Thieme

Covered vs. uncovered self-expandable metal stents for malignant distal biliary strictures: a systematic review and meta-analysis

Authors
Alberto Tringali[1], Cesare Hassan[2], Matteo Rota[3], Marta Rossi[3], Massimiliano Mutignani[1], Lars Aabakken[4]

Institutions
1 Endoscopy Unit, Niguarda Hospital, Milan, Italy
2 Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy
3 Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
4 Endoscopy, Oslo University Hospital – Rikshospitalet, Oslo, Norway

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Corresponding author
Alberto Tringali, MD, Department of Surgery, Endoscopy Unit, Niguarda Hospital, Piazza Ospedale Maggiore 3, 21062 Milan, Italy
Fax: +39-02-64442911
albtri10@gmail.com
alberto.tringali@ospedaleniguarda.it

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ABSTRACT

Background Self-expandable metal stents (SEMS) are used for palliation of distal malignant biliary strictures, but the role of covered SEMS is less clear. We performed an up-to-date meta-analysis to compare the performance of covered and uncovered SEMS in patients with unresectable distal malignant biliary strictures.

Methods A computerized medical search was performed using MEDLINE, EMBASE, and the Cochrane Library between 2000 and December 2016 to identify all randomized trials that compared covered with uncovered SEMS in patients with distal malignant biliary strictures. Primary outcomes were stent failure and patient mortality; secondary outcomes were stent dysfunction and adverse events. Pooled estimates were computed using the random effects model.

Results Overall, 11 RCTs involving 1272 patients were included. The primary outcomes of stent failure and patient mortality did not differ significantly between covered and uncovered SEMS (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.40–1.17; HR 0.89, 95%CI 0.76–1.05, respectively). However, stent migration and sludge formation were much more common with covered SEMS (odds ratio [OR] 5.11, 95%CI 1.84–14.17; OR 2.46, 95%CI 1.37–4.43). The use of covered SEMS was associated with a lower rate of tumor ingrowth (OR 0.21, 95%CI 0.09–0.50) but a higher rate of tumor overgrowth (OR 2.00, 95%CI 1.15–3.48) compared with uncovered stents. The rates of procedure-related adverse events were similar in both groups.

Conclusion There was a risk reduction of about 32% for both stent failure and patient mortality with covered SEMS but this difference was not significant. Migration and sludge rates were higher with covered SEMS, whereas tumor ingrowth was more likely with uncovered SEMS. The data show no added benefit of covered SEMS; further stent evolution is desirable.

Introduction

Distal biliary malignant strictures often present at an unresectable stage, with management restricted to palliation. Endoscopic treatment offers biliary decompression and improved quality of life [1]. Plastic and metal stents have been used to decompress biliary strictures with varying results. A previous meta-analysis showed superiority of self-expandable metal stents (SEMS) over plastic stents, with a reduced risk of recurrent biliary strictures and less need for repeated endoscopy [2]. SEMS have also been associated with improved patency over plastic stents as early as 4 months after insertion [3]. However, uncovered SEMS had a high risk of stent occlusion, occurring 8 months after stent placement in up to 20%–50% of patients following tumor ingrowth through the metal mesh [4].

Covered SEMS may prolong stent patency but are more expensive and more prone to migration. The advantages of using covered over uncovered SEMS in patients with inoperable distal malignant biliary stricture remain uncertain. Although stents have been compared in previous meta-analyses, major methodological flaws prevent definitive conclusions [5–7]. Moreover, no previous systematic review or meta-analysis has assessed stent survival according to the new Tokyo criteria or considered a recently published randomized controlled trial (RCT) [8].

We have conducted the first analysis of primary studies included in a meta-analysis on the basis of the type of covering membrane used and the stent characteristics, as these might have a role in the performance of covered SEMS. Our aim was to perform an up-to-date systematic review and meta-analysis of RCTs to assess differences in performance between covered and uncovered SEMS for the treatment of distal malignant biliary strictures according to the Tokyo criteria.

Methods

The reporting method of this systematic review is based on the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [9]. Methods of analysis and inclusion criteria were specified in advance and documented in a protocol according to the Cochrane guidelines [10].

Search strategy

A computerized medical literature search was performed by using MEDLINE, Embase, Cochrane Library, and the ISI Web of Knowledge between January 2000 and December 2016 to identify available RCTs that compared covered and uncovered SEMS for the treatment of distal malignant biliary strictures. No language or publication status restrictions were imposed.

Eligibility criteria were as follows.

- Types of studies: RCTs comparing efficacy and safety of covered SEMS vs. uncovered SEMS.
- Types of participants: patients older than 18 years with malignant biliary strictures without previous stent placement.
- Types of intervention: endoscopic or percutaneous stent placement.
- Types of outcomes measures: stent and patient survival, cause of stent dysfunction, and adverse events.

Exclusion criteria were hilar tumor and nonrandomized studies.

The keywords "biliary tract disease," "biliary obstruction," "biliary stricture," "pancreas carcinoma," "cholangiocarcinoma," "randomized controlled trial," "stent," "endoprothesis," "metal stent," "covered SEMS," and "uncovered SEMS" were associated in different combinations using the Boolean terms AND/OR. Queries were limited to those involving human subjects. Handsearches of reference lists of relevant literature reviews were used to complement the computer searches. A search strategy is provided in **Supplementary Material 1** (available online). Each article was read and analyzed by at least two members of the research team (A.T. and L.A.), and eligibility assessment was performed independently in an unblinded standardized manner.

Data extraction

Two investigators (A.T. and L.A.) and two biostatisticians (M.R. and M.R.) extracted data from the eligible publications independently. The following data were retrieved and entered into a standardized database: first author, year and type of publication, country of origin, study setting, number of patients, age and sex of patients, stent type and covering material, length of follow-up, tumor type, method of stent insertion, qualitative data (allocation concealment, blinding, lost at follow-up), and primary and secondary outcome data. For primary outcomes, we extracted the hazard ratio (HR) with 95 % confidence interval (CI) when reported in the original publication, or we collected additional information in order to apply statistical methods to compute these values. For secondary outcomes, we extracted the number of patients and events in each arms.

