World Journal of Pediatric Surgery

Early relaparotomy following pediatric living-donor liver transplantation: experience in an Indonesian national referral hospital

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To cite: Rahayatri TH, Soeratman AR, Muhammad Amin RB, *et al*. Early relaparotomy following pediatric living-donor liver transplantation: experience in an Indonesian national referral hospital. *World Jnl Ped Surgery* 2023;**6**:e000511. doi:10.1136/wjps-2022-000511

Received 16 October 2022
Accepted 10 January 2023

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ABSTRACT

Background Living donor liver transplantation (LDLT) remains the only curative treatment for children with end-stage liver disease; however, complications of the procedure are associated with indications for early relaparotomy. Several risk factors associated with early relaparotomy after liver transplantation include pediatric end-stage liver disease (PELD) score, warm ischemia time (WIT), and cold ischemia time (CIT). Our study investigated the incidence and indications of early relaparotomy in postoperative pediatric LDLT recipients and compared the outcomes with patients who did not require relaparotomy.

Methods A retrospective cohort study of pediatric LDLT recipients from Cipto Mangunkusumo Hospital, Jakarta, Indonesia, was collected from 2010 to August 2022. Indications for early relaparotomy were investigated. Factors analyzed in the early relaparotomy group compared with the nonrelaparotomy group included intraoperative blood loss, surgery duration, CIT, WIT, and PELD score.

Results The highest indication for early relaparotomy was biliary leakage. Most patients who underwent early relaparotomy only had one incidence of relaparotomy (60%). The surgery duration in subjects with early relaparotomy was longer by a median of 3 hours compared with those without early relaparotomy (p=0.289). Intraoperative blood loss was greater in early relaparotomy subjects than in subjects without early relaparotomy (95 vs 77 mL/kg, p=0.552). Other factors, such as PELD score, CIT, and WIT, also showed no significant difference between the two groups.

Conclusion Biliary leakage was the most common indication for early relaparotomy in our center. There were no preoperative or intraoperative factors that significantly influenced the incidence of early relaparotomy due to the limited sample size and the early advancement of our liver transplant center.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pediatric living donor liver transplantation (LDLT) is a technically complex procedure.
⇒ Several preoperative and intraoperative factors have been associated with the incidence of complications requiring relaparotomy after LDLT.

WHAT THIS STUDY ADDS

⇒ Biliary leakage has the highest indication for early relaparotomy.
⇒ Prolonged surgery duration and an increase in intraoperative blood loss are evident in the early relaparotomy group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Techniques to prevent preoperative and intraoperative risk factors for early relaparotomy must be avoided to reduce complications and mortality from LDLT.

INTRODUCTION

Living donor liver transplantation (LDLT) is a complex curative procedure for end-stage liver disease.[1] Several early complications of liver transplantation, including hemorrhage and intestinal, biliary, and vascular complications, are possible indications for relaparotomy.[2 3] Early relaparotomy is believed to be associated with intraoperative technical complications and is generally linked to poor prognosis.[3] The significantly rising mortality in liver transplant recipients undergoing early relaparotomy is associated with graft failure. The survival rate declines to 60%–75% in patients requiring relaparotomy compared with those who do not need it, with a survival rate of 96.6%.[4] Pediatric end-stage liver disease (PELD) score, warm ischemia time (WIT), and cold ischemia time (CIT) are among the prognostic factors that contribute to the need to perform relaparotomy.[3]

Numerous studies have extensively discussed the risk factors and complications of early relaparotomy in pediatric LDLT recipients.[5] The incidence of early relaparotomy following LDLT can be used to highlight the progress and learning curve of pediatric LDLT at the national center of

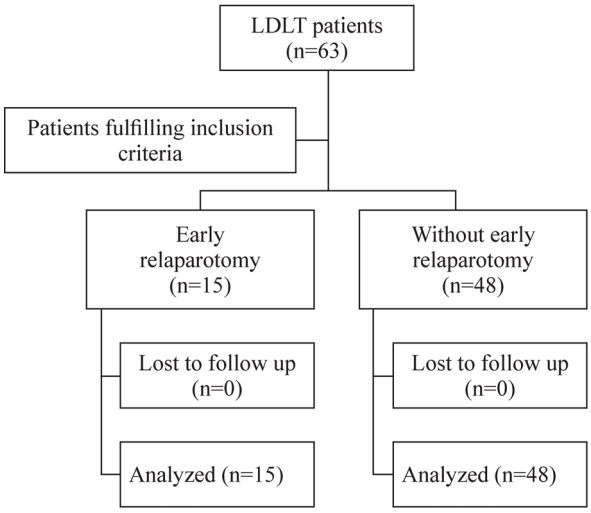

Figure 1 Study flow. LDLT, living donor liver transplantation.

