Endoscopic treatment of biliary complications after living donor liver transplantation in a high volume transplant center in Turkey; a single-center experience

M. Harputluoglu[1], M. Aladag[1], U. Demirel[2], Y. Bilgic[1], R. Dertli[3], M.A. Erdogan[1], M. Karincaoglu[1], R. Kutlu[4], V. Ince[5], S. Karakas[5], E. Parlak[6], S. Yilmaz[5]

(1) Inonu University Medical Faculty, Department of Gastroenterology, Liver Transplantation Institute, Malatya, Turkey ; (2) Firat University Medical Faculty, Department of Gastroenterology, Elazig, Turkey ; (3) Necmettin Erbakan University Medical Faculty, Department of Gastroenterology, Malatya, Turkey ; (4) Inonu University Medical Faculty, Department of Radiology, Liver Transplantation Institute, Malatya, Turkey ; (5) Inonu University Medical Faculty, Department of General Surgery, Liver Transplantation Institute, Malatya, Turkey ; (6) Sakarya University Medical Faculty, Department of Gastroenterology, Sakarya, Turkey.

Abstract

***Background and aim* : Biliary complications are an important cause of mortality and morbidity after living donor liver transplantation (LDLT). We present our endoscopic treatment results after LDLT as a single center with high volume.**

***Methods* : Patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) after LDLT between 2005 and 2015 were included. Clinical data included patient demographics, ERCP indications (stricture or leak), and treatment outcomes, including need for percutaneous and surgical interventions.**

***Results* : ERCP was performed in 446 (39.2%) patients with duct-to-duct anastomosis of 1136 LDLT patients. The most common biliary complication was stricture ± stone (70.6%, 315/446). Stricture and leak occurred in 60 (13.4%) patients. Only biliary leak was found in 40 (8.9%) patients. Our endoscopic treatment success rate in patients with biliary stricture after LDLT was 65.1%. Overall endoscopic success rates in our patients were 55.0% in patients with both leak and stricture, and only leak. In all, our percutaneous transhepatic biliary interventions (PTBI) and ERCP success rate was 90.6% in patients with biliary complications after LDLT.**

***Conclusions* : Endoscopic treatments are highly effective for biliary complications after LDLT. Effective use of percutaneous interventions in collaboration with endoscopic treatments significantly reduces the need for surgical treatment.** (Acta gastroenterol. belg., **2018**, 81, **283-287**).

Key words : Liver transplantation, biliary complication, endoscopic retrograde cholangiopancreatography.

Introduction

Living donor liver transplantation (LDLT) has emerged in recent decades as a critical surgical option to overcome the widespread shortage of cadaveric livers. The reported incidence of biliary complications is 20–34% after LDLT (1). Biliary complications after LDLT include biliary strictures, biliary leak and stone formation, and represent an important cause of postoperative mortality and morbidity. Graft survival rates after 1 year can differ by 45%, based upon the presence or absence of biliary complications (88.5 vs. 43.5%), and by almost 50% after 3 years (2). Therefore, the correct management of these complications is of vital importance. Endoscopic retrograde cholangiopancreatography (ERCP) is first treatment approach in the majority of patients with biliary complications after LDLT.

Our center has become highest volume liver transplantation center in Turkey (200-250 patients per year undergoing primarily LDLT). Herein, we present our endoscopic treatment results after LDLT.

Materials and Methods

We retrospectively reviewed our patient database of the Liver Transplantation Unit of Inonu University between September 2005 and January 2015. Patients who underwent ERCP after LDLT were included in our study cohort. The ethics committee of Inonu University Medical Faculty approved our study.

Clinical data included patient demographics, indication for LDLT, time to ERCP after LDLT, number of ERCP procedures, ERCP indications (stricture or leak), and treatment outcomes, including need for percutaneous and surgical interventions. We also investigated the incidence of hepatic artery complications in liver imaging studies (computed tomography CT or magnetic resonance imaging, MRI).

