ORIGINAL ARTICLE

Risk of Post-ERCP Pancreatitis after placement of Covered versus Uncovered Self-Expandable Biliary Metal Stents: A Systematic Review and Meta-Analysis

Yaseen Alastal[1], Tariq Hammad[1], Muhammad Ali Khan[1,2], Basmah W Khalil[1], Sobia Khan[1], Mohammad Kashif Ismail[2], Ali Nawras[1], Aijaz Sofi[1]

[1]Department of Gastroenterology, University of Toledo, Toledo, OH
[2]Department of Gastroenterology, University of Tennessee, Memphis, TN

ABSTRACT

Background Self-expandable metal stents are commonly used in the management of malignant biliary obstruction due to higher patency rates compared to plastic stents. Development of covered self-expandable metal stents has led to extended stent patency compared to uncovered self-expandable metal stents. However, there are concerns that deployment of covered self-expandable metal stents may be associated with higher risk of post-endoscopic retrograde cholangio-pancreatography pancreatitis, acute cholecystitis and stent migration. **Objective** We performed this meta-analysis to assess the risk of post-endoscopic retrograde cholangio-pancreatography pancreatitis and other adverse events (acute cholecystitis and stent migration) with biliary covered self-expandable metal stents compared to uncovered self-expandable metal stents. We also assessed the proportion of stent patency at 6 and 12 months between the two groups. **Methods** We searched MedLine, EMBASE, Cochrane database, ISI Web of Science and Scopus from January 1989 through June, 2014, to identify randomized controlled trials and observational studies that provided data on the risk of post-endoscopic retrograde cholangio-pancreatography pancreatitis and other adverse events following the placement of covered self-expandable metal stents versus uncovered self-expandable metal stents in patients with biliary obstruction. The Mantel–Haenszel method was used to pool data of post-endoscopic retrograde cholangio-pancreatography pancreatitis, acute cholecystitis, stent migration and proportion of stent patency over 6 and 12 months into fixed or random effect model of meta-analyses. Odds ratio was used to generate an overall effect estimate of the outcome. **Results** Eight studies (6 randomized controlled trials and 2 observational studies) with a total of 1078 patients were included in the meta-analysis. The pooled odds ratio with 95% confidence intervals for risk of post-endoscopic retrograde cholangio-pancreatography pancreatitis with covered versus uncovered self-expandable metal stents was 1.58 (0.65 to 3.86); (Cochran Q test P=0.60, I2=0%). Stent migration was significantly associated with covered self-expandable metal stents, pooled odds ratio with 95% confidence intervals was 10.07 (3.30 to 30.70); (Cochran Q test P=0.80, I2=0%). There was no difference in the risk of acute cholecystitis with either type of stent. Pooled odds ratio with 95% confidence intervals was 1.42 (0.59 to 3.43); (Cochran Q test P=0.75, I2=0%). There was no difference in proportion of stent patency at 6 or 12 months. For 6 months the pooled odds ratio with 95% confidence intervals was 1.55 (0.75 to 3.22); (Cochran Q test P=0.01, I2=68%) and for 12 months the pooled odds ratio with 95% confidence intervals was 1.17 (0.66 to 2.07); (Cochran Q test P=0.03, I2=66%). **Conclusion** This meta-analysis failed to show any association for risk of post-endoscopic retrograde cholangio-pancreatography pancreatitis and acute cholecystitis with use of covered versus uncovered self-expandable metal stents. However, covered self-expandable metal stents was significantly associated with stent migration. There was no superior patency of covered self-expandable metal stents in comparison to uncovered self-expandable metal stents over 6 and 12 months.

