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ORIGINAL ARTICLE

Interventional radiology treatment for vascular and biliary complications following pediatric living donor liver transplantation – a retrospective study

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SUMMARY

There are few long-term outcome reports for interventional radiology (IVR) treatments for vascular and biliary complications following pediatric living donor liver transplantation (LDLT). Herein, we presented our institution's experience and investigated the efficacy and issues of long-term outcome with IVR treatments. Between May 2001 and September 2016, 279 pediatric LDLTs were performed. The median age at LDLT was 1.4 years old, and the median observation period was 8.2 years. All the biliary reconstructions at LDLT were hepaticojejunostomy. The IVR treatments were selected as endovascular, radiological, or endoscopic interventions. Post-transplant hepatic vein, portal vein, hepatic artery, and biliary complications were present in 7.9%, 14.0%, 5.4%, and 18.3%, respectively. IVR treatment was the first treatment option in 81.8%, 94.9%, 46.7%, and 94.1%, respectively. The recurrence and cure rates following IVR treatment were 42.1%, 21.1%, 44.4%, and 34.0% and 84.2%, 97.4%, 100%, and 88.0%, respectively. The graft survival rates in patients with and without post-transplant vascular and biliary complications were 94.4% and 90.6%, respectively ($P = 0.522$). The IVR treatments for vascular and biliary complications following pediatric LDLT are the first choice option. Although the recurrence following IVR treatment is a major problem and it is necessary to carefully perform long-term follow-up, IVR treatments have good treatment outcomes.

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Key words
interventional radiology, pediatric living donor liver transplantation, vascular and biliary complications

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Introduction

Liver transplantation (LT) is an established curative treatment for pediatric patients with end-stage liver disease or acute liver failure. However, vascular and biliary complications following LT are still frequent despite improvements and innovations in surgical techniques [1], and these complications occasionally lead to graft failure or even death.

The cause of post-transplant vascular and biliary complications is multifactorial, but these complications are often related to anastomotic stricture, thrombosis, or

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leakage as a result of transplant surgery. The reported incidence of hepatic vein, portal vein, hepatic artery, and biliary complications following pediatric LT are 5%, 4–8%, 11–20%, and 20–40%, respectively [2]. Although interventional radiology (IVR) treatments for vascular and biliary complications following pediatric LT are the first treatment option, there are few long-term outcome reports.

Herein, we presented our institution's experience and investigated the efficacy and issues of a long-term outcome with IVR treatments for vascular and biliary complications following pediatric living donor liver transplantation (LDLT).

Materials and methods

Patients

Between May 2001 and September 2016, 283 LDLTs were performed for 275 pediatric recipients with end-stage liver disease or acute liver failure at the Department of Transplant Surgery, Jichi Medical University, Japan. Of these, three recipients underwent LDLT with a choledochocholedochostomy, and one recipient underwent LDLT using a posterior graft; these recipients were excluded from this study. Therefore, a total of 279 LDLTs with a hepaticojejunostomy for 271 pediatric recipients were examined in this study. The demographic data for the recipients and information on the grafts are given in Table 1. The median observation period was 8.2 years (range 0.3–15.6 years). Approval to conduct this study was obtained from the Ethics Committees of Jichi Medical University (Ethics Committee Approval Case Number 15-106).

LDLT surgical procedure

The type of donor hepatectomy was determined according to the recipient standard liver volume, recipient body weight and graft volume by preoperative computed tomographic volumetry [3]. If the estimated donor left lateral segment volume by preoperative computed tomographic volumetry was greater than 5% of the graft to recipient weight ratio, such as in neonates, a segment 2 or 3 monosegment graft was selected [4]. The donor biliary anatomy was evaluated using intraoperative real-time cholangiography three times. A routine donor hepatectomy was performed using intraoperative ultrasonic guidance. The donor left hilar plate was transected using a scalpel. The graft was preserved with University of Wisconsin solution, and if necessary, a hepatic vein venoplasty was performed on the back table. If the actual left lateral segment graft volume was greater than 120% of the recipient standard liver volume, an *ex vivo* partial resection from the distal side of the graft was performed.

