Antireflux valve metal stent versus conventional self-expandable metal stent in distal malignant biliary obstruction: a systematic review and meta-analysis

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Abstract

Background In patients with distal malignant biliary obstruction (MBO), endoscopic biliary drainage using the conventional self-expandable metal stent (SEMS) is the gold standard method for palliative treatment. However, there are limited data on the role of the antireflux valve metal stent (ARVMS). The aim of this study was to compare the safety and efficacy of ARVMS and SEMS in patients with distal MBO.

Methods We searched PubMed, Ovid, Embase and the Cochrane Library from inception until April 2019 for relevant randomized controlled trials (RCTs). The selected studies provided data regarding technical and clinical success rates, adverse events, and stent dysfunction. Data were meta-analyzed using RevMan software.

Results Three RCTs were selected, enrolling 293 patients (147 ARVMS and 146 SEMS). The rates of technical success were 95.23% and 99.31% for ARVMS and SEMS groups, respectively (odds ratio [OR] 0.13, 95% confidence interval [CI] 0.01-1.06; P=0.06). The clinical success rates were 91.57% and 89.36% for ARVMS and SEMS groups, respectively (OR 1.30, 95%CI 0.48-3.51; P=0.61). There was no significant difference between the ARVMS and SEMS groups in terms of adverse events (OR 0.61, 95%CI 0.35-1.05; P=0.07) or stent dysfunction (OR 0.77, 95%CI 0.31-1.95; P=0.58), while the incidence of stent occlusion was significantly lower in the ARVMS group (OR 0.44, 95%CI 0.26-0.76; P=0.003).

Conclusion Our study showed that ARVMS and SEMS had similar technical and clinical success rates. Adverse events were comparable between the 2 arms; however, ARVMS was associated with a lower risk of stent occlusion. Larger RCTs are required to verify the benefit of ARVMS in distal MBO patients.

Keywords Biliary malignancy, biliary obstruction, metal stent, meta-analysis

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Introduction

The conventional self-expandable metal stent (SEMS) has been the gold standard for palliative treatment of non-resectable distal malignant biliary obstruction (MBO) because of its longer duration of patency and better conformability to the bile duct compared with plastic stents [1]. However, cholangitis occurs in 6.5-22% of patients with SEMS [2-4]. This adverse event is mainly predicted by the transpapillary insertion of SEMS (which impairs sphincter function) [5] and probably occurs as a result of enteric biliary reflux (as reported in a previous study with barium examination) [6].

The antireflux valve metal stent (ARVMS) has been introduced as an alternative to SEMS to reduce the risk of

cholangitis [7]. The addition of valves of different shapes to the stent was aimed to prevent biliary reflux. Some studies have compared the safety and efficacy of ARVMS to SEMS in patients with distal MBO [7-9]. However, there is still debate regarding the superiority of either of these 2 stent types. For example, Hu *et al* concluded that ARVMS significantly reduced the risk of ascending cholangitis and had longer stent patency [7]. On the other hand, Hamada *et al* showed that ARVMS did not increase the time to recurrent biliary obstruction and was associated with a higher rate of stent migration [8].

This analysis is an attempt to synthesize the evidence from published randomized controlled trials regarding the comparative safety and efficacy of AVRMS and SEMS stents in patients with distal MBO. To our knowledge, this is the first meta-analysis to be conducted with the intention of comparing both stents in this patient population.

Materials and methods

Literature search

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement [10]. We searched PubMed, Medline (Ovid), Embase, and the Cochrane Library for randomized controlled trials (RCTs) published up to and including April 2019. We employed descriptors available from the Medical Subject Headings (MeSH) and, to a lesser degree, other related terms, aiming at a more sensitive strategy. The following terms were used to find eligible trials: antireflux metal stent OR self-expandable metal AND malignant biliary obstruction. Two reviewers (AR,YA) independently screened the database search results for titles and abstracts. If either reviewer felt that a title and abstract met the eligibility criteria of our study, the full text of the study was retrieved**.**

Study eligibility criteria

Only published RCTs were considered eligible, without barriers as to the language or year of publication. We included RCTs that evaluated patients >18 years old, diagnosed with distal MBO (based on lab results and imaging), and undergoing primary drainage of the biliary tract via ARVMS or SEMS. Studies evaluating patients with benign biliary obstruction or published as abstracts only were excluded.