Outcome measures

The primary outcome measures were stent failure and patient mortality, both defined from the time of stent deployment. The stent patency period was computed until primary stent obstruction or further intervention or death with a patent stent, according to the Tokyo criteria [11].

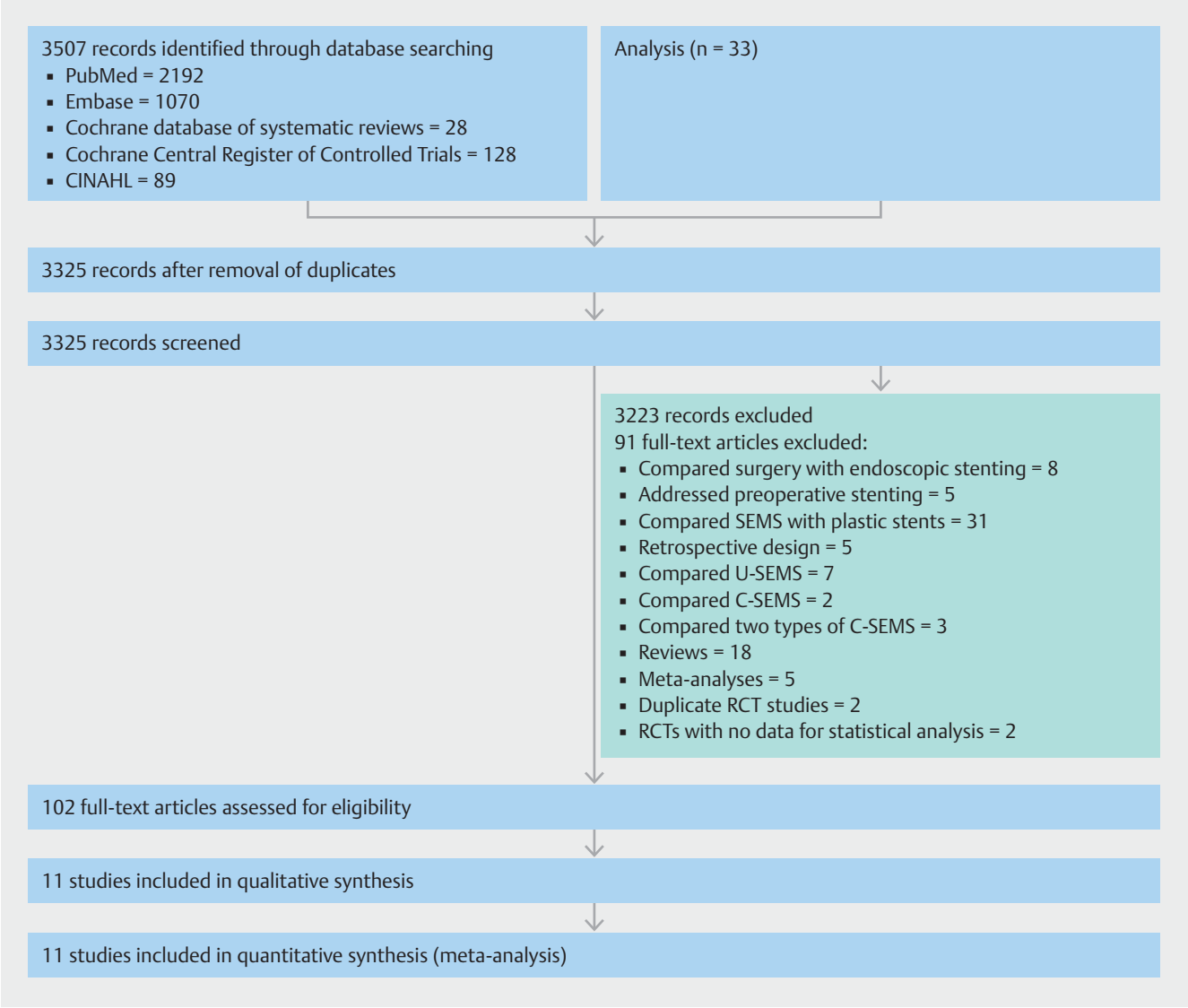
Secondary outcomes included stent migration, tumor ingrowth and overgrowth, and sludge as cause of stent dysfunction. Bleeding, pancreatitis, cholecystitis, perforation, and cholangitis were recorded as adverse events of the procedure.

Unfortunately, none of the RCTs reported cost-effectiveness analyses, so these data were not available for statistical analysis.

Statistical analysis

Statistical analyses were performed using the "meta" package under the R version 3.1.2 (R Foundation for statistical computing, Vienna, Austria). The two primary outcomes – stent failure and patient mortality – were evaluated in terms of HR and corresponding 95 %CI. When studies did not report the HR, we derived its estimate and the corresponding 95 %CI using available additional information, including log-rank *P* values, the given numbers of events for each arm, or Kaplan – Meier curves, applying widely used methods for incorporating summary time-to-event data into meta-analysis [12]. Briefly, when the original publications reported the *P* value derived from the log-rank test for the comparison of the two Kaplan – Meier curves for covered and uncovered SEMS, we derived the observed minus expected count and its variance. Otherwise, if the exact *P* value derived from the log-rank test for the comparison of the two Kaplan – Meier curves for covered and uncovered SEMS was not reported, the observed minus expected count and its variance were derived from the two Kaplan – Meier curves for covered and uncovered SEMS. Finally, the HRs and their corresponding 95 %CIs were derived by assessing the exponential ratio between the observed minus expected count and its variance [12].

Secondary outcomes were evaluated in terms of crude odds ratios (ORs) and their 95 %CIs.



▶ **Fig. 1** Flow diagram according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). SEMS, self-expandable metal stents; C, covered; U, uncovered; RCT, randomized controlled trial.

