

Unilateral versus bilateral endoscopic stenting in patients with unresectable malignant hilar obstruction: a systematic review and meta-analysis




Authors

Mohamad Aghaie Meybodi¹, Delaram Shakoor², Julie Nanavati³, Yervant Ichkhanian¹, Kia Vosoughi¹, Olaya I. Brewer Gutierrez¹, Anthony N. Kalloo¹, Vikesh Singh¹, Vivek Kumbhari¹, Saowanee Ngamruengphong¹, Mouen A. Khashab¹

Institutions

- 1 Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, Baltimore, Maryland, United States
- 2 Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, Maryland, United States
- 3 Welch Medical Library, Johns Hopkins University, Baltimore, Maryland, United States

submitted 31.7.2019

accepted after revision 16.10.2019

Bibliography

DOI <https://doi.org/10.1055/a-1067-4326> |
Endoscopy International Open 2020; 08: E281–E290
© Georg Thieme Verlag KG Stuttgart · New York
eISSN 2196-9736

Corresponding author

Mouen Khashab MD, Associate Professor of Medicine, Director of Therapeutic Endoscopy, Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, 1800 Orleans St, Sheikh Zayad 7E Rm 7125G, Baltimore, MD 21224
Fax: +1-443-287-1960
mkhasha1@jhmi.edu

Supplementary material

Online content viewable at:
<https://doi.org/10.1055/a-1067-4326>

ABSTRACT

Background and study aims Endoscopic stent placement is used for palliative management of unresectable malignant hilar obstruction, which could be achieved by either unilateral or bilateral stent insertion.

Materials and methods A literature search was performed to identify studies that reported outcomes of metallic biliary stent placement in patients with malignant hilar obstruction. Weighted pooled rates (WPR) along with 95% confidence intervals (95%CI) were calculated to determine and compare outcomes including technical and functional success, early and late adverse events, post procedure cholangitis, and stent occlusion between two groups.

Results A total of 21 studies with 1292 patients were included. WPR of technical success was significantly higher in the unilateral group (97%, 95%CI: 93–98%) vs. bilateral group (89%, 95%CI: 84–92%) ($P=0.0003$). WPR for functional success in the unilateral and bilateral groups were 96% (95%CI: 91–98%) and 94% (95%CI: 91–97%), respectively ($P=0.48$). The rate of early and late complications was comparable between the two groups.

Conclusion In patients with unresectable malignant hilar obstruction, unilateral and bilateral metallic stenting techniques are comparable in terms of efficacy and safety.

Introduction

Unresectable malignant hilar biliary obstruction could be caused by a wide variety of neoplasms [1, 2]. Certain malignancies such as Klatskin tumor or hilar cholangiocarcinoma can lead to intrinsic obstruction, while other tumors, including gallbladder carcinoma, hepatomas, pancreatic adenocarcinoma, and metastases contribute to extrinsic obstruction, which ultimately lead to obstructive jaundice [3, 4].

Thus, palliative biliary drainage is absolutely crucial for improving the quality of life of patients with unresectable malig-

nant hilar biliary obstruction. Percutaneous or endoscopic drainage as well as surgical bypass are currently the mainstay of palliative treatment [5, 6]. Due to the limited survival of these patients, minimally-invasive procedures such as endoscopic drainage may be more appealing. Furthermore, prior studies have shown that comparing to surgical bypass procedures, endoscopic drainage could provide better outcomes and lower complication rate in the palliative management of patients with unresectable malignant hilar obstruction [7, 8].

