—Review Article—

# Efficacy and safety of EUS-guided gallbladder drainage for rescue treatment of malignant biliary obstruction: A systematic review and meta-analysis

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## ABSTRACT

ERCP is the first line of treatment for malignant biliary obstruction and EUS-guided biliary drainage (EUS-BD) is usually used for patients who have failed ERCP. EUS-guided gallbladder drainage (EUS-GBD) has been suggested as a rescue treatment for patients who fail EUS-BD and ERCP. In this meta-analysis, we have evaluated the efficacy and safety of EUS-GBD as a rescue treatment of malignant biliary obstruction after failed ERCP and EUS-BD. We reviewed several databases from inception to August 27, 2021, to identify studies that evaluated the efficacy and/or safety of EUS-GBD as a rescue treatment in the management of malignant biliary obstruction after failed ERCP and EUS-BD. Our outcomes of interest were clinical success, adverse events, technical success, stent dysfunction requiring intervention, and difference in mean pre- and postprocedure bilirubin. We calculated pooled rates with 95% confidence intervals (CI) for categorical variables and standardized mean difference (SMD) with 95% CI for continuous variables. We analyzed data using a random-effects model. We included five studies with 104 patients. Pooled rates (95% CI) of clinical success and adverse events were 85% (76%, 91%) and 13% (7%, 21%). Pooled rate (95% CI) for stent dysfunction requiring intervention was 9% (4%, 21%). The postprocedure mean bilirubin was significantly lower compared to preprocedure bilirubin, SMD (95% CI): −1.12 (−1.62–−0.61). EUS-GBD is a safe and effective option to achieve biliary drainage after unsuccessful ERCP and EUS-BD in patients with malignant biliary obstruction.

**Key words:** biliary obstruction, EUS, gall bladder, malignant biliary obstruction, metaanalysis



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## INTRODUCTION

Malignant biliary obstruction is typically managed by ERCP with transpapillary stent placement. In some cases, ERCP can fail for a variety of reasons such as duodenal stenosis, an inaccessible papilla due to tumor invasion or gastric outlet obstruction, or surgically altered anatomy.[1,2] EUS-guided biliary drainage (EUS-BD) or percutaneous transhepatic biliary drainage (PTBD) are effective alternatives in cases of failed ERCP.[3-7] EUS-BD has some potential advantages over PTBD such as avoiding an external drainage catheter, which can affect the quality of life.[8] One meta-analysis found that EUS-BD was associated with better clinical success, fewer adverse events, and lower rates of intervention compared to PTBD.[9]

The reported clinical success of EUS-BD ranges from 62% to 100%.[4,5,10] In some cases, EUS-BD can fail due to intervening vasculature precluding biliary access, inability to advance a guidewire into the bile duct, inability to clearly visualize an appropriate site for biliary access, and other reasons. Conventionally, cases of EUS-BD failures are managed by PTBD.

EUS-guided gallbladder drainage (EUS-GBD) has been suggested as a rescue treatment for patients who fail EUS-BD or are not candidates for it. In 2016, Imai *et al.* reported a series of 12 cases with malignant biliary obstruction who underwent EUS-GBD after failed ERCP and EUS-BD.[11] The rates of clinical success and adverse events were 91.7% and 16.7%, respectively. Since then several studies have evaluated the efficacy and safety of EUS-GBD as a rescue treatment in the management of malignant biliary obstruction after failed ERCP and EUS-BD and reported favorable results.[12-14] In this systematic review and meta-analysis, we have evaluated the efficacy and safety of EUS-GBD as a rescue treatment of malignant biliary obstruction after failed ERCP and EUS-BD.

