META-ANALYSIS

Endoscopic treatment of anastomotic biliary stricture after adult deceased donor liver transplantation with multiple plastic stents versus self-expandable metal stents: a systematic review and meta-analysis

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SUMMARY

Anastomotic biliary strictures (ABSs) occur in up to 15% of patients after liver transplantation (LT). The aim of this study was to compare the efficacy and safety of self-expandable metal stents (SEMS) versus multiple plastic stents (MPS). Databases were searched through April 2017. The outcome measures were technical success, stricture resolution, recurrence and complications. We synthesized the findings descriptively and performed a meta-analysis. Three randomized controlled trials and one retrospective cohort study were identified, including 179 MPS and 119 SEMS patients. Outcome data were pooled in a meta-analysis that showed an advantage of SEMS in terms of the number of ERCP procedures (mean difference: 1.69 ERCP; 95% CI, 1–2.39; $P < 0.00001$) and treatment days (mean difference: 40.2 days; 95% CI, 3.9–76.4; $P = 0.03$), with no differences in terms of ABS resolution or recurrence. Fourteen case series reported MPS outcomes and fifteen reported SEMS outcomes, including 647 and 419 patients, respectively. Based on low-quality evidence, we cannot draw any reliable conclusions on the superiority of MPS or SEMS strategies. Even though shorter treatment times and fewer ERCP procedures support the use of SEMS, whether one technique has well-defined advantages over the other remains unclear.

Transplant International 2018; 31: 131–151

Key words
anastomotic biliary strictures, biliary complications, endoscopic treatment, liver transplantation, multiple plastic stents, self-expandable metal stents

Received: 23 February 2017; Revision requested: 5 April 2017; Accepted: 24 October 2017

Introduction

Despite advances in surgical techniques, organ selection, preservation and immunosuppression, biliary tract complications are the most common complications after liver transplantation (LT), with major impacts on patient and graft survival [1,2]. Anastomotic biliary strictures (ABSs) occur in up to 15% of patients, mainly within the first year after transplantation [1,3–6]. Risk factors for ABS are related to both donor and

doi:10.1111/tri.13089

recipient characteristics (e.g. prolonged ischaemia time, the fibrotic healing process, a mismatch in size between the donor and recipient bile ducts), tension at the anastomosis, the use of electrocauterization, bile leak and infection [2,3,7–10]. The typical presentation involves elevated liver enzymes, obstructive jaundice and cholangitis. Endoscopic treatment is the first-line therapy in patients with duct-to-duct biliary anastomosis [6,11–15].

No standard protocol has emerged for the endoscopic management of ABS. Analogous with the more frequent benign biliary stricture (i.e. postcholecystectomy), endoscopic therapy for ABS usually requires biliary sphincterotomy plus balloon dilatation (BD) and stent placement [16–18]. Multiple plastic stents (MPS) are usually kept in place until stricture resolution or for a period of 12 months [19–21]. An increasing number of stents are placed through the stricture and exchanged every 2–3 months to reduce the likelihood of stent blockage [16,18,22,23]. The reported ABS resolution rate in the literature using the MPS method is between 85% and 97%, with large differences between strategies [11,13,24,25].

Self-expandable metal stents (SEMS), which are usually used in biliary and pancreatic malignancies, have gained popularity in recent years because they may offer the advantages of longer stent patency and a larger diameter, allowing faster benign stricture resolution and requiring reintervention less often compared with MPS [26,27]. SEMS should be kept in place for a minimum of 3 months as a shorter stenting duration could result in slower ABS resolution [28–30]. However, a higher stent migration rate has been described for initial SEMS compared with MPS [24]. Furthermore, SEMS carry a low but significant risk of tissue ingrowth and stent impaction [31].

The current evidence is insufficient to suggest a clear advantage of one strategy over the other in the management of ABS. In a recent large multicentre prospective study [32], the resolution rates using SEMS in 42 post-LT ABS patients were 68% and 75% at 3 and 6 months, respectively. Two recent trials comparing SEMS and MPS in patients with ABS [33,34] found that the resolution rates were similar with both stent protocols, suggesting that SEMS may be a cost-effective alternative to MPS.

The aim of this systematic review was to provide an exhaustive overview of the literature concerning the efficacy and safety of SEMS and MPS techniques in the management of ABS after LT.

Materials and methods

The methodological approach included development of the selection criteria, definition of the search strategies, assessment of study quality and extraction of relevant data. The PRISMA statements checklist for reporting a systematic review was followed [35].

Study inclusion criteria

The study selection criteria were defined before data collection for proper identification of eligible studies for the analysis. All publications in which the primary objective was to describe the efficacy, safety, complications and/or long-term outcomes of endoscopic treatments for ABS in LT patients were retrieved and analysed.

Randomized controlled trials (RCT), cohort studies, case–control studies and case series including more than five patients were considered eligible for inclusion. No trial duration limitation was set. Case reports, review articles and conference abstracts were not considered.

By applying the PICO (Population, Intervention, Comparison, and Outcome) framework, we defined the following study selection criteria:

Populations/participants: Adult deceased donor LT patients with ABS after duct-to-duct reconstruction.

ABS was defined as a dominant narrowing at the anastomotic site as demonstrated by cholangiography. Early ABS was defined as a stricture occurring less than 3 months after LT, and late ABS was defined as a stricture occurring 3 months or more after LT.

Studies on ABS treatment in paediatric patients or after living donor LT were excluded because these cases involve a reduced-size graft from either split-liver transplantation or a living donor that can be associated with different biliary complications and ABS management compared to adult LT patients receiving a whole graft from a deceased donor.

Interventions: Patients who received both primary and secondary treatments for ABS with either MPS or covered (partially or fully) SEMS were eligible.

Primary treatment was defined as the first endoscopic intervention for ABS, and secondary treatment was defined as a salvage endoscopic procedure after primary treatment failure. Studies that included both primary and secondary SEMS patients were analysed within a Secondary subgroup.

Comparison: MPS and SEMS were compared.

Outcome measures included:

Technical success: defined as the ability to obtain a cholangiogram and achieve stenting with or without

previous stricture dilation during endoscopic retrograde cholangiopancreatography (ERCP).
Stricture resolution: defined by easy passage of contrast through the anastomosis during ERCP at the end of endoscopic treatment and improvements in clinical and liver blood chemistry. Resolution is defined as no need for further interventions.
Stricture recurrence: defined by cholangiographic evidence of ABS and the need for endoscopic, percutaneous or surgical treatment related to cholestasis during the follow-up period after initial resolution.
Complications: defined as any adverse effect related to ERCP or stenting procedures.

Studies that did not clearly report ABS outcomes separately from other types of strictures (i.e. chronic pancreatitis) or from other complications (i.e. leaks) were excluded. Studies that focused on patients with nonanastomotic biliary strictures, hepatic artery stenosis and/or thrombosis, and hepaticojejunostomy strictures or on therapy with a single PS or BD only were also excluded.

Literature search strategy

A literature search was performed in the following online databases: MEDLINE, EMBASE, Scopus, Cochrane database and ProQuest Dissertations and Thesis Database. To increase the probability of identifying all relevant articles, a specific research equation was formulated for each database using the following keywords: anastomotic biliary stricture or stenosis or pathologic constriction, biliary duct-to-duct anastomosis, endoscopic biliary stent, liver transplantation, adult deceased donor liver transplant, endoscopic cholangiography, endoscopic treatment or therapy, hepatic artery thrombosis and nonanastomotic biliary strictures. In addition, reference lists from eligible studies and relevant review articles were cross-checked to identify additional publications. No time or language limitation was applied. The literature was searched from inception to April 2017.

Article selection and quality assessment

The titles and abstracts of retrieved articles were independently screened for relevance by two reviewers (FL and NdeA). To enhance sensitivity, records were removed only if both reviewers excluded the record at the title screening level. All disagreements were resolved by discussion with a third reviewer (AM-P). Subsequently, both reviewers performed a full-text analysis of the selected articles. The two reviewers independently assessed the risk of bias using appropriate tools according to the study design. Briefly, the Cochrane criteria described in the Cochrane Handbook for Systematic Reviews of Interventions [36] were applied for RCTs, and the Newcastle–Ottawa Scale (NOS) [37] was used for nonrandomized studies. The NICE checklist (http://www.nice.org.uk/) [38] was used for the quality assessments of case series, which involves ratings on an 8-point scale regarding eight questions concerning the following aspects: setting (i.e. uni-/multicentric), hypothesis/objective, case definition, outcome definition, data collection, patient recruitment, results description and analysis. Additionally, the Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to grade the "body of evidence" arising from this review [39]. GRADE specifies four categories: high, moderate, low and very low. In the context of a meta-analysis, the quality of evidence reflects the confidence that the estimates of the effect are correct and surpass the individual study risk of bias by evaluating the following aspects: study design, imprecision, inconsistency, indirectness of the study results and publication bias.