For the recipient operation, Mercedes-Benz or transverse incisions were made, and total hepatectomy was performed. In many infants, after total hepatectomy, the

Table 1. Demographic data for the recipients and information on the grafts.

Period	May, 2001–September, 2016
Number of cases	279 cases (271 recipients)
Gender	Male: 106 (38.0%), Female: 173 (62.0%)
Age (years old)	1.4 (0.1–16.5)
Body weight (kg)	9.8 (2.6–65.0)
Original disease	Biliary atresia: 200 (71.7%), ornithine transcarbamylase deficiency: 17 (6.1%), graft failure: 11 (3.9%), Alagille syndrome: 10 (3.6%), fulminant hepatitis: 6 (2.2%), others: 35
ABO compatibility	Identical: 183 (65.6%), compatible: 47 (16.8%), incompatible: 49 (17.6%)
PELD/MELD score	6.2 (−25.6–37.0)
Type of graft	Left lateral segment: 196 (70.3%), left lobe: 54 (19.4%), segment 2 monosegment: 12 (4.3%), left lobe + caudate lobe: 11 (3.9%), reduced left lateral segment: 5 (1.8%), segment 3 monosegment: 1 (0.3%)
Observation period (year)	8.2 (0.3–15.6)

MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease.

recipient right, middle and left hepatic veins were formed into a single orifice, which was then anastomosed end-to-end to the graft hepatic vein. The portal vein was reconstructed between the recipient portal vein (branch patch venoplasty, main portal vein, or interposition graft) and the graft left portal vein. Hepatic artery reconstruction was performed using microsurgical techniques. Biliary reconstruction was performed using a Roux-en-Y hepaticojejunostomy. Intraoperative color Doppler ultrasonography was performed to assess blood flow velocity and pattern after vascular reconstruction.

Post-transplant anticoagulation treatment and imaging surveillance

During the post-transplant period, we routinely performed an anticoagulation treatment and Doppler ultrasonography. Anticoagulation treatment was started using intravenous dalteparin sodium (100 U/kg/day) from a few postoperative days. If vascular flow was sufficient, we usually withdrew the anticoagulation treatment on postoperative day 14.

The imaging surveillance methods used for follow-up were Doppler ultrasonography and contrast-enhanced computed tomography (CT). Doppler ultrasonography was performed routinely twice per day until hospital discharge, and thereafter at 1, 3, 5 and 9 months and then every 6 months after LDLT. The CT examination was performed routinely at 1, 2, 6 and 12 months and then every 12 months after LDLT. We evaluate vascular and biliary complications, graft steatosis, and volumetry of graft liver and spleen by CT examination. Magnetic resonance cholangiopancreatography was performed as the evaluation of biliary complications if possible.

Diagnosis and treatments for post-transplant vascular and biliary complications

We defined the post-transplant vascular and biliary complications when radiological, endoscopic, or surgical interventions were performed for treatments. The IVR treatments for vascular and biliary complications were selected endovascular interventions, percutaneous transhepatic biliary drainage (PTBD), or endoscopic interventions under double-balloon enteroscopy (DBE). We performed transjugular venous endovascular interventions for recipients with hepatic vein complications [5], transhepatic portal venous endovascular interventions for recipients with the portal vein complications [6,7], transfemoral arterial endovascular interventions for recipients with the hepatic artery complications [8], and endoscopic interventions under DBE or PTBD for recipients with biliary complications [9]. If percutaneous transhepatic portal vein approach or transfemoral arterial hepatic artery approach was difficult by early stage after LDLT or neonates, we tried to perform IVR treatments via trans-umbilical vein, gastroduodenal artery, or another hepatic artery under a laparotomy. If portal vein thrombosis was diagnosed at a percutaneous transhepatic portography, we tried to perform IVR treatments using the Rendezvous penetration method under a superior mesenteric arteriography. When hepaticojejunal anastomotic obstruction is diagnosed, treatment using the Rendezvous penetration method with DBE and percutaneous transhepatic cholangioscopy was performed after PTBD [10].

