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# EUS- versus ERCP-guided biliary drainage for primary decompression of malignant biliary obstruction: protocol for a systematic review and meta-analysis of randomized controlled trials

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| | |

# Title Page

## Title

EUS- versus ERCP-guided biliary drainage for primary decompression of malignant biliary obstruction: protocol for a systematic review and meta-analysis of randomized controlled trials

## Authors

Zheng Jin MD[1,2,*], Yaping Wei MD[2,*], Huapeng Lin MD[2,*], Haitao Huang MD[2], Wen Lv MD[2], Xiaofeng Zhang MD[2]

[1]Hangzhou Geriatric Hospital, Hangzhou First People's Hospital Group, Hangzhou, China

[2]Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

[*]These authors have contributed equally to this work.

**Correspondence to:** Xiaofeng Zhang, MD, Department of Gastroenterology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, #261 Huansha Road, Hangzhou, 310006, Zhejiang Province, China.

Fax: +86-0571-56006872

E-mail address: gangdaoersan@163.com

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# ABSTRACT

**Introduction:** Current evidence supporting the utility of endoscopic ultrasound-guided biliary drainage (EUS-BD) as a first-line treatment option for malignant biliary obstruction (MBO) is limited. We plan to provide a systematic review and meta-analysis to compare the performance of EUS-BD and endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) as primary palliation of MBO.

**Methods and analysis:** Randomized controlled trials (RCTs) evaluating EUS-BD vs. ERCP-BD in primary drainage of MBO will be searched in MEDLINE, EMBASE, and the Cochrane Library, from database inception to 31 October 2018. Data on study design, participant characteristics, intervention details and outcomes will be extracted. Primary outcomes to be assessed are technical and clinical success. Secondary outcomes include adverse events, stent patency, stent dysfunction, reinterventions, procedure duration, and overall survival. Study quality will be assessed using the Cochrane Risk of Bias Tool. Meta-analysis will be performed using RevMan V.5.3 statistical software. Data will be combined with either the fixed or random effect model based on a heterogeneity test. The

results will be presented as a risk ratio (RR) for dichotomous data, weighted mean difference for continuous data, and hazard ratio (HR) for time-to-event data. Publication bias will be visualized using funnel plots.

**Ethics and dissemination:** This study will not use primary data, and therefore formal ethical approval is not required. The findings will be disseminated through peer-reviewed journals and committee conferences.

# ARTICLE SUMMARY

## Strengths and limitations of this study

1. This is the first meta-analysis comparing EUS- with ERCP-biliary drainage for primary drainage of malignant biliary obstruction.

2. The study selection, data extraction and quality assessment will be performed independently by two researchers.

3. We will calculate time-to-event outcomes using hazard ratios, in contrast to other meta-analyses using risk ratios or weighted mean differences.

4. We will be able to comprehensively survey the literature and identify areas where further study may be required.

5. A possible weakness may be the quality of the trials we include.

# INTRODUCTION

Not uncommonly, malignant biliary obstruction (MBO) is diagnosed at an advanced stage when treatment is mainly palliative. Endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) has been the most commonly used technique for the palliation of MBO.[1] However, a wide range of post-procedure complications has continued to pose a serious challenge.[2] In addition, patients with MBO often have duodenal invasion and surgically altered anatomy, which always preclude accessing bile duct with ERCP.[3]

Since first reported by Giovannini in 2001,[4] endoscopic ultrasound-guided biliary drainage (EUS-BD) has been increasingly used in patients who underwent failed ERCP(3, 5, 6).[3, 5, 6] A recent meta-analysis evaluating EUS-BD reported cumulative technical success and adverse events of 94.71% and 23.32%, respectively.[7] With increasing availability and familiarity with this procedure, several studies have compared EUS-BD vs. ERCP-BD for primary biliary decompression for MBO. These studies have reported variable results and were limited because of small sample sizes. We had planned to

conduct a meta-analysis to compare the performance of EUS-BD with ERCP-BD as primary treatment in relieving MBO.

