

Multiple plastic versus fully covered metal stents for managing post-liver transplantation anastomotic biliary strictures: a meta-analysis of randomized controlled trials

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Abstract

Background Anastomotic biliary strictures (ABS) following liver transplantation (LT) are one of the most common complications, occurring in 4.5-32% of patients. Multiple plastic stenting (MPS) requires multiple sessions, with the associated risk, cost and patient discomfort. Fully covered self-expandable metal stents (FC-SEMS) have increasingly been used in this setting. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs), comparing the role of FC-SEMS and MPS in the treatment of ABS post-LT.

Methods We conducted a bibliographic search using PubMed and EMBASE, aimed at identifying available RCTs that compared MPS to FC-SEMS in patients with ABS post LT from January 2000 to October 2017. Primary outcomes were ABS resolution and recurrence, while secondary outcomes were adverse events and number of procedures performed. Pooled estimates were calculated using random-effects models.

Results Four RCTs (205 patients) were included. ABS resolution and recurrence did not differ significantly between the groups (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.43-2.56, $P=0.92$; and OR 2.37, 95%CI 0.54-10.38, $P=0.25$). The same was true for adverse events (OR 0.91, 95%CI 0.84-3.48, $P=0.86$) and migration rate (OR 1.31, 95%CI 0.46-3.71, $P=0.61$). The mean number of endoscopic retrograde cholangiopancreatography procedures was lower for FC-SEMS (mean difference [MD] -2.08).

Conclusions FC-SEMS and MPS had equal ABS resolution and recurrence, although there was a trend towards a higher recurrence rate in FC-SEMS that disappeared when trials with a shorter stent indwelling time were excluding. No difference was found in overall adverse events or migration rate.

Keywords Randomized controlled trials, meta-analysis, biliary tract disease, stent, self-expandable metal stent, plastic stent, liver transplantation, anastomotic biliary stricture

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Introduction

Anastomotic biliary strictures (ABS) are one of the most common complications following liver transplantation (LT), occurring in approximately 4.5-15% of cases after deceased donor LT and 8-32% after living donor-related LT (LDLT) [1-7]. ABS usually develop within the first year after transplant [1,8,9] and their formation is often due to surgical technical issues, a fibroproliferative response to local ischemia, or both [10].

Endoscopic treatment has become the standard of care for the management of ABS and several techniques have been described, including balloon dilation, multiple plastic stent (MPS) insertion and fully covered self-expandable metal stent (FC-SEMS) insertion. Balloon dilation as monotherapy has been abandoned because of its low success rate and high rate of ABS recurrence [11].

Currently, the standard of care is the placement of plastic stents with or without balloon dilation, with variable timing of subsequent endoscopic retrograde cholangiopancreatography (ERCP); this approach has proven to be effective and safe, with a low rate of ABS recurrence [12-15]. In order to minimize the issues associated with the placement of multiple plastic stents, such as stent occlusion, suboptimal long-term efficacy and the need for multiple endoscopic sessions, several studies have assessed the validity of single FC-SEMS as an alternative to MPS, with heterogeneous results [16-19].

A previous randomized controlled trial (RCT) comparing different types of FC-SEMS showed a clinical success rate of 70%, which was below the reported success rate for MPS [20]. This data was confirmed by 3 previous meta-analyses [15,21,22], comparing the efficacy and safety of FC-SEMS vs. MPS in patients with ABS post-LT and LDLT. These meta-analysis, including only observational studies with low quality, showed that, although FC-SEMS was a promising option in this setting, there was no clear advantage of FC-SEMS over MPS. Recently, 2 new RCTs have been published comparing the efficacy and safety of FC-SEMS vs. MPS [23,24].

The aim of this study was to perform an updated systematic review of the current literature comparing the safety and efficacy of FC-SEMS vs. MPS insertion in the management of post-LT ABS.

Patients and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [25]. The methods of analysis and inclusion criteria were specified in advance and documented in a protocol according to the Cochrane guidelines. A PRISMA checklist is provided in the supplementary materials (S1).

Search strategy

Studies were identified by searching, with the assistance of a research librarian, in PubMed, EMBASE, Google Scholar and the Cochrane Library. The following MESH and keyword search terms were used: “liver transplantation”, “anastomotic biliary stricture”, “biliary strictures”, “self-expandable metal stents”, “plastic stents”. Any duplicate citation was removed.

Inclusion criteria

1. Types of studies: RCTs comparing the efficacy and safety of fully covered SEMs vs. MPS.
2. Types of participants: patients older than 18 years old with ABS following orthotopic LT without previous stent placement.
3. Types of interventions: MPS vs. FC-SEMS placement.
4. Types of outcome measures: ABS resolution and recurrence, cause of stent dysfunction and adverse events.

