ORIGINAL ARTICLE

Cost analysis of a long-term randomized controlled study in biliary duct-to-duct anastomotic stricture after liver transplantation

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SUMMARY

Multiple plastic stent (MPS) for biliary anastomotic stricture (AS) after liver transplantation requires multiple procedures with consequent costs. To compare the success, adverse events and treatment-related costs of fully covered self-expandable metal stents (FCSEMS) versus MPS. Thirty liver transplant (LT) patients with clinically relevant naïve AS were prospectively randomized to FCSEMS or MPS, with stent numbers increased at 3-month intervals. Treatment costs per patient were calculated for endoscopic retrograde cholangiopancreatography (including all devices and stents) and overall hospital stay. Radiological success was achieved in 73% of FCSEMS (median indwelling period of 6 mos) and 93% of MPS patients (P = NS) (median period of 11 mos). AS recurrence occurred in 36% of FCSEMS and 7% of MPS patients (P = NS), and AS re-treatment was needed in 53% and 13% ($P < 0.01$), respectively, during follow-up of 60 (34–80) months. Stents migrated after 29% and 2.6% of FCSEMS and MPS procedures, respectively ($P < 0.01$). Including re-treatments, long-term clinical success was achieved in 28/30 (93%) patients. Overall treatment-related costs were similar between groups. In the subgroup of LT patients in clinical remission after first-line treatment, treatment costs were 41% lower per FCSEMS patient compared with MPS patients. FCSEMS did not perform better than MPS. FCSEMS migration increased the rate of re-treatment and costs.

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Introduction

Stricture of biliary duct-to-duct anastomosis is a common complication after liver transplantation, occurring in up to 15% of patients [1,2]. Endoscopic therapy is the standard treatment for this condition [1,2], although the most cost-effective endoscopic therapy option has not yet been established. Several authors

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have reported optimal results with the traditional multi-stenting technique [3–5], which consists of progressive dilation of the stricture by increasing the number of plastic stents placed side-by-side in multiple procedures. This is the most common option in everyday practice [6]. Recently, fully covered self-expandable metal stents (FCSEMS) have been designed for easy removal in benign biliary strictures [7–14]. In this setting, the use of FCSEMS is appealing in order to decrease the number of procedures and hospitalizations, thus reducing treatment costs. The results of two of the four randomized controlled trials (RCTs), which have compared multiple plastic stents (MPS) with FCSEMS, confirmed that the use of FCSEMS reduced the number of required endoscopic retrograde cholangiopancreatography procedures (ERCPs) [15–18]. Two of these RCTs considered costs, but the results are limited by the small sample size of the study populations and the short follow-up periods [15,18]. The aim of the present randomized controlled study was to compare the costs, long-term effectiveness and adverse events of AS treatment with traditional MPS versus FCSEMS after liver transplantation.

Materials and methods

Study population

Anastomotic stricture (AS) in liver transplant (LT) patients was suspected in the presence of any alteration in liver tests persisting for 3 months whether associated or not with biliary obstructive symptoms (fever, jaundice, itching), and the presence of duct-to-duct anastomosis narrowing on MR or Kehr cholangiography consistent with AS. Liver biopsy and abdominal ultrasonography with Doppler were performed in all LT patients to rule out hepatitis C virus flare, rejection, de novo autoimmunity, and hepatic arterial thrombosis. At our center, the presence of AS was confirmed at ERCP when impaction or difficult passage through the anastomosis of a Fogarty catheter inflated to the same diameter as the common bile duct above the anastomosis was seen. The severity of the stricture was determined according to current international criteria [17]. Briefly, grade A was defined if the diameter at the level of the anastomosis was reduced by 99–100%, grade B if the reduction was 90–99%, grade C if it was 50–90%, and grade D if it was <50%. A severe stricture was considered to be grade A or B, and a mild stricture grade C or D. Only naïve LT patients with duct-to-duct AS were included. The study patients were enrolled since 02.2014 to 07.2016. LT patients with recurrent AS after any previous endoscopic treatment and patients with hepatico-jejunal anastomosis were excluded. LT patients were followed up for a minimum of 24 months after the end of treatments.

