0.004), and postoperative hepatic artery complications (*P* < 0.001) according to the univariate analysis (**Table 4**). Multivariate analysis showed that body weight <6 kg (HR: 2.91, CI: 1.00-8.45, *P*=0.050) (**Figure 2B**), whole-liver DDLT compared to LDLT (HR: 3.93, CI: 1.71-9.03, *P*=0.001) (**Figure 2C**), fulminant liver failure (HR: 3.13, CI 1.35-7.27, *P*=0.008) (**Figure 2D**), and postoperative hepatic artery complications (HR: 6.1, CI: 2.42-15.36, *P*<0.001) (**Figure 2E**) were the only factors that were independently associated with graft survival.

Risk Factors and Outcomes of Hepatic Artery Complications

Hepatic artery complications are surgical complications that are critical (ie, they directly result in patient or graft death); therefore, another univariate analysis was performed to identify the risk factors of postoperative hepatic artery complications.

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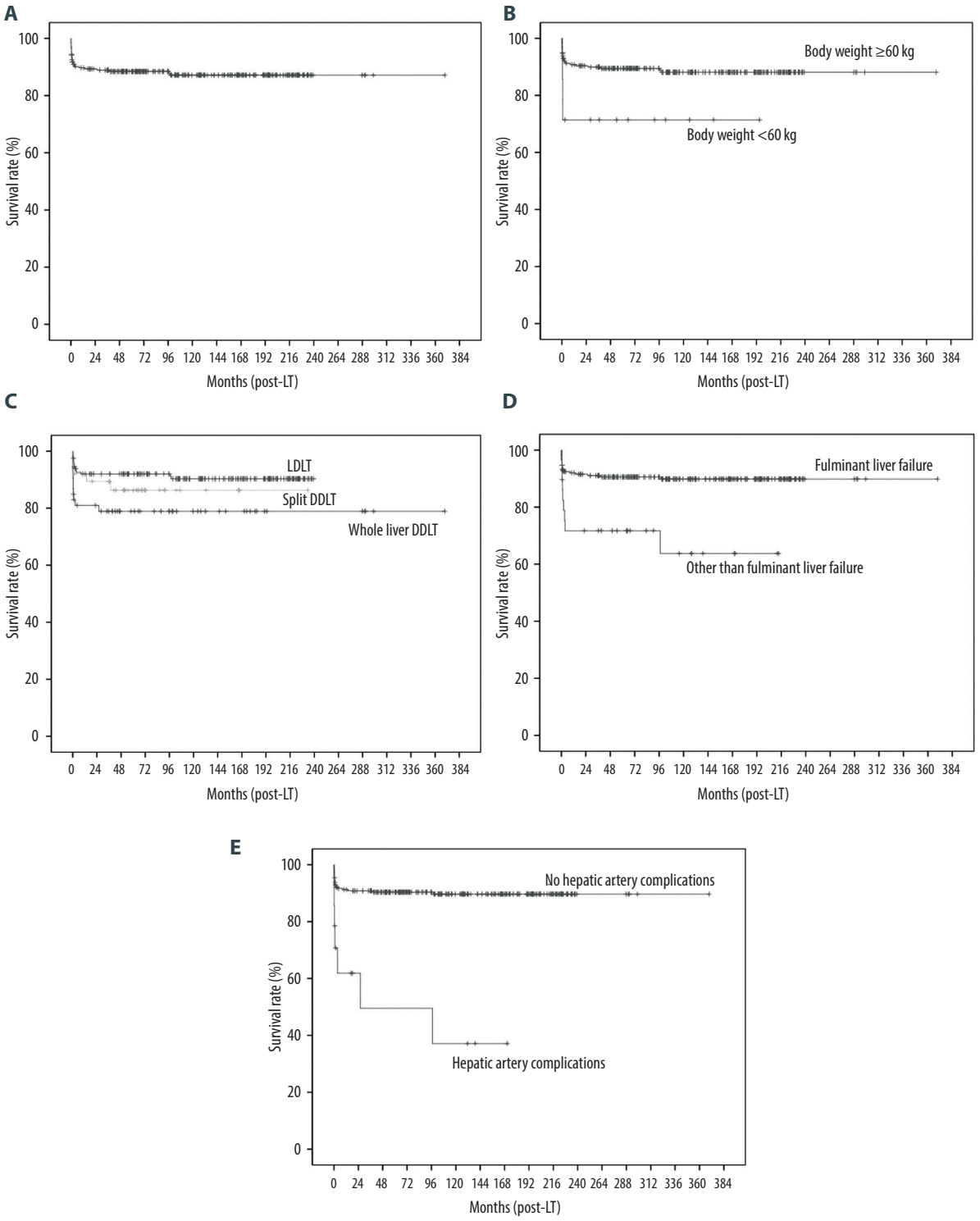