Exclusion criteria

Non-randomized studies, non-anastomotic strictures, and other benign biliary strictures were excluded from the meta-analysis. The keywords “biliary tract disease”, “biliary obstruction”, “biliary stricture”, “anastomotic stricture”, “liver transplantation”, “randomized controlled trial”, “meta-analysis”, “endoprosthesis”, “metal stent”, and “systematic review” were associated in different combinations using the Boolean terms AND/OR. Queries were limited to those involving human subjects. Manual searches of reference lists of relevant literature reviews were used to complement the computer searches. A search strategy is provided in the Supplementary Material (S2). Each article was read and analyzed by at least 2 members of the research team (AT & MM) and eligibility assessment was performed independently in a non-blinded standardized manner.

Definitions

Only one trial [24] reported definitions of measured outcomes that would allow an objective assessment of the results. ABS was defined as a dominant stricture at the anastomotic site without effective passage of contrast medium, as shown by cholangiographic imaging. ABS resolution was defined as cholangiographic resolution of stricture, assessed by easy passage of an 8.5 mm extraction balloon through the anastomosis site, and no need for further interventional procedure. ABS recurrence was defined as relapse characterized by the onset of new clinical symptoms and/or increase in cholestatic enzymes or total bilirubin with cholangiographic evidence of an ABS that requires a subsequent interventional procedure. Adverse events were defined as the occurrence of complications after the procedure and graded according to the Cotton criteria [26].

Data collection

Two investigators (AT & MC) extracted data from the eligible publications independently. The following data were retrieved into a standardized database:

- Descriptive data: first author, year and type of publication, country of origin, study setting, number of patients, age and sex of patients, reason for LT, time to stricture, treatment time, number of ERCPs, stent type and covering material, MPS protocols, length of follow up, adverse events, and procedural related costs.
- Qualitative data: random sequence generation, allocation concealment, blinding of participant and personnel, blinding outcome assessment, incomplete outcome data, selective reporting, and lost to follow up.
- Outcome data: For primary outcomes we extracted the odds ratio (OR) with 95% confidence interval (CI), when reported in the original publication, or we collected additional information in order to apply statistical methods

to compute them. For secondary outcomes, we extracted the number of patients and events in each arm.

- Quality appraisal: Each included study was appraised for quality by 2 independent evaluators (AT & BG). Quality appraisal was performed using the risk-of-bias tool, as recommended by the Cochrane collaboration [27].

Outcome measures

The primary outcome measures were the rates of ABS resolution and recurrence. Secondary outcomes included overall adverse events, pancreatitis, cholangitis and bleeding rate, stent migration and the median number of procedures (ERCP). No RCTs reported cost-effectiveness analysis so that these data were not available for statistical analysis.

Statistical analysis

Dichotomous outcomes were evaluated in terms of ORs with their 95% CIs and summarized across studies through a random-effects model. If no between-study heterogeneity was evident, the pooled estimate from the random-effects model would be equal to the one derived from a fixed-effects model. Procedure time was analyzed using the Hedges' Standardized Mean Difference estimator. When studies used median and range, results were converted to mean and standard deviation using the formula of Hozo *et al* [28]. The hazard ratios (HR) for time to achieve resolution and time to re-obstruction could not be obtained because they were not reported in the trials included in the analysis. Finally, we tried to derive the estimation of an indirect measure of the HRs from log-rank P-values or Kaplan-Meier curves, as previously reported [29], but it was only possible to extract the time to reobstruction for 2 trials [23,24] and the time to achieve ABS resolution for one trial [30], not enough to allow the calculation of relevant outcomes. We performed a cost-analysis converting data from one study from Australian to US dollars and calculating median, range and standard deviation comparing using the Student's *t*-test. Between-studies heterogeneity was assessed using the Q test based on the chi-squared statistics, and inconsistency was quantified in terms of the I² statistic [31]. In order to assess potential sources of heterogeneity, we firstly performed a sensitivity analysis by removing each study in turn (leave-one-out-method) to evaluate its influence on the final pooled estimate. Publication bias was assessed by visual inspection of funnel plots for asymmetry and through Egger's test for asymmetry [32].

Data were synthesized using Review Manager software (version 5.1 for Windows, the Cochrane Collaboration, Oxford, UK). Finally, we graded the quality of evidence using Grade system software—GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.)—according to the GRADE recommendation [33].

Results

Study selection

Eight hundred fifty unique studies were identified through the systematic review of the literature. Following the screening of abstracts and titles, we identified 103 potentially eligible studies for which full-text reading was required. Finally, 4 studies [23,24,30,34] were included, as shown in the PRISMA flow diagram in Fig. 1.