liver transplantation in Indonesia. Our findings will be useful for the development of pediatric liver transplantation centers in novice and expert institutions. Our study aims to explore the incidence, indication, risk factors, and complications of early relaparotomy in postoperative pediatric LDLT recipients in our center compared with previous studies. We compared the outcomes with LDLT patients who did not require relaparotomy.

METHODS

We conducted a retrospective cohort study gathering pediatric LDLT recipients from the electronic medical record database of Cipto Mangunkusumo Hospital National Referral Hospital in Jakarta, Indonesia. We included liver transplant recipients between 2010 and August 2022. Patients over 18 years of age were excluded (figure 1). Early relaparotomy was defined as relaparotomy performed within 30 days of the initial surgery for LDLT. Variables included age, intraoperative blood loss, surgery duration, CIT, WIT, PELD score, and graft size. Reasons for relaparotomy were enlisted. Biliary leakage in our study was defined clinically through evidence of sepsis, evidence of bile fluid leakage in the drain, and analysis of drain fluid.

The immunosuppressive protocol our center adheres to includes the use of tacrolimus starting from 10 to 12 ng/mL for the first month and 8–10 ng/mL for the following 3 months. The regimen is combined with the administration of methylprednisolone starting from 1 mg/kg from postoperative day (POD) 1 until POD 3, 0.5 mg/kg from POD 4 to POD 6, and 0.3 mg/kg at POD 7. In certain cases, mycophenolate mofetil may also be administered. Antibiotic treatment includes empirical antibiotics per the bacterial culture results.[6] The study protocols were performed in accordance with the Declaration of Helsinki and approved by the ethical committee of the Faculty of Medicine, Universitas Indonesia (Ref. No. 20-05-0518).

Data analysis

Collected data were processed through editing, entry, and analysis. The results were analyzed using Statistical Package for the Social Sciences (SPSS) V.20. The normality test used was the Kolmogorov-Smirnov test (>30 samples). All categorical data are presented in the form of n (%). Data were analyzed descriptively and presented with mean±SD for normally distributed data and median (range) for non-normally distributed or skewed data. Unpaired t-test or Mann-Whitney test and χ^2 test were used for the comparison of continuous data and categorical data, respectively, with $p<0.05$ considered statistically significant.

RESULTS

Characteristics of the patients

The study included 63 pediatric liver transplant recipients who underwent LDLT from 2010 to August 2022 and fulfilled the inclusion criteria. The main characteristics of the patients are described in table 1. Most of the patients were diagnosed with biliary atresia (80.9%). In our center, there were two cases of ABO incompatibility, both of which resulted in mortality due to high immunosuppression. Most of the LDLT recipients had one biliary anastomosis (65.1%). The median age of LDLT recipients is 16 months, with a median PELD score of 17. Most LDLT donors were maternal (52.4%), with a median donor age of 32 years old. In our center, the donor age is limited to 21–55 years, with no known comorbidities, and only one donor with 20% steatosis participated in the donation. Others had no or minimal steatosis.

Out of the 63 LDLT recipients, 15 subjects underwent early relaparotomy (23.8%). The highest indication for early relaparotomy was biliary leakage (27%). Table 2 summarizes the indications for early relaparotomy performed in our transplant center. Some subjects have multiple indications for early relaparotomy. Most patients who underwent early relaparotomy only had one incidence of relaparotomy (60%). The most relaparotomies performed on one patient were three times, as recorded in two recipients. One patient had an early relaparotomy performed due to intestinal perforation and another due to intra-abdominal bleeding. A total of four patients were recorded to have two relaparotomies performed after transplantation, with indications of early relaparotomy due to intra-abdominal infection, adhesions, bile leakage, and hepatic vein kinking.

