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Covered and Uncovered Self-Expandable Metallic Stents in the Treatment of Malignant Biliary Obstruction

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Abstract

Context: Self-expandable metal stents (SEMSs) are commonly used in the treatment of malignant biliary obstruction. We performed a meta-analysis to compare the efficacy of covered self-expandable metallic stents (CSEMSs) and uncovered self-expandable metallic stents (UCSEMSs) for patients with malignant distal biliary obstruction.

Methods: A comprehensive search was conducted using PubMed, Embase, Cochrane, and CNKI databases from 2010 to 2019. All randomized controlled trials, which compared the use of the CSEMSs and UCSEMSs for the treatment of malignant distal biliary obstruction were included in this study.

Results: This meta-analysis included 1,539 patients enrolled in 13 trials. There was no difference between the two groups in terms of patients' survival (hazard ratio (HR) 0.96, 95% confidence interval (CI): 0.87 - 1.07; $I^2 = 32.6\%$), stent patency (HR 0.92, 95% CI: 0.69 - 1.22; $I^2 = 56.3\%$), and the overall complication rate (relative risks (RR) 1.35, 95% CI: 0.82 - 2.23; $I^2 = 0\%$). In particular, the CSEMSs group presented a lower rate of tumor ingrowth (RR 0.30, 95% CI: 0.15 - 0.57; $I^2 = 58.5\%$) than the UCSEMSs group. However, the CSEMSs group exhibited a higher rate of tumor overgrowth (RR 1.63, 95% CI: 1.00 - 2.66; $I^2 = 0\%$), sludge formation (RR 2.28, 95% CI: 1.36 - 3.82; $I^2 = 0\%$), and migration (RR 5.14, 95% CI: 1.90 - 13.88; $I^2 = 0\%$).

Conclusions: Our meta-analysis indicated that there was no significant difference between the two stents, and each one had its advantages and disadvantages.

Keywords: Covered Metallic Stent, Uncovered Metallic Stent, Self-Expandable Metallic Stent (SEMS), Malignant Biliary Obstruction, Biliary Stent

1. Context

Malignant biliary obstruction is usually difficult to be diagnosed at onset and development that occurs rapidly, many cases of which cannot utilize surgical methods for removal due to its advanced age, tumor location, or other systematic diseases (1). Therefore, stent placement has been considered a primary palliative treatment for unresectable distal malignant biliary obstruction (2, 3) since Soehendra and Reynders-Frederix (4) first proposed the biliary drainage in 1980. For patients with malignant distal biliary obstruction, inserting stents through the liver or endoscope is an effective way to achieve palliative treatment, relieve biliary obstruction, and improve quality of life. Plastic stents and metal stents are widely used in clinical settings (5, 6); however, the diameter of plastic stents is small and easily blocked, which results in the need to replace the stent repeatedly (7). Owing to the expansion function of the self-expanding metal stents (SEMSs), this stent has a larger diameter and a longer opening time compared with plastic stents (8). Thus, it can effectively reduce the incidence of repeated insertions. However, there are still some dysfunctions in the use of SEMSs such as sludge formation, tumor ingrowth, tumor overgrowth, and migration that also affect the patency of SEMSs (SEMSs include CSEMSs and UCEMSs). Currently, there are several types of stents to choose from, such as plastic stents, covered self-expandable metallic stents (CSEMSs), uncovered self-expandable metallic stents (UCSEMSs), and bioabsorbable stents (5). Self-expandable metallic stents are identified as the most cost-effective biliary stents in the treatment of un-

resectable malignant biliary obstruction (9, 10). However, the topic on which optimal metallic stents to be used is still controversial. The biggest disadvantage of CSEMSs is displacement, whereas UCSEMSs could avoid displacement issues because of its reticular structure and self-expansion system, which allows the stents to be embedded in the biliary wall. Although UCSEMSs may cause stent occlusion along with the growth of tumors. The conclusions of many studies in this field are inconsistent in terms of patency time, patient survival, and the incidence of adverse events, while many randomized studies show that the patency time of CSEMs is significantly higher than that of UCSEMSs (11-15).

Nevertheless, several studies suggested that there was no significant difference between the two stents (16-21). A recent meta-analysis concluded that the incidence of adverse events in the CSEMSs was lower and was a better choice (22). While some researchers also contended that there was no difference in stent patency, patient survival, and the complications between the CSEMSs and UCSEMs groups (23). Therefore, we conducted this meta-analysis to reevaluate the efficacy of CSEMSs and UCSEMSs in treating malignant biliary obstruction.