# METHODS

The review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews.[8] The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[9]

## Criteria for considering studies for this review

Eligibility criteria are established in terms of the Population-Intervention-Comparison-Outcome-Study design framework. Studies will be selected according to the following criteria:

### Participants

Included studies will involve patients who presenting with MBO and initially undergoing endoscopic drainage, with no age limitation. Both distal and hilum MBO will be included. There will be no restrictions on etiology, which include, but are not limited to, pancreatic cancer, cholangiocarcinoma, gallbladder cancer, ampulla of vater cancer, and metastasis. Patients with benign biliary diseases, and those with EUS-BD performing as a salvage procedure for failed ERCP will be excluded.

## Interventions/comparison

The intervention comparisons are EUS-BD vs. ERCP-BD. EUS-BD can be performed in several ways, choledochoduodenostomy, hepaticogastrostomy, antegrade procedure, and rendezvous technique.[10] All these methods of EUS-BD will be included except for rendezvous technique. Because the rendezvous approach is a cross-over technique using EUS to pass a guidewire via the papilla to perform an ERCP. There will be no restrictions on stent type (metal/plastic stent), dilation device (dilation catheter/cystotome/balloon), and whether patient has an indwelling duodenal stent or not.

## Outcomes

There are two primary outcomes for this study: technical success (defined as successful stent placement in the desired location as determined) and clinical success (defined as reduction of total serum bilirubin levels to less than half of the preoperative level within 4 weeks).

There are six secondary outcomes: (i) adverse events: total, pancreatitis, cholangitis, cholecystitis, bleeding and bile peritonitis; (ii) stent patency; (iii) stent dysfunction: stent occlusion, stent migration, and tumor in/overgrowth; (iv) reinterventions; (v) procedure duration; and (vi) overall survival.

## Study design

Only randomized clinical trials (RCTs) will be included. An abstract with sufficient data will also be considered. We will only include studies that are presented in English language due to constraints in translational resources.

Studies will be excluded if it meets at least one of the following criteria: (i) studies without a comparative arm of ERCP-BD; (ii) case reports, reviews, editorials and letters to editor; (iii) duplicate studies, in vitro studies, or animal studies; (iv) no data on any of the primary or secondary outcomes.

## Search methods for identification of studies

### Electronic searches

Two investigators (ZJ and YW) will independently search MEDLINE, EMBASE, and the Cochrane Library, for all entries through 31 October 2018 using the following search terms: “endoscopic ultrasound,” “EUS,” “biliary decompression,” “biliary drainage,” “choledochoduodenostomy,” “hepaticogastrostomy,” “rendezvous,” and “antegrade.” Then, they will compare their lists of potentially eligible titles and abstracts and achieve a consensus on full review. If any up-to-date evidence is published during the review period, we will evaluate the eligibility of each study and consider its addition to the analysis.

### Searching other resources

To further increase the robustness of the literature search, a manual recursive search of the reference sections of the retrieved articles will be carried out to identify other potentially relevant articles. Additional searches of ClinicalTrials.gov and Google Scholar will also be conducted.

## Data collection and analysis

### Selection of studies

Decisions about study inclusion and exclusion will be made independently by two investigators (ZJ and YW). Disagreements will be resolved by consensus after a mutual discussion. The details of the study selection procedure are shown in a PRISMA flow chart. (Figure 1)

### Data extraction and management

Two investigators (YW and HL) will independently extract the appropriate data onto a standardized collection form. Any discrepancies will be resolved by mutual discussion. When necessary data are not included in the published papers, the first or corresponding authors will be contacted for additional information. The following data will be contained in the collection form: country and year of the study, study design, patient demographics and clinical characteristics, methods of EUS-BD, types of stents, technical success, clinical success, procedure duration, stent patency, stent dysfunction, reinterventions, adverse events, overall survival, and follow-up information.

