Metal versus plastic stents for anastomotic biliary strictures after liver transplantation: a randomized controlled trial

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Background and Aims: Biliary anastomotic stricture occurs in 15% to 20% of patients after deceased orthotopic liver transplantation (OLT). It is usually treated endoscopically with multiple plastic stents (MPSs), although the use of fully covered self-expandable metal stents (cSEMSs) is emerging. This study aims to compare the efficacy and safety of cSEMSs versus MPSs in these patients.

Methods: A single-center, open-label, randomized clinical trial was performed. Patients were randomized to single cSEMSs for 6 months or to MPS placement, exchanged every 3 months over 1 year. The primary outcome was stricture resolution. Crossover therapy was considered for failure or recurrence**.** Secondary outcomes were sustained improvement, morbidity, and mortality.

Results: Between October 2009 and January 2014, 162 patients with post-OLT biliary adverse events were assessed for eligibility. Sixty-four were prospectively randomized (1:1) to cSEMSs or MPSs. Baseline characteristics were comparable. Technical success was 100%. Median follow-up was 36.4 and 32.9 months for the cSEMS and MPS groups, stricture resolution at last stent removal was achieved in 83.3% and 96.5% ($P = .19$), and stricture recurrence was observed in 32% and 0%, respectively ($P < .01$). Adverse events occurred in 23.3% and 6.4% of ERCPs in the cSEMS and MPS groups, respectively ($P < .01$), with 13.3% of acute pancreatitis in the cSEMS group and 2.1% in the MPS group ($P < .01$).

Conclusions: cSEMSs were comparable with MPSs regarding post-OLT biliary anastomotic stricture resolution. cSEMSs allowed fewer procedures and had a positive effect on cost. Duration of treatment with cSEMSs should be further investigated. Sphincterotomy should be considered for all patients. (Clinical trial registration number: NCT 01148199.) (Gastrointest Endosc 2018;87:131-40.)

(footnotes appear on last page of article)

BACKGROUND AND AIMS

Biliary lesions are the most frequent complication after orthotopic liver transplantation (OLT).[1-4] Biliary anastomotic strictures (BASs) affect 15% to 20% of patients after deceased OLT and 19% to 40% after living donor liver transplantation.[1-3]

Endoscopy is the first-line therapy for patients with duct-to-duct anastomosis.[1-3] The major drawback of current endoscopic treatment with balloon dilation and multiple plastic stent (MPS) placement is the need for multiple procedures. Covered self-expandable metal stents (cSEMSs) have a plastic covering, which prevents tissue ingrowth, making it very appealing for benign biliary strictures.[4-12]

Early studies with partially and fully covered SEMSs in benign biliary strictures have shown encouraging results.[6,10-13] One randomized trial on post liver transplant with a small sample size demonstrated a reduced number of ERCP procedures needed to achieve stricture resolution with a similar recurrence rate and fewer adverse events, making it cost-effective.[12]

To date, there is no large single-center trial comparing cSEMSs with MPSs in the management of BASs after deceased OLT. The current study was therefore set up to prospectively compare the efficacy and safety of cSEMSs versus MPSs as first-line therapy in patients with BAS after OLT.

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METHODS

This is a single-center, prospective, open-label, randomized (1:1), parallel-group study conducted in Hospital Israelita Albert Einstein (HIAE), São Paulo, Brazil. HIAE is a large, open-access, private tertiary care referral center where approximately 150 OLTs are performed yearly. Our hospital is accredited by the Joint Commission International and is one of the most important transplant centers in South America.

Patients

Eligible participants were those with suspected BAS after deceased OLT without any previous treatment. The suspicion was based on our institution's diagnostic algorithm, presented as Supplementary Figure 1 (available online at www.giejournal.org).

Inclusion criteria were individuals aged between 18 and 75 years old, with diagnosis of post-OLT BAS and indication for endoscopic therapy. The stricture should be located at least 2 cm below hepatic confluence. Randomization occurred after successful passage of a guidewire through the stricture into the proximal biliary tree during index cholangiography. Exclusion criteria were pregnancy, nonanastomotic or hilar stricture, isolated biliary fistulae, hepatic artery stenosis/thrombosis, refusal for randomization, and OLT within 1 month of the endoscopic procedure.

Between October 2009 and January 2014, all consecutive patients referred to our endoscopy center were considered for the study and consented before the examination. Cholangiography was performed to evaluate the presence of BASs and establish compliance with the inclusion and exclusion criteria. Once eligibility was confirmed, individuals were randomized and allocated (1:1) according to a computer-generated randomization sequence enclosed in sequentially numbered, opaque, sealed envelopes containing a card identifying the treatment group. All procedures concerning concealment were conducted by one of the study investigators.

This study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was approved by our Institution's Human Research Committee.

All patients provided written consent before the index ERCP. Patients in whom a guidewire could not be passed through the stricture, although previously consented, were removed from the study and are shown as excluded patients on the flowchart (Fig. 1).

Procedures

All ERCPs were performed with therapeutic videoduodenoscopes (TJF180, TJF160, or TJF140, Olympus Optical Co, Ltd, Tokyo, Japan) with patients under monitored anesthesia. The endoscopists involved had at least 10 years' experience with an average volume of 5 cases a week.

After selective biliary cannulation, a cholangiogram was obtained to evaluate the biliary anastomosis. Anastomotic stricture was defined as a thin, short, localized, and isolated narrowing in the area of biliary anastomosis (Fig. 2A) and usually, but not necessarily, associated with dilated intrahepatic ducts. A guidewire was then passed through and the patient randomized to either a cSEMS or MPS as described above.

