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Original Article

Effect of Recipient Age on Perioperative Complications after Pediatric Liver Transplantation: A Single-Center Retrospective Study

Akira Katayama[a], Satoshi Kimura[b], Takashi Matsusaki[c], and Hiroshi Morimatsu[a]*

[a]*Department of Anesthesiology and Resuscitology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan,*
[b]*Department of Anesthesia, Kyoto University Hospital, Kyoto 606-8507, Japan,*
[c]*Department of Anesthesiology, Mie University Hospital, Tsu 514-8507, Japan*

It has not been clear how recipient age affects the incidence of serious complications after pediatric living donor liver transplantation (LDLT). We investigated the records of 42 pediatric patients receiving LDLT, dividing our sample into two groups: the infant group (aged < 1 year) and the non-infant group (aged ≥ 1 year and ≤ 15 years). The primary outcome was postoperative complications assessed using the Clavien-Dindo classification. Multivariate analysis using the Cox regression model was applied to adjust for confounding factors in assessing the incidence of Clavien-Dindo grade ≥ III (C-D ≥ III) complications. The incidence of C-D ≥ III complications was higher in the non-infant group (46.2%) than in the infant group (12.5%) (odds ratio 6.00, 95% confidence interval [CI] 1.13-31.88, $p = 0.03$). In multivariate analysis using the Cox regression model, the Graft-to-Recipient Weight Ratio (GRWR) was independently associated with the incidence of C-D ≥ III complications (hazard ratio [HR] 0.62, 95%CI 0.40-0.95, $p = 0.03$), but being an infant was not (HR 0.84, 95%CI 0.35-1.98, $p = 0.68$). In conclusion, the incidence of C-D ≥ III complications was higher in the non-infant group than in the infant group, but this was largely a function of GRWR: multivariate analysis revealed that GRWR was independently associated with complications.

Key words: pediatric liver transplantation, postoperative severe complications, Graft-to-Recipient Weight Ratio

Liver transplantation is the treatment of choice for both adults and children with end-stage liver disease. Liver transplantation outcomes have gradually improved owing to developments in surgical techniques, perioperative management, and immunosuppressive agents [1]. Survival rates after living donor liver transplantation are higher in children than in adults [2]. However, young age and/or low body weight are risk factors for high mortality and graft loss, especially in pediatric liver transplantation [3]. Therefore, the Pediatric End-stage Liver Disease (PELD) score was developed, using the 3-month pre-liver transplantation mortality risk as the endpoint. The PELD score contains the component 'age', with patients under 1 year of age being assigned an extra point in the PELD score [4,5]. Graft-to-Recipient Weight Ratio (GRWR) is another important factor associated with graft function after liver transplantation. The ideal range of GRWR is 0.8-4% [6,7], and the use of small-for-size-grafts (< 1%) leads to lower graft survival, probably through enhanced parenchymal cell injury and reduced metabolic and synthetic capacity [6]. This implies that a smaller recipient body weight is beneficial for graft sur-

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*Corresponding author. Phone: +81-86-235-7778; Fax: +81-86-235-6984
E-mail: pb9b45wr@s.okayama-u.ac.jp (H. Morimatsu)

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vival because of a greater GRWR, essentially the reverse assumption of the PELD score.

Therefore, we conducted a retrospective cohort study to determine the incidence of serious postoperative complications after pediatric liver transplantation. We hypothesized that a younger recipient age would not be associated with a greater incidence of serious postoperative complications. In addition, we investigated factors associated with postoperative complications.

Materials and Methods

Study design. In this single-center retrospective observational study, we selected patients who underwent liver transplantation at Okayama University Hospital between September 1, 2009 and November 30, 2020. This study was approved by the Institutional Review Board of our hospital (approval number: 2301-009). The Committee waived the need for obtaining informed consent for studies involving the use of the hospital database. All regulations and measures of ethics and confidentiality were in accordance with the Declaration of Helsinki.