Figure 2. Kaplan-Meier analysis of graft survival: (**A**) all patients, (**B**) according to body weight, (**C**) according to type of LT (LDLT vs split DDLT vs whole-liver DDLT), (**D**) according to liver disease (fulminant liver failure vs other than fulminant liver failure), and (**E**) according to hepatic artery complications.

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Table 2. Cause of graft failure and death.

Variable	Number of patients
Cause of graft failure	
Primary nonfunction	10
Hepatic artery complication	6
Acute rejection	2
Portal vein complication	2
Chronic rejection	1
Bile duct complication	1
Unknown	9
Cause of death other than graft failure	
Infection	10
Cardiogenic shock	1
GVHD	1
Hepatoblastoma recurrence	1

GVHD – graft-versus-host disease

According to the univariate analysis, liver disease other than biliary atresia (*P*=0.036), fulminant liver failure (*P*=0.013) and liver disease without underlying chronic liver disease (*P*=0.004) were significantly associated with postoperative hepatic artery complications (**Table 5**). Multivariate analysis identified that liver disease without underlying chronic liver disease was the only factor independently associated with hepatic artery complications (HR: 5.22, CI: 1.73-15.76, *P*=0.003).

Among 14 patients who experienced postoperative hepatic artery complications (HAT: n=11, HAS: n=3), 4 patients (28.6%) eventually died. Six patients underwent retransplantation; 4 of them underwent thrombectomy and hepatic artery reconstruction before retransplantation. Furthermore, 6 patients underwent hepatic artery reconstruction without retransplantation. Consequently, 2 patients eventually died due to graft failure, while the others survived. One patient who underwent thrombolysis survived without retransplantation while another patient who only underwent arteriography without further intervention died. The details of patients who experienced hepatic artery complications are summarized in **Table 6**.

Discussion

The overall patient and graft survival rates observed in this study were excellent and consistent with previous studies conducted worldwide on LDLT and DDLT [9-11]. The risk factors for overall and graft survival rates from the present study also matched the results of previous studies [9-11].

Children with higher PELD scores were more likely to be hospitalized on parenteral nutrition and under intensive care unit management at the time of LT, which reflects a worse pre-LT condition. The PELD score has been used as a predictor of mortality in children with chronic liver diseases listed for LT as well as in children with acute liver failure [12]. Previous studies showed that patients with PELD scores >20 do not show significantly poorer survival compared to that of those with a PELD score <20; another study showed that the cutoff PELD score was 33 as there was a significant survival difference at that point [3,12]. Similarly, the present study showed no significant survival difference when the PELD cutoff value was 15 or 20, whereas a significant difference in survival was seen when the PELD cutoff value was 30.