## METHODS

### *Data sources and search strategy*

We followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) to conduct this meta-analysis. An experienced medical librarian (W.L.S.) performed a comprehensive search of MEDLINE (PubMed platform), EMBASE (Embase.com, Elsevier), Web of Science Core Collection (Clarivate) the Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) and Global Index Medicus from inception to August 27, 2021. There was no restriction of publication language in conducting the search. The search included truncation-expanded keywords and database-specific subject terms for EUS-GBD and malignant biliary obstruction. Full search strategies from all databases are provided in Supplementary Figure 1. All citations were downloaded into Endnote X9 (Clarivate, Philadelphia, Pennsylvania, USA), a bibliographic database manager. Duplicate citations were removed by successive field matching algorithms with manual inspection. Two authors (F.K. and S.S.) independently reviewed the titles and abstracts of the retrieved publications and excluded those that did not provide data on our outcomes of interest. Full texts of the remaining articles were reviewed. We also reviewed the bibliographies of these articles to identify any additional studies with relevant data. The screening results are illustrated in the form of a PRISMA flowchart in Figure 1.

### *Inclusion and exclusion criteria*

Two authors (F.K. and M.A.K.) independently screened original studies based on predefined inclusion criteria, which are detailed below. We included studies that evaluated the efficacy and/or safety of EUS-GBD as a rescue treatment in the management of malignant biliary obstruction after failed ERCP and EUS-BD. We excluded case reports and review articles. If there were multiple publications from the same cohort, we included only the most recent publication and/or the publication with more information. We included full publications as well as abstracts.

### *Data extraction and quality assessment*

Two authors (F.K. and M.A.K.) independently assessed the eligibility of included studies and collected data using data extraction forms designed for this study. Any disagreement between individual authors was resolved by a repeat review of data and discussion with a third reviewer (D.G.A.). Extracted data included the year of publication, patient demographics, study design, details of stents placed, procedure time, duration of follow-up and number of patients with technical success, clinical success, adverse events, transgastric stents, transduodenal stents, anchoring double-pigtail stents and stent dysfunction requiring intervention.

We performed the quality assessment of studies using a modified version of the Newcastle–Ottawa Scale, which allocates maximum of six points.[15] On this scale, high-quality studies score over 3 while low-quality