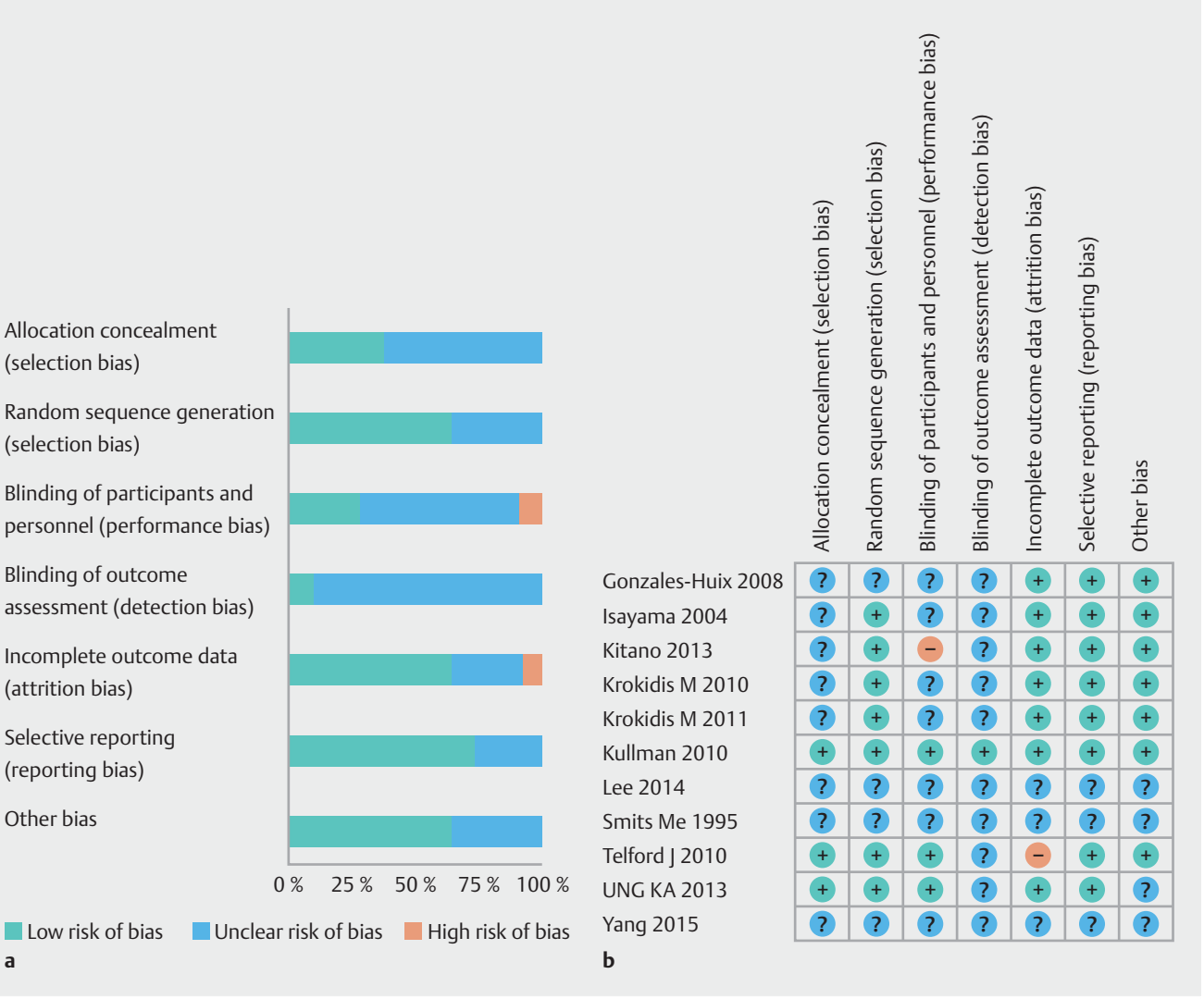
In order to assess heterogeneity, the Q test based on the chi-squared statistics was used to measure data dispersion and the I^2 statistic was used to quantify between-study heterogeneity [13]. As between-study heterogeneity was anticipated, the pooled estimates were computed using the random effect model and the Der Simonian and Laird method based on the moment estimator [14]. When no between-study heterogeneity was detected, the final pooled estimates corresponded to those derived from the fixed effect model.

In order to assess the influence that each individual study had on the final pooled estimates, we performed a sensitivity analysis by omitting one study at a time for each primary and secondary outcome.

For secondary outcomes, we carried out subgroup analyses comparing 1) partially covered SEMS and 2) fully covered SEMS with uncovered SEMS.

Potential sources of bias in individual studies were evaluated through the Cochrane risk of bias tool [15], which is based on the adequacy of randomization and concealment of allocation, blinding of patient and personnel, blinding of outcome, incomplete outcome data, selective outcome reporting, and other potential bias.

Publication bias was initially assessed by visual inspection for the presence of the asymmetry of the funnel plot, and Egger test was carried out to evaluate the presence of asymmetry [16].



▶ **Fig. 2** Cochrane risk of bias. **a** Risk of bias graph. **b** Risk of bias in each study.