INTRODUCTION

Obstructive jaundice secondary to malignant strictures of the biliary tree is not uncommon especially in elderly population. Most of the patients are not eligible for curative surgical intervention at the time of presentation due to locally advanced or metastatic disease. Endoscopic biliary stenting offers the least invasive method for biliary decompression and palliative management [1]. Successful biliary drainage after stent insertion has been shown to improve quality of life in these patients [2]. A vast array of stents is available for biliary stenting in these patients. Self-expandable metal stents (SEMS) are commonly used in the management of malignant biliary obstruction due to their higher patency and lower re-intervention rates compared to plastic stents [3, 4]. Development of covered self-expandable metal stents (CSEMS) was hypothesized to have extended stent patency in comparison to uncovered SEMS (USEMS) by limiting tumor ingrowth. However, this

Received May 05th, 2015-**Accepted** June 5th, 2015
Keywords Pancreatitis
Abbreviations SEMS self-expandable metal stents
Correspondence Aijaz Sofi
University of Toledo
3000 Arlington Avenue, Toledo, OH 43614
Phone +419-383-4000
Fax + 419-383-6127
E-mail aijaz.sofi@utoledo.edu

benefit was not consistently seen in multiple randomized controlled trials, and there were concerns that deployment of CSEMS may be associated with higher risk of Post-ERCP pancreatitis (PEP), acute cholecystitis, and stent migration. We therefore performed this meta-analysis to assess the risk of post-ERCP pancreatitis and other adverse events with biliary CSEMS compared to USEMS.

MATERIALS AND METHODS

Search Strategy

The systematic review was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [5]. The search strategies were developed in PubMed and translated to match the subject headings and keywords for Embase, Cochrane Central Register of Controlled Trials, ISI Web of Science, and Scopus from January 1989 to June 2014. Two authors (Y.A. and M.A.K) searched for randomized controlled trials (RCT), prospective, and retrospective studies comparing the risk of PEP and other adverse events following the placement of covered SEMS versus uncovered SEMS in patients with biliary obstruction. Medical subject headings for our literature review included malignant biliary strictures, biliary stent, post-ERCP pancreatitis, covered biliary stents, uncovered biliary stents, acute cholecystitis and stent migration. To increase the yield of our search strategy, we hand searched related citations in review articles and commentaries, then cross-referencing was performed for identified articles.

Study Selection

Two reviewers (A.S., Y.A.) independently assessed the eligibility of identified studies. Eligible studies were original, longitudinal or randomized studies that reported the association of biliary stenting through ERCP and PEP. Studies in which biliary stents were placed by non-endoscopic techniques were excluded. Any disagreement between reviewers was resolved by consensus.

Data Extraction

Two reviewers (A.S, T.H.) independently extracted data from eligible studies using a predefined form; discrepancies were resolved by a third reviewer (M.A.K). Data related to patient demographics, year of publication, study method, first author, number of patients in every arm of the study and different outcomes were collected.

Quality Assessment

Quality assessment was done by two authors (A.S and M.A.K) independently, using the Newcastle-Ottawa scale (NOS) [6] for cohort studies and Jadad scale for randomized trials [7]. Any disagreements between authors were resolved by consensus. The NOS assessment scale utilizes a tool that measures quality in three parameters of selection, comparability and exposure/outcome, and allocates a maximum of four, two and three points, respectively. High quality studies are scored > 7 on this scale and moderate quality studies between 5 and 7. The Jadad scale assigns one point each for randomization, appropriate method of randomization, double blinding, appropriate method of double blinding and description of dropouts. High quality studies score between 3 and 5, while low quality studies score less than 3

Data Synthesis and Statistical Analysis

Our primary outcome of interest was to evaluate the association between PEP and utilization of covered and uncovered SEMS for attaining satisfactory biliary drainage endoscopically. Secondary outcomes in our work included the association of covered and uncovered biliary stents with other major adverse effects like acute cholecystitis, stent migration and proportion of stent patency at 6 and 12 months. The Mantel–Haenszel method was used to pool data of primary and secondary outcomes of interest into fixed or random effects model of meta-analyses and odds ratio (OR) with corresponding 95% confidence intervals (CI) were calculated. To estimate statistical heterogeneity, we used the Cochrane Q test and I^2 statistics. A p-value of < 0.1 for Cochran Q test was defined as indicating the presence of heterogeneity. All analyses were conducted using Review Manager (RevMan, version 5.3 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Description of Studies