Despite the significance of both fulminant liver failure and liver disease without underlying chronic liver disease as risk factors for overall survival in the univariate analysis, fulminant liver failure was not a significant risk factor in the multivariate analysis. Liver disease not accompanied by chronic liver diseases such as fulminant liver failure, hepatoblastoma, and immature teratoma, and other metabolic liver diseases (glycogen storage disease, tyrosinemia type 1, primary hyperoxaluria, urea cycle defect, and factor H deficiency) were more predictive of the survival outcome than fulminant liver failure alone. On the contrary, isolated fulminant liver failure and not liver disease without chronic liver disease was a significant independent risk factor for graft survival. This can be explained by the fact that 5 patients without chronic liver disease died of causes other than graft failure, and only one of these patients had fulminant liver failure. In other words, a patient with liver disease other than fulminant liver failure without underlying chronic liver disease is likely to die of causes other than graft failure.

Whole-liver DDLT compared to LDLT was another significant independent risk factor for graft survival (*P*=0.001), with similar patient overall survival (*P*=0.471) according to multivariate analysis as a result of an increased retransplantation rate in the whole-liver DDLT group. This finding was similar to that of another study, which reported that graft survival, especially in patients ≤6 years old, was better for LDLT compared to DDLT [13]. Further analysis was performed to identify any difference in the distribution of DDLT and LDLT according to the underlying liver disease. No significant difference in the distribution of DDLT and LDLT was observed in patients with biliary atresia (*P*=0.482). However, more patients with fulminant liver failure underwent LDLT than DDLT (14.6% vs 5.5%, *P*=0.028), showing that poorer graft survival in whole-liver DDLT is not due to the effect of the underlying liver disease. Although patients with fulminant liver failure have a Korean Network for Organ Sharing status 1 priority, similar to United Network for Organ Sharing status 1, most of them undergo

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Table 3. Univariate and multivariate analysis of factors associated with patient survival.

Variables	n	Univariate analysis				Multivariate analysis		
		1-year survival rate (%)	5-year survival rate (%)	10-year survival rate (%)	*P* value	HR	95% CI	*P* value
Sex					0.776			
Male	116	90.5	88.6	88.6				
Female	139	90.6	88.3	87.1				
Age, year					0.491			
<1	72	87.4	85.8	85.8				
≥1	183	91.8	89.4	88.6				
Body weight, kg					0.025			
<6	14	69.6	69.6	69.6		2.78	0.74-10.36	0.130
≥6	241	91.7	89.5	88.8			Reference	
Period of LT					0.274			
Early (1988-2007)	124	87.0	85.4	84.6				
Middle (2008-2011)	54	94.4	90.7	90.7				
Recent (2012-2018)	77	93.4	91.9	–				
Type of LT					0.029			
LDLT	164	93.8	91.9	91.1			Reference	
Whole-liver DDLT	53	79.2	79.2	79.2		1.55	0.47-5.15	0.471
Split DDLT	38	92.1	86.4	86.4		1.70	0.53-5.47	0.372
Underlying disease								
BA vs others					0.058			
BA	142	93.6	92.1	91.1				
Others	113	86.7	83.8	83.8				
Fulminant vs others					0.015			
Fulminant	29	75.7	75.7	75.7		1.73	0.39-7.57	0.469
Others	226	92.4	90.1	89.4			Reference	
Chronic liver disease vs others					0.011			
Chronic liver disease	198	92.9	91.3	90.5			Reference	
Others	57	82.3	78.5	78.5		2.69	1.14-6.38	0.024
PELD score					0.005			
<30	214	94.8	92.8	92.1			Reference	
≥30	25	76.0	76.0	76.0		2.81	1.07-7.37	0.036
Child-Pugh score					0.898			
A	45	95.6	90.8	90.8				
B, C	194	92.2	91.1	90.3				
Postoperative complication								
Hepatic artery					0.024			
Yes	14	69.6	69.6	69.6		2.72	0.82-9.08	0.103
No	241	91.7	89.5	88.8			Reference	

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Table 3 continued. Univariate and multivariate analysis of factors associated with patient survival.