Patient information and data collection. We included patients who were aged ≤15 years and had undergone living donor liver transplantation at Okayama University Hospital. Patients who had undergone multiple liver transplantations were excluded from the study. Data were extracted from the electronic medical record system. We collected data on basic patient characteristics (age, sex, height, weight, etiology, GRWR, and length of intensive care unit [ICU] and hospital stays), preoperative pathological test results, surgical information (operation time, cold ischemic time, warm ischemic time, and anhepatic time), and anesthesia information (amount of red blood cells [RBCs], fresh frozen plasma [FFP], platelet concentrate [PC], and albumin administered, blood loss, and urinary output). The incidence of Clavien-Dindo (C-D) classification grade ≥ III (C-D ≥ III) complications within 30 days was obtained through the electronic medical records. The body weight used to calculate the amount per kg body weight of RBCs, FFP, PC, and albumin administered was derived from anesthetic records. Drainage volumes are routinely measured by ICU nurses every 2 h at each of four drains at the foramen of Winslow, left and right subdiaphragm, and bile duct, and were documented in the medical record.

Anesthetic management. All patients were administered general anesthesia with endotracheal intubation. General anesthesia was induced using 50-100 mg thiopental and 4-5 μg/kg fentanyl with 0.6 mg/kg rocuronium to facilitate endotracheal intubation. Anesthesia was maintained with 1.5-2% sevoflurane and intermittent injections of fentanyl, and muscle relaxation was achieved with intermittent injections of rocuronium. During the surgery, RBCs, FFP, and PC were administered to maintain a hemoglobin level of 8.0 g/dL, prothrombin activity % (PT%) of 50%, and platelet count of 30,000/μL, respectively. All patients were transferred to the ICU after surgery and intubated.

Immunosuppressive management. Immunosuppression was achieved according to the institutional protocol. The basic immunosuppressive regimen comprised a calcineurin inhibitor (tacrolimus or cyclosporine) and corticosteroid (2 mg/kg/day). Additionally, recipients of incompatible-blood-type grafts received preoperative anti-CD20 antibody (rituximab, 375 mg/m^2) and mycophenolate mofetil (20 mg/kg/day) with preoperative blood exchange.

Definitions. We divided the study population into two groups: infants and non-infants. The infant group included patients aged <1 year, and the non-infant group included patients aged ≥1 year and ≤15 years.

We used the C-D classification to assess the severity of postoperative complications. Based on the type of therapy needed for treatment [8], it consists of 7 grades (I, II, IIIa, IIIb, IVa, IVb, and V) with grade III complications requiring surgical, endoscopic, or radiological interventions (either with or without general anesthesia) [9]. In this study, we defined the C-D III or more (C-D ≥III) as the criterion for severe postoperative complications.

Travis *et al.* [10] validated the Sequential Organ Failure Assessment (SOFA) score for critically ill pediatric patients using age-adjusted criteria. The pediatric-SOFA (p-SOFA) score was used to quantify organ dysfunction.

Outcomes. The primary outcome was the incidence of C-D ≥III complications within 30 days after liver transplantation.

Secondary outcomes were the comparisons of the parameters associated with graft function, such as total

bilirubin level (T-Bil), aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, PT%, and drainage volume of ascites, between the infant and non-infant groups from postoperative day (POD) 1 to POD7. We also compared the p-SOFA scores between the infant and non-infant groups from POD1 to POD7.

Statistical analysis. Preoperative and operative data exhibited an abnormal distribution; therefore, they were expressed as medians and interquartile ranges and compared using the Wilcoxon signed-rank test. Categorical variables were expressed as number (proportion) and compared using Pearson's chi-square test. Multivariate Cox regression analyses were used to explore factors independently associated with the incidence of C-D ≥ III complications within 30 days after liver transplantation. GRWR, PELD score, and infant age were included in the multivariate analysis. We selected GRWR and the PELD score because they are well known as predictors of liver transplantation outcomes. The occurrence of C-D ≥ III complications within 30 days was assessed using the Kaplan-Meier method and compared using Cox regression analysis. The postoperative liver function and p-SOFA score were analyzed using repeated measures analysis of variance.

Statistical analyses were performed using STATA/SE (version 17.0; Stata Corp., College Station, TX, USA) and JMP Pro (version 14.0; SAS Institute Inc., Tokyo).