The initial search strategy revealed a total of 528 potentially relevant studies, of which 509 studies were excluded after removal of duplicates and review of title and abstracts. 19 remaining studies were assessed for eligibility. Eventually, eight studies with a total of 1,078 patients were eligible for our analysis. The study selection process is illustrated in **figure 1**. A total of 543 patients received covered SEMS and 535 patients received uncovered SEMS. **Table 1** summarizes the main characteristic of included studies. All 8 studies were published between 2004 and 2013; six of these studies were fully peer reviewed published articles while the other two were abstracts. The studies were published from different countries **(see table 1)**. Six studies were randomized controlled trials (RCT) [8-13] and two studies were observational [14, 15]. Only three RCTs were blinded [9, 11], and four were multicenter studies [9, 12].

Quality Assessment

Four RCTs were high quality studies as per the Jadad scale while one was low quality study. Using the Newcastle Ottawa Scale, for the observational studies group, one was high quality and the other one was of moderate quality **(Tables 2 and 3)**.

Meta-Analyses

Among the 8 studies included, 3 studies [9, 14, 15] did not have any event of PEP in either arm. The pooled OR with 95% (CI) for association of PEP with covered versus uncovered stents was 1.58 (0.65 to 3.86). There was no

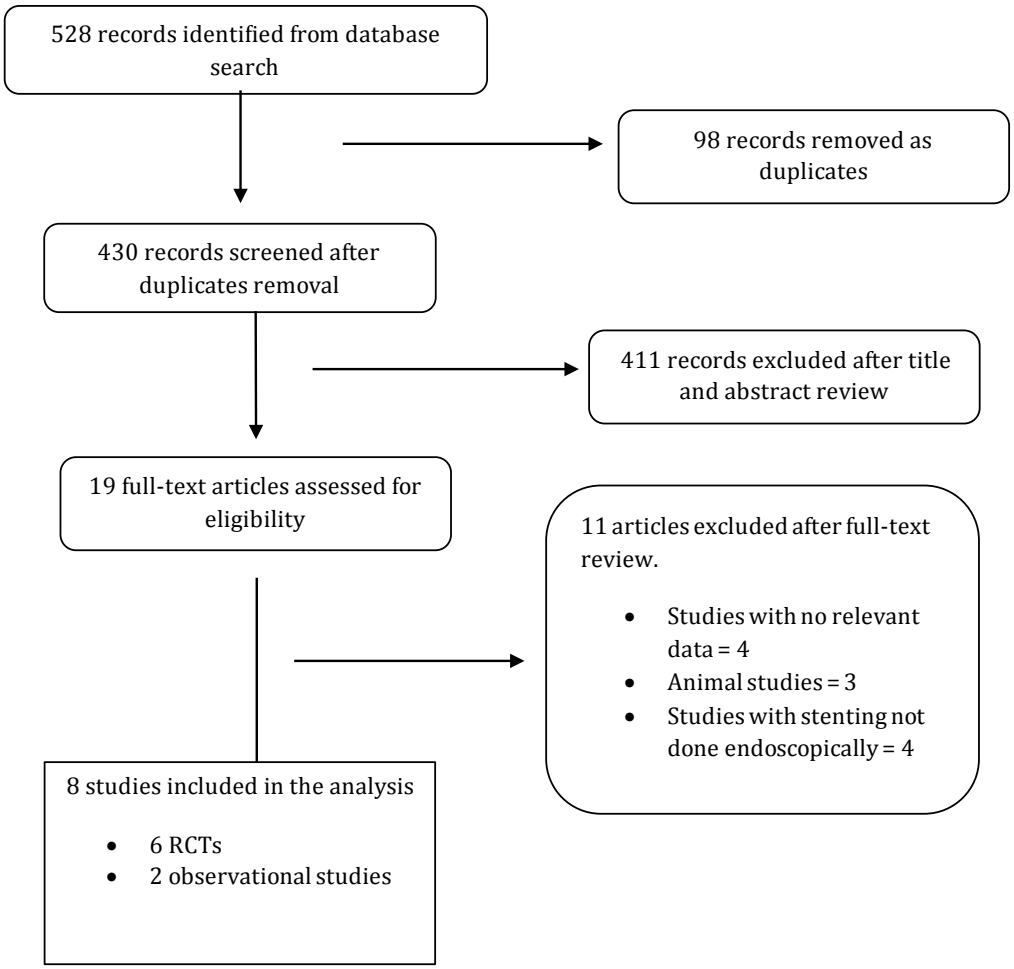

Figure 1. PRISMA flow chart

Table 1: Characteristics of included studies.

Study	Year	Country	Center	Design	Patients (n) (Covered/ uncovered stent)	Type of Stent	Publication Type
Isayama	2004	Japan	Single	RCT	57/55	Ultraflex Diamond	Published article
Yoon	2006	Korea	Single	Retrospective	36/41	Wallstents	Published article
Gonzalhu	2008	Spain	NA	RCT	61/53	Wallstents	Abstract
Gomez	2009	Switzerland	Single	Retrospective	27/31	Wallstents	Abstract
Telford	2010	USA	Multicenter	RCT, blinded	68/61	Wallstents	Published article
Kullman	2010	Sweden	Multicenter	RCT, blinded	200/200	Nitinella	Published article