Endoscopic treatment

ERCP of LT patients was performed under deep (i.v. propofol) or conscious (i.v. midazolam and pethidine) sedation. Aminosalicylic acid was routinely administered to all LT patients for the prevention of hepatic artery thrombosis and maintained before the procedure. In accordance with European guidelines [19], an indometacin 100 mg suppository was administered before ERCP for the prevention of post-ERCP pancreatitis. Intravenous antibiotics were given to prevent biliary sepsis secondary to endoscopic manipulations. After guide-wired cannulation of the common bile duct, occlusive cholangiography was performed and the AS confirmed (see above). Following sphincterotomy, the patient was randomized to one of the two study arms.

When a metal stent was used, a fully covered model was always chosen to allow its easy removal at the end of endoscopic therapy. The brand type was not specified in the protocol. FCSEMS with anti-migration systems was not available at the beginning of the study. No balloon dilation was needed to place FCSEMSs. The FCSEMS was removed after 6 months (Fig. 1). When multi-stenting was employed, a progressive increase in the number of 10 Fr plastic stents at 3-month intervals was planned with an overall duration of treatment of 9 to 12 months according to the rate of improvement of the AS. All stents were removed at each session. Hydrostatic balloon dilatation to assist the placement of multiple stents across the AS was used when the number of stents had to be increased (Fig. 2).

The diameter of the FCSEMS (8 or 10 mm) and the maximum number of plastic stents were chosen according to the diameters of the native and donor common bile ducts.

Treatment success

Radiological (RX) success was evaluated at the time of stent removal and confirmed if the duct diameter at the level of the anastomosis was equal to the diameter below it and an 8.5 mm Fogarty balloon passed easily through the anastomosis. Clinical success was defined as the absence of any increase in laboratory markers of

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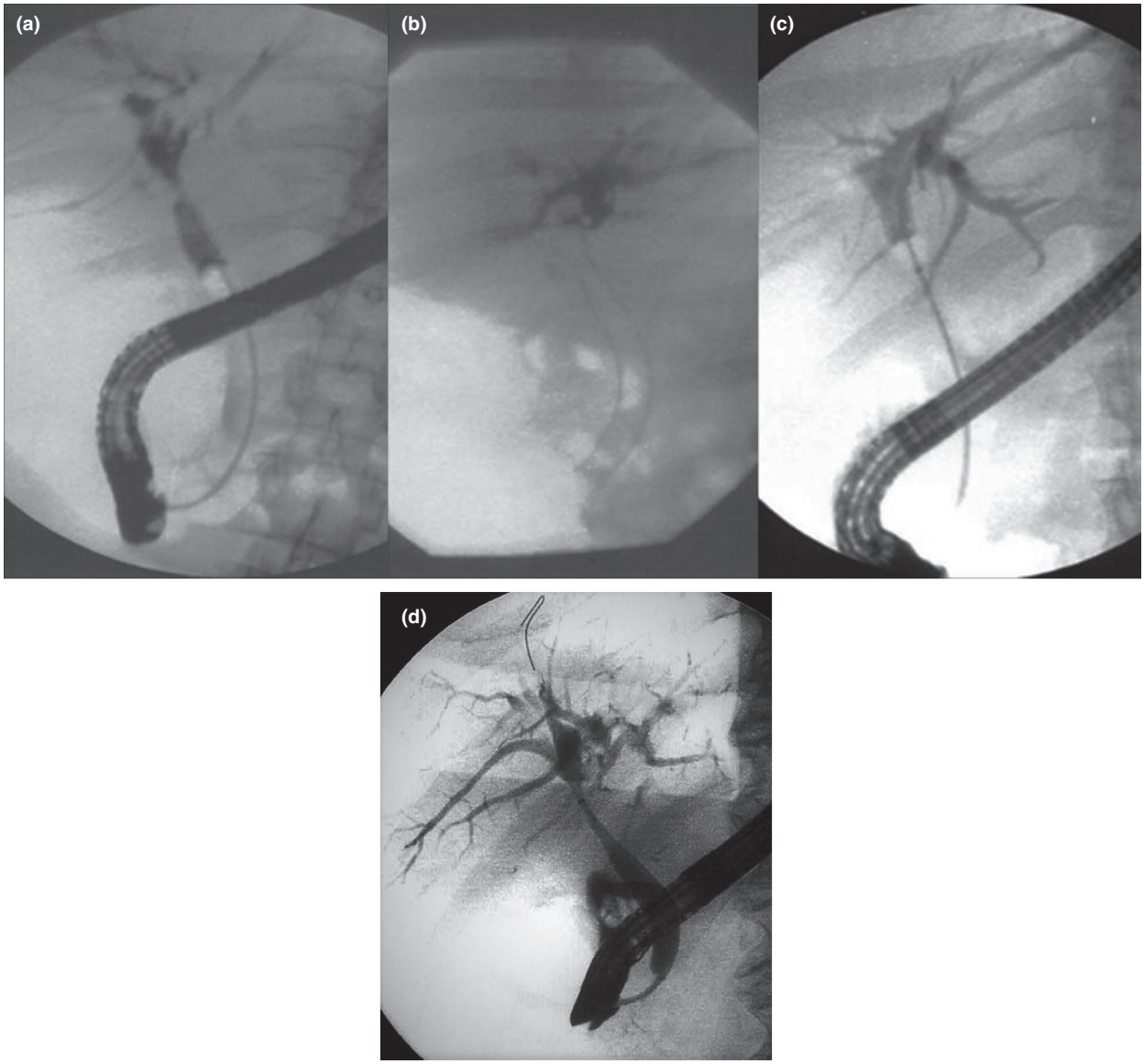

