Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

ASGE guideline on the role of endoscopy in the management of malignant hilar obstruction

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

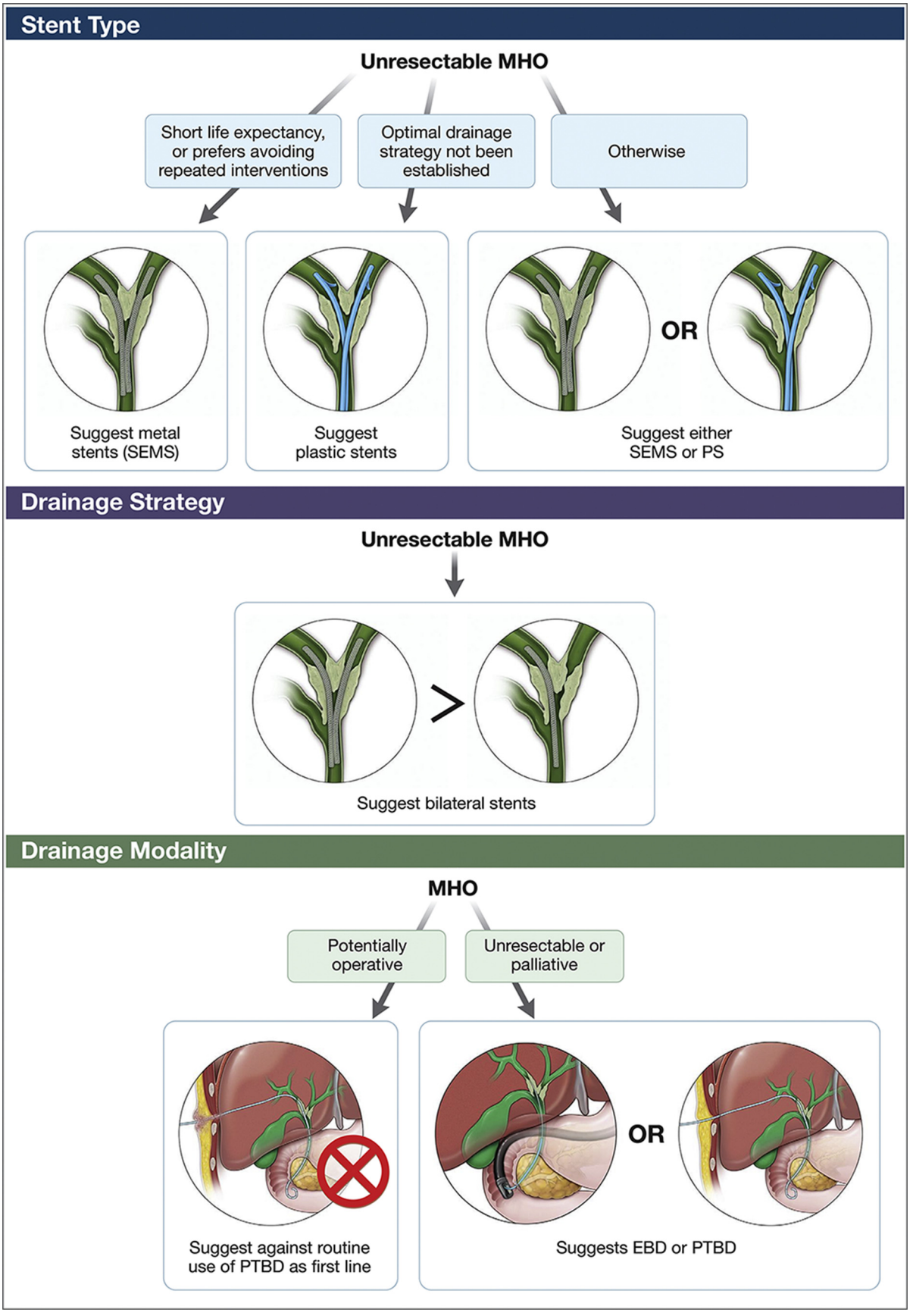
This clinical guideline from the American Society for Gastrointestinal Endoscopy (ASGE) provides an evidence-based approach for the management of patients with malignant hilar obstruction (MHO). This document was developed using the Grading of Recommendations Assessment, Development and Evaluation framework and addresses primary *drainage modality* (percutaneous transhepatic biliary drainage [PTBD] vs endoscopic biliary drainage [EBD]), *drainage strategy* (unilateral vs bilateral), and *stent selection* (plastic stent [PS] vs self-expandable metal stent [SEMS]). Regarding drainage modality, in patients with MHO undergoing drainage before potential resection or transplantation, the panel suggests against routine use of PTBD as first-line therapy compared with EBD. In patients with *unresectable* MHO undergoing palliative drainage, the panel suggests PTBD or EBD. The final decision should be based on patient preferences, disease characteristics, and local expertise. Regarding drainage strategy, in patients with unresectable MHO undergoing palliative stent placement, the panel suggests placement of bilateral stents compared with a unilateral stent in the absence of liver atrophy. Finally, regarding type of stent, in patients with unresectable MHO undergoing palliative stent placement, the panel suggests placing SEMSs or PSs. However, in patients who have a short life expectancy and who place high value on avoiding repeated interventions, the panel suggests using SEMSs compared with PSs. If optimal drainage strategy has not been established, the panel suggests placing PSs. This document clearly outlines the process, analyses, and decision processes used to reach the final recommendations and represents the official ASGE recommendations on the above topics. (Gastrointest Endosc 2021;94:222-34.)

(footnotes appear on last page of article)

Patients with malignant hilar obstruction (MHO) frequently present with signs and symptoms of biliary obstruction. MHO can occur because of several types of malignancies including primary tumors of the biliary tract involving the hilum (Klatskin tumors), local extension of adjacent cancers (gallbladder cancer), and metastatic involvement of lymph nodes with extrinsic hilar compression.[1] MHO is a devastating disease, with a 5-year survival rate of less than 10%.[2] Approximately 73% of lesions causing MHO are either unresectable after preoperative staging or an R0 resection (resection for cure) is not achievable at the time of surgery. Surgery for MHO typically involves partial hepatectomy, or liver transplantation, which is performed in select centers in the United States.[3] Thus, most patients require some form of biliary drainage for symptomatic relief (eg, pain, jaundice, etc) to prevent adverse events (AEs) of cholestasis (pruritus, cholangitis, etc) as part of the preoperative assessment and to preserve liver function.

Accomplishing the goals of biliary drainage in MHO can be challenging. For instance, the optimal drainage strategy and the type of stent (plastic stent [PS] vs self-expanding metallic stent [SEMS]) have not been defined in patients with MHO. Similarly, among patients with potentially resectable MHO, preoperative biliary drainage is often required. There is limited guidance on whether percutaneous transhepatic biliary drainage (PTBD) or endoscopic biliary drainage (EBD) is the most appropriate route for approach in this patient population. In this document, we present the body of evidence and provide guidance in addressing these important clinical questions. We aim

GRAPHICAL ABSTRACT



to provide evidence-based, clinically relevant guidelines addressing management of MHO.

METHODS

This guideline document was conceptualized and conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, as previously described.[4,5] The American Society for Gastrointestinal Endoscopy (ASGE) Governing Board approved the final document before publication.

Panel composition and clinical questions

We invited a panel of stakeholders to be involved in the discussion and formulation of the final recommendations. This included a content expert (B.J.E.), interventional radiologist (A.R.), pancreaticobiliary surgeon (E.P.C.), patient advocate (P.M.), GRADE methodologist (B.J.Q.), and members of the Standards of Pratice committee. The patient advocate was a representative of the Cholangiocarcinoma Foundation (https://cholangiocarcinoma.org). The meeting was held in Chicago, Illinois, USA on March 7, 2020. All members were asked to disclose conflicts of interests based on the ASGE policy (https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf).

Clinical questions were formulated according to the population, intervention, comparison, and outcome, or PICO, format. Critical outcomes included survival, postprocedure mortality, success rates (functional and technical), and adverse outcomes. The questions aimed to address 3 clinically important questions as outlined in Table 3.

Literature search and study selection criteria

Our literature search was done with the help of an expert librarian. We started by searching for existing systematic reviews. If such reviews were identified, the citations from these studies were reviewed for inclusion. The search was updated, and any new studies were also considered based on predefined inclusion and exclusion criteria. Inclusion criteria for all clinical questions were randomized controlled trials, cohort, case-control, retrospective studies, or meeting abstracts from 2018-2019. Included studies have patients with hilar malignancy and assessed survival duration, stent latency, technical and clinical success, therapeutic outcomes, re-intervention rate, or adverse events. A total of 25 studies were used as evidence for all clinical questions. See Appendix (available online at www.giejournal.org) for full search strategies and database details. All citations were imported into covidence.org and reviewed by 2 independent reviewers (B.J.Q. and L.H.J.), and all conflicts were resolved by consensus.

Data extraction and statistical analysis

For all included studies, we extracted data on survival time, mortality rates, stent patency, success rates, reintervention rates, and AEs. Data were extracted into an Excel spreadsheet (Microsoft Corporation, Redmond, Wash, USA). We assessed heterogeneity using the I^2 test, and funnel plots were used to assess for publication bias. Forest plots were constructed to assess the magnitude and direction of effect estimate.

Certainty in evidence (quality of evidence)

Based on the GRADE format,[6] evidence for each outcome was assessed for risk of bias, inconsistency, indirectness, imprecision, and publication bias using the GRADEpro-GDT website (http://gdt.guidelinedevelopment.org/app). The quality of evidence was rated from very low to high. The certainty of evidence was discussed in detail during the panel meeting, and forest and funnel plots were presented.

Considerations in the development of recommendations

In addition to the quality and certainty of the evidence, the panel considered several other factors in making final recommendations: the balance of desirable and undesirable effects, costs, cost-effectiveness, patient values and preference, equity, acceptability, and feasibility of interventions compared with comparisons. Final recommendations used the terms "recommend" to denote strong recommendations or "suggest" to denote conditional recommendations. The categories of GRADE recommendations and their interpretation to patients and clinicians are detailed in Tables 4 and 5.

RESULTS

Details of the primary recommendations from this guideline document are summarized in Table 1 and the graphical abstract. General management concepts are summarized in Table 2.

Recommendation 1: **In patients with unresectable MHO undergoing endoscopic palliative endoscopic stent placement, the panel suggests the following:**

- **SEMSs compared with PSs in patients with a short life expectancy (<3 months) or those who place high value on avoiding repeated interventions.**
- **PSs compared with SEMSs if an optimal drainage strategy has not been established.**
- **Otherwise, either stent type may be used based on local expertise and physician preference.**

(Conditional recommendations, Low quality of evidence)

Summary of evidence and recommendations

We identified an existing systematic review by Sawas et al,[7] which included 5 comparative studies,[2,8-11] 3 of which were randomized controlled trials (RCTs). We identified 3 additional studies, including 1 abstract,[12-14] based on our update of the literature search (from 2016 to 2019).

TABLE 1. Summary of recommendations for the 3 clinical questions in consideration

Category	Population	Considerations	Recommendation
Stent type	Unresectable MHO	Short life expectancy or prefers avoiding repeated interventions	Suggest metal stents (SEMSs)
		Optimal drainage strategy not been established	Suggest PSs
		Otherwise	Suggest either SEMSs or PSs
Drainage strategy	Unresectable MHO	—	Suggest bilateral stents
Drainage modality	MHO	Potentially operative	Suggest *against* routine use of PTBD as first-line treatment
		Unresectable or palliative	Suggest EBD or PTBD

MHO, Malignant hilar obstruction; *SEMS*, self-expandable metal stent; *PS*, plastic stent; *PTBD*, percutaneous transhepatic biliary drainage; *EBD*, endoscopic biliary drainage.

TABLE 2. General concepts in the management of malignant hilar obstruction

1. Review cross-section imaging, with emphasis on volumetric liver assessment
2. Discuss case in a multidisciplinary fashion, especially in patients with potentially resectable disease
3. Limit injection of contrast
4. Avoid injection and attempted drainage of dilated bile ducts within atrophic liver segments
5. Attempt drainage of all injected biliary segments
6. Aim to drain >50% of the viable (nonatrophic) liver volume, which includes the future liver remnant in resectable patients
7. Consider periprocedure antibiotics, especially if drainage of contrast is believed to be incomplete
8. May use a stent-in-stent or stent-by-stent approach
9. Radiofrequency ablation and photodynamic therapy to ablate lesions through self-expanding metal stents can be considered in tertiary centers and research settings

The advantages of SEMSs included higher patency rates, lower reintervention rates, and higher rates of drainage success. Improved survival was also noted in 1 RCT.[8] There was no difference in insertion success rates, 30-day mortality, adverse outcomes, or pancreatitis between SEMSs and PSs. The panel expressed concern about making a strong recommendation for SEMSs compared with PSs because of several factors. First, patients in the RCTs who were randomized to the PS group did not undergo scheduled stent exchanges as would be the case in current practices. Second, in patients who require reintervention, the procedure of exchanging PSs is much easier than restenting an occluded SEMS.

In patients who have short life expectancy (<3 months), the panel suggested the use of SEMSs compared with PSs because of lower rates of reintervention and possibly improved survival based on existing data. In some cases, endoscopists may not know the best side to be drained or cannot confirm that the patient is resectable. The panels suggested placing PSs in such patients while final decisions could be made, at which time SEMSs can be placed if needed.

Evidence synthesis

We extracted data on survival, stent patency, insertion success, drainage success (defined at decrease in serum bilirubin by <75% in 1 month, in most studies), and adverse outcomes (overall AEs, 30-day mortality, cholangitis, and pancreatitis). The evidence profile summarizing each outcome based on GRADE methodology is detailed in Supplementary Table 1 (available online at www.giejournal.org). Forest plots and funnel plots for each outcome are detailed in Supplementary Figures 1 and 2 (available online at www.giejournal.org).

Survival. For the primary outcome of survival, data were used from 2 RCTs. Sangchan et al[8] showed a significant survival benefit in patients who underwent SEMS placement. Mukai et al[2] showed a trend toward better survival with SEMSs, which was not statistically significant. On meta-analysis, there was a significant improvement in survival with SEMSs compared with PSs (difference in means, 56 days [confidence interval {CI}, 12-101]; $I^2 = 33\%$, $P = .01$) (Supplementary Fig. 1A). Evidence was rated down for imprecision because of the assumption of normality (analysis of medians as means). Thus, the quality of evidence was moderate. Adding 3 cohort studies still showed a trend to increased survival but did not reach statistical significance (difference in means, 33 days [CI, –3 to 69]; $I^2 = 55\%$, $P = .07$).