The stricture could not be traversed in 7 patients because it was severely narrowed. We tried different wires (various tips and caliber), a rotational sphincterotome, and occlusion balloon to straighten the choledochal duct. All of these patients were referred to same-day percutaneous drainage.

In the cSEMS group, the length of the stent was determined according to the distance measured from the biliary anastomosis to the papilla. The stents should be long enough to be 1 cm above the stricture, and exteriorize the papilla for no more than 1 cm. A cSEMS (Wallflex, Boston Scientific, 10 mm in diameter, 60 or 80 mm in length) was then advanced over the guidewire, with or without sphincterotomy, until final deployment. Dilation was not performed unless necessary.

Based on the current literature data when the study was initiated, removal was scheduled after 6-month indwelling (Fig. 2B).

In the MPS group, biliary sphincterotomy was performed to allow placement of multiple stents. The BAS was dilated with a hydrostatic balloon (Fig. 3A and B) to the maximum safe diameter at the endoscopist's discretion (6-10 mm), and the maximum number of plastic stents that could be accommodated within the stricture was deployed. ERCP was repeated at 3-month intervals. All plastic stents were then removed, the stricture was progressively dilated, and an increasing number of stents (Fig. 3C) were placed at each session, until 12 months of therapy.

ERCP was performed earlier than per protocol for both groups in all cases of suspicious stent occlusion or migration, usually detected by abnormal liver function tests (LFTs).

Endpoints

The primary endpoint was BAS resolution after cSEMS or MPS therapy. The investigators determined successful stricture resolution if, at the final stent removal, there was no or only minimum waist discerned on cholangiography and a 12-mm extraction balloon could easily pass through the anastomosis (Fig. 3D). Treatment failure was defined as persistence of stricture at the final ERCP for stent removal, at 6 or 12 months after the index therapeutic ERCP for the cSEMS and MPS groups, respectively.

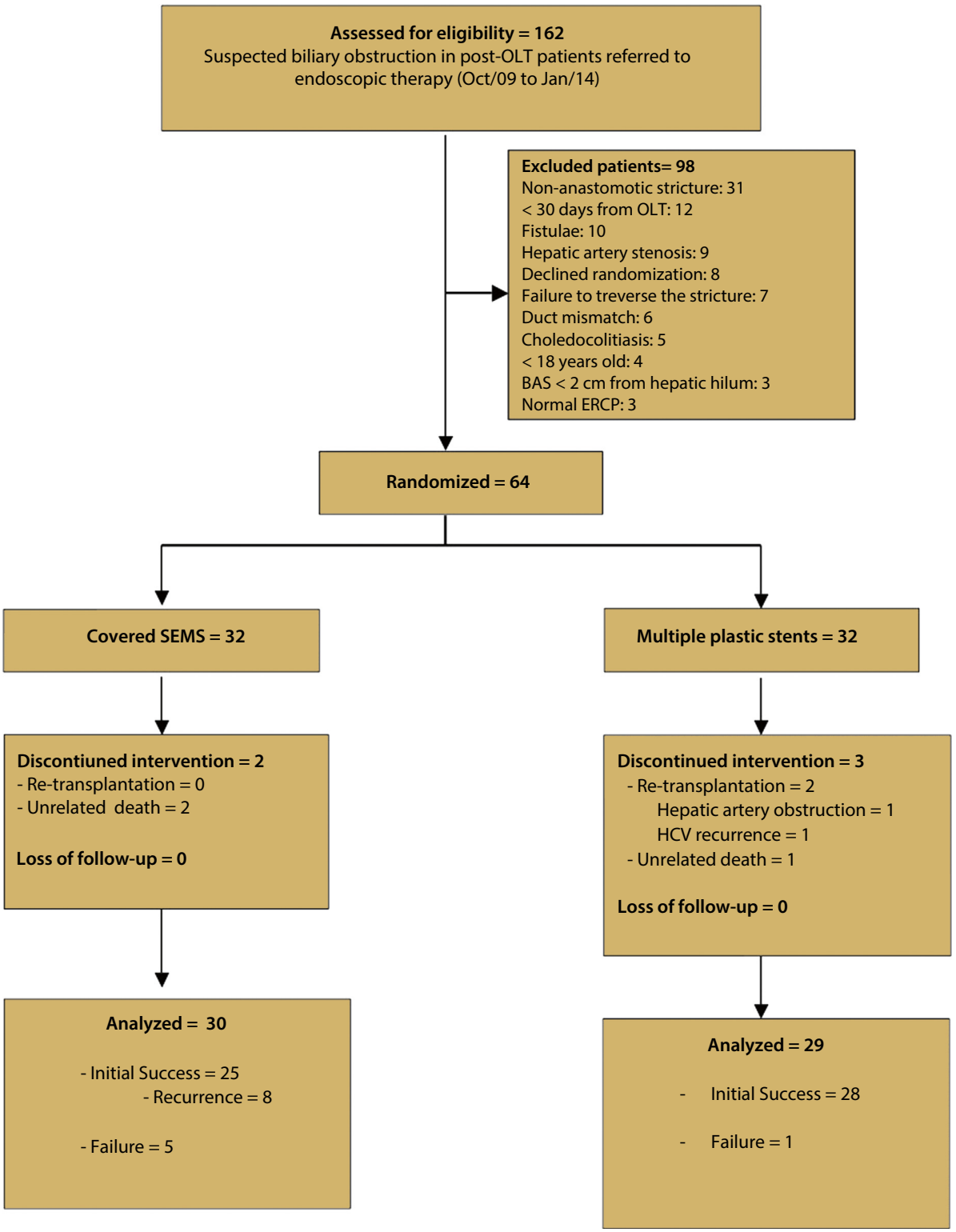

Figure 1. Flowchart of selection of participants in the study. *BAS*, biliary anastomotic stricture; *SEMS*, self-expandable metal stent; *OLT*, orthotopic liver transplantation; *HCV*, hepatitis C virus.