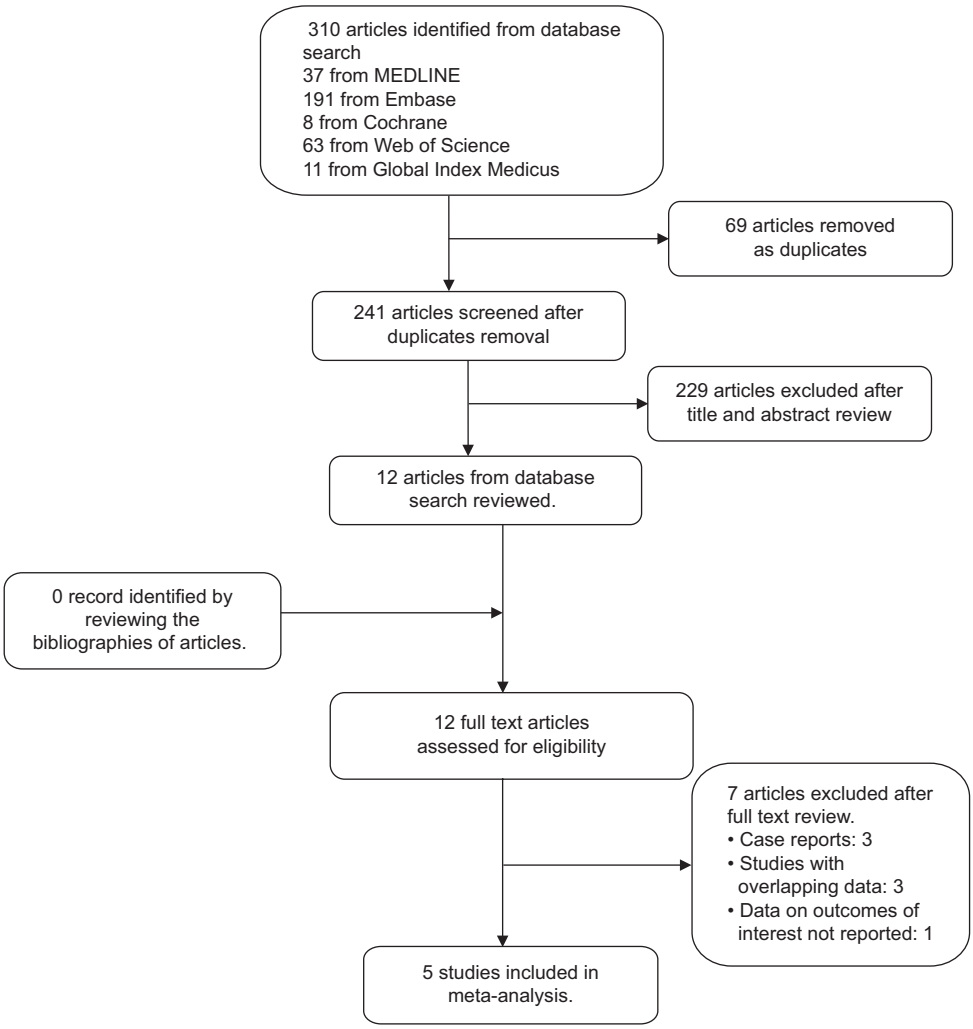


**Figure 1.** Preferred Reporting Items for Systematic Review and Meta-Analysis Flowchart

studies score 3 or below. Two authors (F.K. and U.F.) independently performed the quality assessment and any disagreement was discussed with a third reviewer (D.G.A.). The quality assessment scores of included studies are provided in Table 1.

### *Data synthesis and statistical analysis*

The primary outcome of interest was a clinical success, defined by decrease in postprocedure bilirubin. Secondary outcomes of interest were adverse events, technical success, stent dysfunction requiring intervention, and difference in mean pre- and post-procedure bilirubin. We performed a subgroup analysis by including full publications only and excluding abstracts.

We calculated pooled rates with 95% confidence intervals (CI) for clinical success, adverse events, and stent dysfunction requiring intervention. We calculated standardized mean difference (SMD) with 95% CI to compare mean pre- and postprocedure bilirubin. We used a fixed-effects model for our analyses. Heterogeneity was assessed by $I^2$ statistics. The statistical analysis was performed using comprehensive meta-analysis software. We did not assess for publication bias as the total number of studies that we included was <10.

### *Assessment of quality of evidence*

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess the quality of evidence. For systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. It classifies the quality of evidence as high, moderate, low, or very low. For randomized controlled trials (RCTs), the quality of evidence starts with high confidence; for observational studies, it starts with low confidence. It is further rated based

**Table 1. Characteristics of studies**

| Study, year | Study design | Number of patients | Number of males, *n* (%) | Details of stents placed | Luminal site of stent (transduodenal versus transgastric), *n* (%) | Number of patients with anchoring double pigtail stents, *n* (%) | Procedure time | Adverse events | Follow up | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| Issa *et al.*, 2021 | Retrospective | 28 | 15 (54) | LAMS with a cautery-enhanced tip: 20 (71%) LAMS with a noncautery-enhanced Tip: 6 (21%) SEMS: 2 (7%) | Transduodenal: 15 (54), Transgastric: 13 (46) | 19 (68) | 55 (3-77) min | Food impaction in stent complicated by cholecystitis requiring revision: 3 Delayed bleeding: 2 | 33 (3-64) months | 4 |
| Chang *et al.*, 2018 | Retrospective | 9 | 5 (56) | Electrocautery-enhanced AXIOS stent (Boston Scientific Co., Natick, Massachusetts, United States): 9 (100%) | Trans duodenal: 5 (56), Transgastric: 4 (44) | 3 (33) | NA | 0 | 130.7 days | 4 |
| Imai *et al.*, 2015 | Retrospective | 12 | 8 (67) | SEMS (Wallflex partially covered stent; Boston Scientific, Marlborough Mass): 12 (100%) | Transduodenal: 5 (42), Transgastric: 7 (58) | 7 (58) | NA | Peritonitis: 1 Stent dysfunction: 1 | NA | 6 |
| Binda *et al.*, 2021 | Retrospective | 48 | 23 (48) | LAMS: 48 (100%) | Transduodenal: 20 (42) Transgastric: 28 (58) | NA | 26.4 (17.1) min | 5 details are not available | 122±161 | 4 |
| Paleti *et al.*, 2019 | Retrospective | 7 | 5 (71) | LAMS: 7 (100%) | NA | NA | NA | 0 | NA | 3 |

