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Optimal drainage of anastomosis stricture after living donor liver transplantation

Min Je Sung[1,2] · Jung Hyun Jo[1] · Hee Seung Lee[1] · Jeong Youp Park[1] · Seungmin Bang[1] · Seung Woo Park[1] · Si Young Song[1] · Dong Jin Joo[3] · Moon Jae Chung[1]

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Abstract

Background Endoscopic biliary stenting (EBS) with a fully covered, self-expandable metallic stent (FC-SEMS) and plastic stent (PS) is safe and efficient for biliary anastomotic strictures (ASs) after a deceased donor liver transplantation. Limited studies have investigated the use of FC-SEMSs for biliary strictures post-living donor liver transplantation (LDLT). We compared the resolution rate of biliary ASs post-LDLT and the 12-month recurrence rates post-stent removal between EBS with an FC-SEMS, PS, and percutaneous transhepatic biliary drainage (PTBD).
Methods Patients with biliary ASs after an LDLT (mean age: 57.3 years, 76.1% men) hospitalized between 2014 and 2017 were enrolled. Endoscopic retrograde cholangiopancreatography (ERCP) was repeated every 3–4 months. Patients were followed-up for at least 1-year post-stent removal.
Results Of the 75 patients enrolled, 16, 20, and 39 underwent EBS with an FC-SEMS, PS, and PTBD, respectively. Median follow-up period was 39.2 months. Fewer ERCP procedures were needed in the FC-SEMS group than in the PS group (median, 2 vs. 3; $P=0.20$). Median stent indwelling periods were 4.7, 9.3, and 5.4 months in the FC-SEMS, PS, and PTBD groups, respectively ($P=0.006$). The functional resolution rate was lower in the PS group (16/20) than in the FC-SEMS (16/16) or PTBD (39/39) group ($P=0.005$). The radiologic resolution rate was higher in the FC-SEMS group (16/16) than in the PS group (14/20) ($P=0.07$). The 12-month recurrence rates showed no significant differences (FC-SEMS, 4/16; PS, 3/16; PTBD, 6/39; $P=0.66$). The rates of complications during treatment differed significantly between the groups ($P=0.04$). Stent migration occurred in 1 (6.3%) and 5 (25.0%) patients in the FC-SEMS and PS groups, respectively ($P=0.59$).
Conclusions EBS with an FC-SEMS is comparable with EBS with a PS or PTBD in terms of biliary stricture resolution and 12-month recurrence rates. The use of FC-SEMSs is potentially effective and safe for biliary AS resolution after LDLT.

Keywords Anastomotic biliary stricture · Endoscopic biliary stenting · Intra-ductal fully covered self-expanding metal stent · Plastic stent · Percutaneous transhepatic drainage

Liver transplantation (LT) developed rapidly in the 1980s and is currently the last line of treatment for end-stage liver disease and hepatocellular carcinoma [1–3]. Since 2009, more than 1,000 LTs have been performed annually in Korea [4]. More than 70% of these were living donor liver transplantations (LDLT). Unfortunately, various complications

Dong Jin Joo and Moon Jae Chung have contributed equally to this work.

Min Je Sung and Jung Hyun Jo contributed equally to this work as primary authors.

✉ Dong Jin Joo
DJJOO@yuhs.ac

✉ Moon Jae Chung
mjchung@yuhs.ac

1 Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea

2 Division of Gastroenterology, Department of Internal Medicine CHA Bundang Medical Center, CHA University, Gyeonggi-do, Republic of Korea

3 Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

can occur after an LT. In case of orthotopic liver transplantation (OLT), biliary anastomotic strictures (ASs) are the most common complication, with a reported incidence of 5–37%. ASs are especially common in LDLTs and occur at a rate of 10–37%, as compared to a rate of 5–15% in deceased donor liver transplantations (DDLTs) [5–12]. Biliary drainage through the transpapillary or percutaneous route has been established as a safe management option for biliary ASs after OLT. Endoscopic biliary stenting (EBS) with a plastic stent (PS) is the most commonly used treatment for biliary ASs after DDLTs [13–16]. Recently, EBS with a fully covered self-expandable metallic stent (FC-SEMS) was proposed to be as effective as EBS with a PS [17–20]. However, consensus regarding the optimal treatment option for biliary ASs after LDLT is lacking.

For a biliary AS after OLT, each treatment modality has its advantages and disadvantages. Although it has a success rate of 40–85%, percutaneous transhepatic biliary drainage (PTBD) is still regarded as an alternative treatment option owing to its invasive nature, the inconvenience caused to patients through percutaneous drainage, and the risk of complications, such as hemorrhage, bile leaks, and significant morbidity [11]. Therefore, PTBD is usually used as rescue therapy for patients in whom EBS has failed [21]. In contrast, endoscopic treatment is the recommended standard of care for the management of a biliary AS after OLT, and the usefulness of several techniques has been investigated, including endoscopic balloon dilatation as well as EBS with a PS and an FC-SEMS. Endoscopic balloon dilation as a monotherapy is associated with a low rate of success and a high rate of biliary AS recurrence. Currently, EBS with a PS is widely performed. However, because of the complications associated with the placement of a PS, such as stent occlusion and the requirement of frequent endoscopic sessions, FC-SEMSs were introduced as an alternative to PSs. Several studies, including randomized controlled trials (RCTs), have reported variable results when comparing an FC-SEMS to a PS [17–20]. Moreover, few studies have compared the effectiveness of the three methods—EBS using an FC-SEMS, a PS, and PTBD—for treating a biliary AS after OLT.