Results

Patient characteristics. Forty-three pediatric liver transplantations were performed during the study period. Of these, 42 were analyzed after excluding one patient who had undergone a second liver transplantation. The patient characteristics are shown in Table 1.

The median age of patients in the infant and non-infant groups was 6 (interquartile range, 3.5-8) and 76.5 (22.8-109) months, respectively; no neonate was part of the study. The patients were predominantly male (62.5%) in the infant group while only 42.3% patients in the non-infant group were male. The most common disease requiring liver transplantation in both infant and non-infant groups was biliary atresia.

Table 1 Perioperative clinical characteristics of pediatric liver transplantation recipients

	Infant (n = 16)	Non-infant (n = 26)	*P*-value
Age (months), median [IQR]	6 [3.5, 8]	76.5 [22.8, 109]	<0.01
Sex: Male, n (%)	10 (62.5%)	11 (42.3%)	0.20
Height (cm), median [IQR]	63.2 [60.4, 65.9]	111.6 [76.7, 129.6]	<0.01
Weight (kg), median [IQR]	6.4 [5.9, 7.5]	18.1 [9.8, 25.3]	<0.01
Disease, n (%)			
Biliary atresia	12 (75%)	17 (65.4%)	0.51
Hepatoblastoma	0 (0%)	3 (11.5%)	0.16
Alagille syndrome	0 (0%)	3 (11.5%)	0.16
Others	4 (25%)	3 (11.5%)	0.26
ABO incompatibility, n (%)	4 (25%)	2 (7.7%)	0.12
History of surgery	10 (62.5%)	20 (76.9%)	0.26
Child-Pugh score, median [IQR]	10.5 [8.3, 11.8]	7.5 [6.8, 8.3]	<0.01
PELD score, median [IQR]	16.3 [11.2, 21.4]	5.4 [1.4, 9.5]	<0.01
T-Bil (mg/dL), median [IQR]	11.7 [7.0, 20.0]	3.1 [1.0, 8.8]	<0.01
D-Bil (mg/dL), median [IQR]	7.5 [4.0, 13.9]	2.1 [0.34, 6.2]	<0.01
PT% (%), median [IQR]	56.5 [42.3, 84]	88.0 [70.8, 98.5]	<0.01
PLT ($10^4/\mu$L), median [IQR]	18.5 [11.6, 25.1]	12.9 [7.3, 22.0]	0.28
Hb (g/dL), median [IQR]	8.9 [7.9, 10.3]	9.6 [8.7, 11.1]	0.24
AST level (U/L), median [IQR]	209.5 [122.5, 450.3]	139.5 [72.0, 207.3]	0.06
ALT level (U/L), median [IQR]	88.5 [69.8, 236.5]	85.5 [47.5, 159.5]	0.47
Alb level (g/dL), median [IQR]	2.6 [2.2, 3.0]	3.1 [2.8, 3.6]	<0.01
Cr level (mg/dL), median [IQR]	0.15 [0.087, 0.17]	0.26 [0.19, 0.31]	<0.01

IQR, interquartile range; PELD, Pediatric End-stage Liver Disease; T-Bil, total bilirubin; D-Bil, direct bilirubin; PT, prothrombin time; PLT, platelets; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alb, albumin; Cr, creatinine.

Preoperative severity of liver disease was significantly worse in the infant group, including quantifying variables such as Child-Pugh score, PELD score, T-Bil level, direct bilirubin (D-Bil) level, PT%, and albumin level.

Perioperative data. Comparisons of perioperative data in the infant and non-infant groups are shown in Table 2. There were significant differences between infant and non-infant groups in terms of intraoperative data such as RBC transfusion (33.0 mL/kg vs. 21.3mL/kg; $p=0.02$), operation time (401.0 min vs. 480.0 min; $p=0.02$), and GRWR (3.5% vs. 2.3%; $p<0.01$). Other intraoperative parameters, such as FFP transfusion (30.0 mL/kg vs. 15.8 mL/kg; $p=0.11$), urinary output (2.8 mL/kg/h vs. 2 mL/kg/h; $p=0.07$), and blood loss (37.4 mL/kg vs. 31.1 mL/kg; $p=0.25$) showed nonsignificant trends or no significant difference. Postoperative outcomes including length of ICU stay (22.5 days vs. 23.5 days; $p=0.69$) and length of hospital stay (47.5 days vs. 58.0 days; $p=0.46$) showed no significant difference between the infant and non-infant groups.