Variables	n	Univariate analysis				Multivariate analysis		
		1-year survival rate (%)	5-year survival rate (%)	10-year survival rate (%)	*P* value	HR	95% CI	*P* value
Portal vein					0.802			
Yes	22	95.5	90.9	83.9				
No	233	90.1	88.2	88.2				
Hepatic vein					0.073			
Yes	24	100	100	100				
No	231	89.6	87.3	86.6				
Bile duct					0.720			
Yes	29	93.1	89.4	83.4				
No	226	90.2	88.3	88.3				
Acute rejection					0.179			
Yes	49	95.8	93.4	93.4				
No	206	89.3	87.3	86.5				
Post-transplant lymphoproliferative disorder					0.344			
Yes	19	100	94.7	94.7				
No	236	89.8	88.0	87.3				
Donor sex					0.777			
Male	139	90.6	88.2	87.1				
Female	116	90.5	88.7	88.7				
Donor age, years					0.280			
<18	44	84.0	84.0	84.0				
≥18	211	91.9	89.4	88.7				
Relationship to recipient					0.067			
Mother	79	94.9	93.6	93.6				
Other than mother	176	88.6	86.1	85.2				

HR – hazard ratio; CI – confidence interval; LT – liver transplantation; LDLT – living donor liver transplantation; DDLT – deceased donor liver transplantation; BA – biliary atresia; PELD – pediatric end-stage liver disease.

emergent LDLT instead of DDLT in Korea, an LDLT-dominant country, due to the organ shortage. Among 53 patients who underwent whole-liver DDLT, there were 11 cases of graft failure. The most common cause of graft failure in these cases was unknown (n=7), followed by primary nonfunction (n=3) and hepatic artery complications (n=1). The fact that most cases were due to unknown cause or primary nonfunction and not to other technical issues, suggests potential hidden problems in young, deceased donors.

A bodyweight <6 kg and postoperative hepatic artery complications were also associated with increased graft loss in the multivariate analysis. Young age and/or low body weight are well-known risk factors for high mortality and graft loss after pediatric LT [14-18]. Although assessment of body weight itself may often be misleading because of the effects of organomegaly and ascites, body weight is still a useful variable because it is easy to measure. Various surgical innovations are required to improve the outcomes of pediatric LT, especially in patients with body weight <6 kg and those with a liver disease without underlying chronic liver disease [4,19-24]. Therefore, increased care is required as the number of small children undergoing LT and split LT has recently increased in Korea [25].

Hepatic artery complications, including HAT and HAS, are strong risk factors for graft loss. Hepatic artery complications are well known as one of the most severe complications leading to increased morbidity, graft loss, and, eventually, patient death [26-31]. The incidence of HAT has been reported to be 3-18% after pediatric LT [25,32-34]. In our study, among 14 cases, 2

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Table 4. Univariate and multivariate analysis of factors associated with graft survival.

Variables	n	Univariate analysis				Multivariate analysis		
		1-year survival rate (%)	5-year survival rate (%)	10-year survival rate (%)	*P* value	HR	95% CI	*P* value
Sex					0.412			
Male	116	91.2	90.2	88.8				
Female	139	88.5	87.0	85.8				
Age, year					0.900			
<1	72	88.7	88.7	86.1				
≥1	183	90.1	88.4	87.5				
Body weight, kg					0.035			
<6	14	71.4	71.4	71.4		2.91	1.00-8.45	0.050
≥6	241	90.8	89.5	88.1			Reference	
Period of LT					0.841			
Early (1988-2007)	124	87.8	86.9	86.1				
Middle (2008-2011)	54	94.4	90.4	87.9				
Recent (2012-2018)	77	89.6	89.6	-				
Type of LT					0.043			
LDLT	164	92.0	92.0	90.3			Reference	
Whole-liver DDLT	53	81.0	78.9	78.9		3.93	1.71-9.03	0.001
Split DDLT	38	92.1	86.3	86.3		2.29	0.79-6.64	0.127
Underlying disease								
BA vs others					0.015			
BA	142	93.6	92.9	91.8		0.68	0.26-1.79	0.437
Others	113	84.8	82.9	81.3		Reference		
Fulminant vs others					0.001			
Fulminant	29	71.7	71.7	63.8		3.13	1.35-7.27	0.008
Others	226	92.0	90.6	89.9			Reference	
Chronic liver disease vs others					0.004			
Chronic liver disease	198	92.4	91.3	90.5		1.60	0.43-5.87	0.482
Others	57	80.4	78.4	74.5			Reference	
PELD score					0.072			
<30	214	92.5	91.5	90.7				
≥30	25	83.6	83.6	75.2				
Child-Pugh score					0.433			
A	45	95.6	93.1	93.1				
B, C	194	90.6	90.1	88.4				
Postoperative complication								
Hepatic artery					<0.001			
Yes	14	61.9	49.5	37.1		6.10	2.42-15.36	<0.001
No	241	91.2	90.4	89.7			Reference	