Kitano	2013	Japan	Multicenter	RCT, not blinded	60/60	Wallflex	Published article
Ung	2013	Sweden	Two-centers	RCT, double-blind	34/34	Hanarostent	Published article

Table 2: Quality assessment using the Jadad scale for RCTs

Author	Randomization	Blinding	Account of Patients	Score
Isayama	1 1	0 0	1	3/5
Gonzalez-Huix	1 1	0 0	0	2/5
Telford	1 1	1 1	1	5/5
Kullman	1 1	1 1	1	5/5
Ung	1 1	1 1	1	5/5
Kitano	1 1	0 0	1	3/5

Table 3: Quality assessment using Newcastle Ottawa scale for observational studies

Study	Selection (score)				Comparability (score)	Exposure (score)			Total Score
	Case definition	Representative of cases	Selections of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for participants	Nonresponse rate	
Yoon	1	1	1	1	2	1	1	1	9
Gomez	1	0	0	1	0	1	1	1	5

Figure 2. Forest plot for PEP and covered versus uncovered SEMS

heterogeneity between studies (Cochran Q test P=0.60, I^2=0%) **(Figure 2)**.

Stent migration was reported in 6 studies [8-10, 13-15]. Pooled data showed significantly higher incidence of stent migration in patients who underwent placement of covered SEMS as compared to uncovered SEMS. Pooled OR with 95% (CI) was 10.07 (3.30 to 30.70). There was no heterogeneity between studies (Cochran Q test P=0.80, I^2=0%) **(Figure 3)**. Six studies [8-10, 12-14] reported acute cholecystitis as an adverse event. The pooled OR with 95% (CI) for association of acute cholecystitis and the two types of stents was 1.42 (0.59 to 3.43); Cochran Q test P=0.75, I^2=0%, indicating no heterogeneity between studies **(Figure 4)**. Proportion of stent patency at 6 months was reported in 3 RCTs [8-10] and 2 observational studies [14, 15]. Pooled data did not show any difference in proportion of stent patency at 6 months between covered and uncovered SEMS, OR with 95% (CI) was 1.55 (0.75 to 3.22); Cochran Q test P=0.01, I^2=68% **(Figure 5)**. Likewise, proportion of stent patency at 12 months was no different between the two types of stents. Pooled OR with 95% (CI) was 1.17 (0.66 to 2.07); Cochran Q test P=0.03, I^2=66% **(Figure 6)**.