Results

Study selection and characteristics of included studies

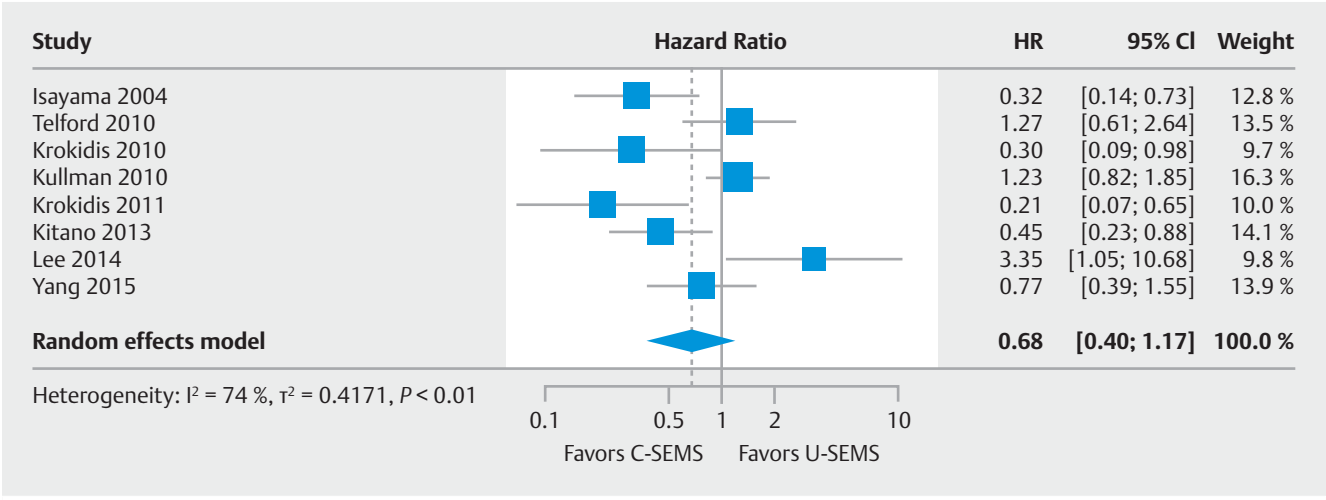
Overall, 102 articles were selected from a total of 3325 identified citations. After full text extraction, 86 articles did not address the topic of our analysis and were excluded. One additional study by Yoon et al. was excluded as it was undertaken retrospectively [17]. An RCT by Lee et al. [18] was excluded as patients had undergone previous stent insertion before study enrollment. We also excluded two conference abstracts by Isayama et al. [19] and Fukuda et al. [20], as there was evidence of data overlapping with full articles respectively by Isayama et al. [21] and Kitano et al. [22]. The study by Ung et al. [23] was not considered in the primary outcome analysis because derivation of patency and survival data was not feasible. In cases of missing data, we contacted authors to retrieve information but we did not get a response. No relevant additional trial was found by handsearching. Thus, 11 studies were considered for the final analysis. A PRISMA flowchart is shown in ▶ **Fig. 1**.

Of the 11 randomized trials included [8, 21 – 30], 2 were conference abstracts [24, 25] and 9 were full published articles [8, 21 – 23, 26 – 30]. Overall, 1272 patients were included, 643 of whom were randomized to receive covered SEMS and 629 to receive uncovered SEMS. ▶ **Table 1** shows the patient and study characteristics. Regarding the type of covered SEMS, partially covered SEMS were evaluated in three trials published in full [8, 21, 30] and one abstract [24], while a mixture of fully covered and partially covered SEMS were used in two full-text articles [26, 29].

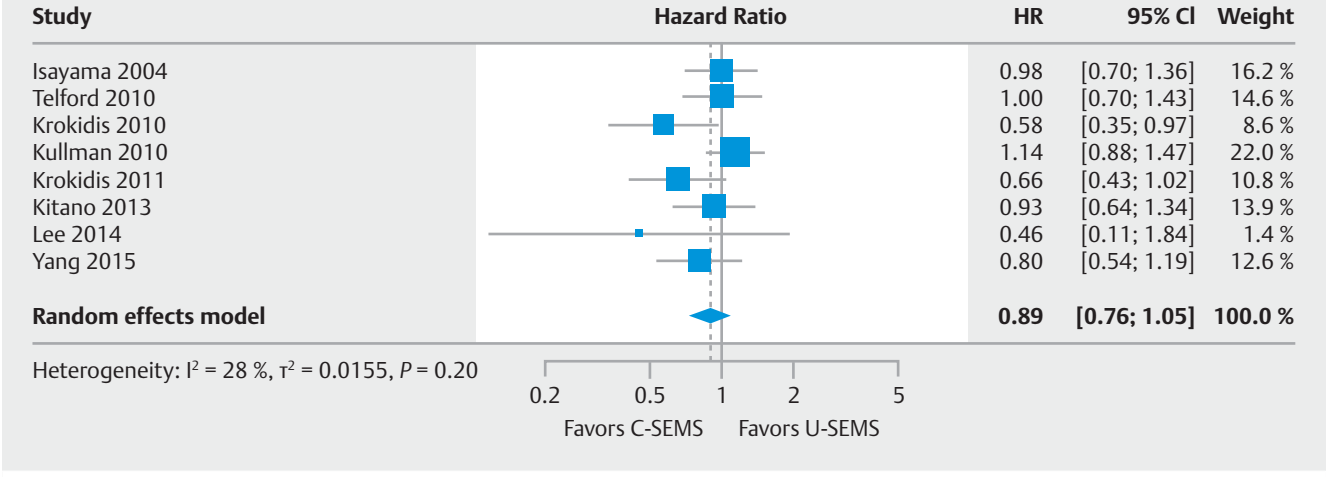
Use of the Cochrane risk of bias tool did not identify any significant bias within individual studies (▶ **Fig. 2**).

Primary outcomes

▶ **Fig. 3** shows study-specific and pooled HRs and 95 %CIs of stent failure from eight trials [8, 21, 22, 26 – 30]. No significant difference between covered and uncovered SEMS was found;



▶ **Fig. 3** Forest plot of stent failure. HR, hazard ratio; CI, confidence interval; SEMS, self-expandable metal stent; C, covered; U, uncovered.



▶ **Fig. 4** Forest plot of patient mortality. HR, hazard ratio; CI, confidence interval; SEMS, self-expandable metal stent; C, covered; U, uncovered

the pooled HR was 0.68 (95 %CI 0.40 – 1.17), in the presence of between-study heterogeneity ($I^2 = 74\%$, $P < 0.01$).

The leave-out sensitivity analysis showed that after exclusion of the study by Lee et al. [30], the stent survival rates were significantly higher in the covered SEMS group than in the uncovered SEMS group (HR 0.58, 95 %CI 0.35 – 0.98).

▶ **Fig. 4** shows study-specific and pooled HRs and 95 %CIs for death from eight trials [8, 21, 22, 26 – 30]. No difference in mortality rate emerged (HR 0.89, 95 %CI 0.76 – 1.05), in the absence of between-study heterogeneity ($I^2 = 28\%$, $P = 0.20$).

