Long-Term Outcome of Percutaneous Biliary Interventions for Biliary Anastomotic Stricture in Pediatric Patients after Living Donor Liver Transplantation with Roux-en-Y Hepaticojejunostomy

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ABSTRACT

Purpose: To retrospectively evaluate long-term outcomes of percutaneous transhepatic biliary drainage (PTBD) followed by balloon dilation and placement of an internal drainage tube for anastomotic stricture in pediatric patients who underwent living donor liver transplantation (LDLT) with Roux-en-Y hepaticojejunostomy (RYHJ).

Materials and Methods: Fifty-two patients (23 male, 29 female; median age, 5 y) with anastomotic biliary stricture were treated with PTBD followed by balloon catheter dilation and long-term placement of an internal drainage tube, which was removed upon cholangiographic confirmation of free flow of bile into the small bowel. Clinical success, tube independence rate, risk factors of recurrent biliary stricture, and patency rates were evaluated.

Results: Thirty-nine patients (75%) had no stricture recurrence. Of 13 patients (25%) with recurrence, six were treated again with the same percutaneous biliary interventions and showed no further recurrence. Clinical success was noted in 43 of 52 patients (83%). Drainage tubes were removed from 49 patients (94%). Multivariate logistic regression analysis indicated that serum alanine aminotransferase level > 53 IU/L at discharge after the initial series of percutaneous biliary interventions was a significant risk factor for recurrent biliary stricture (P = .002). Kaplan–Meier analysis showed 1-, 3-, 5-, and 10-year primary and primary assisted patency rates of 75%, 70%, 70%, and 68%, and 94%, 92%, 88%, and 88%, respectively.

Conclusions: PTBD followed by balloon dilation and internal drainage may be an effective treatment for anastomotic biliary stricture after pediatric LDLT with RYHJ.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, $GGT = \gamma$ -glutamyl transpeptidase, LDLT = living donor liver transplantation, PTBD = percutaneous transhepatic biliary drainage, PTC = percutaneous transhepatic cholangiography, RYHJ = Roux-en-Y hepaticojejunostomy

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Liver transplantation is an established treatment for endstage liver disease (1). Living donor liver transplantation (LDLT) has been widely performed, and the long-term survival outcomes of pediatric patients who have undergone LDLT are satisfactory (1–3). Although improvements in surgical techniques and immunosuppression have contributed to improved outcomes after transplantation, biliary complications remain common and can be serious, with morbidity and mortality rates as high as 19% (4–6).

Anastomotic biliary stricture is the most common biliary complication. Some studies have suggested that

biliary stricture occurs more frequently in LDLT recipients than in deceased-donor liver transplant recipients because of the small diameter of the anastomotic portion of the bile duct, anatomic diversity of bile ducts, or the complicated nature of the surgical procedure (7-9). There are two strategies for treating anastomotic strictures: via the endoscopic retrograde approach (10) or the percutaneous transhepatic approach (11). The endoscopic retrograde approach is feasible for posttransplantation patients with a duct-to-duct anastomosis. Endoscopic stent placement has been reported to be effective for biliary strictures in posttransplantation patients (12). Because the most common disease in pediatric LDLT recipients is biliary atresia, most undergo Kasai surgery and Roux-en-Y hepaticojejunostomy (RYHJ). Although Azeem et al (13) demonstrated the efficacy of endoscopic retrograde cholangiography with a single balloon in the treatment of biliary stricture in posttransplantation patients with RYHJ, they reported that endoscopic retrograde cholangiography was more difficult in LDLT than in deceased-donor liver transplantation. Therefore, percutaneous transhepatic biliary drainage (PTBD) is a first-line treatment.

The purpose of the present retrospective study was to evaluate the effectiveness of percutaneous biliary interventions in the management of anastomotic biliary stricture following pediatric LDLT with RYHJ.

MATERIALS AND METHODS

Our institutional review board approved this retrospective study and waived the informed consent requirement.

Patients

Between October 1997 and August 2014, 539 pediatric patients (age < 18 y) underwent LDLT in the surgical department. During postoperative follow-up, biliary anastomotic stricture was confirmed with percutaneous transhepatic cholangiography (PTC) in 57 patients. The presence of biliary stenosis was suspected in the presence of biochemical cholestasis and dilated intrahepatic bile ducts that appeared on follow-up abdominal ultrasonography (US) and/or computed tomography. Chronic rejection was excluded by needle liver biopsy. Arterial thrombosis, portal venous anastomotic stenosis, or hepatic venous outflow obliteration was excluded with Doppler US. The inclusion criterion for anastomotic biliary stricture was a focal narrowing at the anastomotic site with a proximal dilation of the bile duct. The exclusion criterion was long, diffuse, or multiple strictures of intrahepatic biliary ducts or stones.