In Western countries, DDLTs are performed more often than LDLTs. In contrast, in Asia, LDLTs are more common because of difficulties in organ procurement from deceased donors [22, 23]. Owing to the use of a smaller graft in LDLT compared to the use of a whole liver in DDLT, the diameter of the bile ducts used for anastomosis is smaller, often leading to a size discrepancy between the ducts of the recipient and donor [24]. Moreover, biliary anastomosis following LDLT is more peripheral, smaller, and more complex and is worsened by hypertrophy of the transplanted liver [25]. Thus, LDLT is technically more challenging than DDLT in terms of biliary anastomosis [26]. Therefore, biliary complications occur more often following LDLT than following DDLT [11, 27, 28], and ASs account for approximately 80% of biliary complications occurring after LDLTs [7]. Many studies have investigated EBS as a means of resolving a biliary AS after DDLT [17–20], but relatively few studies have investigated biliary ASs after LDLT [26, 29]. Therefore, the current study focused on biliary ASs occurring after LDLT.

This study aimed to evaluate the differences in the resolution rate of biliary ASs and the 12-month recurrence rates after stent removal between EBS with an FC-SEMS, a PS, and PTBD. This information will allow physicians to optimize the treatment for biliary ASs following LDLT.

Materials and methods

Study cohort

This cohort study included consecutive adult patients (≥ 18 years of age) who underwent OLT and were treated for biliary ASs between 2014 and 2017 at Severance Hospital in Seoul, Korea. Patients were eligible for inclusion if they developed a biliary AS after LDLT, located at least 2 cm below the hepatic confluence. Patients were recruited irrespective of whether the AS was recurrent or refractory, time of AS onset, and objective symptoms or signs (e.g., elevated liver enzyme levels, jaundice, or cholangitis) related to the stricture. Patients were excluded if they were pregnant, showed non-anastomotic or hilar strictures, showed isolated biliary fistulae, showed malignant biliary strictures, or showed hepaticojejunostomy ASs (Fig. 1).

Prospectively collected data were analyzed, which included procedure details (number of endoscopic retrograde cholangiopancreatography [ERCP] procedures, number of strictures, number of stents, number of balloon procedures, history of procedures, and stent indwelling period) and data on treatment outcomes (functional and radiologic stricture resolution, stricture recurrence, time to recurrence, and procedure-related complications).

The protocol of the present study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital (IRB number: 1-2019-0060). The requirement for informed patient consent was waived by the IRB because of the retrospective study design. No organs from executed prisoners were used in this study.

Biliary stenting procedure

All ERCP procedures with therapeutic video duodenoscopy (TJF-260V) were performed by 1 of the 5 interventional endoscopists and attending physicians with an experience of at least 1000 cases (S.Y.S., S.W.P., S.M.B., J.Y.P., and M.J.C.), with or without the assistance of an interventional

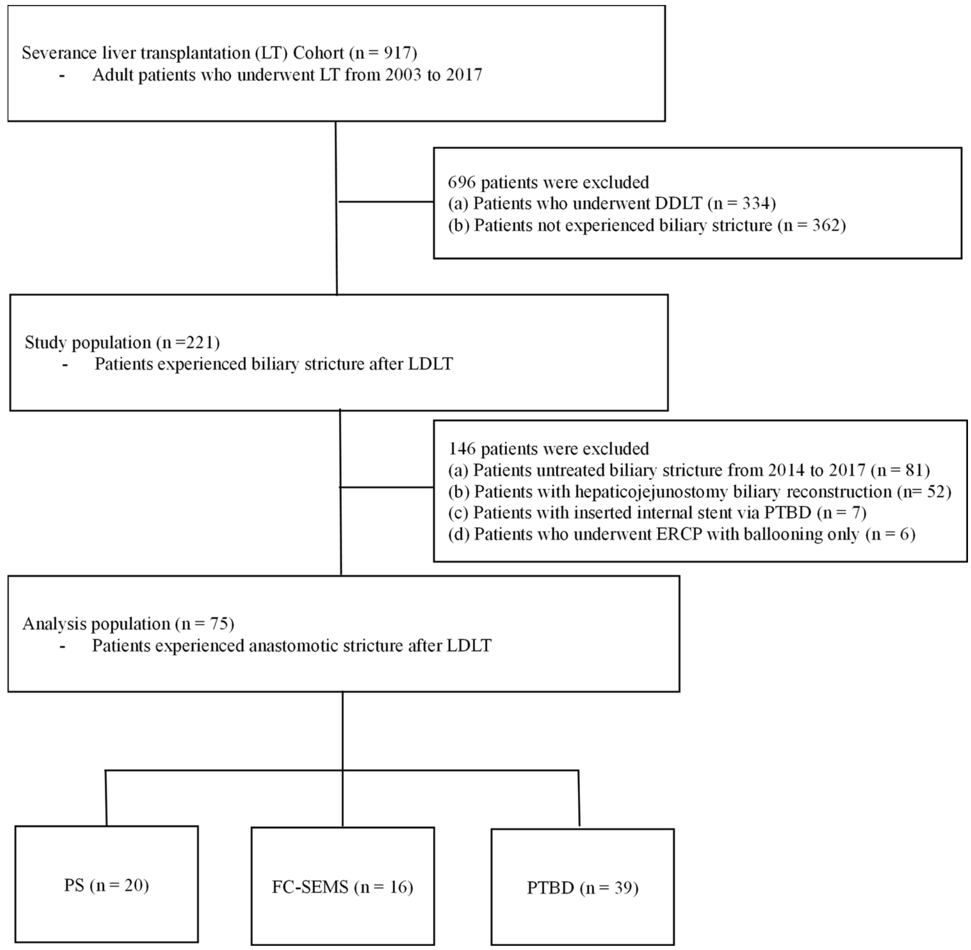

Fig. 1 Flow diagram showing the selection of study participants

endoscopy fellow. All ERCP procedures were performed with patients in the prone position. All the patients were sedated by nurse anesthetists with experience in sedation for endoscopic procedures, under directives from an attending anesthesiologist.