After stricture resolution, all patients were followed clinically for at least 1 year. Secondary endpoints were sustained resolution, morbidity, and mortality.

Stricture recurrence was defined as reappearance of clinical symptoms, with or without increased results for LFTs and imaging evidence of obstruction at the anastomosis site requiring another interventional procedure after

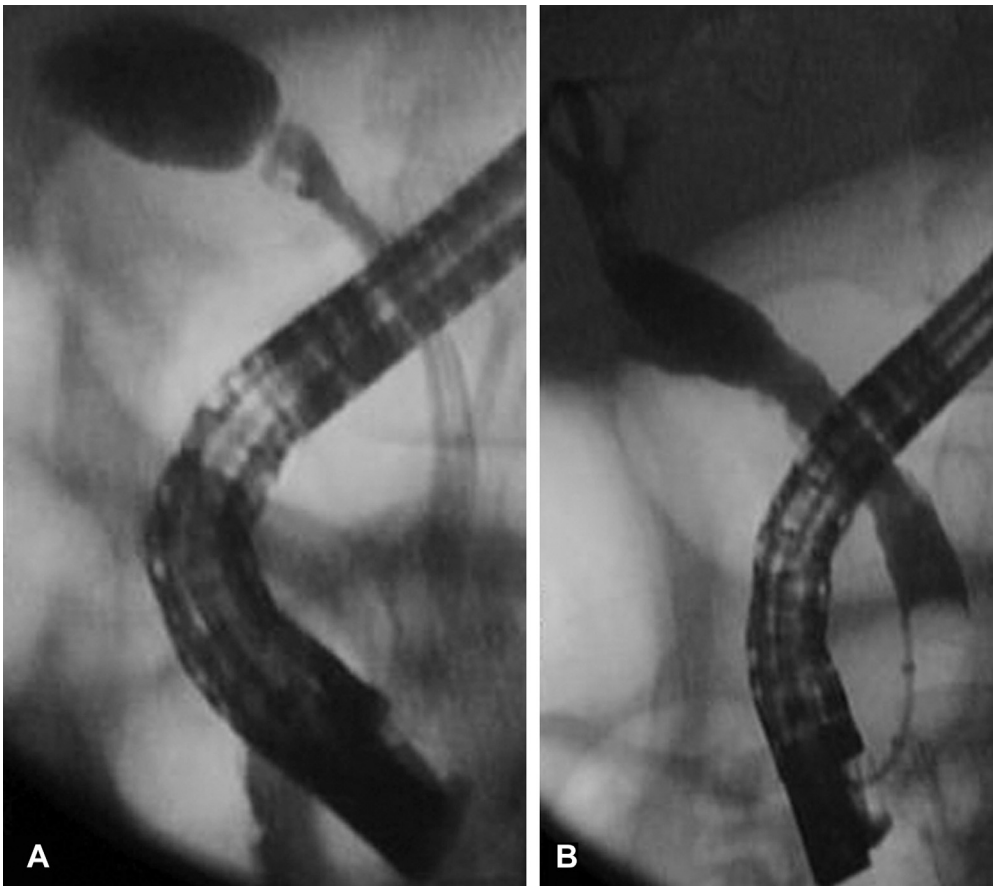

Figure 2. ERCP revealing a post-orthotopic liver transplantation anastomotic biliary stricture (**A**). The patient was treated with a single fully covered self-expandable metal stent, an and occlusion cholangiogram after removal of the stent 6 months later disclosed stricture resolution (**B**).

initial success. Sustained successful outcome after completion of endoscopic therapy was defined as clinical resolution without the need to repeat endoscopic, percutaneous, or surgical treatment until the end of follow-up. Crossover treatment was proposed for all patients presenting treatment failure or recurrence.

Adverse events related to endoscopic therapy were classified as minor (pain, stent migration or clogging, mild cardiopulmonary distress) or major (bleeding, acute pancreatitis, severe cardiopulmonary distress) and graded as previously published by Cotton et al.[14]

Statistics

The expected resolution rate of 90% for the cSEMS group used to calculate the sample size was based on previously published data,[13] and the resolution rate of 73% for the MPS group was based on the current data from our institution.[15] The type 1 error (α) level and statistical power used were 5% and 70%, respectively. The resulting target sample size per study group was 62 (EPI Info 6.0).

As discussed below, we observed a much higher stricture recurrence rate in the cSEMS group, and therefore we decided to evaluate our results when half of the cases had been completed. Consequently, as our final judgment, we interrupted the current study, and changed our treatment approach (see Discussion).

Continuous data were reported using the mean, standard deviation, median, and range. Statistical testing performed between groups was done using the Wilcoxon rank-sum test for continuous variables, a negative binomial model for count data (number of ERCPs), and the Fisher exact test for binary variables. Stricture recurrence was analyzed using the Kaplan-Meier product-limit method and the log-rank test was used to test differences between groups. Multivariate analyses for stricture resolution and stricture recurrence were performed using logistic regression.

All statistical tests were based on a 2-sided α of 5%. All analyses were done using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

A total of 162 post-OLT patients were referred to our endoscopy unit with suspected biliary obstruction between October 2009 and January 2014. Sixty-four patients met the inclusion criteria; the remainder were excluded for various reasons (see Fig. 1).