Of the 57 patients with successful PTC, 54 were treated with a series of percutaneous biliary interventions: PTBD followed by balloon dilation and placement of an internal drainage tube. The other three patients underwent placement of an external drainage tube at PTBD, as placement of the internal drainage tube was

unsuccessful as a result of the tight anastomotic stricture. The three patients with unsuccessful internal drainage underwent surgical reanastomosis of RYHJ and were excluded from this study. The long-term outcomes were evaluated for 52 of the patients who underwent the aforementioned percutaneous biliary interventions, as two patients were lost to follow-up. The baseline characteristics of the 52 patients are shown in Table 1. There were 23 male patients and 29 female patients, whose ages ranged from 6 months to 18 years (median age, 5 y). All 52 patients had received left liver grafts from living donors and underwent reconstruction of RYHJ. The follow-up periods after the first series of percutaneous biliary interventions in the 52 patients ranged from 5 months to 206 months (mean, 100 mo).

Procedures

Procedures were performed by four of the study authors (T.S, M.Y., K.S., and R.I.) with 29, 10, 6, and 6 years of experience in interventional radiology, respectively. Percutaneous interventions were performed under general anesthesia in 50 patients < 15 years of age and under local anesthesia with 1% lidocaine (Xylocaine; Astra-Zeneca, Osaka, Japan) in two patients ≥ 15 years of age. Access to the biliary duct of the left or lateral segment was made under US guidance with a 21-gauge needle. If PTC showed an anastomotic stricture, the bile duct was catheterized by using a SKATER Introducer Set (Argon Medical Devices, Plano, Texas) or Cope Mandril Guide (Cook, Bloomington, Indiana). The stricture was crossed with a 0.035-in angled hydrophilic guide wire (Radifocus; Terumo, Tokyo, Japan) and a 5-F catheter. Dilation of the anastomotic stricture was performed by using a balloon (diameter, 4-10 mm;

Table 1. Patient Characteristics	
Characteristic	Value
Sex	
Male	23
Female	29
Age at first percutaneous biliary intervention (y)	
Range	0.5–18
Median	5
Mode of transplantation	
Lateral segment	48
Left lobe	4
Primary disease	
Biliary atresia	42
Hepatoblastoma	3
Wilson disease	2
Fulminant hepatitis	1
Liver cirrhosis	1
Langerhans cell histiocytosis	1
Hypergalactosemia	1
Hypertyrosinemia	1

Powerflex; Cordis, Bridgewater, New Jersey). The diameter of the balloon was matched to the diameter of the intrahepatic bile duct on the hepatic side of the stricture. The balloon was placed across the stricture and inflated for 180 seconds at an atmospheric pressure of 10 atm. Then, an 8.5-F internal/external drainage tube (Pigtail catheter; Cook) was placed across the anastomotic stricture.

Serial exchanges for a larger 14-F or 16-F drainage tube, with or without balloon dilations, were routinely performed at 1-2-week intervals. At a follow-up session, cholangingraphy was performed to evaluate the persistence of the stricture. When no residual stenosis was noted and free passage of contrast medium across the anastomotic site was observed on cholangiography, we diagnosed the biliary tracts as patent. Then, after resolution of the laboratory data was confirmed, the tube was removed. Following removal of the drainage tube, the patients were evaluated by clinical follow-up, abdominal US, routine laboratory tests every 2-3 months, and liver biopsy when needed. If recurrence of anastomotic stricture was suspected, PTC was performed. When a focal narrowing at the anastomotic site and the absence of fluent passage of contrast medium into the intestinal bowel was observed on PTC, recurrence was confirmed. For patients in whom recurrent anastomotic stricture was diagnosed, the aforementioned series of percutaneous interventions were repeated. During the biliary intervention series, one to four sessions of balloon dilation were performed: one session in six patients, two in 38, three in seven, and four in one.

Study Definitions

Two of the authors (R.I. and T.S.) retrospectively reviewed the patients' medical records and evaluated clinical success, tube independence rate, risk factors for recurrent biliary stricture after the initial percutaneous biliary interventions, and patency rates.

