Biliary Stricture after Adult Right-Lobe Living-Donor Liver Transplantation with Duct-to-Duct Anastomosis: Long-Term Outcome and Its Related Factors after Endoscopic Treatment

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Background/Aims: Biliary stricture is the most common and important complication after right-lobe living-donor liver transplantation (RL-LDLT) with duct-to-duct biliary anastomosis. This study evaluated the efficacy and long-term outcome of endoscopic treatment for biliary stricture after LDLT, with the aim of identifying the factors that influence the outcome.

Methods: Three hundred and thirty-nine adults received RL-LDLTs with duct-to-duct biliary anastomosis between January 2000 and May 2008 at Kangnam St. Mary’s Hospital. Endoscopic retrograde cholangiography (ERC) was performed in 113 patients who had biliary stricture after LDLT. We evaluated the incidence of post-LDLT biliary stricture and the long-term outcome of endoscopic treatment for biliary stricture. The factors related to the outcome were analyzed.

Results: Biliary strictures developed in 121 (35.7%) patients, 95 (78.5%) of them within 1 year of surgery. The mean number of ERCS performed per patient was 3.2 (range, 1 to 11). The serum biochemical markers decreased significantly after ERC (p<0.001). Stent insertion or stricture dilatation during ERC was successful in 90 (79.6%) patients. After a median follow-up period of 33 months from the first successful treatment with ERC, 48 (42.5%) patients achieved treatment success and 12 (10.6%) patients remained under treatment. The factors related to the outcome of endoscopic treatment were nonanastomotic stricture and stenosis of the hepatic artery (p=0.016).

Conclusions: Endoscopic treatment is efficacious and has an acceptable long-term outcome in the management of biliary strictures related to RL-LDLT with duct-to-duct biliary anastomosis. Nonanastomotic stricture and stenosis of the hepatic artery are correlated with a worse outcome of endoscopic treatment.

Key Words: Biliary stenting; Biliary stricture; Duct-to-duct biliary anastomosis; Endoscopic retrograde cholangiography; Liver transplantation

INTRODUCTION

Living-donor liver transplantation (LDLT) has become more popular recently and LDLTs outnumber the cadaveric-donor liver transplantations (CDLTs) in some countries. Among the complications after LDLT, biliary complications are the most common. Biliary complication may become a significant cause of morbidity and mortality in LDLT patients.1,3 Biliary stricture is the major biliary complication in LDLT. The rate of biliary stricture in LDLT ranges from 25% to 32% in different studies.4,8 This rate is higher than the rates reported for CDLT, at less than 15%.5,8,10 Higher incidence of biliary stricture in LDLT is because the anastomosis of the right hepatic duct of donor to the bile duct of the recipient is more complicated than the anastomosis of the common bile duct or left hepatic duct of donor to the bile duct of the recipient. Right hepatic duct has many variations includ-
ing multiple bile ducts and poor blood supply, and the stump of the right hepatic duct for the anastomosis is shorter.3,5,8,11

Endoscopic treatment has become the first-line management for the biliary strictures of LDLT with duct-to-duct (DD) anastomosis because it is less invasive and more convenient for the patient.12 Endoscopic retrograde cholangiography (ERC) has a role not only as the first treatment option but also as the second treatment option for the patients who underwent percutaneous transhepatic biliary drainage (PTBD) successfully after the endoscopic treatment had failed. To date, several reports have shown the usefulness of endoscopic treatment in LDLT with DD biliary anastomosis.3,5,7,8,13,14 However, they have included comparatively small numbers of LDLT patients and have not sufficiently addressed the long-term outcome. Moreover, the factors related to long-term outcome have not been studied even though predictive factors for failure of initial ERC were reported.15,16 Therefore, in the present study, we evaluated the efficacy of the endoscopic treatment of biliary stricture and report the long-term outcome and its related factors in a large number of patients undergoing LDLT with DD anastomosis.