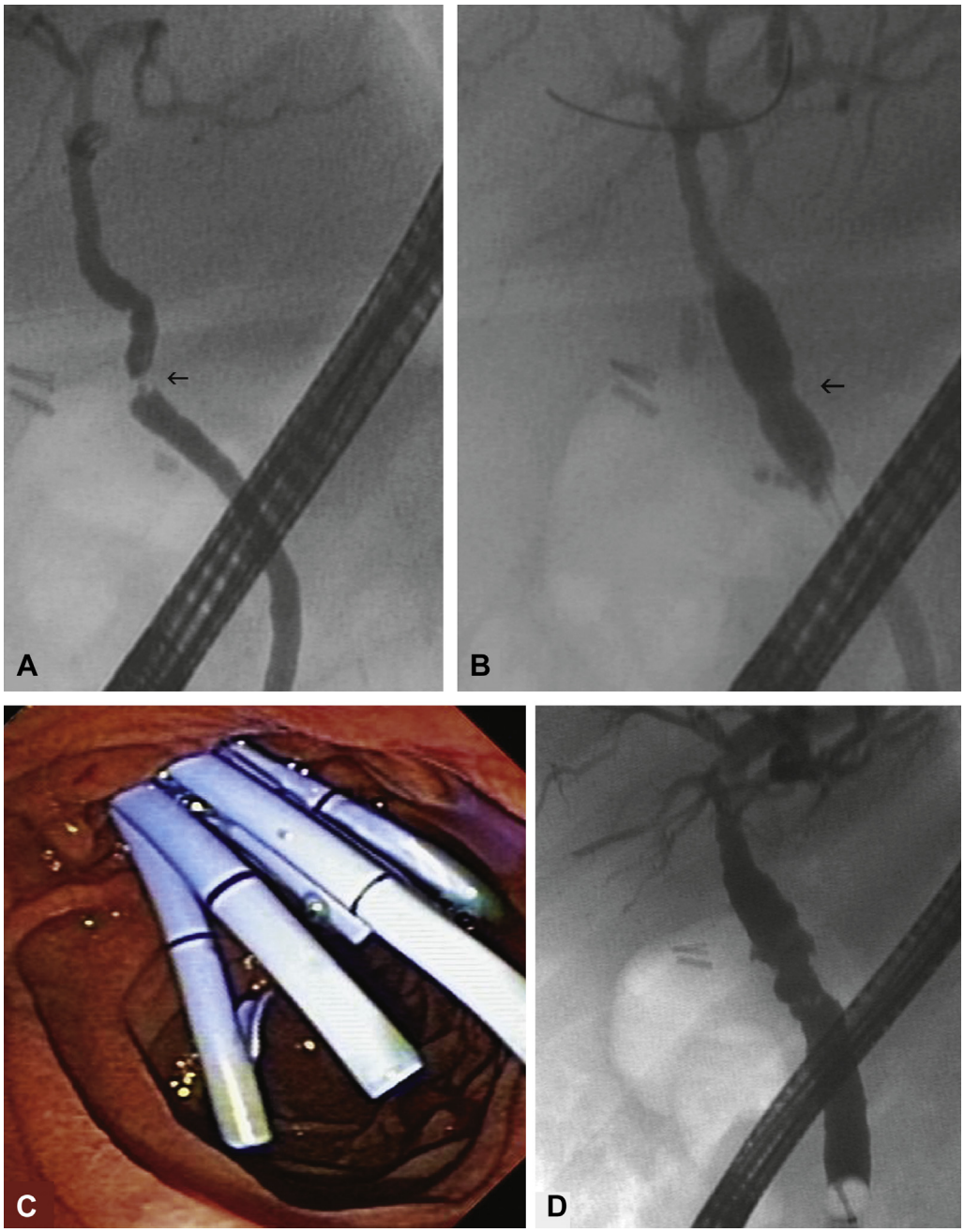

Figure 3. Initial cholangiogram (**A**) of a post-orthotopic liver transplant anastomotic stricture (*arrow*). The patient was treated with 10-mm hydrostatic balloon dilation (**B**) and placement of a progressive number of multiple plastic stents. Endoscopic view of the final number of stents achievable in this particular case (7 plastic stents) placed across the papilla (**C**). The final occlusion cholangiogram demonstrating complete stricture resolution after 12 months of treatment (**D**).

The patients in the study were randomized to receive cSEMS (n = 32; median age, 55 years; 23 male [71.8%]) or to receive MPS (n = 32; median age, 50 years; 22 male [68.8%]). The demographic characteristics were similar for both groups and are presented in Table 1.

Two patients in the cSEMS group died from unrelated causes with the stent in place and were excluded from the analysis of the results. In the MPS group, 3 patients discontinued intervention with plastic stents in situ; 1 died of an unrelated cause and 2 underwent to re-transplantation.

At the index ERCP, 14 patients (46.7%) in the cSEMS group underwent biliary sphincterotomy and 3 (10%) required balloon dilation (6 mm) to have the delivery system placed across the stricture. All cSEMSs could be easily removed either by rat-tooth forceps or standard snare; in one case, the use of argon plasma coagulation was required to dislodge hyperplasic tissue at the distal end of the stent.