Clinical success was defined as resolution or marked improvement of clinical symptoms, including fever or abdominal pain, and improvement of laboratory findings: serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, γ -glutamyl transpeptidase (GGP), and alkaline phosphatase (ALP). These parameters were verified by clinical records and laboratory data, which were

compared immediately before the percutaneous biliary intervention and at the end of the follow-up period. In addition, the patients who died before August 31, 2014, were accepted as cases of clinical failure.

Tube independent rate was defined as the rate at which the patient could undergo tube removal after symptoms were diminished and laboratory findings had improved. Data were evaluated and estimated at the end of the follow-up period or at the time of patient death or repeat transplantation. Balloon dilatation was performed at the initial visit, and exchanges for a larger drainage tube were routinely performed at 1-week intervals thereafter.

Risk Factors for Recurrent Biliary Stricture after Initial Percutaneous Biliary Interventions

Possible risk factors for recurrent biliary stricture were evaluated by univariate and multivariate logistic regression analyses (Tables 1–3). Patency rate was estimated by Kaplan—Meier analysis. Primary patency was defined as the interval between placement of an internal drainage tube and appearance of a recurrent biliary stricture necessitating percutaneous biliary interventions. Primary assisted patency was defined as the interval between placement of an internal drainage tube and the discontinuation of treatment with repeated percutaneous interventions. Repeated percutaneous biliary interventions—PTBD followed by balloon dilation and internal drainage tube placement for restenosis—were included in the evaluation of primary assisted patency. Data were evaluated and estimated at the time of patient death or repeat transplantation.

Statistical Analysis

Data processing and analyses were performed with commercially available software (MedCalc version 12.7.8.0; MedCalc, Ostend, Belgium). Laboratory findings of liver function before and after percutaneous biliary intervention were compared by using a paired t test. Risk factors for recurrent biliary stricture after the initial series of percutaneous biliary interventions were evaluated by univariate logistic regression analysis. Factors showing significant association with recurrence of biliary strictures were further investigated by using a

Table 2. Laboratory Data of Liver Function before and after the Initial Series of Percutaneous Biliary Interventions in 52 Patients

Variable	Before Initial Biliary Interventions	At Discharge after Initial Biliary Interventions
AST (IU/L)	90.4 ± 98.8	61.0 ± 50.9
ALT (IU/L)	98.3 ± 106.5	59.9 ± 47.3
Total bilirubin (mg/dL)	1.3 ± 1.4	1.2 ± 2.4
Direct bilirubin (mg/dL)	0.5 ± 1.0	0.5 ± 1.8
GGT (IU/L)	294.2 ± 306.3	163.5 ± 195.9
ALP (IU/L)	1,755.9 ± 1,105.2	1,718.1 ± 2,017.8

Note-Values presented as mean \pm standard deviation.

Tahla 3	Rick Factors	for Recurrent Rili:	iry Stricture afte	r Initial Spripe	of Percutaneous Biliary	/ Interventions

Variable	No Recurrence (n = 39)	Recurrence (n = 13)	
Sex			
Male	17 (73.9)	6 (26.1)	
Female	22 (75.9)	7 (24.1)	
Age at initial percutaneous biliary intervention (y)	5.4 ± 4.1	5.7 ± 6.2	
Primary disease			
Biliary atresia	30 (71.4)	12 (28.6)	
Others	9 (90)	1 (10)	
Period between LDLT and first biliary intervention (d)	901.2 ± 982	$958.2 \pm 1,984.9$	
Drainage time (d)	121.5 ± 158	71.8 ± 53.4	
Hospital stay after drainage tube removal (d)	9.9 ± 20.6	8.2 ± 9.6	
No. of balloon dilations	2.1 ± 0.6	2.1 ± 0.6	
No. of tube changes	$3.4~\pm~0.6$	3.6 ± 0.8	
Laboratory data at discharge			
AST (IU/L)	52.4 ± 47.2	86.8 ± 54.7	
ALT (IU/L)	47.7 ± 36.9	96.2 ± 57.3	
Total bilirubin (mg/dL)	0.9 ± 1.4	1.9 ± 6.4	
Direct bilirubin (mg/dL)	0.4 ± 1.2	1.0 ± 2.9	
GGT (IU/L)	134.6 ± 190.3	250 ± 193.9	
ALP (IU/L)	1,565.9 ± 2,965.9	2,174.6 ± 1,440.6	

Note–Values presented as mean \pm standard deviation where applicable. Values in parentheses are percentages. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ -glutamyl transpeptidase; LDLT = living donor liver transplantation.

multivariate logistic regression analysis. A final model was determined by including factors that remained significant in the multivariate logistic regression after forward and backward selection. A P value < .05 was considered to indicate a significant difference. Receiver operating characteristic analysis was performed, and the optimal cutoff point was determined by the values that maximized the Youden index (sensitivity and specificity). The patency rate was estimated by Kaplan–Meier analysis.