After selective biliary cannulation, a cholangiogram was acquired to evaluate the biliary AS, defined as a narrowing of more than 75% of the lumen. A guidewire was then passed through the AS, and either an FC-SEMS or a PS was chosen for stenting depending on the physician's discretion. Stricture grade was assessed by fluoroscopic imaging (grade A, 90–100% stricture of the luminal diameter; grade B, 75–90%) [30].

An FC-SEMS consists of an implantable metal stent and a flexible introducer system (Niti-S biliary stent, Taewoong Medical Co Ltd., South Korea). This stent has a central antimigration waist and a 10-cm radiopaque nylon string incorporated into the distal end of the stent to facilitate endoscopic retrieval [31]. The length of the stent was determined according to the length of the biliary stricture. The stents used in this study were available in four different specifications: diameter, 6 mm and length 40 mm; diameter, 8 mm and length 40 mm; diameter, 6 mm and length 60 mm; and diameter, 8 mm and length 60 mm. The decision to perform balloon dilatation of the stricture prior to insertion of the FC-SEMS was based on the physician's judgement of the possibility of the deployment device (8.5Fr) passing through the biliary AS. The stent was left in place for 4–6 months and then removed (Fig. 2A).

In patients who underwent EBS with a PS, a plastic endoprosthesis with the optimal diameter, determined as per the physician's discretion, was inserted (e.g., 7-Fr, 10-Fr). Balloon dilatation of the stricture was performed before inserting the PS. After placement of the PS, ERCP was repeated at 3-month intervals until stricture resolution. The ASs were considered to be resolved when no or minimal waist was recognized on cholangiography after stent removal (Fig. 2B). After confirming the resolution of the AS, patients were followed-up every 2–3 months without further stenting until 1 year after stent removal to evaluate AS recurrence.

Patients treated with EBS with PTBD were premedicated with an analgesic (50 µg of fentanyl); this was followed by skin disinfection and injection of a local anesthetic (20 mL of 1% lidocaine). The PTBD procedures were performed by experienced radiologists following