DISCUSSION

Self-expandable metal stents are being increasingly used as palliative treatment for malignant biliary obstruction because of their superior prolonged patency compared to plastic stents [3]. However, stent dysfunction secondary to tumor ingrowth was one of the major drawbacks with the use of SEMS. To overcome this issue of tumor ingrowth, SEMS were modified to include coating of their inner surface. In this meta-analysis we compared the adverse events resulting from placement of these two types of SEMS, especially the risk of post ERCP pancreatitis. Two previous meta-analyses assessing the patency of these stents have shown conflicting results. Almadi *et al*. [16] concluded that CSEMS does not appear to have longer patency and it has no clear benefit over uncovered SEMS. On the other hand, Saleem *et al* [17] reported that CSEMS have a significantly longer duration of patency as compared to USEMS in patients with distal malignant biliary obstruction. Since the publication of these conflicting meta-analyses, two multicenter RCTs have evaluated the efficacy and adverse events of covered versus uncovered SEMS. In comparison to the previous two meta-analyses [16, 17], we excluded the studies evaluating placement of SEMS through transhepatic route.

Acute pancreatitis can occur as a possible complication of SEMS. Isayama *et al*. [18] related it to the radial and axial forces associated with SEMS. Radial force (RF) is a well-known expansion force related to dilation of the stricture to maintain luminal patency. In comparison to this, the axial force (AF) is the recovery or straightening force when the SEMS is bent. Once SEMS is deployed, it is fixed by the tumor itself. These forces tend to compress the biliary wall, cystic and pancreatic ducts and orifices, which may lead to acute cholecystitis or acute pancreatitis [18-21]. The use of covered SEMS has been postulated to additional risk of pancreatitis and cholecystitis due to pancreatic duct and cystic duct occlusion by the stent covering [8, 22, 23]. Acute pancreatitis was reported higher in CSEMS arm in three studies included in this analysis [8, 11, 12], however, the difference was not statistically significant. All these cases were mild cases of acute pancreatitis which resolved with conservative treatment. Only Kullman *et al*. reported 3 severe cases of acute pancreatitis (one case in CSEMS and two in USEMS). All of these resolved within 2 weeks. Likewise, our meta-analysis did not appreciate any difference in the risk of PEP with covered SEMS as compared to uncovered SEMS.

Acute cholecystitis is another potential adverse effect which can occur more often with placement of covered