Stent patency. For the outcome of stent patency, 2 RCTs[2,8] showed higher median stent patency in patients

TABLE 3. List of 3 clinical questions in the population, intervention, comparison, outcome format with outcomes and ratings

Population	Intervention	Comparator	Outcomes	Rating
Patients with unresectable malignant hilar obstruction	Self-expandable metal stents	Plastic stents	• Survival	Critical
			• Stent patency	Critical
			• Reintervention	Critical
			• Success rate	Critical
			• Adverse events	Critical
Patients with unresectable Malignant hilar obstruction	Bilateral stent placement	Unilateral stent placement	• Survival	Critical
			• Stent patency	Critical
			• Success rate	Critical
			• Adverse events	Critical
Patients with malignant hilar obstruction	Endoscopic biliary drainage	Percutaneous transhepatic biliary drainage	• Postprocedure mortality	Critical
			• Survival	Critical
			• Success rate and conversion rate	Critical
			• Peritoneal metastasis and tube seeding	Critical
			• Adverse events	Critical

TABLE 4. Grading of Recommendations Assessment, Development and Evaluation categories of quality of evidence

Quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

undergoing SEMS placement versus PS placement. On meta-analysis, standardized mean difference (SMD) showed a large improvement in stent patency (SMD, .86 [CI, .55-1.18]; I^2 = 0%, P < .001). Evidence was rated down for imprecision because of assuming normality. Thus, using the data from RCTs, the quality of evidence was moderate. Adding 5 cohort studies also showed an improvement in stent patency (SMD, .64 [CI, .46-.82]; I^2 = 52%, P < .001) (Supplementary Fig. 1B).

Reintervention rates. For the reintervention rate, we found lower odds of reintervention in SEMSs compared with PSs based on 3 RCTs[2,8,9] (odds ratio [OR], .34; confidence interval [CI], .16-.70; I^2 = 0%, P < .001). Evidence was rated down for low number of events, and the quality of evidence was moderate. Adding data from 5 cohort studies did not change the results (OR, .33; 95% CI, .21-.53; I^2 = 38%, P < .001) (Supplementary Fig. 1C).

Success rates. Insertion success was informed by all 3 RCTs that showed no difference between SEMSs and PSs (OR, 6.38; 95% CI, .86-47.45; I^2 = 0%, P = .07) (Supplementary Fig. 1D). Evidence was rated down for imprecision because of low number of events and wide CI, thus ending with a moderate quality of evidence. The outcome of drainage success was informed by 1 RCT and 4 cohort studies. Drainage success was higher in SEMSs

TABLE 5. Interpretation of definitions of strength of recommendation using Grading of Recommendations Assessment, Development and Evaluation framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

compared with PSs (OR, 2.82; 95% CI, 1.19-6.69; $I^2 = 42\%$, $P = .019$) (Supplementary Fig. 1E). The quality of evidence was low.

Adverse outcomes. As summarized in Supplementary Table 1, there was no difference in 30-day mortality or cholangitis rates between the 2 groups (Supplementary Figs. 1F,G). The rate of pancreatitis was assessed in 2 studies. The RCT by Sangchan et al[8] showed 8 cases of pancreatitis in each arm, whereas the study by Gao et al[13] showed 3 cases of pancreatitis in the SEMS group compared with 1 case in the PS group.

Considerations

Cost. The panel recognized that the cost of SEMSs is greater than PSs. However, there is a potential for cost savings from higher stent patency rates and requiring fewer interventions. Two RCTs[2,9] looked at the cost of SEMSs versus PSs and concluded that SEMSs were more cost efficient. One retrospective study by Gao et al[13] found SEMSs to be more costly. The panel recognized there are no true cost-effectiveness analyses in the United States. Walter et al[15] studied the cost efficacy of SEMSs versus PSs in patients with extrahepatic bile duct obstruction and found that the total cost after 1 year did not differ. Yeoh et al[16] compared the cost of SEMSs versus PSs in malignant obstructive jaundice. Their decision analysis showed that initial PS use followed by SEMSs was the most economical option. Based on the above, the panel decided that the overall judgment on cost-effectiveness probably favors SEMSs.

Patient values. We found no studies reporting on patient values. Based on discussion with the patient advocate, the panel assumed that most patients would value survival and lower rates of reintervention. One observational study by Choi et al[12] reported a higher PTBD-free survival in the PS group. The patient advocate on the panel placed a high importance on avoiding permanent stent placement if reintervention may be technically challenging on the next ERCP.

Feasibility, acceptability, and equity. The panel deliberated whether recommending SEMSs could be disadvantageous to resource-poor settings where SEMSs are too expensive or may not be available. However, the final judgment was that there was no overall issue with equity because SEMSs are also available in resource-poor settings. The panel decided that using SEMSs compared with PSs is both feasible and acceptable.

Final comments

Despite the presented data, the panel expressed concern about making a strong recommendation for SEMSs compared with PSs. Some issues outlined by the panel are as follows:

- Patients in the RCTs who were randomized to the PS group did not undergo scheduled stent exchanges but waited until stent occlusion occurred. In patients with prolonged life expectancy (>3 months), this could have caused stent occlusion, which could have resulted in worse survival. Scheduled PS replacement is part of routine real-life clinical practice. Therefore, the noted improvement in survival in the RCTs may not translate to improved survival in daily practice.
- If a patient requires reintervention, the procedure of exchanging PSs is much easier that restenting an occluded SEMS, especially when bilateral SEMSs are placed. This notion is supported by data from Iwasaki et al,[14] who reported higher success rates of reintervention in PSs compared with SEMSs on multivariable analysis.
- Finally, many such patients are referred to open-access calendars in tertiary referral centers. At the index ERCP, the patient and endoscopist may not have definitive answers on pathology, resectability, and the optimal drainage strategy (ie, multisegmental vs unilateral approaches).

Recommendation 2: **In patients with unresectable MHO undergoing palliative endoscopic stent placement, the panel suggests placement of bilateral stents compared with a single unilateral stent.** (*Conditional recommendation, Low quality of evidence*).

Summary of evidence and recommendations

We identified 3 RCTs[2,17,18] and 3 retrospective studies[10,19,20] for this question. All studies assessed patients who had unresectable MHO. Four of the 6 studies reported the use of SEMSs. One study[17] used only PSs, whereas another study[10] used either SEMSs or PSs. Two studies[17,20] used the stent-by-stent (SBS) technique, 1 study[19] used the stent-in-stent (SIS) technique, and 2 studies[10,18] used either SIS or SBS. The type of stent used varied by study.

Based on our analysis of the above data, bilateral stent placement may be associated with an increase in survival, duration of patency, and successful drainage. However, bilateral stent placement was associated with lower technical success rates. Rates of adverse outcomes were similar compared with unilateral stent placement. This evidence suggests that bilateral stent placement is superior to unilateral stent placement, and thus the panel made a recommendation in favor of bilateral stent placement. However, the panel expressed concern that the survival results were mostly based on 1 RCT[18] and a strong recommendation would put excessive burden on endoscopists, some of whom may lack the expertise to place bilateral stents, especially in patients with complex MHO.

Data on the ideal approach to bilateral stent placement are limited. A study by Naitoh et al[20] found no difference between SBS and SIS in success rates. However, AEs were higher in SBS compared with SIS ($P = .016$), and obstruction rates were higher in SBS compared with SIS ($P = .047$). Kim et al[21] found no difference in success rates, AEs, or rates of obstruction.

Further studies are needed before we can make a recommendation on which technique may be superior. Until then, either technique may be used based on availability, local expertise, and anatomic considerations. There are some data on the use of radiofrequency ablation and photodynamic therapy to ablate lesions through SEMSs,[22,23] which could increase stent patency. Such treatments are promising, but the panel cannot make further recommendations regarding their use at this time.

Evidence synthesis

Our initial literature search identified 849 studies. After initial screening, 36 studies were reviewed in full text, and we included 6 studies[2,10,17-20] in this analysis. Of those, we identified 3 RCTs.[2,17,18] Three other studies[10,19,20] were retrospective in nature. All studies assessed patients who had unresectable MHO. The primary outcomes of interest were survival, duration of stent patency, drainage success, technical success, late stent occlusion, and AEs. Evidence profile summarizing each outcome based on GRADE methodology is detailed in Supplemental Table 2 (available online at www.giejournal.org). Forest plots and funnel plots for each outcome are detailed in Supplementary Figures 3 and 4 (available online at www.giejournal.org).

Survival. One RCT by Lee et al[18] showed that bilateral stents were associated with higher survival compared with unilateral stents (adjusted hazard ratio [HR], .42; 95% CI, .26-.67; $P < .01$). Evidence was rated down for imprecision because these are data from a single study. Further evidence was assessed from 2 RCTs[17,18] and 2 cohort studies.[19,20] Median duration, number of patients, and *P*-values were used in the calculation of pooled difference in means. These studies showed a positive trend toward increased survival in bilateral stents. Pooled difference in means was 11 days (CI, –12 to 35; $I^2 = 29\%$ (Supplemental Fig. 3A). However, this did not reach statistical significance ($P = .35$). Evidence was rated down for imprecision because of assumption of normality in distribution, so we had very low quality of evidence.

Stent patency. The best evidence of stent patency came from the RCT by Lee et al.[18] In multivariable Cox proportional hazard modeling assessing stent patency, the study showed that bilateral SEMS placement was a favorable factor in stent patency (adjusted HR, .30; 95% CI, .17-.52; $P < .001$). Evidence was rated down given that these are data are from a single study, and thus the quality of evidence was moderate. Another RCT by Mukai et al,[2] however, failed to show a difference in duration of patency (only *P*-value reported; no HR or median stent patency was reported). In considering the evidence from cohort studies, higher rates of patency were noted in 2 studies: Liberato et al[10] (for SEMS: HR, 3.69 [95% CI, 2.08-6.57]; for PS: HR, 2.24 [95% CI, 1.18-4.24]) and Naitoh et al[20] (median patency 488 days vs 210 days, $P = .009$). Iwano et al[19] showed no difference in median stent patency (129 days vs 133 days, $P = .322$). Evidence was very low in quality given the small cohort studies with results that could not be pooled. Overall median stent patency was reported in 3 studies.[18-20] On meta-analysis, there was no difference in stent patency (SMD, .38 [95% CI, -.22 to .99]; $P = .218$, $I^2 = 78\%$) (Supplementary Fig. 3B). Evidence was rated down for imprecision (assumption of normality), inconsistency (high I^2), and possible publication bias, thus resulting in very low quality of evidence.

Success rate. The technical success rate was lower for bilateral compared with unilateral stents in 2 RCTs[17,18] (OR, .39; 95% CI, .17-.91; $P = .03$, $I^2 = 0\%$). Evidence was rated down for imprecision given the low number of events, resulting in moderate quality of evidence. The same results were true when evidence from 2 cohort studies[19,20] was included (OR, .38; 95% CI, .18-.8; $P = .01$, $I^2 = 0\%$) (Supplementary Fig. 3C). In most studies, successful drainage was defined as a reduction in serum bilirubin level by >75% in 1 month. Based on 2 RCTs,[17,18] there was no difference in drainage success between the 2 groups (OR, 1; 95% CI, .36-2.76; $I^2 = 59\%$, $P = .117$).

Evidence was also rated down for inconsistency given the low number of events. Therefore, the quality of evidence was moderate. These results were consistent when evidence from 1 cohort study[20] was included (OR, .99; 95% CI, .46-2.11; I^2 = 23%, P = .97) (Supplementary Fig. 3D).

Adverse events. Evidence of early AEs, late AEs, and late stent occlusion relied on 2 RCTs[17,18] that were rated down for low number of events. For early AEs, there was no difference based on 2 RCTs (OR, .44; 95% CI, .08-2.33; P = .331, I^2 = 81%, Q = 5.5) or when adding evidence from 2 cohort studies (OR, .6; 95% CI, .15-2.48; P = .484, I^2 = 60%, Q = 7.5) (Supplementary Fig. 3E). For late AEs, there was no difference between bilateral and unilateral stents from 2 RCTs (OR, .92; CI, .56-1.52, I^2 = 0%; P = .661) or when adding evidence from 2 cohort studies (OR, .9; 95% CI, .59-1.38; I^2 = 0%, P = .63) (Supplementary Fig. 3F). For late stent occlusion rates, there was no difference between the 2 groups in the RCTs (OR, .80; 95% CI, .45-1.43; P = .45) or when adding evidence from 2 cohort studies (OR, .76; 95% CI, .44-1.31; P = .33) (Supplementary Fig. 3G).

Considerations

Cost. The panel discussed that bilateral stent placement would add to the cost of the procedure. However, the final judgment was that there are negligible costs or savings for bilateral compared with unilateral stents. There were no studies to inform cost-effectiveness, and none of the RCTs discussed cost.

Patient values. At the present time, there are no data on patient values and preferences. The patient advocate expressed that most patients would place a high value on stent patency, because it would require less-frequent interventions. There was also a high emphasis on drainage success, because this would facilitate the initiation of an appropriate chemotherapeutic regimen.

Feasibility, acceptability, and equity. The panel decided that there is probably no impact on equity in using bilateral compared with unilateral stents. The panel also decided that using bilateral compared with unilateral stents is both feasible and acceptable.

Final comments

Traditionally, it is necessary to drain only one-third of the liver (ie, 1 sector: left, right anterior, or right posterior). More recent data suggests 50% of the liver needs to be drained to prevent jaundice. This corresponds anatomically to 2 sectors or about two-thirds of the liver. All studies reported in our analysis assessed patients with unresectable MHO, which form most hilar malignancies. Therefore, our recommendations and discussion were limited to this patient group. Based on the above evidence and after all considerations, the recommendation was bilateral stent placement. There was also discussion within the panel regarding the accuracy of the term "bilateral stent placement" compared with "multisectoral stent placement" (right anterior, right posterior, or left main duct).[24] Future studies should try to use the term multisectoral stent placement rather than bilateral stent placement. Furthermore, the panel also emphasized the following general guiding principles: avoid draining atrophic portions of the liver, minimize injection into nondilated ducts, and attempt drainage of all injected biliary segments.

Recommendation 3a: **In patients with MHO undergoing *preoperative* drainage, the panel suggests *against* routine use of PTBD as first-line therapy compared with EBD.**
(Conditional recommendation, Low quality of evidence).

Recommendation 3b: **In patients with unresectable MHO undergoing palliative drainage, the panel suggests *EBD or PTBD*. The final decision should be based on patient preferences, disease characteristics, and local expertise.**
(Conditional recommendation, Low quality of evidence)

Summary of evidence and recommendations

Surgical resection of MHO can improve survival and often includes extended liver and extrahepatic bile duct resection.[25] The optimal modality for drainage in the preoperative setting is unclear. We identified a systematic review by Liu et al[26] and updated it from 2016 onward. We only included comparative data from 11 studies.[21,27-36] Three RCTs[27,32,36] assessed the use EBD versus PTBD. The RCT by Coelen et al[27] was stopped early because of higher early mortality in the PTBD group. The only U.S.-based RCT[36] was terminated prematurely because of low recruitment.

EBD is preferred by patients who generally wish to avoid external drainage. Yet, EBD has lower technical success rates with the occasional need for conversion to PTBD and higher rates of pancreatitis and cholangitis. PTBD is associated with a higher success rate combined with a lower risk of AEs such as pancreatitis. However, PTBD appears to be associated with higher rates of peritoneal metastasis and may be associated with higher post-procedure mortality and worse survival compared with EBD. PTBD also involves an external drain (at least temporarily).