## Assessment of risk of bias in included studies

We will assign two independent investigators (YW and HL) to appraise methodological quality of the included trials with the Cochrane Collaboration' s tool for assessing risk of bias.[11] The tool appraises existence of selection bias by assessing methods of randomization and allocation concealment, performance and detection of biases by checking blinding of personnel and outcome assessment, and attrition and reporting bias by evaluating incomplete and selective data reporting. Each of the item is assigned a judgment of high, low, or unclear risk.

## Data synthesis

Hazard ratios (HRs) extrapolated from Kaplan-Meier curves will be calculated for time-to-event outcomes.[12, 13] Weighted mean differences (WMDs) will be calculated for continuous variables. Medians will be used if means are not available and standard deviations (SDs) will be calculated or imputed when possible.[14] Risk ratios (RRs) will be calculated for categorical variables. All outcomes will be analyzed using fixed-effect models, unless statistical heterogeneity is encountered, in which case random-effects models will be used. Heterogeneity among studies will be assessed by calculating the $I^2$ statistics whereby $I^2$<25% indicates no heterogeneity, 25%≤ $I^2$ <50% indicates mild heterogeneity, 50%≤ $I^2$ <75% indicates moderate heterogeneity and $I^2$ ≥75% indicates strong heterogeneity.[15] We had planned that if sufficient studies (≥10) are included in the

analysis of primary outcomes, we would construct funnel plots to evaluate publication bias,[8] otherwise, Egger's test will be applied.[16] All statistical analyses will be performed using Review Manager 5.3 (Cochrane Collaboration, 2014).

### Sensitivity analysis

We will carry out a sensitivity analysis by systematically removing every study and checking the pooled results for the remaining studies to see if there is any significant change in test performance.

### Subgroup analyses

Subgroup analyses will be carried out to investigate heterogeneity between studies based on geographical location, publication form, study design, location of biliary obstruction, indwelling duodenal stent, EUS-BD technique, stent type, and definitions of adverse event. For those subgroups with only 1 study included, subgroup analyses will not be performed.

## DISCUSSION

It has been well established that ERCP-BD is a standard treatment for MBO when curative surgery is not an option.[17, 18] EUS-BD is used as a rescue option when ERCP-BD fails(6, 27, 28).[5, 19, 20] For primary drainage of MBO, several studies have investigated EUS-BD vs. ERCP-BD showing different results.[21-23] A recent meta-analysis [7]reported

that EUS-BD may not be used as an initial modality for relieving biliary obstruction, however none of the included studies were direct-comparative.We therefore propose a meta-analysis to pool the evidence to evaluate the performance of EUS-BD vs. ERCP-BD.

One strengths of our meta-analysis will be that stent patency and overall survival will be calculated using HRs, in contrast to other meta-analyses using RRs or WMDs.[24] Because the included studies had various length of follow-up, and the events might not occur in some patients at the end of study. For these time-to-event outcomes, the most appropriate way of analysis is to use methods of survival analysis and express the intervention effect as a HR.[8]

This will be the first meta-analysis comparing EUS-BD with ERCP-BD for primary drainage of MBO. The results of this study will influence decision making for unresectable MBO, assist in future guideline development and guide future research endeavors.

# ETHICS AND DISSEMINATION

Ethics approval and patient written informed consent will not be required because all analyses in the present study will be performed based on data from published studies. We will disseminate the findings of our work through conference presentations and a peer-reviewed publication.

# AUTHOR STATEMENT

## Author Contributions

ZJ and XZ conceived and designed this study. ZJ and YW searched and selected the studies. YW and HL extracted the essential information. YW and HL assessed the risk of bias. HH, WL, and ZJ performed the statistical analyses. ZJ and YW interpreted the pooled results. ZJ, YW and HL drafted the manuscript. All authors approved the manuscript to be considered for publication.

Competing interests: None.

Funding: None.