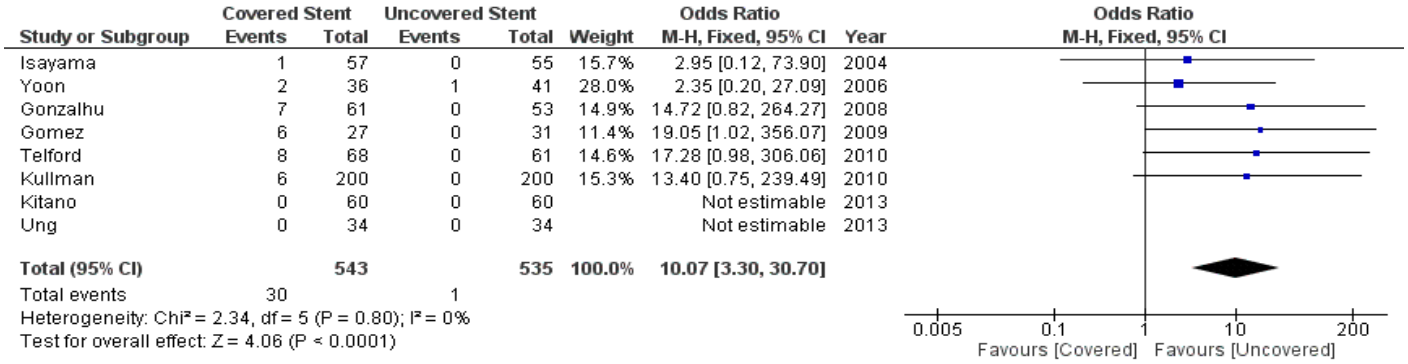

Figure 3. Forest plot for stent migration with covered versus uncovered SEMS

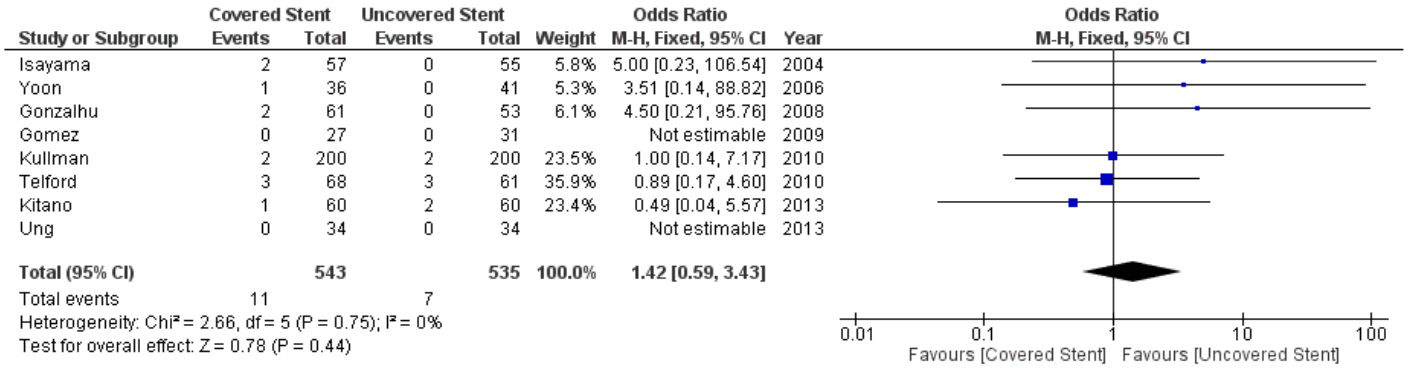

Figure 4. Forest plot for acute cholecystitis with covered versus uncovered SEMS

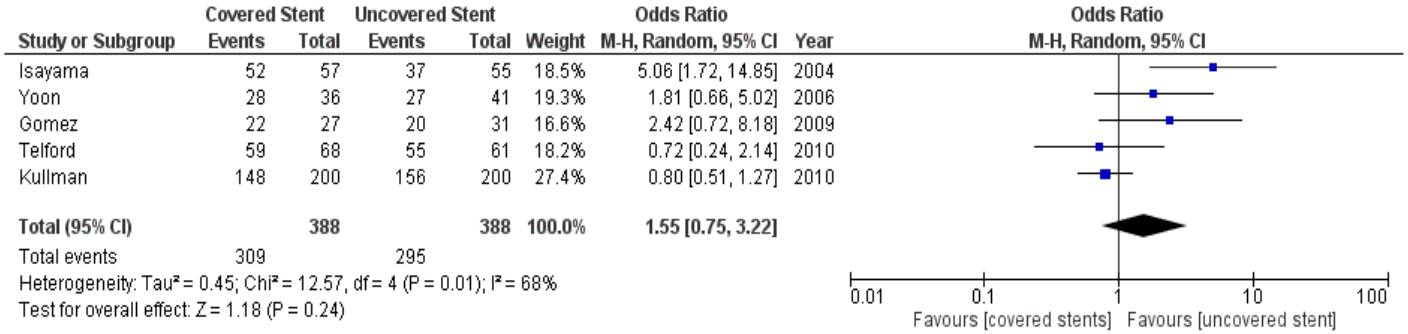

Figure 5. Forest plot for stent patency at 6 months

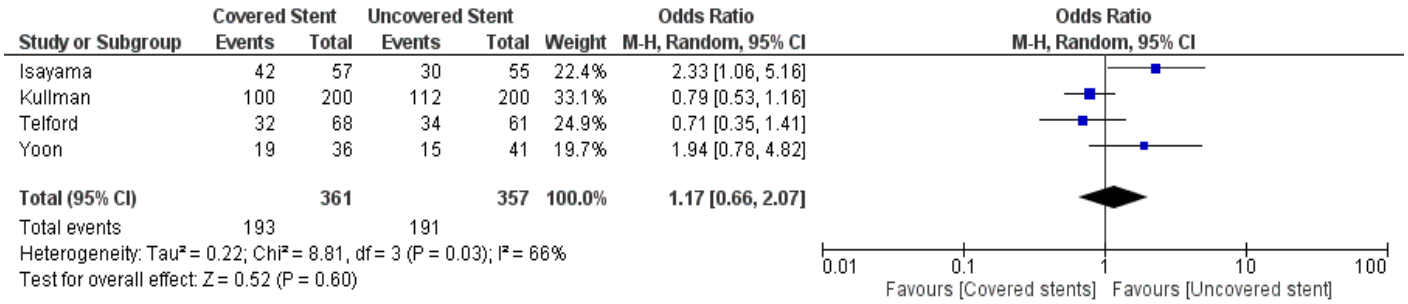

Figure 6. Forest plot for stent patency at 12 months

SEMS as compared to uncovered SEMS. This is because an expanded CSEMS could obstruct the opening of cystic duct into bile duct. Furthermore, contamination of bile duct by instrumentation during ERCP could lead to blocked and infected gall bladder. However, this meta-analysis did not show any significant increase in the risk of acute cholecystitis with CSEMS as compared to USEMS. Few studies have evaluated potential risk factors associated with acute cholecystitis following biliary stenting [24]. In a study by Shimizu *et al*. [25], involvement of cystic duct by a tumor was found to be a significant risk factor for acute cholecystitis after placement of covered SEMS. Similar results were reported by Suk *et al*. [24], who found presence of gall stones as an additional significant risk factor for acute cholecystitis after placement of SEMS. However, the type of stent (covered versus uncovered), was not a significant risk factor in this study.

One of the limitations is the different kind of stents used in the studies. **Table 1** summarized the type of stents in each study. Among the covered stents, the level of coating lining the inner portion of CSEMS also differed in these studies. Isayama *et al*. [8] used Ultraflex partially covered diamond stent with uncovered portions constituting 5 mm at both ends to prevent their migration, and with pores in the mid portion. The covered stents used by Kullman *et al*. [10] had only distal 5 mm of uncovered portion. Ung *et al*. [11] used a covered SEMS coated for the entire length with a silicone membrane. Majority of stents used in other studies had 5-mm uncovered portions at both ends. This variability in the stent coating could affect the studied outcomes; no sub-analysis was done to compare these different types of covered stents due to limited number of events in each category. Another limitation of this meta-analysis is that only three RCTs were reported to be blinded. Lack of blinding could result in detection bias.

On the other hand, our meta-analysis includes the largest number of patients to compare the adverse outcome in CSEMS and USEMS. The search strategy was comprehensive and lead to inclusion of two unpublished abstracts and decreasing publication bias. The method of stent deployment in all included studies was endoscopic route, which decreases the difference between the studies compared to previous meta-analyses.

In conclusion, our meta-analysis shows that placement of covered SEMS is not associated with an increased risk of post-ERCP pancreatitis compared to uncovered SEMS. Similarly, there is no increased risk of acute cholecystitis. However, the risk of stent migration is significantly higher with covered SEMS.

Conflict of interest

Authors declare to have no conflict of interest.

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