The leave-out sensitivity analysis showed that after exclusion of the study by Kullman et al. [27], the pooled HR was 0.84 (95 %CI 0.72 – 0.99), a marginally increased patient survival with covered SEMS compared with uncovered SEMS.

Further analysis excluding studies that placed SEMS percutaneously [21, 26, 29] showed no difference in stent failure (HR 0.74, 95 %CI 0.38 – 1.45) or mortality (HR 1.00, 95 %CI 0.86 – 1.15) for covered vs. uncovered SEMS.

Visual inspection of funnel plots did not reveal asymmetry for any of the outcomes considered, but Egger test for patient mortality did not support the assumption of no publication bias.

Secondary outcomes

The results of secondary outcomes are summarized in ▶ **Table 2**. The use of covered SEMS was associated with a higher rate of migration compared with uncovered stents (OR 5.11, 95 %CI 1.84 – 14.17). The use of covered SEMS was significantly related to a lower rate of tumor ingrowth compared with uncovered stents (OR 0.21, 95 %CI 0.09 – 0.50), while tumor overgrowth and sludge formation rates were higher with covered SEMS compared with uncovered SEMS (OR 2.00, 95 %CI 1.15 – 3.48; OR 2.46, 95 %CI 1.37 – 4.43, respectively). There was no difference in the rates of cholecystitis, cholangitis, pancreatitis, perforation or bleeding between the two groups.

The leave-out sensitivity analysis showed that no single study influenced the final pooled ORs.

▶ **Table 1** Characteristics of studies included in the meta-analysis.

Study characteristics	Smits et al. [24]	Isayama et al. [21]	Gonzalez-Huix et al. [25]	Krokidis et al. [26]	Kullman et al. [27]	Telford et al. [28]	Krokidis et al. [29]	Kitano et al. [22]	Ung et al. [23]	Lee et al. [30]	Yang et al. [8]
Type of publication	Abstract	Full text	Abstract	Full text	Full text	Full text	Full Text	Full text	Full text	Full text	Full text
Year of publication	1995	2004	2008	2010	2010	2010	2011	2013	2013	2014	2015
No. of centers involved	1	4	5	2	10	4	2	22	2	1	1
Duration of follow-up, mean (SD)/median (range), days	N/R	246 (11 – 1155)	N/A	212 (45 – 675)	Unclear	C-SEMS 244 (231) U-SEMS 217 (208)	192 (104 – 603)	233 (17 – 996)	N/A	N/A	N/A
Total no. patients	46	112	114	60	400	129	80	120	68	40	103
Stent type	Wallstent	Ultraflex	Wallstent	Viabil	Nitinella	Wallstent	Viabil	Wallflex	Hanaros-tent	Niti-S Comvi	Bonastent
Covering membrane	Polyure-thane	Polyure-thane	N/R	ePTFE	Polyure-thane-poly-carbonate	Permalume	ePTFE	Silicone	Silicone	PTFE	Silicone
C-SEMS/U-SEMS, n	22/24	57/55	61/53	30/30	200/200	68/61	40/40	60/60	34/34	20/20	51/52
Age, mean (SD)/median (range), years	77 (51 – 2)	N/A	7 (12)	65.3 (46 – 78)	N/A	66 (14)	62.7 (41 – 79)	69.6 (46 – 90)	77/79	62.6 (43 – 86)	C-SEMS: 68.7 ± 11.2 U-SEMS: 68 ± 11.3
Sex, male/female, n	26/20	66/46	54/60	36/24	179/221	61/68	53/27	54/66	27/41	18/22	C-SEMS: 34/17 U-SEMS: 30/22
Type of tumor, C-SEMS/ U-SEMS											
▪ Pancreas	34	34/32	63	0/0	152/155	106	40/40	60/60	30/27	18	29/36
▪ Bile duct	5	6/5	42	30/30	12/10	N/A	0/0	0/0	0/0	2	17/7
▪ Metastatic	0	12/11	0	0/0	16/18	N/A	0/0	0/0	7/9	0	16/15
▪ Gallbldder	0	3/6	0	0/0	8/3	N/A	0/0	0/0	2/5	3	2/5
▪ Papillary	7	2/1	9	0/0	8/9	N/A	0/0	0/0	1/3	0	2/2
Method of insertion, C-SEMS/U-SEMS			N/A								
▪ Endoscopic	46	45/50		0	400	129	0	120	68	40	103
▪ Percutaneous	0	12/5		60	0	0	80	0	0	0	
▪ Combined	0	4/4		0	0	0	0	0	0	0	

SEMS, self-expandable metal stents; C, covered; U, uncovered; PTFE, polytetrafluoroethylene; N/A, not available; N/R, not reported.

▶ **Table 2** Secondary outcomes and subgroup analysis.