TABLE 1. Demographic and baseline characteristics

	cSEMS (n = 30)	MPS (n = 29)
Male:female	22:8	20:9
Age (years)		
Mean	52.9	50.4
Median	54	50
Range	23-73	28-71
Cause		
HCV	8	11
HCV + alcohol	1	1
Alcohol	6	5
Cryptogenic	3	1
NASH	4	3
Autoimmune hepatitis	2	2
Familial amyloidotic polyneuropathy	2	2
Primary biliary cirrhosis	1	1
HBV	1	0
HCV + HBV	0	1
Adenomatosis	1	0
Acute liver failure (drug)	0	1
Budd-Chiari	1	0
Hemochromatosis	0	1
Presence of HCC	8	9
Time from OLT to ERCP (days)		
Mean (±SD)	230.5 (±277)	278.2 (±462)
Median	128.5	139
Range	30-1339	30-2453
Cold ischemia time (hours)		
Mean	7.7	8.4
Median	7.7	8.8
Range	6.2-9.3	4.7-12
Warm ischemia time (minutes)		
Mean	44.9	45
Median	45	45
Range	25-61	33-61
MELD score		
Mean (±SD)	21.8 (±8.5)	21.3 (±8.7)
Median	24	21
Range	5-36	6-42

cSEMS, Fully covered self-expandable metal stent; *MPS*, multiple plastic stent; *HCV*, hepatitis C virus; *NASH*, nonalcoholic steatohepatitis; *HBV*, hepatitis B virus; *HCC*, hepatocarcinoma; *OLT*, orthotopic liver transplantation; *SD*, standard deviation; *MELD*, model for end-stage liver disease.

All patients in the MPS group underwent biliary sphincterotomy at the index ERCP, balloon dilation was performed at the physician's discretion, and 89.6% of patients had at least 2 plastic stents placed at this point.

The total area of MPSs was calculated by the sum of individual stents areas, determined by the following formula: area $= \pi \times r^2$. The area calculated for each stent was as follows: 11.5 mm^2 (11.5F), 8.7 mm^2 (10F), 6 mm^2 (8.5F), and 4.3 mm^2 (7F). The mean final stenting areas were 17.9 mm^2, 31.2 mm^2, 42.4 mm^2, 54.6 mm^2, and 60.9 mm^2, respectively, from the first to fifth endoscopic therapeutic procedure (Supplementary Fig. 2, available online at www.giejournal.org). Not all patients had 5 ERCPs; therefore, taking the final ERCP into account, the average stenting area with MPSs was 52.2 mm^2. Such a large total area is, in our opinion, the goal to be pursued. It can be achieved by placing six 10F stents, or four 11.5F plus one 7F, or a series of other combinations, depending on stent diameter.

Based on procedure and devices costs in our institution, the median treatment cost was USD6,903 and USD16,095 per patient in the cSEMS and MPS groups, respectively ($P < .01$).

Stricture resolution

Stricture resolution was achieved in 83.3% in the cSEMS group and 96.5% in the MPS group ($P = .19$). Multivariate analysis using all baseline variables showed no significant predictors of stricture resolution.

There were 5 failures in the cSEMS group; 1 patient had severe acute pancreatitis, and the metal stent was removed on the advice of the surgeon. The stricture persisted in 1 patient after cSEMS removal. Three patients presented spontaneous incomplete distal stent migration at final ERCP with remnant duct narrowing, although without clinical repercussion.

All 5 patients were offered crossover to MPS therapy and even though this is beyond the study's endpoints, these patients were followed for a median time of 20.4 months. Two patients accepted crossover to MPS; 1 failed endoscopic retreatment and was ultimately referred to surgery. One patient demanded a second cSEMS and was retreated successfully. Two patients were referred to surgery based on the surgeon's advice and the patient's decision. One was lost to follow-up and the other eventually needed retransplantation and died during surgery.

There was 1 failure in the MPS group. This patient accepted crossover to a cSEMS for 6 months. Stricture resolution was achieved and he was uneventful at 3.5 months of follow-up.

Adverse events

Adverse events occurred in 23.3% and 6.4% of ERCPs in the cSEMS and MPS groups, respectively ($P < .01$). Acute pancreatitis was the most common procedure-related adverse event, occurring in 13.3% in the cSEMS group and 2.1% in the MPS group ($P < .01$). Among the 8 cases of acute pancreatitis in the cSEMS group, 2 (25%) were mild, 5 (62.5%) were moderate, and 1 (12.5%) was severe.

In the MPS group, there was 1 (33.3%) mild and 2 (66.7%) moderate cases of acute pancreatitis.

Four patients (6.3%) in the cSEMS group and 1 (0.7%) in the MPS group presented severe abdominal pain, requiring hospital admission to receive intravenous analgesics (Table 2). Another patient in the cSEMS group, although discharged, was readmitted within the next 24 hours for intravenous analgesia.

Among stent-related adverse events, distal migration was the most frequent, occurring in 10% (3/30) and 2.8% (4/141) of procedures in the cSEMS and MPS groups, respectively. There were 2 episodes of symptomatic occlusion in the MPS group (1.4%), and in both cases ERPC intervention had to be anticipated to relieve biliary obstruction.

Stricture recurrence

The median follow-up was 36.4 and 32.9 months for the cSEMS and MPS groups, respectively (Table 3). One patient in the cSEMS group was lost during follow-up after treatment success. Stricture recurrence was observed in 8 patients (32%) in the cSEMS group after a median of 4.9 months and none in the MPS group (Table 3). Kaplan-Meier analysis (Supplementary Fig. 3, available online at www.giejournal.) disclosed a statistically significant difference in time to recurrence between the groups ($P < .01$). Multivariate analysis of all baseline variables showed no significant predictors of recurrence.

All stricture recurrences in the cSEMS group were located at the anastomosis site. We have no cases in which stent-induced stenosis was suspected.

The 8 patients who presented with stricture recurrence were offered crossover: 6 were successfully treated with MPSs for 1 year. The other 2 patients were referred to surgery based on the surgeon's advice and the patient's decision. Analysis of second-line treatment is not an objective of this study.

Three patients in the cSEMS group (12%) presented with choledocolithiasis after stricture resolution, requiring one single ERCP each with no further intervention needed.