Before ERCP, every patient was evaluated at a multidisciplinary meeting including transplant surgeons, radiologists, and gastroenterologists, along with their clinical data and imaging, including MRI or percutaneous cholangiography. Figure 1 shows our procedure algoritm in the presence of biliary complication suspicion.

Biliary stricture was suspected if there were cholangitis symptoms or elevation of liver function tests. Magnetic resonance cholangiopancreatography (MRCP) /computerized tomography (CT) or percutaneous cholangiography was used to diagnose the biliary strictures. If there were findings of biliary stricture, ERCP was preferred as the first choice in patients with duct-

Correspondence to : Murat Harputluoglu, MD. Professor, Inonu University Medical Faculty, Department of Gastroenterology, Malatya, Turkey. Tel : +90 422 3410660/4112. Fax : +90 422 3411149
Email : mharputluoglu@hotmail.com

Submission date : 16/04/2017
Acceptance date : 13/12/2017

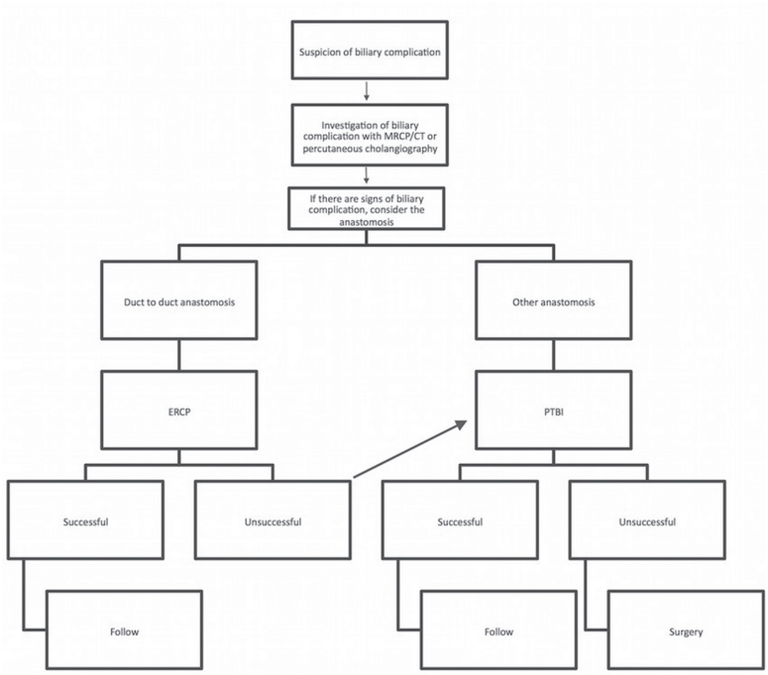

Figure 1. — Our procedure algoritm in the case of biliary complication suspicion (MRCP ; Magnetic resonance cholangiopancreatography, CT ; Computerized tomography, ERCP ; Endoscopic retrograde cholangiopancreatography, and PTBI ; Percutaneous transhepatic biliary interventions).

to duct anastomosis. Percutaneous cholangiograms were performed for clinical indications and performed routinely just prior to catheter removal at approximately 90 days after liver transplantation. During percutaneous cholangiography, we used diluted contrast reagent (Iohexol, (Omnipaque 300™, 647 mg iohexol/ml, GE Healthcare, Oslo, Norway) to confirm the presence of biliary complications. We did not performed ERCP in patients without duct-to duct anastomosis. Three experienced gastroenterologists (M.A., M.H., and Y.B.) performed ERCP using Olympus duodenoscopes (TJF 160, Olympus Optical Co., Ltd., Tokyo, Japan). We performed endoscopic sphincterotomy routinely in every patient during ERCP. A 0.025 or 0.035-inch guidewire (Jagwire, Boston Scientific, Natick, MA, USA) was inserted via the catheter into the intrahepatic bile ducts, if biliary stricture is detected in cholangiography performed with contrast agent. Later, we dilated it using a bougie (7 and 10 French, Wilson-Cook Medical GI Endoscopy, Winston Salem, NC, USA), and/or a balloon catheter (4, 6, or 8 mm, Hurricane RX; Boston Scientific, USA). Then, Amsterdam-type biliary stents (7 and 10 French, 9-18 cm long, Boston Scientific) were placed across the stricture or anastomosis. ERCP and stent revision was performed every 3-6 months. We aimed to improve the stricture as soon as possible. Therefore, we tried to increase the number and diameter of stents in each session. During follow-up ERCP (at approximately 18 months), if the stricture improved, we removed the biliary stents and followed the patient without stents. If stricture persisted, re-dilatation and re-stenting was performed endoscopically.