Characteristics of the included studies

The main characteristics of the 4 included studies are reported in Table 1. The studies were published between 1995 and 2017 and included a total of 205 patients, randomized to FC-SEMS (n=103) or MPS (n=102).

Two studies [23,30] reported the rate of balloon dilation in FC-SEMS and MPS, showing that FC-SEMS group had a lower rate of balloon dilation before stent placement (OR 0.14, 95%CI 0.06-0.30). One trial [30] did not report the primary and secondary outcomes in the setting of LT because it was designed to compare FC-SEMS and MPS for all benign biliary strictures. We obtained the extracted data from the authors.

In the MPS stent group, the 4 RCTs included in the analysis followed different protocols, as shown in Table 1. No RCTs in the MPS group reported how many patients had ABS resolution at 3-6 or 12 months, preventing a direct comparison between the 2 groups. In the FC-SEMS group, there was different time to stent removal protocols, as shown in Table 1. The evaluation using the Cochrane risk-of-bias tool did not show significant bias (Fig. 2).

Primary outcomes

Four studies [23,24,30,34], including 103 FC-SEMS patients and 102 MPS patients, reported the ABS resolution rate. There was no statistically significant difference between FC-SEMS and MPS (OR 1.05, 95%CI 0.43-2.56) (Fig. 3). FC-SEMS showed a trend towards a higher recurrence rate, but the difference was not statistically significant (OR 2.37, 95%CI 0.54-10.38, P=0.25; I² 53%) (Fig. 4).

The sensitivity analysis was performed by removing each trial analysis in turn to assess the influence of each individual study on the global analysis. We noted that excluding the trials in which FC-SEMS were removed later (6 months) [24,30], the trend towards a higher recurrence rate in the FC-SEMS group became more evident (OR 3.90, 95%CI 0.56-27.25, P=0.17), while excluding studies that removed FC-SEMS earlier (12 weeks to 4 months) [23,34] eliminated the difference between the 2 groups (OR 0.89, 95%CI 0.29-2.79, P=0.85). After exclusion of the trial by Martins *et al* [24], the only one to show a higher recurrence rate for FC-SEMS, no statistically significant difference was noted (OR 1.31, 95%CI 0.46-3.74, P=0.61), without heterogeneity (I² 5%).

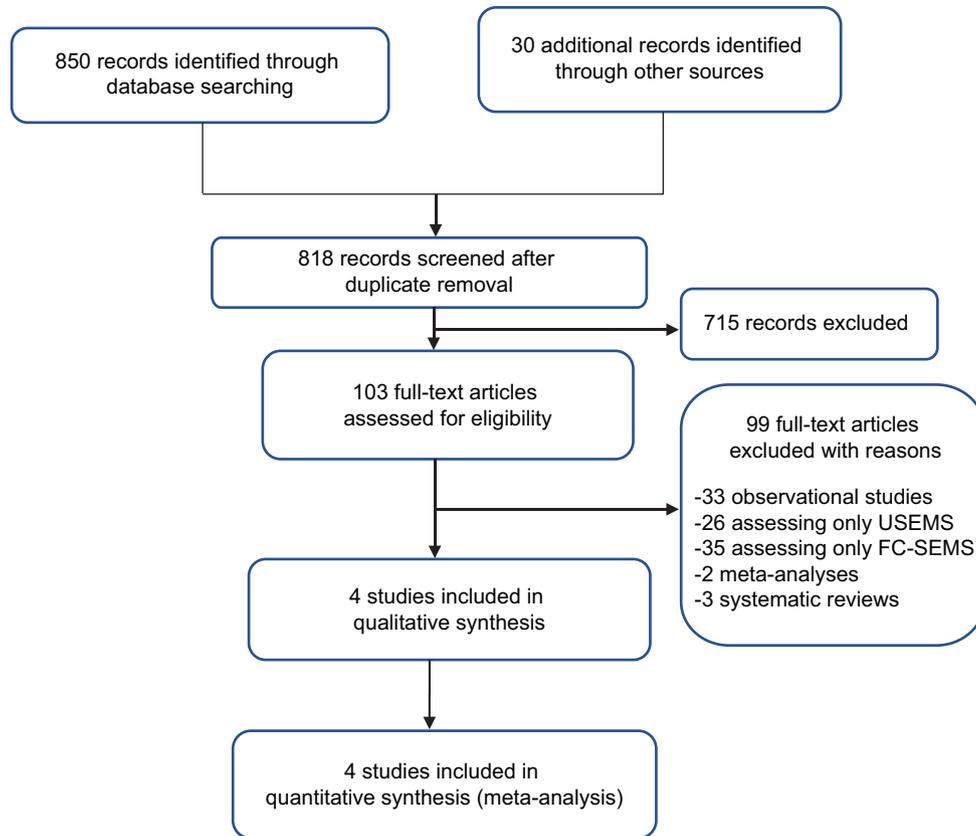


Figure 1 Prisma flow diagram

USEMS, uncovered self-expanding metal stents; FC-SEMS, fully covered self-expandable metal stent