Endoscopic drainage in patients with unresectable malignant hilar obstruction entails using a plastic or self-expandable

metal stent (SEMS). Despite similar technical success rates, metallic stents have been shown to provide longer patency than their plastic counterpart [6]; however, there is no consensus regarding the best treatment option for palliative treatment of patients with unresectable hilar obstruction. In addition, debate remains on the superiority of bilateral stenting over unilateral stenting. While in unilateral stenting there are concerns over suboptimal efficacy in relieving jaundice and bacterial contamination of the undrained segment [9,10], the technical complexity of bilateral stenting has been a major drawback [11]. Therefore, given conflicting outcomes with different endoscopic strategies, we performed a systematic review and meta-analysis to determine the overall technical and functional success rates, as well as the adverse event (AE) rate of unilateral and bilateral metallic stenting and to compare outcomes in management of patients with unresectable malignant hilar obstruction.

Materials and methods

This systematic review was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and meta-analysis of observational studies in epidemiology (MOOSE) [13].

Literature search and study selection

A comprehensive literature search strategy was developed by an experienced medical reference librarian (JN). Four electronic databases – Medline, Embase, Cochrane, and ISI Web of Sciences – were screened to identify relevant studies published through June 1, 2018. The following MeSH and keyword search terms were used: “unilateral stent or drainage, bilateral stent or drainage, malignant hilar obstruction, Klatskin tumor, biliary tract neoplasm, gallbladder tumor”. Literature search was conducted by two investigators (MAM, DS), independently. The retrieved records were screened on the basis of the title and abstract, and the eligible articles were obtained for full-text review. Only English language articles were included. The bibliography of retrieved articles were manually reviewed to reveal any additional relevant studies.

Inclusion and exclusion criteria

Inclusion criteria were determined by two investigators (MAM, MAK). Studies were eligible for inclusion if they described outcomes of unilateral or bilateral endoscopic hepatic duct drainage by SEMS in management of patients with unresectable malignant hilar obstruction. Randomized clinical trials (RCTs) or observational studies that reported technical and functional success rates as well as early and late AEs. Technical success was defined as successful stent insertion across the hilar stricture. Functional success was defined as 50% decrease in bilirubin level within 14 days or a 75% decrease in bilirubin level within a month. Early AEs were defined as any procedure-related complications that occurred within 30 days, while late AEs were described as complications occurring later than 30 days. Cholangitis was reported if the patient had fever, leukocytosis, and increasing bilirubin. Stent occlusion was defined as increase

in bilirubin, recurrence of jaundice, and presence of imaging findings suggestive of intrahepatic bile duct dilation.

Individual case reports or case series with 10 or fewer patients were excluded. Published abstracts of national or international conferences were not included in the study because assessment of risk of bias in them was not possible. Studies that only reported outcomes of plastic stenting were also excluded. Titles and abstracts of obtained records were screened by two investigators (MAM, DS), independently. All eligible articles were downloaded into EndNote 7.0 (Thomson ISI ResearchSoft, Philadelphia, Pennsylvania, United States) and duplicate studies were removed. For final inclusion, eligible studies were reviewed at the full-text level to determine their eligibility. Any disagreement was resolved through discussion with the senior author (MAK).

Data extraction and quality assessment

The following data were extracted from the included studies: study design, year of publication, number of patients, age, sex, type of stent (plastic or SEMS), stenting strategy (unilateral or bilateral), technical success rate, functional success rate, occlusion rate, early and late AEs, post-procedure cholangitis, stent patency, survival and follow-up duration. Two investigators (MAM, DS), independently assessed the quality of included studies using the National Institutes of Health (NIH) quality assessment tool for before–after (pre–post) studies with no control group and the Cochrane tool for RCTs [14].

Statistical analysis and data synthesis

Weighted pooled rates (WPR) along with their 95% confidence intervals (CI) and predictive interval were calculated for technical success, functional success, early and late AEs, post-procedure cholangitis, and stent occlusion. The weight of each study was calculated by the inverse of its variance. Subgroup analysis was performed to compare effect size in studies that employed unilateral or bilateral stent. Cochran Q test and I^2 were assessed for heterogeneity across studies [15]. Presence of significant heterogeneity was considered when $P < 0.1$ for the Cochran Q test. The I^2 values of 0–50%, 50% to 75%, and 75% to 100% were interpreted as low, moderate, and high level of heterogeneity, respectively [16]. Due to heterogeneity between types and sizes of stents, DerSimonian–Laird random-effects model of meta-analysis was applied [17, 18]. A random effects model was also used to combine studies within each subgroup. $P < 0.05$ was considered significant.