In cases where the cholangiogram showed a bile leak, ERCP was decided as treatment modality in patients with duct-to duct anastomosis. If biliary leakage was detected during ERCP, we inserted biliary stents to stop the leak. If biliary stones were found on imaging or during ERCP, we extracted the stones with a balloon or basket catheter.

If ERCP was unsuccessful (failure to pass stricture or persistent biliary complications despite dilatation and stent placement), our multidisciplinary team determined whether percutaneous transhepatic biliary interventions (PTBI) and/or surgical treatments were indicated. After percutaneous drainage with PTBI was shown to be successful, we performed a stent revision with ERCP, at a later point. If endoscopic and percutaneous treatments failed, surgical treatment was offered as a final option. In this study, we accepted as ERCP success if patients included in the study did not have PTBI or surgery due to biliary complication at any time during follow-up after first ERCP.

Data were entered manually and statistically analyzed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). The Kruskal Wallis test was used for comparisons and p-values of less than 0.05 were considered statistically significant.

Results

ERCP was performed in 446 (39.2%) patients with duct-to-duct anastomosis in 1136 cases. Table 1 shows the patient demographics, with the majority of patients (69.3%) being male with hepatitis B as the most common etiology of liver failure (44.1%). Means of

Table 1. — **Baseline patient demographics**

Number of ERCP patients	446
Age (mean)	46.56 ± 14.16
Female/Male	137 (30.7%) / 309 (69.3%)
Means of procedure number	2.54 ± 1.77
Means of time to first ERCP (months)	6.17 ± 9.03
Etiology	Hepatitis B (n=197) 44.1 % Hepatitis C (n=31) 6.9% Hepatitis D (n=23) 5.1 % Others (n=115) 25.7% Criptogenic (n=80) 17.9 %

Table 2. — **ERCP findings**

Findings	Frequency (n, %)
Stricture (± stone)	315 (70.6%)
Leak	40 (8.9%)
Stricture + Leak	60 (13.4 %)
Only stone	4 (0.8%)
Normal ERCP	8 (1.6%)
No cannulation	17 (3.8%)
Failure to pass due to duodenal ulcer	2 (0.4%)
Total	446

ERCP procedure number per patient were 2.54. Means of time to first ERCP after LDLT were 6.17 months. The majority of transplantation had right graft.

The most common biliary complication was stricture (70.6%, 315/446) (Figure 2a and 2b). Almost all of the strictures were anastomotic. Stricture and leak occurred in 60 (13.4%) patients (Figure 2c). Only biliary leak was found in 40 (8.9%) patients. Most of the leaks were from anastomosis. While stricture and stone was detected in 33 patients, only stone was found in four patients. ERCP was unsuccessful in a total of 19 patients due to inability to cannulate and duodenal ulcer. ERCP was normal in eight (1.7%) patients. Table 2 shows the ERCP findings for a total of 446 patients.