Figure 1 (a) Biliary anastomotic stricture. (b) A 10-mm fully covered metal stent was inserted. (c) After six months indwelling period, the anastomotic stricture had disappeared, but (d) a clinically relevant stricture recurred at the level of the anastomosis after 2 months. The patient was crossed over to 12-month MPS treatment and clinical success persisted during the following 45 months of follow-up.

cholestasis secondary to AS and no need for re-treatment after removal of the stents during the entire follow-up period. It was decided that MR cholangiography would be carried out within 6 months after the end of endoscopic therapy if there were any changes in liver test results or biliary obstructive symptoms developed. The diagnostic criteria for recurrent AS were the same as for naive AS. In all cases, re-treatment was considered if there were any changes in laboratory tests associated with AS. Re-treatment was to follow a cross-over design: After FCSEMS failure, the patient underwent MPS and vice versa.

Adverse events

Peri-procedural adverse events were recorded and defined according to international guidelines [20]. Post-ERCP pancreatitis was diagnosed if abdominal pain of pancreatic origin occurred within 24 hours of the procedure, serum amylase was ≥3 times the normal value and hospitalization was prolonged; severe pancreatitis was diagnosed if hospitalization was prolonged by more than 10 days [21]. Cholangitis was diagnosed if new onset of fever > 38°C developed within 48 h of the procedure; bleeding was investigated in case of melena, hematemesis,