TABLE 2. Treatment characteristics

	cSEMS	MPS
Stent treatment duration (days)		
Mean (±SD)	139.4 (±66)	342.8 (±52.5)
Median	158.5	354
Range	9-239	222-442
Total number of ERCP	60	141
Number of procedures per patient		
Mean (±SD)	2	4.9 (± 0.6)
Median	2	5
Range	–	(4-6)
Number of stents per ERCP per patient		
Mean (±SD)	1	4.3 (± 1.1)
Median	1	4.3
Range	–	2-7
Total number of stents per patient		
Mean (±SD)	1	16.7 (± 5.6)
Median	1	16
Range	–	6-30
Final stenting area (mm^2)		
Mean (±SD)	78.5 (N/A)	52.2 (± 14.0)
Median	N/A	52.4
Range	N/A	17.4-95.4
Adverse events, % (n/N)	23.3 (14/60)	6.4 (9/141)
Abdominal pain	1.7 (1/60)	0 (0/141)
Abdominal pain with hospitalization	6.7 (4/60)	0.7 (1/141)
Acute pancreatitis	13.3 (8/60)	2.1 (3/141)
Sphincterotomy bleeding	0 (0/60)	2.1 (3/141)
Bacteremia	1.7 (1/60)	1.4 (2/141)
Stent-related adverse events		
Migration	10 (3/30)	2.8 (4/141)
Occlusion	0 (0/0)	1.4 (2/141)
Death related to ERCP procedure	0 (0/0)	0 (0/0)

cSEMS, Fully covered self-expandable metal stent; *MPS*, multiple plastic stent; *SD*, standard deviation; *N/A*, not applicable.

DISCUSSION

This is the first single-center, prospective, randomized clinical trial (RCT) to compare long-term results of cSEMSs and MPSs for the treatment of post-OLT BAS.

The majority of BASs develop within the first year after OLT; between 8 and 9 months in our series. Patients are usually asymptomatic or may have non-specific symptoms with LFT abnormalities.

Standard endoscopic treatment consists of sphincterotomy, balloon dilation, and subsequent placement of MPSs, repeated at 3-month intervals for 12 to 24 months. Stricture resolution rates reach up to 100%.[16-23] The rational for placement of multiple stents through the stricture is to maintain maximal expansion in luminal diameter, possibly promoting re-shaping of the bile duct stricture over the stents and preventing duct narrowing.[19,22] In addition, the use of MPSs may add biliary drainage through inter-stent channels.[19,21,22]

In our RCT, we adopted an aggressive MPS prophylactic exchange protocol over a 1-year period, achieving a stricture resolution rate of 96.5%, with no recurrence after mean follow-up of approximately 3 years, which compares favorably with the literature results.

The major drawback of endoscopic treatment with MPSs is the need for multiple procedures. Covered metal stents have become an appealing option for benign biliary

TABLE 3. Summary of results

	cSEMS	MPS
Stricture resolution (ITT), % (n/N)		
Success	78.1 (25/32)	87.5 (28/32)
Failure	21.9 (7/32)	12.5 (4/32)
Stricture resolution (per protocol), % (n/N)		
Success	83.3 (25/30)	96.5 (28/29)
Failure	16.6 (5/30)	3.5 (1/29)
Follow-up (days)		
Mean (±SD)	1077.9 (±725.1)	987.3 (±515)
Median	1092	989
Range	0-2318	93-1932
Stricture recurrence, % (n/N)	32 (8/25)	0 (0/28)
Time to recurrent anastomotic stricture (days)		
Mean (±SD)	277.9 (±303.0)	–
Median	147	–
Range	64-940	–
Retreatment after initial failure, n/N (%)		
Success	3/4 (75)	1/1 (100)
Failure	1/4 (25)	0/0 (0)
Retreatment after recurrent anastomotic stricture, n/N (%)		
Success	8/8 (100)	NA

cSEMS, Fully covered self-expandable metal stent; *MPS*, multiple plastic stent; *ITT*, intention to treat; *SD*, standard deviation; *NA*, not applicable.

strictures because their sustained radial force is now associated with removability.[4-12] Therefore, there is a growing interest in cSEMS as first-line option for benign biliary strictures in general. It has been assumed that these patients can be treated with 1 single cSEMS and only 2 ERCPs.

Post-OLT patients present an anatomic advantage for cSEMS placement; the presence of graft duct adds enough space above the stricture to accommodate the stent and still keep it away from hepatic confluence.

Temporary placement of cSEMSs in patients with post-OLT BASs refractory to conventional endoscopic therapy reaches an initial success rate of 87.5% to 100% with 4.5% to 30% recurrence (mean follow-up of 24 months). The major drawback of cSEMS use is migration, occurring in up to 37.5%, although with no clinical consequences.[6,7,9,10,12] The rate of stricture resolution is lower in patients with cSEMS migration.[6,8,24]

In a systematic review including 21 studies, MPSs were compared with metal stents in post liver transplant BAS. There was significant heterogeneity in stent protocols. Patients treated with SEMSs showed a stricture resolution rate of 80% to 94% when the stent was indwelling for longer than 3 months, very similar to the 94% to 100% rate seen with MPSs for at least 12 months. Moreover, SEMSs were used as second-line therapy for refractory strictures in 125 of these patients, which can be considered as selection bias for more difficult strictures. The main problem with SEMSs was stent migration, occurring in 16% of cases.[24]

One small randomized trial conducted in 2 Australian centers compared cSEMSs and MPSs in post-OLT BASs. In the cSEMS group, a reduced number of ERCPs was needed to achieve stricture resolution with similar recurrence rates and fewer adverse events and hospitalization days, resulting in a more cost-effective option according to the authors.[12]

In our study, we analyzed 30 post-OLT patients with BASs treated with cSEMSs as the first-line approach. The resolution rate was 83.3% after the stent was indwelling for a mean of 158.5 days. Although the initial success was comparable with the current standard MPS treatment, there was 32% recurrence after a median of 147 days. This recurrence rate is comparable with that found by Kaffes et al.[12] We debated whether this higher recurrence rate was a result of the shorter stent indwelling time (158.5 versus 354 days) in the cSEMS group or the final stenting area achieved.