Repeated complications, a short-term recurrence of complications, and difficulty with IVR treatments at recurrence were defined as intractable vascular and biliary complications. Thereafter, for recipients with intractable complications, stent placement treatments were performed [8,9,11].

The post-IVR anticoagulation treatment for venous complications included a three-agent combination regimen: dalteparin sodium (100 U/kg/day) by intravenous administration and aspirin and warfarin by oral administration to prevent recurrent complications [7]. Aspirin was given at a dose of 2 mg/kg/day from post-IVR day 1 and continued for 3 months. Warfarin was given at an initial dose of 0.1 mg/kg/day from the day of IVR, and the warfarin dose was adjusted for the following 3 months as needed to maintain an international normalized ratio of prothrombin time between 1.5 and 2.0. The discontinuation of warfarin was considered based on CT examination at post-IVR month 6. When metallic stent placement treatment was performed for intractable venous complications, warfarin was given throughout life. Regarding post-IVR treatments for hepatic artery complications, prostaglandin E1 (0.01 μg/kg/min) administered intravenously was used to prevent recurrent complications [8]. The discontinuation of prostaglandin E1 was considered on post-IVR day 14. When metallic stent placement treatment was performed for intractable hepatic artery complications, aspirin was given throughout life [11]. When plastic stent placement treatment was performed for intractable biliary complications, the plastic stent was removed at post-IVR month 6 [9].

Results

There are no serious complications associated with IVR treatments for vascular and biliary complications.

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Post-transplant hepatic vein complications were present in 22 cases (7.9%), including stricture in 18 cases and thrombosis in four cases. Re-laparotomy as the first treatment option was performed for four cases with thrombosis (re-positioning of the graft in two cases, thrombectomy in one case, and re-LDLT in one case). IVR treatment was performed median one time (1–21 times) per case for 19 cases (including stent placement in two cases). IVR treatment was the first treatment option in 18 cases (81.8%) and IVR treatment was performed for one case with hepatic vein stricture after re-anastomosis for hepatic vein thrombosis. The recurrence rate and cure rate of IVR treatment for hepatic vein complications were 42.1% and 84.2%, respectively. Three cases with IVR treatment failure performed re-LDLT in one case and wait re-transplantation in two cases.

Post-transplant portal vein complications were present in 39 cases (14.0%), including stricture in 37 cases and thrombosis in two cases. Re-laparotomy as the first treatment option was performed for two cases with thrombosis (thrombectomy in two cases). IVR treatment was performed median one time (1–4 times) per case for 38 cases (including stent placement in four cases). IVR treatment was the first treatment option in 37 cases (94.9%) and IVR treatment was performed for one case with portal vein stricture after thrombectomy for portal vein thrombosis. The recurrence rate and cure rate of IVR treatment for portal vein complications were 21.1% and 97.4%, respectively. One case with IVR treatment failure performed re-LDLT, but died due to sepsis after re-LDLT.

Post-transplant hepatic artery complications were present in 15 cases (5.4%), including thrombosis or stricture in 14 cases and spasm or compression by abdominal fluid in one case. Re-laparotomy as the first treatment option was performed for eight cases with thrombosis or stricture (thrombectomy in six cases and re-anastomosis in two cases). IVR treatment was performed median two times (1–3 times) per case for nine cases (including stent placement in one case). IVR treatment was the first treatment option in seven cases (46.7%) and IVR treatment was performed for two cases with hepatic artery stricture after thrombectomy for hepatic artery thrombosis. The recurrence rate and cure rate of IVR treatment for hepatic artery complications were 44.4% and 100%, respectively.

Post-transplant biliary complications were present in 51 cases (18.3%), including stricture in 49 cases, biliary leakage in one case, and residual lost stent in one case. Re-laparotomy as the first treatment option was performed for three cases with anastomotic stricture or leakage (re-anastomosis in three cases). IVR treatment was performed median one time (1–10 times) per case for 50 cases (including stent placement in six cases and the rendezvous penetration method in three cases). IVR treatment was the first treatment option in 48 cases (94.1%); PTBD in 30 cases and DBE in 18 cases. In addition, IVR treatment under DBE was performed for two cases with recurrent biliary stricture after re-anastomosis for biliary anastomotic stricture. The recurrence rate and cure rate of IVR treatment for biliary complications were 34.0% and 88.0%, respectively. Six cases with IVR treatment failure

Table 2. Outcomes of IVR treatments for vascular and biliary complications following pediatric LDLT at our institution.