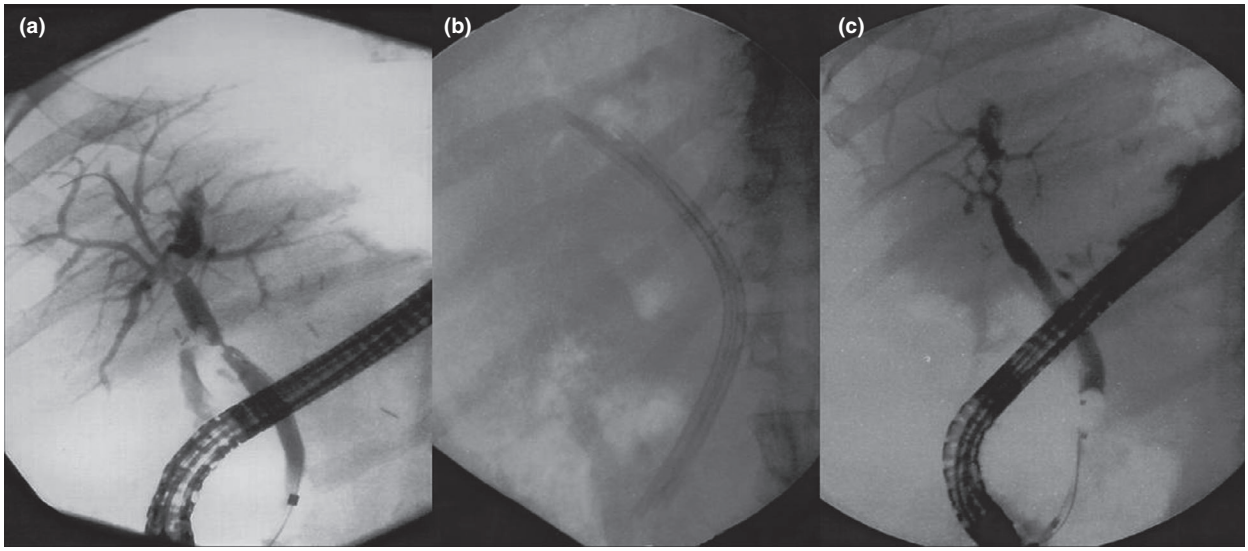

Figure 2 (a) Biliary anastomotic stricture. (b) An increasing number of 10-Fr plastic stents were inserted every 3 months. According to the diameters of the donor and native common bile ducts, four 10-Fr stents were used at the maximal dilation procedure. (c) After removal, occlusive cholangiography confirmed radiological success.

or a decrease in hemoglobin level requiring transfusion or endoscopic hemostasis within 10 days of ERCP [20,22]. Migration of the stent was assessed at the time of the next endoscopic procedure. Distal migration was considered to be complete if the stent was not seen at endoscopy or on abdominal X-ray, and as partial if the stent had migrated partially to the duodenum and its proximal end no longer crossed the AS, as routinely assessed at occlusive cholangiography before removal of the stent. Proximal migration was considered when the duodenal end of the intra-biliary stent was not seen in the duodenum. After removal of stents, LT patients were followed up with monthly laboratory tests for six months, abdominal US at 3 months interval for 1 year after LT, and MR cholangiography at 6 months. Afterward, laboratory tests at 6-month intervals, yearly abdominal US or CT in case of previous HCC, were planned. MR cholangiography was planned in case of recurrent obstructive symptoms or flare of the markers of cholestasis.

Cost analysis

The total cost of endoscopic therapy comprised the cost of endoscopic procedures (€1409/procedure) and biliary devices including plastic (€88) or metal stents (€839–1614, depending on brand), and the cost of hospitalization required for procedures and to deal with adverse events, that is, two days at least. All ERCPs were performed in hospitalized patients in order to have costs reimbursed by the NHS.

The cost of an endoscopic procedure was based on the use of medical, nursing, and administrative resources and of the dedicated endoscopy room, determined as a percentage of working day costs as assessed by the medical staff and approved by the commercial team of our hospital. The costs of devices and biliary stents were determined according to our hospital's financial documents (for the year 2012), that is, papillotome 302 Euros, guide-wire 97 Euros, Fogarty balloon catheter 340 Euros, balloon dilatation catheter 108 Euros, and plastic stent delivery system 84 Euros. The daily cost of hospitalization was determined according to the healthcare system of Lombardy Regional Authority, Italy (for the year 2012).

Ethics

The study was approved by the local Ethics Committee of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy. It was performed in accordance with the ethical standards of the Declaration of Helsinki (year 2000) as well as the Declaration of Istanbul (year 2008). All patients gave their informed consent prior to their inclusion in the study. This study was designed as a continuation of a multicenter European trial (NCT01393067) with the participation of our center (see Discussion). The patient selection criteria and 1:1 randomization set out in the trial protocol were employed in our single-center RCT.

Statistics

The data of the LT patients involved in the study were anonymized in order to ensure blinding in the final statistical analysis. Patient allocation to FCSEMS or MPS treatment was determined according to a randomization table, which was electronically generated. In order to calculate the sample size of the study for cost analysis purposes (continuous variable), which was the primary aim of the study, we assumed that a cost saving of more than 10% with the use of FCSEMS compared with traditional MPS was needed in order to be considered financially relevant. On the basis of the only two previous studies reporting on costs [15,18], the mean costs of FCSEMS and MPS treatment were calculated to be $8288/patient and $16 095/patient, respectively. Assuming a type I error and a statistical power of 5% and 90%, respectively, the sample size required was 12 per study group.

The data were expressed as median (range) or as mean (SD) according to data distribution. Mann–Whitney and chi-squared tests were used when appropriate to compare the patients' characteristics in the FCSEMS and MPS groups. The cost of endoscopic therapy for each patient included the costs of re-treatment, according to an intention-to-treat analysis. A post hoc analysis was performed comparing FCSEMS and MPS patients who achieved clinical success after one treatment only.