The issue of peritoneal metastasis was key to our final recommendation. The meta-analysis by Wang et al[37] showed that patients with PTBD were significantly more likely to have tumor-seeding metastases compared with EBD. Additionally, Hirano et al[28] found that PTBD was a significant predictor of peritoneal metastases when controlling for age and tumor stage. Based on

all considerations, the panel suggested against routine use of PTBD in resectable patients. In palliative cases, the issue of peritoneal metastatic becomes less important, and PTBD or EBD may be used as the initial approach.

Evidence synthesis

The primary outcomes of interest were survival, postprocedure mortality, technical success, and adverse outcomes including tumor seeding and cholangitis. The evidence profile summarizing each outcome is detailed in Supplementary Table 3 (available online at www.giejournal.org). Forrest plots and funnel plots for each outcome are detailed in Supplementary Figures 5 and 6 (available online at www.giejournal.org).

Early mortality. Postprocedure (30-day) mortality was reported in 3 RCTs. There was a trend toward lower mortality in EBD versus PTBD (risk ratio, .53; 95% CI, .28-1.01; I^2 = 24%), although this did not reach statistical significance (P = .05) (Supplementary Fig. 5A). Evidence was rated down for the risk of bias given that 2 of 3 RCTs were terminated early. Thus, we ended up with moderate certainty of evidence. Postprocedure mortality was further assessed with evidence from 6 additional cohort studies.[21,28-31,33] This also showed a trend toward lower mortality in EBD versus PTBD that also did not reach statistical significance (risk ratio, .61; 95% CI, .37-1.01; I^2 = 0%, P = .053). Evidence was rated down for imprecision given the low number of events, and we ended up with very low quality in evidence. Stratifying data by type of patients (preoperative, palliative, or all-comers) did not impact the results of this analysis.

Long-term survival. Because survival varies between resectable and nonresectable MHO, the studies were stratified by population type for this outcome. Hirano et al[28] reported adjusted survival in resectable patients with MHO. The study reported a significant increase in survival in EBD compared with PTBD (HR, 2.08; 95% CI, 1.28-3.71; P = .003). This gave us low quality of evidence. The median survival from Hirano et al and Kim et al[21] was used to assess pooled mean difference in survival among patients with resectable MHO. Mean difference in survival was higher in EBD versus PTBD (mean difference, 27 months [CI, 14-41]; I^2 = 0%, P < .001) (Supplementary Fig. 5B). This was rated down for assumption of normal distribution. We ended up with very low quality of evidence. Two studies of unresectable patients reported patient survival. Median survival was not different in the RCT by Saluja et al[32] or the cohort study by Paik et al.[34]

Peritoneal metastasis and tract seeding. Hirano et al[28] reported an adjusted analysis on factors influencing peritoneal recurrence. When controlling for age and tumor stage, they found that PTBD was the only independent factor predictive of the development of peritoneal recurrence (OR, 6.9; 95% CI, 1.9-25.7; P = .004). This was rated down because data were from a single study, and thus the quality of evidence was rated as very low.

We used data from an existing systematic review by Wang et al[37] assessing metastasis and tube seeding in patients with MHO. Based on 6 studies, EBD was much less likely to be associated with seeding metastasis compared with PTBD (7.8% vs 17.1%; OR, .27; 95% CI, .13-.56); I^2 = 66%, P < .001). Evidence was rated down for imprecision given the very low number of events and for inconsistency given the high I^2, and thus we had very low quality of evidence.

Technical success and conversion to another procedure. The technical success rate was assessed in 1 RCT[32] and 4[21,33-35] cohort studies. Evidence showed lower technical success rates in EBD compared with PTBD (OR, .21; 95% CI, .05-.85; I^2 = 59%, P = .0286) (Supplementary Fig. 5C). Evidence was rated down for imprecision because of the low number of events, and thus the quality of evidence was rated as very low. Conversion to the opposite procedure was assessed in 2 RCTs[27,32] showing higher rates of conversion in EBD (OR, 18.2; 95% CI, 3.1-105.1; I^2 = 0%, P = .001). Evidence was rated down for imprecision given the very low number of events, and thus we had moderate quality of evidence. Adding evidence from 3 retrospective studies[21,30,33] did not change the final results (OR, 14.2; 95% CI, 5.4-37.6; I^2 = 0%, P < .001) (Supplementary Fig. 5D).

Adverse events. Overall AEs were very low in prevalence. Therefore, evidence of each outcome was rated down for imprecision resulting in very low quality of evidence. As expected, pancreatitis was more likely in EBD versus PTBD (OR, 3.69; 95% CI, 1.20-11.33, P = .22) (Supplementary Fig. 5E). There was a trend toward higher overall AEs and cholangitis in EBD versus PTBD, but this did not reach significance (OR, 1.8; 95% CI, 1.03-3.13 and OR, 2.04; 95% CI, 1.00-4.14, respectively) (Supplementary Figs. 5F and 5H). Bleeding was more common in PTBD, but this also did not reach significance (OR, .51; 95% CI, .127-2.01) (Supplementary Fig. 5G).

Considerations

Cost. The direct costs of EBD and PTBD may be comparable. However, patients often do not need general anesthesia when PTBD is performed. The panel judgment believed there was probably negligible cost or cost-savings from EBD compared with PTBD. The data on cost-effectiveness of EBD versus PTBD are limited. One study[38] from Thailand assessed EBD versus PTBD in palliation of MHO and found that EBD was more cost-effective than PTBD, assuming that the willingness to pay is higher than $19,403 for each quality of life-year gained. The panel discussed that generalizability to the United States may be limited.

Patient values. Saluja et al[32] assessed the quality of life in patients with EBD versus PTBD in India using 3 various scores. Unfortunately, the numbers were very small, thus precluding strong conclusions. A study by Nam et al[39] showed that in failed ERCP, most of the 313 patients (>85%) who filled out the survey preferred EUS-guided biliary drainage compared with PTBD. The patient advocate, who was present during the entire presentation, emphasized that many patients view the external drain negatively and it can be a constant reminder of their disease. She also noted that having an external drain becomes a management challenge for patients and caregivers. Regarding patients with tumor seeding at the PTBD tube site, the patient advocate expressed the negative psychological impact of seeing local recurrence at the site of the percutaneous tube.

Feasibility, acceptability, and equity. The panel perceived no issues with regard to equity in performing EBD versus PTBD. The panel found both EBD and PTBD to be feasible and acceptable.

Final comments

One of the driving factors in the panel's decision was the increased risk of peritoneal metastases in PTBD as identified by the meta-analyses by Wang et al.[37] This was further supported by the study by Hirano et al.[28] In palliative cases, where peritoneal recurrence or tumor seeding may not be deciding factors, the final vote among the panel members was to provide a conditional recommendation for the use of PTBD or EBD as first-line options based on patient preference and available resources.

GENERAL CONCEPTS

In addition to addressing the above questions, the panel has also provided general concept statements in managing these patients. No systematic reviews were conducted for these statements, and they represent expert opinions of this multidisciplinary panel (Table 2).

A subset of patients undergo liver transplant for MHO. In such cases, general guiding principles include avoiding EUS with FNA of the lesion; avoiding uncovered SEMSs, which may be difficult to remove surgically; and avoiding PTBD because of the same concerns of seeding as already discussed.

FUTURE DIRECTIONS

This document clearly highlights several gaps in our understanding of the management of MHO. Given the uncertainties outlined above, high-quality randomized and observational data are needed to strengthen existing recommendations and to provide evidence-based guidance in other areas. Regarding the 3 questions addressed in this document, all recommendations are conditional and are based on low-quality evidence. Therefore, additional rigorous investigation addressing prosthesis selection and drainage strategies remains necessary. Below is a brief outline of areas of research that would highly enrich future guideline development on the subject of management of MHO:

- U.S.-based clinical trials: Randomized comparisons of SEMSs versus PSs for MHO would ideally mirror common clinical approaches in both arms, including the routine exchange of PSs, use of smaller-caliber SEMSs when necessary, and establishment of adequate drainage with PSs before randomization to SEMSs versus PSs. Although challenging, research in this area should also consider the impact of prosthesis selection on intraductal ablative therapies. Similarly, given our emerging understanding of volumetric liver assessment and the implications of sectoral anatomy, research on stent placement in MHO should aim to elucidate whether strategies focused on sectoral drainage should replace the traditional unilateral versus bilateral drainage paradigm. As a panel, we encourage participation in future RCTs addressing these critical questions, when they become available.
- Improving study design for stent type: A major limitation we found in answering the first question (stent type) was that the existing RCTs did not schedule patients for stent exchanges on a regular basis in the PS group. Future RCTs should ideally compare SEMSs versus regularly replaced PSs; this mirrors clinical practice and should be reflected in future RCT designs.
- EBD versus PTBD: The question of EBD versus PTBD remains a fundamental unanswered controversy in clinical practice. As mentioned above, a recent U.S.-based randomized trial was terminated because of prohibitively slow accrual. The investigators recommended several research objectives to improve clinical decision-making in this area and to increase the success of a future randomized trial: (1) to better estimate the fraction of PTBD and EBD patients who experience a reduction in bilirubin to a level permitting chemotherapy (important for RCT sample size estimation), (2) to define nonlaboratory patient-centered outcomes that can serve as endpoints in an RCT and may ultimately prove more important in the management of this patient population, and (3) to elucidate patient and stricture characteristics that predict preferential response to EBD versus PTBD.
- Intraductal therapy: Another major priority area for investigation in MHO is the benefit and optimal application of intraductal radiofrequency ablation and/or photodynamic therapy in the treatment of unresectable patients. Additionally, whether the most benefit is realized as a 1-time intervention at the time of initial stent placement or whether there is incremental value

in serial treatments at the time of routine stent exchange remains unclear.
- Patient values: The issue of patient values and preferences continues to be a major deficiency in several GI interventions including the management of MHO. We tried to mitigate this by having a patient representative on our panel. However, this is not a substitute for conducting high-quality studies on how patients value these various treatment options and what can be done to incorporate such values and preferences into our guidelines.
- Cost-effectiveness: For all 3 topics, minimal data are available on cost-effectiveness to inform panel discussions. In making any guideline recommendation, panels need to assess the cost and cost-effectiveness of 1 approach compared with another. Such modeling studies can be done with relatively modest financial resources and will highly enrich future guideline recommendations.
- EUS-guided biliary drainage: Although this topic was not specifically addressed in this guideline document, there is much interest in the role of EUS to drain patients if standard ERCP cannulation could not be achieved. Further RCT on the utility of EUS-guided biliary drainage compared with PTBD in patients with failed cannulation will be helpful for future guideline development.

SUMMARY AND CONCLUSIONS

In this document, the ASGE offers evidence-based, clinically relevant, practical guidelines addressing management of MHO. This guideline followed the GRADE methodology. The final recommendations offer guidance on stent type, drainage strategy, and drainage modality along with key clinical concepts in the management of patients with MHO. Furthermore, the guideline provides a visual representation of the recommendations, which is aimed at making these recommendations easier to understand and disseminate. We believe that this process will help mitigate some of the challenges in dealing with MHO and will hopefully result in an improvement in patient quality of life and outcomes.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years, or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

DISCLOSURE

The following authors disclosed financial relationships: **B. Qumseya** disclosed no financial relationships. **L. Jamil** disclosed no financial relationships. **B. Elmunzer** is a consultant for Takeda Pharmaceuticals. **A. Riaz** disclosed no financial relationships. **E. Ceppa** disclosed no financial relationships. **N. Thosani** is a consultant for Boston Scientific Coporation, TaeWoong Medical; is a consultant and receives research support from PENTAX of America, Inc,; receives royalties from UpToDate; receives research support from Endogastric Solutions; is a speaker for Abbie; and is on the advisory board for ColubrisMX Inc. **J. Buxbaum** is a consultant for Boston Scientific Corporation, Eagle Pharmaceuticals, Inc, Cook Medical LLC, and Olympus America Inc; and receives grant support from Medtronic USA, Inc and Olympus America Inc. **A. Storm** is a consultant for Apollo Endo Surgery, Endo-TAGSS, and Enterasense; data and safety monitoring from ERBE USA Inc and GI Dynamics; and receives research support from Boston Scientific. **M. Sawhney** is a stock holder with Allurion Technology, Inc. **S. Pawa** disclosed no financial relationships. **M. Naveed** disclosed no financial relationships. **J. Lee** disclosed no financial relationships. **J. Law** disclosed no financial relationships. **R. Kwon** disclosed no financial relationships. **T. Jue** disclosed no financial relationships. **L. Fujii-Lau** has received travel compensation from Ovesco. **D. Fishman** disclosed no financial relationships. **A. Calderwood** disclosed no financial relationships. **S. Amateau** is a consultant for Boston Scientific Corporation, Cook Medical LLC, Endo-Therapeutics, Hemostasis LLC, Merit Medical Systems Inc, Olympus Corporation of the Americas, and STERIS Corporation. **M. Al-Haddad** has received research and teaching support from Boston Scientific Corporation. **S. Wani** is a consultant for Boston Scientific Corporation, Medtronic, Exact Sciences and Interpace; and is on the advisory board for Cernostics.