Data extraction

Data related to ARVMS and SEMS biliary drainage of MBO were collected using a preformatted Excel workbook. The data collected included technical and clinical success rates, as well as the duration of the procedure, adverse events, stent patency, and stent dysfunction. In our quantitative analysis, we used the absolute values, means, and standard deviations. If a study

expressed outcomes using median and interquartile range, mathematical formulas were used for data conversion. In cases where the study failed to present means and standard deviations or median and interquartile ranges for the continuous variables of specific outcomes, the variable in question was excluded from the outcome analysis.

Risk of bias assessment (quality assessment)

We assessed the risk of bias in each trial using the Cochrane risk of bias tool for RCTs. Reviewers provided an evaluation for risk of bias as low (bias is not present or unlikely to alter the results seriously), unclear, or high (bias may seriously alter the results) for each of the following domains: sequence generation, allocation sequence concealment, blinding of participants and surgical staff, blinding of outcome assessment, selective outcome data, incomplete outcome data, and other biases [11]. Reviewers' disagreements on risk of bias judgments were resolved by an independent third reviewer.

Publication bias

A funnel plot was used to assess for publication bias.

Data analysis

For dichotomous variables, we calculated the odds ratios (ORs), using the Mantel-Haenszel test, together with the corresponding 95% confidence intervals (CI). The results were displayed as forest plots. We assessed the heterogeneity among studies using the Cochrane Q and I-square (I^2) tests, based on which the fixed- or random-effects model was used (for homogenous and heterogeneous datasets, respectively) [12]. All analyses were carried out using Review Manager software (RevMan 5.3.5; Cochrane Collaboration, Oxford, United Kingdom).

Results

Literature search results

The electronic search of four databases retrieved 254 studies. This number was reduced to 6 after title/abstract screening: i.e., 6 full-text articles were retrieved for full-text screening. Three studies were excluded for not meeting our eligibility criteria and 3 studies were selected for qualitative and quantitative analysis. The search and study selection strategies are illustrated in Fig. 1.

Characteristics of included studies

The 3 eligible studies enrolled a total sample size of 293 patients (147 ARVMS and 146 SEMS). Only one trial
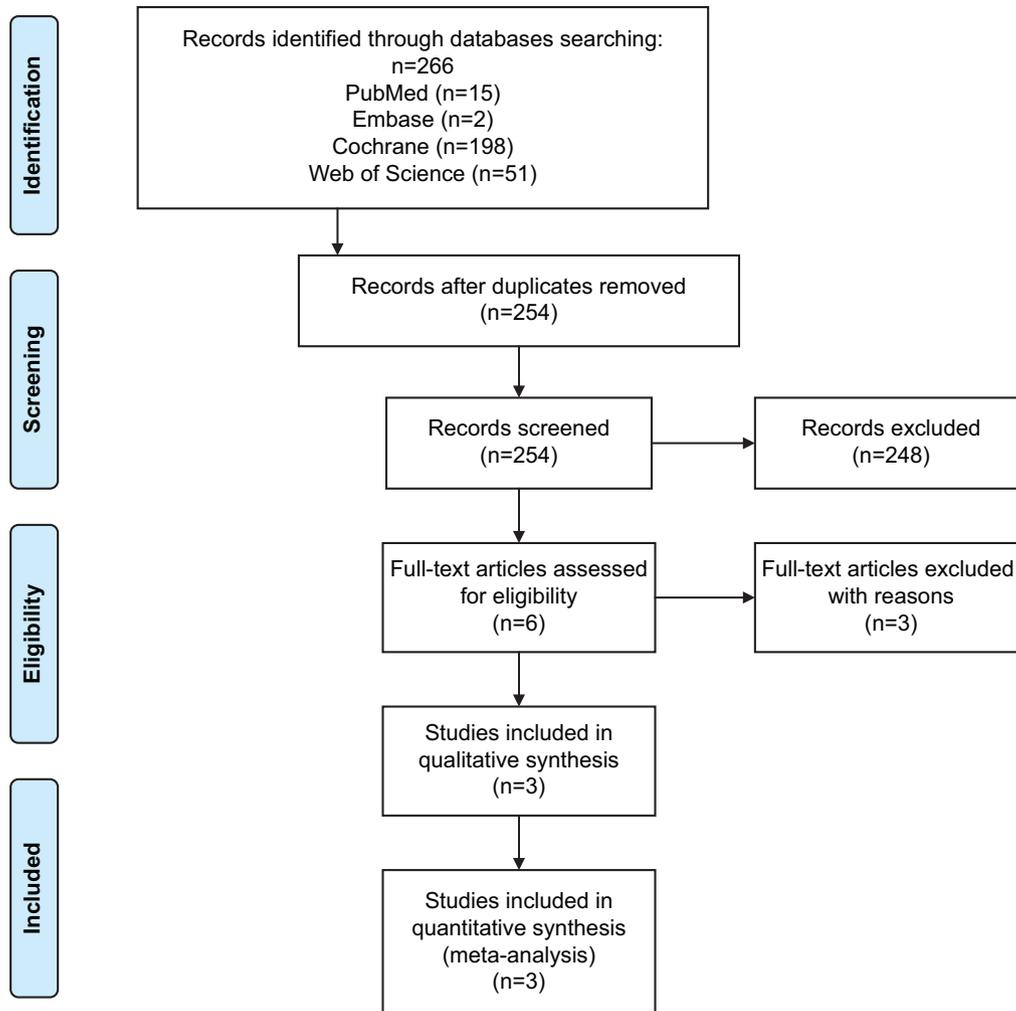
Figure 1 PRISMA flow diagram of literature search and study selection

