International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Safety and Efficacy Comparison of Single-Stage and Two-Stage ERCP Combined with Laparoscopic Cholecystectomy: A Meta-Analysis and Systematic Review

INPLASY2025100075

doi: 10.37766/inplasy2025.10.0075

Received: 21 October 2025

Published: 21 October 2025

Tai, JX.

Corresponding author:
Jianxiong Tai

xiaoyao206444@126.com

Author Affiliation:
The study includes authors from multiple countries, including Europe, Asia, and North America, reflecting a diverse range of clinical practices and patient populations involved in the comparison of LERV and two-stage ERCP + LC.

ADMINISTRATIVE INFORMATION

Support - Not Received.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025100075

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 October 2025 and was last updated on 21 October 2025.

INTRODUCTION

Review question / Objective Population (P): Patients diagnosed with gallstones or choledocholithiasis (common bile duct stones) undergoing surgical management.
Intervention (I): Single-stage Laparoscopic-Endoscopic Rendezvous (LERV) — a combined intraoperative procedure integrating ERCP with laparoscopic cholecystectomy.
Comparison (C): Traditional two-stage approach — Endoscopic Retrograde Cholangiopancreatography (ERCP) followed by delayed Laparoscopic Cholecystectomy (LC).
Outcomes (O): Primary outcomes include the stone clearance success rate, incidence of postoperative complications, occurrence of pancreatitis, and hyperamylasemia. Secondary outcomes include operative time, hospital stay duration, and procedure-related morbidity.
Study Design (S): Prospective randomized controlled trials (RCTs) included in a systematic review and meta-analysis.
This systematic review and meta-analysis aim to evaluate and compare the safety and efficacy of single-stage LERV versus the conventional two-stage ERCP followed by LC in the management of bile duct stones. The study seeks to determine whether LERV improves stone clearance success rates and reduces postoperative complications, particularly pancreatitis and hyperamylasemia, thereby establishing its role as a safe and efficient alternative to sequential surgery.

Condition being studied Condition Being Studied: Gallstones and Choledocholithiasis

Gallstones are solid particles that form in the gallbladder, a small organ located beneath the liver. They primarily consist of cholesterol or bilirubin, and their size can range from very small particles

to large stones. Gallstones are one of the most common disorders of the biliary system, affecting millions of people globally. While many individuals with gallstones remain asymptomatic, some develop symptoms due to complications such as blockage or infection of the bile ducts. The most common symptoms include abdominal pain, nausea, vomiting, and jaundice, which occur when the stones obstruct the flow of bile.

The condition of choledocholithiasis refers to the presence of gallstones within the common bile duct (CBD), a condition that often arises when gallstones from the gallbladder migrate into the bile duct. This can lead to serious complications, including bile duct obstruction, pancreatitis, and cholangitis (inflammation of the bile duct). Choledocholithiasis is a major concern because of its potential to cause significant morbidity and, if untreated, can lead to severe infections, liver damage, and even death.

Treatment for symptomatic gallstones typically involves surgical intervention, with the most common procedure being cholecystectomy—the surgical removal of the gallbladder. In cases where choledocholithiasis is also present, additional procedures are often required to clear the bile duct stones, as these can cause blockage and increase the risk of infections such as cholangitis or pancreatitis.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is a minimally invasive procedure that combines endoscopy and X-ray imaging to diagnose and treat bile duct obstructions. It is commonly used to locate and remove gallstones from the bile ducts in patients with choledocholithiasis. While ERCP is effective for stone retrieval, it carries risks, such as pancreatitis (inflammation of the pancreas) and hyperamylasemia (increased levels of amylase, which is a marker of pancreatic damage).

Laparoscopic Cholecystectomy (LC)

Laparoscopic cholecystectomy is the standard surgical treatment for gallbladder stones. This minimally invasive procedure involves the removal of the gallbladder through small incisions, using a camera to guide the surgeon. It is generally considered safe and effective for managing gallbladder disease but does not address bile duct stones, which may require additional treatment, such as ERCP.