MATERIALS AND METHODS

1. Patients

Three hundred fifty-three consecutive adult right-lobe living-donor liver transplantations (RL-LDLTs) were performed between January 2000 and May 2008 at Kangnam St. Mary’s Hospital, Seoul, Korea. The mean age was 49.1±8.7 years, and 260 (73.7%) patients were men. For the biliary anastomosis, DD anastomosis was performed in 339 patients, Roux-en-Y choledochojejunostomy in 11 patients, and both Roux-en Y choledochojejunostomy and DD anastomosis in three patients. Biliary strictures occurred in 121 (35.7%) of the 339 LDLTs performed with DD anastomosis. Overall, 113 patients underwent ERC for the treatment of biliary stricture. We analyzed the clinical records of these 113 patients retrospectively. Patient anonymity was maintained and the study was carried out in accordance with the ethical guidelines of the Declaration of Helsinki, as revised in 1989.

2. Endoscopic retrograde cholangiography

ERC was performed 364 times in 113 patients. Two hundred ninety-five (81.7%) cases of ERC were performed in Kangnam St. Mary’s Hospital and the remaining cases at another hospital. The process of ERC was as follows. After an overnight fast, ERC was performed with a video duodenoscope (ED-450XT5; Fujinon, Saitama City, Saitama, Japan). After the biliary duct was selectively cannulated, the type and site of the biliary stricture were identified on a fluoroscopic image after the injection of contrast reagent (Telebrix®; Guerbet, Roissy Cdg Cedex, France) through the catheter. A 0.035-inch guidewire (Jagwire; Boston Scientific, Natick, MA, USA) was inserted through the catheter into the intrahepatic bile duct proximal to the site of biliary stricture. If the guidewire did not pass over the stricture site, we replaced it with a 0.025-inch guidewire. To dilate the biliary stricture, a Soehendra bougination catheter (7 F-11.5 F; Wilson-Cook Medical, Winston-Salem, NC, USA), a Soehendra stent retriever (7 F-11.5 F; Wilson-Cook Medical) or a balloon catheter (6 or 8 mm in diameter; Hurricane RX; Boston Scientific) was used, according to the indications. After the stricture was dilated, the endoscopic retrograde biliary drainage stent (ERBD stent) was inserted. We tried to insert as many stents as possible, with the largest diameters possible. Amsterdam-type biliary stents (7 F-11.5 F in diameter, 10-16 cm in length; Wilson-Cook Medical, or Medi-Globe, Achenmuhle, Germany) were inserted across the stricture. The proximal side of the stent was located sufficiently over the stricture and the distal side of the stent was passed 1-2 cm outside the major papilla. A minor sphincterotomy was performed in all patients in whom the ERBD stent was inserted. After the successful insertion of the stent, a follow-up ERC was performed within three to six months. During the follow-up ERC, the previous stent was removed and the degree of improvement in the biliary stricture was evaluated. If the stricture remained, redilatation of the stricture and restenting were performed. If acute cholangitis or obstructive jaundice developed or the ERBD stent was dislodged, the follow-up ERC was performed earlier than scheduled. We did not insert a further stent when the contrast reagent moved easily into the intrahepatic bile duct proximal to the site of the biliary stricture, the dilatation of the intrahepatic duct was minimal, and the stricture did not remain on the fluoroscopic image at the follow-up ERC.

3. Percutaneous transhepatic cholangiography

The patients in whom the endoscopic treatment was unsuccessful were rescued with a percutaneous transhepatic cholangiography (PTC) and PTBD. The process of PTC was as follows. After confirmation of dilatation of intrahepatic duct in the liver on supine position under ultrasonography, a 10 mL of 2% lidocaine HCl was locally infiltrated at the skin surface of the prepared puncture site. Under fluoroscopic guidance, the right intrahepatic duct was punctured with a 21G Chiba needle and then a few mL of bile was aspirated. After insertion of 0.018-
inch hairwire, a yellow sheath followed by a 0.035-inch guidewire was introduced. After confirmation of anastomotic stricture, dilatation of biliary stricture with balloon catheters was performed, if indicated. An 8 F pigtail catheter was inserted over the wire with its tip placed within the common bile duct or duodenum, and tubogram was then obtained. The catheter was anchored to the skin with anchoring device. If the drainage catheter for the PTBD could pass across the stricture, subsequent ERC was performed later. Some of ERCs were performed with the rendezvous method which uses the guidewire inserted by PTC when the placement of the ERBD stent was expected to be difficult because the angle of the bile duct at the stricture site is sharp or twisted.