A sensitivity analysis was performed to determine if one-arm studies had a disparate effect on the pooled effect. We calculated the pooled effect with only two-arm studies. With this approach, if the pooled effect does not change significantly, then the one-arm studies do not disturb the pooled effect. Visual evaluation of funnel plots and the Begg–Mazumdar regression test were performed for evaluation of presence of publication bias [19]. If publication bias was present, Duval and Tweedie’s “trim and fill” method was used to adjust effect size, accordingly. All analysis was performed by one investigator (MAM), using Comprehensive Meta-Analysis software (version 2.0; Biostat; Englewood, New Jersey, United States).

Results

Literature search

Based on our search strategy, we identified 35 records from PubMed, 49 records from Embase, 22 records from Cochrane, and 47 records from ISI Web of Science. Fifty-six duplicate records were removed and an additional 63 studies were excluded after screening titles and abstracts. Thirty-four studies were selected for the full-text review and 16 studies were excluded due to our exclusion criteria; one study [20] was excluded due to serial insertion of stents and another study [21] was excluded due to possible population overlap with another included study [22]. Finally, 18 studies with 911 patients were included in our meta-analysis. Our search strategy and study selection are summarized in a PRISMA flowchart (► Fig. 1).

Study characteristics and quality assessment

Among included studies, 10 [22–31] were retrospective and the rest [32–39] were prospective. Two studies [32, 33] were RCTs. Thirteen studies [23–31, 34, 35, 38, 39] were single-center and the other five studies [21, 32, 33, 36, 37] were multicenter. Two studies [38, 39] evaluated only unilateral stents, 11 studies [21, 23, 25–27, 30, 31, 34–37] evaluated only bilateral stents and five studies [24, 28, 29, 32, 33] compared unilateral vs. bilateral stents.

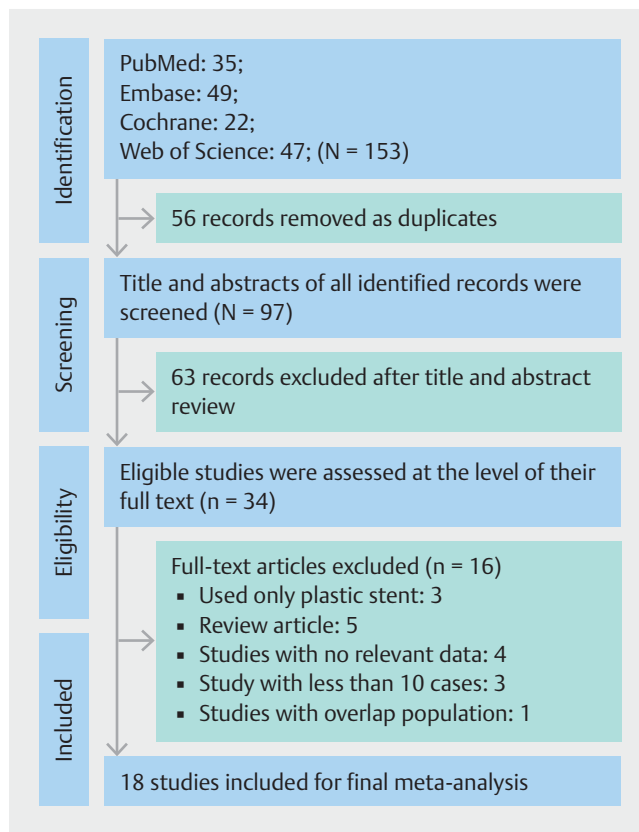
Among 911 patients with malignant hilar obstruction, cholangiocarcinoma was the most frequent etiology (70%). Seventeen percent of patients had stricture due to gallbladder carcinoma, and 13% of patients had obstruction related to other causes. One study [39] did not report the etiology. According to the Bismuth classification, 29.25% of cases were type II, 38.5% of cases were type III, and 32.25% of cases were type IV. Two studies [23, 28] did not report Bismuth classification. Demographic data and study characteristics of included studies are described in ► Table 1 and ► Table 2.