Combination Approaches: Sequential vs. Single-Stage Techniques

In patients with both gallstones and choledocholithiasis, a two-stage approach is often used: ERCP is performed first to clear the bile duct stones, followed by laparoscopic cholecystectomy to remove the gallbladder. While effective, this sequential approach carries the risk of delayed stone clearance and additional complications from multiple procedures.

In contrast, the single-stage technique—known as the Laparoscopic-Endoscopic Rendezvous (LERV) procedure—combines both ERCP and LC into a single, simultaneous operation. This technique is gaining popularity due to its potential advantages, such as reduced hospital stay and fewer complications, including pancreatitis. By performing both procedures in tandem, LERV may offer a more efficient and less risky treatment option for patients with concomitant gallstones and bile duct stones.

In this review, we aim to explore the efficacy and safety of LERV compared to the traditional two-stage approach, focusing on the stone clearance success rate, the incidence of complications, and other clinical outcomes.

METHODS

Participant or population Patient, Participant, or Population

The population targeted in this review consists of adult patients diagnosed with gallstones and choledocholithiasis (common bile duct stones). These patients are typically treated for symptomatic gallstones, which may be associated with complications such as biliary obstruction, inflammation, or infection. The following characteristics define the participant group for this review:

Age Group:
The review focuses on adult patients aged 18 years and older. Gallstones and choledocholithiasis are common conditions in adults, particularly in middle-aged and older populations. While the incidence of these conditions is lower in younger individuals, they are prevalent in older adults, particularly those over 40 years of age.

Diagnosis:
Participants must have been diagnosed with gallstones and/or choledocholithiasis. Diagnosis is

generally confirmed through a combination of clinical symptoms (such as abdominal pain and jaundice), imaging studies (e.g., ultrasound, CT scan), and sometimes, the use of endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP).

Symptomatic Gallstones:
Gallstones are asymptomatic in many patients, but the focus here is on individuals who have developed symptoms, including pain (biliary colic), nausea, vomiting, or jaundice. These symptoms often indicate complications from gallstones, such as gallbladder inflammation (cholecystitis) or common bile duct obstruction (choledocholithiasis), requiring intervention.

Presence of Choledocholithiasis:
Participants will have choledocholithiasis, characterized by the presence of gallstones within the common bile duct. These patients often require a more complex treatment approach to clear the obstructing stones, with additional risks of complications such as pancreatitis and cholangitis.

Indication for Surgical Intervention:
The participants in this review will have been referred for surgical treatment due to symptomatic gallstones and/or choledocholithiasis. The primary intervention options include laparoscopic cholecystectomy (LC) for gallstone removal and ERCP for bile duct stone clearance.

Inclusion Criteria:

Randomized controlled trials (RCTs) and prospective studies comparing single-stage Laparoscopic-Endoscopic Rendezvous (LERV) with the two-stage ERCP + LC approach.

Patients who are eligible for both ERCP and laparoscopic cholecystectomy based on clinical guidelines.

Patients who have not undergone prior biliary surgery, such as previous cholecystectomy or ERCP, unless the trial specifically includes such cases.

Studies including adults from varied demographic backgrounds (including those from Europe, Asia, and North America) and with different ethnicities to ensure broad applicability of results.

Exclusion Criteria:

Patients with contraindications for ERCP or LC, such as severe comorbid conditions (e.g., advanced cardiac disease, severe liver disease, or uncorrectable coagulopathies).

Pregnant patients or individuals who cannot undergo surgery due to specific medical reasons.

Participants who have gallbladder cancer or other cancers affecting the biliary system.

Study Design and Characteristics:
The studies included in this review will focus on prospective randomized controlled trials (RCTs) that compare the efficacy and safety of single-stage LERV with the traditional two-stage approach of ERCP followed by laparoscopic cholecystectomy (ERCP+LC). These studies will provide high-quality evidence by minimizing biases and confounding factors.

By reviewing these criteria, this review will provide clarity on the effectiveness and safety of LERV as a treatment strategy for this specific group of patients with both gallstones and choledocholithiasis, offering insights into the clinical outcomes and potential advantages over the conventional two-stage method.