Results

Study LT population

Thirty LT patients (26 men, 22–69 years old) were enrolled and followed up for a median of 60 (34–80) months. The characteristics of the study population are summarized in Table 1, which shows that the patients' characteristics were similar between the two study groups.

First-line endoscopic therapy

Multiple plastic stenting

Fifteen LT patients (14 men, 22–68 years old) were randomized to MPS treatment and underwent a median of four ERCPs (range 3–7) during a median of 11 months. At the time of the last procedure, a median of four (range 3–6) 10 Fr stents had been placed. Radiological success was achieved in 14/15 (93%) cases. During follow-up, AS recurrence occurred in 1/14 patients (7%). Two patients (13%) (one with a residual and one with a recurrent stricture) had a clinically relevant stricture and needed re-treatment. They were switched to treatment with FCSEMS at 1 and 5 months, respectively, after the removal of the plastic stents.

Fully covered metal stenting

Fifteen LT patients (12 men, 50–69 years old) were randomized to FCSEMS first-line treatment and underwent a median of three ERCPs (range 2–8) during a median of 6 months. A 10-mm metal stent was used in five patients (33%) and an 8-mm stent in the remaining 10 (67%) according to the diameter of the donor and the native common bile duct. Radiological success was achieved in 11/15 patients (73%, P = NS versus MPS) which included 3/5 patients with a 10-mm FCSEMS and 8/10 patients with an 8-mm FCSEMS. During

Table 1. Demographic, laboratory and radiological characteristics of the study population.

	MPS $N = 15$	FCSEMS $N = 15$	P
Sex, male (%)	14 (93)	12 (79)	NS
Age, years (range)	53 (22–68)	59 (50–67)	NS
Etiology, HCV/HBV/ETOH/others	7/3/2/3	11/0/3/1	NS
Time after OLT, months (range)	6 (2–89)	7 (1–58)	NS
Time after OLT, <3 months (%)	2 (13)	5 (33)	NS
Pretreatment ALP, U/L	254 ± 145	260 ± 146	NS
Pretreatment Tot bilirubin, mg/dl	4.0 ± 3.0	2.0 ± 2.0	NS
Stricture severity grade A–B (%)	11 (73)	10 (66)	NS
Stricture length, mm (range)	7 (3–20)	10 (3–15)	NS

Demographic and radiological data are shown as median (range) or percentage values. Laboratory data are shown as mean ± SD values.

MPS, multiple plastic stenting; FCSEMS, fully covered self-expandable metal stent; HCV, hepatitis C virus; HBV, hepatitis B virus; ETOH, ethanol; OLT, orthotopic liver transplantation; ALP, alkaline phosphatase; Tot, total.

follow-up, AS recurred in 4/11 patients (36%, P = NS versus MPS), which included 1/3 patients with a successful 10-mm FCSEMS and 3/8 patients with an 8-mm FCSEMS. Four patients with residual and four with recurrent stricture had a clinically relevant stricture and needed re-treatment (53%; $P < 0.01$ versus MPS).

Second-line endoscopic therapies and clinical outcome

Re-treatment was required in 10 LT patients (33%) previously treated with MPS ($n = 2$) or FCSEMS ($n = 8$). The two patients who failed MPS were treated with an 8-mm metal stent for 4 and 6 months, respectively. Radiological success was achieved in one patient, with no clinically relevant recurrence in the following 71 months. The second patient had a new recurrence of the stricture. As surgery is contraindicated in this patient because of ischemic heart disease, third-line endoscopic therapy with MPS is ongoing.

The eight patients who failed FCSEMS were treated with a median of four (3–6) 10 Fr stents with a median treatment duration of 12 months. Radiological success was achieved in all patients, and no clinically relevant strictures recurred during the median follow-up period of 38 months. One patient did not achieve long-term clinical remission because of recurrent cholangitis secondary to a large intra-hepatic stone which laser lithotripsy failed to fragment. The patient underwent surgery to remove the stone, and a hepatico-jejunal anastomosis was made.