Secondary outcomes

The results of the secondary outcomes are provided in Table 2. There were 4 studies, involving 97 FC-SEMS and 89 MPS patients, that reported overall adverse events. The pooled OR was 0.91 (95%CI 0.32-2.62), showing that there was no statistical difference between FC-SEMS and MPS groups. There was also no statistically significant difference between FC-SEMS and MPS regarding cholangitis rate (OR 0.61, 95%CI 0.16-2.42, $P=0.49$), bleeding rate, perforation rate or migration rate.

Acute pancreatitis was assessed in 2 RCTs [24,30] that showed a higher rate of pancreatitis in the FC-SEMS group (OR 3.41, 95%CI 1.16-10.03, $P=0.03$). An RCT by Martins *et al* [24] had a bias due to the fact that the author did not perform endoscopic sphincterotomy before FC-SEMS placement, as highlighted in the interim analysis. When endoscopic sphincterotomy was performed the rate of pancreatitis was equal in both groups.

The median number of ERCP procedures was lower in the FC-SEMS group compared with MPS group (MD -2.08, 95%CI -3.29 to -0.86) [23,24,30,34]. No RCT reported data to allow a cost-effectiveness analysis. Two RCTs [24,34] reported the total costs for both procedures, showing that FC-SEMS allowed a cost saving of between 9,800 and 10,000 US dollars, favoring FC-SEMS as a less expensive procedure ($P<0.001$).

A subgroup analysis could not be performed because of the small sample size, insufficient to power the results, and the low

number of RCTs published to date. The risk-of-bias analysis of individual studies showed a high risk of performance and detection bias, probably related to the need for ABS assessment, and stent placing and removal by the physicians. The Grade summary of evidence is reported in the Supplementary material (S3).

Publication bias

Visual inspection of funnel plots (Fig. 5) showed no evidence of asymmetry. As a confirmation, Egger's test for funnel plot asymmetry gave a P -value of 0.13, showing no potential publication bias for the outcomes considered.

Discussion

We performed a systematic review and meta-analysis of RCTs specifically designed to assess the efficacy and safety of placement of single FC-SEMS vs. MPS in the management of ABS following LT. In our study, there was no statistically significant difference in the rates of ABS resolution and recurrence between FC-SEMS and MPS in patients with ABS post-LT, although the pooled ORs show that FC-SEMS had

Table 1 Baseline characteristics of included studies

Results	Kaffes <i>et al</i> 2014 [34]		Cotè <i>et al</i> 2016 [30]		Tal <i>et al</i> 2017 [23]		Martins <i>et al</i> 2018 [24]	
	FC-SEMS	MPS	FC-SEMS	MPS	FC-SEMS	MPS	FC-SEMS	MPS
Number of patients	10	10	37	36	24	24	30	29
Age	56.5 (38-67)	49.5 (23-69)	55.4	56.4	57 (32-69)	58.5 (32.72)	54 (23-3)	50 (28-71)
Sex	5/5	5/5	26/11	25/11	14/10	18/6	22/8	20/9
Study type	RCTs 2 centers		RCTs multi		RCTs multi		RCTs single-center	
Stent type	Taewoong		Wallflex 8/10 mm		3 types without anti-migration		Wallflex 10 mm	
FC-SEMS removal (study protocol)	12 weeks		NA		4-6 months		6 months	
MPS protocol	Dilation at endoscopist discretion at 3 month remove PS and if stricture solved not stented		Dilate & place 1-2 PS q3 months, remove all PS, sequentially dilate and upsize PS until stricture solved		As many as possible of varying diameters 7-10-11.5 and type at endoscopist discretion		Dilate with balloon 6-10 mm and as many as PS, remove all PS, dilate restenting until 12 months	
No. of ERCPs/patients	2 (2-2)/4.5 (2-6)		2.21 (\pm 0.48) 3.13 (\pm 0.88)		2 (2-12)/4 (3-12)		2 (2-2)/4.9 (4-6)	
No. of stents/patient	1.0 (1-1)/7.5 (3-13)		NA		1 (1-24)/8 (2-32)		1 (1-1)/16 (6-30)	
Treatment time median (range)	3.8 (2.5-5.0)	10.1 (4-13)	158.2 (\pm 89.7)	193.5 (\pm 88.7)	178.5 (65-551)	229.5 (59-490)	158.5 (9-239)	354 (222-242)
Balloon dilation before stenting	0/1.5 (0-2)		5/37 vs. 31/36		10/24 vs. 14/24		NA	
Costs	10830 AuD	23580 AuD					6903 USD	16905 USD