Data extraction and data analysis

Data from the included studies were processed for qualitative and quantitative analyses. Outcome measures (percentages, mean/median values with standard deviations/ranges) were extracted for each treatment approach. Average technical success, ABS resolution and recurrence rates and various complication rates were calculated as weighted percentages (and ranges) of the values reported. Whenever a meta-analysis of pooled data was possible, the risk ratio (RR) and 95% CI were estimated using the Mantel–Haenszel method for binary outcome data. The mean differences and 95% CIs were estimated using inverse variance weighting for continuous data. Heterogeneity was assessed by the I^2 statistic, and values of 25%, 50% and 75% were considered low, moderate and high, respectively [36,40]. Random-effects models were used for the pooled estimates of the mean differences. The pooled effect was considered significant at $P < 0.05$. The meta-analysis was performed using REVMAN software (version 5.3; Cochrane Collaboration).

Results

Literature search and selection

All database searches were performed in April 2017. A total of 277 articles were retrieved from MEDLINE, 201

from Scopus and 306 from EMBASE. After title and abstract evaluations, 84 articles were retained, 30 of which were ultimately excluded because they were not pertinent to the review question or were conference abstracts. A total of 54 articles underwent full-text evaluations. Among them, 22 were excluded for the following reasons: no relevance to the review question ($n = 11$), review articles ($n = 6$) and case reports including less than 5 patients ($n = 5$). An additional article was retrieved from the reference cross-check. Finally, 33 articles published between 2003 and 2017 were selected and included in qualitative synthesis (Fig. 1). Three RCTs [27,33,34] and one retrospective cohort study [26] compared MPS and SEMS procedures. There were two prospective case series [21,22] and 12 retrospectives case series [19,20,23,41–49] reporting on MPS. We identified five prospective case series [32,50–53] and 10 retrospective case series reporting on SEMS [28–30,54–60]). Among the MPS case series and the RCTs/cohort studies, heterogeneity was observed for the stenting protocol, including the number/diameter of the stents, the interval for stent exchange and the total duration of treatment. Among SEMS case series and RCTs/cohort studies, heterogeneity was also identified for the type of stent and the duration of therapy. A summary of the main characteristics of the included studies is shown in Table 1.

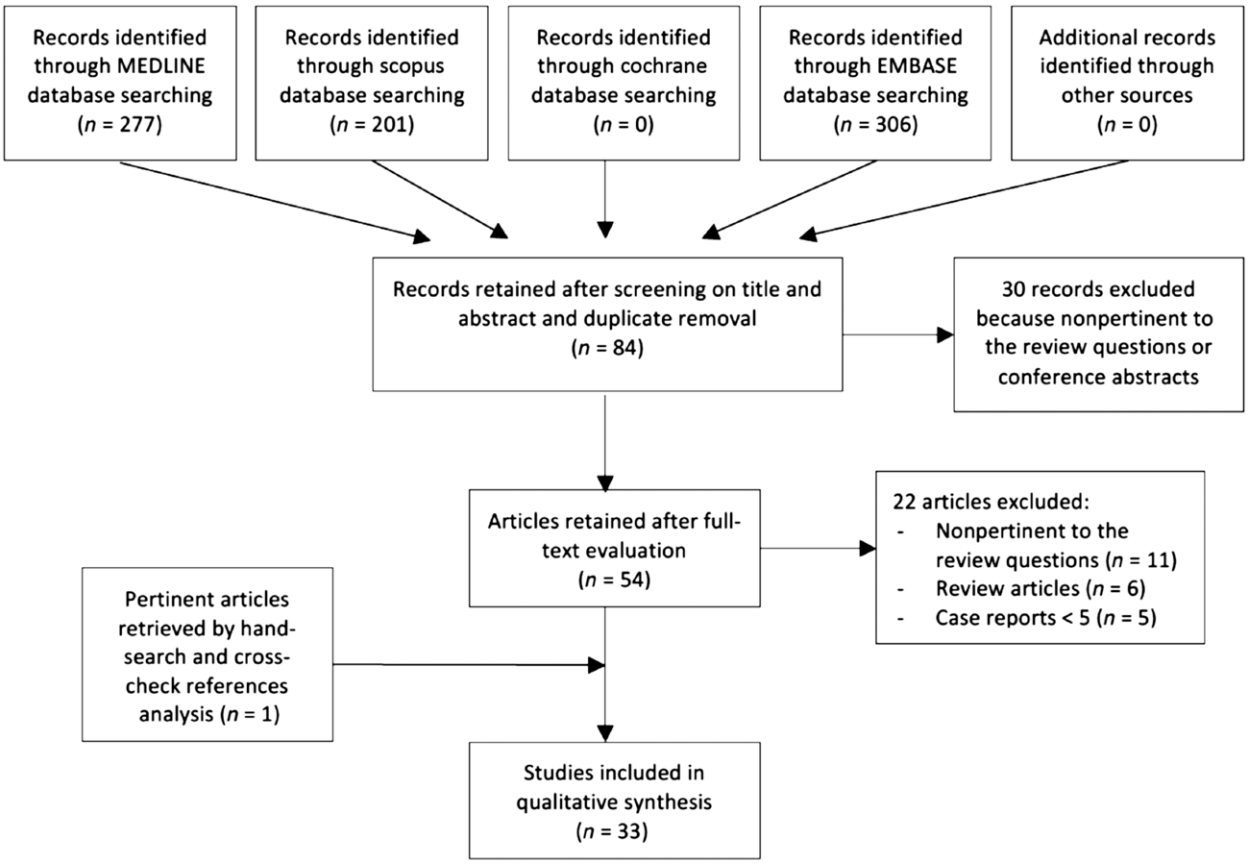

Figure 1 Flow chart of the electronic literature search on MEDLINE, Scopus, EMBASE and other sources (to April 2017). Example of the MEDLINE database equation: ((“endoscopy”[MeSH Terms] OR “endoscopy”[All Fields] OR “endoscopic”[All Fields]) AND (“stents”[MeSH Terms] OR “stents”[All Fields] OR “stent”[All Fields])) AND (biliary[All Fields] AND anastomotic[All Fields] AND (“constriction, pathologic”[MeSH Terms] OR (“constriction”[All Fields] AND “pathologic”[All Fields]) OR “pathologic constriction”[All Fields] OR “strictures”[All Fields])) OR (biliary[All Fields] AND (“constriction, pathologic”[MeSH Terms] OR (“constriction”[All Fields] AND “pathologic”[All Fields]) OR “pathologic constriction”[All Fields] OR “stenosis”[All Fields])) AND (“liver transplantation”[MeSH Terms] OR (“liver”[All Fields] AND “transplantation”[All Fields]) OR “liver transplantation”[All Fields]) NOT ((“hepatic artery”[MeSH Terms] OR (“hepatic”[All Fields] AND “artery”[All Fields]) OR “hepatic artery”[All Fields]) AND (“thrombosis”[MeSH Terms] OR “thrombosis”[All Fields])) NOT (“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields]) NOT (“pediatrics”[MeSH Terms] OR “pediatrics”[All Fields] OR “pediatric”[All Fields]) NOT (“ischemia”[MeSH Terms] OR “ischemia”[All Fields] OR “ischemic”[All Fields]) NOT (“living donors”[MeSH Terms] OR (“living”[All Fields] AND “donors”[All Fields]) OR “living donors”[All Fields] OR (“living”[All Fields] AND “donor”[All Fields]) OR “living donor”[All Fields]) NOT (nonanastomotic[All Fields] AND biliary[All Fields] AND (“constriction, pathologic”[MeSH Terms] OR (“constriction”[All Fields] AND “pathologic”[All Fields]) OR “pathologic constriction”[All Fields] OR “strictures”[All Fields])).

Table 1. Summary of the included studies.

Author, year	Country	*n* ABS post-LT (total)*	Study type	Primary/ secondary treatment	Study design and stenting protocol
RCTs and cohort study on multiple plastic stents					
Tal, 2017	Multinational	24 (48)	RCT	Primary	*Study design*: Open-label, prospective, multicentre RCT (randomization 1:1 for MPS or FCSEMS) *Participants*: Patients underwent LT for ESLD in 4 European centres (2012–2015) with ABS suspected/confirmed by ERCP *Interventions*: Enrolment ERCP + ES ± BD + MPS placement (7F, 10F, 11.5F); stent exchange and upsize every 6–12 weeks, until resolution (if stent migration or dysfunction, crossover to other group is possible); 12 months of follow-up
Coté, 2016	USA	36 (112)	RCT	Primary	*Study design*: Open-label, parallel, multicentre RCT (randomization for MPS or FCSEMS stratified by aetiology and site in blocks of 4) *Participants*: Patients with benign biliary strictures (N = 112) due to LT-ABS (n = 73), chronic pancreatitis (n = 35) and postoperative injury (n = 4) confirmed by cholangiogram in 8 US referral centres (2011–2014) *Interventions*: Enrolment ERCP ± ES ± BD + 1 or 2 PS placement; 2nd ERCP at 3 months, BD and upsize MPS until stricture resolution at 12 months (if no resolution at 12 months, crossover to other group is possible); 12 months of follow-up
Prata-Martins, 2015	Brazil	109 (164)	Retrospective cohort	Primary	*Study design*: Single-centre retrospective cohort study; two groups, selection of treatment on a case-by-case basis: MPS and FCSEMS (N = 32) or PCSEMS (N = 16) *Participants*: Patients underwent LT for ESLD in 1 Brazilian tertiary centre (2006–2014) with ABS confirmed by ERCP *Interventions*: ERCP + ES + BD + progressive stenting exchanged/12 weeks (total 12 months)
Kaffes, 2014	Australia	10 (20)	RCT	Primary	*Study design*: Open-label, prospective bicentric RCT (randomization: 1:1 for MPS or FCSEMS, no sample size calculation) *Participants*: Patients underwent LT for ESLD in 2 Australian centres with ABS confirmed by ERCP *Interventions*: Index ERCP before randomization: 10F stenting ± BD exchanged/12 weeks (total 12 months or less if resolution)
Case series on multiple plastic stents					
Tringali, 2016	Italy	56 (56)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis of a prospective database (ERCP-confirmed ABS treated with MPS between 1994 and 2012) *Protocol*: ERCP ± ES ± BD + MPS placement (8.5F, 10F, 11F); stent exchange and upsize every 12 weeks, until resolution
Fernandez-Simon, 2014	Spain	42 (42)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS, period N/R) *Protocol*: N/R