was multicenter; the other 2 were single-center studies. All studies enrolled patients with distal unresectable malignant obstruction in the biliary tract. All 3 studies were conducted in East Asia (Japan, China, and South Korea). The patients' mean age ranged between 66.3 and 74.5 years, with males representing 54.9% of the pooled population. The characteristics of the eligible studies and their enrolled patients are summarized in Table 1.

Risk of bias assessment results

All 3 studies had a low risk of bias in terms of random sequence generation, allocation concealment, incomplete outcome data, and selective data reporting. The studies were mostly open-label; they had high risks of bias in terms of participants and blinding of outcome assessors (except for 1 study). Insufficient data were provided to assess the existence of other sources of bias. The risk of bias assessment results for the included studies are summarized in Fig. 2.

Efficacy outcomes

The rates of technical success were 95.23% and 99.31% for ARVMS and SEMS groups, respectively. The clinical success rates were 91.57% and 89.36%, respectively. Pairwise meta-analysis showed no significant difference between the ARVMS and SEMS groups in terms of technical success (OR 0.13, 95%CI 0.01-1.06; P=0.06; Fig. 3A) or clinical success (OR 1.30, 95%CI 0.48-3.51; P=0.61; Fig. 3B). No significant heterogeneity was noted (P=0.86, I^2=0%); therefore, the analysis was conducted using the fixed-effects model.

Safety outcomes

The most common adverse event was cholangitis, occurring in 8.6% and 17.2% of the AVRMS and SEMS groups, respectively. This was followed by pancreatitis, occurring in 5.7% and 8.9%, respectively. Other less frequent

Table 1 Baseline characteristics of the enrolled patients in eligible studies

Reference	Design	Country	Study population	Sample size	Sex, male no (%)	Age mean	Intervention	Total bilirubin, mg/dL	Types of outcome measures
Tsuyoshi Hamada *et al* 2019 [8]	Multicenter randomized controlled trial	Japan	Patients who were diagnosed with obstructive jaundice due to non-resectable distal malignant biliary obstruction[a] and did not have a history of biliary metal stent placement	104	60 (57.7%)	74.5	Endoscopic placement of conventional covered self-expandable metal stent[b] vs. fully-covered self-expandable metal stent with an antireflux valve attached to the duodenal end[c]	5.3 mg/dL	Technical success, recurrent biliary obstruction[d], prolong time to recurrent biliary obstruction, stent occlusion[e], Stent migration[f], other morbidities[#], death
Yun Nah Lee *et al* 2016 [9]	Open-label, randomized trial at a single center	South Korea	Patient with unresectable malignant biliary obstruction	77	37 (48.1%)	73.5	Endoscopic placement of conventional covered self-expandable metal stent[g] vs. antireflux valve self-expandable metal stents[h]	4.25 mg/dL	Technical success, clinical success[i], stent patency duration, stent dysfunction[j], tumor overgrowth[k], tumor ingrowth[l], stent migration[m], other morbidities[#], death
Bing Hu *et al* 2013 [7]	Randomized clinical trial at a single center	China	Patients with non-hilar malignant biliary obstruction	112	66 (58.9%)	66.3	Endoscopic placement of Uncovered self-expandable metal stents[n] vs. partly covered metal stents[o]	2.6 mg/dL	Technical success, clinical success[p], ascending cholangitis[q], stent dysfunction[r], stent migration[#] other morbidities[#], death