FC-SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stenting; ERCP, endoscopic retrograde cholangiopancreatography; RCT, randomized controlled trial; AuD, Australian dollars; USD, United states dollars

a trend for a higher recurrence rate compared with MPS, with between-study heterogeneity (I² 53%). This trend was especially apparent when stent removal was performed earlier, but the small sample size was not enough to provide robust data that would allow a definitive conclusion. ABS dilation before stent deployment was performed more frequently in the MPS group than in the FC-SEMS group, but it was not possible to assess the effect of biliary dilation on the ABS recurrence rate.

A crucial issue that remains unsolved is ABS recurrence, because more information would be needed. The study by Martins was the only one to show a significantly higher rate of recurrence in the FC-SEMS group, and the authors suggested that the shorter indwelling time (6 months) in the FC-SEMS group was responsible for this result. We suggest according to our data that should be prolonged the indwelling time in the FC-SEMS group and that future RCTs should take this issue into account.

Another critical point to be stressed is the difference between the 2 procedures (FC-SEMS vs. MPS) because, while FC-SEMS is associated with 2 steps (placement and

removal after a specified time), the MPS technique involves 5 or 6 procedures (placement and removal). Furthermore, the MPS protocol could be different across different centers and protocols, depending on personal technique, for example, stent removal and replacement, or adding one or more stents without stent removal. In the 4 RCTs included in our meta-analysis, the MPS protocols differed significantly, leading to confounding factors that produced a bias.

One unresolved point that should be analyzed in future trials is the method of FC-SEMS placement (transpapillary vs. intraductal), which would be likely to further influence the performance of FC-SEMS, reducing the migration rate and SEMS dysfunction from sludge. Another point that should be mentioned is the ABS location, because no data was available from the primary studies. This could be a factor that limits the use of FC-SEMS placement, if closeness to the bifurcation causes closure of the duct, resulting in cholangitis.

A meta-analysis by Kao *et al* including only observational studies, assessed the role of MPS in 8 studies (446 patients) in CDLT, 3 studies (120 patients) using MPS in LDLT, and

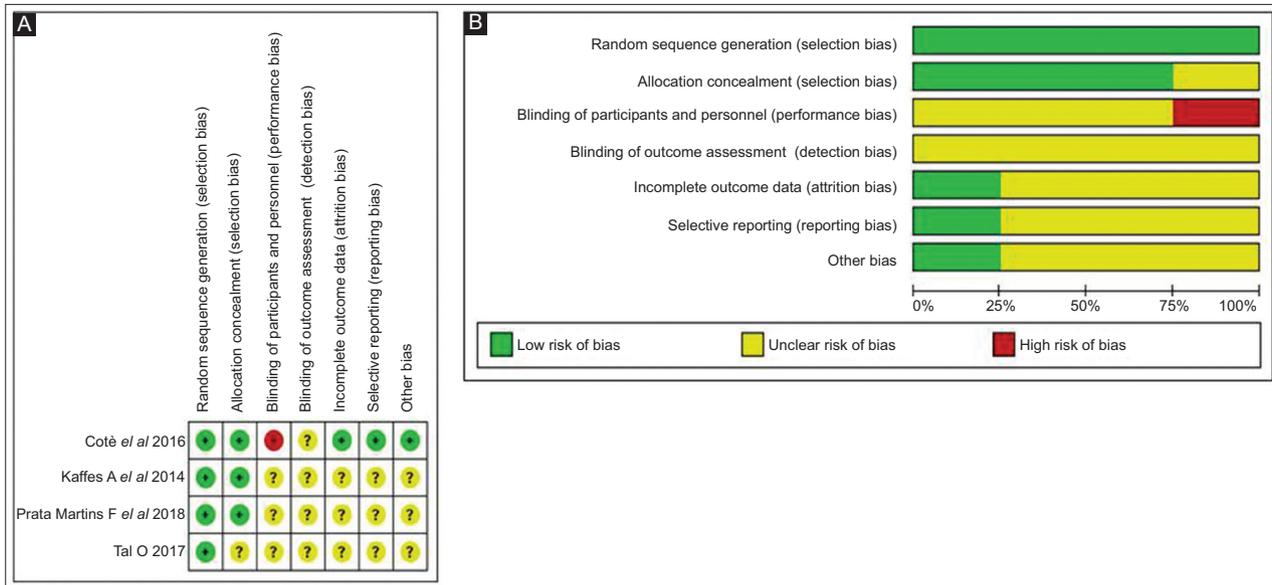


Figure 2 Cochrane risk of bias. (A) Risk of bias summary. (B) risk of bias in the individual study