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Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EBD, endoscopic biliary drainage; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; MHO, malignant hilar obstruction; OR, odds ratio; PS, plastic stents; PTBD, percutaneous transhepatic biliary drainage; RCT, randomized

controlled trial; SEMS, self-expandable metal stent; SBS, stent-by-stent; SIS, stent-in-stent; SMD, standardized mean difference

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APPENDIX. SEARCH STRATEGY FOR PICO 1 AND PICO 2

Search date: September 7, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019; Wiley Cochrane

Limits: Human, English

Excluded: Case reports, comments, editorials, letters, notes

OVID MEDLINE(R), EMBASE

#	Searches	Results
1	*Bile Duct Neoplasms/ use ppez	11140
2	*bile duct tumor/ use emczd	4131
3	exp Cholangiocarcinoma/ use ppez	8663
4	exp klatskin tumor/ use emczd	820
5	((hilar or perihilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenos or constriction or blockage)).ti,ab,kf,kw.	7398
6	or/1-5	23658
7	exp Stents/ use ppez or exp Stent/ use emczd	240788
8	exp Drainage/ use ppez	57353
9	exp biliary tract drainage/ use emczd	22931
10	(stent* or sems or drainage or endoprosthes*).ti,ab,kf,kw.	477976
11	or/7-10	570546
12	6 and 11	4322
13	animals/ not (humans/ and animals/)	5961985
14	12 not 13	4317
15	limit 14 to english language	3562
16	limit 15 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	490
17	Case Report/	4544436
18	15 not (16 or 17)	2705
19	remove duplicates from 18	2096

WILEY COCHRANE

ID	Search	Hits
#1	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	212
#2	MeSH descriptor: [Cholangiocarcinoma] explode all trees	178
#3	MeSH descriptor: [Klatskin Tumor] explode all trees	16
#4	((hilar or perihilar or klatskin) NEAR/2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenos or constriction or blockage)):ti,ab	165
#5	#1 or #2 or #3 or #4	440
#6	MeSH descriptor: [Stents] explode all trees	4003
#7	MeSH descriptor: [Drainage] explode all trees	2667
#8	(stent* or sems or drainage or endoprosthes*):ti,ab	20532
#9	#6 or #7 or #8	22066
#10	#5 AND #9	187

APPENDIX. SEARCH STRATEGY FOR PICO 3

Search date: September 7, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019; Wiley Cochrane

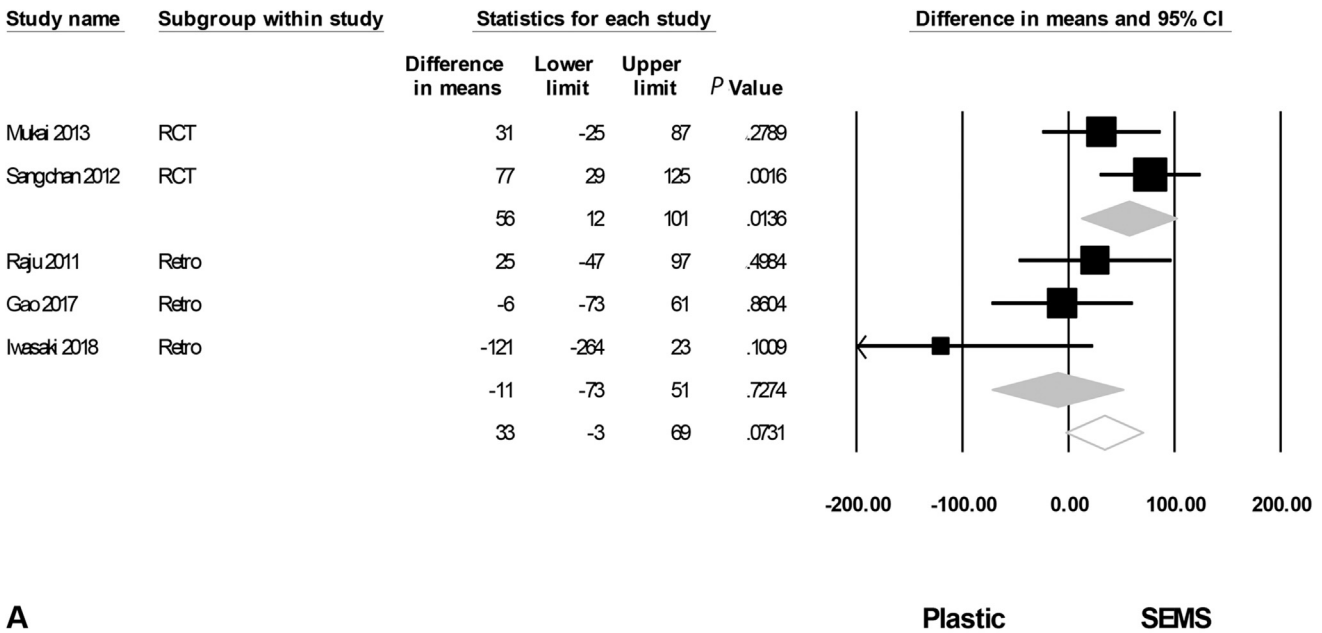
Limits: Human, English

Excluded: Case reports, comments, editorials, letters, notes

Ovid MEDLINE(R), Embase

#	Searches	Results
1	*Bile Duct Neoplasms/ use ppez	11140
2	*bile duct tumor/ use emczd	4131
3	exp Cholangiocarcinoma/ use ppez	8663
4	exp klatskin tumor/ use emczd	820
5	((hilar or perihilar or klatskin) adj2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenos or constriction or blockage)).ti,ab,kf,kw.	7398
6	or/1-5	23658
7	exp Cholangiography/ use ppez or exp percutaneous transhepatic cholangiography/ use emczd	29572
8	(percutaneous adj3 (cholangiography or drainage)).ti,ab,kf,kw.	20729
9	(PTC or ptbd).ti,ab,kf,kw.	25817
10	or/7-9	70893
11	6 and 10	2704
12	animals/ not (humans/ and animals/)	5961985
13	11 not 12	2704
14	limit 13 to english language	2201
15	limit 14 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	577
16	Case Report/	4544436
17	14 not (15 or 16)	1520
18	remove duplicates from 17	1321

Wiley Cochrane		
#1	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	212
#2	MeSH descriptor: [Cholangiocarcinoma] explode all trees	178
#3	MeSH descriptor: [Klatskin Tumor] explode all trees	16
#4	((hilar or perihilar or klatskin) NEAR/2 (carcinoma* or adenoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or cholangiocarcinoma* or malignanc* or stricture* or obstruction or occlusion or stenos or constriction or blockage)):ti,ab	165
#5	#1 or #2 or #3 or #4	440
#6	MeSH descriptor: [Cholangiography] explode all trees	738
#7	(percutaneous NEAR/3 (cholangiography or drainage)):ti,ab	363
#8	(PTC or ptbd):ti,ab	523
#9	#6 or #7 or #8	1546
#10	#5 and #9	64



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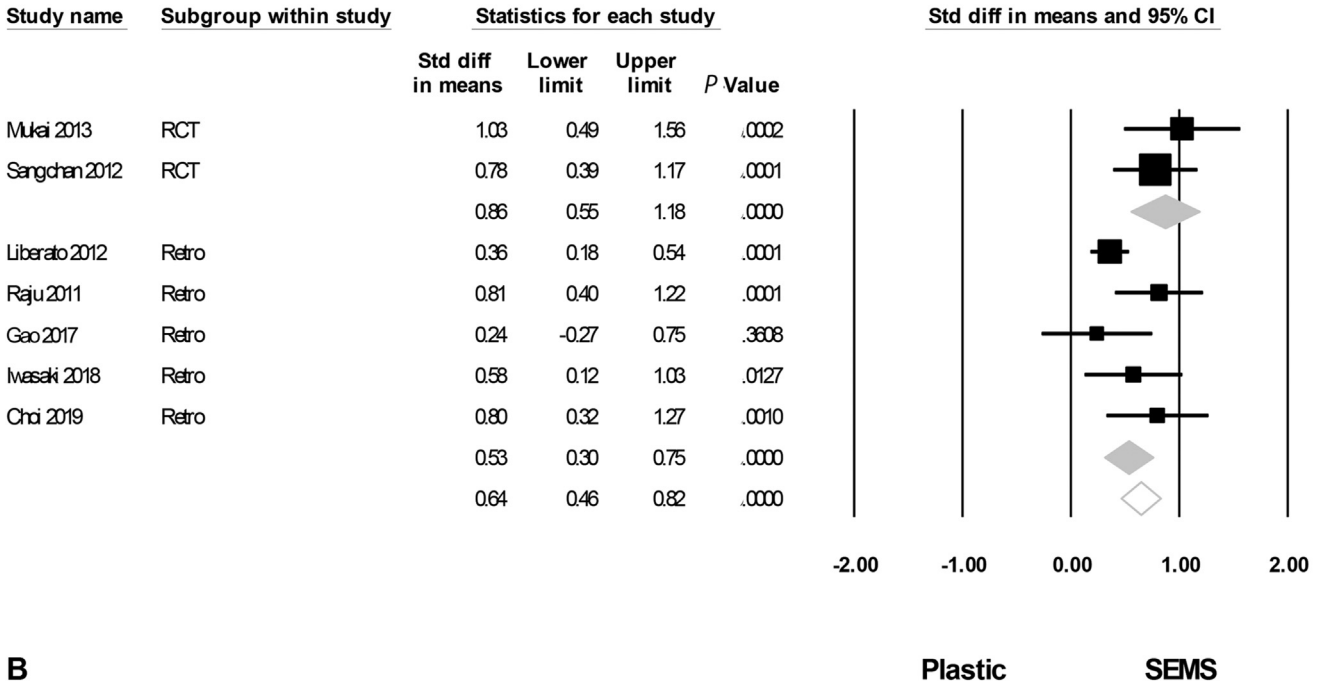
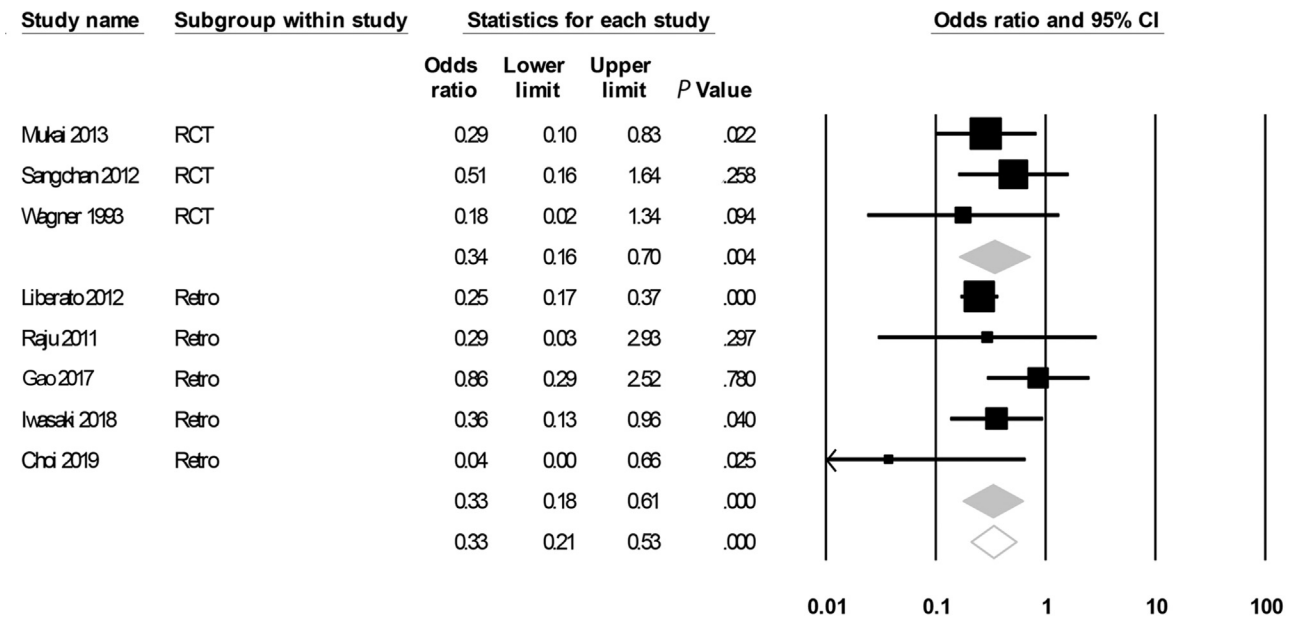


B

Supplementary Figure 1. Forest plots of effect estimates comparing SEMSs with plastic stents for the following outcomes: (A) difference in mean survival (days), (B) standard mean difference for improvement in stent patency, (C) odds of reintervention, (D) odds of insertion success, (E) odds of drainage success, (F) odds of 30-day mortality, and (G) odds of cholangitis. *CI*, Confidence interval; *RCT*, randomized controlled trial; *SEMS*, self-expanding metal stent.



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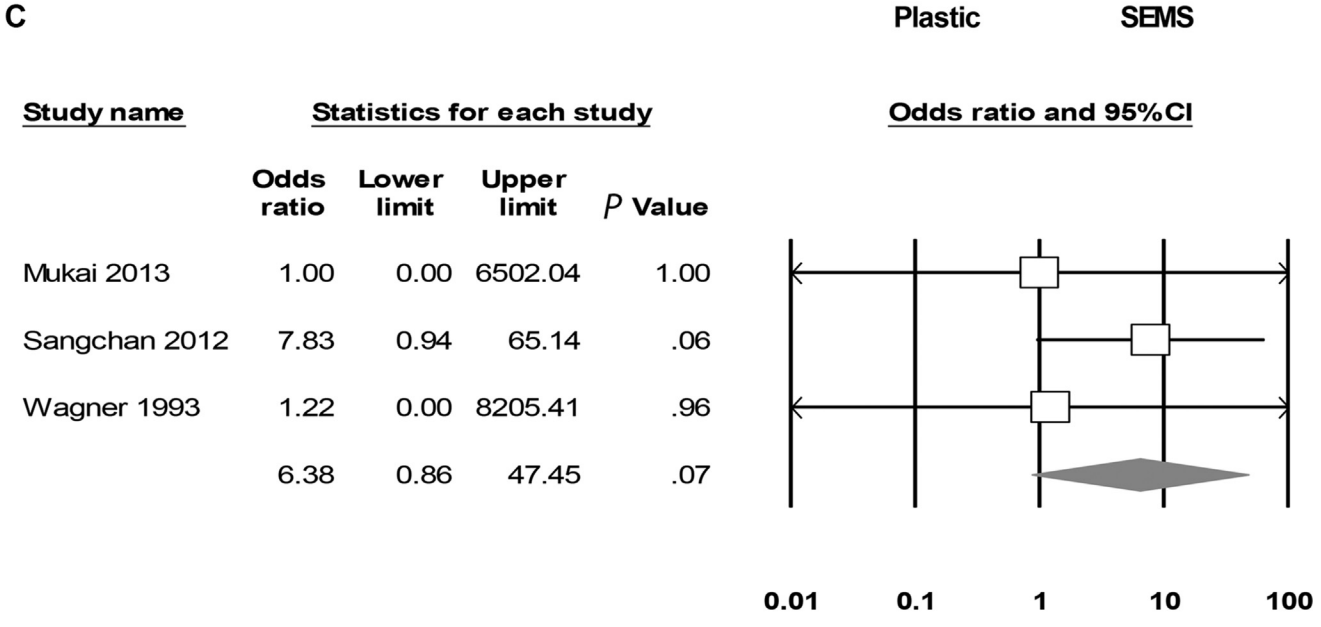

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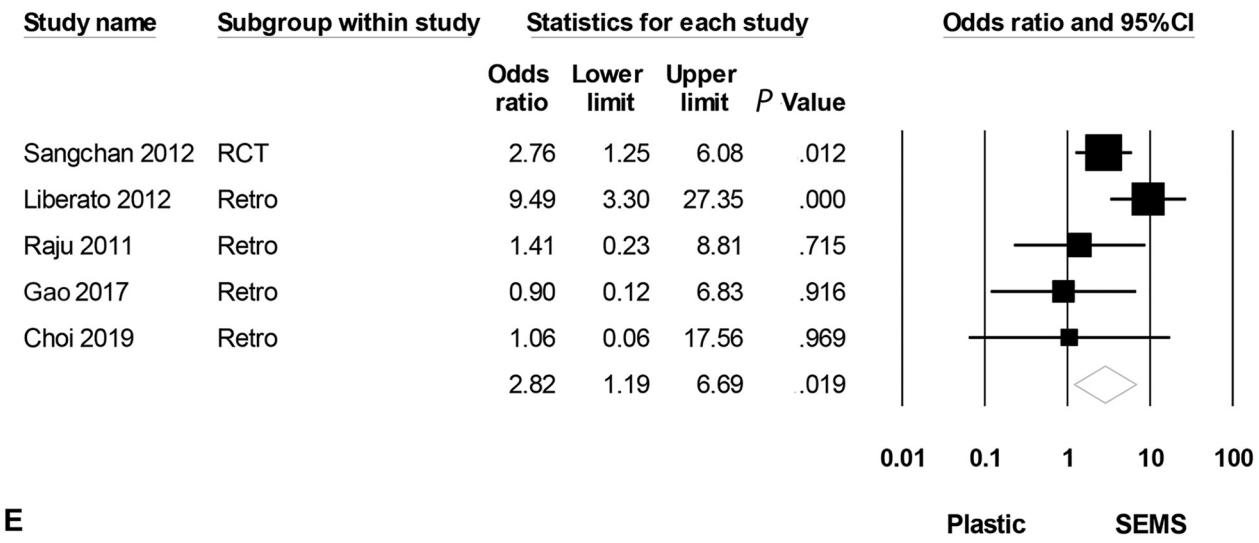
Supplementary Figure 1. Continued.