2. Methods

2.1. Literature Retrieval

The retrieval of literature was obtained from the PubMed database, Embase full-text database, Cochrane library database, CNKI, and all the clinical literature on covered and uncovered metallic stents in the treatment of malignant biliary obstruction that was published in January 2001-April 2019 from the CNKI database. The English index words are “stent”, “randomized controlled trial (Publication Type)”, “cholestasis (MeSH)” and the Chinese index words are “covered”, “metallic stent”, “biliary obstruction”.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for the literature: (1) randomized controlled trials; (2) the clinical control studies of covered and uncovered metallic stents (including partially and fully covered); (3) patients with malignant biliary obstruction; (4) the results of the studies include at least the patency time of stents, survival time, dysfunction of stents or complications. The exclusion criteria for the literature: (1) a lack of corresponding literature on observation data, (2) using other types of stents, like plastic stents.

2.3. Data Extraction

Two independent reviewers completed the work in extracting information from the selected literature independently and according to the inclusion criteria, exclusion criteria, and the keywords. The following information was extracted from each study: first author, year of publication, country of origin, the number of patients with covered and uncovered stents, percent female, mean age, covering material of CSEMSs, patient survival days, and outcome data. Any disagreements were resolved by a third author if the two reviewers could not reach a consensus.

2.4. Statistical Methods

Stata 12.0 software was used for statistical analysis. The hazard ratio (HR) and 95% confidence intervals (CIs) of the patency time of the stents and survival time in the Cox regression model were respectively extracted, and the combined HR and 95% CIs were calculated by metan command. Relative risk (RR) and 95% CIs were utilized to analyze the dichotomous variables. We selected the merger model, according to the consistency test results. The fixed-effect model was applied when there was no significant heterogeneity among the studies, whereas the random effect model was used. $P < 0.05$ was considered statistically significant. I^2 was used to detect statistical heterogeneity, which indicated heterogeneity among studies when a $P < 0.1$ value was present, and the heterogeneity was high when $I^2 > 50\%$. When $I^2 > 25\%$, a sensitivity analysis was performed.

2.4.1. Subgroup Analysis

We conducted a subgroup analysis according to the type of complications. The statistical analysis was performed when the number of the same complication was ≥ 5.

3. Results

3.1. Screening of the Samples

After the initial screening, 14 clinical trials (11-21, 24-26) met the inclusion criteria for the first time, among which one study (26) was excluded due to the lack of data from the corresponding observations. Finally, 13 randomized controlled studies matched the inclusion criteria and were released from 2004 to 2018 (Figure 1). The basic characteristics of these 13 studies are shown in Table 1. A total of 1539 patients were included: 763 in the CSEMS group of covered stents and 776 of uncovered stents. The sample size for each study ranged from 20 to 200 participants, unequally.

Table 1. Baseline Characteristics of Studies[a]