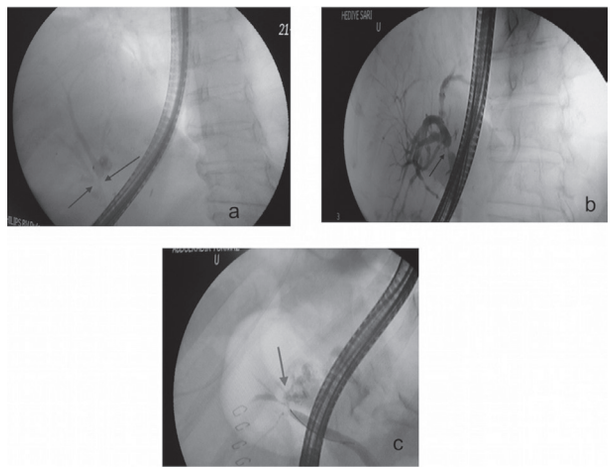

Figure 2. — The fluoroscopic images of the stricture (a and b), and leak and stricture (c) detected during ERCP (Endoscopic retrograde cholangiopancreatography) are shown with black arrows.

PTBI was performed in 110 of 315 (34.9%) patients with stricture ± stone. In this patient group, 27 (8.6%) patients required surgical treatment (Table 3). In patients with leak (with or without stricture), PTBI was performed in 45% of patients. Surgery was performed in six (15.0%) patients for leak, and in seven (11.7%) patients for stricture and leak. In total, 174 (39.1%) patients underwent PTBI. Table 4 shows the causes of endoscopic failure. ERCP and PTBI were unsuccessful in 42 (9.4%) patients, who subsequently required surgery.

The most common complications after ERCP were pancreatitis (12.3%, 55/446), cholangitis (8.3%, 37/446), and bleeding after sphincterotomy (2.9%, 13/446). These complications were treated conservatively. Duodenal perforation developed due to biliary stent migration in one patient, who required surgical treatment. Bleeding after sphincterotomy was treated with angiographic embolization in two patients.

Hepatic artery thrombosis (HAT) was detected in 24 (5.3%) patients on liver imaging studies. PTBI was performed in seven patients and eventually surgery was

Table 3. — **Number of patients who underwent percutaneous transhepatic biliary interventions (PTBI) and surgical treatment**

	PTBI		Surgery		
	No	Yes	No	Yes	Total
Stricture (± stone)	205 (65.1%)	110 (34.9%)	288 (91.4%)	27 (8.6%)	315
Leak	22 (%55.0)	18 (%45.0)	34 (85.0%)	6 (15.0%)	40
Stricture + Leak	33 (%55.0)	27 (%45.0)	53 (88.3%)	7 (11.7%)	60
Only stone	4 (100%)	0	4 (100%)	0	4
Normal ERCP	8 (100%)	0	8 (100%)	0	8
No cannulation	0	17(100%)	15 (88.2%)	2 (11.8%)	17
Failure to pass (duodenal ulcer)	0	2 (100%)	2 (100%)	0	2
Total	272 (60.9%)	174 (39.1%)	404 (90.6%)	42(9.4%)	446

performed in four patients with HAT. There was no statistically correlation with regards to the frequency of HAT in patients who underwent PTBI and surgical treatment (p>0.05).