[a]Defined as a malignant biliary stricture ≥2 cm from the communication of the bilateral hepatic ducts; [b]Niti-S COMVI biliary stent, Taewoong Medical Inc., Gimpo, Korea; [c]Made by Taewoong Medical Inc, Gimpo, Korea; [d]Defined as a composite endpoint of either occlusion or migration of a stent, whichever came first; [e]Considered to be present if elevated liver enzymes were observed along with biliary dilation on imaging studies or endoscopic findings that suggested stent occlusion; [f]Defined as completely-or partially-migrated stent was observed at the time of a reintervention for recurrent biliary obstruction; [g]EGIS Biliary Stent M-Valve; Made by S&G Biotech, Seongnam, South Korea; [h]EGIS Biliary Stent M-Valve; Made by S&G Biotech, Seongnam, South Korea; [i]Defined as at least a 50% decrease in bilirubin levels during the first 7 days after stent insertion; [j]Considered to occur if the patient had obstructive jaundice and a finding of biliary dilation on imaging studie s (CT, magnetic resonance imaging, or US) with or without cholangitis; [k]Defined as stent occlusion by a tumoral mass over the stent; [l]Defined as stent occlusion by the tumor inside the stent; [m]Defined as SEMS movement over the malignant biliary obstruction from the original post-placement position, as documented by the final spot radiograph obtained at the initial endoscopic retrograde cholangio-pancreatography; [n]Modified from a commonly used self-expandable metal stents (Micro-Tech (Nanjing) Co. Ltd. Nanjing, China; [o]Made by Micro-Tech (Nanjing) Co. Ltd. Nanjing, China; [p]Normalized serum bilirubin (less than 18.8 μmol/L) within 1 month; [q]Defined by occurrence of fever (temperature >38°C), associated with upper abdominal pain, minor to moderate abnormality of liver function test results, and increased leukocyte count and/or C-reactive protein levels; Considered to be present if the patient had worsening liver function test results and/or symptoms of cholangitis, which did not respond well to antibiotic treatment for 3 days; [#]Recorded according to normal practice

adverse events included cholecystitis, bleeding, liver abscess, and abscess around the bile duct (Table 2). Pairwise meta-analysis showed no significant differences between ARVMS and SEMS groups in terms of the frequency of all (OR 0.61, 95%CI 0.35-1.05; P=0.07; Fig. 4A), early (OR 0.69, 95%CI 0.27-1.81; P=0.45; Fig. 4B) and late (OR 0.47, 95%CI 0.22-1.02; P=0.05; Fig. 4C) adverse events. No significant heterogeneity was noted across the 3 analyzed outcomes (P>0.1). The funnel plot was symmetrical, consistent with a lower likelihood of publication bias (Fig. 5).
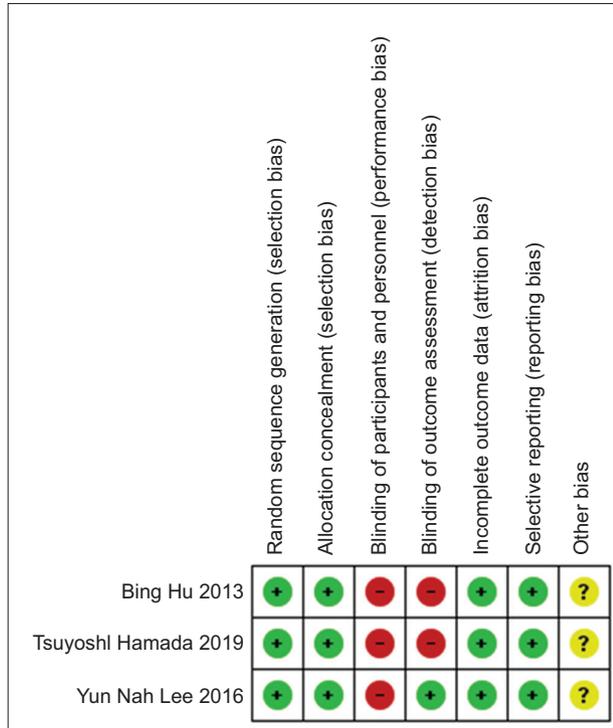

Figure 2 Risk of bias assessment results according to the Cochrane risk of bias tool

Stent dysfunction

The most common cause of stent dysfunction was stent migration, recorded in 16.2% and 7% of the AVRMS and SEMS groups, respectively. This was followed by sludge occlusion, tumor ingrowth, and unknown causes (Table 3). Pairwise meta-analysis showed no significant difference between the stent types in terms of the overall incidence of stent dysfunction (OR 0.77, 95%CI 0.31-1.95; P=0.58; Fig. 6A). Significant heterogeneity was noted (P=0.03, I^2=72%) among the studies [7-9], best resolved when the study by Hamada *et al* [8] was excluded, while the new effect estimate showed a significant reduction in the overall incidence of stent dysfunction in favor of the AVRMS group. However, subgroup analysis by cause of dysfunction showed a greater frequency of stent migration (OR 2.76, 95%CI 1.24-6.17; P=0.01; Fig. 6B) and a lower frequency of stent occlusion (OR 0.44, 95%CI 0.26-0.76; P=0.003; Fig. 6C) in the AVRMS group, in comparison to the SEMS group. The funnel plot was symmetrical, consistent with a lower likelihood of publication bias (Fig. 7).