Study	Country	Group	Number	M/F	Mean Age, y	Approach	Covering Material	Patient Survival, d
Isayama-et al. (11)	Japan	CSEMS	57	35/22	70.5 (48 - 88)	ERCP	Polyurethane	255
		UCSEMS	55	31/24	70.4 (40 - 89)			237
Kullman et al. (16)	Sweden	CSEMS	200	88/112	79.0 (30 - 100)	ERCP	Polycarbonate polyurethane	116
		UCSEMS	200	91/109	76.0 (51 - 95)			174
Krodidis et al. (13)	Greece/Italy	CSEMS	30	20/10	66.5 (52 - 78)	PTC	ePTFE/FEP	243.5
		UCSEMS	30	16/14	63.7 (46 - 73)			180.5
Telford et al. (17)	America/Canada	CSEMS	61	31/49	65 ± 13	ERCP	Permalume	227
		UCSEMS	68	30/56	66 ± 14			239
Krokidis et al. (12)	England/Italy	CSEMS	40	17/23	63.5 ± 9.8	PTC	ePTFE/FEP	248
		UCSEMS	40	36/4	65.0 ± 8.8			203.3
UNG et al. (25)	Sweden	CSEMS	34	18/16	77.0 (54 - 88)	ERCP	Silicone	154
		UCSEMS	34	9/25	79.0 (54 - 92)			157
Kitano et al. (14)	Japan	CSEMS	60	25/35	70.6 ± 10.7		Silicone	285
		UCSEMS	60	29/31	68.7 ± 8.9			223
Hu et al. (15)	China	CSEMS	56	31/25	65.6 ± 14.5	ERCP	Silicone	240
		UCSEMS	56	35/21	66.9 ± 12.2			270
Lee et al. (18)	Korea	CSEMS	20	9/11	62.1 ± 8.6	PTC	Polytetrafluoroethylene	350
		UCSEMS	20	9/11	63.2 ± 11.7			359
Walter et al. (24)	Netherlands	CSEMS	54	NA	NA	ERCP/PTC	Permalume	NA
		UCSEMS	60	NA	NA			NA
Yang et al. (19)	South Korea	CSEMS	51	34/17	68.7 ± 11.2	ERCP	Silicone	219
		UCSEMS	52	30/22	68.0 ± 11.3			245
Lee et al. (20)	Korea	CSEMS	22	16/6	69.0 ± 13.2	ERCP/PTC	Polytetrafluoroethylene	245.7 ± 195.4
Conio et al. (21)	Italy	UCSEMS	21	13/8	65.5 ± 9.2	ERCP	Polytetrafluoroethylene	285.5 ± 243.7
		CSEMS	78	39/39	77.5 (45 - 98)			134.0 (97.8 - 170.2)
		UCSEMS	80	37/43	80 (49 - 101)			112.0 (65.9 - 158.1)

Abbreviations: CSEMSs, covered self-expandable metal stents; ePTFE/FEP, polytetrafluoroethylene, and fluorinated ethylene propylene; ERCP, endoscopic retrograde cholangiopancreatograhy; NA, data not available; PTC, percutaneous transhepatic cholangiography; USEMSs, uncovered self-expandable metal stents;.
[a]Values are expressed as mean ± SD or mean (IQR).

3.2. Patient Survival

The patient's survival time included a total of 12 research reports. The patients' overall survival showed no significant difference between the CSEMSs and the UCSEMSs (HR 0.96; 95% CI: 0.87 - 1.07; I^2 = 32.6%) and a fixed-effect model was used (Figure 2A). The heterogeneity was slightly high, so we performed a sensitivity analysis (Figure 2B).

3.3. Stent Patency

Twelve studies reported stent patency. We did not detect a significant difference between the two groups (HR 0.92, 95% CI: 0.69 - 1.22, I^2 = 56.3%) (Figure 3A). The sensitivity analysis of the stent patency was performed due to high heterogeneity (Figure 3B), and this meta-analysis was estimated using a random-effects model.

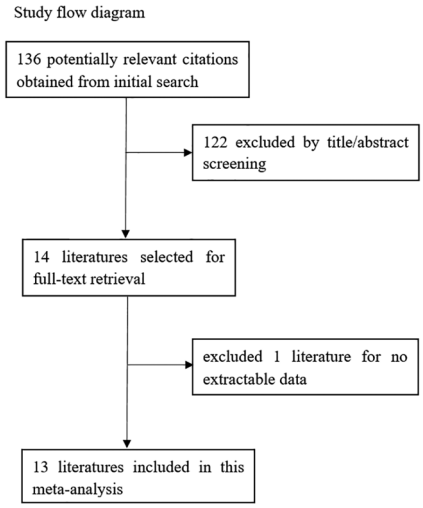

Figure 1. Study flow diagram

3.4. Tumor Ingrowth

This meta-analysis totally included 12 trails. Compared to the rates of tumor in growth in the UCSEMSs group, the rates of tumor ingrowth were significantly lower than in the CSEMSs group (RR 0.30, 95% CI: 0.15 - 0.57, I^2 = 58.5%) (Figure 4A). The heterogeneity among the studies was fairly high, and data were analyzed using a random-effects model. Likewise, we performed a sensitivity analysis (Figure 4B).

3.5. Tumor Overgrowth

Twelve studies were included, this meta-analysis suggested that the rates of tumor ingrowth were significantly higher in the CSEMSs group compared with the UCSEMSs group (RR 1.63, 95% CI: 1.00 - 2.66, I^2 = 0%) (Figure 5). The heterogeneity was low among all studies, so we used a fixed-effect model.