Main outcomes. The incidence of C-D ≥ III complications was significantly higher in the non-infant group (46.2%) than in the infant group (12.5%): odds ratio 6.00; 95% confidence interval (95%CI) 1.13-31.88; $p=0.03$ (Fig. 1). When we analyzed only patients with biliary atresia (29, 69.1%), the pattern was the same: non-infant group 64.7%, infant group 16.7% ($p=0.01$). Seven patients had vascular complications, four had intestinal complications, and three had postoperative bleeding. Vascular complications included hepatic vein stenosis in three patients, thrombosis of the portal vein in two patients, and hepatic artery thrombosis and portal vein anastomotic stenosis in one patient each. Intestinal complications included perforation of the intestine in two patients, and ileus and peritonitis in one patient each. Eight patients (30.8%) in the non-infant group underwent reoperation, but only two (12.5%) in the infant group. Three patients (11.5%) in the non-infant group underwent

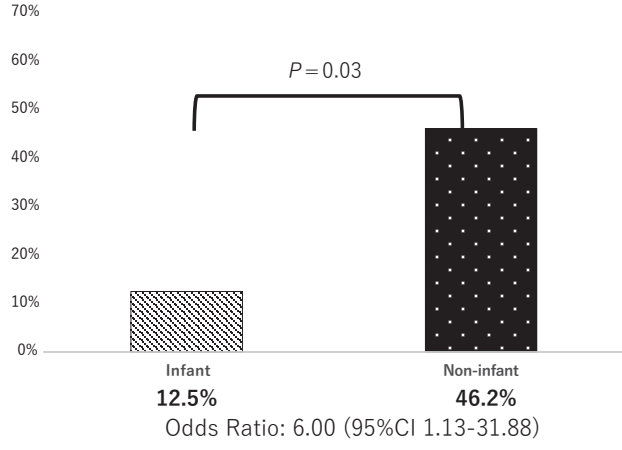

Fig. 1 The incidence of C-D ≥ III complications.
C-D ≥ III, Clavien-Dindo classification grade ≥ III; 95%CI, 95% confidence interval.

Table 2 Intraoperative characteristics of pediatric liver transplantation recipients

	Infant (n = 16)	Non-infant (n = 26)	*P*-value
Crystalloids (mL/kg), median [IQR]	56.1 [31.4, 81.7]	80.3 [61.8, 109.6]	0.07
5% Alb (mL/kg), median [IQR]	44.3 [12.1, 59.4]	40.0 [6, 73.6]	0.79
RBC (mL/kg), median [IQR]	33.0 [22.2, 56.4]	21.3 [8.2, 41.5]	0.02
FFP (mL/kg), median [IQR]	30.0 [14.1, 54.9]	15.8 [2.3, 40.4]	0.11
PC (mL/kg), median [IQR]	0.0 [0.0, 0.0]	0.0 [0.0, 5.5]	0.48
Blood loss (mL/kg), median [IQR]	37.4 [26.8, 77.4]	31.1 [18.5, 64.7]	0.25
Urine (mL/kg/h), median [IQR]	2.8 [2, 3.9]	2 [1.2, 3.5]	0.07
Operation duration (min), median [IQR]	401.0 [354.8, 510.0]	480.0 [439.0, 541.0]	0.02
Cold ischemic time (min), median [IQR]	32.0 [20.5, 70.0]	39.0 [23.0, 58.0]	0.64
Warm ischemic time (min), median [IQR]	40.0 [32.0, 57.0]	46.0 [37.0, 55.0]	0.48
Anhepatic time (min), median [IQR]	152.0 [129.0, 167.0]	152.0 [91.0, 181.0]	0.99
GRWR, median [IQR]	3.5 [2.9, 3.8]	2.3 [1.5, 3.2]	<0.01
ICU stay (days), median [IQR]	22.5 [21.0, 29.8]	23.5 [16.8, 30.3]	0.69
Hospital stay (days), median [IQR]	47.5 [40.8, 66.8]	58.0 [42.8, 70.3]	0.46

IQR, interquartile range; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate; GRBW, Graft-to-Recipient-Weight Ratio; ICU, intensive care unit.

percutaneous ballooning for stenosis of the hepatic vein (Table 3). The median follow-up period was 54.8 months (32.5, 91.8 months, IQR) for the infant group, and 65.7 months (45.6, 105.4 months, IQR) for the non-infant group. No patients died within 30 days after liver transplantation.