LAMS: Lumen apposing metal stents; SEMS: Self-expandable metal stents; NA: Not available; NOS: Newcastle-sOttawa Scale

on methodological quality (risk of bias), directness of evidence, inconsistency, precision of effect estimates, and publication bias. Details of the quality of evidence for the outcomes based on GRADE are summarized in Supplementary Table 1.

## RESULTS

The search strategy yielded 310 articles; 69 of these were removed as duplicates [Figure 1]. Of the remaining 241 articles, 229 were removed after the title and abstract review. No relevant articles were identified by reviewing the bibliographies of articles. We reviewed the full texts of 12 articles. Three were case reports and three studies had overlapping data and were consequently excluded from the study. One study included four patients who underwent EUS-GBD and 56 patients who underwent EUS-BD and data on outcomes were not separately reported for the patients who underwent EUS-GBD, and hence, this study was excluded.[16] We ultimately included five studies with 104 patients in the final analysis.[11-14,17] Three studies with 49 patients were full publications and two studies with 55 patients were abstracts.

### *Clinical success*

The pooled rate (95% CI) of clinical success was 85% (76%–91%), $I^2$ = 0% [Figure 2]. Subgroup analysis, including full publications only, found that the pooled rate (95% CI) of clinical success was 89% (75%–95%), $I^2$ = 0%. Quality of evidence based on GRADE framework was low [Supplementary Table 1].

### *Adverse events*

The pooled rate (95% CI) of adverse events was 13% (7%–21%), $I^2$ = 0% [Figure 3]. Subgroup analysis, including full publications only, found that the pooled rate (95% CI) of adverse events was 16% (8%–29%), $I^2$ = 0%. Details of adverse events are provided in Table 1. The quality of evidence based on GRADE framework was low [Supplementary Table 1].

### *Technical success*

The procedure was technically successful in all 104/104 (100%) of the patients. The stents were placed through transgastric approach in 52 patients and through transduodenal approach in 45 patients. One study did not report data on the luminal site of stent placement. Three studies reported data on anchoring double-pigtail stents placement and these were placed in 29/49 (59%) patients. The quality of evidence based on the GRADE framework was low [Supplementary Table 1].

### *Stent dysfunction requiring intervention*

The pooled rate (95% CI) of stent dysfunction was 9% (4%–21%), $I^2$ = 0% [Figure 4]. 4 patients had stent dysfunction. In three patients, there was food impaction in the stent complicated by recurrent cholecystitis – all of these patients required revision of the anchoring plastic stents and antibiotics. In one case, there was entrapment of the cystic duct by growing tumor and PTBD was performed as a rescue intervention. The quality of evidence based on the GRADE framework was low [Supplementary Table 1].

### *Pre- and post-procedure bilirubin*

The postprocedure mean bilirubin was significantly lower compared to preprocedure bilirubin, SMD (95% CI): −1.12 (−1.62–−0.61), $I^2$ = 0% [Figure 5]. Pooled mean preprocedure bilirubin was 7.5 and pooled mean postprocedure bilirubin was 2.8. The quality of evidence based on GRADE framework was low [Supplementary Table 1].