Including re-treatments, overall clinical success was achieved in 28/30 (93%) LT patients (14/15 in each study group) and maintained for a median of 55 (34–74) months in the MPS group and 63 (41–80) months in the FCSEMS group (P = NS versus MPS). In the FCSEMS group, there was no association between technical failure and patient or stricture characteristics or FCSEMS diameter (8 mm vs. 10 mm).

Stent migration

Stent migration occurred after 2 of 76 (2.6%) MPS treatments, one during first-line and one during second-line treatment. In both cases, a partial distal migration occurred. The two MPS patients with migration achieved the clinical success without re-treatment because the stricture had been already dilated.

In FCSEMS patients, stent migration occurred after five of 17 (29%) treatments ($p < 0.01$ versus MPS), four of which were first-line treatments (one 10-mm and three 8-mm large stent), and one second-line treatment (8-mm large stent). A complete distal migration occurred in four cases and a proximal migration in one. The intra-biliary 8-mm large fully covered SEMS was successfully removed by a rat-tooth forceps under X-ray control. After migration, all FCSEMS patients except one had a clinically relevant relapse of the anastomotic stricture and underwent re-treatment. Thus, among the FCSEMS patients, migration was associated with the need of re-treatment ($P < 0.01$ versus no migration), but it was not influenced by stent diameter (8 mm vs. 10 mm large, P = ns).

Adverse events

Adverse events were recorded after 9 of 122 (7.4%) ERCPs: There were 6 adverse events following 94 (6.4%) MPS procedures and 3 after 28 (11%) FCSEMS procedures (P = NS versus MPS). Mild pancreatitis occurred after 4 (3.3%) ERCPs, that is, after 3/94 (3.2%) MPS and 1/28 (3.6%) FCSEMS procedures (P = NS versus MPS). Two episodes of pancreatitis and three episodes of cholangitis occurred in the same patient, despite prophylactic i.v. antibiotic and pancreatic stent. Because of the occurrence of mild pancreatitis, these three patients had prolongation of their hospital stay by two days. No instances of severe pancreatitis were recorded. Cholangitis occurred after 4 (3.3%) ERCPs, that is, after 2/94 (2.1%) MPS and 2/28 (7%) FCSEMS procedures (P = NS versus MPS). Both patients were successfully treated with a 5-day course of cephalosporin and their hospital stay prolonged by two days. Relevant hemobilia occurred in one patient during an MPS procedure due to injury of the intra-biliary tree by a 0.035-inch hydrophilic guide-wire. The patient underwent transfusion of 2 units of blood red cells, i.v. cephalosporin, and radiologic treatment was not needed.

Cost analysis

Considering first- and second-line treatments together, the number of ERCPs and length of hospital stay were not different between the two study groups (Table 2). Accordingly, the costs of ERCPs and hospital stay in order to achieve clinical remission were also similar (Table 3). The mean cost per patient to achieve and maintain clinical remission was €9550 ± 2497 for the MPS group and €10 490 ± 6709 for the FCSEMS group (P = NS versus MPS) including the cost of endoscopies, accounting for 73% and 72% of the total amount for the MPS and FCSEMS treatments' cost, and of hospital stay, accounting for the 27% and 28%, respectively.

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Table 2. Endoscopic therapy outcomes according to intention-to-treat analysis.

	MPS *N* = 15	FCSEMS *N* = 15	*P*
Rx success of primary endoscopic therapy, *n* (%)	14 (93)	11 (73)	0.14
Stricture recurrence, *n* (%)	1/14 (7)	4/11 (36)	0.07
Stricture re-treatment*, *n* (%)	2 (13)	8 (53)	<0.01
Stent migration, *n* (%)	2/76 (2.6)	5/17 (29)	<0.01
Complicated ERCPs, *n* (%)	6/94 (6.4)	4/28 (14)	NS
ERCP, *n/pt* (range)	4 (3–7)	3 (2–8)	NS
LOS days/pt (range)	8 (6–16)	6 (3–39)	NS
Overall therapy duration, months (range)	10 (4–24)	9 (4–26)	NS
End follow-up ALP, U/L	86 ± 20	92 ± 36	NS
End follow-up Tot bilirubin, mg/dL	1.0 ± 0.1	1.0 ± 0.1	NS
Post-treatment follow-up, months (range)	55 (34–74)	63 (41–80)	NS
Clinical success, *n* (%)	14 (93)	14 (93)	NS

Data are shown as median (range) or percentage values. Laboratory values are shown as mean ± SD.