Comparative study for factors related to early relaparotomy

We analyzed the preoperative and intraoperative factors between the patients who had undergone relaparotomy with those who did not (table 3). The variables observed were PELD score, duration of surgery, hemorrhage during transplantation, WIT, and CIT. All variables showed no significant difference between the early relaparotomy and control groups. The comparative analysis showed that the control group had a higher PELD score

Table 1 General characteristics of research participants (n=63)

Variables	Patients, n (%)
Age (months)*	16 (6–165)
Gender	
Male	34 (54)
Female	29 (46)
Body weight (kg)*	8.7 (6.3–38)
History of growth failure	
Yes	48 (76.2)
No	15 (23.8)
Diagnosis	
Biliary atresia	51 (80.9)
Caroli disease	2 (3.2)
Alagille syndrome	3 (4.8)
Choledochal cyst	3 (4.8)
Autoimmune hepatitis	1 (1.6)
Budd-Chiari syndrome	1 (1.6)
Neonatal hepatitis	1 (1.6)
Extrahepatic portal vein thrombosis	1 (1.6)
History of surgery	
Yes	9 (14.3)
No	54 (85.7)
Donor	
Maternal	33 (52.4)
Paternal	26 (41.3)
Others (aunt/uncle)	4 (6.3)
Donor age (years)*	32 (21–55)
ABO incompatibility	
Yes	2 (3.2)
No	61 (96.8)
Donor macrosteatosis	
None (≤5%)	47 (74.6)
Very mild (>5% to 15%)	12 (19.0)
Mild (>15% to 30%)	2 (3.17)
Moderate (>30% to 60%)	2 (3.17)
Severe (>60%)	0
Billiary anastomosis	
1	41 (65.1)
2	22 (34.9)
Early relaparotomy	15 (23.8)
PELD score*	17 (6–36)
Surgery duration (min)* (n=60)	720 (480–1440)
Blood loss (mL/kg body weight)* (n=58)	81 (17–581)
Warm ischemic time (min)† (n=59)	61±27
Cold ischemic time (min)* (n=59)	62 (19–273)

*Data are presented with median (range).
†Data are presented with mean±SD.
PELD, pediatric end-stage liver disease; SD, standard deviation.

Table 2 Indication for early relaparotomy (n=15)

	Patients, n (%)
Biliary leakage	4 (27)
Intestinal adhesions	3 (20)
Obstructive ileus	2 (13)
Intestinal perforation	2 (13)
Intra-abdominal bleeding	2 (13)
Prolonged ascites	1 (7)
Portal vein thrombosis	1 (7)
Hepatic vein kinking	1 (7)
Intra-abdominal infection	1 (7)

(17 vs 16; p=0.667). However, the results were not statistically significant.

DISCUSSION

This study aimed to report the indication for relaparotomy in pediatric liver transplant recipients and to compare the preoperative and intraoperative factors between the relaparotomy and nonrelaparotomy groups. The incidence of relaparotomy following LDLT ranges from 9.2% to 34%. The relatively high incidence of early relaparotomy is also related to increasing graft failure and mortality.[7 8] In our center, the incidence of early relaparotomy was 23.8%, which is comparable to the range of relaparotomy in other centers. The vitality of identifying factors related to early relaparotomy incidences is crucial to improving surgical care in LDLT recipients and the success of pediatric liver transplantation programs.

Our center's LDLT program commenced in 2010, and to date, it is the only center that performs pediatric LDLT independently in Indonesia. Deceased donor liver transplantation has not yet been established in the country due to many factors. The lack of legal legislation regarding liver transplantation and the absence of liver donors has impeded the growth of the liver transplantation program in Indonesia.[9]

Living donor operations have more technical complexity than deceased donor transplantations.[10] Most patients who arrive at our center requiring liver transplantations present with late conditions, with severe complications such as malnourishment or decompensated stage of liver disease. Although early relaparotomy has been associated with technical issues, the patient's presentation also contributes to the outcome.[5 9]

The advantage of LDLT is the high likelihood of obtaining good graft quality. In our center, the donor selection criteria ensure optimal graft quality. Our donor selection criteria also ensure that the donor has no known comorbidities, and a minimal degree of steatosis must have been adhered. Because our center still has few cases, we aimed to reduce mortality; therefore, our center performs LDLT only in ABO-compatible cases.