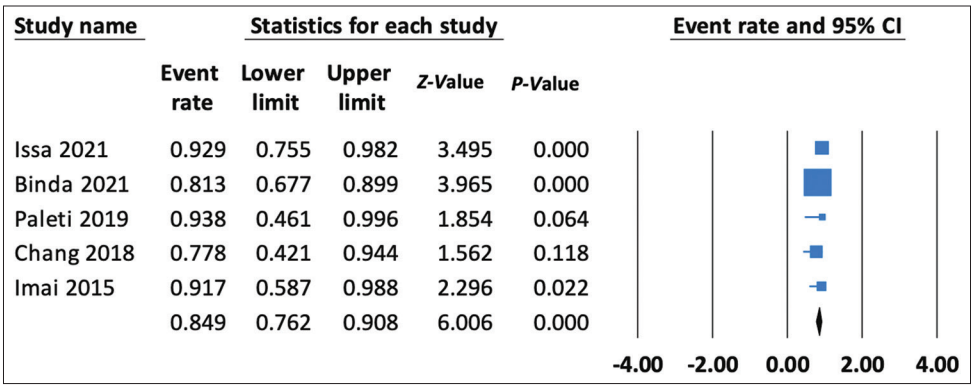


**Figure 2.** Rate of clinical success of EUS-guided gallbladder drainage for malignant biliary obstruction

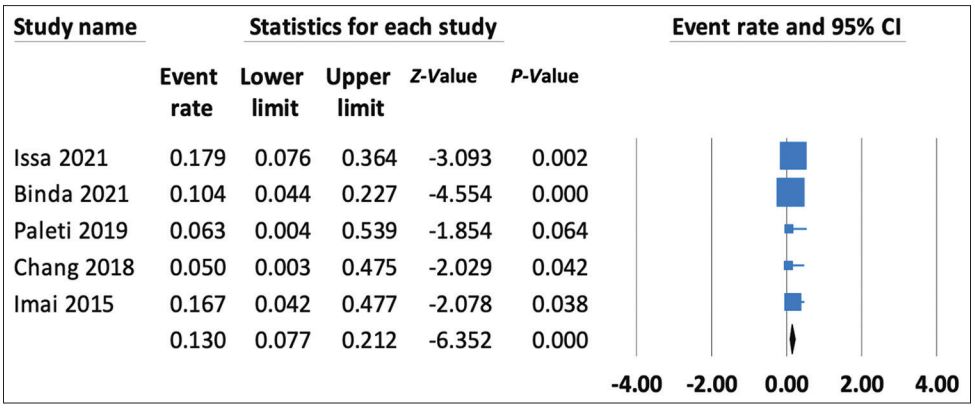


**Figure 3.** Rate of adverse events with EUS-guided gallbladder drainage for malignant biliary obstruction

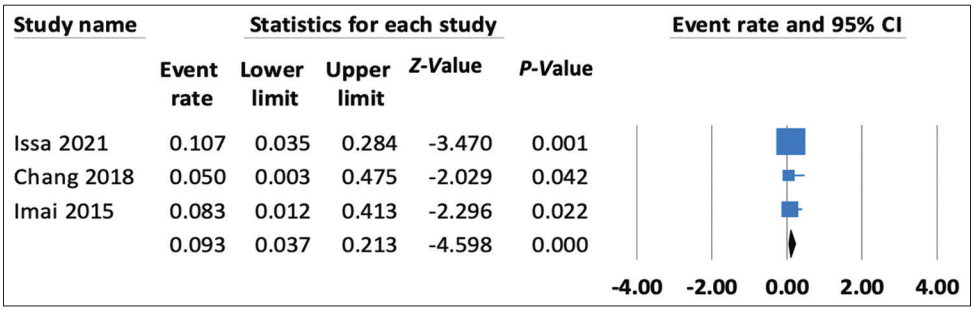


**Figure 4.** Rate of stent dysfunction requiring intervention after EUS-guided gallbladder drainage for malignant biliary obstruction

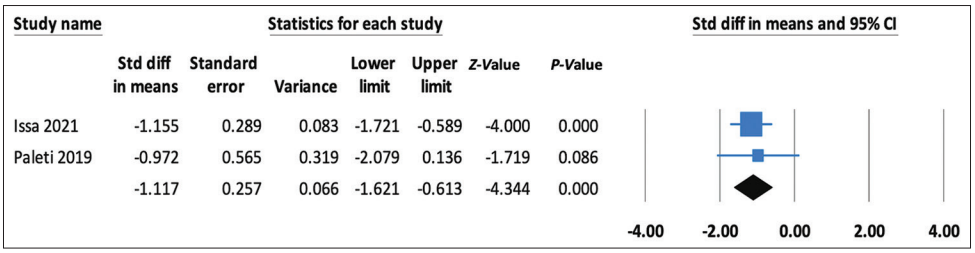


**Figure 5.** The difference in pre-and post-procedure bilirubin after EUS-guided gallbladder drainage for malignant biliary obstruction