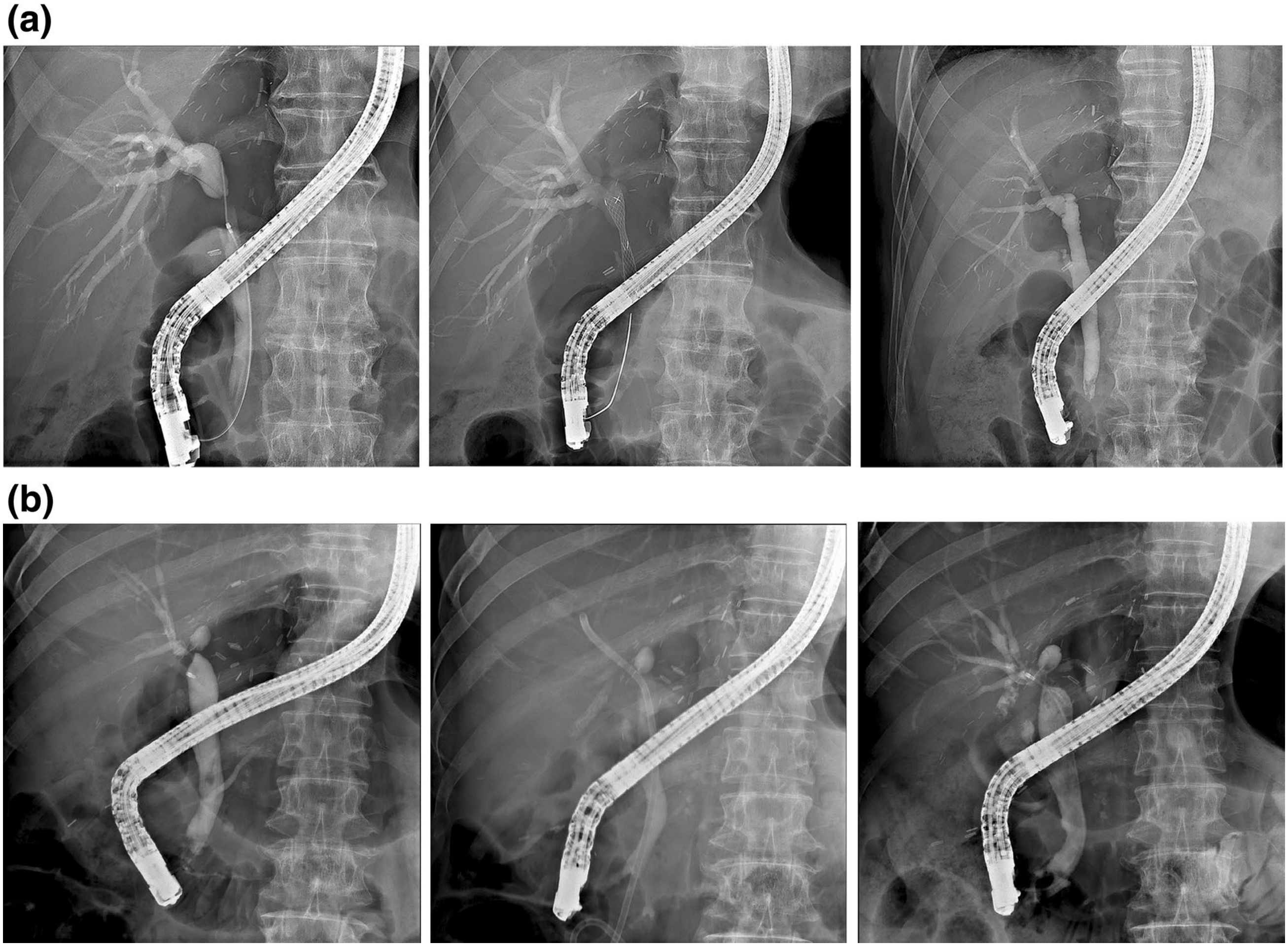

Fig. 2 Fluoroscopy with endoscopic biliary stenting (EBS) with a fully covered self-expandable metallic stent (FC-SEMS) and plastic stent (PS) for an anastomotic stricture (AS) after living donor liver transplantation (LDLT). **A** Fluoroscopy with EBS with a FC-SEMS. (a1) The AS after LDLT is found during endoscopic retrograde cholangiopancreatography (ERCP). (a2) An FC-SEMS is inserted at the AS. (a3) Improvement of AS after stent removal. **B** Fluoroscopy with EBS using a PS. (b1) The AS after LDLT is found during ERCP. (b2) A PS is inserted at the AS. (b3) The AS persists even after stent removal

established and well-described techniques [32]. Either the right-sided subcostal or the intercostal approach was chosen at the discretion of the radiologist. Thereafter, an angioplasty balloon catheter was inserted across the stricture and inflated gradually until the waist disappeared. Following placement of the drainage catheter, cholangiography was repeated at 2-month intervals until stricture resolution.

Outcome measures

The primary endpoints were the rates of functional and radiologic stricture resolution and 12-month recurrence rates. Functional stricture resolution was defined as no or minimal visualization of waist on cholangiography after stent removal. Radiologic resolution was defined based on the following fluoroscopic criterium: the residual diameter of the stricture corresponded to 75% or more of the diameters of the ducts above and below the stricture. We used functional resolution as the standard for stricture resolution, and radiologic resolution was used for comparison with functional resolution. Following stricture resolution, all patients were followed-up clinically for at least 1 year. We defined stricture recurrence as the presence of a bile duct stricture confirmed on ERCP or cholangiography with associated signs or symptoms.

The secondary endpoints were the frequencies of stent-related complications during treatment or at stent removal. Complications included stent migration, jaundice, and cholangitis. During a follow-up period of 1 year, patients presented to our interdisciplinary transplantation clinic routinely every 2–3 months, where liver function tests were performed to evaluate whether relevant biliary AS recurrence had occurred.

Statistical analysis

The normality of data was tested before the application of statistical analysis. For categorical variables, statistical analyses were performed using the Pearson chi-square test, Fisher's exact test, and Fisher–Freeman–Halton exact test. For quantitative variables, we used the Student's *t* test, one-way analysis of variance, Mann–Whitney *U* test, and Kruskal–Wallis test. Continuous variables are presented as medians and ranges, and categorical variables are reported as frequencies and percentages. If there were statistically significant differences between the three groups, an additional pairwise analysis was performed to compare different pairs within the groups. All tests were 2-sided, and a P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 25.0, IBM., New York, NY, USA). All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients

Of the 75 patients who underwent procedures after AS diagnosis, 16 patients underwent EBS with an FC-SEMS, 20 patients with a PS, and 39 patients with PTBD (Fig. 1). The proportion of male participants was 76.1%, and the mean age of the patients was 57.3 years. The median time to AS presentation after OLT was 6.6 (range 0.5–86.8) months. The baseline characteristics of the study population are summarized in Table 1. The proportion of men, cause of LT, and median time to AS onset were not significantly different between patients who were treated with EBS with an FC-SEMS, a PS, and PTBD ($P > 0.05$) (Table 1). The mean age was significantly different between patients who underwent EBS with an FC-SEMS (57.5 years) and a PS (54.2 years) and those who underwent EBS with PTBD (58.7 years) ($P = 0.04$); this difference was especially marked between the PS and PTBD groups (P values: FC-SEMS–PS, 0.37; PS–PTBD, 0.04; FC-SEMS–PTBD, > 0.99) (Table 1). Ten patients who were treated with an FC-SEMS (10/16, 62.5%) had been previously treated with a PS (6 patients, 37.5%), PTBD (3 patients, 18.8%), and both PS and PTBD (1 patient, 6.3%). Five patients treated with a PS (5/20, 25.0%) had been previously treated with PTBD. Nine patients treated with PTBD (9/39, 23.1%) had been previously treated using a PS (5 patients, 12.8%), PTBD (3 patients, 7.7%), and both PS and PTBD (1 patient, 2.6%) (Table 2). Patients who had been previously treated using a PS and PTBD are included under patients treated with PTBD in Fig. 3. In addition, among 39 patients with PTBD, 5 patients (12.8%) underwent PTBD for bile duct anastomosis, such as two separated bile ducts; in addition to 14 (35.9%) for failed ERCP, such as difficult cannulation into anastomosis stricture; 4 (10.3%) for status within 1 month of surgery; and 16 (41.0%) due to surgeon preferences.