GRWR, PELD score, and infant age were included in the multivariate analysis. We selected GRWR and PELD score because they are well known prognostic factors for liver transplantation. The results of multivariate Cox regression analysis for the incidence of C-D ≥III complications showed that GRWR was independently associated with the incidence of C-D ≥III complications (hazard ratio [HR] 0.62; 95%CI 0.40-0.95, $p=0.03$), but other variables such as PELD score (HR 1.02; 95%CI 0.98-1.06, $p=0.26$) and infant age (HR 0.84, 95%CI 0.35-1.98, $p=0.68$) were not (Table 4). Kaplan-Meier analysis of the incidence of C-D ≥III complications showed no significant differences between the infant and non-infant groups ($p=0.44$) (Fig. 2).

Postoperative course of parameters for liver function. While PT% and AST and ALT levels were similar between the infant and non-infant groups, T-Bil, drainage volume of ascites, and p-SOFA scores were higher in the infant group than in the non-infant group. However, repeated measures analysis of variance showed no statistically significant difference between any parameter (PT% $p=0.54$; AST level $p=0.98$; ALT level $p=0.94$; T-Bil level $p=0.11$; occurrence of ascites $p=0.35$; and p-SOFA score $p=0.38$) (Fig. 3).

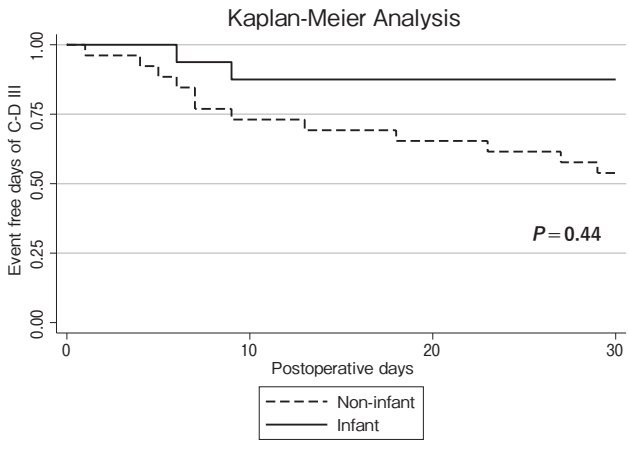

Fig. 2 Kaplan-Meier analysis of the incidence of C-D ≥III complications.
C-D ≥III: Clavien-Dindo classification grade ≥III.

Table 3 Details of C-D ≥III complications

	Infant	Non-infant	*P*-value
Re-operation, n (%)	2 (12.5%)	8 (30.8%)	0.18
Ballooning, n (%)	0 (0%)	3 (11.5%)	0.16

C-D ≥III, Clavien-Dindo classification grade ≥III.

Table 4 Results of multivariate Cox regression analysis for the incidence of C-D ≥III complications

	HR	95%CI	*P*-value
GRWR	0.62	0.40–0.95	0.03
PELD score	1.02	0.98–1.06	0.26
Infant	0.84	0.35–1.98	0.68

C-D ≥III, Clavien-Dindo classification grade ≥III; GRWR, Graft-to-Recipient Weight Ratio; PELD, Pediatric End-stage Liver Disease; HR, hazard ratio; 95%CI, 95% confidence interval.