3.6. Sludge Formation

Ten studies reported data on sludge formation. The pooled results showed that the sludge formation was higher in the CSEMs group when compared to the USCEMs group (RR 2.28, 95% CI: 1.36 - 3.82, I^2 = 0%) (Figure 6A). The heterogeneity was low among all studies, so we used a fixed-effect model.

3.7. Stent Migration

The stent migration was reported in eight trials. Our research suggested that the stent migration of the CSEMSs group was significantly greater than in the UCSEMSs group (RR 5.14, 95% CI: 1.90 - 13.88, I^2 = 0%) (Figure 6B). The heterogeneity was low among all studies, so we used a fixed-effect model.

3.8. Complications

The results showed that there was no statistical difference in the overall complication rates between the two groups (RR 1.35, 95% CI: 0.82 - 2.23, I^2 = 0%) (Figure 6C). The subgroup analysis suggested that there was no difference between the two groups in cholangitis (RR 1.28, 95% CI: 0.69 - 2.38: I^2 = 0%) and pancreatitis (RR 1.50, 95% CI: 0.64 - 3.55, I^2 = 0%). The heterogeneity was low among all studies, so we used a fixed-effect model.

4. Discussion

Changes in the combined results were observed using changing the inclusion criteria, excluding low-quality studies, and using different statistical methods. If excluding a study had a significant impact on the combined results, the study was considered to be sensitive to this study, otherwise, it was not sensitive. If the studies were from the same database, there was no heterogeneity. Therefore, sensitivity analysis was an important index to measure the quality and heterogeneity of literature. Owing to the high heterogeneity of the patients' overall survival (I^2 = 32.6%), stent patency (I^2 = 56.3%), and tumor ingrowth (I^2 = 58.5%) that was the reason why the sensitivity analyses were performed. The result of these sensitivity analyses suggested that the confidence interval of this research was basically within the confidence interval of the total effective value in which the results were stable.

These two manners mentioned in this study are commonly used to prepare endoscopic retrograde cholangiopancreatography (ERCP) surgery, insert duodenoscopy into the descending part of the patient's duodenum, and use an incision combined with a J-head guide through the duodenum. The bile duct was intubated by wire, and biliary angiography was performed after the catheter was successfully placed. Estimating the location and length of biliary obstruction, indwelling guide wire decided whether to perform biliary dilatation according to biliary obstruction and balloon dilatation if necessary.

All the selected studies were randomized controlled clinical studies and included detailed clinical data such as the patient's survival, stent patency, dysfunctions, and complications. The follow-up endpoint of these studies

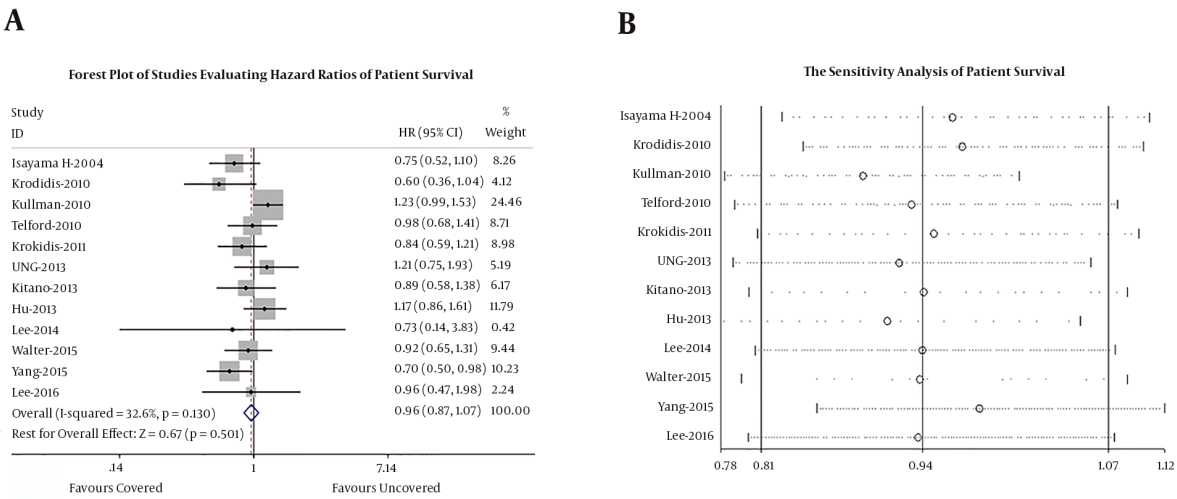

Figure 2. A, Forest plot of studies, evaluating hazards ratios of patients' survival ; B, the sensitivity analysis of patients' survival.