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Table 4 continued. Univariate and multivariate analysis of factors associated with graft survival.

Variables	n	Univariate analysis				Multivariate analysis		
		1-year survival rate (%)	5-year survival rate (%)	10-year survival rate (%)	*P* value	HR	95% CI	*P* value
Portal vein					0.126			
Yes	22	86.4	81.8	75.0				
No	233	90.0	89.1	88.4				
Hepatic vein					0.540			
Yes	24	83.3	83.3	83.3				
No	231	90.4	89.0	87.6				
Bile duct					0.157			
Yes	29	86.2	82.6	77.1				
No	226	90.2	89.2	88.5				
Donor sex					0.685			
Male	139	89.2	87.6	86.5				
Female	116	90.4	89.4	88.0				
Donor age, years					0.123			
<18	44	84.1	81.5	81.5				
≥18	211	90.9	89.9	88.4				
Relationship to recipient					0.450			
Mother	79	91.1	91.1	89.1				
Other than mother	176	89.1	87.2	86.3				

HR – hazard ratio; CI – confidence interval; LT – liver transplantation; LDLT – living donor liver transplantation; DDLT – deceased donor liver transplantation; BA – biliary atresia; PELD – pediatric end-stage liver disease.

underwent non-surgical treatment, 10 underwent surgery, and 6 eventually underwent retransplantation. Owing to the organ shortage in Korea, as in other Asian countries, patients with hepatic artery complications cannot get a deceased organ at the appropriate time despite having a 1A priority status on the waiting list. Among the 8 patients who could not get retransplanted, 5 survived via an aggressive treatment strategy.

Dividing the disease category by biliary atresia vs others, fulminant liver failure vs others, and with vs without chronic liver disease may lead to some overlapping. Biliary atresia, which rapidly progresses to biliary cirrhosis and results in complications related to portal hypertension, would be included in the other than fulminant liver failure group while also being categorized in the liver disease with underlying chronic liver disease group. Considering the confounding effect and the results of multivariate analysis, liver disease without underlying chronic liver disease, rather than biliary atresia or fulminant liver failure itself, is more strongly associated with hepatic artery complications.

According to our previous study that compared the outcomes of pediatric patients with biliary atresia and metabolic liver disease undergoing LT, the rate of hepatic artery complications was higher in patients with metabolic liver disease than in those with biliary atresia [3]. In accordance with the present study, the results indicate that the rate of hepatic artery complications may increase in children without chronic liver disease not characterized by portal hypertension. Several studies reported that smaller or younger children have a higher incidence of hepatic artery complications [26,33-35]. Furthermore, children with chronic liver disease were significantly younger (80.9 vs 53.7 months; *P*=0.010) and tended to have lower body weight (22.8 vs 18.1 kg; *P*=0.053) than children who had liver disease without underlying chronic liver disease. This indicates that the disease category (chronic liver disease *vs* without chronic liver disease) was more strongly associated with HAT or HAS in our study sample rather the recipients' age or weight. There are several reports describing hepatic artery enlargement in biliary atresia [36-38]. A decrease in portal vein flow in chronic liver disease or cirrhosis is compensated for by an increase in hepatic arterial flow to improve the blood supply [37,38]. The hepatic artery enlargement did not lead to a

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Table 5. Univariate and multivariate analysis of factors associated with postoperative hepatic artery complication.