RESULTS

PTBD followed by balloon dilation and placement of an internal drainage tube was performed in 52 patients (Fig 1). After tube removal, 39 patients (75%) had no recurrence (Fig 2) and 13 patients (25%) showed recurrent stricture. In 39 patients, an internal drainage tube was placed for 1-31 months (median, 4 mo) during the initial series of percutaneous biliary interventions and was then removed. No recurrent biliary strictures were observed for 6-150 months (median, 49 mo). However, two of the 39 patients died as a result of acute rejection, and one died as a result of systemic recurrence of hepatoblastoma. The remaining 13 patients showed recurrent stricture at 0.3-63 months (median, 12 mo) after removal of the drainage tube. Among the 13 patients, six underwent a second series of percutaneous biliary interventions, during which an internal drainage tube was placed for 1-12 months (median, 4.8 mo) and was later removed. These patients showed no recurrent biliary stricture for another 45–135 months (median, 84.8 mo). The other seven patients,

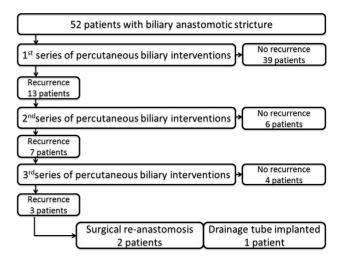


Figure 1. Results in 52 patients confirmed with a biliary anastomotic stricture.

however, showed another recurrent stricture at 0.4–60 months (median, 19.7 mo) after removal of the second drainage tube. Four of these seven patients underwent a third series of percutaneous biliary interventions, during which an internal drainage tube was placed for 1–2.9 months (median, 1.6 mo) and was later removed. These patients showed no recurrent stricture for another 1.4–6 months (median, 4.2 mo), but two of the four patients eventually underwent repeat transplantation as a result of chronic rejection. Of the remaining three patients without relief of biliary stricture, two underwent surgical repeat RYHJ without removal of the drainage tube, and one was

implanted with a third drainage tube subcutaneously. No life-threatening major complications were observed. Figure 2.

Clinical Success

Alleviation of clinical symptoms and improvement in laboratory data were observed in 43 of 52 patients (83%). Of the remaining nine patients, two underwent surgical reanastomosis and one had subcutaneous implantation of a drainage tube because the stricture was not resolved. Among the other six patients, two died of liver failure, one died of hepatoblastoma recurrence, one died of massive hemoptysis, and two underwent repeat transplantation because of chronic rejection. The serum levels (mean ± standard deviation) of AST, ALT, total bilirubin, direct bilirubin, GGP, and ALP of all 52 patients before the initial series of percutaneous biliary interventions and at discharge from the hospital after the series of interventions are summarized in Table 2. Serum ALT (P = .013) and GGP levels (P = .0002) were significantly improved after the biliary interventions.

Tube Independence Rate

Removal of the drainage tube was achieved in 49 of 52 patients (94%). Of the other three patients in whom the drainage tube could not be removed, two underwent surgical reanastomosis and one had a drainage tube implanted subcutaneously. The total time that each patient did not have an indwelling tube ranged from 5 to 203 months (median, 49 mo).

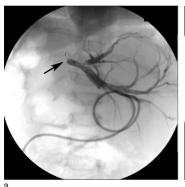
Risk Factors

There were 39 patients with no recurrent stricture after the initial series of percutaneous biliary interventions and 13 patients who showed a recurrent stricture after the initial interventions. Risk factors for recurrent biliary stricture after the initial percutaneous biliary interventions are summarized in **Tables 3** and **4**. The univariate logistic regression analysis showed that there were significant differences in recurrent rates according to the ALT (P=.002) and AST (P=.045) levels. AST and ALT levels at discharge were integrated into the multivariate analysis from the univariate analysis. Multivariate analysis revealed that ALT level at discharge after the initial percutaneous interventions (P=.002) was an independent factor associated with recurrent biliary stricture. The receiver operating characteristic curve showed that the estimated sensitivity and specificity were 76.9% and 76.9%, respectively, when an ALT cutoff value of 53 IU/L was applied.