Discussion

This meta-analysis showed that ARVMS exhibited comparable efficacy and safety profiles to SEMS, evident by the similarities in the rates of clinical and technical success, adverse events and stent dysfunction. No heterogeneity was detected across all outcomes, except in the outcome of overall adverse events. When this heterogeneity was resolved using the leave-one-out sensitivity analysis, a favorable safety profile appeared for ARVMS over SEMS. Interestingly, a lower rate of stent occlusion but a higher rate of stent migration were observed for ARVMS in comparison to SEMS.

ARVMSs were developed based on the notion that preventing biliary reflux using a valve may decrease stent-associated cholangitis [7]. Indeed, we observed from the pooled
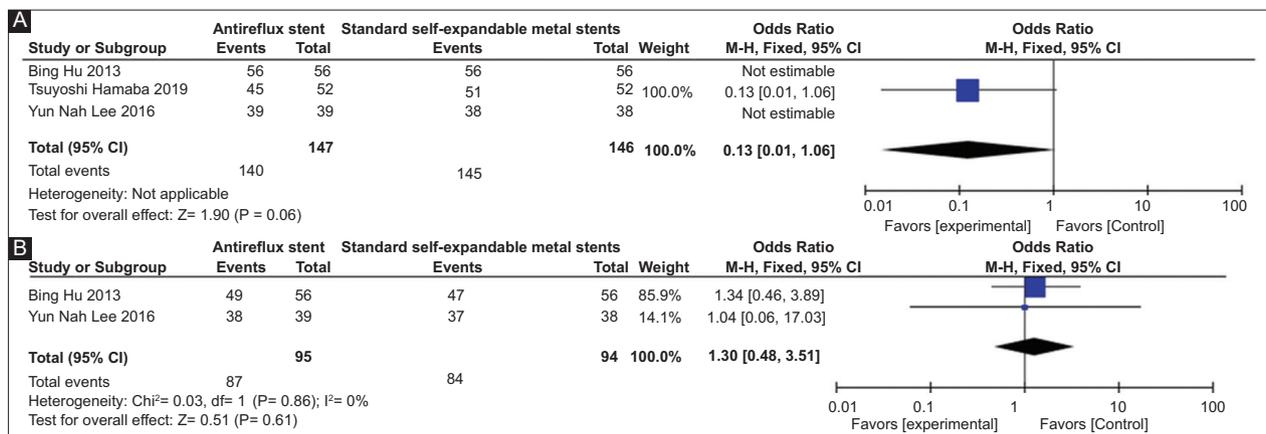

Figure 3 Forest plots representing odds ratios for (A) technical success, and (B) clinical success in the antireflux valve metal stent and the conventional self-expandable metal stent groups
M-H, Mantel-Haenszel; CI, confidence interval

Table 2 Frequency of adverse events and stent dysfunction in groups that received antireflux valve and conventional self-expandable metal stents

Adverse events	Antireflux stent (N=140)	Self-expandable metal stent (N=145)
Pancreatitis	8 (5.7%)	13 (8.9%)
Cholangitis	12 (8.6%)	25 (17.2%)
Cholecystitis	5 (3.6%)	4 (2.7%)
Bleeding	2 (1.4%)	1 (0.7%)
Liver abscess	2 (1.4%)	1 (0.7%)
Abscess around the bile duct	1 (0.7%)	0 (0%)

Data are frequency (percentage)

Table 3 Frequency of stent dysfunction events in groups that received antireflux valve and conventional self-expandable metal stents

| Stent dysfunction	Antireflux stent (N=136)	Self-expandable metal stent (N=144)
Tumor ingrowth	5 (3.7%)	17 (11.8%)
Tumor overgrowth	1 (0.7%)	9 (6.2%)
Sludge occlusion	12 (8.8%)	14 (9.7%)
Food occlusion	0 (0%)	1 (0.7%)
Stent migration	22 (16.2%)	10 (7%)
Valve dysfunction	2 (1.5%)	0 (0%)
Hemobilia	1 (0.7%)	1 (0.7%)
Unknown causes	7 (5.1%)	10 (7%)

Data are frequency (percentage)

data of the included studies that patients who received ARVMS developed markedly fewer cholangitis events than those who received SEMS. This finding is probably due to the antireflux valve. However, Hamada *et al* reported that the antireflux valve was not durable enough to prevent the duodenobiliary reflux after a long follow up [8]. However, one aspect that must be noted is the different shapes and lengths of valves used in the 3 available studies: nipple-shaped, funnel-shaped and windsock-shaped.