Complications	IVR treatment rate as first treatment (%)	Recurrence rate after first IVR treatment (%)	Times of IVR treatment (median)	Stent placement treatment (number)	Graft failure (number)	Cure rate of IVR treatment (%)
Hepatic vein complications (n = 22; 7.9%)	81.8	42.1	1 time (1–21)	2 (thrombus; 2)	3	84.2
Portal vein complications (n = 39; 14.0%)	94.9	21.1	1 time (1–4)	4	1	97.4
Hepatic artery complications (n = 15; 5.4%)	46.7	44.4	2 times (1–3)	1	0	100
Biliary complications (n = 51; 18.3%)	94.1	34.0	1 time (1–10)	6 (removal; 6)	4	88.0

IVR, interventional radiology; LDLT, living donor liver transplantation.

performed re-LDLT in three cases, performed re-anastomosis in one case, wait re-anastomosis in one case, and wait re-transplantation in one case.

The graft survival rates in patients with and without post-transplant vascular and biliary complications were 94.4% and 90.6%, respectively ($P = 0.522$). The causes of graft failure associated with vascular and biliary complications were biliary complications in four cases, hepatic vein complications in three cases, and portal vein complications in one case (Table 2).

Discussion

Post-transplant vascular and biliary complications are major issues that need to be resolved and may occasionally lead to lethal problems, including graft failure. In cases of adult LT, endovascular interventions and conventional endoscopic interventions for these complications have become the first-line treatment because they are less invasive and more convenient for recipients compared with surgical interventions [12–22]. However, in cases of pediatric LT, endovascular instruments and techniques are insufficient, and conventional endoscopy does not approach the biliary anastomotic site because of Roux-en-Y hepaticojejunostomy. In recent years, with advances in endovascular and endoscopic instruments and techniques, reports of novel endovascular and endoscopic treatments for vascular and biliary complications have increased. Therefore, endovascular and endoscopic interventions may become the first-line treatment, even in pediatric recipients [5–11,23–30].

At our institution, the first-line treatment for post-transplant vascular and biliary complications in pediatric recipients is IVR treatment, and the rate of IVR treatment as the first treatment with hepatic vein complications was 81.8%, with portal vein complications was 94.9%, with hepatic artery complications was 46.7%, and with biliary complications was 94.1%. The conclusive cure rate with IVR treatment in hepatic vein complications was 84.2%, in portal vein complications was 97.4%, in hepatic artery complications was 100%, and in biliary complications was 88.0% (Table 2). Furthermore, it has been reported that the cure rate from IVR treatment for hepatic vein, portal vein, and biliary complications was greater than 85% (Table 3) [23–30]. In addition, in the present study, the graft survival rates in patients with and without post-transplant vascular and biliary complications were 94.4% and 90.6%, respectively ($P = 0.522$). On the other hand, there are no serious complications associated with IVR treatments for vascular and biliary complications. Therefore, IVR

Table 3. Recurrence and cure rate of IVR treatments for vascular and biliary complications following pediatric liver transplantation.

Institutions	Hepatic vein complications	Portal vein complications	Hepatic artery complications	Biliary complications
Japan Kyoto University [12–14]	Rec. rate; 41.7% Cure rate 85.4%	Rec. rate; 25.6% Cure rate 86.0%	–	Rec. rate; 41.7% Cure rate 85.4% (PTBD treatment)
Korea Seoul National University [15]	Rec. rate; 41.7% Cure rate 85.4%	–	–	–
Taiwan Kaohsiung Chang Gung Memorial Hospital [16,17]	–	Cure rate 100% (Stent placement treatment)	–	Cure rate 85.4% (PTBD treatment)
Italy ISMETT [18]	–	–	Rec. rate; 20.0% Cure rate 60.0%	–
Brazil Sírio Libanês Hospital [19]	–	–	–	Rec. rate; 41.7% Cure rate 85.4% (PTBD treatment)
Our institution	Rec. rate; 42.1% Cure rate 84.2%	Rec. rate; 21.1% Cure rate 97.4%	Rec. rate; 44.4% Cure rate 100%	Rec. rate; 34.0% Cure rate 88.0% (PTBD and DBE treatment)