Variables	n	Univariate analysis		Multivariate analysis		
		Hepatic artery complication (%)	*P* value	HR	95% CI	*P* value
Sex			0.839			
Male	116	6 (5.2)				
Female	139	8 (5.8)				
Age, year			0.547			
<1	72	5 (6.9)				
≥1	183	9 (4.9)				
Body weight, kg			0.174			
<6	14	2 (14.3)				
≥6	241	12 (5.0)				
Period of LT			0.317			
Early (1988-2007)	117	5 (4.0)				
Middle (2008-2011)	60	4 (7.4)				
Recent (2012-2018)	78	5 (6.5)				
Type of LT			0.475			
LDLT	164	11 (6.7)				
Whole-liver DDLT	53	1 (1.9)				
Split DDLT	38	2 (5.3)				
Underlying disease						
BA vs others			0.036			
BA	142	4 (2.8)		0.78	0.14-4.40	0.781
Others	113	10 (8.8)			Reference	
Fulminant vs others			0.013			
Fulminant	29	5 (17.2)		1.74	0.37-8.07	0.482
Others	226	9 (4.0)			Reference	
Chronic liver disease vs others			0.004			
Chronic liver disease	198	6 (3.0)			Reference	
Others	57	8 (14.0)		5.22	1.73-15.76	0.003
PELD score			0.169			
<30	214	11 (5.1)				
≥30	25	3 (12.0)				
Child-Pugh score			0.307			
A	45	4 (8.9)				
B, C	194	10 (5.2)				

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Table 5 continued. Univariate and multivariate analysis of factors associated with postoperative hepatic artery complication.

Variables	n	Univariate analysis		Multivariate analysis		
		Hepatic artery complication (%)	*P* value	HR	95% CI	*P* value
Donor sex			0.839			
Male	139	8 (5.8)				
Female	116	6 (5.2)				
Donor age, years			1.000			
<18	44	2 (4.5)				
≥18	211	2 (5.7)				
Relationship to recipient			0.768			
Mother	79	5 (6.3)				
Other than mother	176	9 (5.1)				

HR – hazard ratio; CI – confidence interval; LT – liver transplantation; LDLT – living donor liver transplantation; DDLT – deceased donor liver transplantation; BA – biliary atresia; PELD – pediatric end-stage liver disease.

decrease in its quality in children. The intimal hepatic artery changes in patients with portal hypertension progressed gradually over time [38]. Thus, the artery is less likely to be damaged in a pediatric patient than in an adult patient. Moreover, owing to the thickening of the medial layer, the hepatic artery is not friable in patients with chronic liver disease [38]. Taken together, enlargement as a result of compensation, less intimal changes in children, and altered durability owing to medial thickening allows for easier arterial reconstruction.

It is well known that biliary complications occur in up to 50% of patients after HAT [39,40]. The present study also shows a significantly higher frequency of biliary complications in children with hepatic artery complications compared to those without hepatic artery complications (10.0% vs 35.7%; *P*=0.013). Among the 14 patients who suffered from hepatic artery complications, 5 patients experienced bile duct complications requiring percutaneous transhepatic biliary drainage at postoperative days 63, 1031, 381, 324, and 171.