4. Definition

Biliary stricture was diagnosed when the stenosis of the bile duct and the dilatation of the intrahepatic duct proximal to the stricture were observed on abdominal computed tomography or magnetic resonance cholangiography, and the liver biochemical parameters, such as serum bilirubin, \( \gamma \)-glutamyltransferase, and alkaline phosphatase were abnormal, whether or not the patient had symptoms of abdominal pain and fever. A nonanastomotic biliary stricture was diagnosed when the intrahepatic bile ducts proximal to the anastomotic site show strictures or irregularities of moderate or severe degree.\(^{17}\)

We divided the outcome groups into a good outcome group and a poor outcome group. Good outcome group (treatment success group) included the patients who reached stent-free status and had serum total bilirubin <3 mg/dL over 3 months. Poor outcome group included the patients who died or underwent re-liver transplantation because of biliary stricture, or had serum total bilirubin >3 mg/dL over 3 months despite of treatment. We excluded the patients from the good outcome group who had stents (ERBD stents or PTBD) with a good liver function because they were under treatment and the patients from the poor outcome group who died of other causes rather than biliary stricture.

5. Statistical analysis

Student’s t test was used to evaluate the changes in the biochemical test results for serum hepatic markers. A Pearson’s chi-square teat or Fisher’s exact test was used in analysis of the factors related to the outcome of ERC. Statistical analyses were performed with SPSS, ver. 14 (SPSS Inc., Chicago, IL, USA), \( p \) values of <0.05 were considered significant.

RESULTS

1. Biliary complications after LDLT with DD anastomosis

Of the 339 patients who underwent RL-LDLT with DD anastomosis, 147 (43.4\%) developed biliary complications during the follow-up period: biliary stricture occurred in 121 (35.7\%), biliary leakage in 44 (13.0\%), and biliary stones in 35 (10.3\%). Twenty-two patients had a biliary stricture and leakage simultaneously or had leakage followed by a biliary stricture. Most biliary strictures occurred in the early period after transplantation: 95 (78.5\%) occurred within one year of transplantation and 114 (94.2\%) occurred within two years (Fig. 1). Of the
35 patients with biliary stones, only four had biliary stones without a biliary stricture, and the remaining 31 patients had intra or extrahepatic stones with biliary stricture.

2. Outcome of ERC for biliary stricture

Of the 113 patients who underwent ERC for biliary stricture, 102 had anastomotic strictures and 11 had non-anastomotic, multiple intrahepatic strictures (Table 1). The mean age was 49.9±8.2 years and 89 (79%) of them were men. The major underlying diseases indicating liver transplantation were hepatocellular carcinoma (49%) and liver cirrhosis caused by hepatitis B (34%). Single DD anastomosis was performed in 104 patients: one biliary orifice in 76, two biliary orifices in 26, and three biliary orifices in two. Double DD anastomosis was performed in nine patients: using both hepatic ducts in eight and using hepatic duct and cystic duct in one. Ductoplasty was performed in 28 patients. Right hepatic duct of recipient was used for anastomosis in 13 patients and left hepatic duct of recipient was used in 11 patients. Common bile duct of recipient was used in remaining patients. The median period between LDLT and the first ERC was 6 months (range, 1 to 71; Table 2). In total, 364 ERCs were performed per patient was 3.2 (range, 1 to 11). The rendezvous method was used in 16 (4.4%) cases. The serum biochemical tests after ERC showed significant reductions in the levels of serum bilirubin, alkaline phosphatase, and \( \gamma \)-glutamyltransferase (\( p<0.001 \)). The average number of stents inserted per patient was 1.4 (range, 1 to 4) and the mean size of the ERBD stents was 9.2 F (range, 7 F to 11.5 F).

The causes of the treatment failures with ERC were a failure of the selective cannulation of the common bile duct in two patients and the failures of a guidewire to pass across the stricture in 26 patients: in nine patients, there was no passage of contrast reagent across the stricture, so that the intrahepatic bile duct proximal to the stricture was not visualized, and in 17 patients, the contrast reagent passed the stricture but the guidewire did not pass across the stricture because the stricture was tight or there was a sharp angle at the stricture site (the angle between the right hepatic duct of the donor and the bile duct of the recipient).