Patency rates are shown in **Figure 3**. The primary patency rates at 1, 3, 5, and 10 years after initial drainage tube placement were 75%, 70%, 70%, and 68%, respectively. The primary assisted patency rates at 1, 3, 5, and 10 years after initial drainage tube placement were 94%, 92%, 88%, and 88%, respectively.

DISCUSSION

Although biliary complication rates following liver transplantation have been decreasing as a result of improvements in surgical techniques, they remain one of the most important problems associated with liver transplantation because of their high associated morbidity and mortality rates (14). Various biliary complications, including biliary stricture, biliary leak, biliary stones, biloma, and hemobilia have been noted in posttransplantation patients. The two main biliary complications are biliary leaks (which usually occur in the immediate postoperative period) and late-onset biliary strictures (15,16). Biliary strictures are commonly noted at the anastomotic site, although nonanastomotic stricture associated with hepatic artery stenoocclusive disease, primary sclerosing cholangitis, or blood-type incompatibility has been seen (17,18). Without proper and timely treatment, an anastomotic stricture can lead to liver cirrhosis or graft failure. Therefore, it is important to diagnose and treat anastomotic stricture at an early stage.



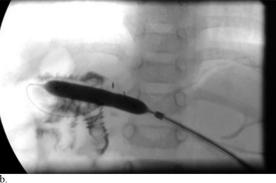


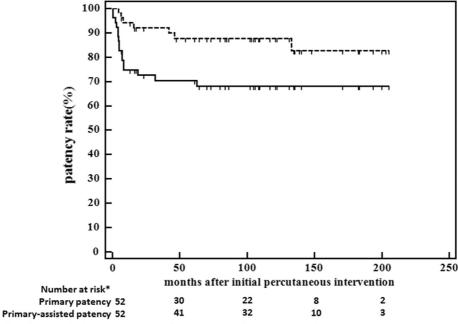


Figure 2. Images from a 2-year-old boy who had undergone LDLT 20 months previously and was suspected of having a biliary anastomotic stricture in view of a fever, increase in serum ALT and AST levels, and slightly dilated intrahepatic bile ducts seen on abdominal US. **(a)** PTC shows an anastomotic stricture (arrow). **(b)** Fluoroscopic view during balloon dilation. Balloon dilation was performed at 10 atm for 3 minutes with a 6-mm-diameter balloon catheter. **(c)** Fluoroscopic view shows an 8.5-F internal/external drainage tube placed across the anastomotic stricture. After serial exchange with a larger-diameter catheter (16 F), the drainage tube was removed. No recurrent stricture was noted for 117 months after the biliary interventions.

Table 4. Logistic Regression Analysis of Variables of Recurrent Biliary Stricture after Initial Percutaneous Intervention: Final Models after Forward and Backward Selection

	Univariate		Multivariate	
Variable	OR (95% CI)	P Value	OR (95% CI)	P Value
Sex	1.11 (0.31–3.91)	.872	_	_
Age at first percutaneous biliary intervention (y)	1.00 (0.99-1.01)	.871	_	_
Primary disease	1.90 (0.36-10.07)	.433	_	-
Period between LDLT and first biliary intervention (d)	1.00 (1.00-1.00)	.89	_	_
Drainage time (d)	0.99 (0.98-1.00)	.154	_	_
Hospital stay after drainage tube removal (d)	0.99 (0.96-1.03)	.76	_	-
No. of balloon dilations	0.78 (0.25-2.44)	.67	_	-
No. of tube changes	1.81 (0.77-4.26)	.18	_	-
Laboratory data at discharge				
AST (IU/L)	1.01 (1.00–1.03)	.045	_	-
ALT (IU/L)	1.02 (1.01–1.04)	.002	1.02 (1.01–1.04)	.002
Total bilirubin (mg/dL)	1.15 (0.90–1.48)	.247	_	-
Direct bilirubin (mg/dL)	1.18 (0.86–1.63)	.293	_	-
GGT (IU/L)	1.00 (1.00-1.01)	.08	_	-
ALP (IU/L)	1.00 (1.00–1.00)	.374	-	-

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; $GGT = \gamma$ -glutamyl transpeptidase; LDLT = living donor liver transplantation; OR = odds ratio.