Intervention The primary intervention evaluated in this review is the Laparoscopic-Endoscopic Rendezvous (LERV) technique. This is a single-stage, combined procedure that integrates endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic cholecystectomy (LC) to treat patients with gallstones and choledocholithiasis (common bile duct stones) concurrently. Below, we provide a detailed description of this intervention:

Overview of LERV Procedure:

The Laparoscopic-Endoscopic Rendezvous (LERV) technique combines two minimally invasive procedures into a single operation to manage bile duct stones and gallbladder stones simultaneously:

Endoscopic Retrograde Cholangiopancreatography (ERCP):
ERCP is performed initially during the procedure. This involves the insertion of an endoscope through the duodenum to access the common bile duct (CBD). A catheter is used to inject contrast dye into the bile ducts, allowing for radiographic imaging. If stones are detected in the CBD, the endoscopist uses specialized tools (such as a stone basket or balloon) to extract the stones. The

ERCP stage may also include sphincterotomy, where the sphincter of Oddi is cut to facilitate stone extraction.

Laparoscopic Cholecystectomy (LC):
Following the ERCP, the laparoscopic surgeon performs a cholecystectomy to remove the gallbladder, which houses the gallstones. This is done via small incisions using a laparoscope, minimizing the need for large incisions and reducing recovery time. The gallbladder is removed, and any remaining stones in the gallbladder or bile ducts are also cleared.

Key Features and Advantages of LERV:

Single-Stage Procedure:
LERV offers the advantage of combining two separate interventions (ERCP and LC) into a single, simultaneous operation. This can potentially reduce hospital stays and minimize the risk of complications associated with multiple procedures.

Minimally Invasive:
Both ERCP and LC are minimally invasive procedures, meaning they use small incisions or endoscopes inserted through natural body openings, resulting in less trauma to the body and faster recovery times compared to traditional open surgery.

Reduced Risk of Postoperative Complications:
By performing the procedures in a single session, the risk of complications such as pancreatitis, biliary leakage, and infections from multiple surgeries may be reduced. Studies suggest LERV can lower the risk of post-ERCP pancreatitis when compared to sequential procedures.

Improved Stone Clearance:
LERV has shown to result in higher stone clearance rates in comparison to the sequential two-stage approach (ERCP followed by LC). The ability to remove stones from the bile duct and gallbladder in one surgical setting improves the chances of complete and effective treatment.

Shorter Hospital Stay and Faster Recovery:
As a single-stage procedure, LERV may reduce hospitalization time and overall recovery time for patients, allowing for a quicker return to daily activities.

Reduced Cost:
Combining both ERCP and LC into a single procedure may result in lower overall healthcare costs, as it eliminates the need for separate surgeries and prolonged hospital stays.

Procedure Workflow:

Preoperative Assessment:
Patients are evaluated to ensure they are eligible for both ERCP and laparoscopic cholecystectomy based on clinical guidelines. Imaging techniques like ultrasound, CT, or MRCP are used to confirm the diagnosis of gallstones and bile duct stones.

Endoscopic Stage (ERCP):
ERCP is performed first to access and remove stones from the common bile duct. If necessary, a sphincterotomy is performed to facilitate the extraction of the stones.

Laparoscopic Stage (LC):
After the ERCP, the patient is positioned for laparoscopic cholecystectomy. The gallbladder is accessed through small abdominal incisions using a camera (laparoscope) and surgical tools. The gallbladder is then removed, and any remaining stones are cleared from the bile ducts if present.

Postoperative Care:
Patients are monitored for any signs of complications such as bleeding, infection, or bile leakage. Due to the minimally invasive nature of the procedure, patients typically experience a shorter recovery and can often be discharged within 24-48 hours after the procedure.

Comparator Comparator: Sequential Two-Stage Approach (ERCP + Laparoscopic Cholecystectomy)

The comparator intervention for this review is the traditional two-stage approach that involves performing Endoscopic Retrograde Cholangiopancreatography (ERCP) followed by Laparoscopic Cholecystectomy (LC) at separate times. This is the standard treatment protocol for patients diagnosed with both gallstones and choledocholithiasis (common bile duct stones).