Successful dilatation of the biliary stricture or the insertion of ERBD stents by ERC were achieved in 90 patients (79.6% of 113 patients), including 27 patients who previously underwent PTBD. After a median follow-up period of 33 months (range, 1 to 82) from the first successful treatment with ERC, 54 patients achieved an inside-stent-free status, seven patients had ERBD stents (under treatment), four patients had PTBD (under treatment, one patient had persistent abnormal liver function despite PTBD), five patients underwent retransplantation, and 14 patients died (Fig. 2). The 54 patients with stent-free status were followed-up for a median period of 22 months (range, 1 to 82) after the removal of the stent, and the mean number of ERCs per patient was 3.8 (range, 1 to 11). Follow-up duration of five patients in the stent-free group was shorter than 3 months (under treatment) and one patient’s serum bilirubin was above 3 mg/dL over 3 months. Therefore, the treatment success was achieved in 48 patients (42.5%). Among them, 30 patients achieved the treatment success by only ERC. Retransplantation was performed in five patients because of biliary hepatic failure. CDLT was performed in four patients and LDLT in one patient. The patient who underwent re-LDLT died two months after transplantation from postoperative bleeding and cytomegalovirus infection. The four patients who underwent re-CDLT were alive at a median follow-up of 34 months. The causes of death who died during follow-up were biliary hepatic failure in 6 patients, recurrent hepatocellular carcinoma in 5 patients, duodenal ulcer bleeding or perforation in two patients, and pneumonia in one patient.

Eleven patients had nonanastomotic strictures. The conditions possibly related to biliary stricture were hepatic artery stenosis or occlusion in four patients, recurrent common bile duct or intrahepatic duct stones in three pa-

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**Table 2. Details and Outcomes of ERC in Patients with Biliary Strictures after RL-LDLT**

<table>
<thead>
<tr>
<th>ERC for biliary stricture (n=113, 364 cases)</th>
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<tbody>
<tr>
<td>Median interval between LDLT and first ERC, mo (range)</td>
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<tr>
<td>Each ERC, mo (range)</td>
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<tr>
<td>Mean no. ERC</td>
</tr>
<tr>
<td>Rendezvous method, cases (%)</td>
</tr>
<tr>
<td>Median follow-up period after LDLT, mo (range)</td>
</tr>
<tr>
<td>Treatment success, No. (%)</td>
</tr>
<tr>
<td>With ERC</td>
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<tr>
<td>With ERC and PTC</td>
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<tr>
<td>Changes in laboratory data, mean (SD)</td>
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<tr>
<td>Before and after ERC</td>
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<tr>
<td>Serum bilirubin*, mg/dL</td>
</tr>
<tr>
<td>Serum alkaline phosphatase*, IU</td>
</tr>
<tr>
<td>Serum ( \gamma )-glutamyltransferase*, IU</td>
</tr>
</tbody>
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ERC, endoscopic retrograde cholangiography; RL-LDLT, right-lobe living-donor liver transplantation; PTC, percutaneous transhepatic cholangiography; SD, standard deviation. *p-value <0.001.
Table 3. Analysis of the Factors Related to Long-term Outcomes after Endoscopic Treatment

<table>
<thead>
<tr>
<th>Related factors</th>
<th>Outcome group</th>
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<tbody>
<tr>
<td></td>
<td>Good, No. (%)</td>
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<tr>
<td>Male sex</td>
<td>37 (77)</td>
</tr>
<tr>
<td>Age (&gt;50)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Onset time of stricture (&lt;6 mo)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Total bilirubin (&lt;5 mg/dL)</td>
<td>30 (63)</td>
</tr>
<tr>
<td>T tube insertion</td>
<td>18 (38)</td>
</tr>
<tr>
<td>Nonanastomotic stricture</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Portal vein stenosis*</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hepatic artery stenosis*</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Rejection activity index (&gt;2, cases)†</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Pre-LT no. of TACE (≥1)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Ductoplasty or ≥2 biliary orifices</td>
<td>11 (23)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; TACE, transarterial chemoembolization.
*Including thrombosis; †Forty-three patients underwent biopsies of transplanted liver.