## DISCUSSION

Our meta-analysis demonstrates the efficacy and safety of EUS-GBD in patients with malignant biliary obstruction following failed ERCP and/or EUS-BD. ERCP is the first line of treatment for malignant biliary obstruction and use of EUS-BD is usually reserved for patients who have failed ERCP or cannot undergo ERCP due to anatomic constraints. Patients in whom both ERCP and EUS-BD are unsuccessful are problematic because these patients are usually poor surgical candidates. Our meta-analysis supports the use of EUS-GBD to achieve biliary drainage in this context.

The concept of gallbladder drainage for malignant biliary obstruction is not novel. EUS-GBD is essentially a modern adaptation of an old concept – this approach was formerly undertaken through a surgical approach in the pre-ERCP era. In the 1970s, surgical cholecystenterostomy and choledochoenterostomy were performed for the treatment of malignant biliary obstruction.[18] Studies comparing the two surgical techniques found comparable rates of relief of jaundice and symptoms, but the incidence of recurrent jaundice or cholangitis was higher in the cholecystenterostomy group.[19,20] With the advent of EUS-BD and improvement in biliary drainage techniques such as ERCP and PTBD, these surgeries have been, essentially, abandoned.

We found that the rate of clinical success of EUS-GBD was 85% (76%, 91%) which is comparable to the reported clinical success of EUS-BD.[21] A patent cystic duct is required for EUS-GBD to be successful.[22] The patency of the cystic duct should be confirmed

by cross-sectional imaging or EUS before proceeding to EUS-GBD. One study[23] evaluating the patency of the cystic duct in patients with malignant obstructive jaundice found that only 50% of these patients had a patent cystic duct and even in 56% of these patients with patent cystic duct, the biliary obstruction was located within 1 cm of the cystic duct. Patients with distal biliary obstruction within 1 cm of the cystic duct may not be ideal candidates for EUS-GBD.[22]

This is the first meta-analysis to evaluate the efficacy and safety of EUS-GBD as a rescue treatment of malignant biliary obstruction. The rate (95% CI) of adverse events was 13% (7%–21%) which is comparable to the reported rate of adverse events of EUS-BD.[21] The details of adverse events are provided in Table 1. All these adverse events were mild to moderate based on the American Society for Gastrointestinal Endoscopy lexicon. There were no serious adverse events. There was no heterogeneity ($I^2$ = 0%) in the analysis of any of our outcomes of interest.

With regard to limitations, the major limitation of this meta-analysis is small sample size. This limitation is inevitable because the traditional procedures to achieve biliary drainages such as ERCP and EUS-BD have a high success rate and only a small proportion of patients require EUS-GBD. In the study by Issa *et al.*, 24,720 ERCPs were performed for malignant distal biliary obstruction and only 1.6% ($n$ = 384) underwent EUS-BD and of those 28 patients (7%) failed EUS-BD and underwent EUS-GBD.[13] All included studies were observational with a risk of measured and unmeasured confounding. Two studies were only available in abstract form.[14,17] As such we performed subgroup analyses by including full publications only.

## CONCLUSIONS

This meta-analysis found that EUS-GBD is a safe and effective option to achieve biliary drainage after unsuccessful ERCP and EUS-BD in patients with malignant biliary obstruction and should be considered a therapeutic option.

### *Supplementary Materials*

Supplementary information is linked to the online version of the article on the *Endoscopic Ultrasound* website.

### *Financial support and sponsorship*

Nil.