Outcome	Comparison groups	Studies, n	Participants, n	OR (95 %CI)	Heterogeneity, I2, %
Stent migration					
	C-SEMS/PC-SEMS vs. U-SEMS	10	1204	5.11 (1.84 – 14.17)	0
	C-SEMS vs. U-SEMS	6	814	4.54 (1.16 – 17.78)	0
	PC-SEMS vs. U-SEMS	4	390	5.92 (1.27 – 27.62)	0
Tumor ingrowth					
	C-SEMS/PC-SEMS vs. U-SEMS	9	1090	0.21 (0.09 – 0.50)	47
	C-SEMS vs. U-SEMS	5	700	0.11 (0.03 – 0.45)	45
	PC-SEMS vs. U-SEMS	4	390	0.34 (0.08 – 1.39)	56
Tumor overgrowth					
	C-SEMS/PC-SEMS vs. U-SEMS	9	1090	2.00 (1.15 – 3.48)	0
	C-SEMS vs. U-SEMS	5	700	1.75 (0.93 – 3.28)	0
	PC-SEMS vs. U-SEMS	4	390	3.17 (0.99 – 10.15)	0
Sludge formation					
	C-SEMS/PC-SEMS vs. U-SEMS	8	1044	2.46 (1.37 – 4.43)	0
	C-SEMS vs. U-SEMS	5	700	2.55 (1.29 – 5.03)	0
	PC-SEMS vs. U-SEMS	3	344	2.21 (0.69 – 7.16)	0
Cholecystitis					
	C-SEMS/PC-SEMS vs. U-SEMS	11	1212	1.50 (0.72 – 3.14)	0
	C-SEMS vs. U-SEMS	8	932	1.32 (0.47 – 3.76)	0
	PC-SEMS vs. U-SEMS	3	280	1.71 (0.60 – 4.84)	0
Cholangitis					
	C-SEMS/PC-SEMS vs. U-SEMS	4	729	0.95 (0.51 – 1.79)	16
	C-SEMS vs. U-SEMS	2	514	0.93 (0.45 – 1.93)	25
	PC-SEMS vs. U-SEMS	2	215	1.30 (0.14 – 12.03)	0
Pancreatitis					
	C-SEMS/PC-SEMS vs. U-SEMS	10	1226	1.61 (0.68 – 3.82)	0
	C-SEMS vs. U-SEMS	7	882	1.22 (0.43 – 3.46)	0
	PC-SEMS vs. U-SEMS	3	344	2.78 (0.46 – 16.84)	23
Perforation					
	C-SEMS/PC-SEMS vs. U-SEMS	4	746	1.76 (0.40 – 7.68)	0
	C-SEMS vs. U-SEMS	2	514	1.52 (0.18 – 12.43)	0
	PC-SEMS vs. U-SEMS	2	232	2.03 (0.26 – 16.01)	0
Bleeding					
	C-SEMS/PC-SEMS vs. U-SEMS	6	884	0.78 (0.24 – 2.48)	I2 = 0 %
	C-SEMS vs. U-SEMS	3	540	0.61 (0.14 – 2.77)	I2 = 0 %
	PC-SEMS vs. U-SEMS	3	344	1.09 (0.18 – 6.81)	I2 = 0 %

SEMS, self-expandable metal stents; C, covered; U, uncovered; PC, partially covered; OR, odds ratio; CI, confidence interval.

▶ **Table 3** Characteristics of previously published meta-analyses investigating differences between covered and uncovered self-expandable metal stents for the treatment of distal biliary strictures.

Data	Saleem et al. [35]	Almadi et al. [34]	Yang et al. [5]	Li et al. [37]	Chen et al. [7]
Journal	Gastrointest Endosc	Clin Gastroenterol Hepatol	Int J Med Sci	PLOS one	Biomed Res Int
Total patients involved	781	1061	801	1417	1067
Publication date	2011	2013	2013	2016	2016
RCTS	5	9	5	14	8
Full text/Abstract	5	5/4	5	7/7	8 (2 not RCTs)
Choice outcome	Stent patency Cause of stent dysfunction	Duration of stent patency Proportion of patency stent at 6 and 12 months Secondary outcome: patient survival, stent migration, and complication	Stent patency and patient survival Rates of technical success, clinical success, tumor ingrowth, tumor overgrowth, and stent migration	Primary outcome: stent patency/patient survival Secondary outcomes: stent dysfunction, overall compli-cation, change in bilirubin level	Not clearly stated Patient survival, stent patency, complications, dysfunction events
Statistical analysis	RR for dichotomous variable WMD for continuous variable	OR for categorical variable WMD for continuous variable	HR for stent and patient survival OR for secondary outcomes	HR for stent and patient survival RR for dichotomous WMD for continuous	HR for stent and patient survival OR for dichotomous data
Stent patency	Mean difference as continuous	OR	N/R	N/R	N/R
Stent survival	Mean difference as continuous C-SEMS better	WMD C-SEMS = U-SEMS	HR C-SEMS = U-SEMS	HR C-SEMS = U-SEMS	HR C-SEMS = U-SEMS
Patient survival	C-SEMS better	C-SEM = U-SEMS	C-SEMS = U-SEMS (HR)	C-SEMS = U-SEMS	C-SEMS = U-SEMS
Tumor ingrowth	C-SEMS better	C-SEMS better	C-SEMS better	C-SEMS better	N/R
Tumor overgrowth	U-SEMS better	U-SEMS better	U-SEMS better	U-SEMS better	N/R
Stent migration	U-SEMS better	U-SEMS better	U-SEMS better	U-SEMS better	N/R
Sludge	U-SEMS better	Reported as dysfunction events	N/R	U-SEMS better	N/R
Adverse events	N/R	Reported as dysfunction events	N/R	N/R	CSEMS better
Complications	N/R	Reported as dysfunction events	N/R	CSEMS = USEMS	CSEMS = USEMS
Dysfunction events	N/R	C-SEMS = U-SEMS	N/R	C-SEMS = U-SEMS	C-SEMS better
Search string	Reported	Reported	Not reported	Reported	Not reported
Heterogeneity	I2	χ2 I2	Not explored (e.g. I2 = 63 % for ingrowth rate)	χ2 I2 I2 = 63 % for stent dysfunction but was not explored	Not explored
Publication bias	Funnel plot (but only 5 RCTs) Egger test	Begg and Egger test	Assessed	Not assessed	Only inspection of funnel plot (but only 8 studies included)
Risk of bias	N/R	Not assessed	Reported	Reported	Not assessed

▶ **Table 3** (Continuation)

Data	Saleem et al. [35]	Almadi et al. [34]	Yang et al. [5]	Li et al. [37]	Chen et al. [7]
Quality	N/R	Jadad	Cochrane	Cochrane	N/R
PRISMA checklist	Reported	N/R	Reported	Reported	N/R
Conclusion	C-SEMS have a significantly longer duration of patency vs. USEMS in patients with distal malignant biliary obstruction. Stent dysfunction occurs at a similar rate, although there is a trend toward later obstruction with CSEMS	The use of C-SEMS vs. U-SEMS in patients with distal malignant biliary obstruction is of unclear benefit; C-SEMS have a higher rate of migration and do not appear to have longer patency	Both C- and U-SEMS are comparable in efficacy for the palliative treatment of malignant obstruction in the digestive tract Each type of stent has its own merit and relative demerit	There is no significant difference in primary stent patency and stent dysfunction between C-SEMS and U-CSEMS However, when taking further management for occluded stents into consideration, C-SEMS is a better choice for patients with malignant biliary obstruction because of their removability	C-SEMS had lower incidence of adverse events There is no significant difference in dysfunction, but C-SEMS tends to be better, with no difference in stent patency, patient survival, and complications

RCT, randomized controlled trial; SEMS, self-expandable metal stents; C, covered; U, uncovered; PC, partially covered; PRISMA, preferred reporting items for systematic reviews and meta-analyses; WMD, weighted mean difference; RR, relative risk; HR, hazard ratio; OR, odds ratio; CI, confidence interval; N/R, not reported.