Table 3 Preoperative and intraoperative factors were compared between groups with a history of early relaparotomy and without

Variable	Early relaparotomy		P value
	Yes (n=15)	No (n=48)	
PELD score*	16 (12–24)	17 (6–36)	0.662
No of biliary anastomosis†			
1	9 (60)	32 (67)	0.636
2	6 (40)	16 (33)	
Duration of surgery* (min) (n=60)	885 (568–1380)	720 (480–1440)	0.289
Hemorrhage* (mL/kg) (n=58)	95 (22–282)	77 (17–581)	0.552
Warm ischemic time‡ (min) (n=59)	65±30	60±27	0.558
Cold ischemic time* (min) (n=59)	71 (19–224)	60 (20–273)	0.337

*Data were presented with median (range).
†Data were presented with number (%).
‡Data were presented with mean±SD.
PELD, pediatric end-stage liver disease; SD, standard deviation.

In this study, biliary leakage accounted for 27% of cases of early relaparotomy. Contrary to previous studies, biliary leakage is not the main indication for relaparotomy in pediatric liver transplant recipients.[3] Biliary leakage post-LDLT falls between 15% and 40%.[11] The cause of biliary leakage is supposedly due to technical issues, necrosis on the anastomosis site, and vascular insufficiency in the biliary drainage.[12] Perioperative factors that give rise to the incidence of biliary leakage are prolonged ischemia time, biliary reconstruction technique, and biliary drainage malfunction.[11] In our study, patients who had biliary leakage as an indication for relaparotomy had not undergone Roux-en-Y anastomosis prior to liver transplantation.

Biliary anastomoses performed in our LDLT all follow the same technique with a duct-to-jejunum anastomosis followed by Roux-en-Y reconstruction. Performing Roux-en-Y anastomosis heavily relies on the surgeon's technical skill in achieving a tension-free anastomosis, preventing obstruction or stricture. In our center, biliary anastomosis is performed by a single surgeon. Thus, experience and technical skills are already established. In contrast to the results reported by Hara *et al*[12] that biliary leakage was treated initially with percutaneous or radiological intervention; however, in our center, we aggressively treated all complications post-LDLT through surgical interventions. Our center provides interventional radiology procedures, such as endoscopic retrograde cholangiopancreatography (ERCP). The duct-to-jejunum anastomosis performed causes technical difficulties for the use of ERCP in biliary leakage complications. Despite the high success rates of ERCP in managing biliary complications, our center-preferred biliary anastomosis for pediatric LDLT makes conservative management and/or surgical intervention with open drainage or extrinsic biliary diversion the better choice.[13] Efforts to reduce the incidence of biliary leakage have been conducted from the start of graft procurement, paying special attention to dissection around the bile duct and the use of bile stents. To reduce the incidence of postoperative biliary leakage in the future, a refined technical procedure is needed for donor hepatectomy and recipient anastomosis. A precise bile duct dissection site during donor hepatectomy is mandatory to ensure the procurement of a single duct bile duct graft. Special attention must be given during bile duct dissection to prevent arterial injury and the risk of ischemia. Although intraoperative cholangiography is used, a technical issue could still result in the presence of multiple. With increased experience, surgeons should strive for improved skills and a lower incidence of technical errors.

Other reported indications for relaparotomy in our study were intestinal adhesions and obstruction. The extension and locations of adhesions were not well documented. Prior surgical history remains the most reported cause of adhesions, which are caused by inflammatory mediators, coagulation reactions, and blood vessel damage. In LDLT indicated for hepatic carcinoma cases, a previous history of liver resection, high blood loss, and prolonged ischemic time presented as increased risks for adhesion formations. Furthermore, adhesions are higher in adults than in pediatric liver recipients. However, the study that made this conclusion had an exceedingly low sample size of pediatric patients.[14] Our center prioritizes aggressive surgical management for adhesiolysis complications. In a systematic review, an emergency exploratory laparotomy was indicated in 42.9% of cases who required adhesiolysis, most commonly in lung and liver transplants without significant morbidity.[15] Obstructive ileus presented the same incidents as bowel perforation that required relaparotomy following LDLT. Intestinal obstruction has an incidence of 3% in postoperative LDLT pediatric patients and is generally due to adhesions.[16]