Fig. 2. Clinical outcomes in 121 patients with posttransplantation anastomotic biliary strictures. RL-LDLT, right-lobe living-donor liver transplantation; ERC, endoscopic retrograde cholangiography; ERBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Patients, moderately or severely active acute rejection in two patients, portal vein stenosis in one patient, and post-transplantation radiation therapy in one patient. Finally, seven patients became stent-free state, two patients underwent retransplantation (CLDT), and the remaining two patients died during follow-up because of hepatic failure.

3. Complications of ERC

Immediate post-ERC cholangitis developed in 38 cases (10.6%) after ERC. Among these cases, dilatation and insertion of stent succeeded in 32 cases and failed in remaining 6 cases. Immediate post-ERC cholangitis was mild in which fever sustained only for 1-3 days and none of them progressed toward sepsis. Delayed post-ERC
cholangitis or liver abscess requiring admission occurred during follow-up in 33 patients (29.2%) who previously underwent sphincterotomy and stenting. They admitted for the treatment of acute cholangitis and improved with conservative management using antibiotics. Twenty-five patients were carrying ERBD stents and eight patients were not carrying an ERBD stent when acute cholangitis developed. Post-ECR pancreatitis developed in 30 cases (8.2%). There were no severe pancreatitis and related death.

4. Factors related to the outcome

We analyzed the factors related to a worse outcome to endoscopic treatment. The nonanastomotic stricture and hepatic artery stenosis were significantly related to a poor outcome (p=0.016; Table 3). Although number of pretransplant transarterial chemoembolization was not significantly related to the final status, it showed a trend toward worse outcome (p=0.097). Sex, age, onset time of biliary stricture, peak total bilirubin before the first treatment, insertion of T tube, portal vein stenosis or thrombosis, rejection activity index, and ductoplasty or ≥2 biliary orifices were not related to the outcome.

DISCUSSION

Despite improvements in surgical techniques and immunosuppressive therapy, biliary complications remain a significant cause of morbidity and mortality after liver transplantation. Because the incidence of biliary stricture in LDLT with DD anastomosis is as high as 30%,4-8 the treatment of biliary strictures has an important role in determining the survival of grafts. Our study showed that successful insertion of ERBD stents or dilatation of biliary stricture was performed in 90 (79.6%) patients. During a median follow-up period of 33 months after successful endoscopic treatment, 48 (42.5%) patients achieved a stent-free status with normal liver function and 12 (10.6%) patients were under treatment. This shows that the endoscopic treatment for biliary strictures is efficacious, and has an acceptable long-term outcome.

Biliary complications occur most frequently in post-LDLT patients and the interventional treatment of biliary complications is mandatory. The long-term outcome for biliary stricture after an endoscopic intervention has not been clearly defined, especially in patients who underwent LDLT with DD anastomosis. Several studies reported the outcome of endoscopic treatment in RT-LDLT and the success rates of endoscopic treatment in these studies were 7/18, 25/75, 4/5, 12/20, 7/14, and 7/7 for median follow-up of 9.5 to 20.3 months.3,5,7,8,13,14 However, all but one5 of these studies included only small numbers of patients who underwent ERC for the treatment of biliary stricture and had short follow-up period after endoscopic treatment. Yazumi et al.5 reported that an incidence of biliary stricture of 29.3% and initial success rate for the endoscopic treatment of anastomotic strictures of 68.0% in a large number of 75 patients. However, their rate of long-term stent-free patients was 33.3% for an average 20 months. As our study shows, patients’ status changed during follow-up. Some patients could remove the ERBD stents, some needed additional endoscopic treatment or PTBD, and some died or underwent re-liver transplantation during follow-up. Our study shows additional gain of 9% in rate of treatment success in comparison with their previous study.