The Cochrane tool for assessing risk of bias was used for quality assessment of the two RCTs. Performance bias was high due to awareness of endoscopists and patients about stent type; however, risk of bias in other domains, including selection, detection, attrition, and reporting was low. Quality assessment of the observational studies was done by NIH quality assessment tool for Before-After (Pre-Post) Studies With No Control Group. Nine studies [24, 25, 28–31, 34, 35, 38] had good quality and seven studies [23, 26, 27, 32, 36, 37, 39] had fair quality (► Table 3).

Meta-analysis

Unilateral vs. bilateral metallic stent

Among included studies, 18 [22–39] recruited the self-expandable metallic stent. The weighted pooled rate (WPR) of technical success was 91% (95%CI: 88–94%, prediction interval: 72–98%), Cochrane Q test $P=0.001$, $I^2=55\%$. The Begg–Mazumdar test revealed no publication bias ($\tau=0.20$, $P=0.17$, two-tailed) (Supplementary Fig. 1). Subgroup analysis was used to compare effect size between unilateral and bilateral



► Fig. 1 PRISMA flowchart. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097.

stenting. The technical success rate was 97% (95%CI: 93–98%, prediction interval: 91–97%) and 89% (95%CI: 84–92%, prediction variable: 69–97%) in the unilateral and bilateral stenting, respectively. The technical success rate was significantly higher in patients who underwent unilateral metallic stenting as compared to those who underwent bilateral metallic stenting ($P=0.003$) (► Fig. 2a). Sensitivity analysis by pooling data from two-arms studies also showed the higher technical success rate in unilateral group (RR=3.82, $P=0.03$).

The WPR of functional success was 95% (95%CI: 92–96%, predictive interval: 87–98%), Cochrane Q test $P=0.24$, $I^2=18\%$. There was no publication bias according to the Begg–Mazumdar regression test ($\tau=0.05$, $P=0.74$, two-tailed). The WPR of functional success of unilateral stenting was 96% (95%CI: 90–98%, predictive interval: 84–99%) and bilateral stenting was 94% (95%CI: 91–96%, predictive interval: 79–98%). There was no statistically significant difference between the functional success rate of unilateral and bilateral stenting ($P=0.481$) (► Fig. 2b). Sensitivity analysis also showed no statistically significant difference between two groups (RR=2.18, $P=0.22$).

In total, 60 early complications happened in the 517 patients. The WPRs of early complication were 15% (95%CI: 7–30%) and 9% (95%CI: 6–15%) in unilateral and bilateral SEMS, respectively (► Fig. 3a). Cholangitis was the most common type

► **Table 1** Demographic and technical data from single-arm studies.