Procedure Overview:

First Stage - ERCP (Preoperative):
The first stage involves the preoperative ERCP procedure, in which an endoscope is inserted into the duodenum, and the common bile duct (CBD) is accessed. If stones are found in the bile duct, stone extraction is performed using specialized instruments (stone baskets, balloons, or mechanical lithotripsy). Additionally, a sphincterotomy (cutting of the sphincter of Oddi)

may be performed to facilitate stone removal. However, ERCP carries risks of complications like pancreatitis, bile duct injury, and infection.

Second Stage - Laparoscopic Cholecystectomy (LC):
After the bile duct has been cleared, the patient undergoes laparoscopic cholecystectomy to remove the gallbladder. The procedure is minimally invasive, performed through small incisions, using a laparoscope and specialized surgical tools. The gallbladder is removed, and any remaining stones in the gallbladder or bile ducts are cleared.

Characteristics of the Two-Stage Approach:

Separate Procedures: ERCP is performed first to address bile duct stones, followed by LC to remove the gallbladder. This requires separate procedures and anesthesia sessions, often days or weeks apart.

Risks: The sequential approach increases the total risk exposure to patients, as they undergo two separate surgeries. Complications such as post-ERCP pancreatitis, infection, and bile leakage may arise, which can result in prolonged hospitalization and recovery.

Hospitalization and Recovery: The need for two separate hospital admissions or a prolonged hospital stay due to complications can increase overall healthcare costs. Patients also experience longer recovery times due to the two distinct interventions.

Effectiveness: While effective in stone removal and gallbladder extraction, the sequential approach is more resource-intensive, requires extended recovery periods, and may be associated with a higher rate of complications compared to the LERV approach.

Comparison with LERV:

Single vs. Multiple Stages: LERV is performed in a single operation, which is intended to reduce hospital stays, the need for additional anesthesia, and the total risk of complications compared to the two-stage approach.

Efficiency: The two-stage approach might be associated with longer hospital stays, increased costs, and a higher risk of postoperative complications, such as pancreatitis and bile leakage, compared to LERV, which combines both procedures into one session, potentially leading to quicker recovery and fewer complications.

The goal of this review is to compare the safety and efficacy of the LERV technique against the two-stage ERCP + LC approach by evaluating key outcomes, such as stone clearance success rates, postoperative complications, hospital stay duration, and recovery time.

Study designs to be included The review will include prospective randomized controlled trials (RCTs), as these provide the highest level of evidence by minimizing bias through random allocation of participants to either the LERV or two-stage ERCP + LC intervention groups. Additionally, prospective cohort studies will be included if RCTs are unavailable, as they can offer valuable insights into the real-world application of these interventions. Systematic reviews and meta-analyses of RCTs will also be included to strengthen the evidence base.

Eligibility criteria Eligibility Criteria
Inclusion Criteria:

Study Design:

Prospective randomized controlled trials (RCTs) comparing Laparoscopic-Endoscopic Rendezvous (LERV) with two-stage ERCP + laparoscopic cholecystectomy (LC).

Prospective cohort studies where RCTs are unavailable.

Systematic reviews and meta-analyses that include RCTs or cohort studies focusing on LERV versus the two-stage approach.

Population:

Adults aged 18 years and older with gallstones and choledocholithiasis (bile duct stones).

Patients who have been diagnosed with symptomatic gallstones and/or choledocholithiasis and require surgical intervention (i.e., ERCP and/or LC).

Intervention:

Studies where LERV (single-stage laparoendoscopic rendezvous) is used as the intervention for managing both gallstones and bile duct stones.

Comparator:

Studies comparing LERV to the two-stage ERCP + LC approach.

Outcomes:

Studies that report on stone clearance rates, complication rates (e.g., pancreatitis, hyperamylasemia), hospitalization duration, and overall recovery time.

Language:

Studies published in English.

Exclusion Criteria:

Study Design:

Retrospective studies, case reports, and reviews without primary data.