Discussion

In this retrospective study, we assessed the incidence of C-D ≥III complications in 42 patients aged 2 months to 15 years who underwent living-donor liver transplantation. We found that the incidence of C-D ≥III complications was higher in the non-infant group (46.2%) than in the infant group (12.5%). We performed subgroup analysis of cases with biliary atresia because different etiologies may lead to different prognosis. We confirmed similar findings even in this subgroup. Multivariate analysis revealed that only GRWR was independently associated with the incidence of C-D ≥III complications (HR: 0.62, 95%CI: 0.40-0.95, $p=0.03$). Furthermore, the T-Bil level, Child-Pugh score, PELD score, and PT% were significantly worse in the infant group than in the non-infant group. These results indicate that the incidence of postoperative complications was lower in the infant group despite preoperative laboratory findings being worse in this group.

Because few studies have employed the Clavien-Dindo classification to quantify serious postoperative complications after pediatric liver transplantation, we cannot compare our results with those of previous reports. However, with regard to other parameters such as 1-year or 5-year survival, Kasahara *et al.* [2] reported 1-year survival as 88.3% and 5-year survival as

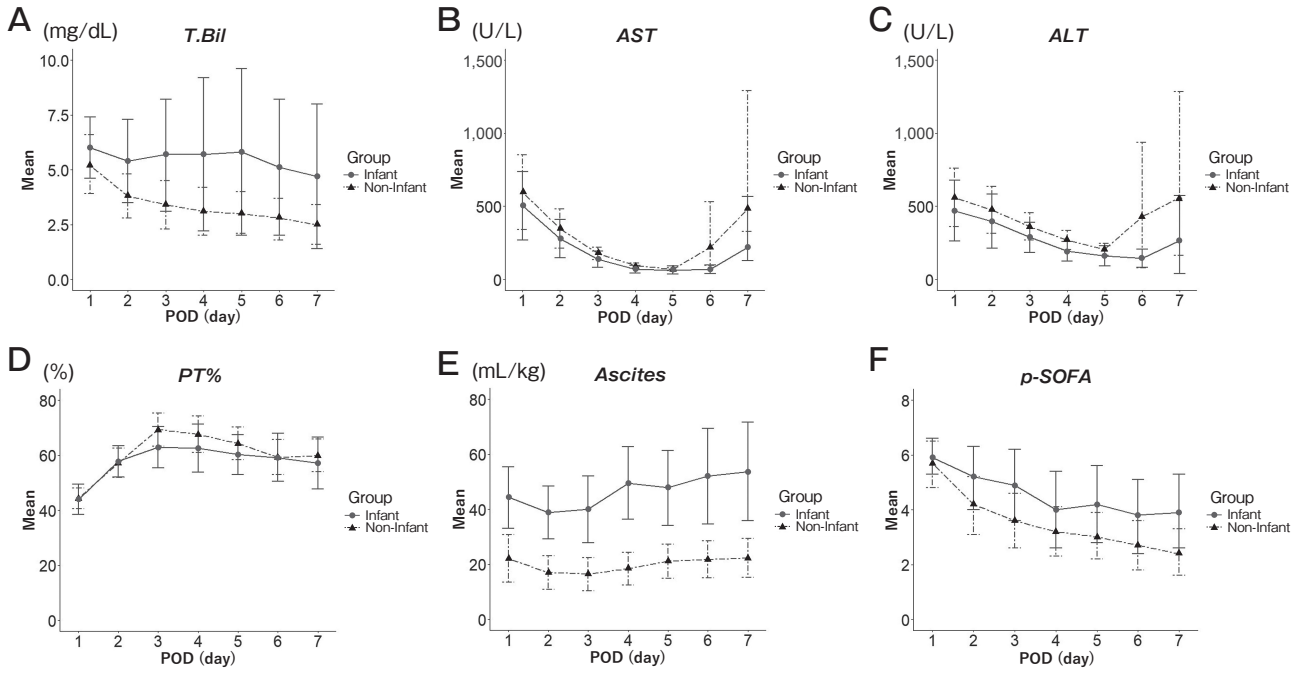

Fig. 3 Postoperative course of parameters for liver function. **A**, T-Bil; **B**, AST; **C**, ALT; **D**, PT%; **E**, Ascites; **F**, p-SOFA. POD, postoperative day; T-Bil, total bilirubin; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; p-SOFA, Pediatric-Sequential Organ Failure Assessment.

85.4% after pediatric liver transplantation, whereas our study results indicated 97.6% and 85.2%, respectively, which is not inferior. We set the outcome as occurrence of C-D ≥III complications because we believe that perioperative management affects short-term outcomes.