Study	Stent	Number of patients (male)	Age (mean ± SD)	Technical success, %	Functional success, %	Stent patency, (day, median)	Survival, (day, median)	Follow-up
De Palma et al 2003	Unilateral stent	61 (40)	62.5 ± 11.2	96.7	100	169	140	N/A
Singh et al 2004	Unilateral stent	18 (7)	53.7 ± 11.1	100	100	N/A	N/A	N/A
Chahal et al 2010	Bilateral stent	21 (15)	63.7 ± 13.9	100	N/A	189	N/A	6.14 months
Hwang et al 2011	Bilateral stent	30 (20)	68 ± 8	86.7	100	140	176	5.8 months
Kim et al 2012	Bilateral stent	97 (48)	71 median	78.4	97.4	159	226	234 days
Kim et al 2009	Bilateral stent	34 (19)	68.3 median	85.3	100	186	239	21 months
Kitamura et al 2017	Bilateral stent	17 (9)	78 median	100	82	N/A	N/A	192 days
Law et al 2013	Bilateral stent	24 (19)	68 ± 13	100	N/A	N/A	N/A	97 days
Lee et al 2013	Bilateral stent	84 (48)	68.3 ± 15.8	95.2	97.5	238	256	N/A
Park et al 2016	Bilateral stent	31 (16)	67 ± 14	83.9	92.3	188	175	N/A
Park et al 2009	Bilateral stent	35 (21)	66	94.3	100	150	180	142 days
Yang et al 2018	Bilateral stent	43 (22)	72.9 ± 9.1	88.4	100	198	300	184 days
Dumas et al 2000	Bilateral stent	45 (28)	72	73.3	100	N/A	N/A	8.5 months

► **Table 2** Demographic and technical data from two-arm studies.

Study	Number of patients (male)		age		Technical success%		Functional success%		Stent patency, (day, median)		Survival, (day, median)	
	Uni	Bi	Uni	Bi	Uni	Bi	Uni	Bi	Uni	Bi	Uni	Bi
Lee et al 2017	66 (33)	67 (36)	74.1 ± 10.42	73.5 ± 10.42	100	95.5	95.3	87.5	139	252	178	270
Iwano et al 2011	63 (35)	19 (11)	71.6	66.6	95.2	89.4	N/A	N/A	133	125	170	184
Naitoh et al 2009	17 (9)	29 (12)	69 ± 14	70 ± 11	100	90	94.1	96.1	210	488	166	205
Mukai et al 2012	14	16	N/A	N/A	100	100	100	100	363	295	N/A	N/A
Liberato et al 2012	35	45	N/A	N/A	100	93.3	N/A	N/A	24 weeks	29 weeks	N/A	N/A