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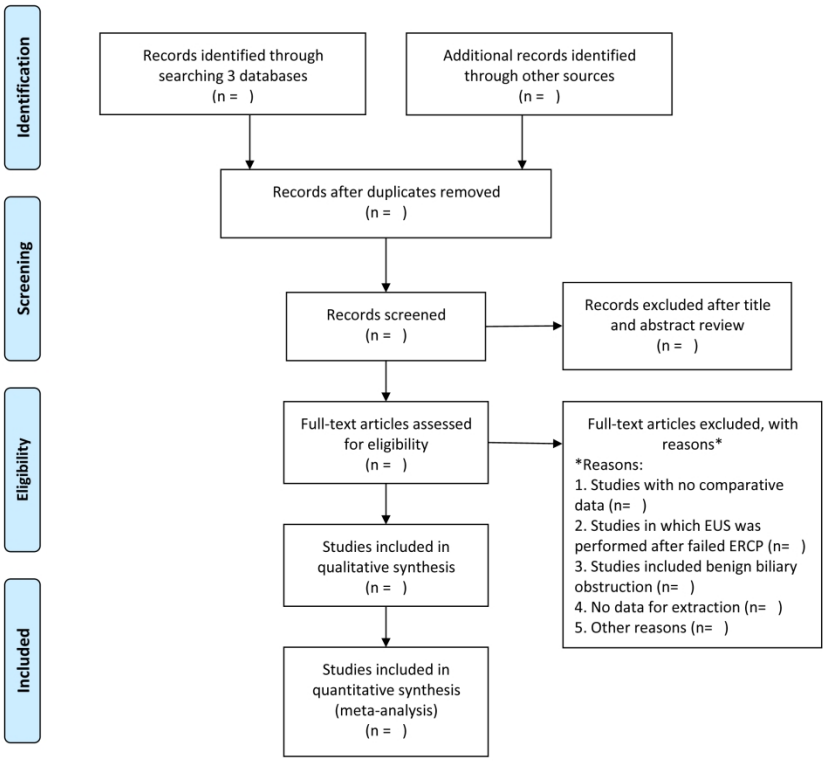


Figure 1 Flow diagram of the study selection process.

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | ☒ | ☐ | Page 1 Line 11 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☒ | Not applicable |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | ☐ | ☒ | Not applicable |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | ☒ | ☐ | Page 1 Line 24 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | ☒ | ☐ | Page 12 Line 24 |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☐ | ☒ | Not applicable |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | ☒ | ☐ | Page 12 Line 45 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | ☒ | ☐ | Page 12 Line 45 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☒ | ☐ | Page 12 Line 45 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | ☒ | ☐ | Page 4 Line 19 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | ☒ | ☐ | Page 4 Line 54 |
| **METHODS** | | | | | |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | ☒ | ☐ | Page 5 Line 25 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | ☒ | ☐ | Page 7 Line 31 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | ☐ | ☒ | |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | ☒ | ☐ | Page 8 Line 34 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | ☒ | ☐ | Page 8 Line 19 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | ☒ | ☐ | Page 8 Line 34 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | ☒ | ☐ | Page 8 Line 48 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | ☒ | ☐ | Page 6 Line 27 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☒ | ☐ | Page 9 Line 4 |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | ☒ | ☐ | Page 9 Line 27 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | ☒ | ☐ | Page 9 Line 27 |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ☒ | ☐ | Page 10 Line 13 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | ☒ | ☐ | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☒ | ☐ | Page 10 Line 13 |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | ☒ | |

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[1]Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China

[*]These authors have contributed equally to this work.

**Correspondence to:** Xiaofeng Zhang, MD, Department of Gastroenterology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, #261 Huansha Road, Hangzhou, 310006, Zhejiang Province, China.

Fax: +86-0571-56006872

E-mail address: gangdaoersan@163.com

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# ABSTRACT

**Introduction:** Current evidence supporting the utility of endoscopic ultrasound-guided biliary drainage (EUS-BD) as a first-line treatment option for malignant biliary obstruction (MBO) is limited. We plan to provide a systematic review and meta-analysis to compare the performance of EUS-BD and endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) as primary palliation of MBO.