We consider the post-stenting follow-up period (average of approximately 3 years) adequate for evaluating stricture recurrence, which was statistically significantly ($P < .01$) higher in the cSEMS group.

In our study, the average estimated stenting area accomplished at the final ERCP with MPSs was 52.2 mm^2 versus 78.5 mm^2 achieved with a 10-mm cSEMS. On the basis that the final stenting area was higher in the cSEMS group, we may theorize that stent indwelling is the most likely explanation for the higher stricture recurrence rate in this group.

When we started our series, most of the reported literature considered leaving cSEMSs in place for no longer than 6 months. This approach has been changing in recent years, and there are some reports of the stents being left for longer periods.[6] Although longer cSEMS indwelling could improve the resolution rate, it could also increase the rate of migration or secondary bile duct injuries. A single-arm prospective study evaluating treatment with cSEMS indwelling for 1 year is already being conducted at our institution. Preliminary results of this study have not been published.

Stent migration remains the most important limitation for cSEMS use.[6-10,24] Three patients presented stent migration, and although there were no symptoms associated with migration, they all required retreatment because the stricture persisted. These 3 patients had not undergone any kind of dilation procedure before metal stent deployment and only one had undergone sphincterotomy.

As we demonstrated in our study, cSEMSs allowed anastomotic biliary stricture resolution with fewer procedure

sessions and reduced treatment costs, confirming the results of Behm et al.[25] Even considering the higher recurrence rate, if these patients were treated once again with cSEMSs, treatment would be cheaper. A better analysis of the overall treatment cost (including adverse events and lost days at work) is underway.

Postprocedure acute pancreatitis occurred in 2.1% of patients in the MPS group, which compares favorably with the literature reports.[26,27] However, the rate of pancreatitis in the cSEMS group was 13.3%, which is high, even for a high-risk population.

Biliary sphincterotomy is usually not performed before SEMS placement for malignant biliary obstructions, and there is a lack of conclusive data about the increased risk of acute pancreatitis after placing cSEMSs across an intact sphincter of Oddi.[28]

Assuming that sphincterotomy increases the chances of stent migration, in our study, the first 16 cSEMSs were deployed without one. The high incidence of acute pancreatitis (8 patients among the first 16) came to our attention. The main hypothesis was that placing a trans-papillary metal stent in a native papilla without sphincterotomy was the main reason for the high rate of postprocedure pancreatitis. Currently in our practice, all cSEMSs are now placed after biliary sphincterotomy, which drastically decreased acute pancreatitis to 1 case in the next 14 patients. Although our adverse event rate in the cSEMS group was higher than those of published studies, we assume this was probably because we did not perform sphincterotomy before stent deployment.

Our study is the first single-center RCT comparing cSEMSs with MPSs in post-OLT patients. We have demonstrated that cSEMSs are as effective as MPSs in the management of post-OLT BASs. The main advantages of cSEMSs proved to be lower cost and reduced number of procedures. The discrepancy in the acute pancreatitis rate was attributed to the initial decision to not perform sphincterotomy before cSEMS deployment. This observation is limited by the number of patients but is still remarkable.

This study was limited by the variable period of stent indwelling according to treatment allocation. Moreover, the generalizability of our findings is compromised by the study's enrollment criteria, particularly by excluding patients in whom a guidewire could not be passed through BASs.

In conclusion, cSEMSs were comparable with MPSs regarding BAS resolution. cSEMSs allowed fewer procedures and had a positive effect on cost. The duration of treatment with cSEMSs should be further investigated. Sphincterotomy should be considered for all patients.

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Abbreviations: BAS, biliary anastomotic stricture; cSEMS, fully covered self-expandable metal stent; LFT, liver function test; MPS, multiple plastic stent; OLT, orthotopic liver transplantation; RCT, randomized clinical trial; SEMS, self-expandable metal stent.

DISCLOSURE: *Angelo Paulo Ferrari has acted as an independent consultant for Boston Scientific.*