DBE, double-balloon enteroscopy; IVR, interventional radiology; PTBD, percutaneous transhepatic drainage; Rec., recurrence.

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treatments for hepatic vein, portal vein, and biliary complications following pediatric LDLT are the first choice option and have good treatment outcomes.

Regarding IVR treatments for hepatic artery complications, endovascular interventions remain controversial in view of the potential risks of hemorrhage in the early post-transplant period and their uncertain long-term patency. There have been few reports and a low cure rate (Table 3) [29]. However, we reported that endovascular interventions in the early post-transplant period were safer and less invasive than surgical interventions [8]. In addition, the cure rate from endovascular interventions was 100% in the present study. On the other hand, the rate of IVR treatment as the first treatment was low because there was compressive or spastic artery hypoperfusion due to hematoma or abscess as the causes of hepatic artery complications. We decided that the only exclusion criterion for IVR treatments should be the presence of compressive or spastic artery hypoperfusion due to hematoma or abscess and that age should not be considered a contraindication. Therefore, the IVR treatments for hepatic artery complications following pediatric LDLT are a significant challenge for the future.

The IVR treatments for vascular and biliary complications following pediatric LT remain controversial due to recurrence. In the present study, the recurrence rate following IVR treatments was 42.1% for hepatic vein complications, 21.1% for portal vein complications, 44.4% for hepatic artery complications, and 34.0% for biliary complications (Table 2). It has been reported that the recurrence rate following IVR treatments was greater than 20% (Table 3) [12–15,18,19]. It is difficult for recipients with recurrent and intractable vascular and biliary complications to receive additional treatments because the radical treatment is re-laparotomy and re-transplantation. Therefore, recurrence of these complications remains important problems to solve. As we experienced a case of recurrent portal vein stricture with portal vein thrombosis following endovascular balloon dilatation for portal vein stricture, the post-IVR anticoagulation treatment for venous complications included a three-agent combination regimen: dalteparin sodium by intravenous administration and aspirin and warfarin by oral administration to prevent recurrent complications [7]. The recurrence rate of portal vein stricture following IVR treatment was significantly decreased [7]. In addition, if recurrent portal vein stricture occurs, we perform the IVR treatment using stent placement. However, although stent placement for recurrent portal vein stricture is effective, stent placement for recurrent hepatic vein stricture remains a controversial because all our recipients suffered from a thrombotic occlusion in stent. As for recurrent biliary stricture, we may perform the IVR treatment using internal stent placement under DBE for the purpose of preventing re-stricture after balloon dilatation [9]. However, internal stent placement for recurrent biliary stricture causes stent occlusion due to biliary cast, leads to calculus formation, and also leads to granulation due to mechanical stimulation, and therefore, periodic replacement or removal is necessary, requiring repeated DBE [9]. Therefore, we think that early diagnosis and treatment of biliary strictures should be performed as DBE can be performed on pediatric recipients with mild intrahepatic bile duct dilatation.

In conclusion, IVR treatments for vascular and biliary complications following pediatric LDLT are the first choice option. Although the recurrence following IVR treatment is a major problem and it is necessary to carefully perform long-term follow-up, IVR treatments have good treatment outcomes. Further studies of our treatment strategy and the accumulation of prospective experience are necessary.

Authorship

SY: designed and performed study. SY, KT, HY, YN, ON, IY, OK, OS, ID and UK: collected data and discussion. SY: analyzed and interpreted the data. SY: wrote the paper. MK: revised the manuscript.

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Conflict of interest

No commercial organizations. This manuscript has no conflict of interest to disclose as described by the Transplant International.

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