Procedure details

The number of strictures was not significantly different between any pair of methods ($P > 0.05$). The number of ERCPs required was lower in the FC-SEMS group than

Table 1 Baseline characteristics

	FC-SEMS (*N* = 16)	PS (*N* = 20)	PTBD (*N* = 39)	*P*-value (FC-SEMS:PS/PS:PTBD/FC-SEMS:PTBD)
Male sex, *N* (%)	13 (81.3%)	17 (85.0%)	27 (69.2%)	0.401
Age, mean ± SD	57.5 ± 6.1	54.2 ± 6.3	58.7 ± 6.6	0.041 (0.366/0.039/ > 0.999)
Cause of LT, *N* (%)				0.455
B viral LC	5 (31.3%)	4 (20.0%)	7 (17.9%)	
C viral LC	0 (0.0%)	0 (0.0%)	0 (0.0%)	
B viral HCC	5 (31.3%)	9 (45.0%)	22 (53.8%)	
C viral HCC	1 (6.3%)	0 (0.0%)	1 (2.6%)	
Non-B non-C LC	2 (12.5%)	6 (30.0%)	8 (20.5%)	
Non-B non-C HCC	3 (18.8%)	1 (5.0%)	2 (5.1%)	
Time of AS onset, months, median (IQR)	9.8 (0.5–37.2)	6.0 (0.5–72.9)	5.4 (0.4–86.8)	0.923

PS plastic stent, *FC-SEMS* full covered self-expanding metal stent, *PTBD* percutaneous transhepatic biliary drainage, *SD* standard deviation, *LT* liver transplantation, *LC* liver cirrhosis, *HCC* hepatocellular carcinoma, *AS* anastomosis stricture, *IQR* interquartile range

Table 2 Procedure details

	FC-SEMS (*N* = 16)	PS (*N* = 20)	PTBD (*N* = 39)	*P*-value (FC-SEMS:PS/PS:PTBD/FC-SEMS:PTBD)
Previous procedures, *N* (%)				0.005 (0.012/0.282/0.075)
Naive	6 (37.5%)	15 (75.0%)	30 (76.9%)	0.013 (0.069/ > 0.999/0.015)
Plastic stent	6 (37.5%)	0 (0.0%)	5 (12.8%)	0.005 (0.012/0.468/0.183)
PTBD	3 (18.8%)	5 (25.0%)	3 (7.7%)	0.188
Plastic stent and PTBD	1 (6.3%)	0 (0.0%)	1 (2.6%)	0.452
Number of strictures, median (range)	1	1 (1–2)	1 (1–2)	0.045 (> 0.999/0.576/0.144)
Number of ERCPs, median (range)	2 (2–5)	3 (1–9)	–	0.197
Number of stents, median (range)	1.0 (1–3)	2 (1–8)	–	0.043
Number of ballooning, median (range)	0.5 (0–2)	1.5 (0–7)	1 (0–4)	0.010 (0.492/ > 0.999/0.003)
Stent indwelling period, months, median (range)	4.7 (3.0–7.0)	9.3 (0.5–48.5)	5.4 (3.2–9.1)	0.006 (0.105/0.249/0.006)

PS plastic stent, *FC-SEMS* full covered self-expanding metal stent, *PTBD* percutaneous transhepatic biliary drainage, *ERCP* endoscopic retrograde cholangiopancreatography