Studies that do not directly compare LERV with the two-stage ERCP + LC approach.

Population:

Studies including pediatric patients or those younger than 18 years.

Patients with contraindications to ERCP or laparoscopic surgery (e.g., severe cardiovascular or hepatic diseases, uncorrectable coagulopathies).

Patients with gallbladder cancer or other malignancies affecting the biliary system.

Intervention:

Studies evaluating other procedures for gallstones and choledocholithiasis, such as open surgery, percutaneous interventions, or non-surgical treatments.

Outcomes:

Studies that do not report on key outcomes such as stone clearance, postoperative complications, or hospital stay/recovery time.

Publication Type:

Unpublished studies, conference abstracts, and studies with incomplete data or lack of clear statistical reporting.

These criteria ensure that the studies included in the review provide robust, relevant data on the comparison between LERV and the conventional two-stage ERCP + LC approach for treating gallstones and choledocholithiasis.

Information sources Information Sources

To address the objective of this review and ensure comprehensive coverage of the topic, the following information sources will be utilized:

1. Electronic Databases:

PubMed: A comprehensive resource for biomedical literature, including studies related to gallstones, choledocholithiasis, and ERCP + laparoscopic cholecystectomy.

Embase: A biomedical database offering a broad selection of peer-reviewed journals, including international studies that may not be present in PubMed.

Cochrane Library: A trusted source for high-quality systematic reviews and meta-analyses, as well as clinical trials related to the treatment of gallstones and bile duct stones.

Web of Science: A multidisciplinary database providing access to high-impact research articles, reviews, and clinical studies, relevant to ERCP and laparoscopic cholecystectomy interventions.

CINAHL (Cumulative Index to Nursing and Allied Health Literature): For studies related to surgical nursing, post-operative care, and management of gallstone-related diseases.

2. Trial Registers:

ClinicalTrials.gov: To identify ongoing or completed clinical trials on the use of LERV and the two-stage ERCP + LC approach in the treatment of gallstones and choledocholithiasis.

WHO International Clinical Trials Registry Platform (ICTRP): To ensure inclusion of trials that may not have been indexed in traditional databases, especially those from non-English-speaking countries.

EU Clinical Trials Register: For trials conducted in Europe, focusing on novel interventions like LERV in bile duct stone management.

3. Grey Literature:

Conference Proceedings: Abstracts and posters from major gastroenterology and surgical conferences (e.g., American Society of Gastrointestinal Endoscopy (ASGE), Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), and European Association for

Endoscopic Surgery (EAES)) will be reviewed for unpublished studies or preliminary results.

Dissertations and Theses: Relevant dissertations and theses that might not yet be published in journals but contribute to the understanding of LERV versus two-stage procedures.

Government and Health Organization Reports: Reports from health organizations and government bodies (e.g., National Institute for Health and Care Excellence (NICE), World Health Organization (WHO)) may provide relevant clinical practice guidelines and evidence on the treatment of gallstones and choledocholithiasis.

4. Contact with Authors:

Direct contact with study authors: If necessary, we will contact the authors of studies that have incomplete data or require additional clarification. This will be particularly useful for acquiring data on outcomes like complication rates, hospitalization duration, or stone clearance rates.

5. Other Sources:

Reference Lists: The reference lists of all included studies, relevant systematic reviews, and meta-analyses will be examined to identify any additional studies that might be missed in the primary search.

Non-English Sources: When possible, translations of studies in non-English languages will be sought, particularly in Chinese, Spanish, German, and French, which are common languages for clinical studies on ERCP and laparoscopic cholecystectomy.

By searching across multiple sources, this review will ensure that a comprehensive range of high-quality evidence is included, providing the most accurate and up-to-date information on the effectiveness and safety of LERV versus the traditional two-stage approach.

Main outcome(s) The primary outcomes of this review will focus on effectiveness and safety of the Laparoscopic-Endoscopic Rendezvous (LERV) technique compared to the traditional two-stage ERCP + laparoscopic cholecystectomy (LC) approach. The outcomes will be as follows:

Stone Clearance Success Rate:

Definition: The proportion of patients who achieve complete clearance of bile duct stones during the procedure.