The incidence of C-D ≥III was lower in the infant group, but multivariate Cox regression analysis revealed that while GRWR was independently associated with the incidence of C-D ≥III, being an infant was not. It has been demonstrated that younger age and/or low body weight are risk factors for high mortality and graft loss, especially in pediatric liver transplantation [11-13]. However, a recent study by Neto *et al.* [14], which included 1,078 patients aged under 18 years, indicated that body weight is not significantly associated with patient and graft survival after adjusting for other risk factors. This finding is consistent with our results. Moreover, our study showed that the infant group had a lower incidence of C-D ≥III complications than the non-infant group. Furthermore, the Cox regression analysis in our study suggested that GRWR may play a more significant role than age in terms of short-term postoperative complications of living-donor liver transplantation in children. However, although past history of abdominal surgery was not different among the infant group and the non-infant group (n=10 [62.5%] vs. n=20 [76.9%], $p=0.26$), the non-infant group had a longer length of surgery. This fact might have affected the incidence of C-D ≥III complications.

The postoperative bilirubin levels were higher in the infant group than in the non-infant group. Hyperbilirubinemia can be caused by preoperative liver failure, massive transfusion, or cholestasis [15,16]. The infant group had higher preoperative bilirubin levels, which may have influenced the higher postoperative bilirubin levels. Furthermore, the infant group was transfused with more RBCs intraoperatively, and the higher bilirubin levels could be attributed to increased heme breakdown resulting from bulk transfusions [17]. Additionally, the hepatic artery is the only blood supply to the biliary system, and hepatic artery complications may lead to elevated bilirubin levels [18]. Gu *et al.* [19] reported that the incidence of hepatic artery thrombosis was high in younger recipients, especially those aged

less than one year, and this may be attributed to the higher bilirubin levels in the infant group. Although there are many possible causes, it is unclear exactly why the bilirubin levels were higher in the infant group in this study.

With regard to the drainage volume of ascites, it was higher in the infant group than in the non-infant group. Herzog *et al.* [20] reported the overall incidence of ascites after pediatric liver transplantation as 31.2%. Another report by Antonio *et al.* [21] showed an inverse relationship between patient weight and severity of ascites. These results are similar to those of this study, which suggest that the volume of ascitic fluid depends on the fluid status of the patient. Our findings showed that although the infant group had higher bilirubin levels and larger amounts of ascitic fluid, their incidence of C-D ≥ III complications was lower than that of the non-infant group. In clinical practice, we use data mainly associated with liver function, such as AST, ALT, and platelet counts, PT%, bilirubin level, and occurrence of ascites, to predict graft function. However, higher bilirubin levels and larger amounts of ascitic fluid may not necessarily lead to serious postoperative complications as defined by C-D ≥ III.

The limitations of this study were as follows. First, Kaplan-Meier analysis of the incidence of C-D ≥ III complications showed no significant difference between the infant and non-infant groups. One possible reason for this may be the small number of patients included in this study and consequent low statistical power. Further study with larger enrollment numbers is called for. Nonetheless, we found a significant difference in the incidence of C-D ≥ III based on GRWR, and we believe that this result has important implications for clinical decision making. Second, this was a single-center retrospective study, which may have affected the generalizability of the results. Third, the study period was so long that the standard perioperative management protocols, including surgical techniques, anesthetic agents, and immunosuppressant agents, may have changed. These changes may have influenced the results of the present study. Fourth, all patients in this study underwent living-donor liver transplantation. We cannot confirm whether our findings can be applied to patients undergoing deceased-donor liver transplantation. Fifth, we did not have information on the preoperative status such as acute-on-chronic liver failure, acute liver failure, hepatopulmonary syndrome, portopulmonary hypertension, or hepatic encephalopathy. These conditions may have affected the outcome of liver transplantation.

In conclusion, the incidence of C-D ≥ III complications was higher in the non-infant group (46.2%) than in the infant group (12.5%). However, this was largely a function of the GRWR, as the incidence of C-D ≥ III complications after pediatric liver transplantation was independently associated with GRWR.

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