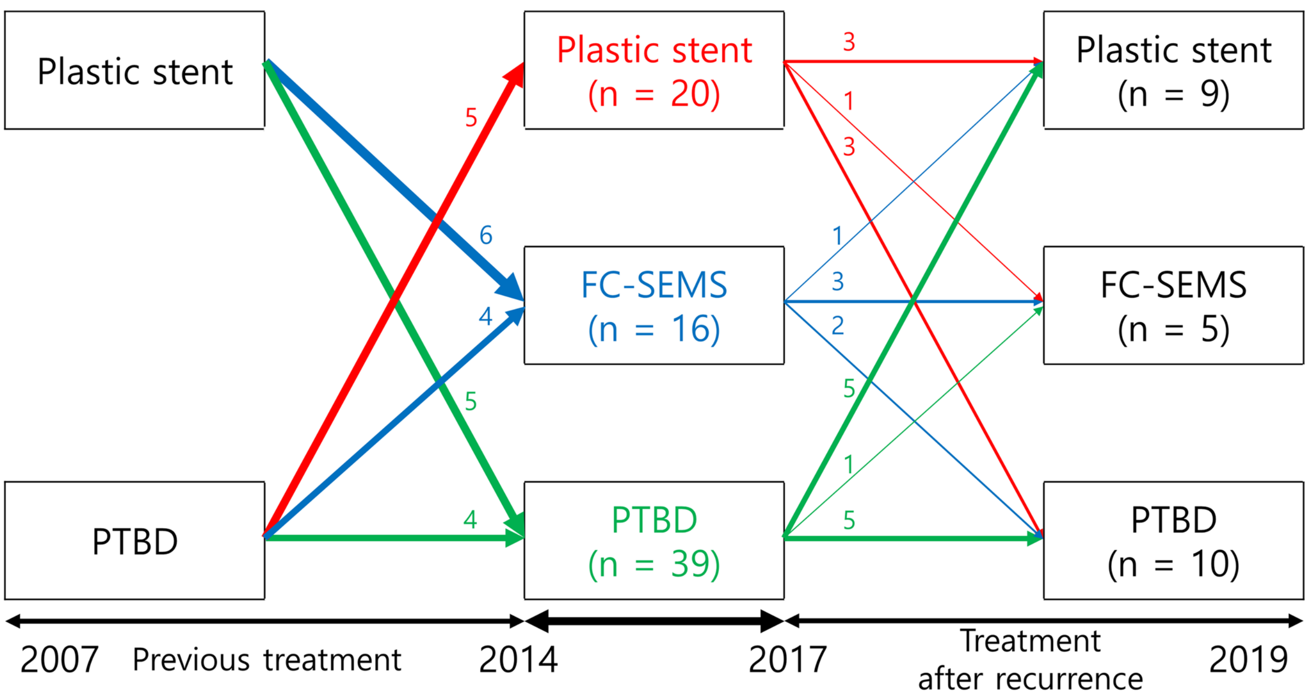

Fig. 3 Flow chart showing previous treatments and treatments after recurrence

in the PS group (median: 2 vs. 3, respectively), but the difference was not statistically significant ($P = 0.20$). The number of stents inserted during the treatment period was significantly lower in patients treated with a FC-SEMS than in those treated with a PS (median: 1 vs. 2; $P = 0.04$). The number of balloon procedures was significantly different during the 3-month follow-up interval ($P = 0.01$), and this difference was especially marked between those treated with an FC-SEMS and PTBD (median: 0.5 vs. 1; $P = 0.003$). The stent indwelling period was 4.7 months (range, 3.0–7.0) in the FC-SEMS group, 9.3 months (0.5–48.5) in the PS group, and 5.4 months (3.2–9.1) in the PTBD group. There was a marked difference in stent indwelling period between the FC-SEMS and PTBD groups (*P* values: FC-SEMS–PS, 0.11; PS–PTBD, 0.25;

Table 3 Treatment outcomes

	FC-SEMS ($N=16$)	PS ($N=20$)	PTBD ($N=39$)	P-value (FC-SEMS:PS/PS:PTBD/FC-SEMS:PTBD)
Stricture resolution (functional), N (%)	16 (100.0%)	16 (80.0%)	39 (100.0%)	0.005 (0.339/0.033/-)
Stricture resolution (Radiologic), N (%)	16 (100.0%)	14 (70.0%)	35 (89.7%)	0.019 (0.072/0.222/0.933)
Stricture recurrence, N (%)*	6/16 (37.5%)	7/16 (43.8%)	11/39 (28.2%)	0.509
3 months	1/16 (6.3%)	1/16 (6.3%)	1/39 (2.6%)	0.585
6 months	2/16 (12.5%)	1/16 (6.3%)	4/39 (10.3%)	>0.999
12 months	4/16 (25.0%)	3/16 (18.8%)	6/39 (15.4%)	0.659
Time to recurrence, mo., median (range)	8.8 (2.8–22.7)	12.1 (2.3–35.7)	11.0 (2.6–43.9)	0.908
Treatment after recurrence, N (%)[a]				0.455
FC-SEMS	3/6 (50.0%)	1/7 (14.3%)	1/11 (9.1%)	
PS	1/6 (16.7%)	3/7 (42.9%)	5/11 (45.5%)	
PTBD	2/6 (33.3%)	3/7 (42.9%)	5/11 (45.5%)	

PS plastic stent, *FC-SEMS* full covered self-expanding metal stent, *PTBD* percutaneous transhepatic biliary drainage

[a]Stricture recurrence rate was calculated in patients with stricture resolution after treatment

FC-SEMS–PTBD, 0.006; Table 2). Differences in stricture grade before treatment were not statistically significant among three groups ($P=0.115$) (Supplementary Table 1).

Treatment outcomes

The rate of functional resolution tended to be lower in the PS group than in the FC-SEMS or PTBD group. The stricture resolution rate was different between EBS with a PS and EBS with PTBD (16/20 vs. 39/39, respectively; $P=0.03$). The rates of radiologic resolution were different between all three treatment methods ($P=0.02$), but there were no significant differences between any pair of methods (Table 3).

The 12-month recurrence rate was not significantly different between patients who underwent EBS with an FC-SEMS (4/16), a PS (3/16), or PTBD (6/39) ($P=0.66$). On analysis after dividing the follow-up period into 3, 6, and 12 months, there was still no significant difference between the three methods. Moreover, with regard to the time to recurrence, which was defined as the time between stent removal and recurrence after stricture resolution, there was no significant difference between the three methods ($P=0.91$). Six cases of AS recurrence (6/16, 37.5%) within a median follow-up duration of 8.8 (2.8–22.7) months were observed in patients treated with an FC-SEMS; six (7/16, 43.8%) cases were observed within 12.1 (2.3–35.7) months of treatment with a PS, and 11 (11/39, 28.2%) cases were observed within 11.0 (2.6–43.9) months of treatment with PTBD (Table 3). Patients who experienced AS recurrence were treated successfully with EBS with an FC-SEMS (5/24, 20.8%), a PS (9/24, 37.5%), and PTBD (10/24, 41.7%) ($P=0.46$) (Table 3, Fig. 3).