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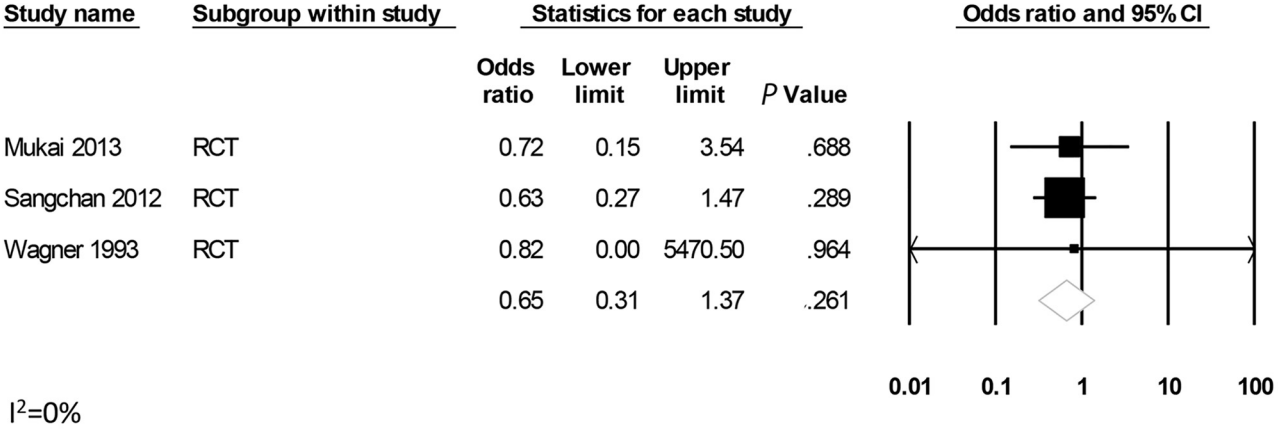

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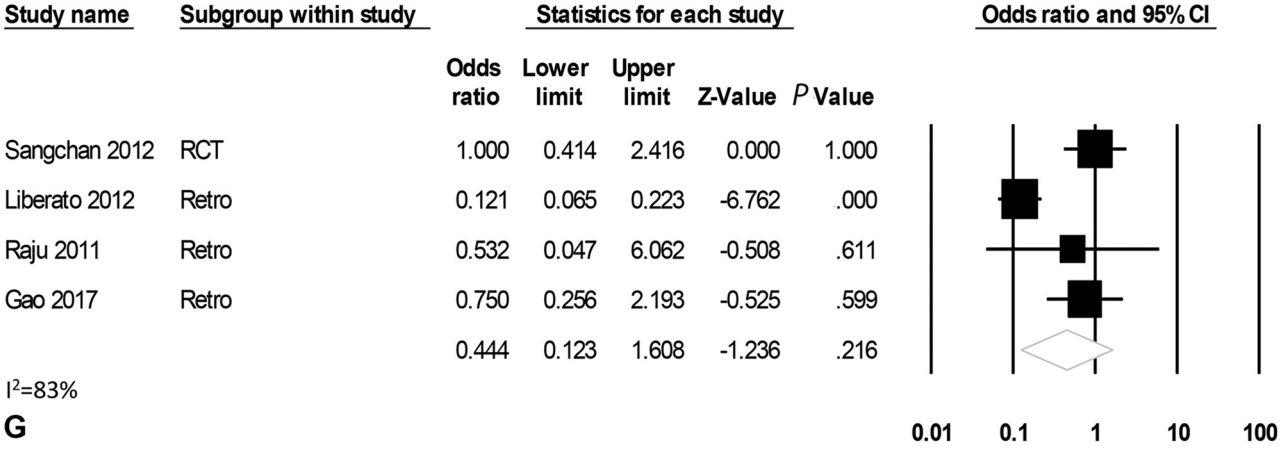
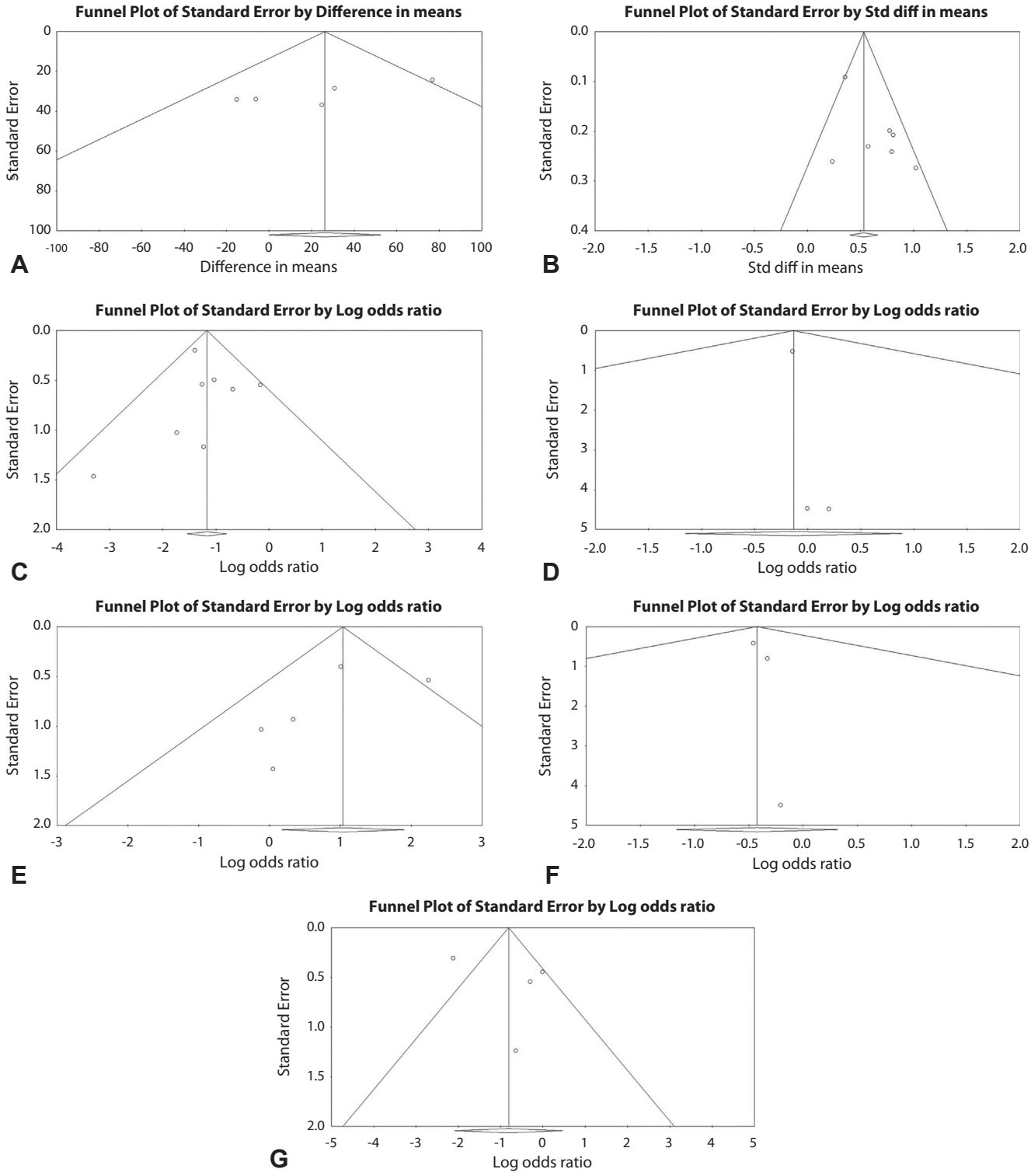
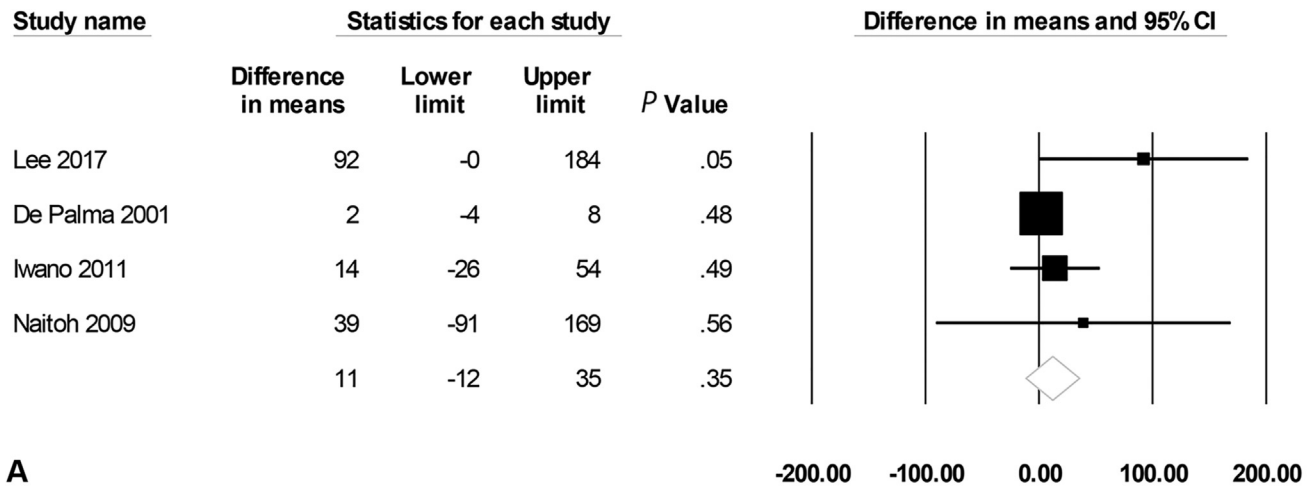


G

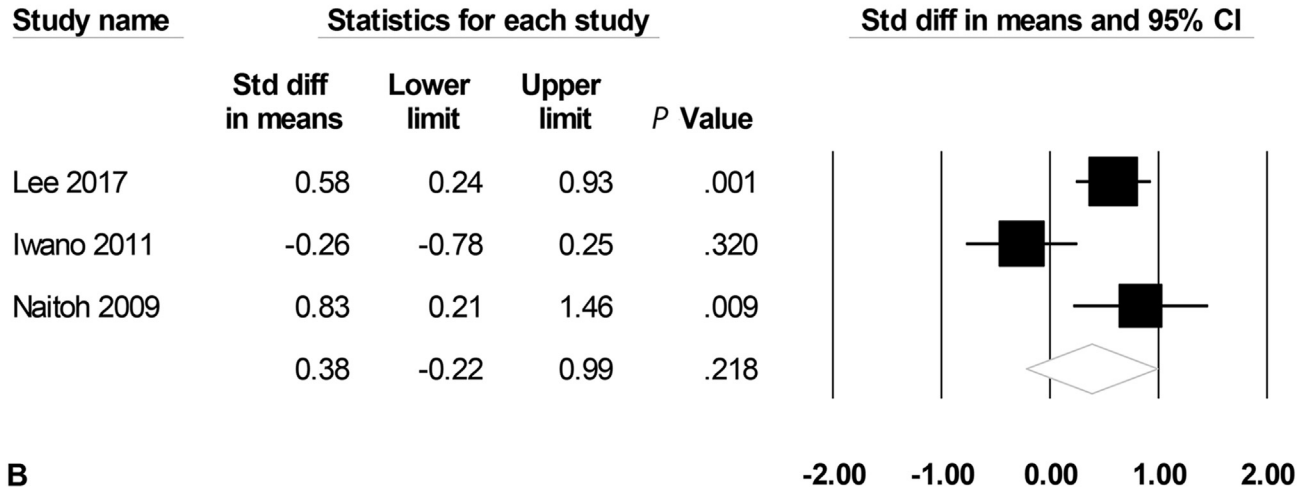
Supplementary Figure 1. Continued.



Supplementary Figure 2. Funnel plots for outcomes of (A) survival, (B) stent patency, (C) reintervention, (D) insertion success, (E) early stent occlusion, (F) 30-day mortality, and (G) cholangitis.



A



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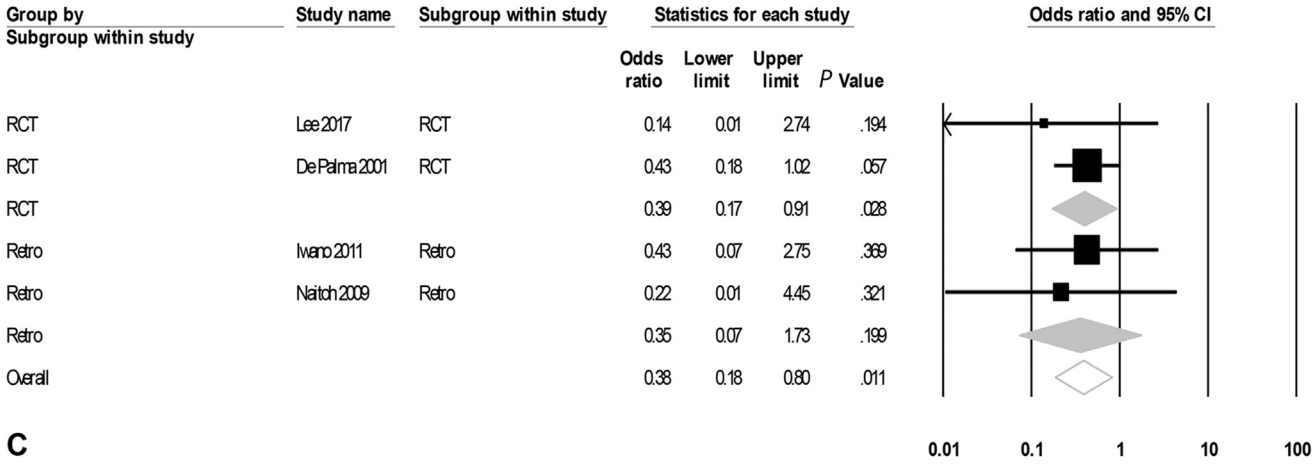
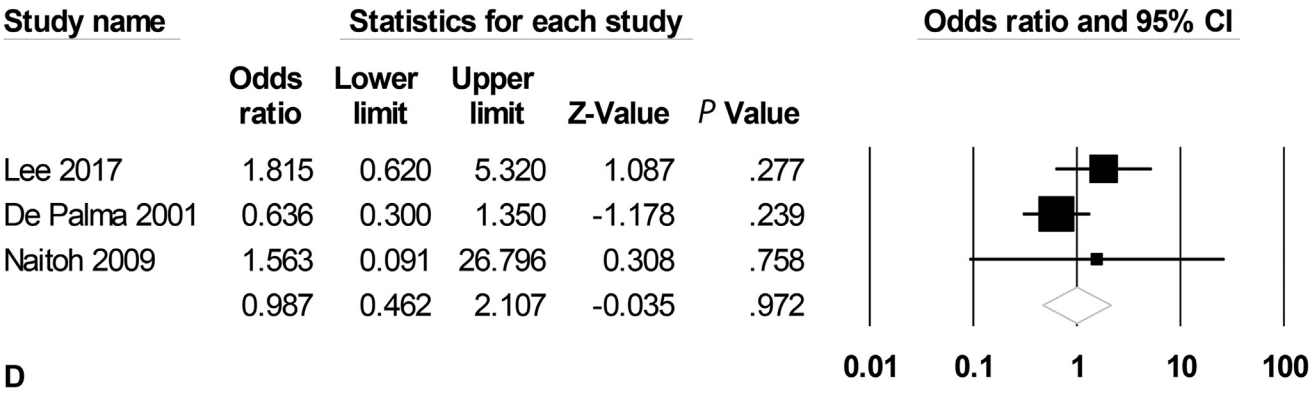


C

Supplementary Figure 3. Forest plots of effect estimates comparing bilateral stents with unilateral stent for the following outcomes: (A) difference in mean survival (days), (B) standard mean difference in stent patency (days), (C) odds technical success, (D) odds of drainage success, (E) odds of early adverse events, (F) odds late adverse events, and (G) odds of late stent occlusion. *CI*, Confidence interval; *RCT*, randomized controlled trial; *SEMS*, self-expanding metal stent.