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**PROSPERO registration number:** CRD42018117040

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1. This is the first meta-analysis comparing EUS- with ERCP-biliary drainage for primary drainage of malignant biliary obstruction.

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4. We will be able to comprehensively survey the literature and identify areas where further study may be required.

5. A possible weakness may be the quality of the trials we include.

# INTRODUCTION

Not uncommonly, malignant biliary obstruction (MBO) is diagnosed at an advanced stage when treatment is mainly palliative. Endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) has been the most commonly used technique for the palliation of MBO.[1] However, a wide range of post-procedure complications has continued to pose a serious challenge.[2] In addition, patients with MBO may be accompanied by duodenal invasion and altered anatomy from the previous surgeries, which could increase ERCP difficulty.[3]

Since first reported by Giovannini in 2001,[4] endoscopic ultrasound-guided biliary drainage (EUS-BD) has emerged as an alternative procedure to percutaneous transhepatic biliary drainage (PTBD) after failed ERCP[5-8] A recent meta-analysis evaluating EUS-BD reported cumulative technical success and adverse events of 94.71% and 23.32%, respectively.[9] With increasing availability and familiarity with this procedure, several studies have compared EUS-BD vs. ERCP-BD for primary biliary decompression for MBO[10-12]. These studies have reported variable results and were limited because of small sample sizes. We had planned to conduct a meta-analysis to compare the performance of EUS-BD with ERCP-BD as primary treatment in relieving MBO.

# METHODS

The review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews.[13] The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[14] The systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018117040).

## Criteria for considering studies for this review

Eligibility criteria are established in terms of the Population-Intervention-Comparison-Outcome-Study design framework. Studies will be selected according to the following criteria:

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Included studies will involve patients presenting with MBO and initially undergoing endoscopic drainage, with no age limitation. Both distal and hilum MBO will be included. There will be no restrictions on etiology, which include, but are not limited to, pancreatic cancer, cholangiocarcinoma, gallbladder cancer, ampulla of vater cancer, and metastasis. Patients with benign biliary diseases, and those with EUS-BD performing as a salvage procedure for failed ERCP will be excluded.

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The intervention comparisons are EUS-BD vs. ERCP-BD. EUS-BD can be performed in several ways, choledochoduodenostomy, hepaticogastrostomy, antegrade procedure, and rendezvous technique.[15] All these methods of EUS-BD will be included except for rendezvous technique. Because the rendezvous approach is a cross-over technique using EUS to pass a guidewire via the papilla to perform an ERCP. There will be no restrictions on stent type (metal/plastic stent), dilation device (dilation catheter/cystotome/balloon), and whether patient has an indwelling duodenal stent or not.

## Outcomes

There are two primary outcomes for this study: technical success (defined as successful stent placement as determined endoscopically or radiographically) and clinical success (defined as reduction of total serum bilirubin levels to less than half of the preoperative level within 4 weeks[10]).

There are six secondary outcomes: (i) adverse events: total, pancreatitis, cholangitis, cholecystitis, bleeding and bile peritonitis; (ii) stent patency (hazard ratio [HR] for interval from initial insertion to recurrence of obstruction); (iii) stent dysfunction: stent occlusion, stent migration, and tumor in/overgrowth; (iv) reinterventions; (v) procedure duration; and (vi) overall survival (HR for death).

## Study design

Only randomized clinical trials (RCTs) will be included. Unpublished trials and abstracts will be included if the methodology and data are accessible. We will only include studies that are presented in English language due to constraints in translational resources.

Exclusion criteria will be: (i) studies without a comparative arm of ERCP-BD; (ii) observational studies, case reports, reviews, editorials and letters to editor; (iii) duplicate studies, in vitro studies, or animal studies; (iv) no data on any of the primary or secondary outcomes.