Hemorrhage was mainly reported due to bleeding at the anastomosis site or cutting surface of the liver. Previous studies have shown intra-abdominal bleeding

to be the leading cause of early relaparotomy.[12] Yoshiya *et al*[5] identified that intra-abdominal bleeding post-transplantation was due to prolonged coagulopathy, anastomosis hemorrhage, arterial bleeding from the splenic hilum stump, or bleeding from drain site insertion. Similar to our study, Yoshiya *et al*[5] and Hara *et al*[12] identified no significant risk factors associated with any relaparotomy indications. Intraoperative blood loss was not a significant factor for relaparotomy post-LDLT. Intraoperative blood loss was documented to be higher in the relaparotomy group. This finding is similar to that reported by Okada *et al*.[4] Massive blood transfusion has been reported to be associated with postoperative complications.[12 17 18]

Bacterial infection was one of the most common complications reported within a month post-liver transplantation, which may manifest as spontaneous bacterial peritonitis intra-abdominal abscess, hospital-acquired infection, cholangitis, pneumonia, or donor-acquired infection.[4 12 19] In contrast, our center showed only one case of early relaparotomy due to intra-abdominal infection. In our center, all intra-abdominal infections post-LDLT are managed aggressively with surgical management to prevent further complications in the recipient. Multiple factors, such as hepatocellular dysfunction, mucocutaneous barrier damage, use of invasive medical devices, and immunosuppressive therapy, contribute to the development of intra-abdominal infection. Other contributing perioperative factors include age, nutritional status, anhepatic phase, Roux-en-Y anastomosis, and duration of hospitalization in the intensive care unit.[3]

The LDLT for the early relaparotomy group was more prolonged than that for the non-early relaparotomy group with a median duration of almost 3 hours. Our study did not show a significant difference in operation duration between the two groups. A prognostic study accomplished by Kawaguchi *et al*[7] revealed a similar result that the time of operation did not provide prognostic relevance in the event of relaparotomy. Other studies reported an association between the duration of operation and complications, namely, ascites, intestinal perforation, vascular complications, biliary complications, bowel obstruction, and intra-abdominal bleeding that required relaparotomy.[3 4 7] Another study showed that operation duration longer than 2 hours doubled the risk of developing postoperative complications due to the deteriorating effect of sedation on the heart and kidneys.[20] The average difference in operation durations between the two groups in our study was approximately 5 hours. Effective management of anesthesia may have contributed to the tolerance of the patients.

Differences in CIT and WIT were not significant between the two groups. Previous studies have shown contradictory results.[3 5 20] The duration of WIT is associated with complications such as hemorrhage, biliary duct injury, and thrombosis due to ischemic–reperfusion injury.[5] Several studies have determined that the maximum cut-off time for CIT ranges from 7 to 12 hours. The morbidity increases as the transplantation procedure extends every hour due to ischemic–reperfusion injury, potentially leading to graft failure and postoperative complications.

Our study showed that transplant surgery duration and blood loss were higher in subjects who underwent relaparotomy, which is congruent with risk factors associated with early relaparotomy; however, the results were not significant. Most of our patients were indicated for relaparotomy due to biliary leakage. The sample obtained in this study was limited due to a single-center setting and the emerging liver transplantation program in the country, and our center is the only independent center performing liver transplantation at the moment. Several confounding factors, such as donor age, stage of primary non-function, donor operative time, and donor intraoperative blood loss, were not considered. Intraoperative technical factors were also not included, such as the extent of adhesions, diameters of biliary ducts, and blood vessels.

In conclusion, biliary leakage was the most common indication for early relaparotomy in pediatric LDLT. Preventive measures to reduce the risk of biliary leakage may reduce the likelihood of requiring relaparotomy in these patients. Our centers' protocol in aggressively managing complications through surgical interventions to limit mortality in LDLT has resulted in various indications for early relaparotomy that differ from previous studies. In our center, there were no preoperative or intraoperative factors that significantly influenced the incidence of early relaparotomy, which may be due to the limited sample size and the early advancement of our liver transplant center.

Contributors THR: conceptualization, methodology, formal analysis and investigation, writing—original draft preparation, writing—review and editing andguarantor. ARS: conceptualization, methodology, formal analysis and investigation, writing—original draft preparation and writing—review and editing. RBMA: conceptualization, methodology, formal analysis and investigation, writing—original draft preparation and writing—review and editing. DBM: methodology, formal analysis and investigation and writing—review and editing. RPT and MK: supervision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required as the identities of patients is not identifiable within the study.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo Hospital (Ref. No. 20-05-0518).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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