Subgroup analysis was performed to identify any specific disease associated with poor prognosis in patients with and without chronic liver disease. Disease entities with <5 patients were grouped to strengthen the statistical power. There was no statistically significant in-group disease entity associated with poor overall survival both in patients with and without chronic liver disease (*P*=0.152 and *P*=0.840). However, there was a significant difference in graft survival among patients with different disease entities in the chronic liver disease group (*P*=0.009). Patients with Alagille syndrome had poorer graft survival among patients with chronic liver disease (*P*<0.001). Alagille syndrome is a multisystem autosomal dominant disorder [41]. Several studies reported poor outcomes after LT given the multisystemic nature of this condition [41,42]. Our subgroup analysis also showed poorer graft survival in Alagille syndrome compared with other chronic liver diseases. Among the 9 patients with Alagille syndrome in the present study, 2 patients with primary nonfunction (0.2 months and 2.4 months after LT) and one patient with portal vein complication (13.7 months after LT) eventually died. One patient who experienced recurrent cholangitis immediately after LT the graft was affected by the same disease entity as his mother, which led to the need for retransplantation. The poor outcome of these patients is caused by the multisystemic nature of the disease rather than by the low body weight or hepatic artery complications.

There are some limitations to our study. This was a retrospective study that depended on the completeness of the medical records. Since this study was performed in a single center which mostly performs LDLT, the results may not be directly generalizable to other centers that frequently perform DDLT. To draw a definitive and general conclusion, a multicenter study including all patients who are considered for LT would be needed. The Korean Organ Transplantation Registry is an ongoing prospective multicenter registration database that has been in operation since 2014. Further studies using this database after adequate long-term follow-up are needed to validate the results.

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Table 6. Details of patients who had hepatic artery complication after LT.

Patient	Age (months)	Body weight (kg)	Underlying liver disease	Type of LT	Year of LT	Onset of HA complication	Management	Outcome	Cause of death
1	4.6	6.7	Fulminant	LDLT	2000	POD 4	HA reconstruction after arteriography	Dead	Acute rejection
2	13.1	5.9	Biliary atresia	LDLT	2001	POD 7	Retransplantation	Alive	
3	73.5	28.0	Fulminant	LDLT	2004	POD 22	HA reconstruction after arteriography	Alive	
4	80.0	35.7	Fulminant	LDLT	2004	POD 12	Arteriography and conservative management	Dead	Infection
5	11.9	11.4	Fulminant	LDLT	2007	POD 11	HA reconstruction	Alive	
6	102.1	23.4	Langerhans cell histiocytosis	LDLT	2008	POD 3	Thrombolysis and angioplasty	Alive	
7	4.4	6.7	Primary hyperoxaluria	Split DDLT	2009	POD 5	HA reconstruction	Dead	Infection
8	150.0	24.0	Glycogen storage disease	Whole DDLT	2009	POD 3	HA reconstruction and eventually retransplantation	Alive	
9	9.9	10.4	Fulminant	LDLT	2010	POD 8	HA reconstruction and eventually retransplantation	Alive	
10	4.7	5.1	Biliary atresia	LDLT	2016	POD 7	Retransplantation	Dead	Infection
11	153.7	33.9	Caroli's disease	LDLT	2017	POD 1	Arteriography, reconstruction, and eventually retransplantation	Alive	
12	101.2	30.8	Biliary atresia	LDLT	2017	POD 4	HA reconstruction	Alive	
13	77.3	18.4	Primary hyperoxaluria	Split DDLT	2017	POD 1	HA reconstruction and eventually retransplantation	Alive	
14	182.5	40.0	Biliary atresia	LDLT	2017	POD 1	HA reconstruction	Alive	

LT – liver transplantation; HA – hepatic artery; LDLT – living donor liver transplantation; POD – postoperative day; DDLT – deceased donor liver transplantation.

Conclusions

Greater caution is recommended in pediatric patients with a high PELD score and/or without chronic liver disease undergoing LT to improve patient survival. To improve graft survival, greater caution is recommended for patients with low body weight and/or patients with liver disease not accompanied by underlying chronic liver disease. Hepatic artery complications were the only surgical complications affecting graft survival. Therefore, further technical innovations and careful management are required to deal with hepatic artery reconstruction, especially in patients without chronic liver disease.

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