## Search methods for identification of studies

### Electronic searches

Two investigators (ZJ and YW) will independently search MEDLINE, EMBASE, Web of Science, the Cochrane Library, ClinicalTrials.gov, and Google Scholar, for all entries through 31 October 2018. The search strategies will be decided on after a discussion among all reviewers. The primary search strategy will be used for PubMed MEDLINE (Online Supplementary Appendix I). Modifications to the search strategy will be made for other databases. We will assess eligibility of the retrieved articles by title and abstract using predetermined inclusion criteria. If this information is insufficient for eligibility assessment, we will review the full article. If any up-to-date evidence is published during the review period, we will evaluate the eligibility of each study and consider its addition to the analysis.

### Searching other resources

To further increase the robustness of the literature search, a manual recursive search of the reference sections of the retrieved articles, as well as the related articles option in PubMed, will be carried out to identify other potentially relevant articles.

## Data collection and analysis

### Selection of studies

Decisions about study inclusion and exclusion will be made independently by two investigators (ZJ and YW). Disagreements will be resolved by consensus after a mutual discussion. The details of the study selection procedure are shown in a PRISMA flow chart. (Figure 1)

### Data extraction and management

Two investigators (YW and HL) will independently extract the appropriate data onto a data collection form (Online Supplementary Appendix II). The following variables will be contained in the collection form: country and year of the study, study design, patient demographics and clinical characteristics, methods of EUS-BD, types of stents, technical success, clinical success, procedure duration, stent patency, stent dysfunction, reinterventions, adverse events, overall survival, and follow-up information. When necessary data are not included in the published studies, the corresponding authors will

be contacted for additional information. If there is no reply, we will analyze only the available data. If there is no data on any of the primary or secondary outcomes, those studies will be excluded from the meta-analyses.

## Assessment of risk of bias in included studies

We will assign two independent investigators (YW and HL) to appraise methodological quality of the included trials with the Cochrane Collaboration' s tool for assessing risk of bias.[16] The tool appraises existence of selection bias by assessing methods of randomization and allocation concealment, performance and detection of biases by checking blinding of personnel and outcome assessment, and attrition and reporting bias by evaluating incomplete and selective data reporting. Each of the item is assigned a judgment of high, low, or unclear risk.

## Data synthesis

The HRs (hazard ratios) for time-to-event outcomes (stent patency and overall survival) will be calculated using the Excel sheet published by Tierney et al[17], based on Parmar' s method of data extraction[18] from Kaplan-Meier curves. Weighted mean differences (WMDs) will be calculated for continuous variables. Medians will be used if means are not available and standard deviations (SDs) will be calculated or imputed when possible.[19] Risk ratios (RRs) will be calculated for categorical variables. Owning to the assumption of inherently various study scenarios and study populations, a random effects

model for all analyses will be assumed[13]. Heterogeneity among studies will be assessed by calculating the $I^2$ statistics whereby $I^2$<25% indicates no heterogeneity, 25%≤ $I^2$ <50% indicates mild heterogeneity, 50%≤ $I^2$ <75% indicates moderate heterogeneity and $I^2$ ≥75% indicates strong heterogeneity.[20] We had planned that if sufficient studies (≥10) are included in the analysis of primary outcomes, we would construct funnel plots to evaluate publication bias,[13] otherwise, Egger's test will be applied.[21] All statistical analyses will be performed using Review Manager 5.3 (Cochrane Collaboration, 2014).

### Subgroup analyses

In the case of possible strong heterogeneity, we will explore the possible sources using subgroup and meta-regression analyses. Subgroup analyses will be carried out based on geographical location, publication form, study design, location of biliary obstruction, indwelling duodenal stent, EUS-BD technique, stent type, and definitions of adverse event. For those subgroups with only 1 study included, subgroup analyses will not be performed.

### Sensitivity analysis

We will carry out a sensitivity analysis by systematically removing every study and checking the pooled results for the remaining studies to see if there is any significant change in test performance.