Effect Measure: Risk ratio (RR) with a 95% confidence interval (CI).

Timing: Measured intraoperatively or immediately post-surgery.

Incidence of Postoperative Complications:

Definition: Includes complications such as pancreatitis, hyperamylasemia, infection, and bile leakage.

Effect Measure: Risk ratio (RR) with a 95% confidence interval (CI).

Timing: Measured within 30 days postoperatively or the duration of hospitalization.

Hospitalization Duration:

Definition: The total length of hospital stay from the time of the procedure to discharge.

Effect Measure: Mean difference (MD) with a 95% confidence interval (CI).

Timing: Recorded from admission to discharge.

Recovery Time:

Definition: Time taken for patients to return to normal daily activities.

Effect Measure: Mean difference (MD) with a 95% confidence interval (CI).

Timing: 1-3 months post-surgery, based on patient reports.

Incidence of Pancreatitis:

Definition: Occurrence of post-ERCP pancreatitis, a common complication in bile duct stone treatments.

Effect Measure: Risk ratio (RR) with a 95% confidence interval (CI).

Timing: Measured within 30 days postoperatively.

These outcomes will provide a comprehensive understanding of the comparative safety, efficacy, and practicality of the two treatment approaches.

Quality assessment / Risk of bias analysis To ensure the reliability and validity of the studies included in this review, the risk of bias in the primary studies will be assessed using the

Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials (RCTs). For cohort studies, we will use the Newcastle-Ottawa Scale (NOS) to evaluate study quality.

Cochrane Risk of Bias Tool (RoB 2) for RCTs:

The RoB 2 tool will assess the risk of bias across five key domains:

Random Sequence Generation: Evaluates whether randomization was appropriately conducted to reduce selection bias.

Allocation Concealment: Assesses whether the method of allocation was concealed to prevent selection bias.

Blinding of Participants and Personnel: Determines if participants and healthcare providers were blinded to group allocation, minimizing performance bias.

Blinding of Outcome Assessment: Reviews if the assessment of primary and secondary outcomes was blinded to prevent detection bias.

Incomplete Outcome Data: Assesses whether there were any missing outcome data and if the handling of missing data was appropriate to prevent attrition bias.

Selective Reporting: Examines whether the study reported all outcomes as planned in the protocol or if there were selective reports of favorable outcomes.

Other Bias: Identifies any other biases in the study design or conduct that could impact the results.

Each domain will be rated as Low, High, or Unclear risk of bias. The overall risk of bias will be classified as Low, Moderate, or High based on the assessment across all domains.

Newcastle-Ottawa Scale (NOS) for Cohort Studies:

The NOS will evaluate the quality of prospective cohort studies across three domains:

Selection: Assesses the representativeness of the exposed cohort, the selection of the non-exposed cohort, and the ascertainment of exposure.

Comparability: Evaluates whether the cohorts are comparable based on the design or analysis.

Outcome: Reviews the assessment of the outcome, including whether the outcome is clearly defined and the method of outcome assessment.

Each cohort study will be awarded stars (up to a maximum of 9) based on the NOS criteria, and studies will be classified as Low, Moderate, or High quality.

Handling of Studies with High Risk of Bias:

Studies identified with a high risk of bias will be carefully considered in the analysis. Sensitivity analyses may be performed to assess the robustness of the results, potentially excluding high-bias studies.

If significant bias is detected in a large number of studies, this will be noted, and conclusions will be drawn cautiously, indicating the limitations.

Strategy of data synthesis The data synthesis for this review will follow a quantitative approach, using meta-analysis to combine the results of included studies, when appropriate. The synthesis will focus on comparing the effectiveness and safety of the Laparoscopic-Endoscopic Rendezvous (LERV) technique with the traditional two-stage ERCP + laparoscopic cholecystectomy (LC) approach for patients with gallstones and choledocholithiasis. The strategy will include the following steps:

1. Data Extraction

Data will be extracted independently by two reviewers using a standardized extraction form. Relevant information to be extracted includes:

Study characteristics (e.g., author, year, country, study design)

Participant demographics (e.g., age, gender, clinical characteristics)

Intervention details (e.g., type of procedure, timing)

Outcome data (e.g., stone clearance rate, incidence of complications, hospital stay)

Discrepancies between reviewers will be resolved through discussion or a third reviewer.