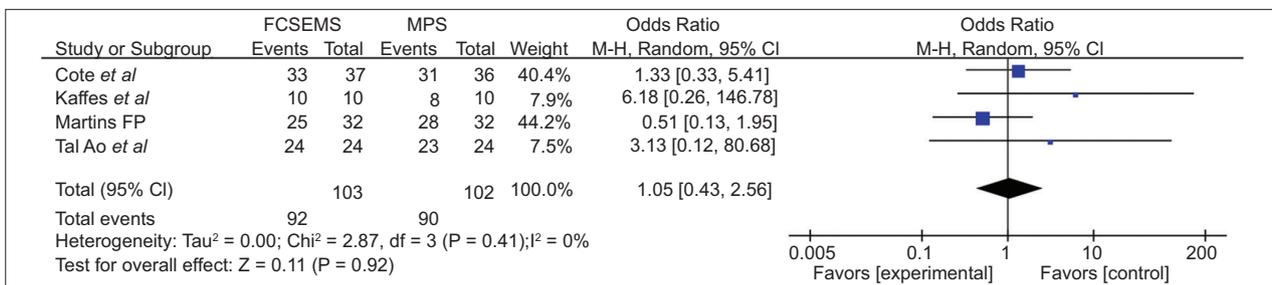


Figure 3 Forest plots showing the results of a meta-analysis comparing stricture resolution between FC-SEMS and MPS
CI, confidence interval; FC-SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stenting

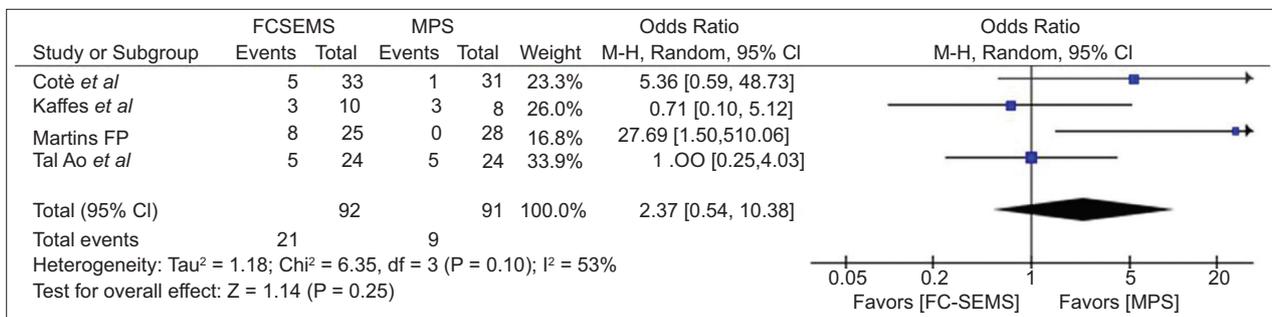


Figure 4 Forest-plots showing the results of meta-analysis comparing stricture recurrence between FC-SEMS vs. MPS
CI, confidence interval; FC-SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stenting

10 studies (200 patients) using SEMs without a direct comparing of the two treatments. The authors concluded that ABS resolution and recurrence rate were higher in cases with a longer stent indwell duration (>12 months) compared with a shorter duration (<12 months); this is similar to our own findings.

In the meta-analysis by Kao *et al* [15] available data were in the form of case series. Each study had small numbers of patients, with 148 being the highest number of participants,

and none fulfilled all the criteria for high-quality studies. Significant heterogeneity existed among the studies with respect to primary outcome, patient selection, stent protocol, stent duration, types of SEMs and follow-up periods; this made it difficult to compare FC-SEMS with MPS.