Table 1. Continued.

Author, year	Country	*n* ABS post-LT (total)*	Study type	Primary/ secondary treatment	Study design and stenting protocol
Albert, 2013	Germany	47 (47)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1996 and 2009) *Protocol*: ERCP + ES ± BD (6–8 mm) and/or stenting (7F–11.5F)/exchange frequency not specified
Poley, 2013	Netherlands	31 (63)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis of a prospective database (ERCP-confirmed late ABS treated with MPS between 2000 and 2009) *Protocol*: ERCP + ES ± BD + *x*1 Stent 10F exchanged/12 weeks until maximum number of stents
Ribeiro, 2012	Brazil	13 (15)	Retrospective case series	Primary	*Design*: Bicentric retrospective analysis (ERCP-confirmed ABS treated with MPS, between 2004 and 2011) *Protocol*: ERCP + BD + Stent 10F exchanged/12 weeks until maximum number of stents
Sanna, 2011	Italy	45 (94)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1990 and 2007) *Protocol*: ERCP + BD + Stent 10F (Max 3) exchanged/12 weeks
Tabibian, 2010	USA	69 (69)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis of a prospective database (ERCP-confirmed ABS treated with MPS between 2002 and 2007) *Protocol*: Early ABS: ERCP + ES + BD + MPS (8.5–11.5F) exchanged/12 weeks; Late ABS: ES + BD + MPS exchanged/12 weeks only if <3 stents; otherwise, exchanged only if obstruction
Morelli, 2008	USA	38 (38)	Prospective case series	Primary	*Design*: Single-centre prospective observational study (ERCP-confirmed ABS treated with MPS between 2003 and 2005) *Protocol*: ERCP + ES ± BD (4–10 mm) and stenting (10F)/exchanged/2 weeks until maximum dilatation and then every 12 weeks
Holt, 2007	UK	53 (53)	Prospective case series	Primary	*Design*: Single-centre prospective observational study (ERCP-confirmed ABS treated with MPS between 2000 and 2006) *Protocol*: ERCP (early ABS) and single stent (7F); ES + BD 24F (late ABS) and MPS (10F) exchanged/12 weeks
Pasha, 2007	USA	25 (25)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1999 and 2004) *Protocol*: ERCP + ES ± BD (4–10 mm) and stenting (7–11.5F) exchanged/8–12 weeks
Solmi, 2007	Italy	12 (34)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1999 and 2004) *Protocol*: ERCP + ES ± BD (10–24F) and stenting (10F) exchanged/16 weeks
Alazmi, 2006	USA	148 (148)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1994 and 2004) *Protocol*: ERCP + ES ± BD (4–10 mm) and stenting (7F–11.5F) exchanged/8–16 weeks

Table 1. Continued.

Author, year	Country	*n* ABS post-LT (total)*	Study type	Primary/ secondary treatment	Study design and stenting protocol
Morelli, 2003	USA	25 (25)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1990 and 1999) *Protocol*: ERCP + ES ± BD (4–8 mm) and stenting (7F–10F) exchanged/12 weeks
Rerknimitr 2002	USA	43 (121)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with MPS between 1988 and 1999) *Protocol*: ERCP + ES ± BD (6–10 mm) or bougies and stenting (5F–11.5F); exchange frequency variable
RCTs and cohort study on self-expandable metal stents					
Tal, 2017	Multinational	24 (48)	RCT	Primary	*Study design*: Prospective, open-label, multicentre trial (randomization 1:1 for MPS or FCSEMS) *Participants*: Patients underwent LT for ESLD in 4 European centres (2012–2015) with ABS suspected/confirmed by ERCP *Interventions*: Enrolment ERCP + ES ± BD + FCSEMS placement (10 mm, without antimigration flaps); stent removed at 4–6 months (if stent migration or dysfunction, crossover to other group is possible); 12 months of follow-up
Coté, 2016	USA	37 (112)	RCT	Primary	*Study design*: Open-label, parallel, multicentre RCT (randomization for MPS or FCSEMS stratified by aetiology and site in blocks of 4) *Participants*: Patients with benign biliary strictures (*N* = 112) due to: LT-ABS (*n* = 73), chronic pancreatitis (*n* = 35), postoperative injury (*n* = 4) confirmed by cholangiogram in 8 US referral centres (2011–2014) *Interventions*: ERCP + BD + 1 FCSEMS 8 or 10 mm diameter (WallFlex; Boston Sci.); 2nd ERCP at 6 months, stent removed; replaced only if no stricture resolution at 12 months (if no resolution at 12 months, crossover to other group is possible); 12 months of follow-up
Prata-Martins, 2015	Brazil	48 (164)	Retrospective cohort	Primary	*Study design*: Single-centre retrospective cohort study; two groups, selection of treatment on a case-by-case basis: MPS and FCSEMS (*N* = 32) or PCSEMS (*N* = 16) *Participants*: Patients underwent LT for ESLD in 1 Brazilian tertiary centre (2006–2014) with ABS confirmed by ERCP *Interventions*: ERCP ± ES + SEMS, removed after 12 weeks if PCSEMS or 24 weeks if FCSEMS
Kaffes 2014	Australia	10 (20)	RCT	Primary	*Study design*: Open-label, prospective bicentric RCT (randomization: 1:1 for MPS or FCSEMS, no sample size calculation) *Participants*: Patients underwent LT for ESLD in 2 Australian centres with ABS confirmed by ERCP *Interventions*: Index ERCP and randomization: FCSEMS (Taewoong Medical, Co., Ltd.; 10 mm diameter with central narrowing 8 mm; 40 mm length) removed after 12 weeks, if resolution no further stenting

Table 1. Continued.

Author, year	Country	*n* ABS post-LT (total)*	Study type	Primary/ secondary treatment	Study design and stenting protocol
Case series on self-expandable metal stents					
Aepli, 2016	Australia	31 (31)	Retrospective case series	Secondary	*Design*: Multicentre (3 centres) retrospective analysis (ERCP-confirmed ABS treated with FCSEMS between 2008 and 2014) *Protocol*: ERCP + ES + intraductal FCSEMS (Niti-S biliary stent; Taewoong Medical, Co., Ltd., 8 mm diameter × 40 mm length); stent removed at 3 months
Jimenez-Perez, 2016	Spain	44 (44)	Retrospective case series	Secondary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with FCSEMS between 2009 and 2014) *Protocol*: ERCP + ES ± BD (if BD, temporary PS placement for 1 month) + FCSEMS placement (WallFlex; Boston Sci.; 8–10 mm diameter; 6–12 cm length); stent removed at 3–6 month
Tarantino, 2015	Italy	70 (70)	Retrospective case series	Secondary	*Design*: Single-centre retrospective analysis of a prospective database (ERCP-confirmed ABS treated with FCSEMS between 2008 and 2012) *Protocol*: ERCP + ES + BD + progressive MPS/12–16 weeks until resolution; if failure, FCSEMS was placed (Niti-S Com-Vi; Taewoong Medical; 10 × 10 or 8 mm)
Deviere, 2014	Multinational	42 (187)	Prospective case series	Secondary	*Design*: Multicentre prospective observational study (ERCP-confirmed ABS treated with FCSEMS, period N/R) *Protocol*: ERCP + FCSEMS (WallFlex; Boston Sci.; 8 or 10 mm diameter; 60–80 mm length) removed at 4–6 months
Cerecedo-Rodriguez, 2013	USA	55 (55)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis of a prospective database (ERCP-confirmed ABS treated with FC/PCSEMS between 2002 and 2010) *Protocol*: ERCP + ES + PCSEMS (Wallstent; Boston Sci.) 10 mm diameter; 60–100 mm lengthERCP + ES + FCSEMS (Gore Viabil; Conmed) 10 mm diameter; 40–100 mm lengthERCP + ES + FCSEMS (WallFlex; Boston Sci.) 10 mm diameter; 60–80 mm length
Kahaleh, 2013	USA	35 (133)	Retrospective case series	Secondary	*Design*: Multicentre (6 centres) retrospective analysis of a prospective database (ERCP-confirmed ABS treated with FCSEMS between 2009 and 2010) *Protocol*: ERCP and deployment of FCSEMS (WallFlex; Boston Sci.) with flared ends (40, 60, 80 mm)
Haapamaki, 2012	Finland	16 (17)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with FC/PCSEMS between 2008 and 2010) *Protocol*: ERCP ± ES ± BD + FCSEMS (Allium; Caesarea Ind.) or PCSEMS (Wallstent; Boston Sci.) 10 mm diameter; 60–100 mm length; exchanged/3–4 months, total 6 months
Sauer, 2012	Germany	9 (19)	Prospective case series	Secondary	*Design*: Single-centre prospective observational study (ERCP-confirmed ABS treated with FCSEMS, between 2009 and 2010) *Protocol*: ERCP + ES + FCSEMS (WallFlex; Boston Sci.) × 3 months
Tarantino, 2012	Italy	15 (54)	Retrospective case series	Primary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with FCSEMS between 2008 and 2010) *Protocol*: ERCP + ES + BD + FCSEMS (Niti-S Com-Vi; Taewoong Medical) removed after 2 months (10 × 10 or 8 mm)