2. Descriptive Analysis

A descriptive summary of the studies will be provided, including details on study designs, participant characteristics, interventions, and

outcomes. This will help contextualize the findings and assess the scope of the data.

3. Statistical Analysis

Effect Measures:

For dichotomous outcomes (e.g., stone clearance success, complications like pancreatitis, hyperamylasemia), the Risk Ratio (RR) with 95% Confidence Intervals (CI) will be calculated.

For continuous outcomes (e.g., hospital stay duration, recovery time), the Mean Difference (MD) or Standardized Mean Difference (SMD) with 95% CI will be calculated.

Heterogeneity:

Heterogeneity between studies will be assessed using the I^2 statistic.

Low heterogeneity ($I^2 \leq 25\%$) will indicate minimal variability across studies.

Moderate ($I^2 = 25\text{-}50\%$) and high ($I^2 \geq 50\%$) heterogeneity will suggest significant variability, and the analysis will use a random-effects model to account for this variation.

If heterogeneity is low, a fixed-effects model will be used.

Meta-Analysis:

A meta-analysis will be performed if the studies are sufficiently homogeneous in terms of outcome measures and study design.

The random-effects model will be preferred when significant heterogeneity is present. This model assumes that the true effect varies between studies, allowing for more conservative estimates of treatment effects.

If inappropriate statistical pooling (due to too much heterogeneity or insufficient data) occurs, a qualitative synthesis will be provided instead of a quantitative meta-analysis.

Sensitivity Analysis:

Sensitivity analysis will be conducted to examine the impact of high-risk bias studies on the overall results. Studies identified as having high risk of bias will be excluded from the sensitivity analysis to test the robustness of the results.

4. Subgroup and Meta-Regression Analysis:

If enough data are available, subgroup analyses will be performed to assess the effect of variables such as:

Age: Elderly versus younger populations.

Severity of disease: Symptomatic versus asymptomatic gallstone disease.

Geographic region: Differences in outcomes across geographical settings (e.g., Western vs. Asian populations).

Meta-regression may be employed to explore the impact of potential effect modifiers, such as study quality, sample size, or treatment variations.

5. Assessment of Publication Bias:

Funnel plots will be used to visually assess publication bias for the primary outcomes (stone clearance rate, complications).

Egger's test will be performed to statistically assess asymmetry in funnel plots.

6. GRADE Framework for Assessing Evidence Quality

Subgroup analysis Subgroup analysis will be conducted to explore potential differences in treatment effects across various patient and study characteristics. The goal is to understand how factors such as patient demographics, disease severity, and study quality might influence the outcomes of Laparoscopic-Endoscopic Rendezvous (LERV) versus the two-stage ERCP + laparoscopic cholecystectomy (LC) approach. The following subgroup analyses will be performed:

1. Age Group

Young Adults vs. Elderly:
Older patients (typically over 65) may have different surgical risks and outcomes due to comorbidities, and the effectiveness of LERV versus the traditional two-stage approach may vary across these groups.

2. Disease Severity

Symptomatic vs. Asymptomatic Gallstones:
The efficacy of LERV may differ between patients with symptomatic gallstones (requiring intervention due to complications) versus asymptomatic individuals. Symptomatic patients might have more

severe disease, which could influence outcomes such as recovery time and complication rates.

Mild vs. Severe Choledocholithiasis:
Subgroup analysis will consider patients with mild choledocholithiasis (fewer stones or minimal ductal obstruction) versus those with more severe conditions (multiple stones, large obstructive stones). The complexity of the disease could affect the success of stone clearance and complication rates.