On subgroup analysis, there were no significant differences in the rate of stricture recurrence after radiologic resolution between the three methods (Supplementary Table 2). In addition, we analyzed the correlation between the onset of biliary AS and stricture recurrence between the three methods. When the onset cutoff was 3 months, there were no significant differences between the three methods (Supplementary Table 3).

Procedure-related adverse events

All attempted stent removal procedures were successful without any technical problems. Analysis of the rate of complications during treatment showed a significant difference between the three methods ($P=0.04$). Stent migration was seen in only 1 patient (6.3%) treated with a FC-SEMS and in 5 patients (25.0%) treated with a PS ($P=0.59$). There was also a significant difference among the three methods in the rate of complications at stent removal ($P=0.009$), especially between patients treated with a PS and PTBD ($P<0.001$). At stent removal, biliary sludge and stones were present in 45% of patients treated with a PS, and cholangitis occurred in 10.3% of patients treated with PTBD. Biliary stones were present in 5 patients (25.0%) treated with a PS, but this value was not significantly different between patients treated with an FC-SEMS and a PS ($P=0.05$). Cholangitis did not develop in any patient treated with a PS, but developed in 2 patients treated with an FC-SEMS (12.5%) and in 4 patients

Table 4 Adverse events

	FC-SEMS ($N=16$)	PS ($N=20$)	PTBD ($N=39$)	P-value (FC-SEMS:PS/PS:PTBD/FC-SEMS:PTBD)
Rate of complication during treatment, N (%)	3/16 (18.8%)	10/20 (50.0%)	8/39 (20.1%)	0.038 (0.156/0.060/ > 0.999)
Cholangitis	2 (12.5%)	3 (15.0%)	6 (15.4%)	> 0.999
Migration	1 (6.3%)	5 (25.0%)	2 (5.1%)	0.061
Jaundice	0 (0.0%)	2 (10.0%)	0 (0.0%)	0.112
Rate of complication at removal, N (%)	5/16 (21.3%)	9/20 (45.0%)	4/39 (10.3%)	0.009 (> 0.999/ < 0.001/0.309)
Sludge	3 (18.8%)	4 (20.0%)	–	0.999
Stone	0 (0.0%)	5 (25.0%)	–	0.053
Cholangitis	2 (12.5%)	0 (0.0%)	4 (10.3%)	0.285

PS plastic stent, *FC-SEMS* full covered self-expanding metal stent, *PTBD* percutaneous transhepatic biliary drainage

treated with PTBD (10.3%); however, there was no significant difference among the three groups ($P=0.29$) (Table 4).

Discussion

In the current study, we performed analyses designed to evaluate the resolution rates and 12-month recurrence rate after stent removal among patients who underwent EBS with an FC-SEMS, a PS, and PTBD for the management of biliary ASs after LDLT. Of these methods, the use of FC-SEMSs tended to be superior to the use of PSs in terms of the rate of functional resolution (100 vs. 80.0%, respectively); EBS with the former required fewer ballooning procedures than EBS with the latter (FC-SEMS 0.5 [0–2] vs. PS 1.5 [0–7]), although the differences were not significant ($P=0.34$). We suspect that the resolution rate of biliary AS is higher with EBS with an FC-SEMS than with EBS with a PS because of the difference in radial forces exerted by both stents. In contrast, there was no significant difference in 12-month recurrence rates among the three methods ($P=0.51$). Three previous RCTs have shown that the use of FC-SEMSs is associated with a higher rate of biliary stricture recurrence than the use of PSs; however, Kaffes et al.'s study did not show this result [17–20]. Although the indwelling period of an FC-SEMS was 4 months in our study, the optimal duration for metal stent placement is unclear. This is one key area that needs further investigation. A longer duration of stent placement without the risk of stent migration would be beneficial and would allow for longer in situ stent placement and fibrous tissue remodeling [33]. Moreover, the longer indwelling period of an FC-SEMS may contribute to the lower recurrence rate, although there is a risk of complications, such as bile duct injuries, migration, and stent occlusion [18, 20].

In the United States, where DDLTs have been mainly performed for end-stage liver disease, the number of living donor transplants has gradually increased since 2010 [34]. Thus, complications of LDLT, such as biliary AS, have drawn greater interest. The current study focused on the treatment of biliary ASs after LDLT and not DDLT. Most previous studies conducted in Western countries have examined patients who underwent DDLT; therefore, only the results of few studies are applicable to Asian patients, who mainly undergo LDLT [17–20, 23, 35]. Hence, there is a need to identify a suitable treatment modality for biliary ASs that occur following LDLT. In our study, compared with the use of a PS, use of an FC-SEMS required fewer ERCP procedures and showed a shorter stent indwelling period, which implies that an FC-SEMS is more convenient for the use in patients with a biliary AS than a PS. The reduced requirement for ERCP procedures also reduces the risks of procedure-related adverse events (AE) as well as the length of hospital stay, which consequently reduces the overall medical cost.