Uni, unilateral; Bi, bilateral

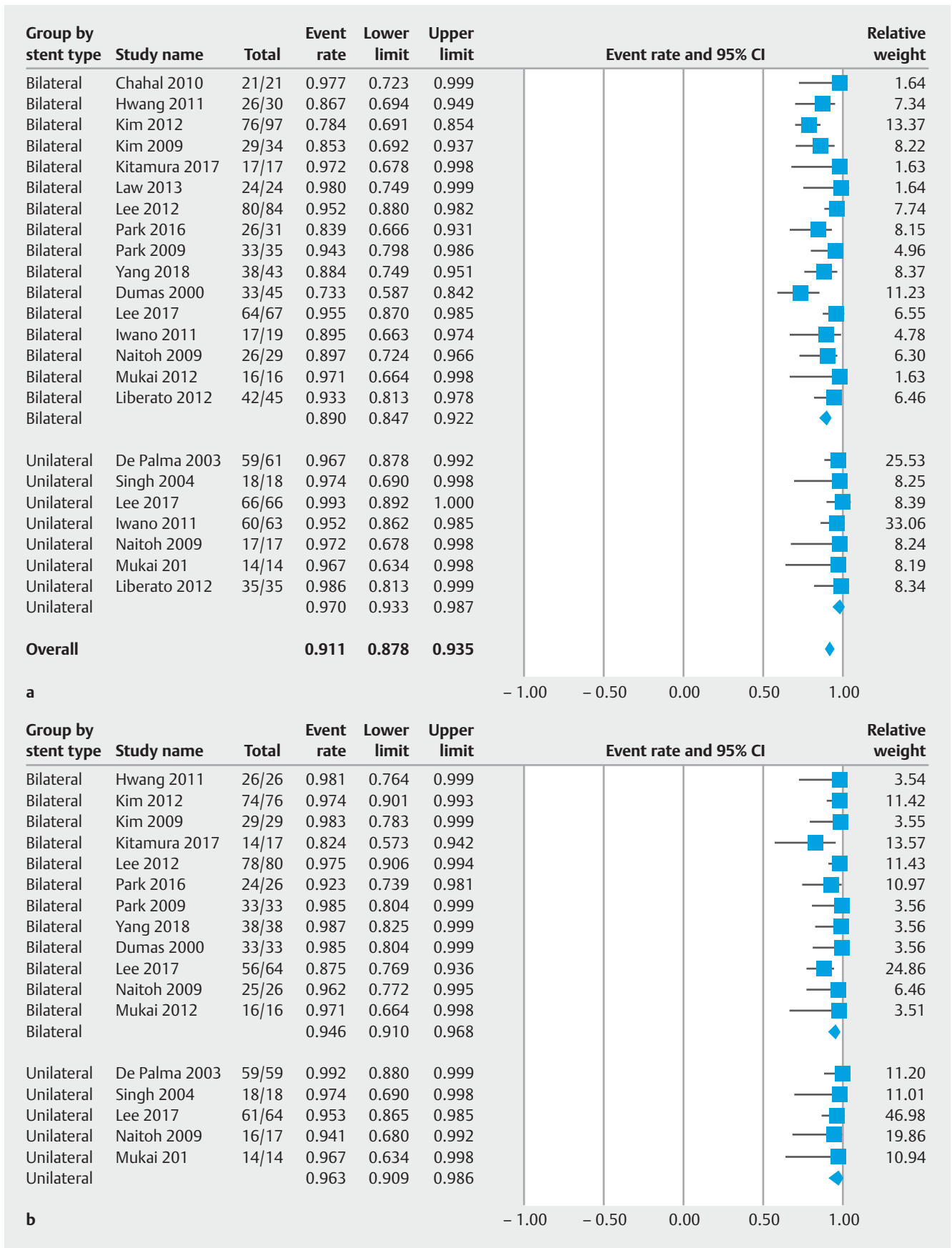
► **Table 3** Quality assessment of studies with NIH quality assessment tool for before–after studies with no control group.

Criteria	De Palma et al 2002	Singh et al	Chahal et al	Hwang et al	Kim et al 2012	Kim et al 2009	Kita-mura et al	Law et al	Lee et al 2013	Park et al 2016	Park et al 2009	Yang et al	Iwano et al	Naitoh et al	Liberato et al	Dumas et al
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