Table 1. Continued.

Author, year	Country	*n* ABS post-LT (total)*	Study type	Primary/ secondary treatment	Study design and stenting protocol
Hu, 2011	China	13 (13)	Prospective case series	Primary	*Design*: Single-centre prospective observational study (ERCP-confirmed ABS treated with FCSEMS between 2008 and 2010) *Protocol*: ERCP + ES + BD (6–10 mm) + FCSEMS (length 4 cm, narrow distal end and wide proximal end) removed after 3–6 months
Chaput, 2010	France	22 (22)	Prospective case series	Secondary	*Design*: Multicentre (3 centres) prospective observational study (ERCP-confirmed ABS treated with FCSEMS between 2007 and 2008) *Protocol*: ERCP ± ES ± BD + PCSEMS (Wallstent; Boston Sci.) 10 mm diameter; 60–100 mm length; removed after 2 months
Garcia-Pajares, 2010	Spain	22 (22)	Retrospective case series	Secondary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with FCSEMS between 2001 and 2009) *Protocol*: ERCP + ES + single/MPS; salvage SEMS at 2nd ERCP in 14 patients, at 3rd ERCP in 7 patients and at 4th ERCP in 1 patient
Marin-Gomez, 2010	Spain	8 (11)	Retrospective case series	Secondary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with FCSEMS between 2006 and 2009) *Protocol*: ERCP + ES + PS. If failure after 9 months FCSEMS (WallFlex Biliary RX; Boston Sci.) removed after 4 months
Kahaleh, 2008	USA	16 (79)	Prospective case series	Primary	*Design*: Single-centre prospective observational study (ERCP-confirmed ABS treated with FCSEMS between 2001 and 2005) *Protocol*: ERCP + PCSEMS (Wallstent; Boston Sci.; covered Permalume) 10 mm diameter, 40, 60, or 80 mm length
Vandenbroucke, 2006	Canada	21 (21)	Retrospective case series	Secondary	*Design*: Single-centre retrospective analysis (ERCP-confirmed ABS treated with PCSEMS between 1999 and 2004) *Protocol*: ERCP + ES + PS exchanged/6 weeks until resolution; salvage PCSEMS if persistence after 3 BD or late stricture >6 months after OLT not responding to BD

N/R, not reported; ABS, anastomotic biliary stricture; LT, liver transplantation; ESLD, end-stage liver disease; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; BD, balloon dilatation; MPS, multiple plastic stents; FCSEMS, full-covered self-expandable metal stents; PCSEMS, partially covered self-expandable metal stents; RCT, randomized controlled trial.

*Proportion of patients with ABS in studies including biliary strictures of different aetiologies.

Multiple plastic stents studies

Three RCTs and one cohort study included a total of 179 patients with MPS aged between 49 and 58 years [26,27,33,34]. Technical success was between 95% and 100%, the resolution rate was 80–95%, the recurrence rate was 3–37%, treatment duration was 6–10 months and the number of ERCPs/patient was 3–4.5 (Table 2).

Multiple plastic stents case series

Overall, fourteen case series reported outcomes for MPS [19–23,41–49], including 647 patients with ages between 35 and 61 years (Table 2). BD before stent placement was performed in approximately two-thirds of the patients. In most case series, the stent exchange interval was 3 months and the mean number of ERCP procedures per patient ranged between 2.5 and 5.

Technical success: The technical success rate of MPS in the case series was between 91.6 and 100%.
Stricture resolution: The ABS resolution rate in the MPS case series was between 53.8 and 100%, and the mean stent duration was between 3.5 and 15.8 months.
Stricture recurrence: The ABS recurrence rate for the MPS case series was between 0 and 21% after widely variable follow-up periods.
Complications: There was an overall per-ERCP complication rate between 0 and 16.2% and a per-patient complication rate between 0% and 71% (Table 5).

Self-expandable metal stents studies

Three RCTs and one cohort study included a total of 119 patients with SEMS aged between 48 and 57 years [26,27,33,34]. Technical success was 100%, the resolution rate was 86–100%, the recurrence rate was 15–30%, treatment duration was 4–6 months and the average number of ERCPs/patient was 2 (Table 3).

Self-expandable metal stents case series

Overall, fifteen case series reported outcomes of SEMS procedures for ABS treatment, which were used as primary treatment in five of them [29,30,52,53,55], including 115 patients with ages between 40 and 59 years. The mean number of ERCP procedures per patient ranged between 3 and 6.8 (Table 3). These procedures were used as secondary intervention in five of the studies [50,54,56–58]. The other five studies [28,32,51,59,60] included SEMS as both primary and secondary treatments in a total of 304 patients with an age range of 49–59 years. The mean number of ERCP procedures per patient was between 2.7 and 3.7 (Table 3).

Technical success: The technical success rates were 100% for the primary SEMS case series and 86–100% for the secondary SEMS case series.

Stricture resolution: The ABS resolution rate in the primary SEMS case series was 53.3–100%, with a mean stent duration between 2 and 6.8 months. In the secondary SEMS cases series, the rate was 50–100%, with a mean stent duration between 2 and 9.2 months.

Stricture recurrence: The overall ABS recurrence rate in the primary SEMS case series was 8.3–30.3%. In the secondary SEMS case series, the rate was 4.5–47.4%.

Complications: The per-patient complication rate in the primary SEMS case series was 10–46.7%. In the secondary SEMS cases series, the rate was 12.9–63.6% (Table 5).

Meta-analysis of the RCTs and cohort study

Three RCTs [27,33,34] and one cohort study [26] were included in the meta-analysis for different outcomes.

Overall analysis: The pooled data from the three RCTs [27,33,34] and the cohort study [26] showed ABS resolution in 153 (91%) of 167 patients who received MPS and in 100 (92%) of 108 patients who received SEMS (RR: .89; 95% CI, 0.40–2.02; $P = 0.79$; heterogeneity $I^2 = 0\%$) (Fig. 2). The same studies showed recurrence in 16 (10.5%) of the 152 MPS patients and in 23 (23%) of the 100 SEMS patients (RR: .55; 95% CI, 0.22–1.38; $P = 0.20$; heterogeneity $I^2 = 20\%$). The pooled data from the RCTs [27,34] and cohort study [26] found no differences in treatment duration (mean difference of 83.5 days; 95% CI, −4.1 to 171 days; $P = 0.06$; heterogeneity $I^2 = 91\%$). The pooled data of the three RCTs [27,33,34] and cohort study [26] found a number of ERCPs/patient in favour of SEMS (mean difference of 1.69 ERCP procedures; 95% CI, 1–2.39 ERCP procedures; $P < 0.00001$; heterogeneity $I^2 = 86\%$).