The stent migration rate can be reduced by using an FC-SEMS with an antimigration waist rather than a conventional FC-SEMS. In previous studies, which used a conventional FC-SEMS, the stent migration rate was 10–33.3%, whereas in the current study, it dramatically reduced to 6.3%. However, an exact comparison of stent migration rates with those of conventional FC-SEMSs may be problematic due to the variety of LT procedures used. In our study, the stent migration rate with a PS (5/20, 25.0%) was higher than that with an FC-SEMS with an antimigration waist. Although FC-SEMSs are gaining acceptance for the treatment of benign biliary stricture (BBS), in this scenario, stent migration remains the most concerning complication due to poor durability. In a large multinational study by Devière et al. [36], it was suggested that a traditional FC-SEMS is more suited for distal strictures associated with chronic pancreatitis; however, these stents perform poorly in cases of strictures in the upper common bile duct (CBD), such as ASs, or those in the common hepatic duct, such as post cholecystectomy strictures. In this study, we used intraductal FC-SEMSs designed for BBS with characteristics such as an antimigration waist, a short stent length, and a long removal string. This appears to be a suitable stent, especially for strictures of the upper CBD or common hepatic duct, and they had a low rate of migration in cases of ASs after OLT [17, 31].

Many studies have compared the outcomes of endoscopic treatment using a FC-SEMS and a PS; however, few studies have compared the usefulness of PTBD [29]. In comparison to EBS with a FC-SEMS and a PS, PTBD can cause severe pain to the patient during or after the procedure. Patients treated with PTBD also require additional time for tube management, which consists of dressing and drainage of the bile bag during the treatment period. Therefore, PTBD is inconvenient for patients and is usually used as an alternative treatment when effective endoscopic drainage cannot be achieved by ERCP. Our study showed that there were no significant differences between PTBD and endoscopic treatment with an FC-SEMS or a PS in terms of stricture resolution rate ($P = 0.51$) or the rate of complications during treatment (P values: FC-SEMS–PTBD, > 0.99; PS–PTBD, 0.06). This implies that if there is no difference in clinical outcomes between the three methods used for treating a biliary AS following LDLT, EBS should be considered as the first choice of treatment from the patient's point of view.

The onset of AS most often occurs within the first year after OLT [30, 37]. When ASs occur within the first month of LT, they are usually caused by technical surgical problems [38]. Bile leakage, one of the commonly encountered postoperative complications, is closely associated with biliary strictures, and the high incidence of bile leakage may be the most important factor in stricture formation after LDLT [27, 39, 40]. Bile leakage can occur 75 days after LDLT [30]. Therefore, we set 3 months as the cutoff period for measuring the onset of AS. No case of biliary leakage could be confirmed in our study; however, to exclude strictures due to biliary leakage, we conducted a comparison of recurrence rates or the time to recurrence between patients with early (≤ 3 months) and late onset (> 3 months) of AS. We found that the recurrence rate and time to recurrence were not significantly different between the early and late groups (recurrence rate, $P = 0.68$; time to recurrence, $P = 0.39$). Although previous studies have reported varying results, some studies have reported that early ASs had lower recurrence rates [27, 38]. Therefore, our study showed that the onset of AS did not correlate with the recurrence rate and time to recurrence.

Our study had several limitations. First, the sample size was not large enough to conclusively establish the effectiveness of each modality. Since the number of patients investigated is small, even one outlier can greatly affect the median values. For example, patients treated with FC-SEMSs tended to have a shorter time to recurrence than patients treated with PSs because of one outlier (35.7 months). Moreover, the mean age of the patients among the three groups was significantly different ($P = 0.04$), especially between patients treated with EBS with a PS and those treated with PTBD (54.2 vs. 58.7, $P = 0.01$). Although recipient age is not a predisposing factor for biliary strictures following OLT, donor age is correlated to biliary strictures [41, 42]. Therefore, small differences in the patients' age and baseline characteristics would not have a big enough impact for these factors to be classified as confounding factors. Furthermore, there was a small number of patients treated with EBS with FC-SEMS as the initial treatment modality: EBS with FC-SEMS was not commonly used when the patients with biliary AS were treated by EBS with PS or PTBD. Recently, EBS with FC-SEMS has been performed mainly in biliary AS of LDLT. In previous studies, the number of stents used in patients who underwent EBS with a PS was higher than that in our study. Endoscopic therapy is the preferred treatment for a biliary AS post-LT, and PSs are the gold-standard of stents used to treat an AS. Presently, the use of a single PS is not recommended, as reported by van Boeckel et al. who published an excellent and comprehensive review that showed the limitations of the use of a single PS for BBS [43]. A single PS has poor durability, and the occurrence of AEs is unacceptably high. Hence, single PS interventions should only be used as an initial approach in very select cases before applying definite strategies [33]. However, most of the previous studies were performed on patients who underwent DDLT, while our study was performed on patients who underwent LDLT. Deployment of a large-bore or multiple PSs is challenging, especially in patients who have undergone LDLT, because the small donor bile duct and angulated biliary system in LDLT patients often precludes the deployment of multiple PSs [44, 45]. Therefore, compared to the previous studies that mainly investigated patients who underwent DDLT, our study included a relatively large number of patients who underwent the insertion of only one PS.

Conclusion

The use of an FC-SEMS was comparable with the use of PSs or PTBD in terms of stricture resolution rates and 12-month recurrence rates for the treatment of biliary ASs after LDLT. EBS with an FC-SEMS led to the need for fewer ERCP procedures and a shorter treatment period than EBS with a PS. Furthermore, the rates of complications during treatment or at stent removal in the FC-SEMS group were not different than those in the PS and PTBD groups. Our study suggests that EBS with FC-SEMSs may be an effective and safe treatment option for biliary ASs after LDLT. A well-designed prospective study will be required for the verification of these results.

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Compliance with ethical standards

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