MPS, multiple plastic stenting; FCSEMS, fully covered self-expandable metal stent; Rx, radiological; ERCP, endoscopic retrograde cholangiopancreatography; pt, patient; LOS, length of hospital stay; ALP, alkaline phosphatase; Tot, total.

*For residual or recurrent stricture.

Table 3. Endoscopic therapy-related costs according to intention-to-treat analysis.

	MPS *N* = 15	FCSEMS *N* = 15	*P*
Stent cost/patient, €	1206 ± 598	2054 ± 980	<0.05
Endoscopy cost/patient, €	6937 ± 2050	7503 ± 4191	0.4
Hospitalization cost/patient, €	2613 ± 831	2982 ± 2815	0.3
Treatment cost/patient*, €	9550 ± 2497	10 490 ± 6709	0.4

Data are shown as mean ± SD values.

MPS, multiple plastic stenting; FCSEMS, fully covered self-expandable metal stent.

*Sum of stent, endoscopy and hospitalization costs.

Considering the subgroup of patients who achieved and maintained clinical remission after first-line treatment only (13 patients in the MPS and seven patients in the FCSEMS group), the mean endoscopy cost was €6551 ± 1389 for the MPS (72% of the total cost) and €4211 ± 378 for the FCSEMS group (78%) ($P < 0.001$ versus MPS). Moreover, the mean hospitalization-related cost was €2542 ± 745 for MPS (28% of the total cost) and €1160 ± 193 for FCSEMS patients (22%) ($P < 0.001$ versus MPS). Thus, the mean overall cost per patient was €9092 ± 1544 for the MPS and €5371 ± 237 for the FCSEMS group ($P < 0.001$ versus MPS) with a mean cost saving of around 41% for each FCSEMS patient. Difference in hospitalization costs between the two subgroups is due to the lower number of endoscopy sessions in FCSEMS patients, as stated per protocol. Occurrence of adverse events (one mild PEP in the MPS group) did not determine relevant extra-costs, that is, increase of 7% secondary to prolongation of hospital stay.

Discussion

Endoscopic therapy is considered the first-line treatment for biliary complications after liver transplantation [1,2]. Traditional progressive plastic multi-stenting has the best success rate especially when a sufficient number (≥4) of 10 Fr plastic stents are placed side-by-side [3–5]. This type of treatment requires three to five endoscopic procedures a year and thus impacts into associated costs, which includes the costs of stents, ERCPs, devices other than stents, human resources, and

repeated hospitalizations. Fully covered metal stents, initially designed for palliation of malignant strictures, have been tested and approved for the treatment of benign strictures [6–14]. The large diameter of metal stents can achieve a sudden maximal dilation and shorten the duration of treatment as only two procedures (for insertion and removal) are required, thus reducing costs. Their easy removal 3–6 months after implantation also offers an extra benefit.

Four studies so far have compared covered metal stenting with traditional multi-stenting in RCTs [15–18]. Two recent meta-analyses of these studies have shown that fully covered stenting and plastic multi-stenting had similar rates of stricture resolution (89% FCSEMS versus 88% MPS) [23,24] at a median follow-up of ≤36 months. All authors agreed the use of fully covered metal stents reduced the number of ERCPs (<50%) needed to treat AS, with a consequent reduction in treatment costs.

Only two of the four RCTs considered costs in their analysis [15,18]. Kaffes *et al.* studied the costs of endoscopic treatment including ERCPs, stents, and overnight hospital stay [15]. When the costs of re-treatment for 30% of FCSEMS and 50% of MPS patients were included, FCSEMS resulted in a 56% cost saving compared with MPS. Martins *et al.* considered the costs related to ERCPs and devices. They reported that FCSEMS use saved 57% of costs compared with MPS use, but the costs for hospital stay and re-treatment were not included [18].