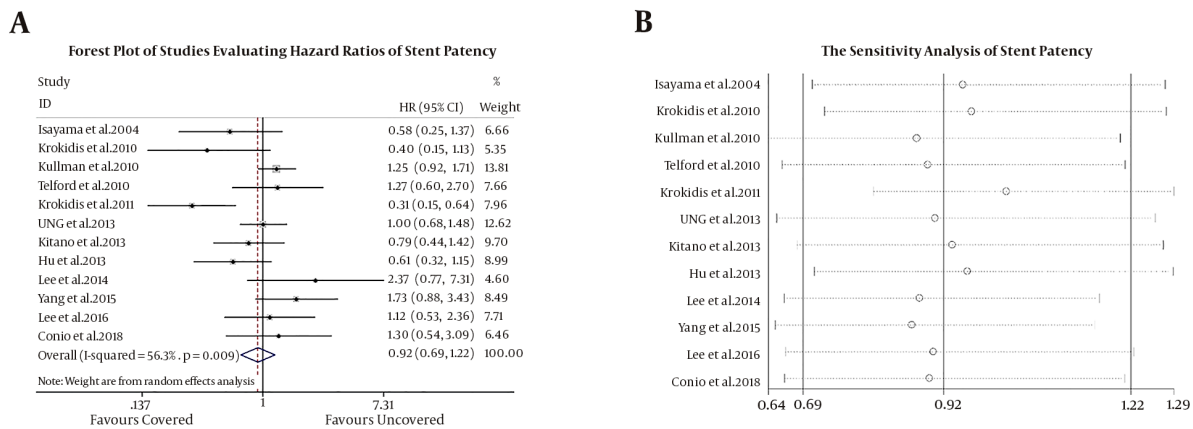

Figure 3. A, Forest plot of studies, evaluating hazards ratios of sent patency; B, the sensitivity analysis of sent patency.

was either the last follow-up or patient death. This meta-analysis showed that there was no difference in the patients' survival between the use of CSEMSs and UCSEMSs. The stent patency and the overall complications were also not statistically different between the two groups. The patency time of the stent is affected by various factors, such as the structural characteristics and the type of covering materials, etc. (27). There were various types of covering materials included in this study, such as polyurethane, polytetrafluoroethylene, and fluorinated ethylene propylene polyurethane, permalume, silicone, and polytetrafluoroethylene. It is well known that the main factors affecting the stent patency are tumor ingrowth, tumor overgrowth, sludge formation, and migration. The scaffold (Wallstent endoscopic biliary endoprosthesis with permalume covering) consisted of a biomedical superheat resistant alloy monofilament that is interwoven into a pipe network structure and coated with a silicone polymer (Permalume coating). The covered stent had uncoated portions approximately 5 mm in length at each end. Uncovered self-expandable metallic stents did not have the covered stent. Our meta-analysis suggested that the CSEMSs group had a lower rate of tumor ingrowth. However, the CSEMSs group exhibited a higher rate of tumor overgrowth, sludge formation, and migration than that of the UCSEMSs group. The results indicated that the covering material can re-