We also carried out stratified analyses according to the type of stent – fully covered [22, 23, 25 – 27, 29, 30] or partially covered SEMS [8, 21, 24, 28] – and did not find substantial differences when compared with the overall estimates.

No evidence of publication bias emerged from visual inspection of funnel plots and Egger test for all secondary outcomes.

Discussion

According to our meta-analysis, there was no statistically significant difference for either stent or patient survival between covered and uncovered SEMS in patients with distal malignant biliary strictures, although the pooled HRs for covered vs. uncovered SEMS were below unity for both stent failure and mortality. In particular, the stent failure rate reduction of covered vs. uncovered SEMS was about 32 %, suggesting a possible benefit of covered stents in terms of stent survival. However, covered SEMS were affected by a higher rate of sludge formation and migration, while uncovered SEMS had a higher rate of tumor ingrowth. No difference in stent-related adverse event rates emerged between the two groups.

The results of this meta-analysis are relevant for the following reasons. First, we do not exclude a benefit of covered SEMS in term of clinical efficacy. The lack of a statistically significant difference between covered and uncovered stents in terms of stent survival in our systematic review may be explained by the fact that the benefit of preventing tumor ingrowth is offset by the adverse events caused by the covering membrane. In particular, covered SEMS are associated with higher rates of migration, sludge formation, and tumor overgrowth, which are the causes of stent dysfunction in the covered group.

Unfortunately, stent characteristics have never been evaluated systematically and the RCTs available for statistical analysis used covered SEMS without the recent technical improvements developed to overcome the limitations of the covering membranes. In particular, the only rational conclusion about the higher rate of tumor overgrowth in the covered SEMS group is that the covering membrane did not inhibit tumor overgrowth.

We speculate that the type of covering membrane, technical characteristics of the covered SEMS, such as the axial and radial force of the stents, and the anti-migration system might play significant roles.

Biodurability and biodegradation of the covering membrane vary according to the different covering material used [31], and a strong tensile/tear strength of membrane may be more resistant to tumor ingrowth and thus be the preferred material for covering metallic stents [32].

To date, there are no new studies that include covered SEMS with newer stent characteristics compared with uncovered SEMS. Most of the covered stents in the RCTs were characterized by inefficient covering membrane or unfavorable axial or radial force, which may have influenced the comparison between covered and uncovered SEMS. Thus, the current statistical analysis may prompt many physicians to continue to place uncovered SEMS. However, we suggest that, on the basis of a stent failure rate reduction of 32 % favoring covered SEMS,

these stents should be considered as the first option until new, better designed RCTs are published. In support of this, when the data by Lee et al. [30] were excluded from the sensitivity analysis, the stent failure rate was 42 %, with statistical significance.

Second, our subgroup analysis revealed no difference in the rate of migration or any other outcomes between partially covered SEMS and uncovered SEMS. Although an RCT showed higher insertion-related adverse events when stents were placed percutaneously compared with those placed endoscopically [33], such difference in insertion technique did not affect stent outcome. Third, our analysis demonstrated a higher migration rate with covered SEMS than with uncovered SEMS, in agreement with two previous meta-analyses [34, 35] (▶ **Table 3**). The higher migration rate in covered SEMS is likely to be due to the covering membrane as well as the higher axial force [36]. Fourth, our analysis showed no difference in the rate of cholecystitis between the covered and uncovered SEMS.

Fifth, similarly to previous meta-analyses [7, 34, 35, 37], we found no difference in pancreatitis rates between covered and uncovered SEMS. Covered stents have been associated with a higher rate of pancreatitis perhaps because the pancreatic duct may be occluded by the stent covering. SEMS with high axial force and nonpancreatic cancer were significant risk factors for pancreatitis, as described in a study by Kawakubo et al. [38].

Our results on the primary end points are not in disagreement with those from two previous meta-analyses [34, 35], although there are some differences in methodology and outcome definitions (▶ **Table 3**). In detail, the meta-analysis by Almadi et al. [34], included nine randomized trial, and reported higher stent patency duration with covered SEMS than with uncovered SEMS (67.9 days, 95 %CI 60.3 – 75.5). However, stent patency at 6 and 12 months was similar (OR 1.82; OR 1.25).

The meta-analysis by Saleem et al. [35], included five trials, and demonstrated longer stent patency and stent survival with covered SEMS compared with uncovered SEMS using mean difference. However, data for stent survival, derived from four studies, was heterogeneous ($I^2 = 79\%$) and the limited number of studies available for analysis did not permit sensitivity or stratified analyses to identify potential sources of heterogeneity.

An important caveat is that patients with unusually prolonged survival would not affect the stent patency, but could bias stent survival.

Our analysis also addresses methodological flaws present in two more recent meta-analyses [7, 37]. In the meta-analysis by Li et al. [37] including 14 RCTs (7 in full text and 7 in abstract form), the authors did not explore the presence of heterogeneity for stent dysfunction, and the reported HRs were not comparable. In the Chen et al. meta-analysis [7], HRs were more reproducible, but the trial quality was not assessed.

A new system to report stent outcome has been proposed recently [11]. Application of a uniform system would allow more accurate meta-analyses, and by avoidance of different terminologies make data more comparable [11]. In clinical trials, stent survival or time to recurrent biliary obstruction should be primary end points. To our knowledge, this is the first meta-analysis to be conducted in accordance with the recommendations of the Tokyo criteria [11].