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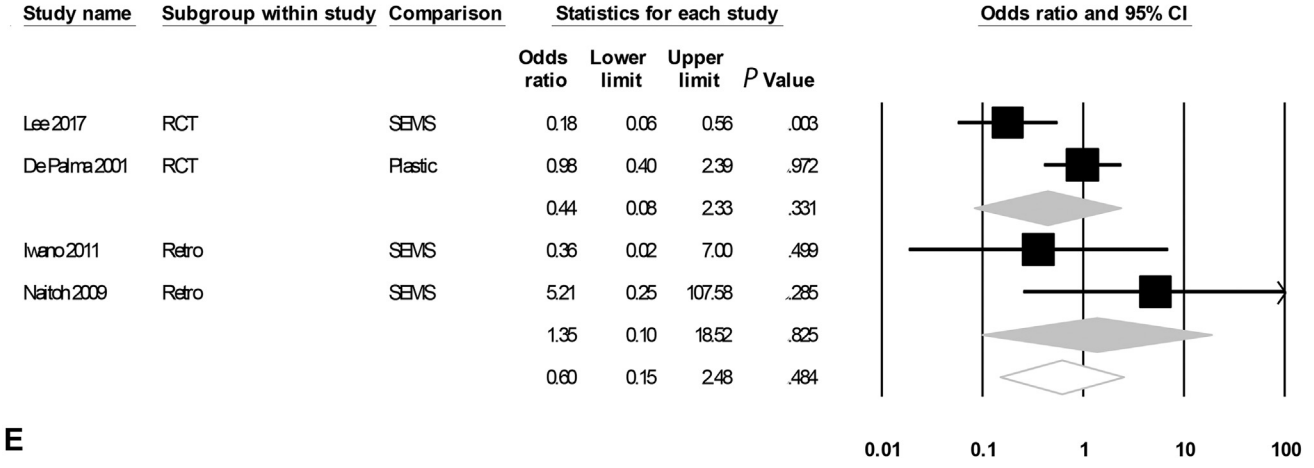

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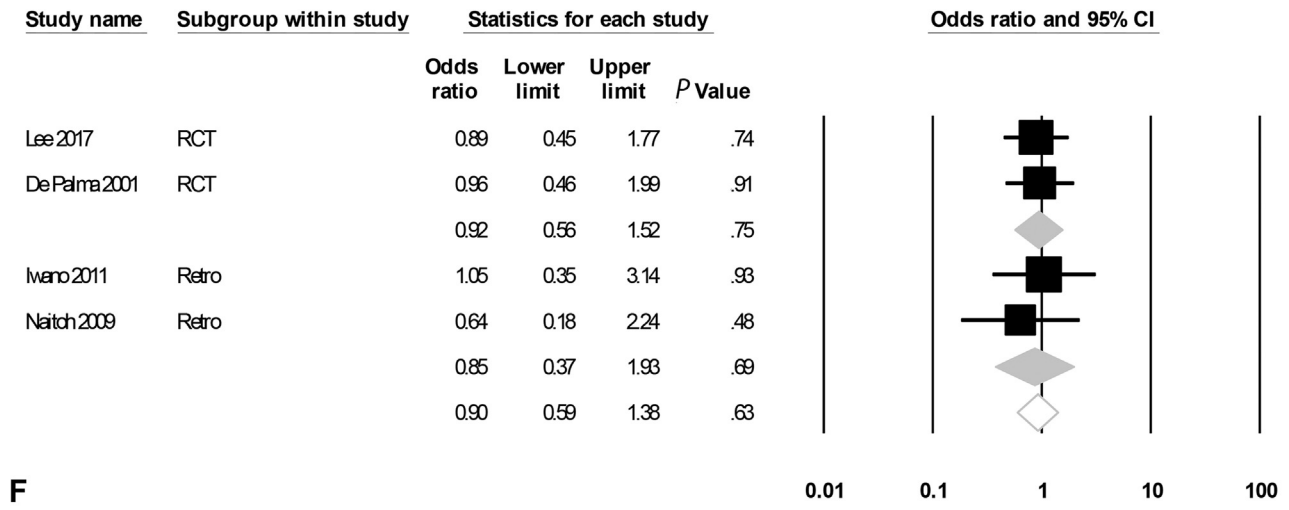

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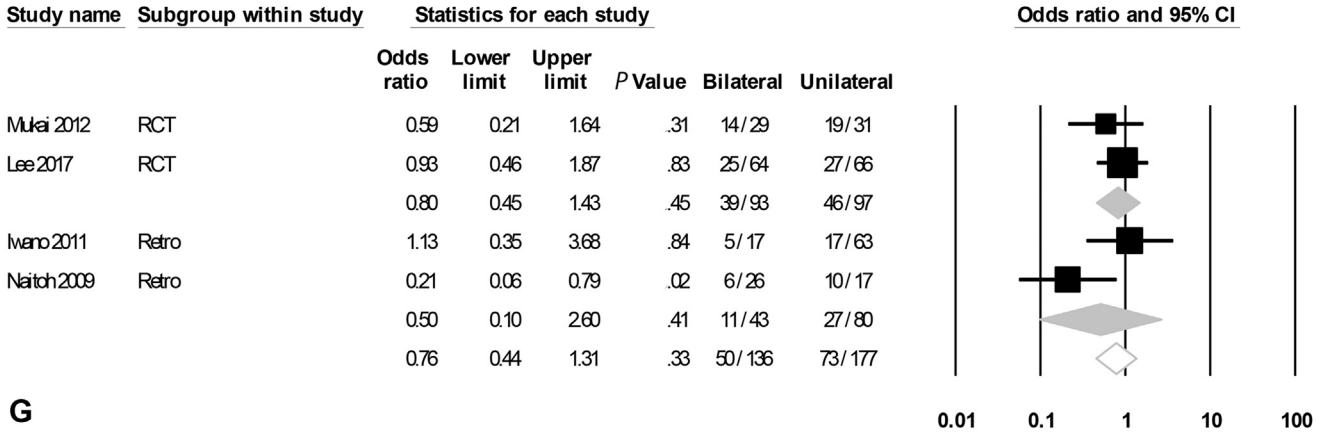

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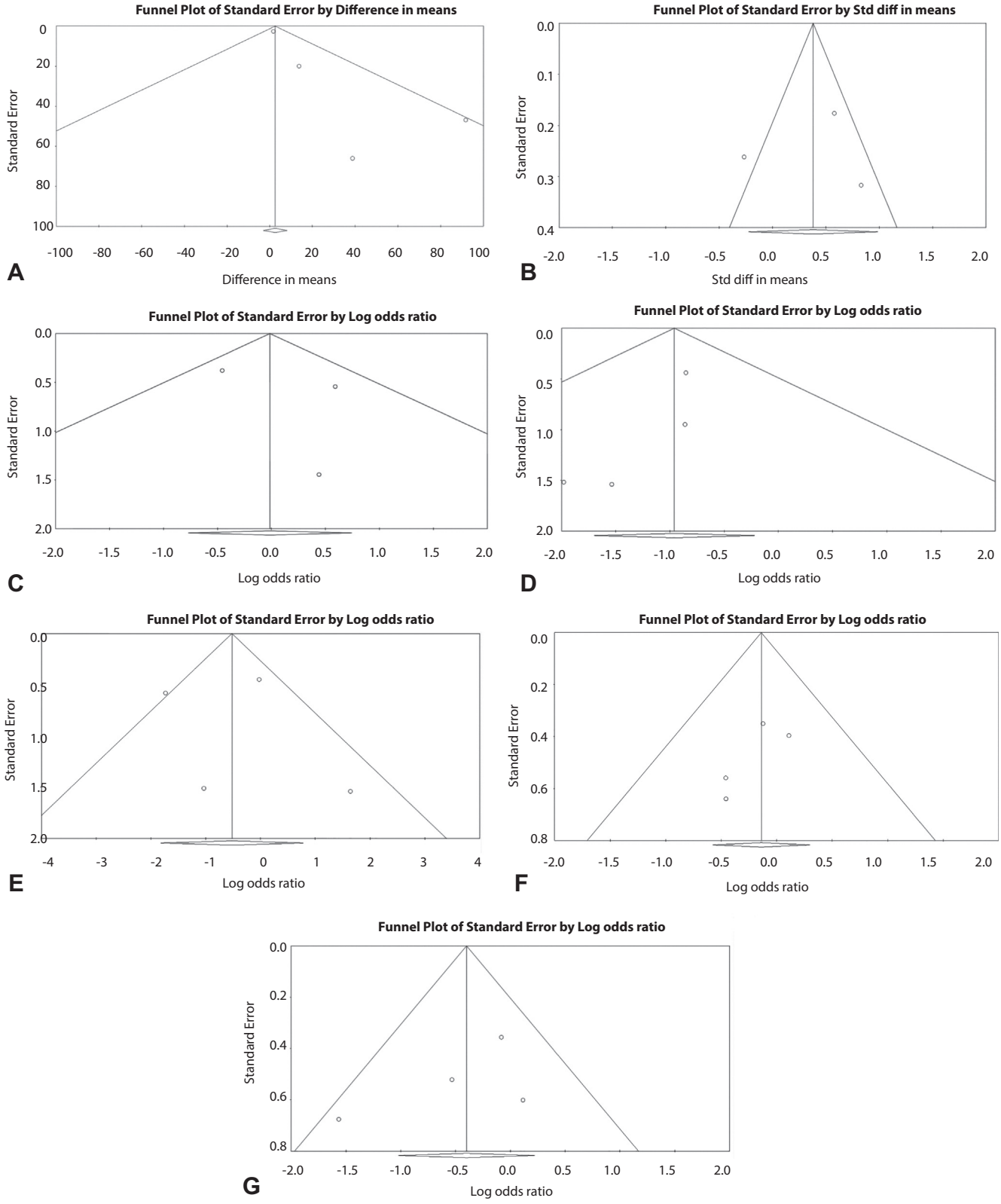
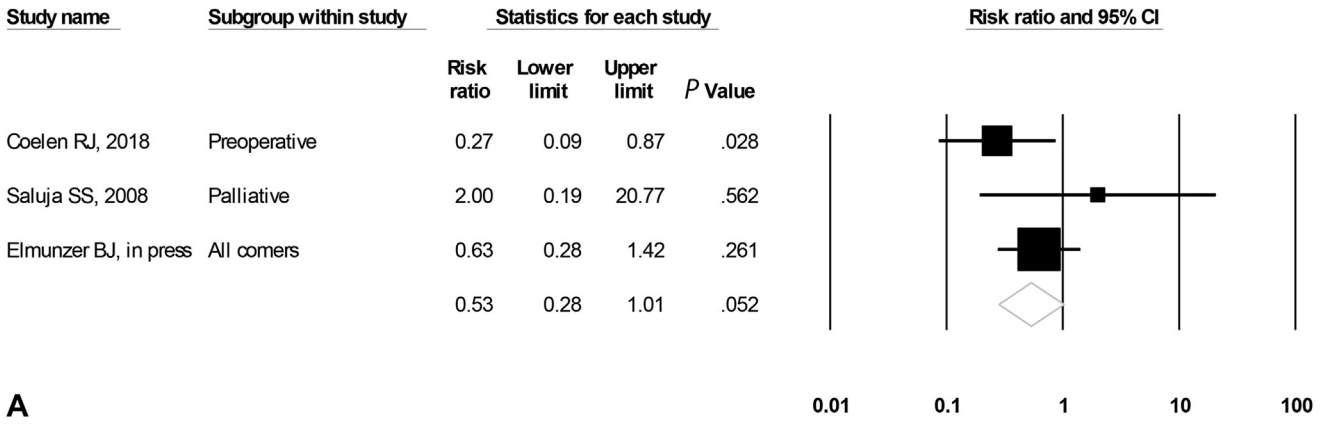
Supplementary Figure 3. Continued.



Supplementary Figure 4. Funnel plots for outcomes of (A) survival (days), (B) stent patency (days), (C) technical success, (D) drainage success, (E) early adverse events, (F) late adverse events, and (G) late stent occlusion.