Sensitivity analysis: The pooled data from the three RCTs [27,33,34] (excluding the cohort study [26]) found ABS resolution in 62/67 MPS patients (92.5%) and 67/70 SEMS patients (95.7%) (RR: 1.42; 95% CI, .37–5.43; $P = 0.61$; heterogeneity $I^2 = 0\%$) (Fig. 3). The same studies found recurrence in 9/61 MPS patients (14.7%) and in 13/67 SEMS patients (19.4%) (RR: 0.88; 95% CI, .38–2.02; $P = 0.76$; heterogeneity $I^2 = 9\%$). The pooled data from two

Table 2. Summary of patient characteristics and outcomes in studies and case series using MPS for ABS after LT

Author, year	*n* ABS	Mean age, year	Gender, F/M	Mean LT-ABS interval, mo	Prestenting BD (%)	Technical success (%)	Mean stent duration, mo	ABS resolution (%)	Mean ERCPs/ patient	ABS recurrence (%)	Complications per ERCP (%)	Complications per patient (%)
RCTs and cohort study on multiple plastic stents												
Tal, 2017	24	58.5*	6/18	7.3*	14/24 (58.3)	23/24 (95.8)	7.5*	23/24 (95.8)	4*	5/23 (21.7)	N/R	2/24 (8.3)
Coté, 2016	36	56.7†	N/R	4*	N/R	36/36 (100)	6.3	31/33 (93.9)	3.1	1/30 (3.3)	N/R	N/R
Prata-Martins, 2015	109	48.8	33/76	7	N/R	109/109 (100)	9.3	91/100 (91)	3.9	7/91 (7.7)	26/271 (9.6)	26/109 (23.9)
Kaffes, 2014	10	49.5*	5/5	26*	N/R	10/10 (100)	10.1*	8/10 (80)	4.5*	3/8 (37.5)	N/R	5/10 (50)
Case series on multiple plastic stents												
Tringali, 2016	56	51*	10/46	6.8*	22/50 (44)	55/56 (98.2)	11.5	50/51 (98)	4*	3/50 (6)	N/R	3/56 (5.3)
Fernandez-Simon, 2014	42	52.5	N/R	16.5	N/R	42/42 (100)	N/R	37/42 (88)	3.1	3/37 (8.2)	N/R	N/R
Albert, 2013	47	50	28/29	16.2	33/47 (70.2)	47/47 (100)	7	31/47 (66)	4.2	16/47 (34)	32/198 (16.2)	32/47 (68)
Poley, 2013	31	61*	10/21	N/R	29/31 (93.5)	31/31 (100)	N/R	25/31 (80.6)	5*	6/31 (19.4)	22/155 (14.2)	22/31 (71)
Ribeiro, 2012	13	49.5	5/10	12.7	13/13 (100)	13/13 (100)	8.7	7/13 (53.8)	2.5	1/7 (14.3)	0/33 (0)	0/13 (0)
Sanna, 2011	45	N/R	N/R	N/R	34/34 (100)	34/34 (100)	3*	28/34 (82.4)	2.5	6/28 (21.4)	N/R	N/R
Tabibian, 2010	69	52.5	24/45	7*	69/69 (100)	69/69 (100)	15*	65/69 (94)	3*	2/65 (3.1)	4/286 (1.4)	4/69 (5.8)
Morelli, 2008	38	52.6	12/26	2.9	38/38 (100)	38/38 (100)	3.5	38/38 (100)	3.45	5/38 (13.2)	2/131 (1.5)	2/38 (5.3)
Holt, 2007	53	48.5*	32/21	30.5*	N/R	49/53 (92)	11*	34/49 (69.4)	3*	2/34 (5.9)	11/180 (6.1)	11/53 (20.8)
Pasha, 2007	25	46.8	5/20	2*	25/25 (100)	25/25 (100)	5.4	22/25 (88)	3.5*	4/22 (18.1)	5/105 (4.8)	5/25 (20)
Solmi, 2007	12	N/R	N/R	N/R	11/11 (100)	11/12 (91.6)	15	11/11 (100)	3.6	0/11 (0)	0/54 (0)	0/11 (0)
Alazmi, 2006	148	N/R	N/R	2.1	64/131 (48.8)	143/148 (96.6)	4.8	131/143 (91.6)	3.1	24/131 (18.3)	N/R	N/R
Morelli, 2003	25	48	9/16	1.7	17/25 (68)	24/25 (96)	6*	22/24 (91.6)	3*	2/22 (9)	3/79 (3.7)	3/24 (12.5)
Rerknimitr, 2002	43	35.6	27/28	8.3	N/R	43/43 (100)	15.8	43/43 (100)	3.8	0/43 (0)	N/R	N/R

N/R, not reported; MPS, multiple plastic stents; ABS, anastomotic biliary stricture; LT, liver transplantation; F/M, female/male; BD, balloon dilatation; ERCP, endoscopic retrograde cholangiopancreatography; mo, months.

*Median.

†Relative to whole group of MPS patients (including other type of strictures).

Table 3. Summary of patient characteristics and outcomes in studies using SEMS for ABS after LT.

Author, year	Primary versus secondary treatment	*n* ABS	Mean age, year	Gender, F/M	Mean LT-ABS interval, mo	Technical success (%)	Mean stent duration, mo	Mean ERCPs/ patient	ABS resolution (%)	ABS recurrence (%)	Complications per patient (%)	Stent migration (%)
RCTs and cohort study on primary self-expandable metal stents												
Tal, 2017	Primary	24	57*	10/14	5.4*	24/24 (100)	5.9*	2 (2–12)*	24/24 (100)	5/24 (20.8)	8/24 (33.3)	8/24 (33.3)
Coté, 2016	Primary	37	54.5‡	N/R	3*	37/37 (100)	5.2	2.2	33/36 (91.7)	5/33 (15.1)	N/R	13/37 (35.1)
Prata-Martins, 2015	Primary	48	48.8	12/36	7.3	48/48 (100)	4	2	33/38 (86.8)	10/33 (30.3)	17/48 (35.4)	3/48 (6.3)
Kaffes, 2014	Primary	10	56.5*	5/5	11.8*	10/10 (100)	3.8*	2	10/10 (100)	3/10 (30)	1/10 (10)	0/10 (0)
Case series on primary self-expandable metal stents												
Cerecedo-Rodriguez, 2013	Primary	55	54.74	15/40	44.4/6/ 20.8†	55/55 (100)	4.1–4.5	6.8/3.5/ 2.9†	38/55 (69)	N/R	10/55 (18)	4/55 (7.2)
Haapamaki, 2012	Primary	16	40 *	N/R	N/R	16/16 (100)	6.8*	3*	16/16 (100)	N/R	N/R	N/R
Tarantino, 2012	Primary	15	59.1	5/10	11.4	15/15 (100)	2	N/R	8/15 (53.3)	2/8 (25)	7/15 (46.7)	7/15 (46.7)
Hu, 2011	Primary	13	51.2	3/10	25.7	13/13 (100)	5.4	N/R	12/13 (92.3)	1/12 (8.3)	2/13 (16.6)	0/13 (0)
Kahaleh, 2008	Primary	16	55	N/R	N/R	16/16 (100)	4*	N/R	15/16 (93.8)	N/R	N/R	N/R
Case series on secondary self-expandable metal stents												
Aepli, 2016	23 primary/8 secondary	31	56	12/19	20.3	31/31 (100)	3.8	N/R	29/29 (100)	7/29 (24.1)	4/31 (12.9)	1/31 (3.2)
Jimenez-Perez, 2016	24 primary/20 secondary	44	57.1	8/36	22.8–25.1¶	44/44 (100)§	4.5–3.8¶	2.8–3.7	41/41 (100)	9/41 (22)	31/44 (70.5)	17/41 (41.4)
Tarantino, 2015	Secondary	70	59.3	22/48	9.8	70/70 (100)	2.8	N/R	46/70 (65.7)	18/46 (39)	32/70 (45.7)	32/70 (45.7%)
Deviere, 2014	22 primary/20 secondary	42	56.5	7/35	N/R	42/42 (100)	5*	N/R	28/41 (68.3)	N/R	17/42 (40.5)	0/42 (0)
Kahaleh, 2013	Secondary (50% previous PS)	35	59.2	N/R	N/R	35/35 (100)	3.1	N/R	19/31 (61.3)	N/R	5/31 (16.1)	5/31 (16.1)
Sauer, 2012	Secondary	9	55	N/R	N/R	9/9 (100)	3	N/R	6/9 (66.6)	1/6 (17)	N/R	N/R
Chaput, 2010	Secondary (77% previous PS)	22	49.7	4/18	5	22/22 (100)	2	N/R	19/22 (86)	9/19 (47.4)	12/22 (54.5)	6/22 (27.2)
Garcia-Pajares, 2010	Secondary	22	55*	4/18	0.9	22/22 (100)	N/R	3.4	21/22 (95.5)	1/22 (4.5)	14/22 (63.6)	4/22 (18)

Table 3. Continued.

Author, year	Primary versus secondary treatment	*n* ABS	Mean age, year	Gender, F/M	Mean LT-ABS interval, mo	Technical success (%)	Mean stent duration, mo	Mean ERCPs/ patient	ABS resolution (%)	ABS recurrence (%)	Complications per patient (%)	Stent migration (%)
Marin-Gomez, 2010	Secondary	8	54	4/4	4.4	8/8 (100)	9.2	N/R	4/8 (50)	3/8 (37.5)	2/8 (25)	5/8 (62.5)
Vandenbroucke, 2006	Secondary	21	57	11/10	N/R	18/21 (86)	N/R	2.7	14/21 (67)	N/R	N/R	0

N/R, not reported; SEMS, self-expandable metal stents; PS, plastic stents; ABS, anastomotic biliary stricture; LT, liver transplantation; F/M, female/male; ERCP, endoscopic retrograde cholangiopancreatography; mo, months.

*Median.