Whether ERC or PTC is chosen as the first treatment of posttransplantation biliary stricture could depend on the status of the biliary stricture and the patients’ condition. In general, ERC is recommended as the first approach and PTC is reserved for rescue therapy,10,12,18 for following reasons. First, the rates of successful interventions and patency do not differ for ERC or PTC, and the numbers of necessary interventions are higher for PTC.12 Second, patient comfort is greater with ERC and the inconvenience of the PTBD catheter cannot be ignored. The discomfort caused by carrying a PTBD catheter reduces the patient’s quality of life and disturbs the usual course of daily routine. PTBD-related complications, such as leakage, pain, infection, and the accidental removal of the PTBD catheter, are not uncommon. Therefore, we recommend that ERC be performed first and that PTC follows ERC. If primary or rescue PTC is successfully performed with internal drainage, subsequent ERC with the insertion of ERBD stents is recommended for the second reason. With subsequent ERC, the PTBD catheter can be removed earlier and the complications related to the PTBD catheter can be reduced. If the insertion of stents is expected to be difficult because of the sharp or twisted angle of the anastomosis or for other reasons, ERC can be successfully performed with the rendezvous method, as in our study.

Only eight (7.1%) patients with biliary stricture were treated with a single ERC in our study. In most cases, several ERCS (mean, 3.2) were required, and the mean interval between ERCS was 4 months. The optimal interval between ERCS is unclear. As in our study, ERC is performed at intervals of about three to six months at the many centers. One study reported that rapid dilatation and stenting with ERC at intervals of two weeks resulted in the good long-term resolution of strictures.19 Although the mean number of ERCS performed did not differ from
that in our study, the total stenting period was significantly reduced. However, the patient’s inconvenience or unwillingness toward ERC sometimes does not allow short-term ERC. It is sometimes difficult to further dilate a biliary stricture and to insert a greater number of ERBD stents during a short-term follow-up ERC than previous ERC. Further comparative studies are required to assess the usefulness of short-term ERC.

Cholangitis related to ERC often occur in immuno-compromised transplant patient. In our study, immediate post-ERC cholangitis developed in 38 cases (10.6%) and delayed post-ERC cholangitis or liver abscess requiring admission occurred in 33 patients (29.2%). The our incidence of post-ERC cholangitis (10.6%) in LDLT was higher than in non-transplant patients (3.4%) in meta-analysis. However, post-ERC cholangitis in LDLT was mild and improved in a few days. We performed a minor sphincterotomy in all patients in whom the ERBD stent was inserted. Sphincterotomy and stenting outside of major papilla might raise possibility of duodenobiliary reflux and development of cholangitis. Sphincterotomy was not performed and ERBD stents were inserted inside of common bile duct, not outside of ampulla in order to reduce cholangitis in a previous study. That study showed that there was no infection after removing the ERBD stents. This approach could be valuable especially in transplant patients who are vulnerable to infections caused by immunosuppressive therapy. Besides cholangitis, biliary stones, carcinoma, and liver abscess could be developed after sphincterotomy. Therefore, comparative further studies assessing the incidence of biliary tract infection in post-transplant patients between stenting with and without sphincterotomy are needed in the future.

The predictive factors for a long-term outcome to the treatment of biliary strictures in LDLT patients have not been studied. For the initial response to endoscopic treatment, anastomotic strictures had a good initial response, and patients with multiple stricture or late biliary stricture over 24 weeks had a worse response to endoscopic management. In the present study, nonanastomotic stricture and hepatic artery stenosis were significant negative prognostic factors related to the outcome after treatment. The blood supply to the biliary system has been shown to be almost arterial. Thus, hepatic artery stenosis or thrombosis is related to biliary stricture. The important cause of nonanastomotic stricture is known as insufficient blood supply from hepatic artery. Nonanastomotic stricture is difficult to treat, and any generalized treatment recommendations are difficult to make. Therefore, the outcome after endoscopic treatment is expected to be worse in the patients with nonanastomotic stricture or hepatic artery stenosis. Because of lack of patients with poor outcome, we could not perform a multivariate analysis. The further study is expected to find independent prognostic factor to outcome after endoscopic treatment.

In conclusion, endoscopic treatment is efficacious and has an acceptable long-term outcome in the management of biliary strictures related to RL-LDLT with DD biliary anastomosis. Nonanastomotic stricture and hepatic artery stenosis were related to worse outcome after treatment. Further studies should be performed to improve the outcome of endoscopic treatment for posttransplant biliary stricture in the future.

REFERENCES