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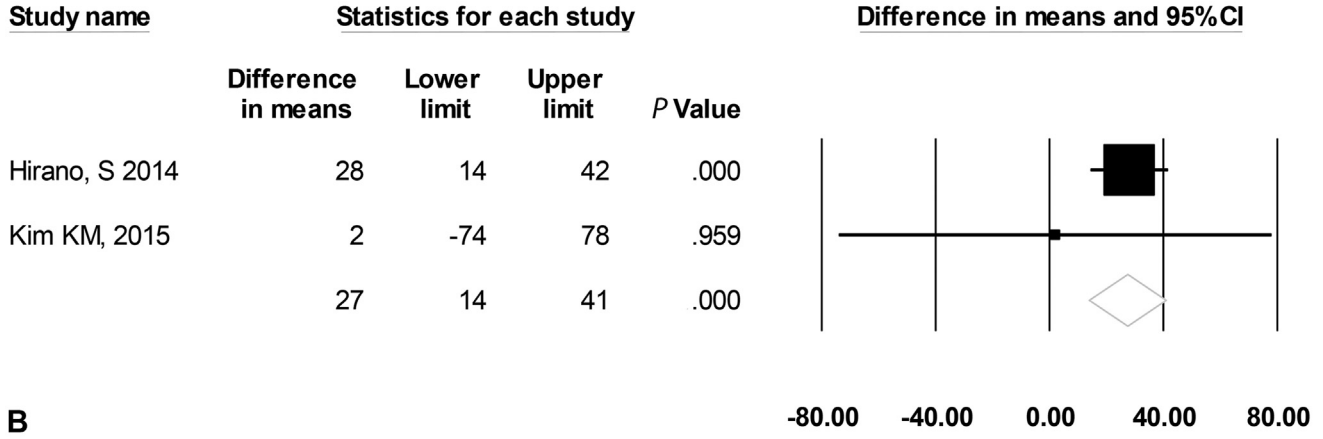

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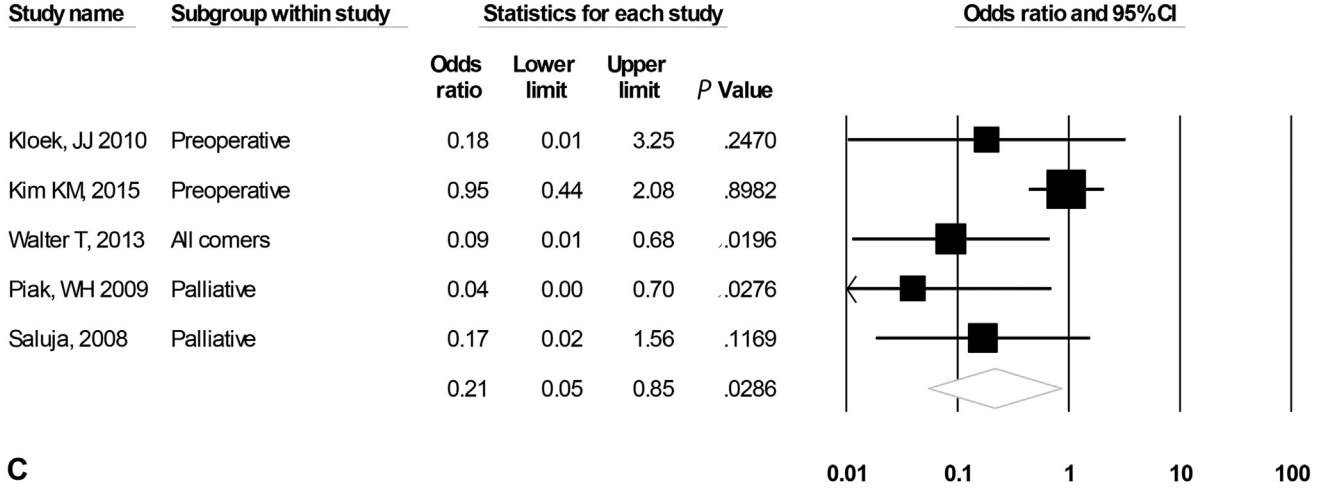
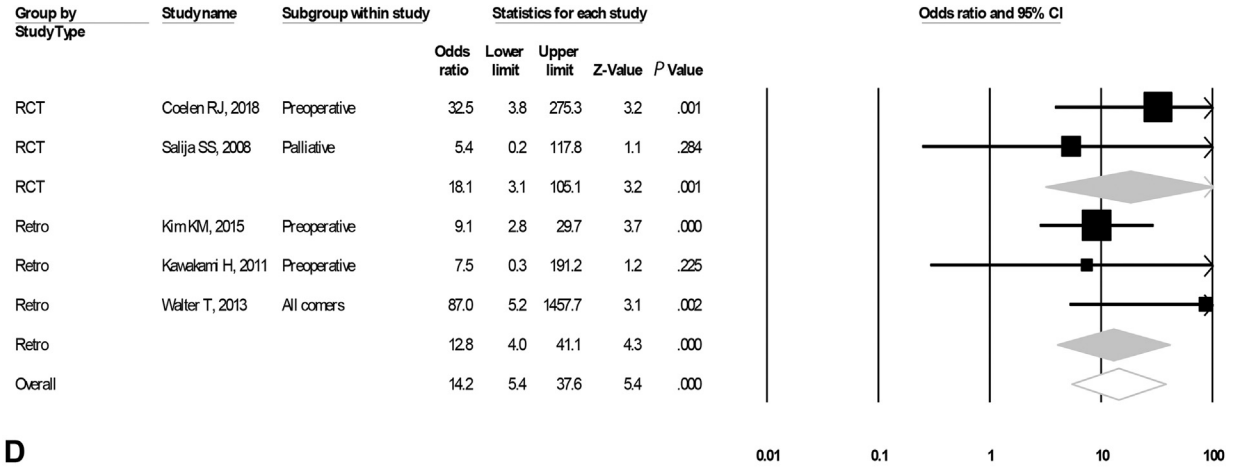


C

Supplementary Figure 5. Forest plots of effect estimates comparing endoscopic biliary drainage with percutaneous transhepatic biliary drainage for the following outcomes: (A) risk of postprocedure mortality, (B) mean difference of survival, (C) odds of technical success, (D) conversion to opposite procedure, (E) odds pancreatitis, (F) odds of overall adverse events, (G) odds of bleeding, and (H) and odds of cholangitis. *CI*, Confidence interval; *RCT*, randomized controlled trial.



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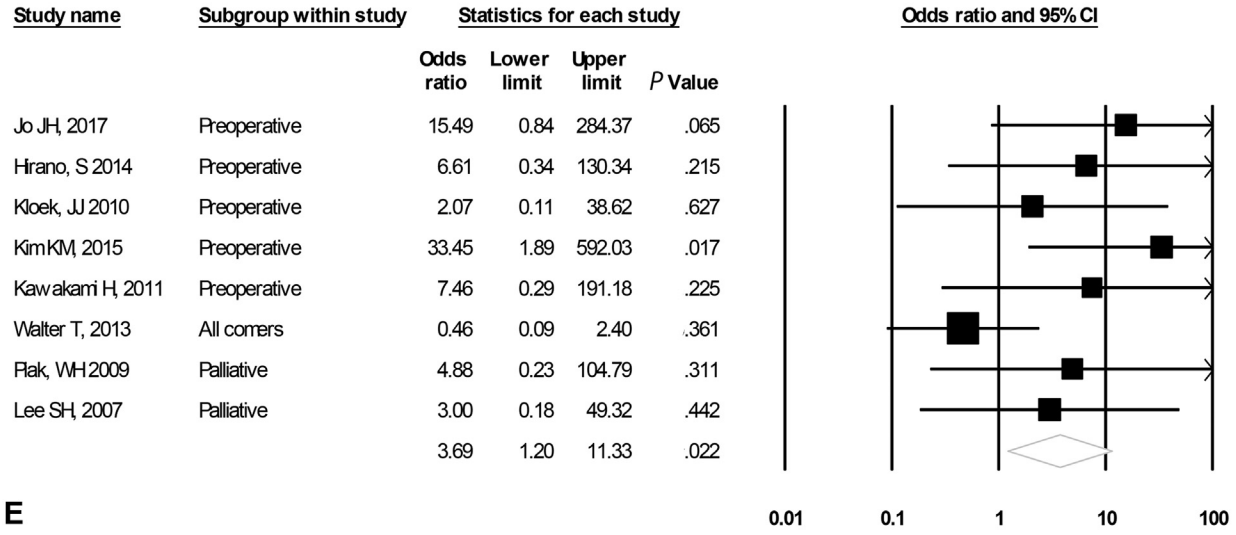

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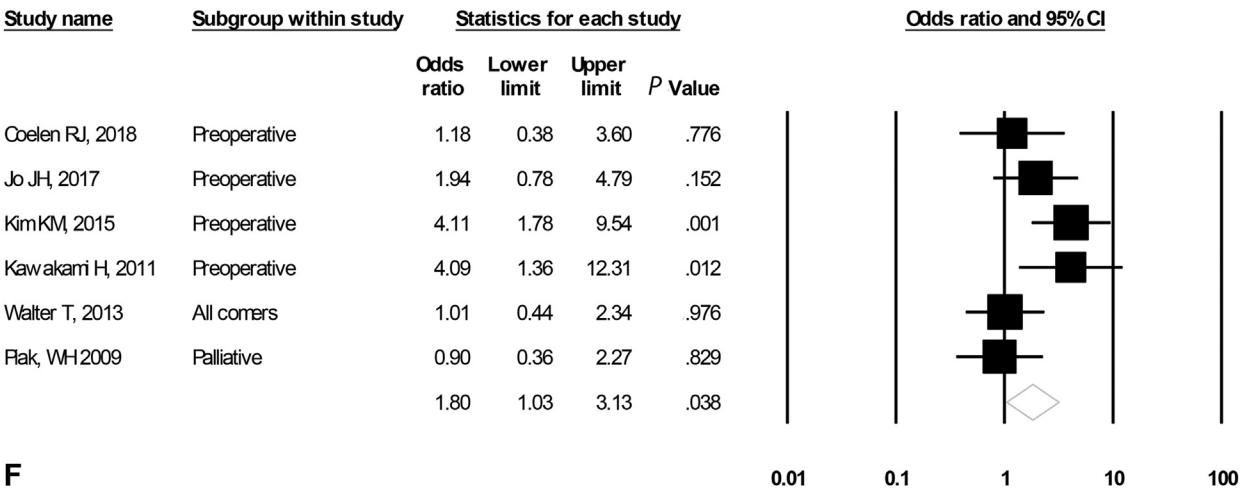

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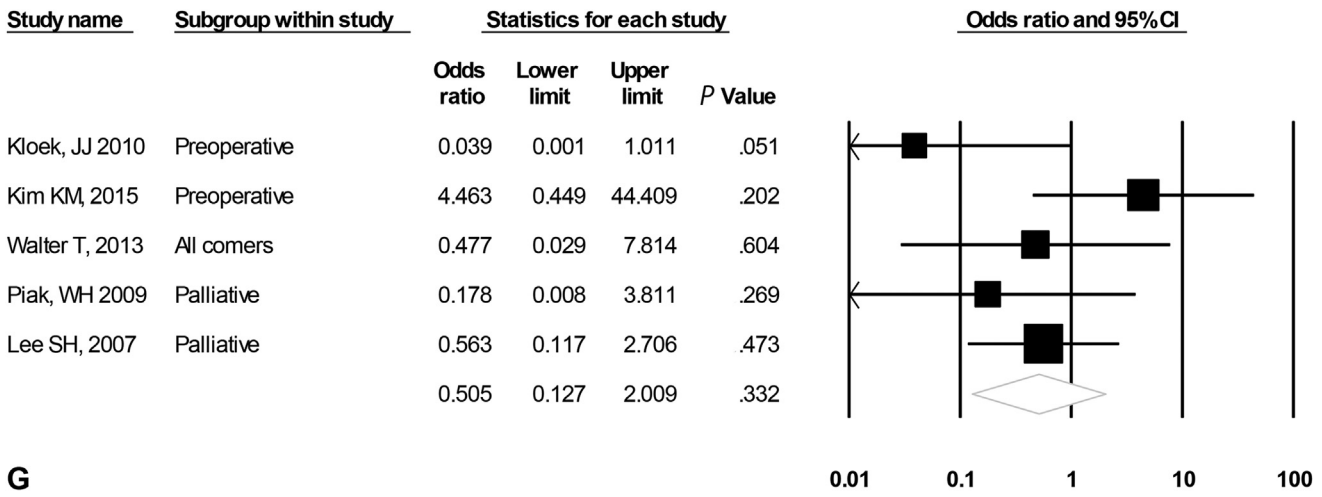
Supplementary Figure 5. Continued.



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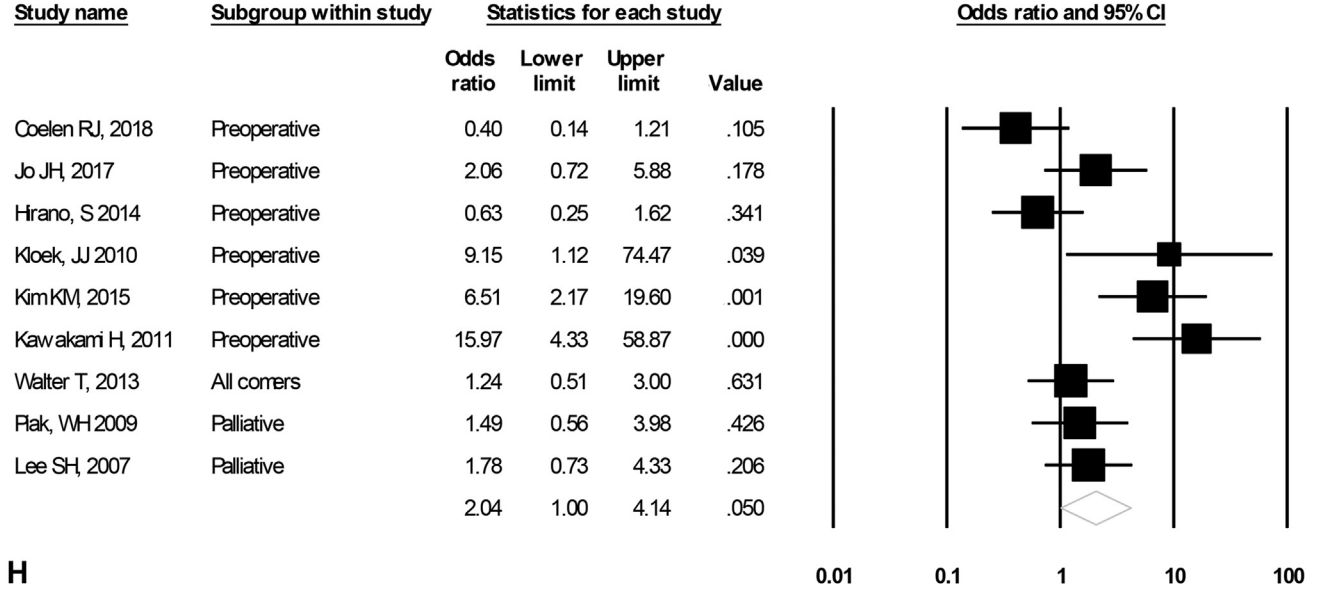
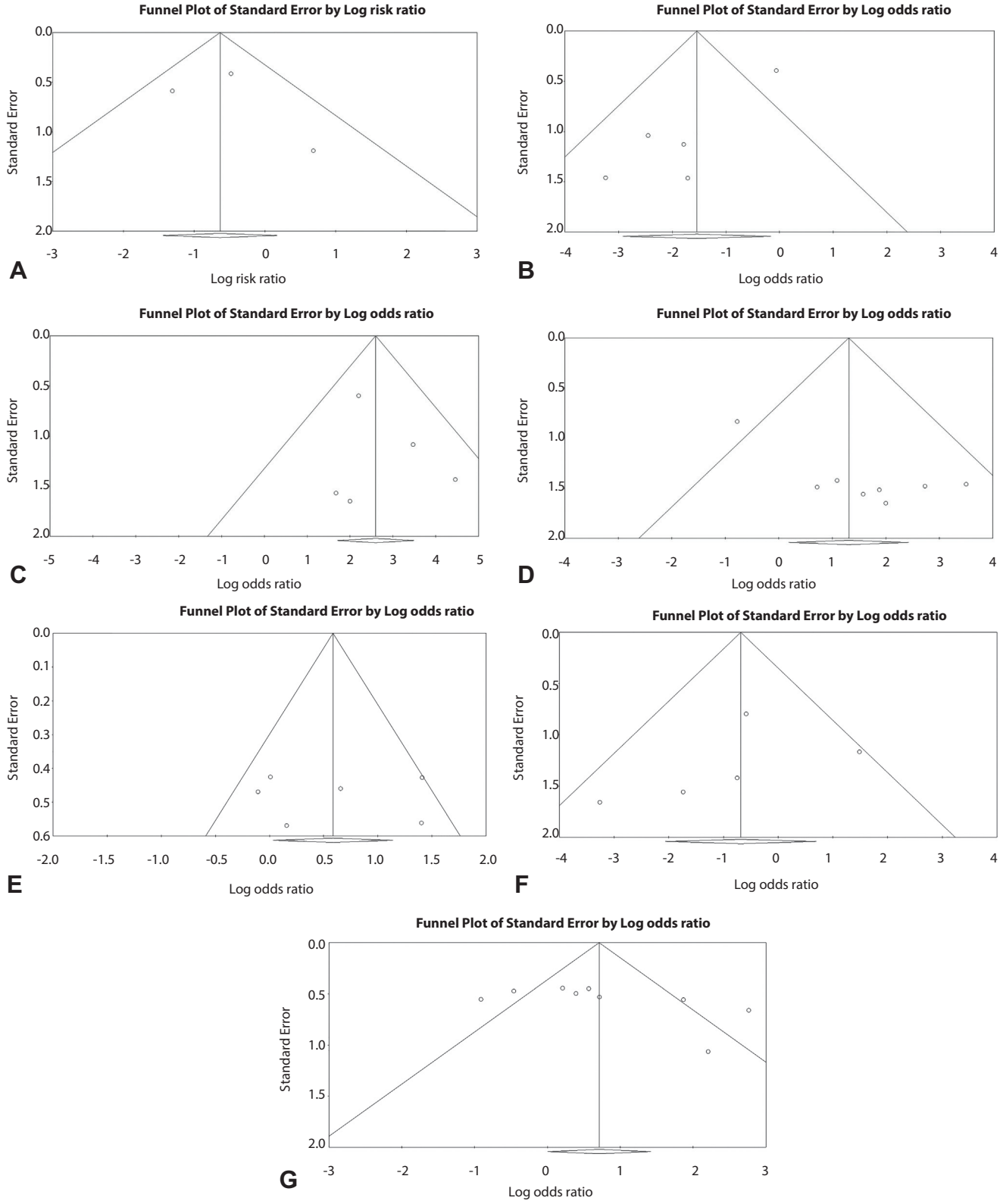