Discussion

In our cohort of patients who underwent ERCP after LDLT, percutaneous and surgical treatments were performed in 39.1% and 9.4% of patients, respectively. ERCP frequency was 39.2% (446/1136) in our LDLT patients. The most common biliary complication was stricture (84%, 375/446) (Figure 2a and 2b). Of 375 patients, stricture ± stone occurred in 315, and leak accompanied by stricture (Figure 2c) in 60 patients. Our endoscopic treatment success rate in patients with biliary stricture after LDLT was 65.1%. Figure 3 shows the fluoroscopic images of balloon dilation and stenting in patients with stricture. Figure 4 is the final state of the stricture after removal of the stents in a patient with stricture. Wadhawan et al. reported that the success rate of ERCP alone and combined ERCP + PTBI in patients with biliary stricture after LDLT was 75% and 91%, respectively (1). Chan et al. reported that 75% of LDLT patients had a successful response to endoscopic therapy in a small patient group (3). Yazumi et al. reported the endoscopic success rate to be 68% for anastomotic strictures (4). In contrast to these studies, others reported lower endoscopic success rates after LDLT (5, 6). Chang et al. reported an overall ERCP success rate of 42.4% (only ERCP 26.5%, and ERCP and PTBI 42.4%) in 113 patients with biliary stricture after LDLT (5). Kim et al. reported that immediate endoscopic success was achieved in 82/147 (55.8%) patients and final endoscopic success in 52/141 (36.9%) after LDLT (6). In these studies, the primary reason for endoscopic failure was an inability to traverse the guidewire across the stricture in 23% and 44% of patients, respectively. In a small patient cohort, Gomez et al. demonstrated an endoscopic treatment success rate of 20% in LDLT patients with stricture; failure to traverse the stricture occurred in 60% (7). In our study, the major causes of endoscopic failure were cannulation problems, (17/446, 3.8%), failure to pass the pylorus due to duodenal ulcer (2/446, 0.4%), and failure to traverse the stricture or persistent biliary problems despite dilatation and stent placement (155/446, 34.7%) (Table 4). Akamatsu et al. reported an overall ERCP success rate of 57% in the largest patient group with biliary stricture, including 11,547 deceased donor liver transplantation (DDLT) patients and 2812 LDLT patients with biliary complications (8). They reported that ERCP was performed in 136 (25.6%) of 530 patients with biliary stricture. There is no data in this meta-analysis about the ERCP success rate for LDLT patients. Moreover, they reported that PTBI and surgery were chosen as the first approach more frequently for biliary complications after LDLT. Conversely, ERCP was the first approach for biliary complications in our study. The most important features of our study are (i) large patient volume, (ii) homogeneity of expert surgeons and endoscopists, (iii) single center experience, (iiii) preference for ERCP as first line treatment. Our success rate for endoscopic treatment of biliary stricture after LDLT was 65.1%. These data suggest that individually, ERCP is an important and first-line treatment modality for the management of biliary stricture.

The second biliary complication in our cohort was biliary leak (22.4%, 100/446). Only leak occurred in 40 patients. Stricture was accompanied by leak in 60 patients. Overall, endoscopic success rates were 55% in patients with both leak and stricture. It has been reported

Table 4. — **The causes of endoscopic failure**

Causes	Number of patients (%)
Cannulation problems	17/446 (3.8%)
Failure to pass the pylorus due to duodenal ulcer	2/446 (0.4%)
Failure to traverse the stricture or persistent biliary problems despite dilatation and stent placement	155/446 (34.7)
Total	174/446 (39.1%)

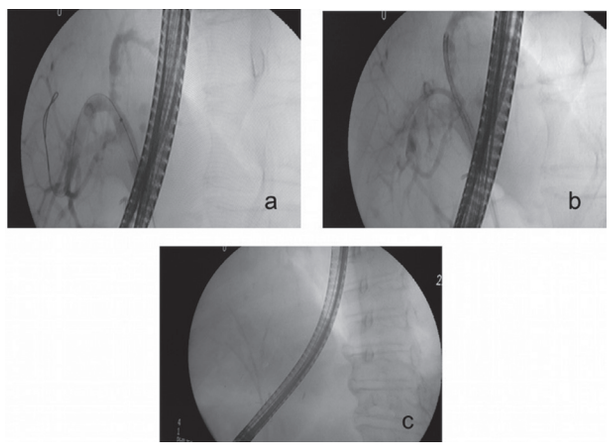

Figure 3. — The fluoroscopic images of balloon dilation (a) and stenting (b, and c) in patients with stricture.