## Patient and public involvement

Because the collected data within this systematic review and meta-analysis originates from previously published studies, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

# DISCUSSION

ERCP-BD has been a generally preferred treatment for inoperable MBO.[22-24] Conventionally, when ERCP fails for achieving biliary drainage, patients undergo PTBD and EUS-BD.[5, 8, 25] For primary drainage of MBO, several studies have investigated EUS-BD vs. ERCP-BD showing different results.[10-12] A recent meta-analysis [9]reported that EUS-BD may not be used as an initial modality for relieving biliary obstruction, however none of the included studies were direct-comparative. We therefore propose a meta-analysis to pool the evidence to evaluate the performance of EUS-BD vs. ERCP-BD.

One strength of our meta-analysis will be that stent patency and overall survival will be calculated using HRs, in contrast to other meta-analyses using RRs or WMDs.[26] Because the included studies had various length of follow-up, and the events might not occur in some patients at the end of study. For these time-to-event outcomes, the most appropriate way of analysis is to use methods of survival analysis and express the intervention effect as a HR.[13] This will be the first meta-analysis of RCTs comparing

EUS-BD with ERCP-BD for primary drainage of MBO. The results of this study will influence decision making for unresectable MBO, assist in future guideline development and guide future research endeavors.

# ETHICS AND DISSEMINATION

Ethics approval and patient written informed consent will not be required because all analyses in the present study will be performed based on data from published studies. We will disseminate the findings of our work through conference presentations and a peer-reviewed publication.

# AUTHOR STATEMENT

## Author Contributions

XZ is the guarantor. ZJ drafted the manuscript protocol. YW, HL, and WL contributed to the development of the selection criteria, article screening strategy, risk of bias

assessment strategy and data extraction criteria. ZJ developed the search strategy. HH provided statistical expertise. All authors read, provided feedback and approved the final protocol.

Competing interests: None.

Funding: None.

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**Figure 1:** Flow diagram of the study selection process.

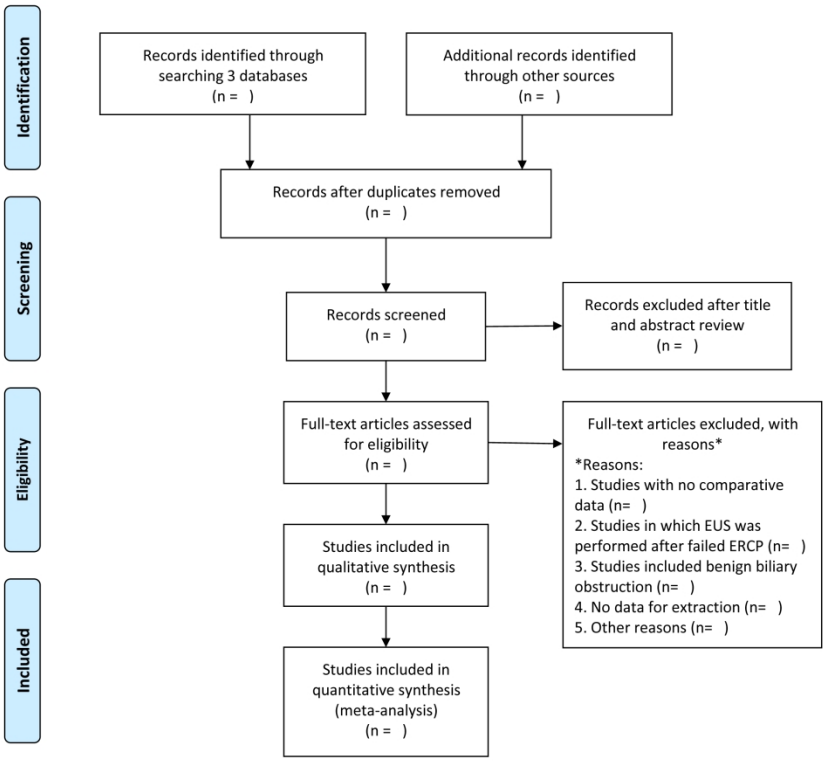


Figure 1 Flow diagram of the study selection process.