As few data have been published and the studies reporting procedure-related costs have limitations, the most cost-effective endoscopic treatment for AS after liver transplantation cannot be determined. We conducted an RCT to study the costs of endoscopic therapy including ERCPs, stents, and hospital stay. The healthcare system in Italy is organized on a regional basis, and so the costs of metal and plastic stents, the overall endoscopic procedure, and hospital stay vary among centers. Accordingly, this study was based on a single-center and tertiary referral centers participating in the national BASALT study group were not included. All procedures were planned as inpatients to have full reimbursement from the healthcare system, similarly to other European Countries. Excluding the costs of hospital stay (27% and 28% for the MPS and FCSEMS group, respectively), comparisons between the study groups did not change.

All patients were followed up for more than 34 months with a median follow-up duration of 5 years after the end of endoscopic therapy. This is the longest follow-up reported in the literature and ensured the inclusion of all re-treatment for stricture relapse. No differences in costs were seen between FCSEMS and MPS patients. The rate of re-treatment after FCSEMS use was 53% and secondary to radiological failure or stricture relapse. The study was ended after the data of the 30 LT patients were analyzed; the findings are in line with recent larger RCTs [17,18].

Thus, we confirm the suboptimal performance of FCSEMS as first-line treatment for biliary AS after liver transplantation. We hypothesize that the abrupt expansion of the metal meshes caused ischemic damage to the anastomotic tissue as compared with the progressive dilation seen during traditional multi-stenting. Moreover, we confirmed the high rate of migration of fully covered stents as also seen in recent RCTs [17,18], leading to the requirement for re-treatment in the majority of affected patients. At the time of the present study, no anti-migration systems (flaps, fins) were yet available at our center. Kaffes *et al.* [15] proposed the use of a 3-cm suspended, fully covered cylindrical metal stent. In their small RCT (10 patients per arm), no migration events were recorded and the stent was easily removed using a long duodenal lasso. At that time, the stent proposed by Kaffes *et al.* was a prototype and not yet available on the market. We are currently using FCSEMS with anti-migration systems, and future studies will define their usefulness in reducing migration rate and the need for re-treatment.

Our data suggest caution in the use of FCSEMS as first-line treatment in patients with a naïve duct-to-duct stricture. This is in line with the findings of Tarantino *et al.* who in a retrospective study involving 15 naïve LT patients showed that radiological success was achieved in 53% and stricture relapse was seen in 25% of their patients at a median of 14 months after FCSEMS [25]. Migration of FCSEMS occurred in 46% of the cases in that study.

As expected in our series, analysis comparing patients treated with FCSEMS and with MPS in prolonged clinical remission after first-line endoscopic therapy only showed that a reduction in costs of up to 40% was achieved with the use of FCSEMS. Further study with larger data series should examine whether patient selection and stricture characteristics can predict long-term success with the use of FCSEMS.

The limitations of the present study include the small number of patients treated, possibly causing a type II error. The sample size was calculated on the basis of the few published reports that included endoscopic treatment-related costs but not data on stricture resolution.

The suboptimal results in LT patients treated with FCSEMS after 30 patients were enrolled caused the authors to prematurely end the study. Secondly, the treatment duration of MPS patients was assessed at the time of radiological success that was checked every 3 months, and of FCSEMS patients when they were assessed after at least 6 months to limit the risks of sepsis of biliary origin. This difference in procedure suggests the protocol should assign different treatment durations to the two arms, in line with all RCTs published so far, with a median duration of 3–6 months in FCSEMS patients and 9–12 months in MPS patients [15–18].

The cost analysis showed similar results between the two endoscopic therapies, mainly because 53% of the patients needed second-line treatment after FCSEMS, which also led to termination of the study. Which endoscopic therapy is better as first-line treatment for AS remains undecided. An intriguing future perspective should be a cost-effectiveness analysis based on larger long-term series of LT patients to compare different endoscopic strategies considering the variability of cost of devices and stents and modality of hospitalization across countries.

In summary, at long-term follow-up, multi-stenting seems a better option for treating naïve patients with a duct-to-duct AS after liver transplantation. The use of next-generation FCSEMS with anti-migration systems and the selection of patients with characteristics favorable for FCSEMS treatment are suggested in order to achieve optimal results and contain costs.

Authorship

PC and RP: designed the study, collected data and wrote the paper; GS: collected data, analyzed data and wrote the paper; RR, IP, FM, AT, IF, FI and FD: collected data, analyzed data and reviewed the paper; PL, PR, GR and MV: reviewed the paper.

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Conflict of interest

The authors have declared no conflicts of interest.

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