†Values are relative to PCSEMS and two types of FCSEMS, respectively.

‡Relative to whole group of SEMS patients (including other type of strictures).

§In 24/44 (54%), it was possible to directly set the SEMS in place at the 1st attempt, whereas in 20/44 (46%) PS were initially placed and then replaced 1 month later with SEMS.

¶Values in relation to patients without and with ABS recurrence, respectively.

RCTs [27,34] found a total duration of treatment in favour of SEMS (mean difference of 40.2 days; 95% CI, 3.9–76.4 days; $P = 0.03$; heterogeneity $I^2 = 0\%$). The pooled data of the three RCTs [27,33,34] confirmed a number of ERCP procedures per patient in favour of SEMS (mean difference of 1.64 ERCP procedures; 95% CI, .62–2.65 ERCP procedures; $P < 0.002$; heterogeneity $I^2 = 80\%$).

Management of recurrence

Treatments after recurrence are summarized in Table 4. For the patients who previously underwent MPS placement, repeat ERCP was the most frequent treatment, followed by surgery and SEMS placement. For the patients who initially underwent SEMS placement, repeat SEMS or MPS placement was the most common treatment after recurrence, followed by surgical procedures. Overall, three patients [42,58] needed a second LT for ABS recurrence, including one after MPS therapy and two after SEMS therapy.

Quality assessments of the studies and case series

Most of the publications were case series without a control group. Only three RCTs were found. By applying the Cochrane criteria, the risk of bias was considered low in one study [34] and high in two studies [27,33]. The quality of the retrospective cohort study [26] according to the NOS was 7/9, and the risk of bias was classified as low (Table S1). Based on the NICE checklist, eight case series received a score of 7/8 [19,21,22,42,45,49,51,59], seven received a grade of 6/8 [28,29,32,41,44,56,60], nine case series received a grade of 5/8 [20,23,30,46–48,52,54,57] and the other five received a grade of 4/8 [43,50,53,55,58] (Fig. S1).

Based on the GRADE concerning the quality of evidence for meta-analysis, one RCT had high-quality evidence [34] and three studies had moderate-quality evidence [26,27,33].

Discussion

The present systematic review describes the outcomes of two endoscopic treatments for ABS in adult LT patients. The outcomes summarized in the present systematic review, which are based on low-quality evidence, do not allow the determination of any reliable conclusion regarding the superiority of one technique over another in terms of efficacy and safety. However, the data from the meta-analysis of the RCTs suggest advantages in

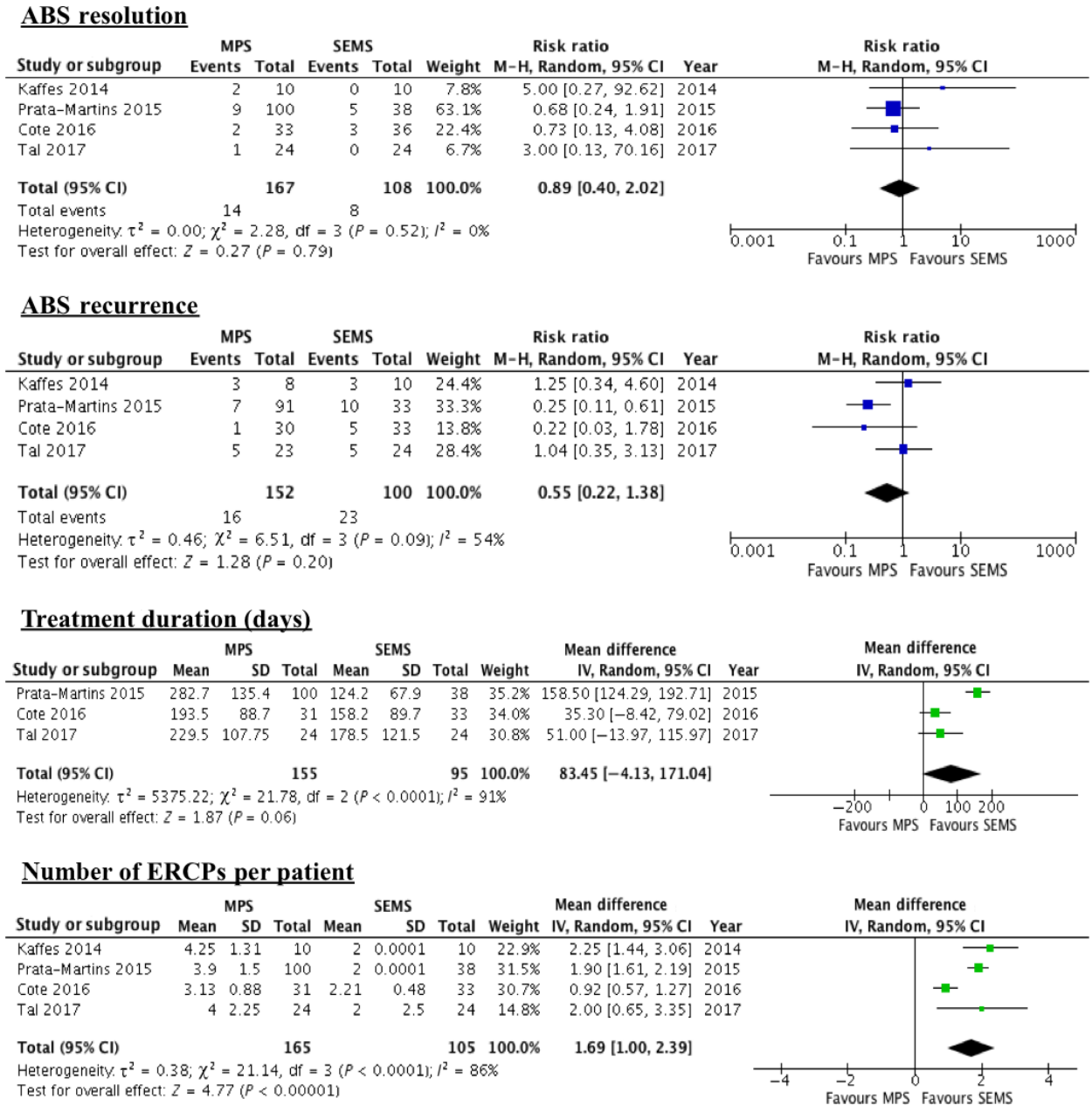

Figure 2 Forest plots of the overall analysis.

terms of fewer ERCP procedures and shorter treatment durations in favour of SEMS.

In recent years, the standard of care for symptomatic ABS has been ERCP as a first-line intervention, with MPS exchanged every 3 months over a 12-month period. There is no consensus on this treatment, with some authors supporting alternative timing while others preferring single stents or dilation alone to minimize complications [8,13,16,43,61]. However, this strategy requires repeated hospital admissions and endoscopic procedures and exposes patients to ERCP-associated morbidity [6,62]. Kobayashi *et al.* [63] demonstrated that endoscopic manoeuvring for biliary dilatation and stent placement following LT resulted in a higher risk of post-ERCP pancreatitis than the use of the same technique for the treatment of other types of biliary stricture. The potential benefit of a single covered self-expandable metal stent is related to its relatively simple management compared with MPS. SEMS have larger diameters and are easily removed and can potentially limit costs by reducing the number of procedures needed to achieve ABS resolution [33]. However,