Conclusion

Our results do not exclude a possible benefit with covered SEMS in terms of patient and stent survival compared with uncovered SEMS in patients with distal malignant biliary strictures, at the expense of a higher risk of migration in the covered stent group. Further developments in stent design are still required.

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Competing interests

None.

References

[1] Abraham NS, Barkun JS, Barkun AN. Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life. Gastrointest Endosc 2002; 56: 835 – 841

[2] Moss AC, Morris E, Leyden J et al. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev 2007; 33: 213 – 221

[3] Almadi MA, Barkun A, Martel M. Plastic vs. self-expandable metal stents for palliation in malignant biliary obstruction: a series of meta-analyses. Am J Gastroenterol 2017; 112: 260 – 273

[4] Davids PH, Groen AK, Rauws EA et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992; 340: 1488 – 1492

[5] Yang Z, Wu Q, Wang F et al. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. Int J Med Sci 2013; 10: 825 – 835

[6] Moole H, Puli SR. Comparison of complications for covered versus uncovered metal stents in malignant biliary strictures: a meta-analysis and systematic review. Gastroenterology 2015; 148: S – 400

[7] Chen MY, Lin JW, Zhu HP et al. Covered stents versus uncovered stents for unresectable malignant biliary strictures: a meta-analysis. Biomed Res Int 2016; 2016: 640806

[8] Yang MJ, Kim JH, Yoo BM et al. Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: a randomized controlled trial. Scand J Gastroenterol 2015; 50: 1490 – 1499

[9] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097

[10] Green S, Higgins JP. Chapter 2: Preparing a Cochrane review. In: Higgins JP, Green S eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008

[11] Isayama H, Hamada T, Yasuda I et al. TOKYO criteria 2014 for transpapillary biliary stenting. Dig Endosc 2015; 27: 259 – 264

[12] Tierney JF, Stewart LA, Ghersi D et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16

[13] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539 – 1558

[14] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177 – 188

[15] Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928

[16] Egger M, Davey SmithG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629 – 634

[17] Yoon WJ, Lee JK, Lee KH et al. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc 2006; 63: 996 – 1000

[18] Lee BS, Ryu JK, Jang DK et al. Reintervention for occluded metal stent in malignant bile duct obstruction: a prospective randomized trial comparing covered and uncovered metal stent. J Gastroenterol Hepatol 2016; 31: 1901 – 1907

[19] Isayama H, Komatsu Y, Tsujino T et al. A prospective randomized study of "covered" vs "uncovered" metallic stent for distal malignant biliary obstruction. Gastrointest Endosc 2000; 51: AB191

[20] Fukuda W, Konishi H, Kamada K et al. A randomized multicenter study comparing covered and uncovered self-expandable metal stents for malignant distal biliary obstruction – Kansai EDS study group. J Gastroenterol Hepatol 2012; 27: 54 – 55

[21] Isayama H, Komatsu Y, Tsujino T et al. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. Gut 2004; 53: 729 – 734

[22] Kitano M, Yamashita Y, Tanaka K et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. Am J Gastroenterol 2013; 108: 1713 – 1722

[23] Ung KA, Stotzer PO, Nilsson A et al. Covered and uncovered self-expandable metallic Hanarostents are equally efficacious in the drainage of extrahepatic malignant strictures. Results of a double-blind randomized study. Scand J Gastroenterol 2013; 48: 459 – 465

[24] Smits ME, Rauws EAJ, Groen AK et al. Preliminary results of a prospective randomized study of partially covered wallstents vs noncovered wallstents. Gastrointest Endosc 1995; 41: 416

[25] Gonzalez-Huix F, Huertas C, Figa M et al. A randomized controlled trial comparing the covered (CSEMS) versus uncovered self-expandable metal stents (USEMS) for the palliation of malignant distal biliary obstruction (MDBO): interim analysis. Gastrointest Endosc 2008; 67: AB166

[26] Krokidis M, Fanelli F, Orgera G et al. Percutaneous treatment of malignant jaundice due to extrahepatic cholangiocarcinoma: covered Viabil stent versus uncovered Wallstents. Cardiovasc Intervent Radiol 2010; 33: 97 – 106

[27] Kullman E, Frozanpor F, Soderlund C et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc 2010; 72: 915 – 923

[28] Telford JJ, Carr-Locke DL, Baron TH et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc 2010; 72: 907 – 914

[29] Krokidis M, Fanelli F, Orgera G et al. Percutaneous palliation of pancreatic head cancer: randomized comparison of ePTFE/FEP-covered versus uncovered nitinol biliary stents. Cardiovasc Intervent Radiol 2011; 34: 352 – 361

[30] Lee SJ, Kim MD, Lee MS et al. Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial. J Vasc Interv Radiol 2014; 25: 1912 – 1920

[31] Meng B, Wang J, Zhu N et al. Study of biodegradable and self-expandable PLLA helical biliary stent in vivo and in vitro. J Mater Sci Mater Med 2006; 17: 611 – 617

[32] Bang BW, Jeong S, Lee DH et al. The biodurability of covering materials for metallic stents in a bile flow phantom. Dig Dis Sci 2012; 57: 1056 – 1063

[33] Smith AC, Dowsett JF, Russell RC et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. Lancet 1994; 344: 1655 – 1660

[34] Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol 2013; 11: 27 – 37

[35] Saleem A, Leggett CL, Murad MH et al. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. Gastrointest Endosc 2011; 74: 321 – 327

[36] Isayama H, Kawabe T, Nakai Y et al. Management of distal malignant biliary obstruction with the ComVi stent, a new covered metallic stent. Surg Endosc 2010; 24: 131 – 137

[37] Li J, Li T, Sun P et al. Covered versus uncovered self-expandable metal stents for managing malignant distal biliary obstruction: a meta-analysis. PLoS One 2016; 11: e0149066

[38] Kawakubo K, Isayama H, Nakai Y et al. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. Surg Endosc 2012; 26: 771 – 776