A meta-analysis by Aparicio *et al* [21] that included 10 studies (1 RCT, 6 non-randomized prospective studies and 3 cohort studies) showed an equal ABS resolution with FC-SEMS and MPS, but only the single RCT assessed the

Table 2 Primary and secondary outcome

Author	Total n. pts	FC-SEMS/MPS	Stricture resolution (n/%) FC-SEMS/MPS	Stricture recurrence (n/%) FC-SEMS/MPS	Overall adverse events (n/%) FC-SEMS/MPS	Migration rate (n/%) FC-SEMS/MPS	Acute pancreatitis (n/%) FC-SEMS/MPS	Cholangitis rate (n/%) FC-SEMS vs MPS
Martin <i>et al</i> , 2017 [24]	59	30/29	25/30 vs. 28/29	8/25 vs. 0/28	14/30 vs. 9/30	3/30 vs. 4/30	8/60 vs. 3/141	1/60 vs. 2/141
Tal <i>et al</i> , 2017 [23]	48	24/24	24/24 vs. 23/24	5/24 vs. 5/24	3/24 vs. 3/24	5/24 vs. 0/24	NA	NA
Kaffes <i>et al</i> , 2014 [33]	20	10/10	10/10 vs. 8/10	3/10 vs. 3/8	6/10 vs. 5/10	0/10 vs. 1/10	NA	1/10 vs. 4/10
Cote <i>et al</i> , 2016 [30]	73	37/36	33/37 vs. 31/36	5/33 vs. 1/31	12/33 vs. 17/25	15/33 vs. 8/25	2/33 vs. 2/25	1/33 vs. 0/25
Overall	205	103/102	92/103 vs. 90/102	21/92 vs. 9/91	35/97 vs. 34/89	23/101 vs. 13/89	10/93 vs. 5/166	3/103 vs. 6/176
OR (95%CI)			1.05 (0.43,2.56)	2.37 (0.54-10.38)	0.91 (0.84-3.48)	1.31 (0.46-3.71)	3.41 (1.16-10.03)	0.61 (0.16-2.42)
P value			0.92	0.25	0.86	0.61	0.03	0.49

FC-SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stenting; OR, odds ratio; CI, confidence interval

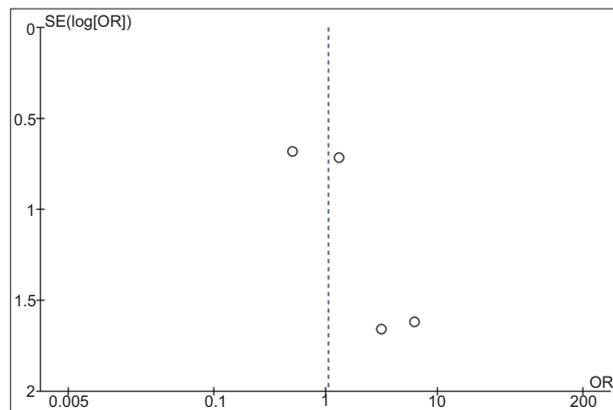


Figure 5 Funnel plot showing no publication bias
SE, standard error; OR, odds ratio

ABS resolution rate between FC-SEMS and MPS. A recent meta-analysis was published by Landi *et al* [22], including 3 RCTs and 1 observational study with a total of 119 patients receiving FC-SEMS and 179 MPS. The results showed that FC-SEMS were superior in terms of the number of ERCP procedures and days of treatment, whereas ABS resolution and recurrence rate showed equal efficacy in both groups. This meta-analysis is underpowered to draw definitive conclusions and the consistent heterogeneity observed in the included studies suggest caution for interpreting the results. The authors did not consider the results of previous meta-analyses, while the findings regarding ABS resolution and recurrence from the randomized trials by Cote *et al* [30], designed for all benign biliary strictures, included in their meta-analysis, did not report the real results for the subgroup of ABS post-LT.

Only 2 RCTs, those by Kaffes *et al* [34] and Martins *et al* [24], reported the cost-analysis, which included the cost of the procedure and the health personnel involved, and

both showed a cost-saving favoring FC-SEMS. Furthermore, an economic analysis published in abstract form found that FC-SEMS were overwhelming favored as the more economical strategy, offering an overall less expensive hospital stay and fewer lost days of work compared to MPS, even with the more expensive implant cost.

The limitations of our meta-analysis are based on the missing relevant data from the primary studies, such as risk factors for biliary complications, different protocols, need for balloon dilation, SEMS type, type of covering, different axial and radial force, and the different protocols used in the RCTs for the MPS group. Another limitation is the absence of cost-analysis and cost-benefit studies that could allow a choice of better treatment approach, taking into account the costs to the health system. The small sample size (205 patients) of the RCTs included could have affected various results and limited the conclusions; it did not allow us to determine the reasons for the trend noted towards a higher recurrence rate in the FC-SEMS group. Finally, we assessed ABS resolution and recurrence as a dichotomous variable and not as a time to event, because, unfortunately, the HRs of the 2 primary outcomes were often unavailable or not obtainable.