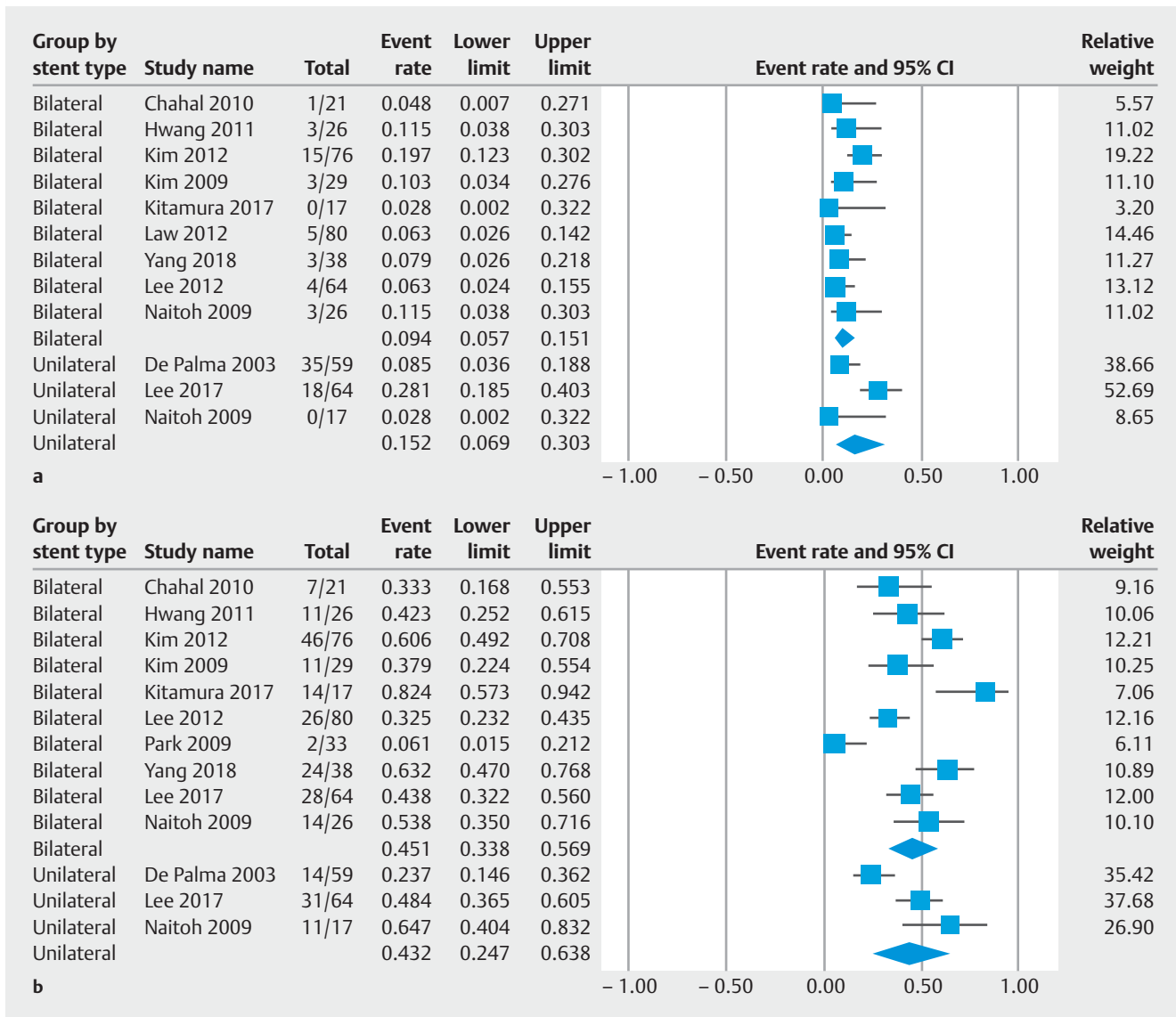
▶ **Table 3** (Continuation)

Criteria	De Palma et al 2002	Singh et al	Chahal et al	Hwang et al	Kim et al 2012	Kim et al 2009	Kita-mura et al	Law et al	Lee et al 2013	Park et al 2016	Park et al 2009	Yang et al	Iwano et al	Naitoh et al	Liberato et al	Dumas et al
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i. e., did they use an interrupted time-series design)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If the intervention was conducted at a group level (e. g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Results	Good	Fair	Fair	Good	Good	Good	Fair	Fair	Fair	Good	Fair	Fair	Good	Good	Good	Good

NIH, National Institutes of Health



► **Fig. 2** Forest plots displaying weighted pool rate of **a** technical success and **b** functional success.



► **Fig. 3** Forest plots displaying weighted pool rate of **a** early complications and **b** late complication.

of early complication, which occurred in 5.5% of unilateral and 6.3% of bilateral groups. In 550 patients, 550 late complications were reported. The WPR of late complication was 43% (95%CI: 25–64%) in the unilateral group and 45% (95%CI: 33–56%) in the bilateral group (► **Fig. 3b**). Obstruction after 30 days occurred in 33.7% of the unilateral group and 33.1% in the bilateral group. Fifty-two percent of cases with stent occlusion were managed by insertion of a plastic stent through the metal stent. The remaining patients were managed by SEMS (20%), percutaneous drainage (24%), nasobiliary drainage (2%), and cleaning of sludge (2%). Subgroup analysis demonstrated no statistically significant difference in AEs between unilateral and bilateral metal stent drainage. No mortality related to the procedure was reported.