3. Surgical Experience and Facility Type

Surgeon Expertise:
The outcomes of LERV may differ based on the surgeon's experience with the technique. More experienced surgeons might have better outcomes, particularly in minimizing complications such as pancreatitis or biliary leaks.

Institutional Setting:
Differences between studies conducted in high-volume centers with access to advanced technologies and expertise versus community hospitals with less specialized teams will be explored. High-volume centers may report better outcomes for LERV due to more refined techniques and experienced teams.

4. Geographic Region

Western vs. Non-Western Populations:
Subgroup analysis will also consider the geographic origin of the studies. Differences in patient characteristics, healthcare systems, and procedural expertise could lead to variability in the outcomes of LERV compared to the two-stage approach.

5. Type of Procedure (LERV vs. ERCP + LC)

Timing of the Procedures:
Differences in the timing of the two-stage procedures (whether ERCP is performed days or weeks prior to LC) could influence the outcomes. The analysis will examine whether there are advantages to performing both procedures in one session (LERV) compared to the conventional sequential approach.

6. Study Quality

High vs. Low Risk of Bias Studies:
We will evaluate whether study quality (as assessed by the Cochrane Risk of Bias tool or Newcastle-Ottawa Scale for cohort studies) influences the results.

Sensitivity analysis To assess the robustness and reliability of the review's findings, sensitivity analysis will be conducted. This will help determine whether the results are affected by decisions made during the study selection process, study quality, or assumptions made during data analysis. The following approaches will be used:

1. Excluding High-Risk Bias Studies

Objective:
The first step in sensitivity analysis will be to assess the impact of studies with high risk of bias (as determined by the Cochrane Risk of Bias tool or the Newcastle-Ottawa Scale for cohort studies) on the overall findings.

Approach:
Studies identified as having a high risk of bias (e.g., issues with randomization, blinding, or incomplete data) will be excluded from the analysis to see if their inclusion has influenced the pooled results. This will allow us to determine whether the conclusions hold up when only high-quality studies are considered.

Outcome:
We will compare the results of the meta-analysis with and without high-risk bias studies, examining if the magnitude of treatment effects changes significantly.

2. Sensitivity Based on Study Design

Objective:
Since RCTs and cohort studies may yield different results, we will conduct a sensitivity analysis by excluding cohort studies or randomized controlled trials (RCTs) to explore if the effect estimates vary by study design.

Approach:
Separate meta-analyses will be conducted for RCTs only and cohort studies only. The results of these analyses will be compared to identify any significant discrepancies in treatment effects between different study designs.

Outcome:
This will help assess whether the study design influences the overall effectiveness and safety outcomes of LERV versus the two-stage ERCP + LC approach.

3. Impact of Subgroup Definitions

Objective:

Sensitivity analysis will also evaluate the influence of subgroup definitions on the findings. For example, if a subgroup based on disease severity (mild vs. severe choledocholithiasis) has a disproportionate influence on the results, this may bias the overall conclusions.

Approach:
We will re-run the analysis by adjusting subgroup definitions or excluding specific subgroups that might skew the data.

Outcome:
This will confirm whether the observed treatment effects remain consistent across various patient groups, or if certain subgroups disproportionately impact the results.

4. Influence of Outlier Studies

Objective:
To assess whether any outlier studies with extreme effect sizes are driving the results.

Approach:
We will use leave-one-out sensitivity analysis, where one study is removed at a time, and the pooled estimates are recalculated. If the results change significantly when a particular study is excluded, it may indicate that the study is exerting undue influence on the outcome.

Outcome:
This will help identify whether the overall findings are sensitive to the inclusion of specific studies or if the conclusions are stable.

5. Influence of Assumptions in Statistical Models.

Country(ies) involved The study includes authors from multiple countries, including Europe, Asia, and North America, reflecting a diverse range of clinical practices and patient populations involved in the comparison of LERV.

Keywords Bile duct stones; ERCP; Laparoscopic-Endoscopic Rendezvous; Laparoscopic cholecystectomy; Meta-analysis.

Contributions of each author

Author 1 - Jianxiong Tai.
Email: xiaoyao206444@126.com