Another interesting finding in our study was the lower risk of stent occlusion in ARVMS compared with SEMS. This may be because: (i) the large lumen of SEMS may predispose to reflux and accumulation of enteric contents; and (ii) uncovered stents, such as those used in the study by Hu *et al*, may suffer from tumor ingrowth through their mesh openings [13-15]. The initial event in stent occlusion appears to be the formation of a biofilm from bacterial and host proteins adhering to the stent wall. Bacterial enzymes then act on bile components, forming biliary sludge (bacterial products, calcium bilirubinate, and calcium fatty acid soaps) [16,17]. This finding was again debated in the study by Hamada *et al* who showed no prolongation of patency benefit for ARVMS over SEMS, but acknowledged that the closed and longer valve structure in other studies may have been responsible for the potential benefit [8].

The greater stent migration rate in the ARVMS group in the current study is worthy of attention. The most common cause of stent dysfunction in the included studies was stent migration, a major cause of recurrent biliary obstruction. It may occur as a result of increased bile outflow pressure on the antireflux valve, or because the attachment of the antireflux valve at the duodenal end may prevent full expansion. Notably, Hamada *et al* indicated that chemotherapy may play
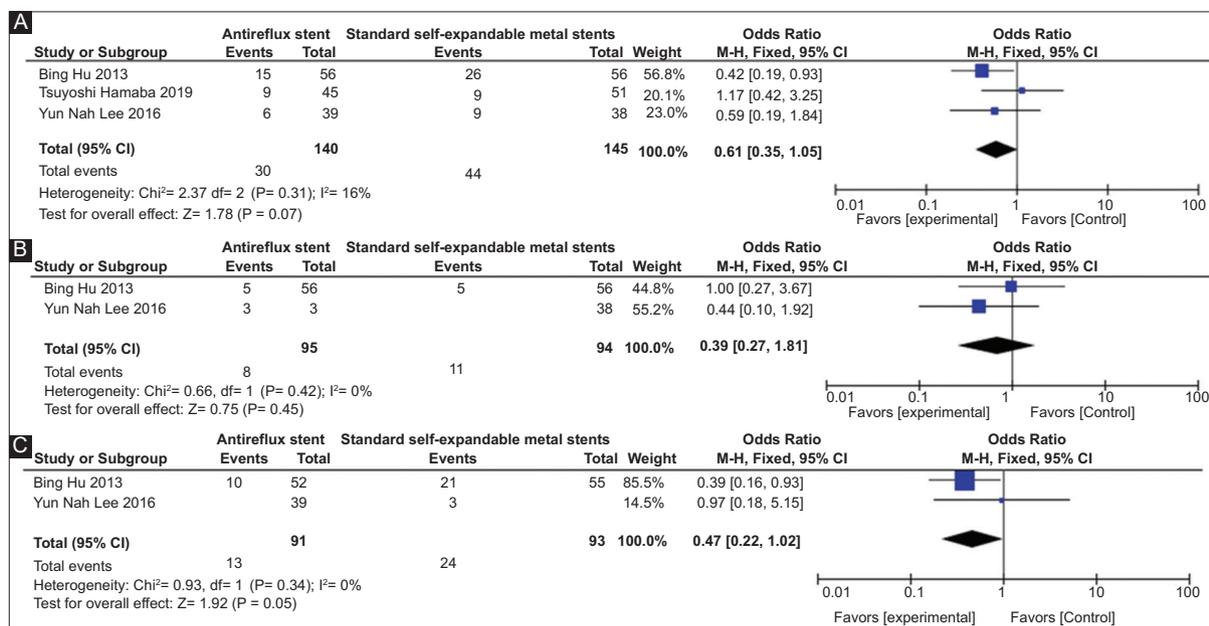
Figure 4 Forest plots representing odds ratios for (A) all adverse events, (B) early adverse events, and (C) late adverse events in the antireflux valve and the conventional self-expandable metal stent groups
M-H, Mantel-Haenszel; CI, confidence interval
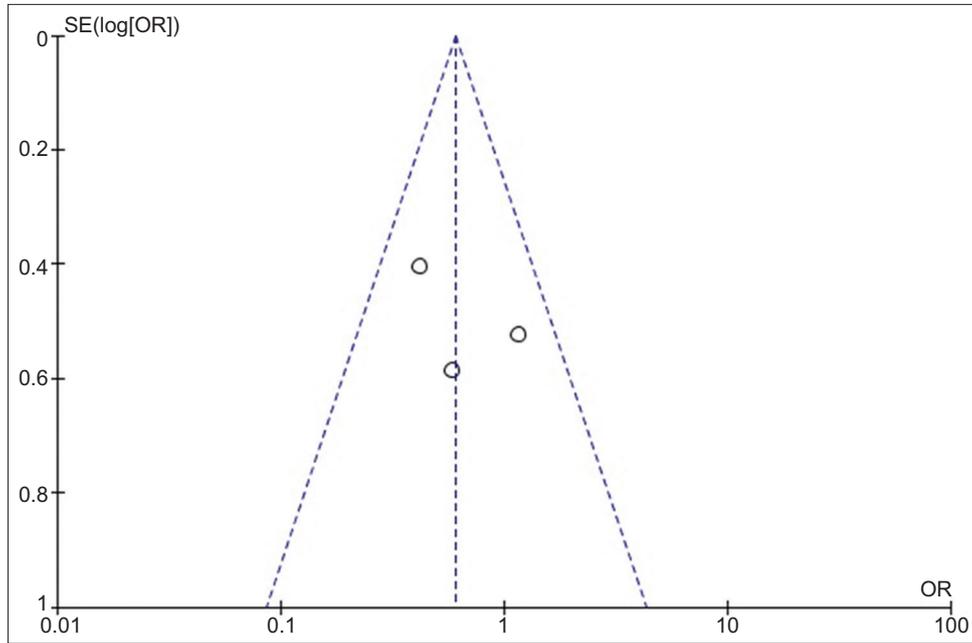
Figure 5 Funnel plot for the identification of publication bias for adverse events
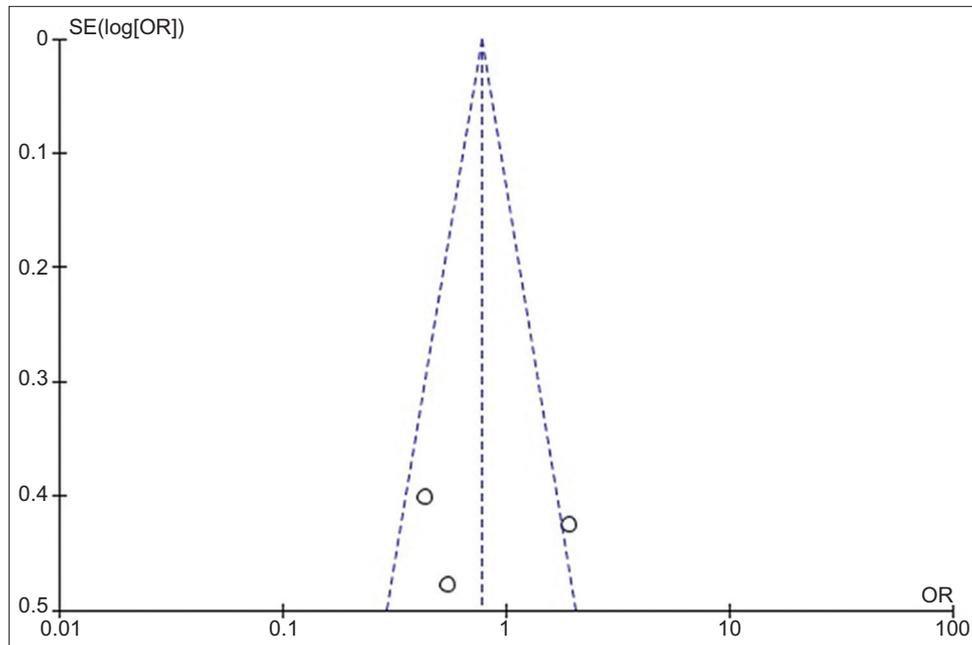*SE, standard error; OR, odds ratio*
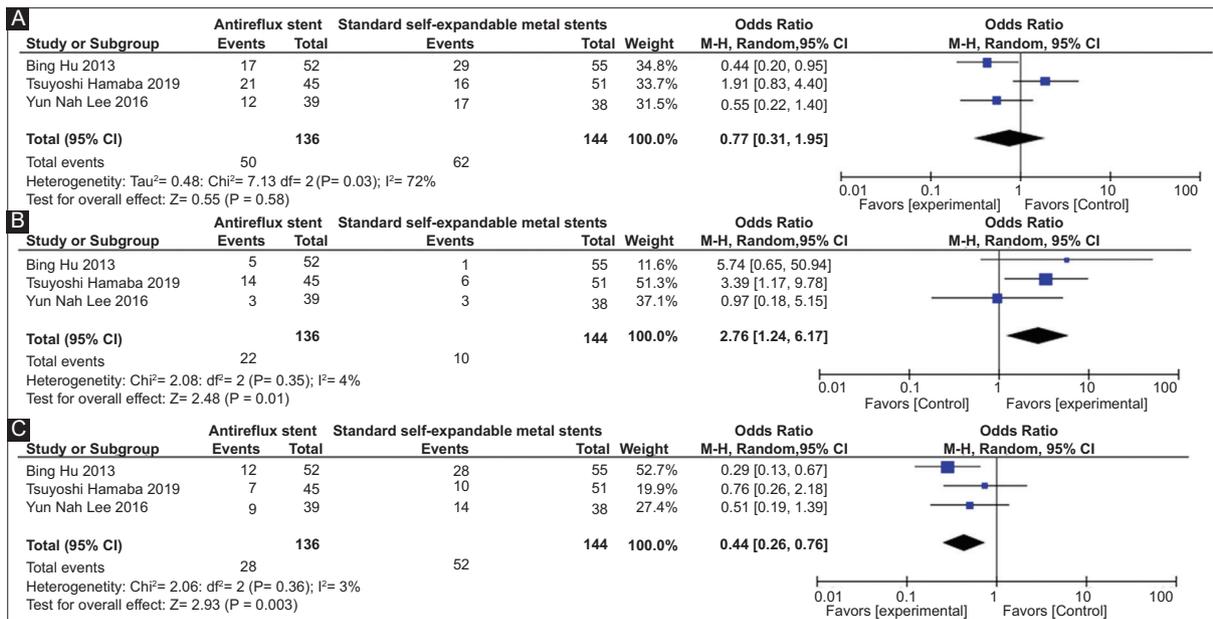
Figure 6 Forest plots representing odds ratios for (A) overall stent dysfunction, (B) stent migration, and (C) stent occlusion in the antireflux valve and the conventional self-expandable metal stent groups
M-H, Mantel-Haenszel; CI, confidence interval