### *Conflicts of interest*

Douglas G. Adler is a Co-Editor-in-Chief of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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**Supplementary Table 1. Assessment of certainty of evidence by Grading of Recommendations Assessment, Development, and Evaluation for outcomes of interest**

| Outcomes | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Quality of evidence |
|---|---|---|---|---|---|---|
| Clinical success | Low | No serious indirectness | Low heterogeneity | No serious imprecision | Not assessed[a] | Low (due to observational nature of studies) |
| Adverse events | Low | No serious indirectness | Low heterogeneity | No serious imprecision | Not assessed[a] | Low (due to observational nature of studies) |
| Technical success | Low | No serious indirectness | Low heterogeneity | No serious imprecision | Not assessed[a] | Low (due to observational nature of studies) |
| Stent dysfunction requiring intervention | Low | No serious indirectness | Low heterogeneity | No serious imprecision | Not assessed[a] | Low (due to observational nature of studies) |
| Pre and postprocedure bilirubin | Low | No serious indirectness | Low heterogeneity | No serious imprecision | Not assessed[a] | Low (due to observational nature of studies) |

[a]Due to small number of studies

**Supplementary Figure 1.** Search strategies from all databases

| EMBASE search (Embase.com, Elsevier. August 27, 2021) | | |
|---|---|---|
| **Number** | **Query** | **Results** |
| #1 | 'interventional ultrasonography'/exp OR 'endoscopic ultrasonography'/exp OR echoendoscop* OR 'endoscopic echograph*' OR 'endoscopic ultrasonograph*' OR 'endoscopic ultrasound*' OR endosonograph* OR 'eus' OR 'interventional ultrasonograph*' OR 'interventional ultrasound*' OR 'intravascular ultrasonograph*' OR 'echo endoscop*' OR 'ultrasonic endoscop*' OR 'eus-gd' OR 'eus-bgd' OR 'eusbgd' | 58,864 |
| #2 | 'gallbladder'/exp OR gallbladder* OR 'gallbladder*' | 74,413 |
| #3 | 'stent'/exp OR 'biliary tract drainage'/exp OR drain* OR stent* | 474,431 |
| #4 | 'malignant neoplasm'/exp OR 16:cl OR malignant*:ti, ab, kw, de OR cancer*:ti, ab, kw, de OR neoplasm*:ti, ab, kw, de OR tumor*:ti, ab, kw, de OR tumor*:ti, ab, kw, de | 6,475,686 |
| #5 | 'cholestasis'/exp OR 'cholecystitis'/exp OR cholangio cholecystitis* OR cholecystitis* OR cholestas* OR 'biliary stasis' OR obstruct* OR stricture* OR stenos* | 1,014,157 |
| #6 | #1 AND #2 AND #3 AND #4 AND #5 | 389 |
| #7 | #6 NOT ([animals]/lim NOT [humans]/lim) | 383 |
| #8 | #7 NOT ('conference review'/it OR 'editorial'/it OR 'review'/it OR 'short survey'/it) | 334 |
| #9 | #8 NOT ('case report'/de OR 'consensus development'/de OR 'meta analysis'/de OR 'meta analysis topic'/de OR 'practice guideline'/de OR 'systematic review'/de OR 'systematic review topic'/de) | 191 |

| MEDLINE/PubMed search (PubMed, NCBI. August 27, 2021) | |
|---|---|
| **Query** | **Results** |
| "Endosonography"[Mesh] OR "Ultrasonography, Interventional"[Mesh] OR echoendoscop* OR endoscopic-echograph* OR endoscopic-ultrasonograph* OR endoscopic-ultrasound* OR endosonograph* OR "eus" OR interventional-ultrasonograph* OR interventional-ultrasound* OR intravascular-ultrasonograph* OR echo-endoscop* OR ultrasonic-endoscop* OR "EUS-GD" OR "EUS-BGD" OR "EUSBGD" | 52,046 |
| "Gallbladder"[Mesh] OR gallbladder* OR gallbladder* | 49,265 |
| "Drainage"[Mesh] OR "Stents"[Mesh] OR drain* OR stent* | 293,781 |
| #1 AND #2 AND #3 | 345 |
| "Cholecystitis"[Mesh] OR "Cholestasis"[Mesh] OR (cholangio cholecystitis* OR cholecystitis* OR Cholestas* OR biliary-stasis OR obstruct* OR stricture* OR stenos*) | 629,499 |
| "Neoplasms"[Mesh] OR "cancer"[sb] OR (malignant* OR cancer* OR neoplasm* OR tumor* OR tumor*) | 6,963,996 |
| #5 AND #6 | 138,960 |
| #4 AND #7 | 89 |
| #8 NOT ("animals"[mh] NOT "humans"[mh]) | 88 |
| #9 NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "guideline"[Publication Type] OR "introductory journal article"[Publication Type] OR "meta analysis"[Publication Type] OR "news"[Publication Type] OR "retracted publication"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Publication Type]) | 37 |

| Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley. Issue 8 of 12, August 27, 2021) | | |
|---|---|---|
| **Number** | **Query** | **Results** |
| #1 | [mh "Endosonography"] OR [mh "Ultrasonography, Interventional"] OR echoendoscop* OR endoscopic-echograph* OR endoscopic-ultrasonograph* OR endoscopic-ultrasound* OR endosonograph* OR "eus" OR interventional-ultrasonograph* OR interventional-ultrasound* OR intravascular-ultrasonograph* OR echo-endoscop* OR ultrasonic-endoscop* OR "EUS-GD" OR "EUS-BGD" OR "EUSBGD" | 4379 |
| #2 | [mh "Gallbladder"] OR gallbladder* OR gallbladder* | 3177 |
| #3 | [mh "Drainage"] OR [mh "Stents"] OR drain* OR stent* | 30,055 |
| #4 | #1 AND #2 AND #3 | 41 |
| #5 | [mh "Neoplasms"] OR (malignan* OR cancer* OR neoplasm* OR tumor* OR tumor*) | 243,263 |
| #6 | [mh "Cholecystitis"] OR [mh "Cholestasis"] OR (cholangio cholecystitis* OR cholecystitis* OR Cholestas* OR biliary-stasis OR obstruct* OR stricture* OR stenos*) | 56,529 |
| #7 | #5 AND #6 | 6340 |
| #8 | #4 AND #7 | 15 |
| #9 | Trials matching "#8 - #4 AND #7" | 8 |

| Web of Science Core Collection, Including ESCI (Web of Science, Clarivate. August 27, 2021) | |
|---|---|
| **Query** | **Results** |
| echo-endoscop* OR ultrasonic-endoscop* OR "EUS-GD" OR "EUS-BGD" OR "EUSBGD" (Topic) AND gallbladder* OR gallbladder* (Topic) AND drain* OR stent* (Topic) AND (malignant* OR cancer* OR neoplasm* OR tumor* OR tumor *) (Topic) AND (cholangio cholecystitis* OR cholecystitis* OR Cholestas* OR biliary-stasis OR obstruct* OR stricture* OR stenos*) (Topic) AND Editorial Materials or Review Articles (Exclude – Document Types) | 63 |

| Global Index Medicus* (GlobalIndexMedicus.net, World Health Organization. August 27, 2021) | |
|---|---|
| **Query** | **Results** |
| (echoendoscop* OR endoscopic-echograph* OR endoscopic-ultrasonograph* OR endoscopic-ultrasound* OR endosonograph* OR "eus" OR interventional-ultrasonograph* OR interventional-ultrasound* OR intravascular-ultrasonograph* OR echo-endoscop* OR ultrasonic-endoscop* OR "EUS-GD" OR "EUS-BGD" OR "EUSBGD") AND (gallbladder* OR gallbladder*) AND (drain* OR stent*) AND (malignant* OR cancer* OR neoplasm* OR tumor* OR tumor*) AND (cholangio cholecystitis* OR cholecystitis* OR cholestas* OR biliary-stasis OR obstruct* OR stricture* OR stenos*) | 11 |

*Includes African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for South-East Asia Region, Latin America and the Caribbean Literature on Health Sciences, and the Western Pacific Region Index Medicus