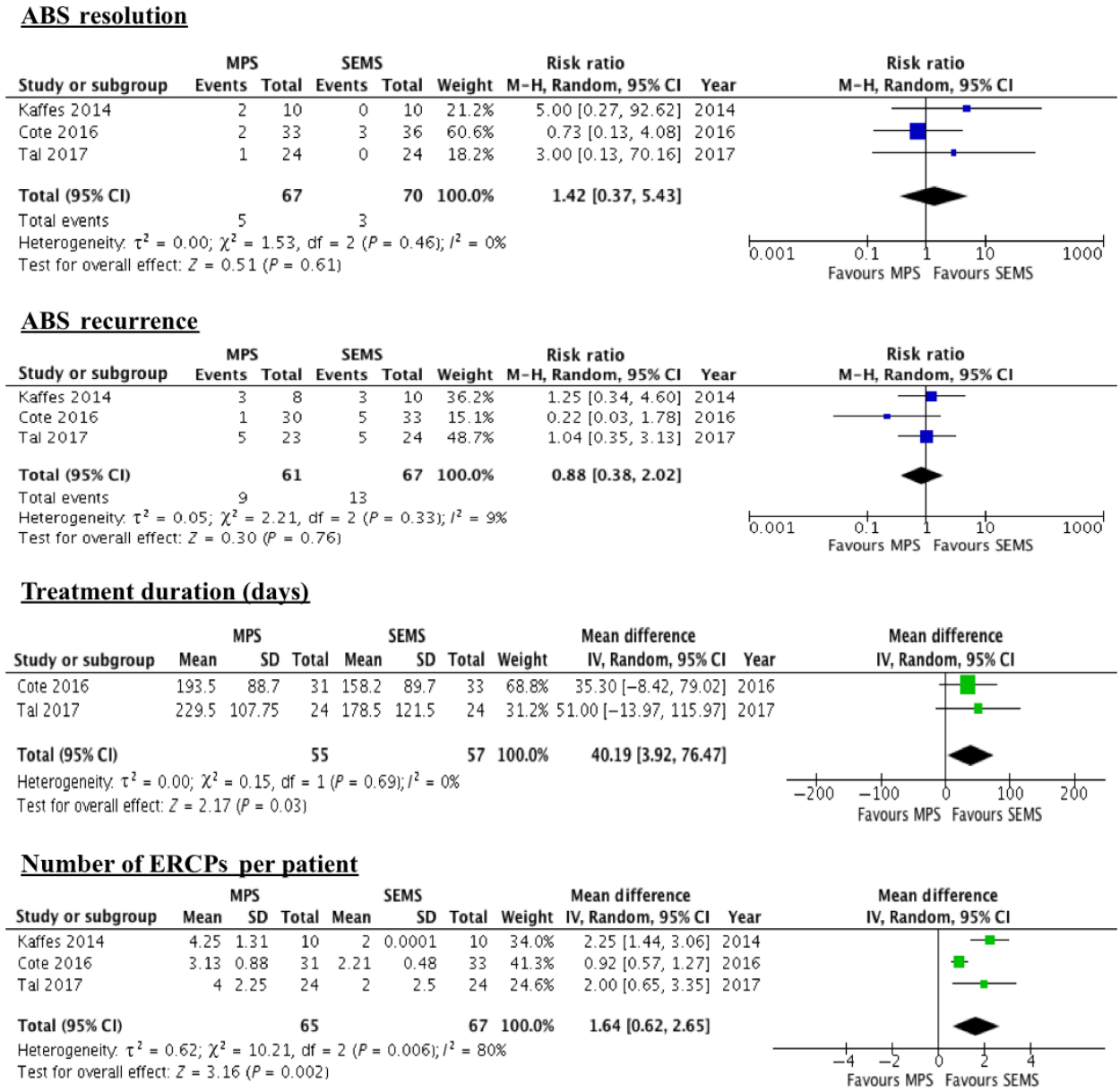

Figure 3 Forest plots of the sensitivity analysis.

disadvantages such as a higher complication rate and migration may affect both patient tolerability and costs [27,30,64,65].

The technical success rates of both strategies are close to 100% in the studies and case series summarized in the present review. Relatively easy access to the stricture and stenting without any major complications with either technique represent ideal conditions for future RCTs.

For the MPS group, most authors (13/18) [19,21–23,26,27,33,34,44–47,49] conform to a stent exchange policy of every 12 weeks, and this period was chosen by all RCTs. Two case series [42,43] did not report a replacement frequency, and the other three case series [20,41,48] reported a variable frequency between 8 and 16 weeks. Such heterogeneity does not allow the determination of a reliable conclusion regarding the best timing strategy for MPS. The impact of closer surveillance or more frequent stent replacements should be investigated in a specifically designed RCT. Based on the limited available evidence, we recommend MPS replacement every 12 weeks with a monthly outpatient physical examination and blood test surveillance to detect early signs of complications. For the SEMS

Table 4. Management of ABS recurrence.

Author, year	*n* ABS	Mean F/U, mo	ABS recurrence (%)	Need for surgery/PTC after recurrence *n* (%)	Type of treatment after recurrence
RCTs and cohort study on multiple plastic stents					
Tal, 2017	24	16.4*	5/24 (20.8)	N/R	N/R
Coté, 2016	36	12	1/30 (3.3)	0	ERCP and repeat stenting
Prata-Martins, 2015	109	22.7	7/91 (7.7)	3/7 (42.9)	SEMS, MPS, surgery (HJ)
Kaffes, 2014	10	25.5*	3/8 (37.5)	0	16 ERCP
Case series on multiple plastic stents					
Tringali, 2016	56	60	3/50 (6)	0	ERCP and repeat MPS
Fernandez-Simon, 2014	42	41.5	3/37 (8.2)	N/R	3 ERCP
Albert, 2013	47	35.2	16/47 (34)	2/16 (12.5)	1 surgery/1 re-LT/14 ERCP (MPS)
Poley, 2013	31	28*	6/31 (19.4)	5/0 (16.1)	5 HJ/1 ERCP (SEMS)
Ribeiro, 2012	13	28*	1/7 (14.3)	0/0	1 ERCP
Sanna, 2011	45	88*	6/28 (21.4)	6/28 (21.4)	HJ/PTC
Tabibian, 2010	69	12	2/65 (3.1)	0/0	1 ERCP/patient
Morelli, 2008	38	12	5/38 (13.2)	1/0 (2.6)	4 ERCP/1 HJ
Holt, 2007	53	18*	2/34 (5.9)	0	2 ERCP
Pasha, 2007	25	21.5*	4/22 (18.1)	2/0 (9)	2 ERCP/2 HJ
Solmi, 2007	12	19	0/11	0/0	–
Alazmi, 2006	148	28	24/131 (18.3)	N/R	1–4 ERCP/patient
Morelli, 2003	25	54	2/22 (9)	0/1 (4)	1 ERCP/patient
Rerknimitr, 2002	43	39.6	0/43	0/0	–
RCTs and cohort study on self-expandable metal stents					
Tal, 2017	24	16.4*	5/24 (20.8)	N/R	N/R
Coté, 2016	36	12	5/33 (15.2)	0	ERCP and repeat stenting
Prata-Martins, 2015	48	20.4	10/38 (30.3)	7/0 (70)	8 MPS, 2 SEMS, 4 HJ
Kaffes, 2014	10	26*	3/10 (30)	0/10	19 ERCP
Case series on self-expandable metal stents					
Aepli, 2016	31	12.8	7/29 (24.1)	0	ERCP and stenting (2 SEMS and 4 MPS)
Jimenez-Perez, 2016	44	27.8–29.5†	9/41 (22)	0	ERCP and repeat FCSEMS in all cases
Tarantino, 2015	70	48	18/46 (39)	N/R	N/R
Deviere, 2014	42	20.3*	N/R	N/R	N/R
Cerecedo-Rodriguez, 2013	55	4.6–38.9	N/R	3/55 (5.4)	N/R
Kahaleh, 2013	35	N/R	N/R	N/R	N/R
Haapamaki, 2012	16	21.7*	N/R	0/0	1 FCSEMS
Sauer, 2012	9	12	1/6 (17)	0/0	1 SEMS
Tarantino, 2012	15	14.4	2/8 (25)	N/R	N/R
Hu, 2011	13	12.1	1/12 (8.3)	0	SEMS
Chaput, 2010	22	12	9/19 (47.4)	1/0 (10)	4 PS, 6 SEMS, 1 HJ
Marin-Gomez, 2010	8	N/R	3/8 (37.5)	3	1 HJ/2 re-LT
Garcia-Pajares, 2010	22	12.5*	1/22 (4.5)	0/0	Repeat SEMS
Kahaleh, 2008	16	12*	N/R	N/R	N/R
Vandenbroucke, 2006	21	37.8	N/R	N/R	N/R

*Median values.

†Values related to patients without and with ABS recurrence, respectively.

N/R, not reported; LT, liver transplantation; ABS, anastomotic biliary stricture; F/U, follow-up; PTC, percutaneous transhepatic catheter; HJ, hepaticojejunostomy; ERCP, endoscopic retrograde cholangiopancreatography; LT, liver transplantation; SEMS, self-expandable metal stents; MPS, multiple plastic stents; PS, plastic stents; FCSEMS, full-covered self-expandable metal stents.

group, only nine articles [26,27,29,30,33,34,52,53,55] concerning primary treatment were analysed to deduce the best strategy to prevent complications. Again, the significant variability in timing (replacement between 2 and 6 months) prevents the determination of any conclusions. Interestingly, both major trials using FCSEMS

Table 5. Most common complications.