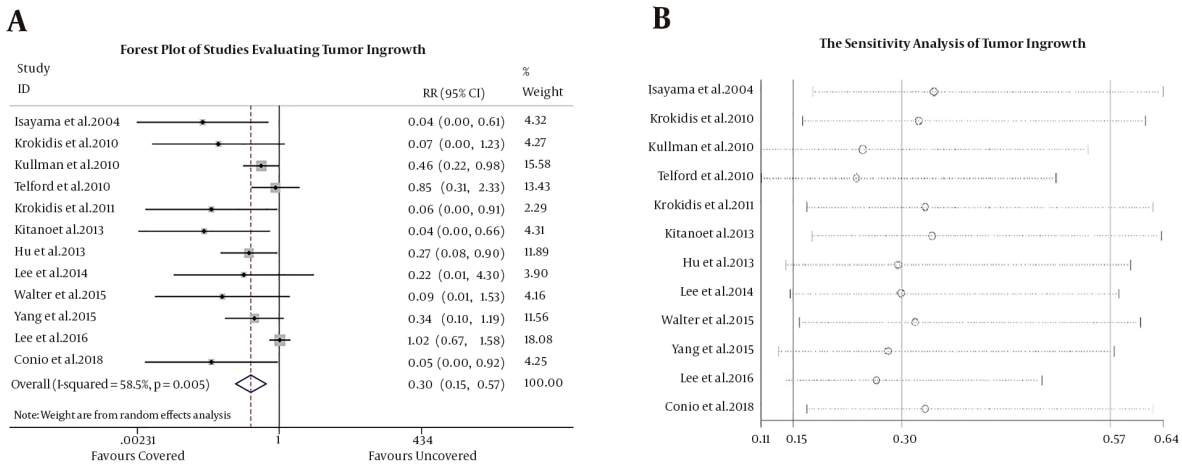

Figure 4. A, Forest plot of studies, evaluating tumor ingrowth; B, the sensitivity analysis of tumor ingrowth.

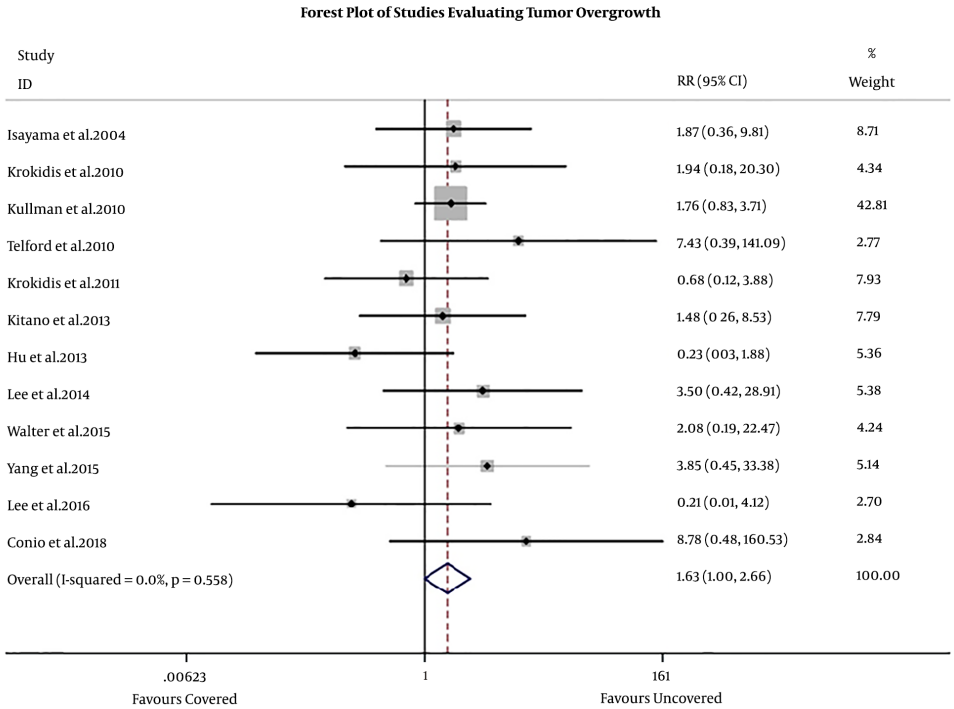

Figure 5. Forest plot of studies evaluating tumor overgrowth

duce the ingrowth of tumors and also prevent the stent from embedding and subsequent stent anchoring at the same time. The final comprehensive factors that influence stent patency, such as the ingrowth rate of tumors, stent displacement, tumor overgrowth, and other factors offset with each other. Our results indicated that the covered stents had a higher rate of sludge formation than the uncovered stents. This might be related to the coatings of