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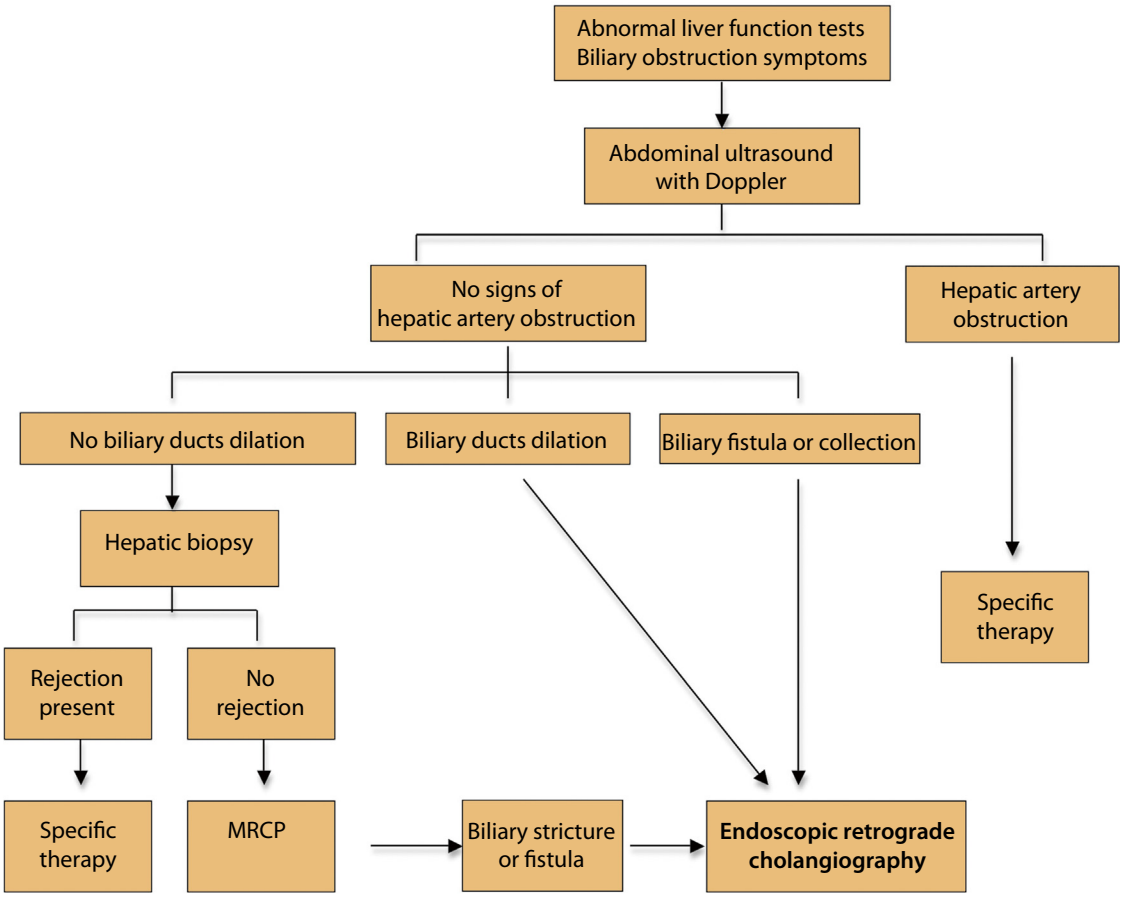
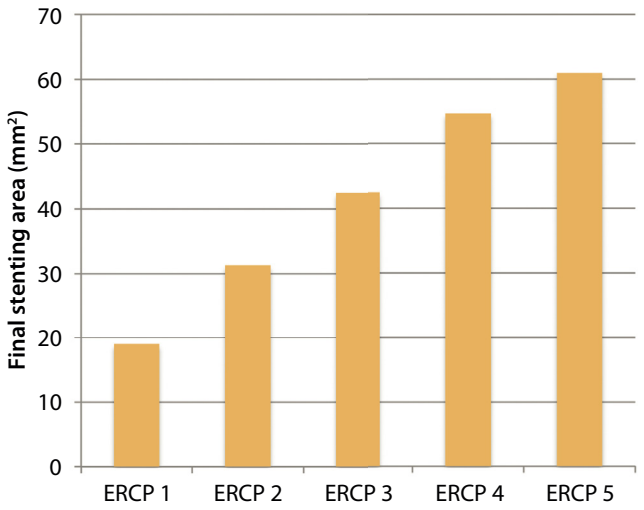
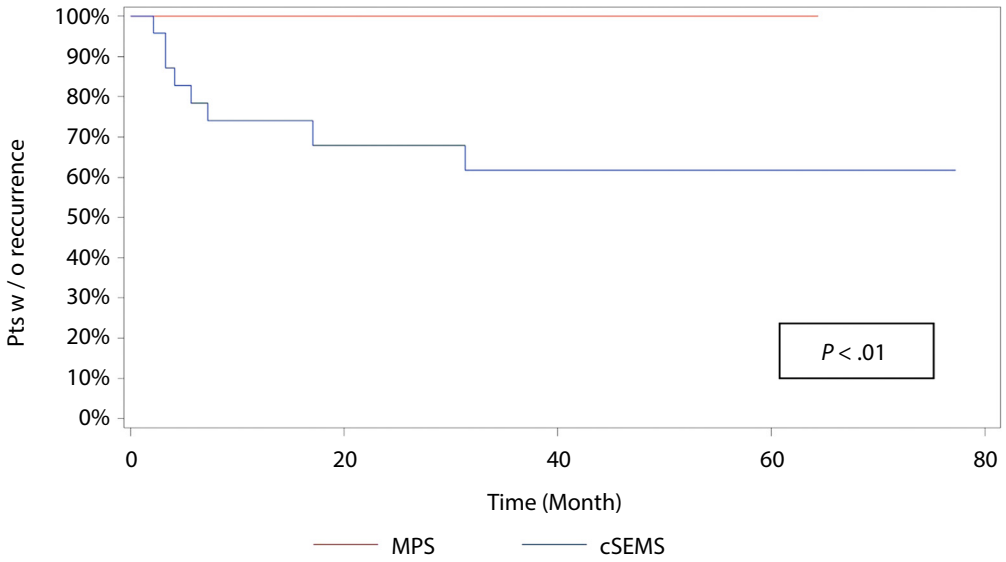


Supplementary Figure 1. Work-up algorithm for the diagnosis of biliary adverse events after liver transplant.



Supplementary Figure 2. Average stenting area (mm^2) in the multiple plastic stent group for each ERCP procedure.



Patients at risk

Group	Month 0	Month 20	Month 40	Month 60	Month 80
MPS	29	29	22	9	3
cSEMS	25	24	11	6	5

Supplementary Figure 3. Kaplan-Meier analysis of time to recurrence.