Author, year	*n* ABS	Total ERCP	Complications per ERCP, *n* (%)	Complications per patient, *n* (%)	Type of complication
RCTs and cohort study on multiple plastic stents					
Tal, 2017	24	N/R	N/R	2/24 (8.3)	1 severe haemobilia (crossover to SEMS arm to stop bleeding); 1 bilio-duodenal fistula.
Coté, 2016	36	N/R	N/R	N/R	
Prata-Martins, 2015	109	271	26/271 (9.6)	26/109 (23.9)	11 pancreatitis, 7 bleeding, 2 duodenal perforation, 15 stent migration (5.5%)
Kaffes, 2014	10	N/R	N/R	5/10 (50)	4 cholangitis, 1 abdominal pain
Case series on multiple plastic stents					
Tringali, 2016	56	N/R	N/R	3/56 (5.3)	1 mild pancreatitis, 1 severe pancreatitis, 1 bleeding
Fernandez-Simon, 2014	42	N/R	N/R	N/R	
Albert, 2013	47	198	32/198 (16.2)	32/47 (68)	19 cholangitis, 6 pancreatitis, 5 bleeding, 2 duodenal perforation
Poley, 2013	31	155	22/155 (14.2)	22/31 (71)	12 cholangitis, 7 pancreatitis, 3 abdominal pain
Ribeiro, 2012	13	33	0/33	0/13 (0)	–
Sanna, 2011	45	85	N/R	N/R	
Tabibian, 2010	69	286	4/286 (1.4)	4/69 (5.8)	2 pancreatitis, 2 bacteremia (moderate cholangitis)
Morelli, 2008	38	131	2/131 (1.5)	2/38 (5.3)	2 mild cholangitis
Holt, 2007	53	180	11/180 (6.1)	11/53 (20.8)	5 mild pancreatitis, 5 mild/moderate cholangitis, 1 stent migration
Pasha, 2007	25	105	5/105 (4.8)	5/25 (20)	3 mild pancreatitis, 2 stent migration
Solmi, 2007	12	54	0/54 (0)	0/11 (0)	–
Alazmi, 2006	148	423	N/R	N/R	
Morelli, 2003	25	79	3/79 (3.7)	3/24 (12.5)	3 mild cholangitis
Rerknimitr, 2002	43	157	N/R	N/R	
RCTs and cohort study on self-expandable metal stents					
Tal, 2017	24	N/R	N/R	8/24 (33.3)	8 stent migration (4 crossover to MPS arm)
Coté, 2016	37	NR	N/R	13/37 (35.1)*	13 stent migration
Prata-Martins, 2015	48	70	17/70 (24.3)	17/48 (35.4)	12 pancreatitis, 1 mild cholangitis, 4 abdominal pain, 3 stent migration
Kaffes, 2014	10	20	1/20 (5)	1/10 (10)	1 cholangitis
Case series on self-expandable metal stents					
Aepli, 2016	31	N/R	N/R	4/31 (12.9)	2 cholangitis, 1 embedding, 1 migration
Jimenez-Perez, 2016	44	N/R	N/R	31/44 (70.5)	1 severe embedding, 8 pancreatitis (3 severe), 5 cholangitis, 17 stent migration
Tarantino, 2015	70	NR	N/R	32/70 (45.7)	32 stent migration
Deviere, 2014	42	NR	N/R	17/42 (40.5)	10 cholangitis, 4 abdominal pain, 2 cholestasis, 1 bleeding
Cerecedo-Rodriguez, 2013	55	N/R	N/R	10/55 (18)	2 cholangitis, 1 pancreatitis, 3 stent occlusion, 4 stent migration
Kahaleh, 2013	35	N/R	N/R	5/31 (16.1)	5 stent migration
Haapamaki, 2012	16	58	9/58 (15.5)	9/17 (53)	5 cholangitis, 1 pancreatitis, 1 bleeding, 4 stent migration
Sauer, 2012	9	N/R	N/R	N/R	
Tarantino, 2012	15	N/R	0	7/15 (46.7)	7 stent migration
Hu, 2011	13	N/R	N/R	2/13 (16.6)	1 mild pancreatitis, 1 complicated cholangitis
Chaput, 2010	22	N/R	N/R	12/22 (54.5)	2 mild cholangitis, 1 minor bleeding, 3 mild pancreatitis, 6 stent migration
Marin-Gomez, 2010	8	N/R	N/R	2/8 (25)	5 stent migration
Garcia-Pajares, 2010	22	75	14/75 (18.7)	14/22 (63.6)	4 abdominal pain, 1 bleeding, 4 stent migration, 1 stent occlusion, 1 stent embedding

Table 5. Continued.

Author, year	*n* ABS	Total ERCP	Complications per ERCP, *n* (%)	Complications per patient, *n* (%)	Type of complication
Kahaleh, 2008	16	N/R	N/R	N/R	
Vandenbroucke, 2006	21	N/R	N/R	N/R	

N/R, not reported; LT, liver transplantation; ABS, anastomotic biliary stricture; ERCP, endoscopic retrograde cholangiopancreatography; SEMS, self-expandable metal stent; MPS, multiple plastic stents; PS, plastic stents; CBD, common bile duct.

*Only stent migration; no subgroup analysis was carried out on general complications for post-LT ABS patients.

[27,34] replaced them after a relatively long period (every 6 months [27] and every 4–6 months [34]) compared with previous publications [30,33,55]. These RCTs reported a stent migration rate of approximately 30%, which is similar to others studies and case series on SEMS. Based on current evidence, we believe that stent replacement every 4–6 months is feasible and safe under close clinical surveillance.

Only Kaffes *et al.* [33] provided a reliable cost analysis of both strategies. They found that the SEMS strategy was more cost-effective than the MPS strategy. The cost of completing the protocol for ABS treatment (Australian $) was lower for SEMS compared with MPS: 10.830 versus $23.580 ($P = 0.02$). They also analysed the costs for any additional procedures required during follow-up and found that SEMS were still more cost-effective ($12.913 vs. $29.280), but without statistical significance ($P = 0.08$).

A recent randomized controlled trial of noninferiority studied SEMS versus MPS in benign biliary strictures of different aetiologies [27]. The study enrolled 112 patients stratified by stricture aetiology and conducted endoscopic reassessments for resolution every 3 months (MPS) or every 6 months (FCSEMS), and 65% of the patients had ABS after LT. As reported by this study, among the patients with benign biliary strictures, SEMS were not inferior to MPS in achieving stricture resolution after 12 months of treatment. In a particular subgroup of LT patients, the observed resolution rate after 12 months of stenting was noninferior (SEMS 91.7% vs. MPS 93.9%), but a higher recurrence rate was observed among those randomized to receive SEMS (15.2% vs. 3.3%) compared to those who received MPS. Even if these outcomes are consistent with the results of the literature summarized in the present review, we cannot draw any definitive conclusions from this trial because the enrolment criteria included benign biliary strictures of other aetiologies (i.e. chronic pancreatitis). Consequently, the study was not adequately powered to conduct subgroup analyses to compare the efficacy of SEMS vs. MPS relative to various aetiologies. Despite this limitation, among LT patients who achieved ABS resolution, the number of ERCP procedures required to achieve stricture resolution was significantly lower for those randomized to receive SEMS vs. MPS (mean, 2.2 vs. 3.1). The same trend towards fewer ERCP procedures per patient in SEMS patients was reported by Tal *et al.* [34] and was confirmed by the results of the meta-analysis. Another important element that can be argued from the study of Coté *et al.* is that endoluminal migration of SEMS remains a relevant clinical issue. In this clinical trial, the observed migration rate was 43%, which is consistent with previous case series in which Tarantino *et al.* [30,56] reported a migration rate greater than 40% for both primary and secondary treatments with SEMS. The overall migration rate of the summarized studies and case series included in this review represents a probable underestimation of this particular complication due to the retrospective design of most of the articles. Some reports suggest that patients treated with SEMS with some kind of inherent antimigration design (i.e. modified SEMS with a central waist and a long removal string) showed fewer complications [33,59,66]. Park *et al.* [65] showed that significantly less stent migration occurred among patients treated with SEMS anchored with a 5F double-pigtail plastic stent compared to a nonanchored group (6.3% vs. 41.2%).

Although the heterogeneity of the studies and case series does not allow any reliable comparison between SEMS and MPS patients, substantial qualitative differences in terms of the types of complications between the groups are not apparent (Table 5). Interestingly, only one anastomosis rupture was described in the SEMS group [53], and four duodenal perforations were reported in the MPS group [26,42]. Among comparative studies, Prata-Martins *et al.* [26] reported a per-patient complication rate of 23.9% for MPS versus 35.4% for SEMS. Cote *et al.* [27]

reported a similar mean number of adverse events per ERCP procedure (although a subgroup analysis dedicated to post-LT ABS patients was not available) for both study arms (0.23 MPS vs. 0.36 SEMS; $P = 0.31$).

Our systematic review attempted to summarize the current literature on the endoscopic treatment of duct-to-duct ABS after LT. Although a considerable number of publications were retrieved overall, the total evidence is insufficient and is often underpowered to draw definitive conclusions. Moreover, heterogeneity was observed in endoscopic management across different studies and case series, indicating that caution is required when interpreting the results. Despite these limitations, the present systematic review and meta-analysis highlights the efficacy and safety of both strategies to achieve ABS resolution and manage biliary complications via minimally invasive methods. Future RCTs should aim to establish the best therapeutic strategy between SEMS and MPS to reduce the number of per-patient endoscopic procedures, decrease the complication rate and reduce costs.

Because of the low-quality evidence, we cannot draw any reliable conclusions on the superiority of MPS or SEMS strategies. Even though shorter treatment durations and fewer ERCP procedures advocate in favour of SEMS, whether one technique has clear advantages over the other remains unclear. This issue should be addressed in further adequately powered, randomized clinical trials.

Funding

The authors have declared no funding.

Conflicts of Interest

All authors have no conflict of interests or financial ties to disclose.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Study quality assessments using the NICE checklist.

Table S1. Quality assessment of RCTs (according to Cochrane collaboration handbook for systematic review of interventions) and cohort study (according to Newcastle-Ottawa scale).

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