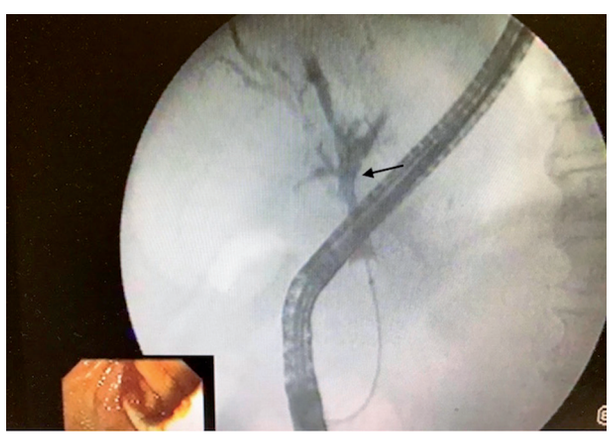

Figure 4. — The final state of the stricture (black arrow) after removal of the stents in a patient with stricture.

that endoscopic therapy resolves bile leak in more than 85% of patients after orthotopic liver transplantation (OLT) (7, 9-13). In a small patient group with bile leak after OLT, the endoscopic success rate was 100% (14). There are a few studies reporting outcomes of endoscopic management of biliary leak in patients who underwent LDLT. Wadhawan et al. reported the endoscopic success rate in patients with bile leak after LDLT to be 82% (14/17 patients) (1). Chok et al. reported that half were successfully treated with the endo-radiological method in a very small patient group (n=12) after LDLT (15). Akamatsu et al. found that biliary leak could often be managed conservatively, as 34% of cases reviewed were cured without aggressive treatment (8). However, ERCP was chosen in the minority of patients with biliary leak (40/268), such as biliary stricture patients in this meta-analysis. In light of this data, it is difficult to interpret the efficiency of ERCP alone in the management of the biliary leak after LDLT.

Another nonsurgical treatment option for biliary complications after LDLT is percutaneous intervention. In our center, if ERCP was unsuccesful, PTBI was performed. After successful percutaneous drainage with PTBI, we performed stent revision with ERCP at a later point. PTBI was performed in 34.9% of patients with stricture. In this patient group, 8.6% of patients required surgical treatment. PTBI was performed in 45% of patients with leak (with or without stricture). Surgery was performed 15.0% of patients with only leak, and 11.7% of patients with stricture and leak. These results show that ERCP combined with PTBI has a higher success rate in the treatment of biliary stricture compared with biliary leak. In total, 174 (39.1%) patients underwent PTBI. ERCP and PTBI were unsuccesful in 42 (9.4%) patients, and in these cases surgery was required. ERCP combined with PTBI resolved biliary problems in 90.6% of patients. These results suggest that endoscopic and percutaneous interventions are complementary treatments in the management of biliary complications after LDLT.

Biliary anastomosis is the Achilles' heel of liver transplant. Because of the small diameter of the bile ducts in the anastomoses from the donor right hepatic lobe and the frequent need for two anastomoses, biliary complications are known to be more frequent in LDLT compared with DDLT (16). The lower success rate for LDLT patients versus DDLT patients can be attributed to multiple, small-caliber anastomoses, peripheral locations, and twisted structures, which probably result from anastomotic fibrosis and hypertrophy of the transplanted liver (17). Despite our conventional ERCP experience, in early periods, ERCP was very difficult for us in patients with LDLT due to reasons above. We observed that our ERCP success rates increased as we experienced. Although ERCP is the first choice, high PTBI rates reflect our low experience in early periods.

In conclusion, endoscopic treatments are highly effective for biliary complications after LDLT. Effective usage of percutaneous interventions in combination with endoscopic treatments significantly reduces the need for surgical treatment.