H

Supplementary Figure 5. Continued.



Supplementary Figure 6. Funnel plots for outcomes of (A) postprocedure mortality, (B) technical success, (C) conversion to opposite procedures, (D) pancreatitis, (E) overall adverse events, (F) bleeding, and (G) cholangitis.

SUPPLEMENTARY TABLE 1. Evidence profile for use of SEMSs compared with PSs in patients with unresectable malignant hilar obstruction

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Survival: RCT						
2	Randomized trials	Serious*	Not serious†	Not serious	Not serious‡	None
Survival: 2 RCTs + 3 cohort						
5	Observational studies	Serious*	Not serious	Not serious	Not serious	None
Stent patency: RCT						
2	Randomized trials	Serious*	Not serious	Not serious	Not serious	None
Stent patency: 2 RCTs + 4 cohort						
7	Observational studies	Serious*	Not serious	Not serious	Not serious	None
Insertion success						
3	Randomized trials	Not serious	Not serious	Not serious	Serious§	None
Drainage success: 1 RCT, 4 cohort						
5	Observational studies	Not serious	Not serious	Not serious	Not serious	None ¶
Reintervention: RCT						
3	Randomized trials	Not serious	Not serious	Not serious	Serious§	None
Reintervention: 3 RCTs + 4 cohort						
7	Observational studies	Not serious	Not serious	Not serious	Not serious	None
30-day mortality						
3	Randomized trials	Not serious	Not serious	Not serious	Serious§	None
Cholangitis: 1 RCT, 3 cohort						
4	Observational studies	Not serious	Serious‖	Not serious	Serious§	Publication bias strongly suspected¶

CI, Confidence interval; *SMD*, standardized mean difference; *SD*, standard deviation; *OR*, odds ratio; *SEMS*, self-expanding metal stent; *PS*, plastic stent; *RCT*, randomized controlled trial.

*Rated down because we assumed normal distribution and used medians as means.

†I^2 = 0.99%.

‡Two studies (Mukai et al[2] and Sangchan et al[8]) with a low number of patients.

§Small number of events.

¶Asymmetry in funnel plot.

‖I^2 = 83%.

SUPPLEMENTARY TABLE 1. Continued

No. of patients		Effect			
SEMSs	PSs	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
	Difference in mean (median) survival 56 days (range, 12-101)			⊕⊕⊕◯ MODERATE	CRITICAL
	Difference in mean 33 day (range, –3 to 69)			⊕◯◯◯ VERY LOW	CRITICAL
462	147	—	SMD .864 SD higher (.547 higher to 1.18 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
1385	561.2	—	SMD .639 SD more (.457 more to .821 more)	⊕◯◯◯ VERY LOW	CRITICAL
86/87 (98.9%)	85/93 (91.4%)	OR 6.38 (.86-47.45)	71 more per 1000 (from 13 fewer to 84 more)	⊕⊕⊕◯ MODERATE	CRITICAL
393/417 (94.2%)	342/404 (84.7%)	OR 2.82 (1.19-6.69)	93 more per 1000 (from 21 more to 127 more)	⊕⊕◯◯ LOW	CRITICAL
19/95 (20.0%)	35/93 (37.6%)	OR .34 (.16-.70)	206 fewer per 1000 (from 288 fewer to 79 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
172/398 (43.2%)	254/363 (70.0%)	OR .33 (.21-.53)	265 fewer per 1000 (from 371 fewer to 147 fewer)	⊕⊕◯◯ LOW	CRITICAL
16/99 (16.2%)	22/99 (22.2%)	OR .65 (.31-1.37)	66 fewer per 1000 (from 141 fewer to 59 more)	⊕⊕⊕◯ MODERATE	CRITICAL
24/322 (7.5%)	82/287 (28.6%)	OR .440 (.123-1.608)	136 fewer per 1000 (from 239 fewer to 106 more)	⊕◯◯◯ VERY LOW	IMPORTANT

SUPPLEMENTARY TABLE 2. Evidence profile for use of bilateral stents compared with unilateral stents in patients with unresectable malignant hilar obstruction

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Survival: adjusted RCT						
1	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Survival: overall (2 RCTs + 2 cohort)						
4	Observational studies	Serious†	Not serious	Not serious	Not serious	None
Duration of patency: adjusted, RCT						
1	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Duration of patency: unadjusted RCT						
1	Randomized trials	Serious‡	Not serious	Not serious	Serious*	None
Duration of patency: unadjusted retrospective						
3	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Duration of patency: 1 RCT + 2 cohort						
3	Observational studies	Not serious	Serious§	Not serious	Serious*	Publication bias strongly suspected¶
Late adverse events						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Successful drainage: RCTs						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Successful drainage: overall (2 RCTs + 1 cohort)						
3	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Technical success: RCTs						
2	Randomized trials	Not serious	Not serious	Not serious	Serious‖	None¶
Technical success: overall (2 RCT + 2 cohort)						
4	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Late stent occlusion: RCT						
2	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Late stent occlusion: overall (2 RCTs + 2 cohort)						
4	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Early adverse event						
2	Randomized trials	Not serious	Serious§	Not serious	Serious*	None

CI, Confidence interval; *MD*, mean difference; *HR*, hazard ratio; *OR*, odds ratio; *SEMS*, self-expanding metal stent; *PS*, plastic stent; *RCT*, randomized controlled trial.
*Low number of events.
†Assumed normal distribution.
‡Unadjusted (compared with RCT with adjusted HR).
§d. High I^2.
¶Wide confidence intervals.
‖Based on funnel plot.

SUPPLEMENTARY TABLE 2. Continued

No. of patients		Effect			
Bilateral stent placement	**Unilateral stent placement**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Lee at al[18] showed survival benefit for bilateral drainage when adjusting for covariates: HR = .415 (.259-.666)				⊕⊕⊕◯ MODERATE	CRITICAL
701	624	—	MD 11 days higher (12 lower to 35 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Lee et al. bilateral SEMS was positively associated with stent patency:				⊕⊕⊕◯	CRITICAL
Adjusted HR .30 (.172-0.521), $P < .001$.				MODERATE	
Mukai et al[2]: No difference in patency period $P = .3477$				⊕⊕◯◯	IMPORTANT
Median not reported				LOW	
Liberato et al[10] (SEMS): HR, 3.69 (2.08-6.57)				⊕◯◯◯	IMPORTANT
Liberato et al[10] (PS): HR, 2.24 (1.18-4.24)				VERY LOW	
Naitoh et al[20] (SEMS): .006					
Iwano et al[19] (SEMS): .322					
115	146	—	MD 96 days higher (29 lower to 220 higher)	⊕◯◯◯ VERY LOW	CRITICAL
33/83 (39.8%)	31/80 (38.8%)	OR .92 (.56-1.52)	20 fewer per 1000 (from 126 fewer to 103 more)	⊕⊕⊕◯ MODERATE	CRITICAL
118/145 (81.4%)	120/145 (82.8%)	OR 1.00 (.36-2.76)	0 fewer per 1000 (from 194 fewer to 102 more)	⊕⊕⊕◯ MODERATE	CRITICAL
143/171 (83.6%)	126/163 (77.3%)	OR .99 (.46-2.11)	2 fewer per 1000 (from 163 fewer to 105 more)	⊕◯◯◯ VERY LOW	IMPORTANT
124/145 (85.5%)	136/145 (93.8%)	OR .39 (.17-.91)	83 fewer per 1000 (from 218 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
167/193 (86.5%)	213/226 (94.2%)	OR .38 (.18-.80)	81 fewer per 1000 (from 196 fewer to 13 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
33/83 (39.8%)	31/80 (38.8%)	OR 1.17 (.45-3.04)	38 more per 1000 (from 166 fewer to 270 more)	⊕⊕⊕◯ MODERATE	CRITICAL
47/131 (35.9%)	68/160 (42.5%)	OR .92 (.40-2.09)	20 fewer per 1000 (from 197 fewer to 182 more)	⊕◯◯◯ VERY LOW	IMPORTANT
15/124 (12.1%)	31/136 (22.8%)	OR .44 (.08-2.23)	113 fewer per 1000 (from 205 fewer to 169 more)	⊕⊕◯◯ LOW	CRITICAL

SUPPLEMENTARY TABLE 3. Evidence profile for EBD compared with PTBD in patients with malignant hilar obstruction

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Mortality: RCT						
3	Randomized trials	Not serious	Not serious	Not serious	Serious*	None
Mortality: all studies						
9	Observational studies	Not serious	Not serious	Not serious	Serious†	None
Survival: resectable patients, adjusted						
1	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Survival: resectable, unadjusted						
2	Observational studies	Not serious	Not serious	Not serious	Serious†‡	None
Technical success						
5	Observational studies	Not serious	Not serious§	Not serious	Serious†	None ¶
Peritoneal recurrence: adjusted						
1	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Peritoneal metastasis and tube seeding						
6	Observational studies	Not serious	Serious‖	Not serious	Serious†	None
Overall adverse events						
6	Observational studies	Not serious	Not serious	Not serious	Serious†	None
Cholangitis						
9	Observational studies	Not serious	Serious‖	Not serious	Not serious	Publication bias strongly suspected¶
Pancreatitis						
8	Observational studies	Not serious	Not serious	Not serious	Serious†	None
Bleeding						
5	Observational studies	Not serious	Not serious	Not serious	Serious†	None
Conversion to another drainage						
4	Observational studies	Not serious	Not serious	Not serious	Serious†	None

CI, Confidence interval; *EBD*, endoscopic biliary drainage; *PTBD*, percutaneous transhepatic biliary drainage; *MD*, mean difference; *HR*, hazard ratio; *OR*, odds ratio; *RCT*, randomized controlled trial.

*One study only.

†Low number of events.

‡Normal distribution assumed.

§I^2 = 59%.

¶On funnel plot.

‖High I^2.

SUPPLEMENTARY TABLE 3. Continued

No. of patients		Effect		Certainty	Importance
EBD	PTBD	Relative (95% CI)	Absolute (95% CI)		
9/62 (14.5%)	17/59 (28.8%)	Risk ratio .53 (.28-1.01)	14 fewer per 100 (from 21 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
18/363 (5.0%)	32/421 (7.6%)	Risk ratio .61 (.35-1.01)	30 fewer per 1000 (from 49 fewer to 1 more)	⊕◯◯◯ VERY LOW	CRITICAL
		Adjusted HR, 2.075 (1.279-3.709), $P = .003$		⊕⊕◯◯ LOW	CRITICAL
118	129	—	MD 27 months higher (14 higher to 41 higher)	⊕◯◯◯ VERY LOW	CRITICAL
222/292 (76.0%)	155/183 (84.7%)	OR .21 (.05-.85)	309 fewer per 1000 (from 630 fewer to 22 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
3/74 (4.1%)	17/67 (25.4%)	OR 6.9 (1.9-25.7)	447 more per 1000 (from 139 more to 644 more)	⊕◯◯◯ VERY LOW	
64/649 (9.9%)	138/716 (19.3%)	OR .27 (.13-.56)	132 fewer per 1000 (from 163 fewer to 75 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
109/264 (41.3%)	82/263 (31.2%)	OR 1.80 (1.03-3.13)	137 more per 1000 (from 6 more to 275 more)	⊕◯◯◯ VERY LOW	CRITICAL
148/462 (32.0%)	83/441 (18.8%)	OR 2.04 (1.00-4.14)	133 more per 1000 (from 0 fewer to 302 more)	⊕◯◯◯ VERY LOW	CRITICAL
32/435 (7.4%)	4/414 (1.0%)	OR 3.69 (1.20-11.33)	25 more per 1000 (from 2 more to 90 more)	⊕◯◯◯ VERY LOW	CRITICAL
6/299 (2.0%)	15/256 (5.9%)	OR .505 (.127-2.009)	28 fewer per 1000 (from 51 fewer to 53 more)	⊕◯◯◯ VERY LOW	IMPORTANT
77/178 (43.3%)	5/179 (2.8%)	OR 14.590 (5.759-36.975)	267 more per 1000 (from 114 more to 487 more)	⊕◯◯◯ VERY LOW	CRITICAL