Discussion

The majority of patients with malignant hilar biliary obstruction present with non-curative disease which makes palliative care the mainstay of management. Surgical biliary bypass procedures have a higher risk of morbidity and mortality with comparable efficacy to other therapeutic options [40–42]. Therefore, endoscopic and percutaneous stent insertions are frequently used for management of advanced hilar carcinoma. Percutaneous stenting requires external tube placement and is associated with longer hospital stays, which could be less comfortable for patients [7]. Thus, endoscopic biliary drainage has been introduced as a less invasive alternative for palliation of biliary obstruction and is considered as the first choice for management of malignant hilar obstruction [43].

The findings from our meta-analysis revealed that both unilateral and bilateral hilar stenting are associated with comparable efficacy and safety for palliative management of patients

with malignant hilar obstruction. It should also be noted that a high level of heterogeneity was revealed in the technical success rate of metallic stenting. This could be explained by the different etiologies of malignant hilar obstruction in the patient populations of the included studies. In addition, hilar cholangiocarcinoma, which was the most common etiology among included patients, is anatomically categorized by Bismuth classification into five different groups and the pooled population consisted of patients with various Bismuth classification. Unfortunately, we were unable to perform subgroup analysis based on etiology or Bismuth classification because the included studies did not report their outcome based on these covariates.

Our findings also suggest that the technical success rate of unilateral metallic stenting was significantly higher than that for bilateral metallic stenting. This may be due to the challenges that are associated with insertion of a bilateral metallic stent. Prior studies have also reported on the technical challenges of insertion of a bilateral metal stent, and recommended stricture dilation before stent insertion as a solution, to improve the technical success rate of second metallic stent insertion [44]. In addition, multiple techniques have been described for bilateral stent insertion. Most of them were developed as to “stent-by-stent” or “stent-in-stent” techniques [27]. However, detailed categorization based on different insertion techniques was not possible because the included studies did not report their outcomes based on these categories. Further investigations are warranted to compare outcomes of different insertion techniques and determine the most effective method. In our meta-analysis no significant difference was observed in terms of functional success or early and late complications between the unilateral and bilateral metallic stenting groups. These findings are in contrast with a previous systematic review which showed lower overall, early and late complication rates for bilateral metallic stent [44]. This discrepancy may be explained by the distinct differences in the methodology and execution of these two studies. The mentioned systematic review included published abstracts and no quality assessment was performed for observational studies whereas in our meta-analysis, we excluded published abstracts due to the discrepancy between full-text articles and published abstracts [46,46]. Small case series were also excluded to decrease the effects of small studies on the results. We also performed a quality assessment for both RCTs and observational studies.

We acknowledge that our study has several limitations. First, the majority of included studies were observational, which could raise concerns about presence of selection bias. Second, we could not categorize our results based on type of malignant neoplasm or bismuth classification because the included studies did not report patient outcomes based on their etiologies and classification. Finally, included studies used different types, brands, and sizes of stents, which could increase the level of heterogeneity of our results.

Conclusion

In conclusion, the findings from our study suggest that both unilateral and bilateral drainage of malignant hilar obstruction can effectively relieve biliary obstruction. Although unilateral metallic stent insertion had a significantly higher technical success rate, no significant difference was observed in terms of functional success rates. Early and late complication rates were also comparable between the two groups.

Competing interests

Dr. Kalloo is a founding member of, and equity holder in, Apollo Endosurgery. Dr. Kumbhari is a consultant for Boston Scientific, Reshape Life Science, Medtronic, Pentax Medical and Apollo Endosurgery. Dr. Singh is a consultant for Akeca Therapeutics, AbbVie and Ariel Precision Medicine. Dr. Khashab is a consultant for Boston Scientific, Olympus and Medtronic and is on the medical advisory board for Boston Scientific and Olympus.

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