References

1. WADHAWAN M., KUMAR A., GUPTA S., GOYAL N, SHANDIL R., TANEJA S., *et al.* Post-transplant biliary complications: an analysis from a predominantly living donor liver transplant center. *J. Gastroenterol. Hepatol.,* 2013, **28** : 1056-1060.
2. PASCHER A., GERLACH U., NEUHAUS P. Bile duct strictures after liver transplantation. *Curr. Opin. Gastroenterol.,* 2014, **30** : 320-325.
3. CHAN C.H., DONNELLAN F., BYRNE M.F., COSS A., HAQUE M., WIESENGER H., *et al*. Response to endoscopic therapy for biliary anastomotic strictures in deceased versus living donor liver transplantation. *Hepatobiliary. Pancreat. Dis. Int.,* 2013, **12** : 488-493.
4. YAZUMI S., YOSHIMOTO T., HISATSUNE H., HASEGAWA K., KIDA M., TADA S., *et al*. Endoscopic treatment of biliary complications after right-lobe living-donor liver transplantation with duct-to-duct biliary anastomosis. *J. Hepatobiliary. Pancreat. Surg.,* 2006, **13** : 502-510.
5. CHANG J.H., LEE I.S., CHOI J.Y., YOON S.K., KIM D.G., YOU Y.K., *et al.* 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. *Gut Liver.,* 2010, **4** : 226-233.
6. KIM T.H., LEE S.K., HAN J.H., PARK DO H., LEE S.S., SEO D.W., *et al*. The role of endoscopic retrograde cholangiography for biliary stricture after adult living donor liver transplantation: technical aspect and outcome. *Scand. J. Gastroenterol.,* 2011, **46** : 188-196.
7. MACÍAS-GÓMEZ C., DUMONCEAU J.M. Endoscopic management of biliary complications after liver transplantation: an evidence-based review. *World J. Gastrointest. Endosc.,* 2015, **7** : 606-616.
8. AKAMATSU N., SUGAWARA Y., HASHIMOTO D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. *Transpl. Int.,* 2011, **24** : 379-392.
9. RERKNIMITR R., SHERMAN S., FOGEL E.L., KALAYCI C., LUMENG L., CHALASANI N., *et al.* Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. *Gastrointest. Endosc.,* 2002, **55** : 224-231.
10. JOHNSTON T.D., GATES R., REDDY K.S., NICKL N.J., RANJAN D. Nonoperative management of bile leaks following liver transplantation. *Clin. Transplant.,* 2000, **14** : 365-369.
11. DUMONCEAU J.M., TRINGALI A., BLERO D., DEVIERE J., LAUGIERS R., HERESBACH D., *et al*. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy*., 2012, **44** : 277-298.
12. MORELLI J., MULCAHY H.E., WILLNER I.R., CUNNINGHAM J.T., DRAGANOV P. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. *Gastrointest. Endosc.,* 2003, **58** : 374-379.
13. SOLMI L., CARIANI G., LEO P., MIRACOLO A., NIGRO G., RODA E. Results of endoscopic retrograde cholangiopancreatography in the treatment of biliary tract complications after orthotopic liver transplantation: our experience. *Hepatogastroenterology*., 2007, **54** : 1004-1008.
14. SANNA C., GIORDANINO C., GIONO I., BARLETTI C., FERRARI A., RECCHIA S., *et al.* Safety and efficacy of endoscopic retrograde cholangiopancreatography in patients with post-liver transplant biliary complications: results of a cohort study with long-term follow-up. *Gut Liver*., 2011, **5** : 328-334.
15. CHOK K.S., CHAN A.C., SHARR W.W., CHEUNG T.T., FUNG J.Y., CHAN S.C., *et al.* Outcomes of endo-radiological approach to management of bile leakage after right lobe living donor liver transplantation. *J. Gastroenterol. Hepatol.,* 2016, **31** : 190-193.
16. RANJAN P., BANSAL R.K., MEHTA N., LALWANİ S., KUMARAN V., SACHDEVA M.K., *et al.* Endoscopic management of post-liver transplant billiary complications: A prospective study from tertiary centre in India. *Indian J. Gastroenterol*., 2016, **35** : 48-54.
17. WANG S.F., HUANG Z.Y., CHEN X.P. Biliary complications after living donor liver transplantation. *Liver Transpl*., 2011, **17**: 1127-1136.