*Number at risk of primary patency and primary-assisted patency is based on 52 patients at any time, respectively.

Figure 3. Kaplan–Meier curves of primary and primary assisted patency rates. Solid and dotted lines indicate primary patency and primary assisted patency, respectively. Vertical lines indicate censored observations. Primary and primary assisted patency rates at 1, 3, 5, and 10 years were 75%, 70%, 70% and 68%, and 94%, 92%, 88%, and 88%, respectively.

Greif et al (19) showed that anastomotic strictures were more common after choledochojejunostomy than duct-to-duct anastomosis because of the direct bilioenteric connection. In posttransplantation pediatric patients with RYHJ, percutaneous transhepatic biliary interventions may be preferred because of easier access to biliary tracts compared with endoscopic double-balloon techniques (13,20).

Several reports (21–25) have described the effectiveness of PTBD followed by balloon dilation and internal drainage for biliary anastomotic strictures at the RYHJ site. Moreira et al (21) described the long-term outcomes of percutaneous transhepatic biliary intervention in 35 pediatric patients in whom biliary anastomotic stenosis developed at the RYHJ site after liver transplantation.

Among them were 16 patients after LDLT and 19 after deceased donor liver transplantation. In their study (21), 23 of 35 patients (65.7%) were free of a drainage tube after the first interventional session. The mean drainage time for the 23 patients was 10 months. Miraglia et al (22) reported success rates of 56% for a single course of percutaneous therapy and 74% for repeated percutaneous therapy in 27 pediatric liver transplant recipients with biliary stricture at a median follow-up of 13 months.

In the present study, 39 of 52 patients (75%) had no recurrent biliary stricture for 6-150 months (median, 49 mo) after the initial series of percutaneous biliary interventions. These outcomes might be comparable to or better than those reported in the previous studies (21– 25). However, a number of patients (13 of 52; 25%) showed recurrent stricture after the initial series of percutaneous biliary interventions, although the recurrence rate was lower than those in some of the previous reports (21-25). Multivariate analysis indicated that a risk factor for recurrent biliary stricture was a high level of serum ALT (> 53 IU/L) at discharge following the percutaneous biliary interventions, although the cohort size was not ideal to conduct a multivariate analysis. Serum ALT level reflects the degree of ischemic and reperfusion hepatocellular injury. Under conditions of hepatocellular injury around peribiliary glands by sustained inflammation, the incidence of biliary stricture increases as a result of the loss of epithelial cells of the deep peribiliary glands and insufficient supply of oxygen (26). In some patients with recurrent stenosis and high levels of serum ALT, intrahepatic bile duct injuries as well as anastomotic stricture might exist, but these findings were not shown on PTC.

Various strategies have been performed to obtain better patency after PTBD followed by balloon dilation and internal drainage, including placement of a metallic stent or dilation with a cutting balloon (27–30). A metallic stent can provide a large-caliber bile duct, but stent restenosis rates are fairly high, ranging from 38% to 58% (28–30). Additionally, a metallic stent could complicate future surgical revisions of the RYHJ or repeat transplantation. The placed stent also migrates more frequently in patients with RYHJ than in those with duct-to-duct anastomosis. Placement of a metallic stent is not preferred in the treatment of biliary strictures in pediatric transplant recipients given its unknown long-term patency. Cutting balloons are not used in the treatment of biliary strictures in cases of LDLT in our center.

There were several limitations to the present study. First, it had a retrospective design. Second, the therapeutic strategies for biliary anastomotic stricture were not unified. The timing of balloon dilation and exchange with drainage tube was not established early in the study. In our current series of biliary interventions, balloon dilation was performed at the initial visit, and exchanges for larger drainage tubes were routinely performed at 1-week intervals thereafter. In patients in whom recurrence was noted after

three series of biliary interventions, surgical revision was recommended. Third, complications might have been underreported given the retrospective design of the study. Finally, a case-control design was impossible before and after establishment of our protocols for biliary percutaneous interventions for biliary anastomotic stricture because the number of patients in this study was too small.

In conclusion, PTBD followed by balloon dilation and internal drainage may be a safe and effective treatment with long-term patency for biliary anastomotic stricture after pediatric LDLT.

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