a role in stent migration, as the between-group difference in stent migration was more pronounced in patients receiving chemotherapy [8,18]. Anti-migration properties, such as flared ends or low axial force, might overcome this drawback [19,20].

Although not analyzed in the present study, Hu *et al* reported that, despite the better stent patency, ARVMS was not associated with a higher rate of patient survival. They iterated that the prognosis of these patients is more dependent on the tumor prognosis and therapy rather than the stent type [7]. However, their finding needs further confirmation in larger clinical trials to complete the picture on the ARVMS-SEMS comparison.

This study had some limitations. First, the low numbers of studies included and patients enrolled limit the generalizability and external validity of our findings. Furthermore, 2 of these were single-center studies. Second, owing to the nature of the

Figure 7 Funnel plot for the identification of publication bias for stent dysfunction
SE, standard error; OR, odds ratio

Summary Box

What is already known:

- The conventional self-expandable metal stent (SEMS) has been the gold standard for palliative treatment of non-resectable distal malignant biliary obstruction
- The antireflux valve metal stent (ARVMS) has been introduced as an alternative to SEMS to reduce the risk of cholangitis with SEMS
- Debate continues regarding the superiority of either of the 2 stent types

What the new findings are:

- No significant difference was found between ARVMS and SEMS regarding technical and clinical success rates
- Overall adverse events were comparable between ARVMS and SEMS; however, ARVMS had a lower risk of stent occlusion and a higher risk of migration

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procedure, patients, physicians, and outcome assessors were often not blinded to the treatment arms. Third, the limited follow-up duration in all included studies precluded any long-term assessment of the durability of these stents. Fourth, different types of stents were used in the included studies: in the conventional SEMS arm, 2 studies [8,9] used covered

SEMS, while the third study used uncovered SEMS [7]; in the ARVMS arm, 1 study used fully covered stents [8], while the other 2 used partially covered stents [7,9]. The difference in the type of stents could affect some reported outcomes, such as stent migration. The limited number of studies included in our meta-analysis made it impossible to perform a subanalysis based on the stent type to adjust for this difference. Further multicenter trials with longer follow-up periods are needed to establish the superiority of either stent type in patients with distal MBO.

In conclusion, our study showed no significant difference between ARVMS and SEMS regarding technical and clinical success rates. Overall adverse events were comparable between the 2 arms; however, ARVMS was associated with a lower risk of stent occlusion and a higher risk of migration. Larger RCTs are required to verify the benefit of ARVMS in distal MBO patients.

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