**Appendix I. PubMed-MEDLINE search strategy**

up to 31 October 2018.

#1 "Endosonography"[MeSH] OR "endoscopic ultrasonography"[tiab] OR "endoscopic ultrasound"[tiab] OR "EUS"[tiab] OR "choledochoduodenostomy"[tw] OR "hepaticogastrostomy"[tw]

#2 "Cholangiopancreatography, Endoscopic Retrograde"[MeSH] OR "ERCP"[tiab]

#3 "Cholestasis, Extrahepatic"[MeSH] OR "Jaundice, Obstructive"[MeSH] OR "biliary obstruction"[tiab] OR "biliary stricture"[tiab]

#4 "Carcinoma"[MeSH] OR "malign* "[tiab] OR "cancer"[tiab]

#5 #3 AND #4

#6 "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomly"[tiab]

#7 #1 AND #2 AND #5 AND #6

## Appendix II. Data extraction form

| | | |
|---|---|---|
| Article title | | |
| First author | | |
| Year of publication | | |
| Location | | |
| Setting | | |
| Study design | | |
| Study quality | | |
| Patient demographics characteristics | EUS-BD | ERCP-BD |
| Sample size, n | | |
| Age (y), mean ± SD | | |
| Sex, male, % | | |
| Patient clinical characteristics | | |
| Etiology (n) | | |
| Duodenal invasion, n/N (%) | | |
| Indwelling duodenal stent, n/N (%) | | |
| Indications for reintervention (n) | | |
| Chemotherapy, n/N (%) | | |
| EUS-BD technique | | |
| Type of stents | | |
| **Technical success, n/N (%)** | | |
| **Clinical success, n/N (%)** | | |
| **Procedure Duration (mins), mean ± SD** | | |
| **Stent dysfunctions, n/N (%)** | | |
| **Stent occlusion** | | |
| **Stent migration** | | |
| **Tumor in/overgrowth** | | |
| **Reinterventions, n/N (%)** | | |
| **Adverse events, n/N (%)** | | |
| **Total** | | |
| **Pancreatitis** | | |
| **Cholangitis** | | |
| **Cholecystitis** | | |
| **Bleeding** | | |
| **Bile peritonitis** | | |
| **Stent Patency (HR)** | | |
| **Overall survival (HR)** | | |
| Follow-up (days), median (IQR) | | |
| Patients lost to follow-up, n/N (%) | | |

EUS-BD, EUS-guided biliary drainage; ERCP-BD, ERCP-guided biliary drainage; HR, hazard ratio; IQR, interquartile range, SD, standard deviation.
Bold items are outcomes of our analysis.

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | ☒ | ☐ | Page 1 Line 11 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☒ | Not applicable |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | ☐ | ☒ | Not applicable |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | ☒ | ☐ | Page 1 Line 24 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | ☒ | ☐ | Page 12 Line 24 |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☐ | ☒ | Not applicable |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | ☒ | ☐ | Page 12 Line 45 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | ☒ | ☐ | Page 12 Line 45 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | ☒ | ☐ | Page 12 Line 45 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | ☒ | ☐ | Page 4 Line 19 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | ☒ | ☐ | Page 4 Line 54 |
| **METHODS** | | | | | |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | ☒ | ☐ | Page 5 Line 25 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | ☒ | ☐ | Page 7 Line 31 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | ☐ | ☒ | |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | ☒ | ☐ | Page 8 Line 34 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | ☒ | ☐ | Page 8 Line 19 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | ☒ | ☐ | Page 8 Line 34 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | ☒ | ☐ | Page 8 Line 48 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | ☒ | ☐ | Page 6 Line 27 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☒ | ☐ | Page 9 Line 4 |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | ☒ | ☐ | Page 9 Line 27 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | ☒ | ☐ | Page 9 Line 27 |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ☒ | ☐ | Page 10 Line 13 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | ☒ | ☐ | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☒ | ☐ | Page 10 Line 13 |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | ☒ | |