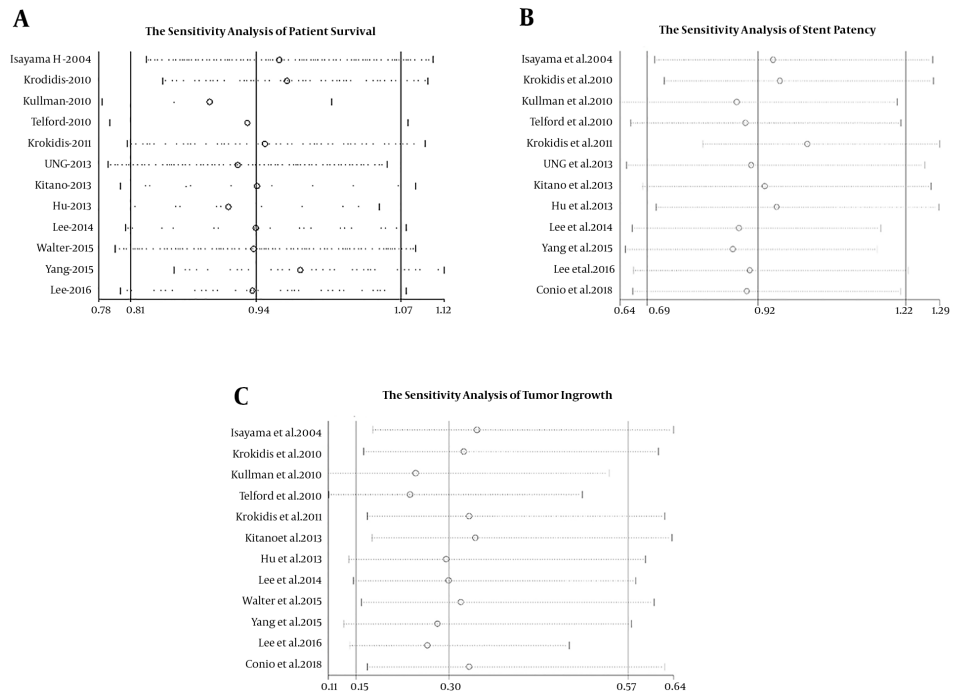

Figure 6. A, Forest plot of studies, evaluating sludge formation; B, forest plot of studies, evaluating stent migration; C, forest plot of studies, evaluating complication.

the covering material, which provides a biofilm surface on which bacteria can cling, similar to plastic scaffolds. We analyzed the overall complications and found that there was no significant statistical difference concerning cholangitis and pancreatitis. Although there was no difference in the incidence of complications, the incidence of acute pancreatitis and cholecystitis were increased when the CSEMSs were placed on the cystic or pancreatic duct. The reason why this would happen is that the CSEMSs may block the cystic duct or pancreatic duct (28). Several studies suggested that we should take measures to reduce the incidence of complications and CSEMSs dysfunction. For patients with unresectable malignant distal biliary obstruction, both endoscopic and percutaneous could help to relieve jaundice. Endoscopic stent placement is considered the better choice; endoscopic biliary stent placement could reduce the incidence of complications and improve the quality of life (29). Percutaneous transhepatic cholangiography is also a good choice, while endoscopic retrograde cholangiopancreatography cannot be performed. In this meta-analysis, the original data on how many cases were treated with percutaneous biliary stents were not available, and the overall incidence of complications was provided without distinction. Therefore, clinicians could choose the appropriate approach based on the type of tumor and the extent of the biliary obstruction.

5. Conclusions

Our meta-analysis indicated that there was no significant difference in patient survival, stent patency, and the overall complications between CSEMSs and UCSEMSs stents. However, according to stent dysfunction, each type of stent has its advantages and disadvantages.

Footnotes

Authors' Contribution: Wen-Yan Qin and Lian-Biao Li did substantial contributions to the conception and design of the work, and draft the work. Wen-Yan Qin, Wen-Ping Peng, Jin-Zhen Li, Ming-Ming Zhang, Bo Lao, Jie-Ming Hong, and Lian-Biao Li did the acquisition, analysis, and interpretation of data for the work. Wen-Ping Peng, Jin-Zhen Li, Ming-Ming Zhang, Bo Lao, Jie-Ming Hong, and Lian-Biao Li did revising it critically for important intellectual content. Wen-Ping Peng, Jin-Zhen Li, Ming-Ming Zhang, Bo Lao, Jie-Ming Hong, and Lian-Biao Li did final approval of the version to be published. Wen-Ping Peng, Jin-Zhen Li, Ming-Ming

Zhang, Bo Lao, Jie-Ming Hong, and Lian-Biao Li did agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Clinical Trial Registration Code: n/a

Conflict of Interests: All authors declare that they have no conflict of interest to disclose.

Ethical Approval: This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Second Hospital of Yinzhou District.

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