In conclusion, our systematic review shows that FC-SEMS had equal stricture resolution, stricture recurrence and overall adverse events compared with MPS, although there was a trend toward a higher recurrence rate in the FC-SEMS groups when the stents were removed early. Our meta-analysis is the first systematic review including only RCTs that have conducted to a more robust conclusion. FC-SEMS are associated with reduced number of procedures overall a cost sparing procedure. According to our data and cost-analysis data, the use of new FC-SEMS with an antimigration system for a longer dwell time could be the best approach. Further RCTs with larger sample size and longer follow up focusing on risk factors of recurrence rate and using FC-SEMS with anti-migration features with appropriate dwelling time are warranted.

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Summary Box

What is already known:

- Multiple plastic stents (MPS) are the gold standard for the treatment of anastomotic biliary strictures post-liver transplantation
- Fully covered self-expandable metal stents (FC-SEMS) are increasingly used as rescue treatment in case of refractory strictures or as primary treatment
- Many trials and meta-analyses addressed the comparison between MPS and FC-SEMS without finding any relevant difference, but those studies had many flaws

What the new findings are:

- Our study for the first time analyzed only randomized controlled trials (RCTs) and showed that MPS and FC-SEMS are equally effective and safe procedures
- We stressed the difference between the 2 procedures because, while FC-SEMS is associated with 2 steps (placement and removal after a specific time), the MPS technique involves 5 or 6 steps (placement and removal)
- The study highlights the missing relevant data from the primary studies, such as risk factors for biliary complications, different protocols, need for balloon dilation, SEMS type, type of covering, different axial and radial forces, the different protocols used in the RCTs, as well as the absence of cost-analysis that could allow a choice of better treatment approach considering health system costs

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Supplementary Table 1 PRISMA check list
PRISMA 2009 Checklist to be included with meta-analyses

Section/topic	Item #	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1-3
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	7
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	9

(Contd...)

Supplementary Table 1 (Continued)

Section/topic	Item #	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	9
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include confidence intervals and measures of consistency for each	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16])	9-10
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome: consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	12

Search strategy

Supplementary material 1

Search strategy PubMed

1. Biliary stricture (exp)
2. Bile duct disease
3. Cholestasis
4. Common bile duct disease
5. Jaundice, obstructive
5. Or/ 1-5
6. Liver transplantation
7. OLT
8. Or/6-7
9. Stent
10. Plastic stent
11. Or/ 9-10
12. Metallic stent
13. SEMS
14. Self-expandable metal stent
15. Or/12-14
16. Randomized controlled trial (pt)
17. Controlled clinical trial
18. Randomized (tiab)
19. Randomly (tiab)
20. Trial (tiab)
21. Groups (tiab)
22. Or/16-21
23. 5 and 8 and 11 and 15 and 22

Grade summary of evidence

[FC-SEMS] compared to [MPS] for anastomotic biliary stricture (ABS) post-LT

Patient or population: Anastomotic biliary stricture (ABS) post LT

Setting: Liver transplantation

Intervention: [FC-SEMS]

Comparison: [MPS]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with [MPS]	Risk difference with [FC-SEMS]
Stricture resolution	205 (4 RCTs)	⊕⊕⊕⊕ HIGH	OR 1.05 (0.43 to 2.56)	88 per 100	0 fewer per 100 (12 fewer to 7 more)
Stricture recurrence	183 (4 RCTs)	⊕⊕⊕⊕ HIGH	OR 2.37 (0.54 to 10.38)	10 per 100	11 more per 100 (4 fewer to 43 more)
Adverse events	186 (4 RCTs)	⊕⊕⊕⊕ HIGH	OR 0.91 (0.84 to 3.48)	38 per 100	2 fewer per 100 (4 fewer to 30 more)
Stent migration	190 (4 RCTs)	⊕⊕⊕⊕ HIGH	OR 1.31 (0.46 to 3.71)	15 per 100	4 more per 100 (7 fewer to 24 more)
Treatment time assessed with: days	203 (4 RCTs)	⊕⊕⊕⊕ MODERATE ^a	-	The mean treatment time was 266.7	MD 104.99 lower (202.19 lower to 7.79 lower)
Cholangitis	279 (3 RCTs)	⊕⊕⊕⊕ HIGH	OR 0.61 (0.16 to 2.42)	34 per 1,000	13 fewer per 1,000 (28 fewer to 45 more)
Acute pancreatitis	259 (3 RCTs)	⊕⊕⊕⊕ MODERATE	OR 3.41 (1.16 to 10.03)	30 per 1,000	66 more per 1,000 (5 more to 207 more)

^aThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI)

FC-SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stenting; LT, liver transplantation; CI, confidence interval; OR, odds ratio; MD, mean difference; RCT, randomized controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect