**HEALTH TECHNOLOGY ASSESSMENT REPORT**

**ON**

# CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS OF CHOLECYSTECTOMY COMPARED WITH CONSERVATIVE MANAGEMENT IN PEOPLE PRESENTING WITH UNCOMPLICATED SYMPTOMATIC GALLSTONES (BILIARY PAIN) OR CHOLECYSTITIS IN INDIA

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| | |
|---|---|
| ACC | Acute Calculous Cholecystitis |
| BMI | Body Mass Index |
| CBD | Common Bile Duct |
| CE | Cost Effectiveness |
| CEA | Cost Effectiveness Analysis |
| CEAC | Cost Effectiveness Acceptability Curve |
| CGHS | Central Government Health Scheme |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CI | Confidence Interval |
| CM | Conservative Management |
| CMCHIS | Chief Minister's Comprehensive Health Insurance Scheme |
| CPI | Consumer Price Index |
| CUA | Cost Utility Analysis |
| DC | Delayed Cholecystectomy |
| DLC | Delayed Laparoscopic Cholecystectomy |
| DOC | Delayed Open Cholecystectomy |
| EC | Early Cholecystectomy |
| ELC | Early Laparoscopic Cholecystectomy |
| EOC | Early Open Cholecystectomy |

| | |
|---|---|
| EM | Endoscopic Management |
| EmLC | Emergency Laparoscopic Cholecystectomy |
| EmOC | Emergency Open Cholecystectomy |
| EQ-5D | EuroQol's 5-Dimensional |
| ERCP | Endoscopic Retrograde Cholangiopancreatography |
| EUS | Endoscopic Ultrasound |
| GB | Gall Bladder |
| GBC | Gall Balder Cancer |
| GDP | Gross Domestic Product |
| GSD | Gallstone Diseases |
| GSS | Gallstone Symptoms |
| HICs | High Income Countries |
| HRQoL | Health-Related Quality of Life |
| ICER | Incremental Cost-Effectiveness Ratio |
| IMF | International Monitory Fund |
| INB | Incremental Net Benefit |
| INR | Indian Rupees |
| IQR | Interquartile Range |
| IV | Intravenous |
| LC | Laparoscopic Cholecystectomy |

| | |
|---|---|
| LICs | Low Income Countries |
| LMIC | Lower Middle-Income Countries |
| LNF | Laparoscopic Nissen Fundoplication, |
| MIC | Middle Income Countries |
| MLC | Mini Laparoscopic Cholecystectomy |
| MRCP | Magnetic Resonance Cholangiopancreatography |
| NABH | National Accreditation Board for Hospitals |
| NICE | National Institute for Health and Care Excellence |
| NMB | Net Monetary Benefit |
| NNTH | Number Needed to Treat Harm |
| NOS | Newcastle-Ottawa Scale |
| OC | Open Cholecystectomy |
| OM | Observation Management |
| OPD | Out Patient Department |
| OR | Operation Room |
| OWSA | One Way Sensitivity Analysis |
| PC | Percutaneous Cholecystostomy |
| PCLC | Percutaneous Cholecystostomy followed by LC |
| PEER | Patient Expected Event Rate. |
| PGIMER | Post Graduate Institute of Medical Education and Research |

| | |
|---|---|
| PICO | Population, Intervention, Comparator, and Outcome |
| PMJAY | Pradhan Mantri Jan Arogya Yojana |
| PMRSSM | Pradhan Mantri Rashtriya Swasthya Suraksha Mission |
| PPP | Purchasing Power Parity |
| PPPI | Purchasing Power Parity Index |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSA | Probabilistic Sensitivity Analysis |
| QALY | Quality-Adjusted Life Years |
| QoL | Quality of Life |
| RCT | Randomized Control Trial |
| RD | Risk Difference |
| RIOCP | Routine Intra Operative Cholangiography |
| RoB | Risk of Bias |
| RR | Risk Ratio |
| SAL | Single Access Laparoscopic |
| SD | Standard Deviation |
| SE | Standard Error |
| SILC | Single-Incision Laparoscopic Cholecystectomy |
| SILS | Single Incision Laparoscopic Surgery |
| SIOC | Small Incision Open Cholecystectomy |

| | |
|---|---|
| SPL | Single Port Laparoscopic |
| SRMA | Systematic Review and Meta-Analysis |
| TN | Tamil Nadu |
| UK | United Kingdom |
| UMICs | Upper-Middle Income Countries |
| USA | United States of America |
| USD | United States Dollars |
| VAS | Visual Analogue Scale |
| WHO | World Health Organisation |
| WSES | World Society of Emergency Surgery |
| WTP | Willingness to Pay |

# EXECUTIVE SUMMARY

Gallstone disease or cholelithiasis/cholecystitis is the sixth universal problem requiring surgery and emergency hospitalization in India. Gallstone disease is associated with higher overall and cause-specific mortality and affects the patient's quality of life. Gallstone disease treatment is expensive and represents a significant burden for the healthcare systems worldwide. In India, the risk of gallbladder diseases is high, with a prevalence of 6 to 20% among the adult population. Cholecystectomy or surgical removal of the gallbladder is the recommended treatment for cholecystitis. Laparoscopic cholecystectomy is the most preferred and effective treatment for cholelithiasis/cholecystitis but is expensive. Conservative management involves symptomatic management without the need for surgical intervention. Conservative management also carries a lower risk of complications and is considered an alternative to surgical treatment. Considering the significant economic burden on the healthcare systems imposed by gallbladder diseases, it's critical to determine which management option is most efficient and cost-effective for implementation into the Indian health system. Also, increasing pressure on all aspects of health service delivery warrants the need for such a decision regarding the effective allocation of scarce resources. Hence, we have performed a health technology assessment to determine the cost-effectiveness of cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis. Further, there were no standard guidelines/uniform methods of conservative management for gallstone disease.

For evidence synthesis, we have conducted the systematic review and meta-analysis for clinical and economic outcomes of gallstone disease treatments separately. The SRMA on clinical effectiveness concluded that early cholecystectomy is more effective and results in fewer biliary complications with lower rates of reduced abdominal pain than conservative

management/delayed cholecystectomy. The pooled incremental net benefit from the SRMA of cost-utility studies revealed that early laparoscopic cholecystectomy is cost-effective compared to delayed laparoscopic cholecystectomy. The systematic review of costing studies identifies that early laparoscopic cholecystectomy is less costly than open cholecystectomy/delayed cholecystectomy. The systematic review of cost minimization studies showed that laparoscopic cholecystectomy is less expensive than open cholecystectomy.

To assess the cost-effectiveness, we constructed an analytical decision Markov model to evaluate the cost-effectiveness of laparoscopic cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis in India. Study results indicate that early laparoscopic cholecystectomy (<72 hours) is cost-saving compared to delayed laparoscopic cholecystectomy as well as conservative management. Also, the delayed laparoscopic cholecystectomy is cost-effective than conservative management. Hence, early laparoscopic cholecystectomy could be prioritized as the treatment for people presenting with gallstones/cholecystitis in India. We checked the robustness of our results using one-way sensitivity analyses, probabilistic sensitivity analysis, scenario analysis and observed that the results were valid.

Last, we did a budget impact analysis with an incremental increase in the treatment coverage for Tamil Nadu in India to determine the impact on the state treasury if cholecystectomy is offered to the entire eligible population of the state. We found that early cholecystectomy would lead to net cost savings for the state compared to conservative management and delayed cholecystectomy if the state's entire population is covered for symptomatic gallstones.

Early laparoscopic cholecystectomy is a cost-effective intervention than conservative management or delayed cholecystectomy; hence, the early cholecystectomy within 72 hrs of symptom onset for may be preferable option for symptomatic uncomplicated cholelithiasis and acute cholecystitis. Also, we recommend reducing the delay in elective surgery through active participation and encouragement of primary care needs in acute cholecystitis by the surgical team.

# CHAPTER 1

# INTRODUCTION

## 1.1 BACKGROUND

### 1.1.1 Pathology and clinical presentation

Gallstone disease or cholelithiasis is the sixth commonest problem requiring surgery and emergency hospitalization in India [1]. Gallstones usually form when there is a concentration of bile in the gallbladder due to sluggish emptying of bile, which precipitates as sludge and later develops into gallstones [2]. It can also be developed as a result of biliary obstruction. There are several gallstones types, including cholesterol gallstones, pigmented gallstones, mixed pigmented gallstones, and calcium stones. Cholesterol gallstones form from precipitates of cholesterol from cholesterol-rich bile, which is the most predominant type. Pigmented gallstones, the second most common type, develop from the breakdown of red blood cells and tend to be black. Mixed pigmented stones are a combination of calcium carbonate or calcium phosphate, cholesterol, and bile, whereas Calcium stones are precipitates of serum calcium, particularly in patients with hypercalcemia [2]. Black stones predominate in hemolytic disorders, and brown stones are most common in Asian patients [3]. Brownstones are related to biliary tract infections, including bacterial and parasitic infections [3].

When migrated to the cystic duct opening, these gallstones block the bile flow, resulting in biliary pain. When the obstruction persists for a long time, it can lead to gallbladder inflammation, defined as cholecystitis [2]. These gallstones could stay asymptomatic as silent gallstones or turn to be symptomatic. Symptomatic gallstone disease is characterized as episodes of epigastric pain, ultrasonographic signs of gallbladder stone, and other possible causes ruled out by laboratory evidence. Severe symptoms include frequent and intense pain attacks hindering the patient’s quality of life [4]. Patients with acute cholecystitis usually present with abdominal pain in the right upper region, nausea, vomiting, and fever

accompanied by tenderness in the right upper abdomen, a palpable gallbladder, and Murphy's sign which involves exacerbation of tenderness and pain below the cartilage by inspiration [5]. A positive Murphy's sign has a specificity of 79–96% for acute cholecystitis. Although asymptomatic gallstones usually require no treatment, treating symptomatic gallstones with or without complications is imperative [5].

### 1.1.2 Epidemiology

The prevalence of gallstones was found to be in the range of 6 to 20% in the adult Indian population [6] [1] [7]. It is 2-4 times higher in North Indians than the South Indians, thus showing a varied prevalence in different communities [8]. There is also gender-specific variation observed in the prevalence where it is 1.7 times higher in females than males placing the females at higher risk. Furthermore, pigment gallstones were predominantly reported in South Indians, whereas cholesterol gallstones were predominant among North Indians. Age-specific differences in the prevalence of gallstones were not noted among North Indians and South Indians [6]; however, it has been reported elsewhere that the incidence of gallbladder disease increases with age [9].

### 1.1.3 Disease burden

Gallbladder diseases are considered expensive which costs about 6.5 billion dollars to the US per year, thus representing a significant burden for the healthcare systems worldwide [10]. Direct mortality of gallstone disease or cholelithiasis is considerably low as deaths caused directly due to gallstone-associated complications are rare these days. However, gallstone disease has been associated with higher overall and causes specific mortalities. Cardiovascular disease, Cancer, and Diabetes mortality was 50%, 30%, and two and a half times higher among persons with gallstone disease, respectively, but unrelated to mortality from digestive and infectious diseases [11]. 80% of Indian patients with gallbladder cancer possess gallstones,

increasing their risk of mucosal injury [12]. GBC risk increases further with the increasing size and number of gallstones, especially if the stones occupy a significant volume of the GB [13].

### 1.1.4 Risk Factors

Physical inactivity, tobacco, smoking, nonvegetarian, and high-fat diet have shown to be potentially modifiable risk factors for GSD development, whereas family history, female gender, and ethnicity are unmodifiable risk factors [14]. Some risk factors for the formation of gallstones specific for the South Indian population have also been identified, including higher BMI and use of tamarind, which is the most used ingredient in the south Indian diet [15]. The presence of type 2 diabetes also seems to increase the probability of having GS compared to the general population [16]. Although gallstones are usually asymptomatic, some individuals have a higher risk of progression to symptomatic disease and complications. The risk factors that pose these individuals for higher risk include age <55 years, smoking, female sex, greater body weight, presence of three or more GS, and floating stones. Calculi >2 cm in diameter, calculi <3 mm, and patent cystic duct, non-functioning gallbladder, and perioperative detection of incidental stones have also been quoted as potential risk factors for progression [17].

## 1.2 TECHNOLOGY IN QUESTION

### 1.2.1 Intervention- Cholecystectomy

***Open Cholecystectomy versus Laparoscopic Cholecystectomy***

Cholecystectomy is the surgical removal of the gallbladder, performed either as open cholecystectomy with a single large incision or laparoscopically with four small, minimally invasive incisions. With the advent of laparoscopic cholecystectomy in the 1990s, it has become the gold standard approach for gallbladder removal. It is preferred over open cholecystectomy in terms of shorter hospitalization, early return to work, and reduced expense. However, 2-10% of open cholecystectomies are performed when converting from a

laparoscopic to open cholecystectomy (NBK448176). The overall mortality rate for laparoscopic cholecystectomy was reported to be 0.16% [18]. Open cholecystectomy compared to laparoscopic cholecystectomy had significantly higher mortality, Perioperative complications, Surgical postoperative complications, and Medical postoperative complications. Reoperation rate also seemed to be high in open cholecystectomy compared to laparoscopy. However, the laparoscopy was converted to open cholecystectomy in few patients due to the major intraoperative complications, which include frozen Calot's triangle, injury to the common bile duct (CBD), bile leak from a slipped clip or an accessory duct, uncontrolled bleeding, major vessel injury, duodenal injury, and diaphragmatic tear. Postoperative complications were reportedly higher in the laparoscopic cholecystectomies converted group than in the non-converted group [19]. The main postoperative complications were bile leakage, bleeding, sub-hepatic abscess, and retained bile duct stones. Some patients with post-operative complications require revisional surgeries [20].

***Laparoscopic Cholecystectomy versus Single-incision cholecystectomy***

Unlike laparoscopic cholecystectomy, single-incision laparoscopic cholecystectomy (SILC) aids the removal of the gallbladder with a single incision which is usually made near the umbilicus. Compared to laparoscopic cholecystectomy, single-incision cholecystectomy incurs less pain, shorter recovery time, fewer wound complications and improved cosmesis despite the longer operative time. In terms of clinical effectiveness and safety, single-incision cholecystectomy has been comparable to the laparoscopic method with similar mortality and conversion rates. It was also not associated with more complications compared to the conventional laparoscopic approach [21].

### 1.2.2 Comparator- Conservative Management

Conservative management of cholelithiasis involves administering intravenous (IV) fluids, narcotic analgesics, and non-steroid anti-inflammatory drugs [22] to relieve biliary pain and Proton pump inhibitors to prevent acid-related conditions and dietary restrictions. In patients with cholecystitis or with signs of inflammation, broad-spectrum antibiotics are prescribed until symptoms subside and a normal body temperature is reached [22]. In a systematic review of Conservative treatment for acute cholecystitis, the pooled success rate of conservative treatment during index admission was reported to be 86 % (95 % CI 0.8 to 0.9) [23]. In contrast, a pooled analysis of only randomized controlled trials showed a success rate of 91 % (95 % CI 0.9–1.0) [23]. The pooled mortality rate was 0.5 % (95 % CI 0.001–0.009) [23]. The pooled recurrence rate of gallstone-related disease during long-term follow-up was 19.7 % (95 % CI 0.1–0.3) [23]. Another systematic review (including only randomized studies) conducted to assess the success rate of antibiotics in the treatment of acute calculous cholecystitis (ACC) revealed a 10 % (5 to 20) pooled recurrence rate for ACC [22]. In a recent research that studied the outcomes of conservative management of cholelithiasis in the elderly population, a recurrence rate of 39.8% has been reported over a 2-year follow-up period which constitutes 58% of study subjects with acute cholecystitis and 18.1% with biliary pancreatitis [24].

## 1.3 REVIEW OF LITERATURE

***Clinical effectiveness of cholecystectomy compared with conservative management***

A systematic search was performed to retrieve the existing evidence on the clinical effectiveness of cholecystectomy compared with conservative management for uncomplicated symptomatic gallstones/cholecystitis. Relevant articles comparing cholecystectomy and conservative management were alone selected based on the title and abstract screening, reviewed, and summarized. A recent randomized control trial (RCT) conducted in Norway

compared the non-inferiority of a restrictive strategy with stepwise selection(cholecystectomy) with usual care (conservative management) demonstrated a suboptimal pain reduction in patients with gallstones and abdominal pain with a similar rate of gallstone related complications in both groups which substantiate the effectiveness of conservative management in cholelithiasis [25]. Another RCT that examined the long-term feasibility and safety of observation compared with surgery in patients with acute cholecystitis reported that among those randomized to observation, 33% of patients underwent cholecystectomy, and 33% experienced a new event of gallstone-related disease within five years of follow up. The mortality was reported to be similar in both the intervention groups and was not related to gallstone disease/gallbladder cancer [4]. Another RCT conducted in patients with uncomplicated gallstone disease demonstrated that 88% of people randomized to surgery and 45% of people randomized to observation eventually underwent cholecystectomy during the 14-year follow-up period. 4% of people randomized to observation had a gallstone-associated event, including acute cholecystitis, common bile duct stones, and acute pancreatitis [26]. The results of both the RCTs suggest that watchful waiting could be a safe option, at least in the elderly population. A systematic review that assessed cholecystectomy's clinical effectiveness compared with observation/conservative management included only the above two RCTs and concluded that 55% of the people randomized to observation and 12% of the people randomized cholecystectomy did not require/undergo surgery during the 14-year follow-up period. Participants randomized to observation were significantly more likely to experience gallstone-related complications (RR = 6.69), in particular, acute cholecystitis (RR = 9.55) and less likely to undergo surgery (RR = 0.50) or experience surgery-related complications (RR = 0.36) than those randomized to surgery [27]. An earlier study has also shown that more than 80% of patients randomized to observation did not require surgery, indicating that even patients with complicated gallstone disease may not require surgical intervention [28].

In contrast, an Indian RCT which has compared conservative management versus cholecystectomy in patients who have had endoscopic sphincterotomy who also presented with cholelithiasis have concluded that early cholecystectomy is a must in patients with CBD stones, cholelithiasis, and significant co-morbid illnesses. Whether accompanying co-morbid diseases affects the effectiveness of conservative management needs clarity [29]. From the currently available evidence, it is known that, although cholecystectomy is the treatment of choice for symptomatic gallstone disease/cholecystitis, conservative management carries a low risk of complications thus can be considered as an alternative to surgery in elderly patients [30].

***Cost-effectiveness of cholecystectomy compared with conservative management***

A systematic search was performed to review the existing evidence on the cost-effectiveness of cholecystectomy compared with conservative management for uncomplicated symptomatic gallstones/cholecystitis. Relevant articles comparing cholecystectomy and conservative management were alone selected based on the title and abstract screening, reviewed, and summarized. Apart from that, relevant literature from the CEA registry was also considered. A recent health technology assessment has been conducted in the United Kingdom (UK) to compare the cost-effectiveness of cholecystectomy with conservative management, whose results indicate that surgery strategy was more effective on average than the conservative management and incurred an additional cost of £1236 per patient. More people in the conservative management group required surgery which led to a reduction in the cost-effectiveness of the conservative strategy [31]. However, another CEA study showed that elective cholecystectomy compared to observation in all patients involved an additional cost of $3,422.83 per patient and had lower effectiveness (-0.10 QALYs) at 2-year follow-up [32]. Many other cost-utility studies have compared early versus delayed laparoscopic cholecystectomy for cholelithiasis/acute cholecystitis, which have revealed that early

cholecystectomy is less costly and more effective than delayed cholecystectomy [33], [34], [35], [36]. Contrastingly, one CUA analysis performed alongside an RCT has shown that despite the cost-utilities of the early and delayed approaches being similar, the incremental cost per additional QALY gained favored conventional management [37]. Though there is evidence on the cost-effectiveness of cholecystectomy compared with conservative management, none of them was conducted in India.

## 1.4 RATIONALE FOR CONDUCTING THE STUDY

Cholelithiasis/cholecystitis is one of the expensive diseases imposing a significant burden on the healthcare systems worldwide. In India, the risk of gallbladder diseases is high. Although gallstone disease is asymptomatic and might requires no treatment, certain risk factors drive the progression from asymptomatic to symptomatic disease with or without complications and make it imperative to treat. With the advent of laparoscopic cholecystectomy, it has become the most preferred treatment for cholelithiasis/cholecystitis and has proven effective. Though effective, it also seems to be costly. Conservative management, on the other hand, involves pain and symptom management has also shown effectiveness towards cholelithiasis and cholecystitis and carries a low risk of complications and is considered an alternative to surgery in the clinical practice. Considering the significant economic burden on the healthcare systems imposed by gallbladder diseases, determine which management options are most likely to be efficient and cost-effective for implementation into the Indian health system. This substantiates the importance of conducting health technology assessments to determine the cost-effectiveness of cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis.

## 1.5 AIM / RESEARCH QUESTION

To determine the clinical and cost-effectiveness of cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis

### 1.5.1 Objectives

#### 1.5.1.1 Primary Objectives

1. To conduct a systematic review & meta-analysis of available evidence on the clinical effectiveness of surgical intervention compared with conservative cholelithiasis management
2. To conduct a systematic review & meta-analysis of available evidence on economic evaluations of surgical intervention compared with conservative cholelithiasis management.
3. To develop an economic model to determine the cost-effectiveness of cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis.

#### 1.5.1.2 Secondary Objectives

1. To analyze the budget impact of cholecystectomy compared with conservative management.
2. To formulate policy implications on optimal treatment strategy for people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis.

# CHAPTER 2

# SYSTEMATIC REVIEW AND META-ANALYSIS- CLINICAL EFFECTIVENESS

## 2.1 SYSTEMATIC REVIEW AND META-ANALYSIS OF GALLSTONE-DISEASE TREATMENT OUTCOMES IN EARLY CHOLECYSTECTOMY VERSUS CONSERVATIVE MANAGEMENT/DELAYED CHOLECYSTECTOMY

### 2.1.1 Introduction

Cholelithiasis/gallstone disease management imposes a significant burden on healthcare systems worldwide, costing about 6.5 billion dollars/year only in the USA itself[10]. The prevalence of gallstones ranges from 0.1 to 50.5% worldwide[38]. Although gallstone disease is usually asymptomatic, certain risk factors drive the progression from asymptomatic to symptomatic illness, with or without complications, making it imperative to treat[5]. Gallstone-related complications include common bile duct stones (CBD stones)/Choledocholithiasis, acute-cholecystitis, cholangitis, gallstone-pancreatitis, and others[5]. Surgical removal of the gallbladder (known as cholecystectomy) is the treatment of choice for symptomatic gallstones[39]. Laparoscopic cholecystectomy is the preferred treatment option over open cholecystectomy for gallstones and cholecystitis[40]. However, approximately 12% of patients who have undergone cholecystectomy continue to experience pain and recurrent gallstone-related symptoms[41].

Conservative management, involving pain and symptomatic treatment with gallbladder in situ, carries no risk of operative complications and is also considered an alternative to cholecystectomy[23]. However, among conservatively managed patients with uncomplicated gallstones, recurrence of gallstone symptoms and subsequent development of gallstone-related

complications often lead to cholecystectomy[42]. Similarly, several randomized control trials (RCTs) comparing early versus delayed cholecystectomies for gallstone disease reported recurrence of symptoms/complications in the waiting period before surgery and reported higher post-surgical complications with delayed surgery[43]. Thus, the effectiveness of early cholecystectomy over conservative management/delayed cholecystectomy is ambiguous. Therefore, we conducted this systematic review and meta-analysis to synthesize treatment outcomes between early cholecystectomy and conservative management/delayed cholecystectomy. The study's objective is to synthesize treatment outcomes such as (i) gallstone-related complications between early cholecystectomy and conservative management/delayed cholecystectomy (ii) surgical complications, length of hospital stays, and operative time between early and delayed cholecystectomy.

### 2.1.2 Methods

#### 2.1.2.1 Screening and Study Selection

We carried out this systematic review and meta-analysis in compliance with PRISMA guidelines and registered the protocol at PROSPERO (PROSPERO ID: 2020 CRD42020192612) [44]. We systematically searched the studies indexed in PubMed-Medline, Scopus, and Embase. We constructed the search terms based on domains of population, intervention, comparator, and outcome (PICO) as described below. The search terms were combined using Boolean operator "OR" within the same domains and Boolean operator "AND" between domains of PICO as described in the supplementary Tables 5-7. An initial search was performed on 16$^{th}$ June 2020, and an updated search was performed on 12$^{th}$ January 2021.

According to the inclusion criteria, search results were screened for eligibility. The population included gallstones (cholelithiasis/cholecystolithiasis), CBD stones (choledocholithiasis), acute cholecystitis, or gallstone-pancreatitis. The intervention included surgical removal of the gallbladder through open or laparoscopic methods, where surgery was performed on an emergency basis or within seven days, treated as early cholecystectomy (EC). The comparator is conservative management (CM) and delayed cholecystectomy (DC). Conservative management included both Observation management (OM) (also known as wait and watch strategy) and Endoscopic management (EM). Under observation management, this study considered patients with gallstones who were symptomatically managed using painkillers, antibiotics, diet, and lifestyle changes. Under endoscopic management, this study considered patients who underwent endoscopic removal of CBD stones with gallbladder left in-situ. In delayed cholecystectomy, we considered patients initially managed conservatively and later underwent cholecystectomy after six weeks. Outcomes included complications related to gallstone disease, perioperative, intraoperative, and postoperative complications with cholecystectomy, length of hospital stays, operative time, and the studies included were RCTs. Non-randomized trials, observational studies, reviews, and studies published in non-English languages for which a translation could not be obtained were excluded. Studies were also excluded for their selection of the population, intervention, comparator, and outcome that is not of the study's interest.

Titles and abstracts of studies listed from the electronic database search were meticulously screened independently by authors (BSB, MH, AS) using the Rayyan-web application [45]. After screening, authors independently reviewed and selected studies based on inclusion and exclusion criteria with authors' mutual consensus (Figure 1).

#### 2.1.2.2 Data extraction and management

All relevant details were extracted from the studies included, using a specific data extraction form. Data extracted included study characteristics (study design, location of study, etc.), participant characteristics (age, gender, duration of symptoms, and timing of surgery), intervention, comparators, and treatment outcomes (gallstone symptoms and complications, surgical complications). All the data for pooling were extracted as reported in the primary studies. For quality control, data extraction was performed by one reviewer and cross-checked by another reviewer (BSB, MH). Any discrepancies between authors were resolved by discussion and consulting with a third reviewer (AS) whenever necessary. The extracted data was checked and used for further analysis after confirmation of its consistency.

#### 2.1.2.3 Assessment of Risk of bias

We assessed the risk of bias using a revised Cochrane risk of bias tool for randomized trial (RoB-2 tool)[46]. RoB-2 tool comprises five domains: bias arising from randomization process, deviation from intended intervention, missing outcome data, bias in the measurement of outcome, and selection of reported results. The judgment regarding the risk of bias was determined through signaling questions with responses as “Yes", “Probably yes,” “Probably No,” “No,” and “No information.” Two authors (MH and KVJ) independently assessed the risk of bias; later, a consensus was reached for any disagreement through discussion. However, a third reviewer’s opinion (BSB) was obtained wherever necessary. The overall risk of bias was ascertained as high, some concerns or low for each study.

#### 2.1.2.4 Statistical analysis

The risk ratio and its 95% confidence interval (CI) were estimated for each complication from individual studies. Subsequently, risk ratios were pooled across studies using a random-effects DerSimonian and Laird method considering possible heterogeneity. For continuous variables,

such as operation time and duration of hospital stay, mean difference and 95% CI were estimated for individual studies and then pooled using a random-effects DerSimonian and Laird method. While performing the analysis, zero cells were corrected by adding 0.5.

#### 2.1.2.5 Assessment of heterogeneity

Heterogeneity was assessed using visual inspection of forest plots, Cochran-Q test, and $I^2$ statistics. $I^2$ describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error (chance). $I^2$ values in our analysis were interpreted using the standards laid down in Cochrane's handbook for Systematic Reviews of Interventions[47]. Cochran's Q is the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q is a chi-square statistic with k (number of studies) minus one degree of freedom. If the Q(k-1) value is greater than the tabulated value (obtained using degrees of freedom) and the p-value is <0.1, then the heterogeneity is considered to be present [48].

#### 2.1.2.6 Analysis of sub-groups

Results were further explored using subgroup analysis based on intervention and comparators: early cholecystectomy versus observation management (EC *vs.* OM), early cholecystectomy versus endoscopic management (EC *vs.* EM), and early cholecystectomy versus delayed cholecystectomy (EC *vs.* DC). A subgroup analysis of baseline gallstone complications (CBD stones/acute-cholecystitis/gallstone-pancreatitis) was performed within each comparison to address the heterogeneity of patients included in the systematic review. We also conducted a subgroup analysis to determine whether the timing of surgery influenced the surgical complications. We have also performed a separate analysis of early cholecystectomy with conservative management alone (combining observation management and endoscopic management) (EC *vs.* CM). Risk ratios and mean differences were pooled between all

interventions and comparators; however, perioperative and intra-operative complications were pooled only among early versus delayed cholecystectomy studies.

#### 2.1.2.7 Estimation of Number of needed to harm

In this systematic review and meta-analysis, we also estimated the Number needed to treat harm (NNTH) for each outcome[49]. NNTH is defined as "The number of people exposed to a given treatment such that on average and over a given follow-up period one additional person experiences the adverse effect of interest because of the treatment." It expresses the additional absolute risk of an adverse effect conferred by treatment and is, therefore, a useful and intuitively understandable decision-making tool for practicing clinicians[49]. As there is no consensus for the calculation of NNTs from pooled meta-analysis, we estimated the number needed to treat to harm (NNTH) for each outcome using the two approaches suggested[50]. In the first approach, the log of risk difference (RD) and 95% CIs between intervention and comparator for each complication were estimated. Risk differences were then pooled across studies using a random-effect model. Following, mean NNTH for each complication and its 95%CI were calculated as the inverse of mean and inverse of upper and lower limits of 95% CI of pooled RD, respectively[51].

$$NNTH = \frac{1}{pooled\ RD}$$

We also calculated adjusted NNTH using the method suggested by Furukawa[52] and recent evidence synthesis[50]. We calculated adjusted NNTH using the following formula.

$$NNTH_{adjusted} = \frac{1}{(1 - RR) * PEER}$$

Where RR is pooled relative risk, PEER is the patient expected event rate. The PEER was calculated as the ratio of the total frequency of complication among comparators to that of the total number of comparators in respective pooled studies.

#### 2.1.2.8 Assessment of Publication bias

Publication bias was assessed using a funnel plot (asymmetry) and Egger's test ($p < 0.05$) of the effect measures only if a sufficient (at least 10) number of studies were available for pooling[53, 54]. Further, on identifying asymmetry in the funnel plot, the source of asymmetry was explored using a contour-enhanced funnel plot. Data was recorded using a Microsoft Excel sheet and analyzed using Stata software version 16 [55]. Two-sided $p<0.05$ was considered statistically significant except for the subgroup analysis and heterogeneity test, wherein $p<0.10$ was considered significant.

### 2.1.3 Results

#### 2.1.3.1 Description of included studies

We retrieved a total of 6,494 studies through our initial and updated search, out of which 40 studies were included for systematic review, as shown in the PRISMA flow diagram (Figure 2.1.1). We had excluded one study from the meta-analysis since no information on complications was reported[56]. Therefore, 39 studies with 4,483 gallstone disease patients [Intervention- early cholecystectomy, n=2,265 and Comparator (conservative management/delayed cholecystectomy), n=2,218] were included in meta-analysis[57] [58-70, 37, 71-85] [86-88, 42, 89, 90] [91-93]. Characteristics of included studies are provided in Table 2.1.1.

Patients' mean age was 53.47 years and 54.41 years in intervention and comparators, respectively. Sample sizes in individual studies ranged from 15 to 314 patients. In total, 6, 3 and 31 studies that compared EC *vs* OM[86-88, 42, 89, 90], EC *vs* EM[91-93], and EC *vs* DC[57, 56, 58-70, 37, 71-85] respectively, were analyzed. Among the 32 studies which reported gender proportions, 26 studies (81.25%) had a higher proportion of female

participants. Only nine out of the forty included studies for systematic review were multi-centric RCTs, and the rest were conducted in single centers. The baseline gallstone complications reported were acute cholecystitis, CBD-stones, gallstone-pancreatitis, and uncomplicated gallstones in 20, 12, seven, and one study. Out of the 40 studies included in the systematic review, open cholecystectomy was reported among nine studies and, cholecystectomy was performed laparoscopically among the rest. Duration of symptoms was reported only in seven studies, in which duration varied from 35.1 to 96 hours. In all the EC vs. DC studies, EC was performed within seven days of randomization, and DC was performed after six weeks.

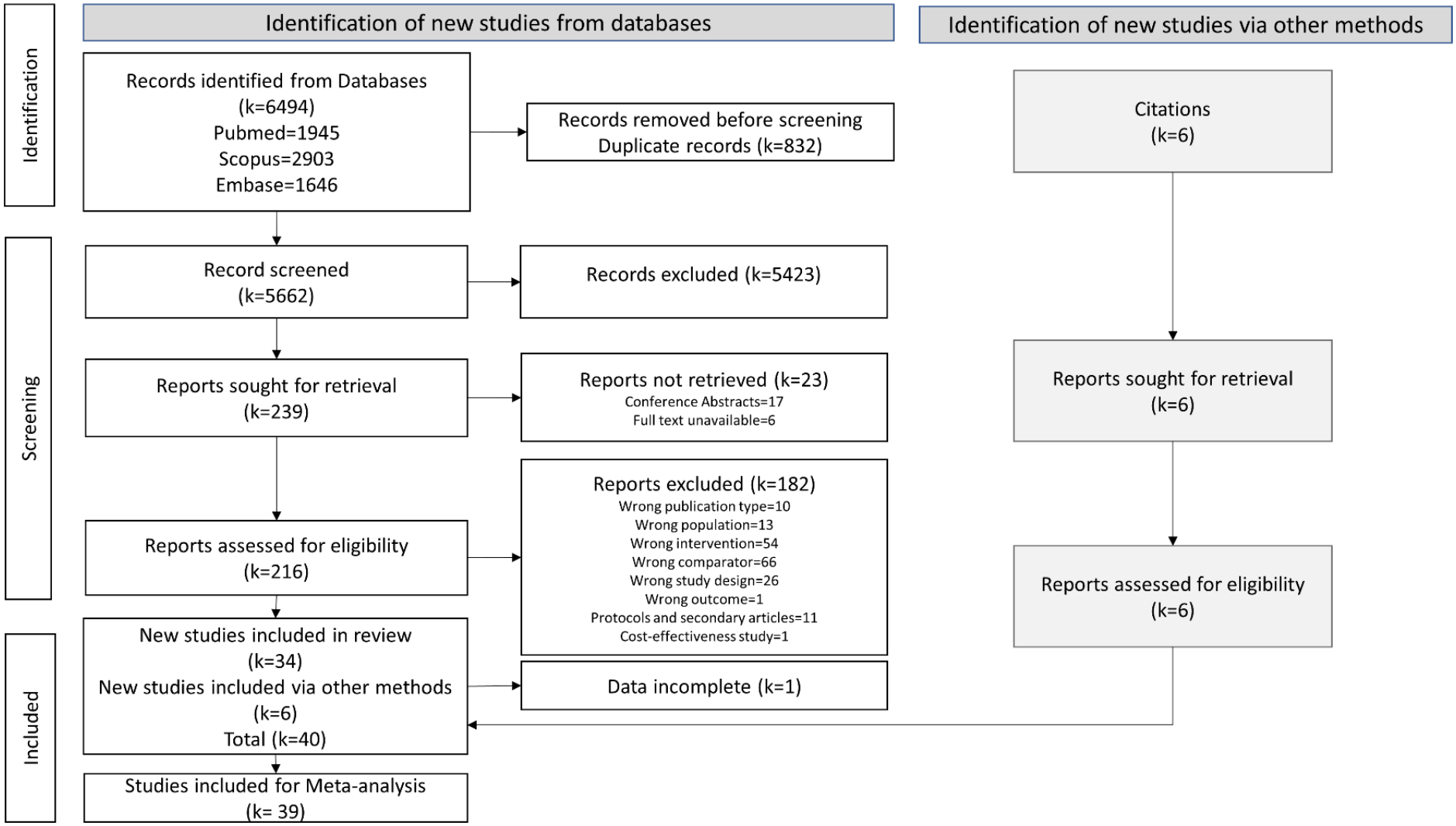



**Figure 2.1.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection**

**Table 2.1.1 Characteristics of included studies**

| Study | Country | Study Design | Baseline gallstone complication | Type of surgery | Groups (Sample size) | Age (Mean years) | Gender (%) | Duration of symptoms (hours) | Timing of surgery |
|---|---|---|---|---|---|---|---|---|---|
| Muhammedoğlu et al 2020 | Turkey | RCT-SC | CBD stones | LC | EC (n=82) | 61.5 | - | - | Not Specified |
| | | | | | DC (n=37) | 53.5 | - | - | 6-8 weeks |
| Noel et al 2018 | Sweden | RCT-SC | Gallstone Pancreatitis | LC | EC (n=32) | 48.0 | 62.5% | - | within 48 hours |
| | | | | | DC (n=34) | 43.5 | 55.9% | - | 6 weeks |
| Khalid et al 2017 | Pakistan | RCT-SC | Cholecystitis | LC | EC (n=90) | - | - | - | within 72 hours |
| | | | | | DC (n=90) | - | - | - | 6-8 weeks |
| El Nakeeb et al 2016 | Egypt | RCT-SC | CBD stones | LC | EC (n=55) | 43.0 | 70.9% | - | within 72 hours |
| | | | | | DC (n=55) | 47.0 | 65.5% | - | after 1 month |
| Rajcok et al 2016 | Slovakia | RCT-SC | Cholecystitis | LC | EC (n=31) | 56.3 | 48.3% | - | within 72 hours |
| | | | | | DC (n=31) | 59.8 | 45.1% | - | 6-8 weeks |
| Roulin et al 2016 | Switzerland | RCT-SC | Cholecystitis | LC | EC (n=42) | 55.8 | 43.0% | 96 | within 72 hours |
| | | | | | DC (n=44) | 57.9 | 43.0% | 96 | after 6 weeks |
| Zhang et al 2016 | China | RCT-SC | Gallstone Pancreatitis | LC | EC (n=49) | 62.1 | 57.1% | - | within 7 days |
| | | | | | DC (n=53) | 63.5 | 62.26% | - | >7 days |
| Jee et al 2016 | Malaysia | RCT-SC | Gallstone Pancreatitis | LC | EC (n=38) | 42.5 | 52.63% | - | within 7 days |
| | | | | | DC (n=34) | 42.5 | 61.76% | - | 6-8 weeks |
| da Costa et al 2015 | Netherlands | RCT-MC | Gallstone Pancreatitis | LC | EC (n=128) | 53.0 | 59.0% | - | within 72 hours |
| | | | | | DC (n=136) | 54.0 | 62.0% | - | 25-30 days |
| Agrawal et al 2015 | India | RCT-SC | Cholecystitis | LC | EC (n=25) | 47.28 | 68.0% | 35.44 | within 24 hours |
| | | | | | DC (n=25) | 50.96 | 68.0% | 36.8 | 6-8 weeks |
| Ammar et al 2014 | Egypt | RCT-SC | CBD stones | LC | EC (n=31) | 46.2 | 67.7% | - | within 24 hours |
| | | | | | DC (n=29) | 47.3 | 72.4% | - | >24 hours |

| Study | Country | Study Design | Baseline gallstone complication | Type of surgery | Groups (Sample size) | Age (Mean years) | Gender (%) | Duration of symptoms (hours) | Timing of surgery |
|---|---|---|---|---|---|---|---|---|---|
| Heo et al 2014 | Korea | RCT-SC | CBD stones | LC | CH (n=43) | 64.02 | 41.9% | - | - |
| | | | | | CM (n=45) | 63.96 | 44.4% | - | - |
| Zahur et al 2014 | Pakistan | RCT-SC | Cholecystitis | LC | EC (n=47) | - | - | - | within 48 hours |
| | | | | | DC (n=41) | - | - | - | 6-8 weeks |
| Zargar et al 2014 | India | RCT-SC | CBD stones | - | CH (n=80) | 78.2 | - | - | - |
| | | | | | CM (n=82) | 77.3 | - | - | - |
| Gul et al 2013 | India | RCT-SC | Cholecystitis | LC | EC (n=30) | 39.83 | - | - | within 72 hours |
| | | | | | DC (n=30) | 38.27 | - | - | 6-12 weeks |
| Verma et al 2013 | India | RCT-SC | Cholecystitis | LC | EC (n=30) | 31.73 | 86.6% | - | within 72 hours |
| | | | | | DC (n=30) | 32.8 | 93.3% | - | 6-8 weeks |
| Schmidt et al a et al 2011 | Norway | RCT-MC | Cholecystitis | LC | CH (n=31) | 55.5 | 60.6% | - | - |
| | | | | | CM (n=33) | 61.0 | 54.8% | - | - |
| Schmidt et al b et al 2011 | Norway | RCT-MC | Uncomplicated gallstones | LC | CH (n=68) | 52.0 | 80.9% | - | - |
| | | | | | CM (n=69) | 54.0 | 82.6% | - | - |
| Aboulian et al 2010 | USA | RCT-SC | Gallstone Pancreatitis | LC | EC (n=25) | 33.0 | 8% | 48.0 | within 48 hours |
| | | | | | DC (n=25) | 41.0 | 12% | 48.0 | Not specified |
| Reinders et al 2010 | Netherlands | RCT-MC | CBD stones | LC | EC (n=47) | 55.0 | 76.5% | - | within 72 hours |
| | | | | | DC (n=47) | 47.0 | 61.7% | - | 6-8 weeks |
| Salman et al 2009 | Turkey | RCT-SC | CBD stones | LC | EC (n=39) | 43.5 | 66.6% | - | within 48 hours |
| | | | | | DC (n=40) | 44.6 | 70.0% | - | within 7 days |
| Yadav et al 2009 | Nepal | RCT-SC | Cholecystitis | LC | EC (n=25) | 42.68 | - | - | within 48 hours |
| | | | | | DC (n=25) | 40.26 | - | - | 6-8 weeks |
| Kolla et al 2004 | India | RCT-SC | Cholecystitis | LC | EC (n=20) | 41.5 | 85.0% | 35.1 | within 24 hours |
| | | | | | DC (n=20) | 38.6 | 75.0% | 36.1 | 6-12 weeks |
| Lai et al 1998 | Hong Kong | RCT-SC | Cholecystitis | LC | EC (n=53) | 55.8 | 56.6% | - | within 24 hours |
| | | | | | DC (n=51) | 56.1 | 70.5% | - | 6-8 weeks |

| Study | Country | Study Design | Baseline gallstone complication | Type of surgery | Groups (Sample size) | Age (Mean years) | Gender (%) | Duration of symptoms (hours) | Timing of surgery |
|---|---|---|---|---|---|---|---|---|---|
| Mau Lo et al 1998 | Hong Kong, China | RCT-SC | Cholecystitis | LC | EC (n=45) | 59.0 | 42.2% | 48.0 | within 72 hours |
| | | | | | DC (n=41) | 61.0 | 48.7% | 48.0 | 8-12 weeks |
| Norby et al 1983 | Swedon | RCT-MC | Cholecystitis | OC | EC (n=101) | 58.0 | 65.30% | - | within 7 days |
| | | | | | DC (n=91) | 58.0 | 61.50% | - | Not specified |
| Jarvinen et al 1980 | Finland | RCT-SC | Cholecystitis | OC | EC (n=80) | 57.8 | 50.0% | 52.8 | within 7 days |
| | | | | | DC (n=75) | 56.7 | 52.0% | 55.2 | 8-16 weeks |
| Mcarthur et al 1975 | United Kingdom | RCT-SC | Cholecystitis | OC | EC (n=15) | 48.9 | 82.3% | 38.1 | Not Specified |
| | | | | | DC (n=17) | 49.8 | 93.3% | 47.9 | 8-12 weeks |
| Ozkardes et al 2014 | Turkey | RCT-SC | Cholecystitis | LC | EC (n=30) | 58.03 | 66.70% | - | within 24 hours |
| | | | | | DC (n=30) | 59.43 | 56.70% | - | 6-8 weeks |
| Saber et al 2014 | Egypt | RCT-MC | Cholecystitis | LC | EC (n=60) | | 75.0% | - | within 72 hours |
| | | | | | DC (n=60) | | 70.0% | - | 6-8 weeks |
| Abbas et al 2013 | Pakistan | RCT-SC | Gallstone Pancreatitis | OC | EC (n=31) | 40.22 | 83.8% | - | Not Specified |
| | | | | | DC (n=31) | 53.51 | 83.8% | - | 6-8 weeks |
| Gutt et al 2013 | Germany | RCT-MC | Cholecystitis | LC | EC (n=304) | 55.6 | 62.8% | - | within 24 hours |
| | | | | | DC (n=314) | 56.8 | 54.8% | - | 7-45 days |
| Macafee et al 2009 | United Kingdom | RCT-SC | Cholecystitis | LC | EC (n=36) | 52.0 | 72.2% | - | within 72 hours |
| | | | | | DC (n=36) | 53.0 | 58.3% | - | after 3 months |
| Lau et al 2006 | China | RCT-SC | CBD stones | LC | CH (n=89) | 43.0 | 51.7% | - | - |
| | | | | | CM (n=89) | 49.0 | 44.9% | - | - |
| Boerma et al 2002 | Netherlands | RCT-MC | CBD stones | LC | CH (n=56) | 60.0 | 59.0% | - | - |
| | | | | | CM (n=64) | 63.0 | 51.0% | - | - |
| Suc et al 1998 | France | RCT- | CBD stones | OC | CH | 66.7 | 68.5% | - | - |

| Study | Country | Study Design | Baseline gallstone complication | Type of surgery | Groups (Sample size) | Age (Mean years) | Gender (%) | Duration of symptoms (hours) | Timing of surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | MC | | | (n=105) | | | | |
| | | | | | EM (n=97) | 66.8 | 68.04% | - | - |
| Targarona et al 1996 | Spain | RCT-SC | CBD stones | OC | CH (n=48) | 80.0 | 68.75% | - | - |
| | | | | | EM (n=50) | 79.0 | 70.0% | - | - |
| Hammarstrom et al 1995 | Sweden | RCT-SC | CBD stones | OC | CH (n=41) | 73.5 | - | - | - |
| | | | | | EM (n=39) | 75.0 | - | - | - |
| Stone et al 1981 | Georgia | RCT-SC | Gallstone Pancreatitis | OC | EC (n=36) | - | - | - | within 72 hours |
| | | | | | DC (n=34) | - | - | - | 3-6 months |
| Lahtinen et al 1978 | Finland | RCT-SC | Cholecystitis | OC | EC (n=47) | 63.8 | 60.0% | - | within 7 days |
| | | | | | DC (n=44) | 62.8 | 60.0% | - | 8-12 weeks |

RR-Risk Ratio; NNTH- Number needed to treat to harm; CI- confidence interval; EC- Early Cholecystectomy; DC- Delayed Cholecystectomy; OM-Observation Management; EM- Endoscopic Management; CBD- Common Bile Duct

#### 2.1.3.2 Risk of bias assessment:

Out of forty studies included in the systematic review, 31 (77.5%) studies adequately followed the randomization process. None of the included studies reported that patients and caregivers were blinded for the intervention under study, which might be due to the involvement of surgical intervention. Nine (22.5%) studies had shown deviations from the intended intervention. There were seven (17.5%) studies under the missing outcome data domain, one study (2.5%) in each domain for measurement of outcome data, and selection of the reported results were assessed as a high risk of bias. The overall risk of bias was estimated as low in 22 (55.0%), some concerns in 6 (15.0%), and high in 12 (30.0%) studies (Figure 2.1.2).

| S. No | Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|
| 1 | Aboulian_2010 | + | + | + | + | + | + |
| 2 | Ammar_2014 | + | + | + | + | + | + |
| 3 | El_Nakeeb_2016 | + | + | + | + | + | + |
| 4 | Ozkardes_2014 | + | + | + | + | + | + |
| 5 | Saber_2014 | + | + | + | + | + | + |
| 6 | Abbas_2013 | - | - | - | + | + | - |
| 7 | Gul_2013 | + | + | ! | + | + | ! |
| 8 | Khalid_2017 | - | + | + | ! | + | - |
| 9 | Kolla_2004 | + | + | + | + | + | + |
| 10 | Lai_1998 | + | - | - | + | + | - |
| 11 | Gutt_2013 | + | + | + | + | + | + |
| 12 | Muhammedoğlu_2020 | + | + | + | + | + | + |
| 13 | Macafee_2009 | + | + | + | + | + | + |
| 14 | Mau Lo_1998 | + | + | + | + | + | + |
| 15 | Rajcok_2016 | - | - | - | - | ! | - |
| 16 | Roulin_2016 | + | + | + | + | + | + |
| 17 | Agrawal_2015 | - | + | + | + | + | - |
| 18 | da Costa_2015 | + | + | + | + | + | + |
| 19 | Boerma_2002 | + | ! | + | + | + | ! |
| 20 | Stone_1981 | - | - | - | + | ! | - |
| 21 | Lahtinen_1978 | + | - | - | + | - | - |
| 22 | Lau_2006 | + | + | + | + | + | + |
| 23 | Norby_1983 | - | ! | + | + | ! | - |
| 24 | Salman_2009 | ! | + | + | + | + | ! |
| 25 | Reinders_2010 | + | + | + | + | + | + |
| 26 | Heo_2014 | + | - | + | + | + | - |
| 27 | Mcarthur_1975 | + | - | - | + | ! | - |
| 28 | Noel_2018 | + | - | - | + | + | - |
| 29 | Jarvinen_1980 | + | + | + | + | + | + |
| 30 | Zahur_2014 | - | - | + | ! | ! | - |
| 31 | Jee_2016 | + | ! | + | + | ! | ! |
| 32 | Zargar_2014 | + | + | + | + | ! | ! |
| 33 | Verma_2013 | + | + | + | + | + | + |
| 34 | Yadav_2009 | + | + | + | + | + | + |
| 35 | Hammarstrom_1995 | + | + | + | + | + | + |
| 36 | Suc_1998 | + | + | + | + | + | + |
| 37 | Targarona_1996 | + | + | + | + | + | + |
| 38 | Schmidt_b_2011 | + | + | + | + | + | + |
| 39 | Schmidt_a_2011 | + | + | + | + | + | + |
| 40 | Zhang_2016 | ! | + | + | + | ! | ! |

**Figure 2.1.2 Assessment of risk of bias**

Bias due to D1-Randomization process; D2-Deviation from intended intervention;
D3-Missing outcome data; D4- Measurement of outcome; D5-Selection of reported result.

+ indicates low bias ! indicates moderate bias — indicates serious bias

**Table 2.1.2 Pooled risk ratios and NNTH of gallstone related complications with subgroups based on intervention**

| Complications | Subgroup (No. of studies) | RR (95% CI) | $I^2$ (%) | *Q* | NNTH_adjusted (95% CI) | NNTH_Unadjusted (95% CI) | References |
|---|---|---|---|---|---|---|---|
| Pain/biliary colic | Overall (n=12) | 0.38 (0.2 to 0.74) | 51.57 | 22.72 | 14.0 (10.9 to 33.4) | 12.5 (8.3 to 33.3) | |
| | EC vs OM (n=5) | 0.39 (0.16 to 0.94) | 39.70 | 6.63 | 10.4 (7.6 to 105.97) | 12.5 (5.9 to 100.0) | [86, 88, 42, 89, 90] |
| | EC vs EM (n=2) | 0.35 (0.06 to 2.28) | 0 | 0.27 | 34.2 (17.4 to 23.7) | 33.33 (12.5 to 100.0) | [91, 93] |
| | EC vs DC (n=5) | 0.33 (0.08 to 1.33) | 74.68 | 15.80 | 14.8 (10.8 to 30.0) | 14.0 (6.7 to very high) | [60, 63, 65, 73, 77] |
| CBD stones | Overall (n=4) | 0.50 (0.14 to 1.78) | 0 | 0.40 | 81.4 (47.3 to 52.2) | 100.0 (33.3 to 100.0) | |
| | EC vs OM (n=2) | 0.35 (0.06 to 2.15) | 0 | 0 | 39.2 (27.1 to 22.2) | 50.0 (25 to 100.0) | [42, 89] |
| | EC vs EM (n=0) | - | - | - | - | - | - |
| | EC vs DC (n=2) | 0.70 (0.12 to 4.23) | 0 | 0.12 | 203.3 (19.0 to 69.3) | 100.0 (33.3 to 50.0) | [60, 77] |
| Biliary Pancreatitis | Overall (n=8) | 0.47 (0.22 to 1.03) | 0 | 3.90 | 44.9 (30.5 to 794) | >1000 (50 to 100.0) | |
| | EC vs OM (n=3) | 1.48 (0.24 to 9.29) | 0 | 0.30 | -383.3 (22.2 to 242.1) | 100.0 (33.3 to 100.0) | [42, 89, 90] |
| | EC vs EM (n=2) | 0.58 (0.07 to 4.67) | 0 | 0.25 | 161.9 (18.5 to 73.1) | 100.0 (33.3 to 50.0) | [91, 92] |
| | EC vs DC (n=3) | 0.34 (0.13 to 0.86) | 0 | 1.34 | 16.3 (12.3 to 76.7) | 17.0 (9.1 to 100.0) | [60, 65, 73] |
| Cholangitis | Overall (n=6) | 0.52 (0.28 to 0.97) | 0 | 3.76 | 29.6 (19.8 to 474.4) | 100.0 (25.0 to 100.0) | |
| | EC vs OM (n=4) | 0.79 (1.47 to 0.10) | 0 | 2.96 | 5.8 (4.2 to 9.4) | Could not be calculated | [86-88, 90] |
| | EC vs EM (n=2) | 1.00 (0.21 to 4.84) | 0 | 3.76 | Could not be calculated | | [92, 93] |
| | EC vs DC (n=0) | - | - | - | - | - | - |
| Mortality/Death | Overall (n=15) | 0.74 (0.48 to 1.15) | 0 | 6.81 | 118.3 (59.2 to 205.1) | >1000 (100 to 100000) | |
| | EC vs OM (n=4) | 0.80 (0.48 to 1.35) | 0 | 2.83 | 54.3 (20.9 to 31.0) | 100.0 (25.0 to 100.0) | [86, 88-90] |
| | EC vs EM (n=2) | 0.75 (0.17 to 3.29) | 0 | 0.03 | 147.0 (16.0 to 44.3) | >1000 (33.3 to 50.0) | [92, 93] |
| | EC vs DC (n=10) | 0.55 (0.20 to 1.50) | 0 | 3.56 | 186.9 (105.1 to | >1000 (100.0 to 100.0) | [57, 60, 63, |

| **Complications** | **Subgroup (No. of studies)** | **RR (95% CI)** | **$I^2$ (%)** | ***Q*** | **NNTH_adjusted (95% CI)** | **NNTH_Unadjusted (95% CI)** | **References** |
|---|---|---|---|---|---|---|---|
| | | | | | 168.2) | | 65-68, 74, 77, 81] |
| Total no. of biliary complications | Overall (n=11) | 0.33 (0.2 to 0.55) | 68.24 | 31.48 | 5.7 (4.8 to 8.5) | 5.9 (4.3 to 9.1) | |
| | EC vs OM (n=5) | 0.33 (0.19 to 0.56) | 38.13 | 6.47 | 5.2 (4.3 to 7.9) | 5.3 (3.7 to 10) | [87, 88, 42, 89, 90] |
| | EC vs EM (n=1) | 0.31 (0.09 to 1.07) | - | - | 7.2 (5.5 to 71.4) | 7.1 (3.7 to 100) | [93] |
| | EC vs DC (n=5) | 0.29 (0.1 to 0.85) | 83.75 | 24.62 | 6.6 (5.2 to 31.4) | 6 (3.8 to 16.7) | [60, 63, 65, 73, 77] |
| Conversion to laparotomy | EC vs DC (n=19) | 0.98 (0.71 to 1.36) | 0 | 22.45 | 586.2 (32.6 to 40.4) | >1000 (50 to 50) | [67, 69, 82, 85, 70, 80, 83, 63, 59, 75, 79, 84, 58, 60, 61, 76, 78, 65, 73] |

RR-Risk Ratio; NNTH- Number needed to treat to harm; CI- confidence interval; EC- Early Cholecystectomy; DC- Delayed Cholecystectomy; OM-Observation Management; EM- Endoscopic Management; CBD- Common Bile Duct

**Table 2.1.3 Risk ratios of biliary complications in early cholecystectomy versus conservative management (Observation and Endoscopic management)**

| Complications (no. of studies) | RR (CI) | $I^2$ | Q | Reference |
|---|---|---|---|---|
| Pain/Biliary Colic (7) | 0.39 (0.21 to 0.75) | 13.2% | 6.91 | [91, 93] [86, 88, 42, 89, 90] |
| Biliary Pancreatitis (5) | 0.99 (0.25 to 3.90) | 0% | 0.98 | [91, 92] [42, 89, 90] [38] |
| Acute cholecystitis (9) | 0.09 (0.03 to 0.23) | 0% | 1.13 | [91-93] [86-88, 42, 89, 90] |
| CBD stones (2) | 0.35 (0.06 to 2.15) | 0% | 0.00 | [42, 89] |
| Cholangitis (6) | 0.52 (0.28 to 0.97) | 0% | 3.76 | [92, 93, 86, 88, 90] |
| Total Biliary complications (6) | 0.33 (0.21 to 0.51) | 22.7% | 6.47 | [93, 87, 88, 42, 89, 90] |
| Mortality (6) | 0.80 (0.49 to 1.30) | 0% | 2.86 | [92, 93, 86, 88-90] |

### 2.1.3.3 Pooling of risk ratios

**Pain/Biliary Colic**

We pooled the risk ratios of pain/biliary colic from twelve studies comparing early cholecystectomy(EC) and conservative management(CM)/delayed cholecystectomy (DC), consisting of subgroups EC *vs* OM (n=5)[86, 88, 42, 89, 90], EC *vs* EM (n=2)[91, 93] and EC *vs* DC (n=5)[60, 63, 65, 73, 77]. The pooled risk ratio was 0.38 (0.20-0.74, $I^2$=51.57%) with moderate heterogeneity indicating significantly lower pain events with early cholecystectomy (Table 2.1.2). However, subgroups had significantly lower pain events, only in EC vs. OM with EC (0.39, 0.16-0.94, $I^2$=39.4%). The adjusted and unadjusted NNTH was 14.0 (10.9-33.4) and 12.5 (8.3-33.3), respectively. Sub-group analysis was conducted based on baseline gallstone complications within each comparison (EC *vs.* OM, EC *vs.* EM, and EC *vs.* DC). In EC *vs.* OM, subgroups included were patients with i. CBD stones, ii. uncomplicated gallstones, and iii. acute-cholecystitis. The pooled risk ratio shows significantly lower pain events with EC than OM in CBD stones and uncomplicated gallstones, whereas no significant difference was observed (Figure 2.1.3). In EC *vs.* EM, sub-grouping based on baseline gallstone

complications was not performed due to a lack of published studies. In EC *vs.* DC, one study for acute cholecystitis [63] and CBD stones[77] and three studies for gallstone pancreatitis[22 27 36] were identified. Significantly lower pain was observed in the EC compared to DC for acute cholecystitis and CBD stones, whereas for gallstone-pancreatitis, no significant difference was observed between EC and DC (Figure 2.1.4). The funnel plot for EC vs. DC shows asymmetry (p=0.508), indicating publication bias (Figure 2.1.5). A separate analysis of pain in EC *vs.* CM alone (combining OM and EM) showed significantly lower pain events in EC (Table 2.1.3)

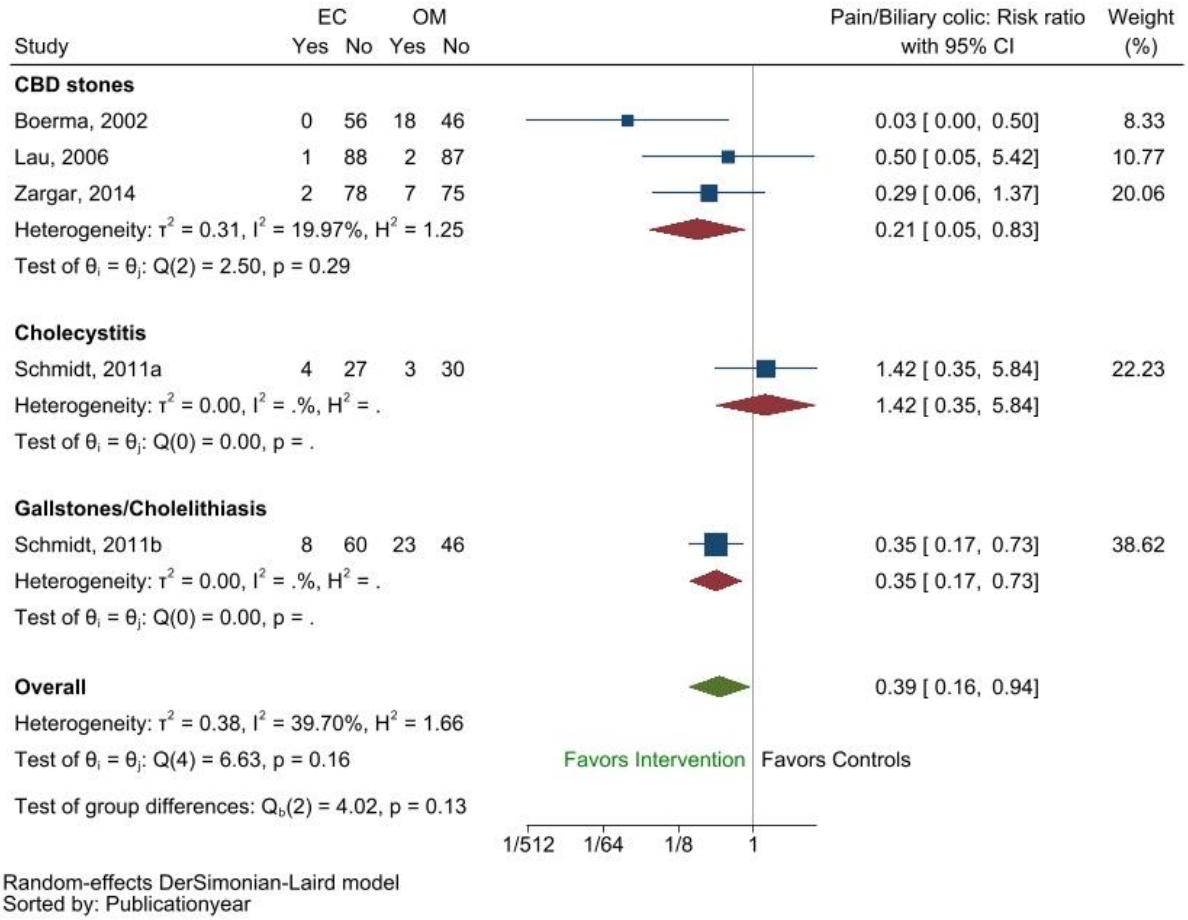



**Figure 2.1.3 Subgroup analysis of Pain/Biliary Colic in early cholecystectomy (EC) versus observation management (OM) by Baseline gallstone complication.**

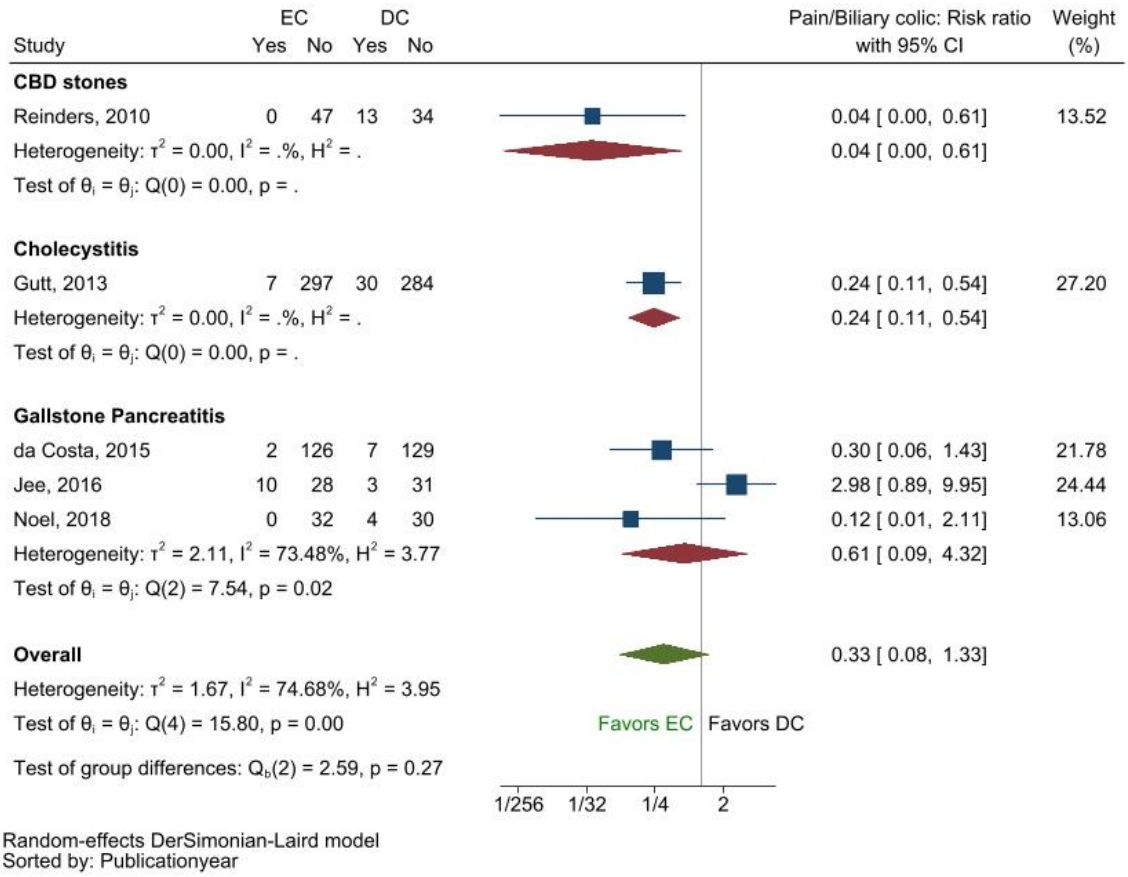



**Figure 2.1.4 Subgroup analysis of Pain/Biliary Colic in Early Cholecystectomy (EC) versus Delayed Cholecystectomy (DC) by Baseline gallstone complication.**

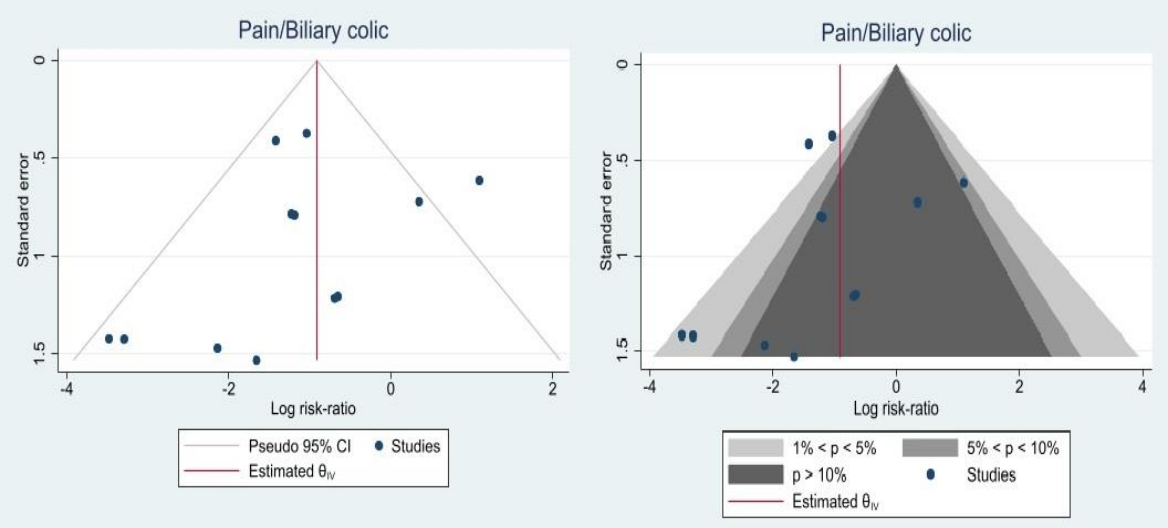



**Figure 2.1.5 Funnel and contour-enhanced funnel plots of early versus delayed cholecystectomy for Pain/Biliary Colic**

**Biliary Pancreatitis**

We pooled the risk ratios of biliary pancreatitis from eight studies consisting of sub-groups EC *vs* OM (n=3)[42, 89, 90], EC *vs* EM (n=2)[91, 92] and EC *vs* DC (n=3)[60, 65, 73]. The pooled risk ratio was estimated as 0.47 (0.22-1.03, $I^2$=0%) with low heterogeneity, indicating no significant difference between intervention and comparators (Table 2.1.2). The adjusted and unadjusted NNTH were 44.9 (30.5-793.9) and >1000 (50.0-100.0), respectively. Among subgroups, in EC *vs.* DC alone, significantly lower biliary pancreatitis events were observed in EC. Sub-group analysis based on baseline gallstone complications was not performed due to insufficient published literature. A separate analysis of biliary pancreatitis in EC *vs.* CM alone (combining OM and EM) showed no significant difference in biliary pancreatitis between EC and CM (Table 2.1.3)

**CBD Stones**

We pooled the risk ratios of CBD stones from four studies consisting of EC *vs* OM (n=2) [42, 89]and EC *vs* DC (n=2) [60, 77]. No studies with EC *vs.* EM were available. The pooled risk ratio was 0.50 (0.14-1.78, $I^2$=0%) with low heterogeneity, indicating no significant difference between intervention and comparator. Results were found similar within each of the subgroups (Table 2.1.2). The adjusted and unadjusted NNTH was 81.4 (47.3-52.2) and 100.0 (33.3-100.0), respectively. Sub-group analysis based on baseline gallstone complications was not performed due to insufficient published studies. A separate analysis of CBD stones in EC *vs* CM alone (combining OM and EM) showed no significant difference in CBD stones between EC and CM (Table 2.1.3)

**Cholangitis**

We pooled the risk ratios of cholangitis from six studies consisting of EC *vs* OM (n=4)[86-88, 90] and EC *vs* EM (n=2)[92, 93]. No studies with EC *vs.* DC were available; the pooled risk ratio was 0.52 (0.28-0.97, $I^2$=0%) with no heterogeneity, indicating significantly lower cholangitis events with intervention (Table 2.1.2). The adjusted and unadjusted NNTH was 21.6 (14.4-345.7) and 100.0 (25.0-100.0), respectively. Among sub-groups, in EC *vs.* OM, significantly lower cholangitis events were observed in the EC group (RR=0.46, 0.23-0.91, $I^2$=0%) (Table 2.1.2). Sub-group analysis based on baseline gallstone complications was not performed due to insufficient published studies. A separate analysis of cholangitis in EC *vs.* CM alone (combining OM and EM) showed significantly lower cholangitis events in EC (Table 2.1.3)

## Total Biliary Complications

We pooled the risk ratios of total biliary complications from eleven studies, including subgroups EC *vs.* OM (n=5), EC *vs.* EM (n=1), and EC *vs.* DC (n=5) (Table 2.1.2). The pooled risk ratio was 0.33 (0.20-0.55, $I^2$=68.24%) with moderate heterogeneity indicating significantly lower total biliary complications with EC (Figure 2.1.6).

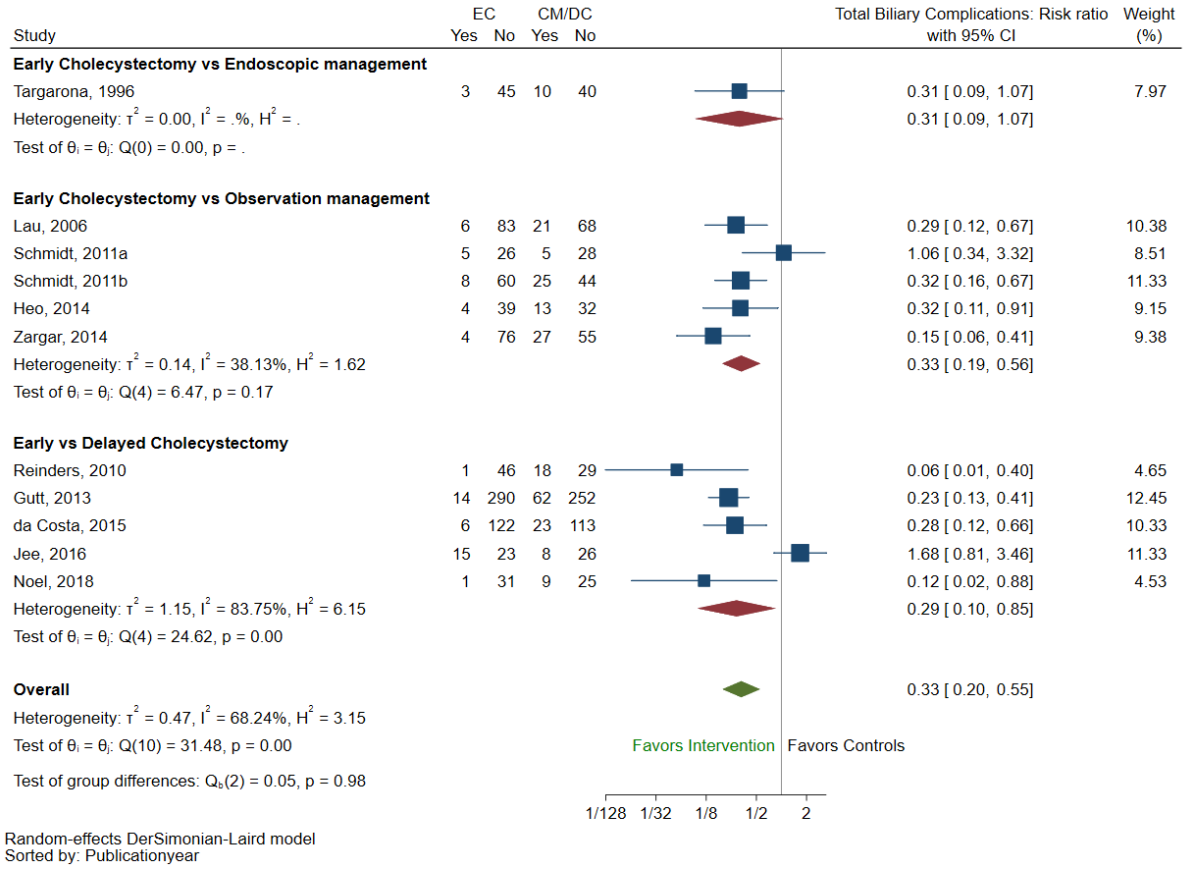



**Figure 2.1.6 Forest plot showing risk ratio of total biliary complications between**

The adjusted and unadjusted NNTH was 6.3 (5.2-9.3) and 5.9 (4.3-9.1), respectively. Among the subgroups, EC vs. OM and EC vs. DC, there were significantly lower biliary complications with EC, but not in the EC *vs.* EM subgroup. On subgroup analysis based on baseline gallstone complications, EC *vs.* OM showed substantially lower total biliary complications in the EC for CBD stones and cholelithiasis (Figure 2.1.7). In EC *vs.* DC, only one study for acute-cholecystitis[63] and CBD stones[77] was identified, showing significantly lower total biliary

complications in EC than DC. Three studies[61, 66, 74] were included for gallstone-pancreatitis, which showed no significant difference between EC and DC (Figure 2.1.8). The funnel plot showed asymmetry (p=0.476), indicating publication bias (Figure 2.1.9). A separate analysis of total biliary complications in EC *vs.* CM alone (combining OM and EM) showed significantly lower total biliary complications in EC (Table 2.1.3)

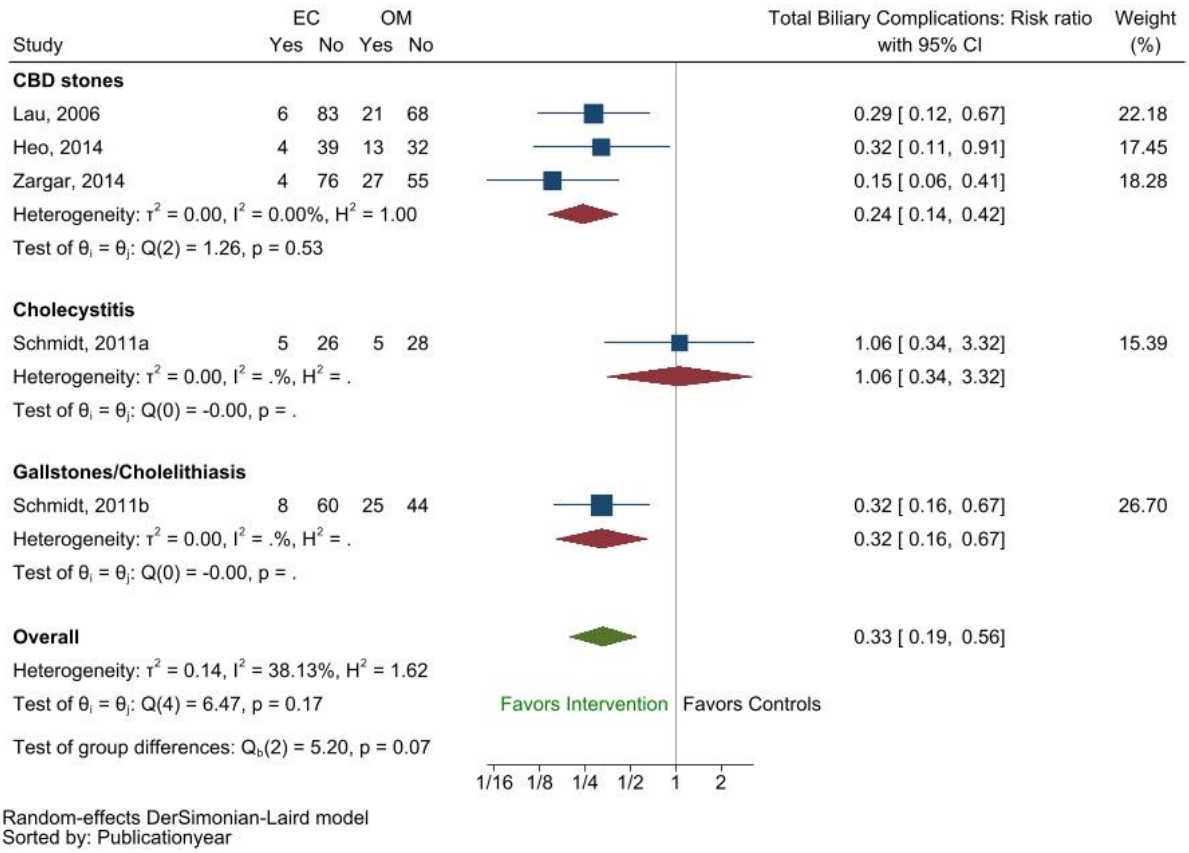



**Figure 2.1.7 Subgroup analysis of Total biliary complications in early cholecystectomy (EC) versus observation management (OM) by Baseline gallstone complication.**

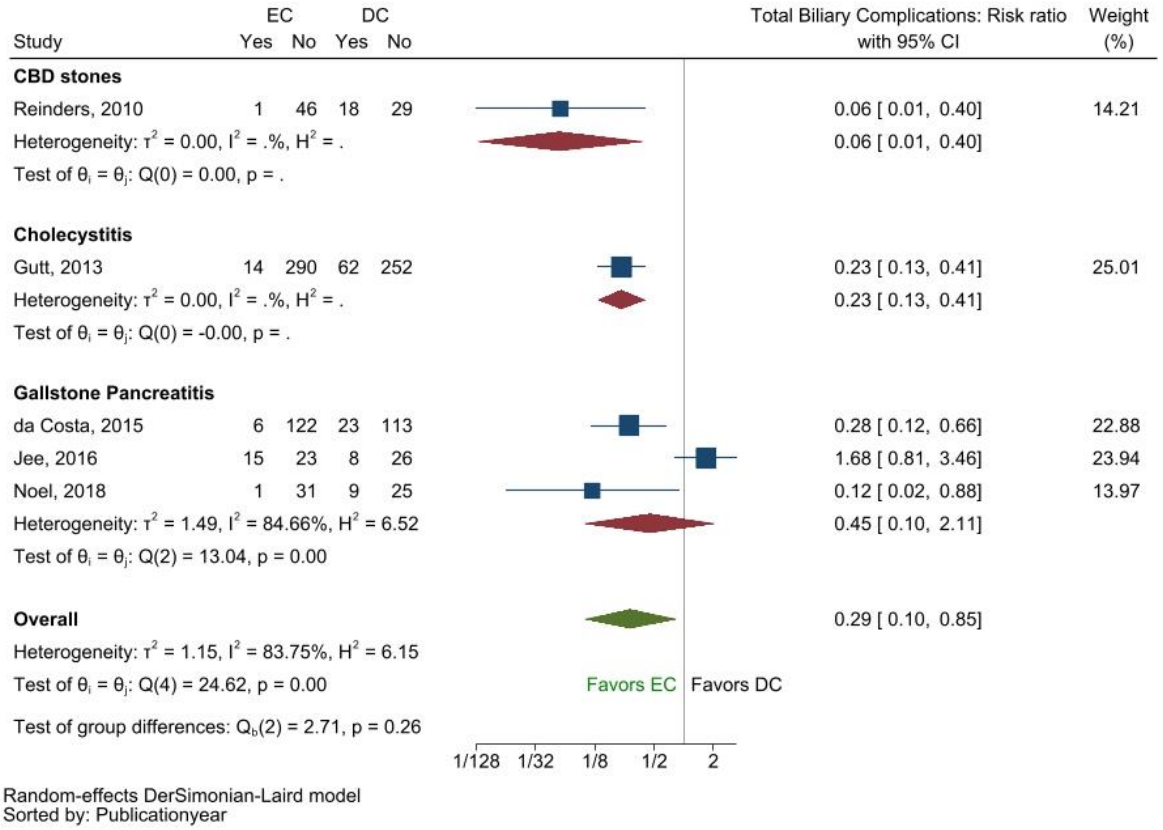



**Figure 2.1.8 Subgroup analysis of Total biliary complications in Early Cholecystectomy (EC) versus Delayed Cholecystectomy (DC) by Baseline gallstone complication.**

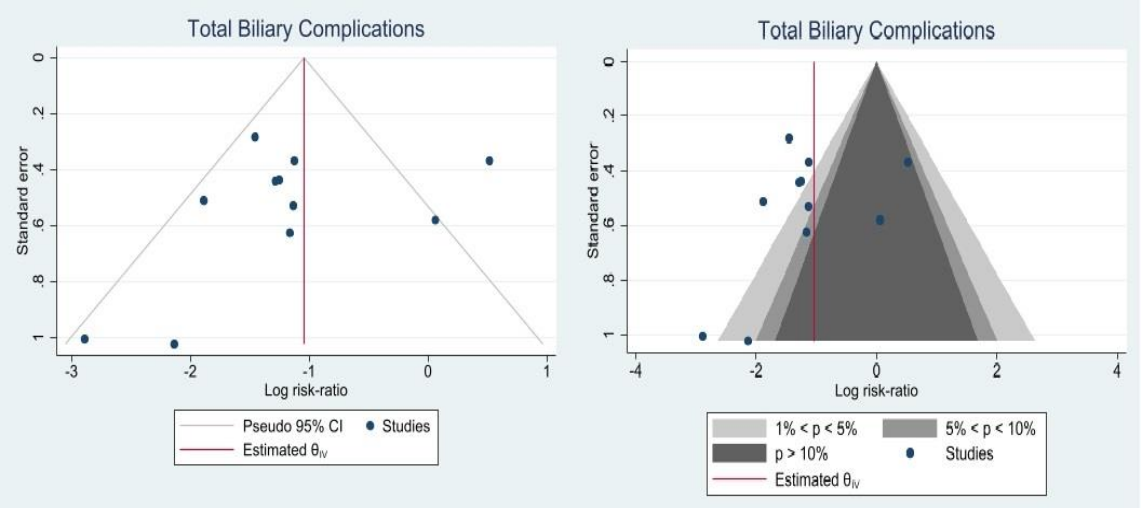



**Figure 2.1.9 Funnel and contour-enhanced funnel plots of early cholecystectomy versus entirely/relatively conservative management for Total Biliary Complications**

**Mortality**

We pooled the risk ratios of mortality from fifteen studies, including subgroups EC *vs* OM (n=4)[86, 87, 89, 90], EC *vs* EM (n=2)[92, 93] and EC *vs* DC (n=9)[57, 60, 63, 65, 67, 68, 74, 77, 81] (Table 2.1.2). The pooled risk ratio was 0.74 (0.48-1.15, $I^2$=0%) with no heterogeneity, showing no significant difference between intervention and comparator. Similar results were found within each of the subgroups. The adjusted and unadjusted NNTH were 118.3 (59.16-205.1) and >1000 (100.0->1000), respectively. Further, subgroup analysis based on baseline gallstone complication showed no significant difference in mortality EC *vs.* DC and EC *vs.* OM (Figure 2.1.10). Similarly, in EC *vs.* DC, no significant difference in mortality was observed between the sub-groups (Figure 2.1.11). The funnel plot showed asymmetry (p=0.553), indicating publication bias (Figure 2.1.12). A separate analysis of mortality in EC *vs.* CM alone (combining OM and EM) showed no significant difference in mortality between EC and CM (Table 2.1.3)

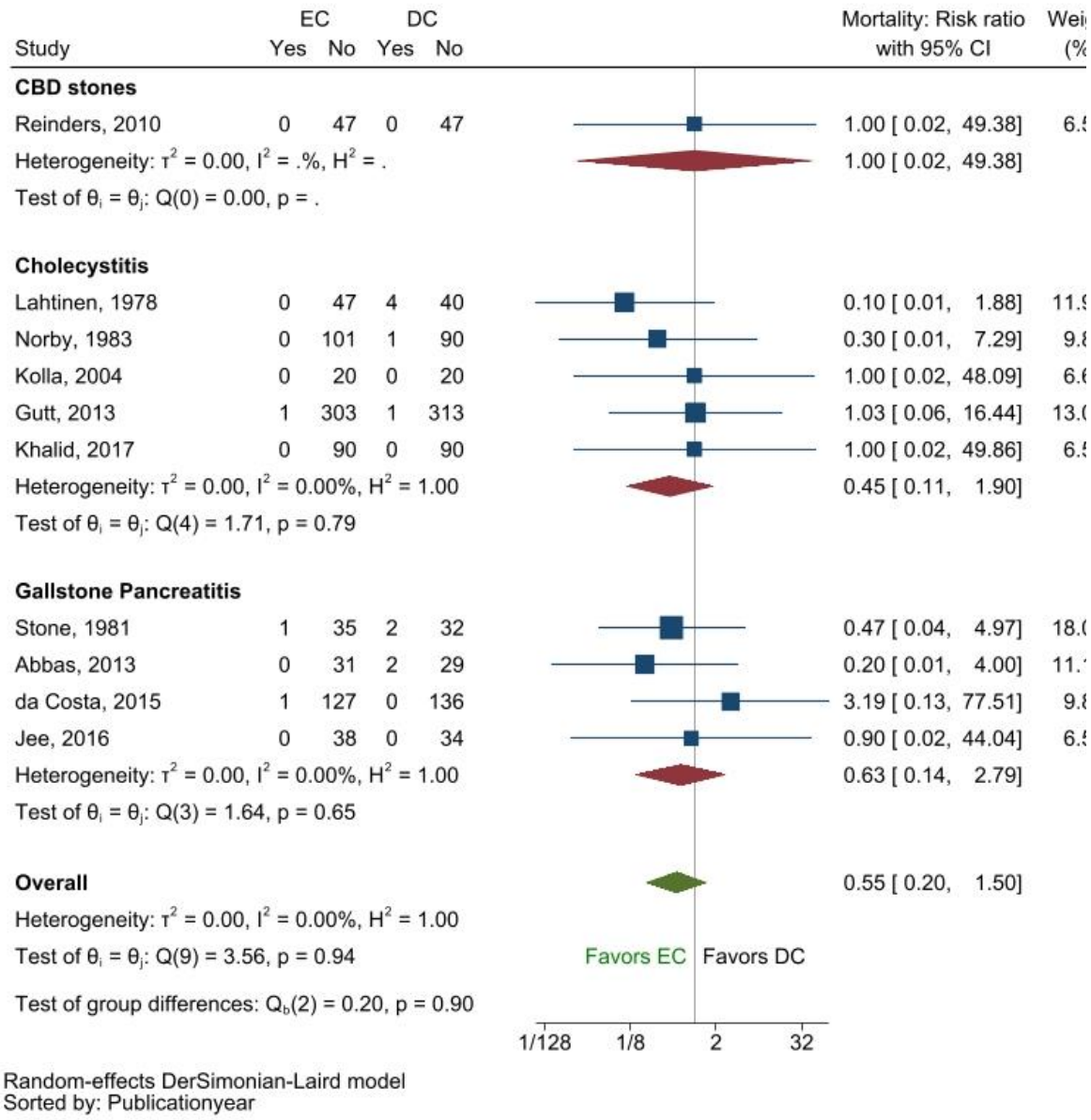



**Figure 2.1.10 Subgroup analysis of Mortality in Early Cholecystectomy (EC) versus Delayed Cholecystectomy (DC) by Baseline gallstone complication.**

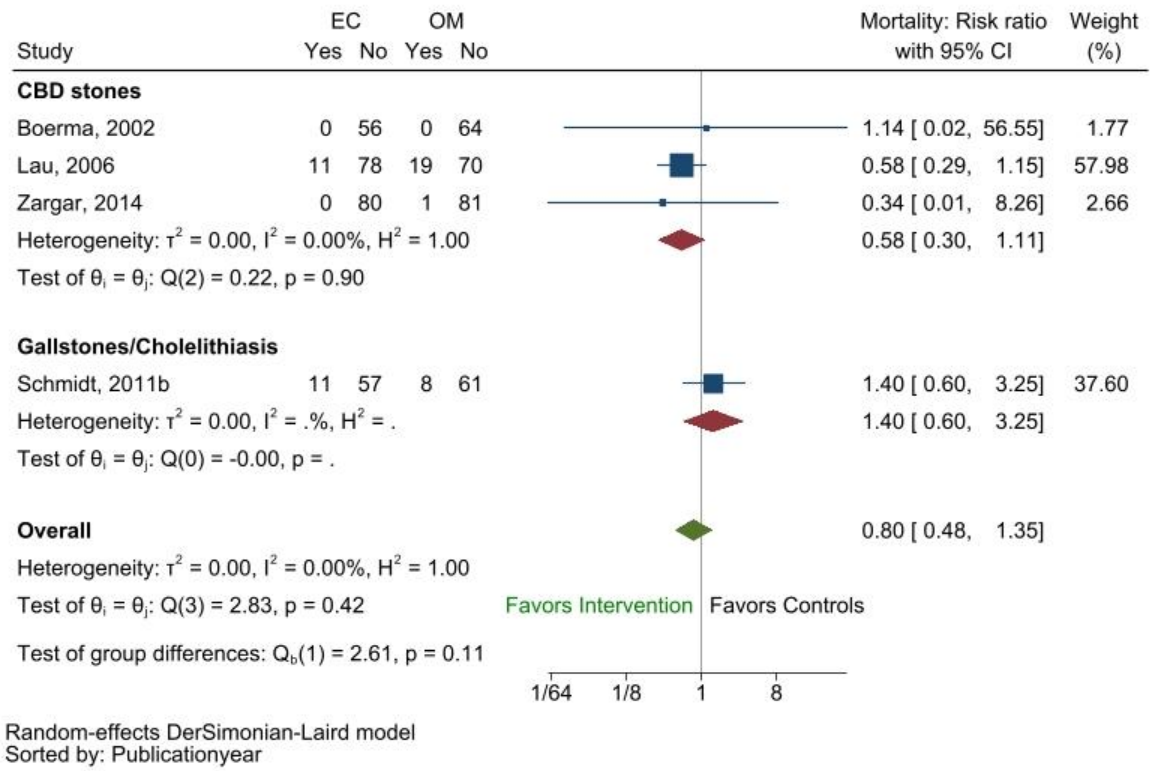



**Figure 2.1.11 Subgroup analysis of Mortality in early cholecystectomy (EC) versus observation management (OM) by Baseline gallstone complication**

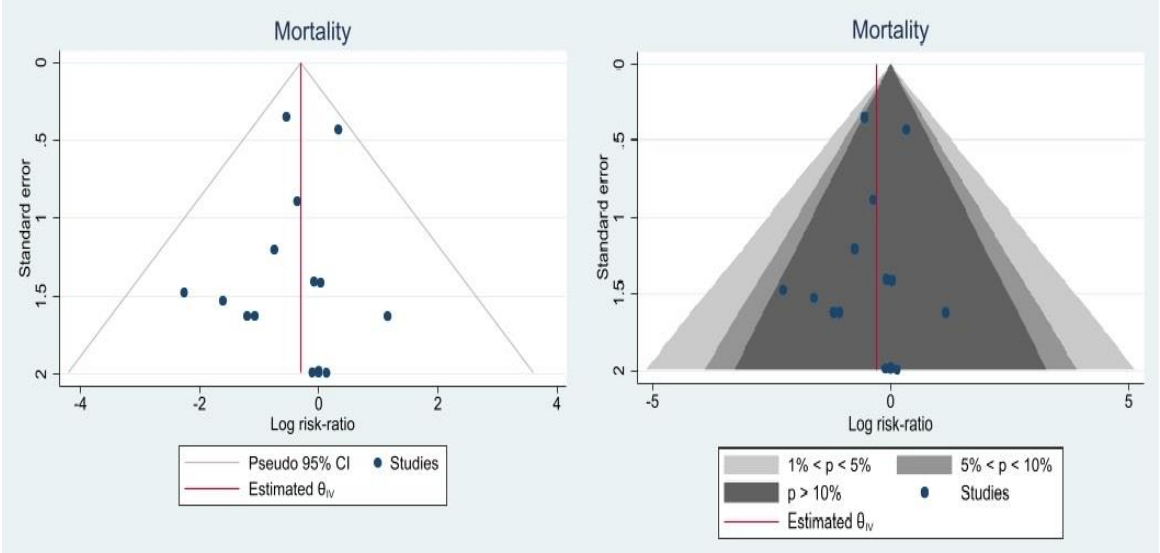



**Figure 2.1.12 Funnel and contour-enhanced funnel plots of early cholecystectomy versus conservative management for Mortality**

**Conversion to laparotomy**

We pooled the risk ratios of conversion to laparotomy from 19 studies comparing EC and DC [58-62, 65, 67, 69, 70, 73, 75, 76, 78-80, 82-85] (Table 2.1.2). The pooled risk ratio was 1.08 (0.18-1.43, $I^2$=2.01%) with low heterogeneity showing no significant difference between the intervention and comparator. The adjusted and unadjusted NNTH was>1000 (100.0->1000). Subgroup analysis based on baseline gallstone complication showed no significant difference between sub-groups (Figure 2.1.13). The funnel plot showed asymmetry (p=0.553), indicating publication bias (Figure 2.1.14).

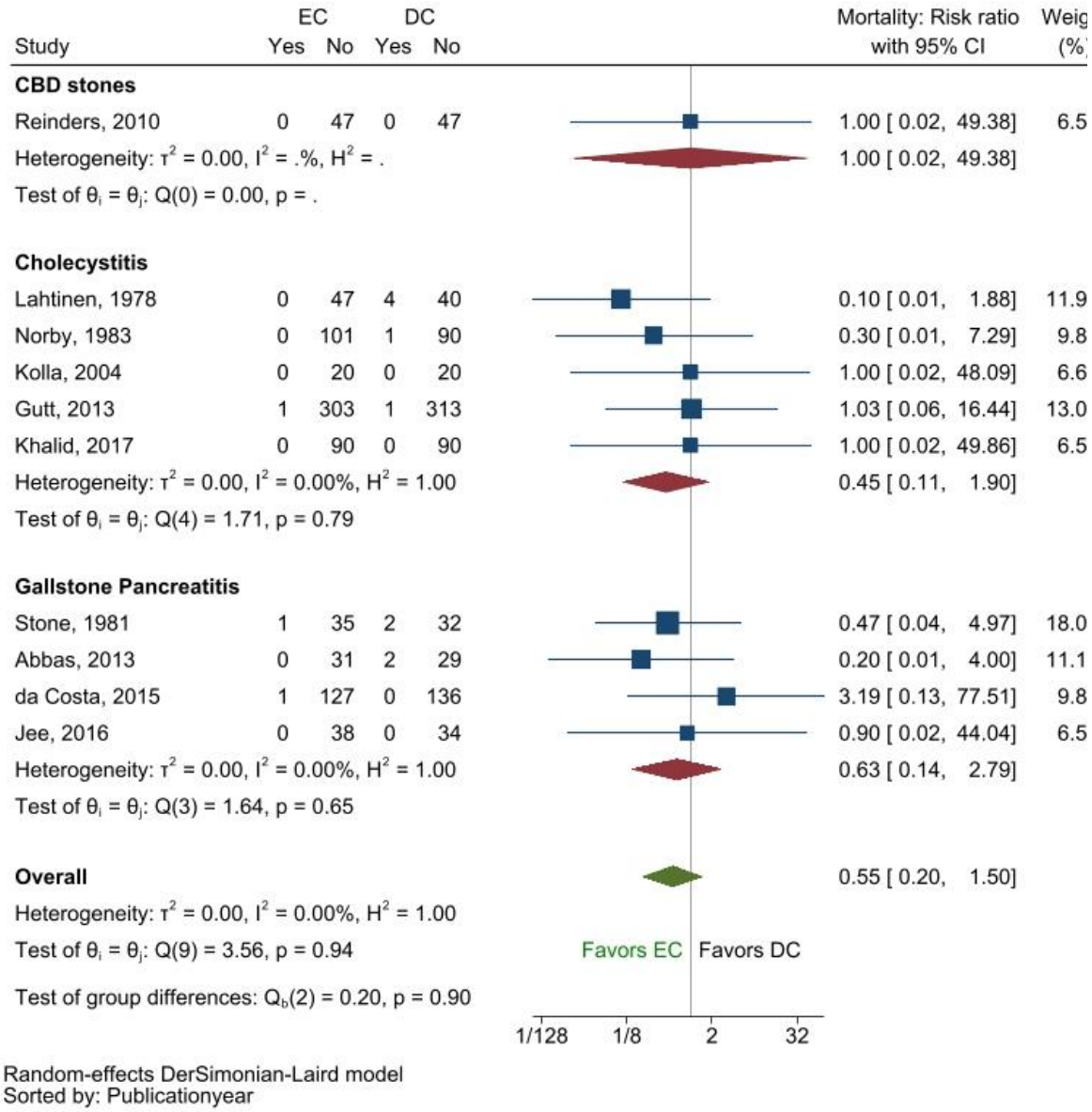



**Figure 2.1.13 Subgroup analysis of Conversion to laparotomy in Early Cholecystectomy (EC) versus Delayed Cholecystectomy (DC) by Baseline gallstone complication.**

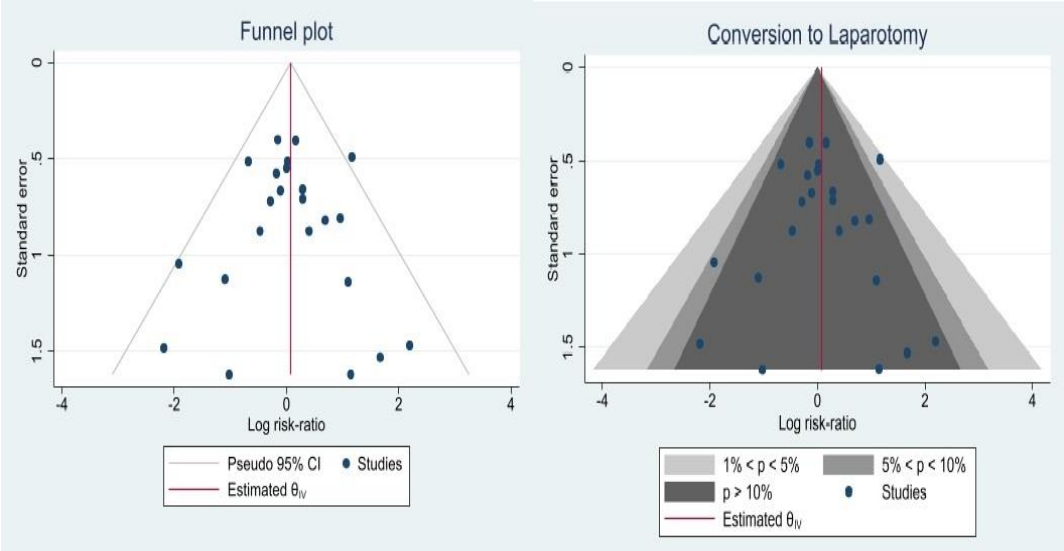



**Figure 2.1.14 Funnel and contour-enhanced funnel plots of early versus delayed cholecystectomy for Conversion to Laparotomy**

**Surgical Complications**

All surgical complications, including perioperative, intraoperative and postoperative complications, were compared between EC *vs* DC groups (See Table 2). The perioperative and intraoperative complications, including a requirement of decompression, use of endoscopic pouches to retrieve specimen, enlargement of sub umbilical incision events, were significantly found higher in EC, indicating complexity. In contrast, adhesion events were lower in EC significantly. Other complications such as drain placement, bile leak, CBD injury, bleeding, and total operative complications reported in the studies did not differ between EC and DC. On subgroup analysis, based on baseline gallstone complications, the events of perioperative and intraoperative complications did not vary between sub-groups (Data not shown). Subgroup analysis on the timing of surgery had shown similar results within the subgroups (Supp Table 2).

**Table 2.1.4 Subgroup analysis of surgical complications of early cholecystectomy (EC) versus delayed cholecystectomy (DC) based on the timing of surgery**

| Surgical Complications | Timing of surgery (no. of studies) | RR (95% CI) | $I^2$ (%) | Q | References |
|---|---|---|---|---|---|
| Total Intra-operative complications | within 7 days (2) | 1.21 (0.15 to 9.65) | 18.99% | 1.23 | [65, 74] |
| | within 72 hours (3) | 0.95 (0.28 to 3.20) | 61.33% | 5.17 | [70, 80, 83] |
| | <6 weeks (1) | 1.02 (0.02 to 50.42) | - | - | [80] |
| | >6 weeks (3) | 0.83 (0.24 to 2.84) | 64.54% | 5.64 | [65, 70, 83] |
| | Overall (5) | 1.00 (0.40 to 2.51) | 38.64% | 6.52 | |
| Total Post-operative complications | within 7 days (1) | 0.89 (0.19 to 4.14) | - | - | [65] |
| | within 72 hours (11) | 0.94 (0.68 to 1.29) | 0% | 8.01 | [58, 62, 66, 67, 69, 37, 73, 77, 78, 80, 83] |
| | <6 weeks (1) | 0.26 (0.03 to 2.19) | - | - | [80] |
| | >6 weeks (11) | 0.97 (0.70 to 1.32) | 0% | 6.58 | [58, 62, 66, 67, 69, 37, 73, 77, 78, 80, 83] |
| | Overall (12) | 0.94 (0.69 to 1.28) | 0% | 8.02 | |
| Total Surgical complications | within 7 days (3) | 0.83 (0.53 to 1.31) | 0% | 0.16 | [64, 65, 74] |
| | within 72 hours (12) | 1.35 (1.02 to 1.79) | 0% | 9.52 | [58, 60, 63, 66, 67, 37, 73, 75, 77, 79, 81, 83] |
| | <6 weeks (2) | 0.98 (0.50 to 1.91) | 0% | 0.09 | [60, 63] |
| | >6 weeks (14) | 1.23 (0.94 to 1.62) | 3.51% | 13.47 | [57, 58, 64-67, 37, 71, 73, 75, 77, 79, 81, 83] |
| | Overall (17) | 1.15 (0.91 to 1.45) | 0% | 14.63 | |
| Mortality | within 7 days (3) | 0.25 (0.04 to 1.62) | 0% | 0.78 | [65, 68, 74] |
| | within 72 hours (6) | 0.97 (0.27 to 3.51) | 0% | 0.9 | [60, 63, 66, 67, 77, 81] |
| | <6 weeks (2) | 1.67 (0.21 to 13.55) | 0% | 0.27 | [60, 63] |
| | >6 weeks (7) | 0.59 (0.21 to 1.69) | 0% | 3.40 | [56, 65-68, 77, 81] |
| | Overall (9) | 0.63 (0.22 to 1.8) | 0% | 3.06 | |
| Conversion to Laparotomy | within 7 days (2) | 0.78 (0.23 to 2.63) | 0% | 0.27 | [65, 85] |
| | within 72 hours (18) | 1.01 (0.75 to 1.37) | 0% | 12.97 | [58-62, 66, 67, 69, 70, 73, 75, 76, 78-80, 82-84] |
| | <6 weeks (5) | 0.71 (0.36 to 1.43) | 0% | 3.46 | [59-61, 80, 85] |
| | >6 weeks (15) | 1.07 (0.78 to 1.48) | 0% | 8.87 | [58, 62, 65-67, 69, 70, 73, 75, 76, 78, 79, 82-84] |
| | Overall (20) | 1.00 (0.74 to 1.34) | 0% | 13.40 | |

The postoperative complications reported by the studies, were wound infection, sepsis, postoperative bleeding, cystic duct leakage, chest infection, pneumonia, retained CBD stones, reoperation due to bile leak, pulmonary embolus, subphrenic abscess and readmission rate. Among the postoperative complications reported, only the readmission rate was significantly lower in the EC group. All other complications had shown no significant difference between EC *vs* DC groups. Subgroup analysis also showed similar results between subgroups based on baseline gallstone complications (Data not shown) and timing of surgery (Table 2.1.4).

The length of hospital stay was significantly lower in the EC group with a mean difference of -3.00 (-3.99- -2.02) days with high heterogeneity ($I^2$=92.61%) (Figure 2.1.15). However, operative time (in minutes) did not differ between EC *vs* DC groups, with a mean difference of -4.84 (-12.35-2.66) with high heterogeneity ($I^2$=90.34%).

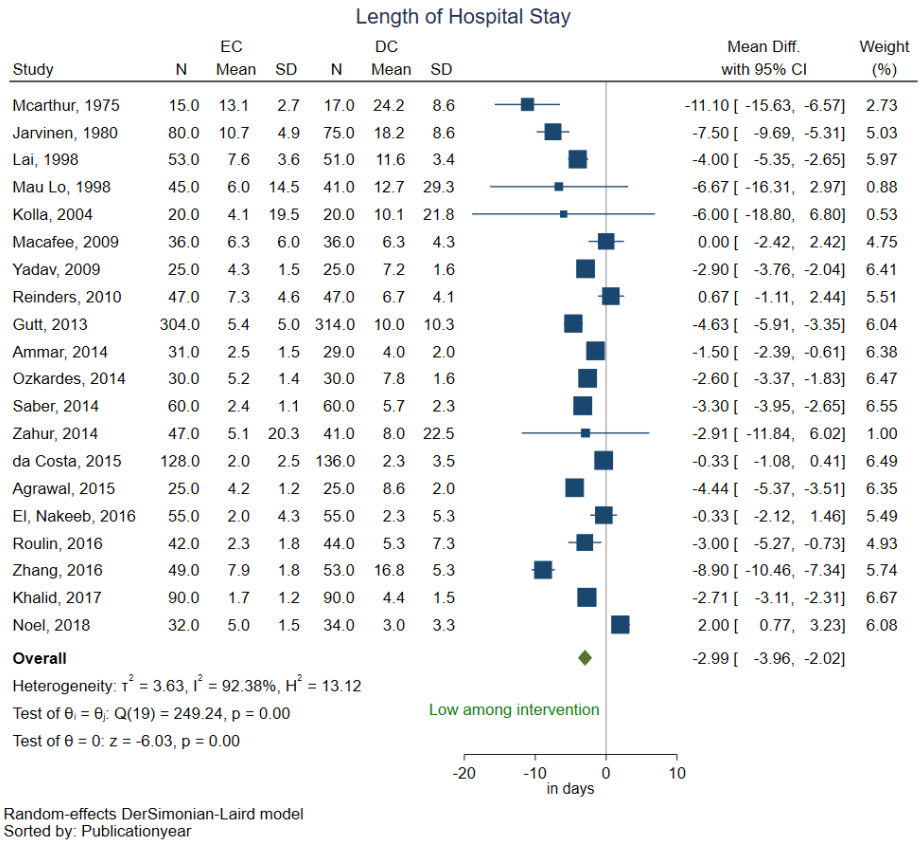


**Figure 2.1.15 Forest plot showing mean difference in length of hospital stay between early and delayed cholecystectomy**

### 2.1.4 Discussion:

In this systematic review and meta-analysis of RCTs, we compared the clinical effectiveness of early cholecystectomy with conservative management/delayed cholecystectomy in reducing the recurrence of gallstone symptoms and the occurrence of related complications. We also compared the surgical complications between EC and DC. Meta-analysis results showed that the gallstone-related complications, particularly pain/biliary colic, acute cholecystitis, and cholangitis, were significantly lower among early cholecystectomies than conservative management/delayed cholecystectomy. The total biliary complications reported in the studies were significantly lower with early cholecystectomy in the EC *vs* OM subgroup. No significant difference was observed in the EC *vs.* EM and EC *vs.* DC subgroups. The perioperative and intraoperative complications, including the requirement of decompression, use of endoscopic pouches to retrieve specimen, enlargement of sub umbilical incision except for adhesion, were significantly higher in EC, indicating the complexity of the procedure. Other perioperative and major postoperative complications, such as wound infection and bile leak, did not differ between EC *vs.* DC groups.

Existing systematic review and meta-analysis, comparing EC *vs.* DC, had focused mainly on surgical complications, length of hospital stays, and operative time with no/less emphasis on gallstone-related complications [43]. Also, as this review mainly focussed on recurrent gallstone complications, thereby observing lower effectiveness of conservative management/delayed cholecystectomy from the pooled analysis. However, only fewer RCTs had reported these outcomes[60, 63, 65, 73, 77]. We also included a few additional studies

comparing EC vs. DC, not included in any previous systematic review and meta-analysis[58, 64, 66, 68, 74, 84].

We also compared surgical outcomes in EC and DC groups to assess the impact of delayed surgery on surgical complications. Although studies involving conservative management reported surgical outcomes, not all the patients in the conservative arm underwent surgery. Therefore, we considered it appropriate to compare the surgical complications between EC and DC alone. Even though many previously published observational studies reported a higher risk for bile duct injury with EC in acute-cholecystitis[94, 95], this meta-analysis suggests that there is no significant difference in terms of major postoperative complications such as bile duct injury, wound infection and bile leak between EC and DC. Our meta-analysis observed a higher risk for perioperative and intraoperative complications in EC, similar to previous systematic review and meta-analysis[43]. Although there was no significant difference in major surgical complications, this meta-analysis results revealed the recurrence or aggravation of gallstone symptoms during the waiting period of delayed cholecystectomy. Thus, early cholecystectomy seems to be a safer option based on existing pieces of evidence.

Our meta-analysis has also reported both adjusted and unadjusted NNTH, a beneficial measure to arrive at appropriate clinical decisions[96, 97], which added strength to our systematic review and meta-analysis. From this meta-analysis, it was clear that 12.5, >1000, 100, 100, 5.9, and >1000 patients need to undergo early cholecystectomy for one additional patient to have pain, biliary pancreatitis, CBD stones, cholangitis, total biliary complications, and mortality respectively as compared to conservative management/delayed cholecystectomy. The review findings favor early cholecystectomy, as a better treatment option, compared to conservative management/delayed cholecystectomy.

This systematic review and meta-analysis have some limitations. We compared early cholecystectomy with conservative management (including observation management and endoscopic management) and delayed cholecystectomy, which might have contributed some heterogeneity in data.

However, we have tried to address it through subgroup analysis. Few RCTs included in this study had a high risk of bias in randomization and deviation from intended intervention. In most of the outcomes analyzed, publication bias was also observed. We could not collect all the evidence since full texts of some published studies that met the inclusion criteria were unavailable even after requesting the corresponding authors. The presence of many zero cells indicates rare events, which were statically handled through zero correction in our meta-analysis. We found that there are insufficient studies in many subgroups. Mainly, there was only one study that compared EC with OM for acute cholecystitis. Therefore, it is recommended to conduct further RCTs in the future, which may bridge this knowledge gap.

### 2.1.5 Conclusion

In conclusion, early cholecystectomy is more effective in gallstone disease management, as it results in fewer biliary complications and a reduction in reported abdominal pain than delayed cholecystectomy/conservative management.

## 2.2 HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH GALLSTONE DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EUROQOL (EQ-5D) UTILITY SCORES

### 2.2.1 Introduction

Gallstone or cholelithiasis is a chronic disease formed by the deposition of cholesterol or bilirubin in the gallbladder. The prevalence of gallstones varies from 0.1 to 50.5% across the globe, which increases with age. Gallstones are predominant in females, with the highest prevalence of 57%, observed among 70-79 years old gall stone patients [98, 99]. Patients with gallstones could be either asymptomatic or symptomatic. Asymptomatic gallstones usually require no treatment, whereas symptomatic gallstone often causes persistent pain in the right upper abdomen and other symptoms like nausea, vomiting, and indigestion, limiting the activities of the affected individuals, thus making the treatment imperative [100]. Gallstones are associated with various complications, including common bile duct (CBD) stones (choledocholithiasis), acute cholecystitis, cholangitis, and biliary pancreatitis; these complications could be potentially life-threatening and require appropriate clinical management [101, 102, 100].

Cholecystectomy (a surgical procedure to remove the gall bladder) is the preferred treatment for cholelithiasis [100]. Laparoscopic cholecystectomy (multi/single incision) is preferred over open cholecystectomy for its cosmetic advantages and fast recovery [103, 104]. About 75,000 gallstone patients undergo cholecystectomy every year in the USA, making it a common surgery[105]. Alternative treatments for gallstone include conservative management, Extracorporeal shockwave lithotripsy, stone dissolution therapy, etc. [106]. Considering the

high prevalence and the significant economic burden it imposes on the healthcare systems, identifying cost-effective management for gallstones through cost-utility analysis (CUA) is crucial. In CUAs, the effect of an intervention is measured as ‘healthy years,’ which are estimated by combining utility score with life-years gained with some judgment on the quality of those life years [27]. The health state utility scores are measured using various generic instruments such as EuroQoL 's Five-Dimensional Questionnaire [EQ-5D], Short Form (SF)-6D, Health Utilities Index, etc. [107]. EQ-5D is the preferred generic instrument for assessing the health-related quality of life (HRQoL) as recommended by the NICE (National Institute for Health and Care Excellence) [108]. EQ-5D (EuroQol Group, Rotterdam, The Netherlands) utility score covers the five dimensions to measure the quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [109-111]. Each dimension has five levels or three levels of responses; the obtained scores are compared with the standard score for each country or region to obtain a single utility score ranging from 0 (death) to 1 (perfect health).

Systematic review and meta-analysis of EQ-5D utility scores would provide precise and generalizable utility estimates, which are inevitable for CUAs on gallstone management. Currently, there are no systematic reviews and meta-analyses of EQ-5D utility scores for gallstone disease. Therefore, we systematically reviewed the studies on HRQoL obtained using EQ-5D and provided EQ-5D utility and EQ-5D VAS pooled estimate scores for gallstone disease.

### 2.2.2 METHODS

A systematic review and meta-analysis was conducted adhering to the guidelines of Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) [44], and the protocol was registered in PROSPERO (CRD42021234467). Search terms were formulated based on the PICO method (i.e. population [adult Gallstone patients], intervention [none], comparator [none], and outcome health-related quality of life measures] and systematically searched in Medline (Pubmed), Embase, and Scopus databases since inception through February 2021. Conventional sensitivity and precision maximizing strategy was adopted during the selection of studies. Studies that reported EQ-5D utility scores for gallstone disease were included in the systematic review. Reviews, conference abstracts, letters to the editor were excluded from the systematic review.

**Screening and reviewing of studies:** After removing the duplicates, articles were screened by title and abstract independently by the reviewers (AAD and BSB) using the Rayyan-web app for systematic reviews [45]. AAD and MK performed the full-text screening. The studies that reported EQ-5D utility scores for gallstone disease were included in the systematic review on mutual agreement of the reviewers.

**Data extraction:** The necessary information required for achieving the study's objective was extracted from the selected studies using a data extraction form created in - Microsoft Excel (2016). The data extraction form included general information such as author name, the title of the study, the country in which the study was conducted, author's email address, characteristics such as study population, intervention, and comparator, and sample size; patient characteristics such as mean age, gender, and body mass index (BMI). Data on central tendency (mean/median) and dispersion (standard deviation (SD) / Standard error (SE) / Interquartile

range (IQR) / 95% confidence interval (CI)) for the primary outcome variable, EQ-5D utility score, EQ-5D VAS, and other available parameters were extracted from the included studies by AAD and verified independently by BSB.

**Risk of bias assessment:** The risk of bias in the included studies was assessed independently by two reviewers (MK and HM), and disagreements were solved by consensus. Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [112], AXIS tool for cross-sectional studies [113], and Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) for randomized control trials (RCTs) were used [114].

**Statistical analysis:** The weighted mean of EQ-5D utility and EQ-5D visual analogue score (VAS) were pooled using STATA 16 [55]. In studies that reported EQ-5D utility scores at baseline and follow-up post-intervention, the mean difference method pooled the incremental differences in the EQ-5D utility scores. The heterogeneity was assessed by visual inspection of forest plots, $I^2$ statistics, and Cochran Q test. $I^2$ values greater than 25% or Cochrane-Q >0.1 were considered to be heterogeneous. The random-effects model with DerSimonian and Laird method was used if heterogeneity was observed between the studies [115]; otherwise, a fixed-effect model was used. In the event of missing data, an attempt was made to contact the authors of the studies by email to obtain the missing information. When no response was received from the authors, the studies were omitted from the meta-analysis. Publication bias could not be assessed due to insufficient studies.

### 2.2.3 RESULTS

**Selection of studies:** The electronic search retrieved 4,871 studies after removing the duplicates. 3,702 articles were screened by title and abstract, after which 324 studies were considered for the full-text screening. Finally, eleven eligible studies were included for systematic review. The reasons for excluding articles include inappropriate population, Different outcomes, study design, etc., summarised in the PRISMA flowchart (Figure 2.2.1). Among the eleven studies, five reported EQ-5D utility scores, and three reported EQ-5D visual analogue scores. The measure of dispersion was not specified in the three studies; hence they were not included in the meta-analysis.

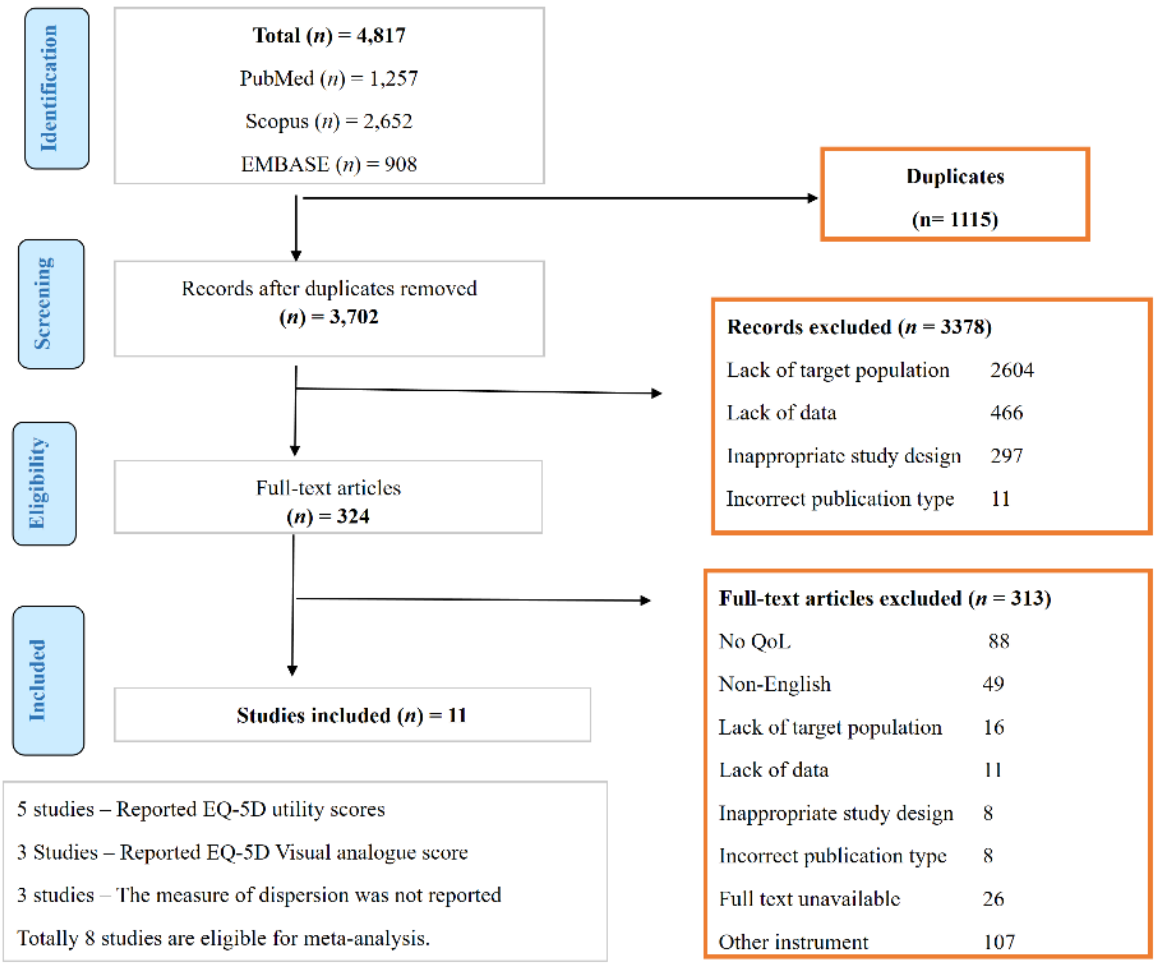


**Figure 2.2.1 PRISMA flow chart of selection of studies**

**Description of studies:** The characteristics of the included studies are given in Table 2.2.1. The sample size of the individual studies ranged from 13 to 451 patients. Finally three studies (27%) conducted in Canada [116-118], two (18%) each from Egypt [119, 120], and Sweden [121, 122], one each (9%) from Mongolia [123], Netherland [124], German [125], and turkey [126] seven out of eleven studies were cohort studies [119, 116, 120, 126, 117, 118, 124, 125] , two case-control study [121, 122] and two clinical trial [116, 120]. Seven studies [116, 120] out of 11 reported EQ-5D-5L, and four studies [116, 120, 117, 118] reported EQ-5D-3L. Among the eleven studies, seven studies reported the EQ-5D utility scores [116, 120, 117, 118] [121, 122] [126], whereas four studies reported the EQ-5D VAS score [119] [123-125].

**Table 2.2.1 Characteristics of included studies**

| Study | Country | Study design | Year | Sex (Female %) | Groups | Sample size | Age |
|---|---|---|---|---|---|---|---|
| Ellatif_2012 | Egypt | Cohort study | 2012 | 76.0 | SAL<br>LC | 125<br>125 | 47.7±10.6<br>46.9±11.4 |
| Karimuddin _2021 | Canada | Cohort study | 2021 | 71.3 | Elective Cholecystectomy | 195 | NA |
| Lombardo_2018 | Mongolia | Cohort study | 2018 | 68.8 | OC<br>LC | 93<br>122 | 49.8±14.1<br>47.7±12.9 |
| Rosemuller _2017 | Egypt | Pragmatic randomized clinical trial | 2017 | 62.0 | LC<br>SIOC | 177<br>156 | 52.0±16.5<br>51.5±16.0 |
| Rystedt_2017 | Sweden | Cohort study | 2017 | NA | OC, LC & Endoscopic Cholecystectomy of BDI | 101 | NA |
| Sutherland_2020 | Canada | Cohort study | 2019 | 73.3 | Elective Cholecystectomy | 135 | NA |
| Sutherland_2021 | Canada | Cohort study | 2020 | 73.0 | Elective Cholecystectomy | 188 | 58.7±13.3 |
| Sinam_2018 | Turkey | Cohort study | 2018 | 57.1 | SIL<br>LC | 16<br>13 | 46.2±14.3 |
| Vlug _2009 | Netherlands | Cohort study | 2009 | 81.3 | LC<br>LNF | 48<br>22 | 46.0±11.8<br>47.0±11.8 |
| Wagner_2017 | Germany | Cohort study | 2017 | 78.6 | SPL<br>LC | 122<br>100 | 45.0±10.3<br>54.0±10.0 |
| Wanjura_2015 | Sweden | Case Control | 2015 | 72.5 | Acute and Elective Cholecystectomy | 451 | 55.1±13.5 |

**BDI-Bile duct injury, LC- Laparoscopic Cholecystectomy, LNF- Laparoscopic Nissen fundoplication, NA- Not Available, OC-Open Cholecystectomy, SAL-Single Access Laparoscopic, SIOC- Small Incision open Cholecystectomy, SPL- Single Port Laparoscopic, SIL- Single-incision Laparoscopic.**

**Risk of bias:** We analyzed seven cohorts [117, 118] [119] [121] [123, 126, 124, 125] and two case-control [121, 122] studies using NOS found no evidence of serious risk of bias, and all studies scored high (≥7). Similarly, the ROB-2 tool assessed the risk of biases in randomized controlled trials; two RCTs [116, 120] found low risk. Although Jenny et al. 2017 lost points in two domains, there was no evidence of serious risk of bias across the included studies assessing EQ-5D. Two authors (MH & MK) independently evaluated the quality of included studies, and disagreements were resolved by consensus (Table 2.2.2, 2.2.3, and 2.2.4).

**Table 2.2.2 ROB assessment of RCTs using ROB-2**

| **Domains** | Rosenmüller MH et al 2017 | Abd Ellatif ME et al 2013 |
|---|---|---|
| Randomisation process | + | + |
| Deviations from the intended interventions | + | + |
| Missing outcome data | + | + |
| Measurement of the outcome | + | + |
| Selection of the reported result | + | + |
| **Overall** | + | + |
| + Low ? Moderate − Serious | | |

**Table 2.2.3 ROB assessment of cross-sectional studies using Axis tool**

| **Signaling Questions** | Asai 2019 |
|---|---|
| Were the aims/objectives of the study clear? | + |
| Was the study design appropriate for the stated aim(s)? | + |
| Was the sample size justified? | + |
| Was the target/reference population clearly defined? (Is it clear who the research was about? | + |
| Was the sample frame taken from an appropriate population base? | ? |
| Was the selection process likely to select subjects/participants? | + |
| Were measures undertaken to address and categorise non-responders? | + |
| Were the risk factor and outcome variables measured appropriate to the aims of the study? | + |
| Were the risk factor and outcome variables measured correctly using instruments published previously? | + |
| Is it clear what was used to determined statistical significance and/or precision estimates? | + |
| Were the methods (including statistical methods) sufficiently described to enable them to be repeated? | + |
| Were the basic data adequately described? | + |
| Does the response rate raise concerns about non-response bias? * | − |
| If appropriate, was information about non-responders described? | ? |
| Were the results internally consistent? | + |
| Were the results for the analyses described in the methods, presented? | − |
| Were the authors' discussions and conclusions justified by the results? | − |
| Were the limitations of the study discussed? | + |
| Were there any funding sources or conflicts of interest? * | + |
| Was ethical approval or consent of participants attained? | + |
| + indciates 'YES', − indicates 'NO', ? indicates 'DO NOT KNOW'<br>* + indciates 'NO', − indicates 'YES', ? indicates 'DO NOT KNOW' | |

**Table 2.2.4 ROB assessment of cohort studies using Newcastle Ottawa scale**

| | Vlug et al 2009 | Markus J.et al 2013 | Wanjura et.al 2016 | Lombardo, MD et al 2018 |
|---|---|---|---|---|
| Representativeness of the Exposed Cohort | * | * | * | * |
| Selection of the non-exposed cohort | * | * | * | * |
| Ascertainment of exposure | * | * | * | * |
| Demonstration that outcome of interest was not present at start of study | * | * | * | * |
| Comparability of cases and controls on the basis of the design or analysis | ** | ** | ** | * |
| Assessment of outcome | * | * | * | * |
| Was Follow-Up Long Enough for Outcomes to Occur | * | * | * | * |
| Adequacy of follow up of cohorts | * | * | * | * |
| Total | 9 | 9 | 9 | 8 |
| * indicates 'One star', ** indicates 'Two stars', – indicates 'No star | | | | |

**Pooling of EQ-5D utility and VAS scores:** EQ-5D mean utility scores of patients with Gallstone disease who have yet to undergo any treatment were reported in five studies [116, 120, 117, 118]. The Pooled EQ-5D utility score for patients with gallstone disease was 0.87 (0.82 to 0.91) with an $I^2$ value (93.73%) and a Q value (63.80), indicating high heterogeneity (Figure 2.2.2). The pooled EQ-5D VAS score was 83.3 (60.59 to 106.12) with high heterogeneity ($I^2$=99.30%, Q= 143.87) from two studies [119, 123] (Figure 2.2.3).

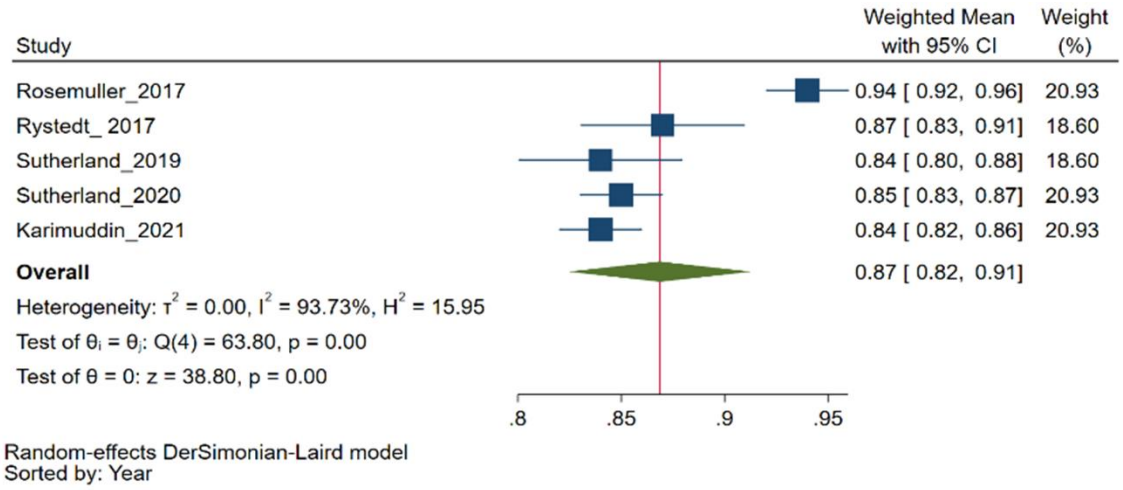



**Figure 2.2.2 Pooled EQ5D utility score of individuals with gallstone disease**

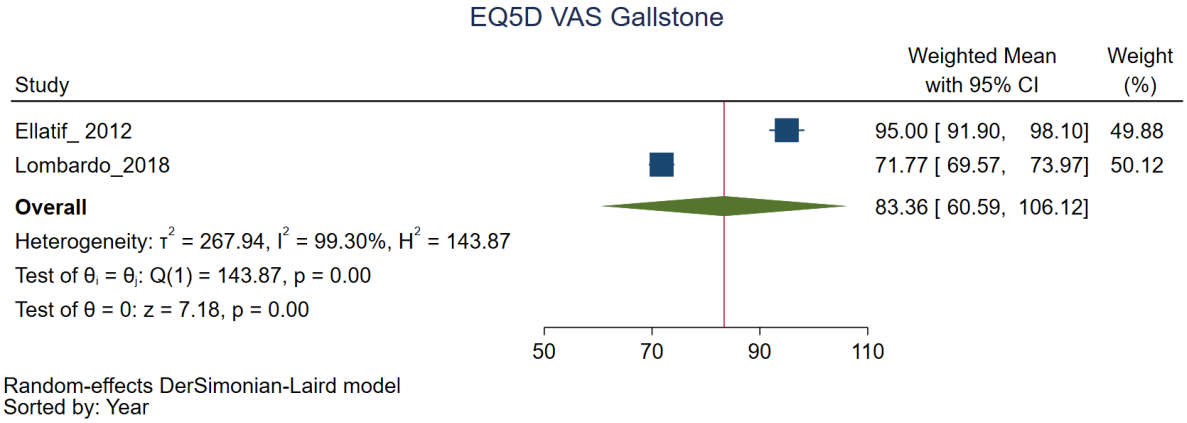



**Figure 2.2.3 Pooled EQ-5D VAS score for Gallstone Disease**

**Pooling of EQ-5D utility and VAS scores post-cholecystectomy:** The EQ-5D utility scores reported during the follow-up six months after surgery (cholecystectomy) were pooled from five studies [119, 123]. The pooled EQ-5D utility score was 0.93(0.91 to 0.95) with high

heterogeneity ($I^2$=90.17%, Q=28.90) (Figure 2.2.4). The pooled EQ-5D VAS post-cholecystectomy at six months follow-up was 91.7 (85.99 to 96.35). High heterogeneity ($I^2$= 97.93%, Q= 96.49) was present between the studies as noted by visual inspection of forest plot and $I^2$ value greater than 25% (Figure 2.2.5).

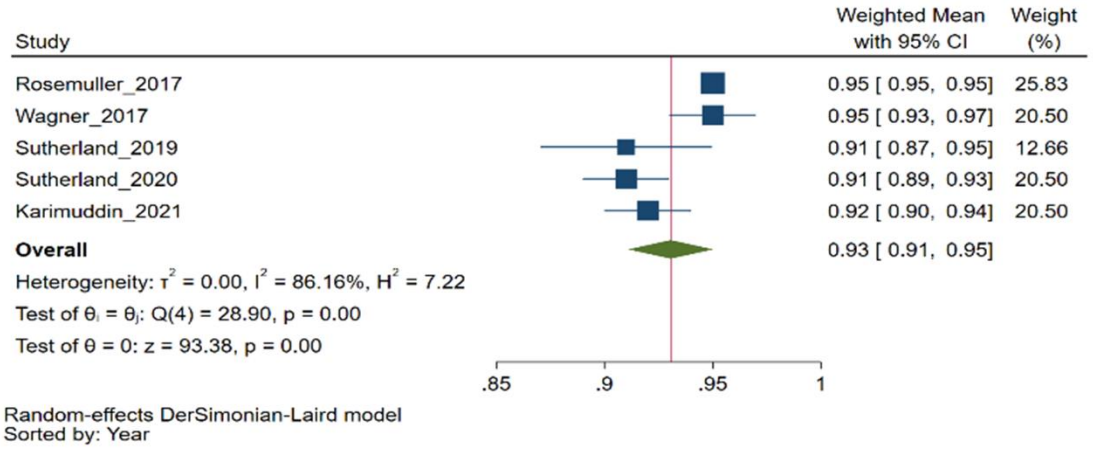



**Figure 2.2.4 Pooled EQ-5D utility score of gallstone disease six months post-cholecystectomy**

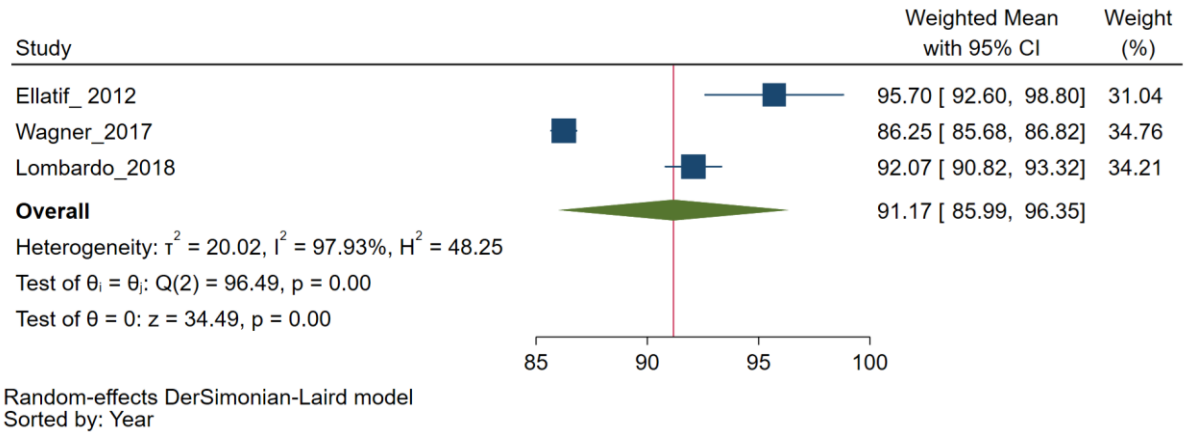



**Figure 2.2.5 EQ-5D Visual analogue score utility score post cholecystectomy**

**Pooling of mean differences in EQ-5D scores, pre and post cholecystectomy:** The mean differences in EQ-5D utility and VAS score pre and post-cholecystectomy were pooled to assess the influence of treatment on the quality of life of gallstone patients. The pooled mean difference in EQ-5D utility score was 0.05 (0.01 to 0.10) from the four studies [119, 123], which have reported the utility scores at baseline (pre-cholecystectomy) and follow-up (post-Cholecystectomy) (Figure 2.2.6). Considering a minimal clinically important difference (MCID) ranging from 0.03 to 0.50 [127], a pooled mean difference of 0.05 indicates a significant improvement in quality of life following cholecystectomy.

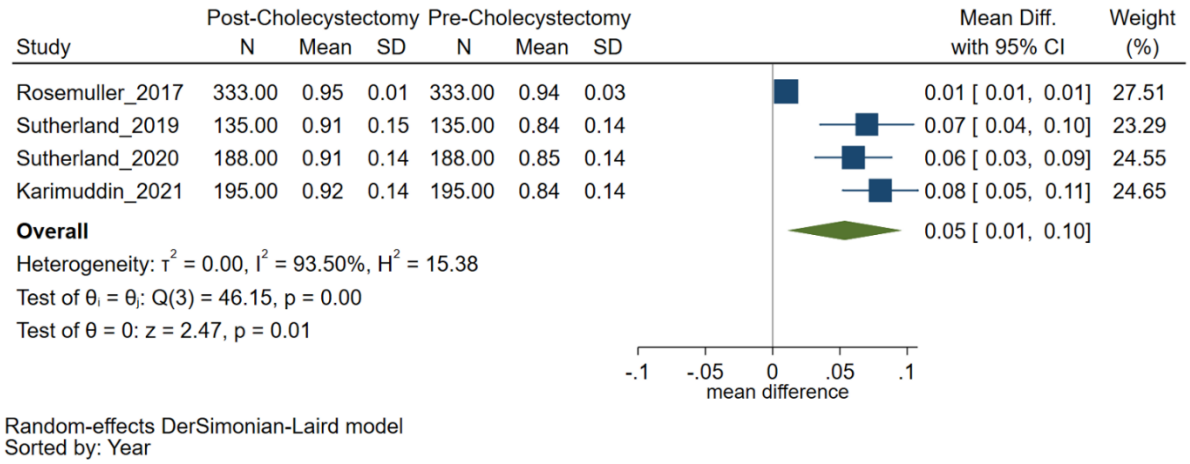



**Figure 2.2.6 Pooled EQ-5D incremental Mean change Post-Cholecystectomy**

The pooled mean difference in EQ-5D VAS was 10.58 (-8.63 to 29.79) from two studies [119, 123] which have reported the utility scores at baseline (pre-cholecystectomy) and follow-up (post-cholecystectomy)(Figure 2.2.7). The forest plot showed considerable heterogeneity between studies ($I^2$ = 98.32%, Q=59.63). The test for group difference indicates that the mean difference is equal to zero, and hence there is no significant difference in utility scores between

baseline and follow-up.

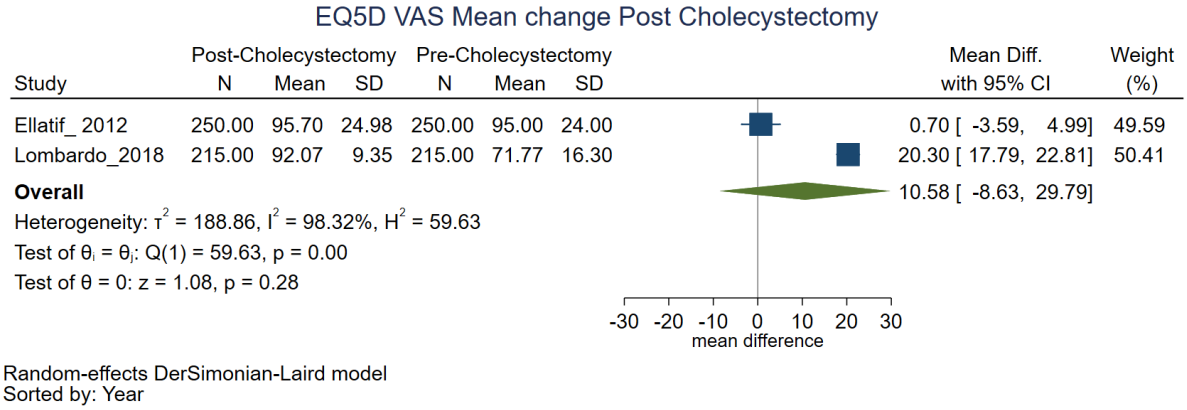



**Figure 2.2.7 Pooled EQ-5D Visual analogue score incremental mean change Post Cholecystectomy**

### 2.2.4 DISCUSSION

The purpose of this systematic review and meta-analysis was to synthesize the evidence on HRQoL estimated using EQ-5D for gallstone disease and provide a pooled estimate of HRQoL, specifically the EQ-5D utility and VAS scores specific to gallstone disease. The improvement in quality of life post-treatment for gallstones was also synthesized by pooling the mean change of EQ-5D scores.

Though several treatments are available for gallstone management, cholecystectomy is the preferred treatment of choice currently. Our systematic review also noted that most of the interventional studies that have assessed the EQ-5D utility score involve cholecystectomy as the intervention. However, the literature observed that complete recovery is not achieved even after cholecystectomy, and approximately 22% of the patients continue to experience pain and recurrent gallstone-related symptoms [41]. Therefore, we have assessed the quality of life of

gallstone patients post-cholecystectomy, which could be a piece of helpful information for cost-utility studies on cholecystectomy. In this study, the pooled EQ-5D score post-cholecystectomy was 0.93. The incremental mean change of EQ-5D scores was 0.05, greater than the MCID, indicating significant improvement in quality of life following cholecystectomy. It is important to remember that cholecystectomy is associated with several post-surgical complications such as bile duct injury, wound infection, etc. However, the current interventional studies included in this systematic review have not provided the utility scores of such surgical complications except one study that provided separate EQ-5D scores for bile duct injury, indicating paucity in such data. Also, the heterogeneity was observed to be high between studies showing the requirement of more high-quality studies.

We have also identified limited/no data on health-related quality of life for specific gallstone complications such as cholecystitis, choledocholithiasis, cholangitis, and biliary pancreatitis. It is important to note that gallstone disease varies widely in its presentation. Some people remain asymptomatic throughout their lifetime, some exhibit mild symptoms like pain, and some may experience fatal complications, including pancreatitis, cholangitis, etc. Thus, the health utility is not the same for all patients with gallstones. Therefore, health state-specific utility scores using EQ-5D are critical for gallstone disease, lacking in the currently available literature. Existing CUAs have used the health state utilities from much older studies that have reported the utility scores obtained using different approaches [128].

The limitations in this systematic review are primarily due to limited high-quality evidence rather than the methods used in this review. In general, health-related quality of life could be influenced by various factors such as age, gender, and comorbidities, etc. However, our

systematic review could not examine the impact of co-morbid conditions and demographic factors due to limited data availability. There is a high risk of type I (incorrectly concluding an intervention as beneficial when it is not) and type II (incorrectly concluding that an intervention is not beneficial when it is beneficial) because of paucity in studies. The studies were insufficient for conducting the meta-regression. Publication Bias was also not assessed due to insufficient studies.

### 2.2.5 CONCLUSION

Current systematic review and meta-analysis pooled EQ-5D utility score and EQ-5D VAS scores of patients with gallstone disease, could provide valuable inputs for CUAs on gallstone management. Our systematic review has identified several evidence gaps, which warrants new HRQoL studies in gallstone patients with specific complications to obtain a precise utility estimate for gallstone disease.

# CHAPTER 3

# SYSTEMATIC REVIEW AND META-ANALYSIS OF ECONOMIC EVALUATIONS IN GALLSTONE DISEASE

## 3.1 INCREMENTAL NET BENEFIT OF CHOLECYSTECTOMY COMPARED WITH ALTERNATIVE TREATMENTS IN PEOPLE WITH GALLSTONES OR CHOLECYSTITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF COST-UTILITY STUDIES

### 3.1.1 Introduction

Gallstones constitute one of the most common and expensive gastrointestinal disorders and cause significant epidemiologic and economic burdens worldwide. Approximately 20% of people with gallstones experience symptoms requiring medical attention or surgery, while the remaining people persist as asymptomatic for many years [31]. Treatment options for cholecystitis include surgical (cholecystectomy-open and laparoscopic) or conservative management. The treatment of gallstone disease was expensive and often engendered substantial economic and social burden if symptoms or complications occur. United States healthcare system alone reported treatment costs as 6.5 billion US$ per year [129].

The optimal timing and the treatment choice for cholecystectomy in patients with acute cholecystitis have always been contentious [130]. In earlier days, several weeks of hospital stay and an initial intense medical management were the norm before an open cholecystectomy (OC) [131]. Introducing early cholecystectomy (open or laparoscopic) reduced the overall treatment duration considerably [130]. Performing an early surgery for cholecystitis has the

advantage of reduced hospital stay and circumvents the risk of emergency surgery in the wake of a non-resolved or recurrent issue [131].

Delayed laparoscopic cholecystectomy (DLC) and OC requires multiple hospital visits considering the conservative treatment, surgery, and recovery period. Hence, it was associated with a higher rate of morbidity, hospital stays, pain, and time to return to work [132]. Early laparoscopic cholecystectomy (ELC) was associated with a lower risk of wound infection, shorter hospital stay, better cost-effectiveness, and higher patient satisfaction and quality of life [131]. Studies have confirmed that ELC also reduces treatment costs significantly [133-135]. However, uncertainty still prevails around the ELC, conceivably due to fear of complication. Moreover, the unpredictability in health outcomes and the cost makes the comparison of the overall effectiveness of one intervention over another debatable as well as imperative [31].

Most of the reported studies on gallstone disease management were clinical or partial economic evaluations. These studies covered the costs of treatments but failed to capture the combined measure of the cost and effectiveness of both intervention and comparators in terms of the monetary cost and a generic measure of health gain [136]. Concurrently, even the reported cost-effectiveness studies depict conflicting results, as some studies have reported ELC as cost-effective [134, 137, 138]. In contrast, some others [139, 37] concluded it as only cost-saving and not cost-effective. The lack of existing evidence and its discord on the cost-effectiveness of cholecystectomy compared with other treatment options was evident; hence, a systematic reappraisal of the literature is critical. Therefore, we systemically reviewed the economic evaluation studies of cholecystitis/cholelithiasis management. Also, we synthesised the

evidence on the cost-effectiveness of the various treatment options. This systematic review and meta-analysis summarise the cost-effectiveness of an intervention (Early/Open- LC) compared with a comparator intervention [delayed/open- Laparoscopic Cholecystectomy (LC), conservative management]. Therefore, the results could provide appropriate information to choose the cost-effective method.

### 3.1.2 Methods

We conducted a systematic literature search in PubMed, Scopus, and Embase databases in compliance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [140]. The protocol was registered with the international register of systematic reviews (PROSPERO ID: CRD42020194052).

**Data Sources, Screening, and Study Selection:** The search was performed from inception to July 1$^{st,}$ 2020 in PubMed, Embase, Scopus databases, and Tufts Registry[141][141]. We followed the PICO approach (Population, Intervention, Comparator, Outcome) to construct the search terms. The desired population for the study included all the adult patients presenting with cholelithiasis or acute cholecystitis who were being considered for a cholecystectomy. Surgical removal of the gallbladder using early, open, or LC was the intervention, and non-surgical methods like conservative management, wait-and-watch, endoscopic management cover the comparator strategy. The possible economic outcomes included were incremental cost-effectiveness ratio (ICER), incremental net benefit (INB), quality-adjusted life years (QALY) gained, Life Years saved, and costs saved.

The detailed search terms and search strategies were reported in the appendix. The total number of studies identified from the databases search was 8,710, includes 2,977 from PubMed, 3,696

from Scopus, and 2,037 from Embase. After removing the duplicates (n=1,414), 7,296 studies were selected for an initial title and abstract screening.

Titles and abstracts of the studies listed from the electronic database search were screened independently by the authors (BSB, MK, and AS) for their potential inclusion using the Rayyan software [45]. After screening, authors (BSB, MK, AS) independently reviewed the full-text articles (n= 660). The final list of studies that met the inclusion and exclusion criteria was prepared on the authors' mutual consensus (BS, MK, AS).

All full economic evaluation studies with a study population of cholelithiasis or cholecystitis that compared the costs and consequences of intervention along with comparator in terms of quality-adjusted life-years (QALYs), ICER, or INBs were included in the study. Studies other than Cost-Utility Analysis (CUA), reviews, letters, editorials, abstracts, books, reports, grey literature, and methodological articles were excluded from the study. Based on these inclusion-exclusion criteria, we identified twenty-eight studies for systematic review, and the data were extracted from these papers using a data extraction form. PRISMA flow chart of the screening process appended as figure 3.1.1.

The data extraction form captured general study characteristics, characteristics of the studied population, economic input parameters - cost and incremental/delta costs (C and ΔC), clinical effectiveness and its incremental/delta effectiveness (E and ΔE), ICERs, INB values and its measures of dispersion [i.e., standard deviation (SD), standard error (SE), or 95% confidence interval (CI)], and willingness to pay (WTP) threshold (K) as well as details of intervention and comparator outcomes data for the pooling domain. From the cost-effective (CE) plane graph, we have extracted ΔC and ΔE using webplot-digitizer software [142][142]. The

intervention of interest was early surgical removal (within seven days of symptoms) of the gallbladder (OC or LC). The comparator delayed surgical removal (after 6-8 weeks) of the gallbladder (OC or LC) and included non-surgical methods like conservative management, wait-and-watch, and endoscopic management. Three reviewers (BSB, AK, SK) independently extracted the data from the finally selected 28 studies; any disagreement was resolved by consensus.

We assessed the risk of bias using the modified economic evaluations bias (ECOBIAS) checklist [143]. It considers overall biases (11 items) and biases from model-specific aspects, i.e., structure (4 items), data (6 items), and internal consistency (1 item). Each item was graded as yes, partly, unclear, no, or not applicable (figure 3.1.2).

**The outcome of interest:** The primary outcome parameter of interest was INB, defined as, $INB=K*\Delta E-\Delta C$, where K was the willingness to pay threshold, $\Delta C$-incremental cost (i.e., the difference in costs between intervention and comparator), $\Delta E$-incremental effectiveness (i.e., the difference in effectiveness between intervention and comparator). The positive INB favours treatment, i.e., the intervention was cost-effective. In contrast, a negative INB suggests favouring the comparator, i.e., the intervention was not cost-effective. We used INB instead of ICER as the effect measure because of limitations with ICER and the ambiguity in interpreting them [144]. In addition, since all monetary units were being reported in different currencies and at different periods (years), we converted them to purchasing power parity (PPP), adjusted to US$ for the year 2019 [145].

**Data preparation and statistical analysis:** We followed the data preparation method and analysis as detailed in Bagepally et al. [146]. Briefly, to calculate the INB and its variance,

mean values along with dispersions (SD, SE, 95% CI) of ΔC and ΔE were required. However, economic studies reported different parameters; therefore, we designed five scenarios to deal with the data available from different studies. Using the data as reported by the primary research publications and following the approach detailed in Bagepally et al., we calculated the INB and its variances for each intervention comparator duo [144].

Following the data preparation, INBs were pooled across studies stratified by low (LIC), lower-middle (LMIC), upper-middle (UMIC), and high (HIC) income countries as per the World Bank classification. Meta-analysis was applied to pool the INBs using a random-effects model if heterogeneity was present (i.e., $I^2 \geq 25\%$ or Q p-value < 0.1). We did subgroup analysis wherever appropriate to explore the source of heterogeneity and provide subgroup-specific pooled INBs. Subsequently, we assessed the publication bias using funnel plots and Egger's test. Further, we explored the sources of asymmetry using contour-enhanced funnel plots. All data were prepared using Microsoft Excel version 2016 and analysed by Stata software version 16 [55]. Two-sided $p<0.05$ was considered statistically significant.

### 3.1.3 Results

We retrieved 8,710 potentially relevant studies through our search. Twenty-eight studies were eligible for the systematic review, as shown in the PRISMA flow diagram (Figure 3.1.1, Table 3.1.1). Of the identified studies, eight were diagnostic, and the remaining twenty were therapeutic. Only seven out of the twenty therapeutic studies were included in the meta-analysis [138, 147, 148, 135, 139, 149, 37]. Among those twenty excluded studies, three

studies conducted before the year 2000 presented a considerable variation in the cost data, and ten studies were with no similar intervention-comparators duos to pool.

On analytic approach and design, 78.57% (N=22) studies were model-based, and the remaining 21.43% (N=6) studies were primary economic evaluations [150-152, 137, 37, 153]. The model-based techniques used in these studies were decision tree (N= 19, 67.86%) and Markov model (N= 3, 10.71%) [135, 154, 134]. Most studies (N=11, 39.29%) adopted the payer perspective, followed by the health system perspective (N =10, 35.71%). Four studies adopted a societal perspective [155, 153, 156, 157], and the remaining three studies have not mentioned the study perspective [158, 37, 159].

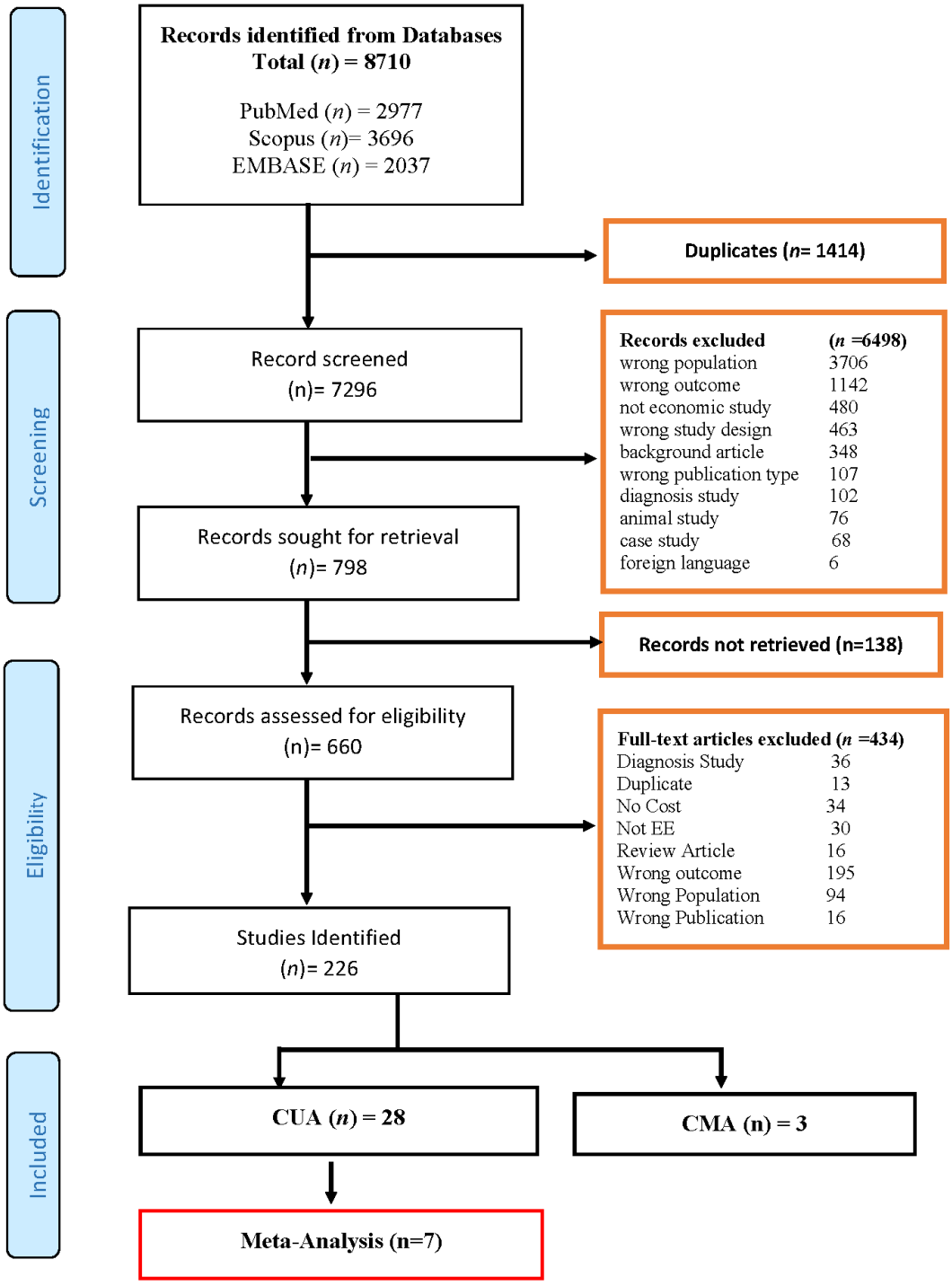



**Figure 3.1.1 PRISMA flow diagram**

The time horizons used in these studies vary from one year to a lifetime. The majority of the studies used a one-year time horizon (N=13, 46.43%), followed by five years (N=5, 17.86%). Two studies each used two and three-year time horizons [138, 158], [160, 155], and only one study used lifetime horizons [161]. Five studies failed to mention a time horizon, and three were from before the year 2000 [151, 137, 157, 162, 159].

All the diagnostic studies evaluating the effectiveness of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) over magnetic resonance cholangiopancreatography (MRCP) reported MRCP as the dominant strategy, either as cost-effective or by providing more QALYs compared with the alternatives. The initial diagnosis with MRCP was reported as the most cost-effective option, with the highest monetary net benefit [162-166].

Among therapeutic studies, three studies [134, 135, 158] compared conservative management with surgery (LC), of which two studies reported that early detection and treatment of cholecystitis become cost-saving and ELC was less expensive and provided greater QALY gains compared to DLC and watchful waiting. Both these studies confirmed DLC was the most expensive treatment and implied the need for early treatment [135, 134]. In contrast, the study conducted by Parmer et al. (2014) recounted that observation was the most cost-effective approach [158].

Similarly, three other studies comparing the cost-effectiveness of LC with OC also favoured Laparoscopic surgery as it was less costly and more effective, concluding that LC dominates OC [151, 137, 154]. Contrastingly, the study by Teerawattananon et al. (2005) found that LC was not cost-effective compared with OC [155].

**Table 3.1.1- Characteristics of studies included in the systematic review**

| Author, Year | Country | Setting | Study perspective | Target population | Time Horizon (Year) | Discount Rate (%) | Intervention | Comparator | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Weinstein, 1990 | USA | Risk group | Societal | Biliary colic, non-calcified gall stones | NA | 5 | Elective Chole | Ursodiol with surgery | Not Cost effective |
| Eric B Bass, 1991 | USA | Others | Payers | bile duct stones with gallstones | 5 | No | ESWL | Surgery | NA |
| Eric B Bass, 1993 | USA | Others | Payers | Acute/chronic biliary pain | 5 | 5 | LC | OC | Dominant |
| Johanna Cook, 1994 | Australia | Others | Payers | Underwent cholecystectomy | NA | No | LC, OC | LC, ESWL | LC dominant |
| Gregor, 1996 | Canada | Others | Third Party Payers | CBD Patients | NA | 5 | ERCP | No ERCP | ERCP dominant |
| Teerawattanam, 2005 | Thailand | Country | Societal | Gall stone Pancreatitis, Bile duct stones | 3 | 3.5 | LC | OC | Not Cost-effective |
| Howard, 2006 | Australia | NA | Health System | Post Cholecystectomy Patients with biliary obstruction | 1 | No | MRCP | ERCP | Dominant |
| YB Vergel, 2006 | UK | Risk group | Healthcare provider | CBD Patients with biliary obstruction | 1 | No | MRCP | ERCP | Dominant |
| B K Paulose, 2007 | USA | Others | Payers | symptomatic Cholelithiasis and incidental | 1 | No | LCBDE | ERCP | Dominant |

| Author, Year | Country | Setting | Study perspective | Target population | Time Horizon (Year) | Discount Rate (%) | Intervention | Comparator | Findings |
|---|---|---|---|---|---|---|---|---|---|
| | | | | CDL at the time of LC | | | | | |
| Keranen, 2007 | Finland | Hospital | Healthcare Provider | Bile Duct Stone, Diagnosed with Cholelithiasis | 1 | No | From home to Operation | Ward | Dominant |
| Macafee, 2009 | UK | Hospital | Societal | Acute Biliary Cholic | 1 | No | Early LC | Delayed LC | ELC cost-saving |
| E. Wilson, 2010 | UK | Country | Payers | gallstone pancreatitis, cholecystitis | 1 | No | Emergency LC | Delayed LC | ELC dominant |
| Dageforde, 2012 | USA | Others | Societal | underwent cholecystectomy | 1 | 3 | Early HBS | Late HBS, | Dominant |
| Gurusamy, 2012 | UK | Country | Payers | gall bladder stones with CBD stones | 3 | 3.5 | IOES | POES | Dominant |
| Amanda Johner, 2013 | Canada | Others | Healthcare Provider | Acute cholecystitis | 1 | No | Early LC | Delayed LC | Dominant |
| A D. Parmar, 2014 | USA | NA | NA | bile duct stones /cholecholithiasis | 2 | No | CM | Elective LC | CM cost effective |
| Morris, 2014 | UK | Others | UK NHS | LC for Mild, acute gallstone pancreatitis | 1 | No | Early LC | Late LC | ELC cost saving |
| Brazzelli, 2014 | UK | NA | UK NHS | symptomatic uncomplicated gallstone, cholecystitis | 5 | 3.5 | Surgery (LC) | CM | LC cost-effective |
| Morris, 2015 | UK | NA | UK NHS | CBD Stone Patients | 1 | No | EUS, MRCP | ERCP | MRCP cost effective |

| Author, Year | Country | Setting | Study perspective | Target population | Time Horizon (Year) | Discount Rate (%) | Intervention | Comparator | Findings |
|---|---|---|---|---|---|---|---|---|---|
| JB Oliver, 2015 | USA | Others | Healthcare provider | Biliary stricture without mass | 5 | 3 | ERCP | EUS, Surgery | EUS cost effective |
| Javid, 2016 | Iran | Hospital | Healthcare Provider | Undergone Cholecystectomy | NA | No | LC | OC | Cost effective |
| De Mestral, 2016 | Canada | Hospital | Third-party payer | Cholecystitis | 5 | 5 | Delayed LC | Early LC | ELC cost saving |
| Sun, 2016 | USA | Others | NA | Intermediate Bile duct stones | NA | No | IOUS, IOCP | EM | IOUS dominat |
| A.J.Sutton, 2016 | UK | NA | Payers | Bile duct stones with gallstones | 1 | No | Delayed LC | Early LC | ELC dominant |
| Rosenmuller, 2017 | Sweden | Others | Societal | Acute Emergency Gall stone Pancreatitis Bile duct stones | 1 | No | LC | SIOC | SIOC cost saving |
| Stella K. Kang, 2017 | USA | Country | US Health system | Symptomatic bile duct stones with gallstones | Lifetime | 3 | MRCP | ASGE | Cost effective |
| J M L Rystedt, 2017 | Sweden | Country | Payers | Symptomatic bile duct stones with gallstones, | 10 | 3 | Routine IOCP | On demand IOCP | Not cost effective |
| Doa'a Kerwat, 2018 | UK | Country | Payers | acute bile duct stones with gallstones | 2 | No | Early LC | Delayed LC | ELC cost-effective |

LC- Laparoscopic Cholecystectomy, OC- Open Cholecystectomy, POES- Pre-Operative Endoscopic Sphincterotomy, IOES- Intra Operative Endoscopic Sphincterotomy, MRCP- Magnetic Resonance Cholangiography, ASGE- American Society for Gastrointestinal Endoscopy, ERCP- Endoscopic Retrograde Cholangiopancreatography, LCBDE- Laparoscopic common bile duct Exploration, CM- Conservative management, EUS- Endoscopic Ultra sound, HBS- Hepatobiliary surgeon, IOCP- Intra operative Cholangiography, EM- Expectant management, IOUS- intraoperative ultrasonography, SIOC- Single Incision open Chole, ESWL- Extracorporeal Shock Wave Lithotripsy, RIOCP- Routine Intra operative cholangiography

**Risk of bias assessment:** The ECOBIAS checklist shows that for most of the studies, the best current practice was chosen as a comparator, and all the comparators have been described in adequate detail. Studies also reported a clear presentation of data used in the model, provided sufficient detail for the costs, applied recommended discount rates, and outwardly disclosed details of funding received. Bias related to a time horizon was high because most of the studies used a short-term horizon. Limited scope bias is very likely in almost all studies, and the internal consistency related to mathematical logic was unclear (Appendix Figure 3.1.1).

**Pooled INBs of Early versus Delayed Laparoscopic Cholecystectomy**

The INBs of ELC versus DLC varied across the seven studies [138, 135, 147, 139, 149, 37, 148], with high heterogeneity ($I^2$ =73.32) and a pooled INB of $1,221 (187 to 2,255) (figure 3.1.2). The calculated overall INB and 95% CI values of the selected studies favour the intervention; infers that ELC was cost-effective compared to the DLC.

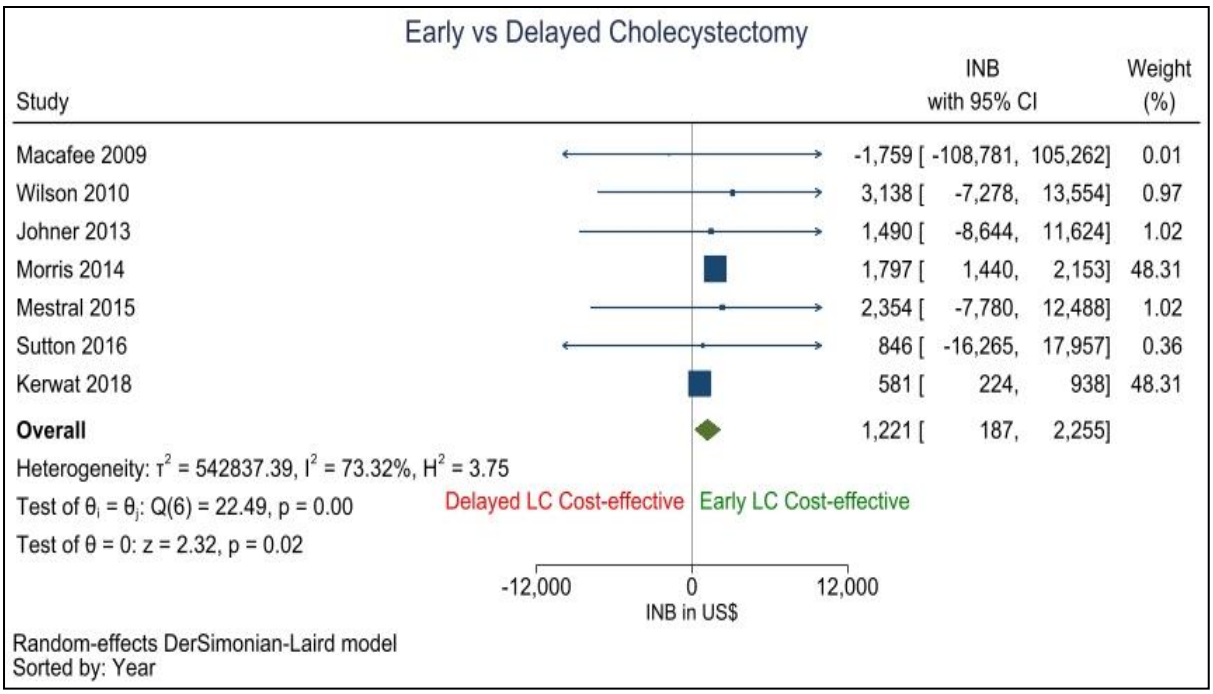



**Figure 3.1.2 Forest plot for Pooled INBs of ELC versus DLC**

Examination of the evidence of publication bias on the funnel plot (Figure 3.1.3) shows evidence of asymmetry. Egger's test with a p-value of 0.912 also indicated a significant asymmetry. No study fell in the area of significance on contour enhanced funnel plot, making publication bias plausible (Figure 3.1.4). To distinguish between publication bias or other causes would be a challenge due to high between-study heterogeneity.

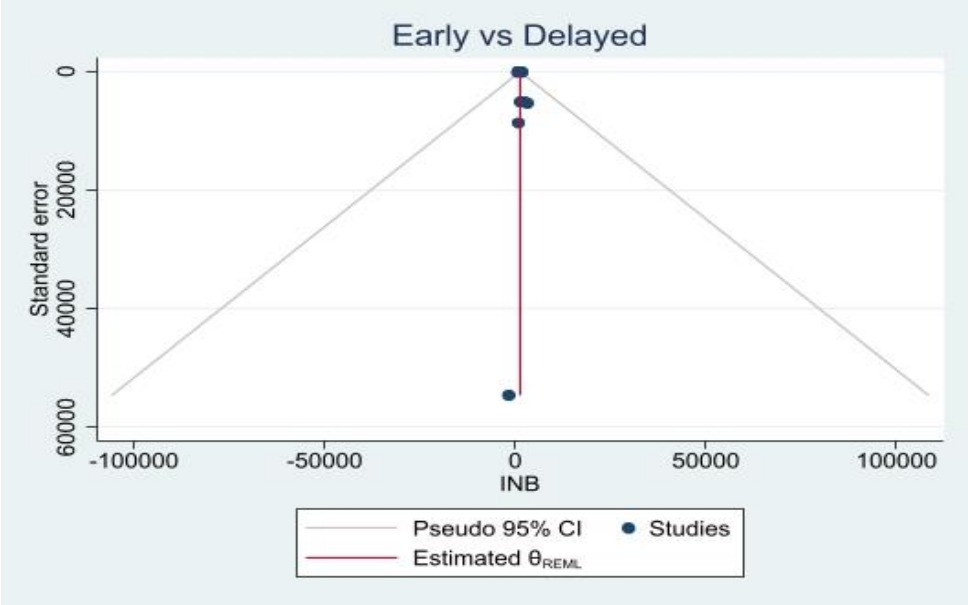



**Figure 3.1.3 Funnel plot to distinguish publication bias**

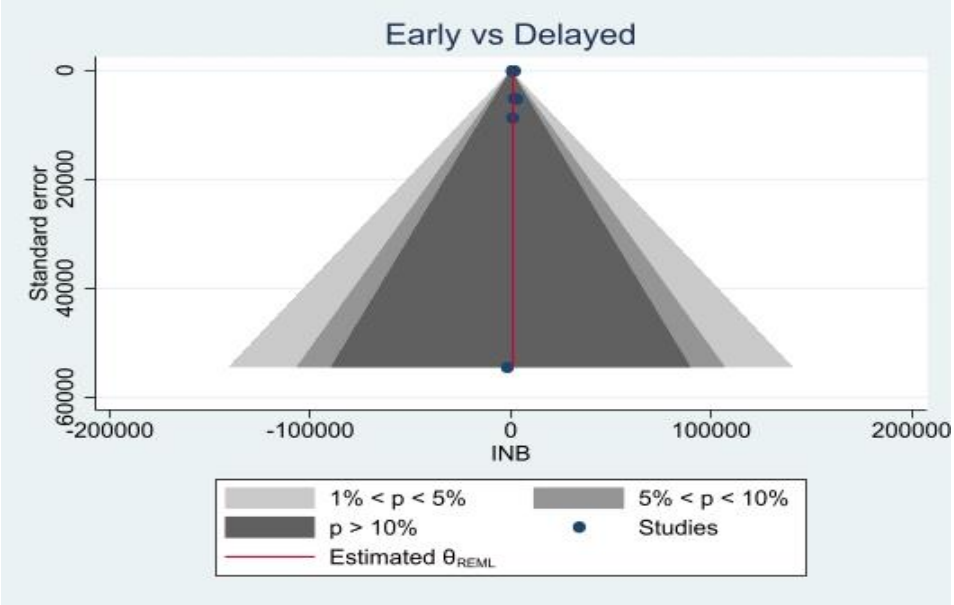



**Figure 3.1.4 Contour-enhanced funnel plot to distinguish publication bias**

Subgroup analysis of the time horizon used for the study also indicates that ELC was significantly cost-effective compared with DLC for one year and five-year time frames. The pooled INBs of studies with one-year and five-year time horizon with 95% CI values was $1,797 (1,441 to 2,154) and $583 (227 to 940), respectively (Figure 3.1.5). In addition, six out of the seven selected studies for meta-analysis were model-based studies, and the sensitivity analysis of these six studies also supports the Intervention (ELC) with a pooled INBs of $1,223 (161 to 2 285) (Figure 3.1.6).

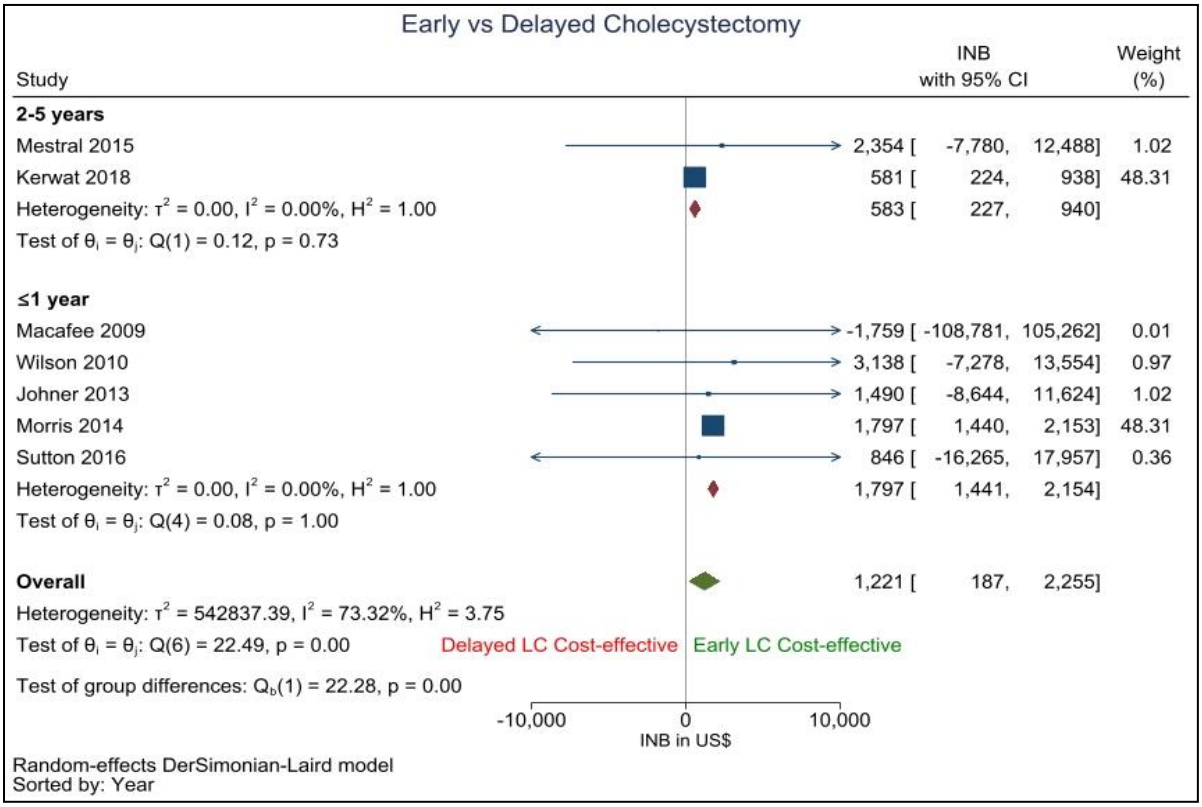



**Figure 3.1.5 Subgroup analysis of pooled INBs based on different Time horizon**

Country-wise pooled INB statistic from the subgroup analysis revealed that intervention was not cost-effective in Canada [$1,922 (-5,244 to 9,088)], and there was no heterogeneity between these studies ($I^2$ =0). Conversely, ELC was cost-effective in the UK with a positive pooled INB of $1,209 (106 to 2,311) but with substantial heterogeneity ($I^2$ = 82.17%) (fig 3.1.8). The study by Sutton, 2017 has examined cholecystectomy outcomes in both the UK and Ireland. However, to make a sufficient capacity to be pooled for INBs, we considered the country UK only in subgroup analysis.

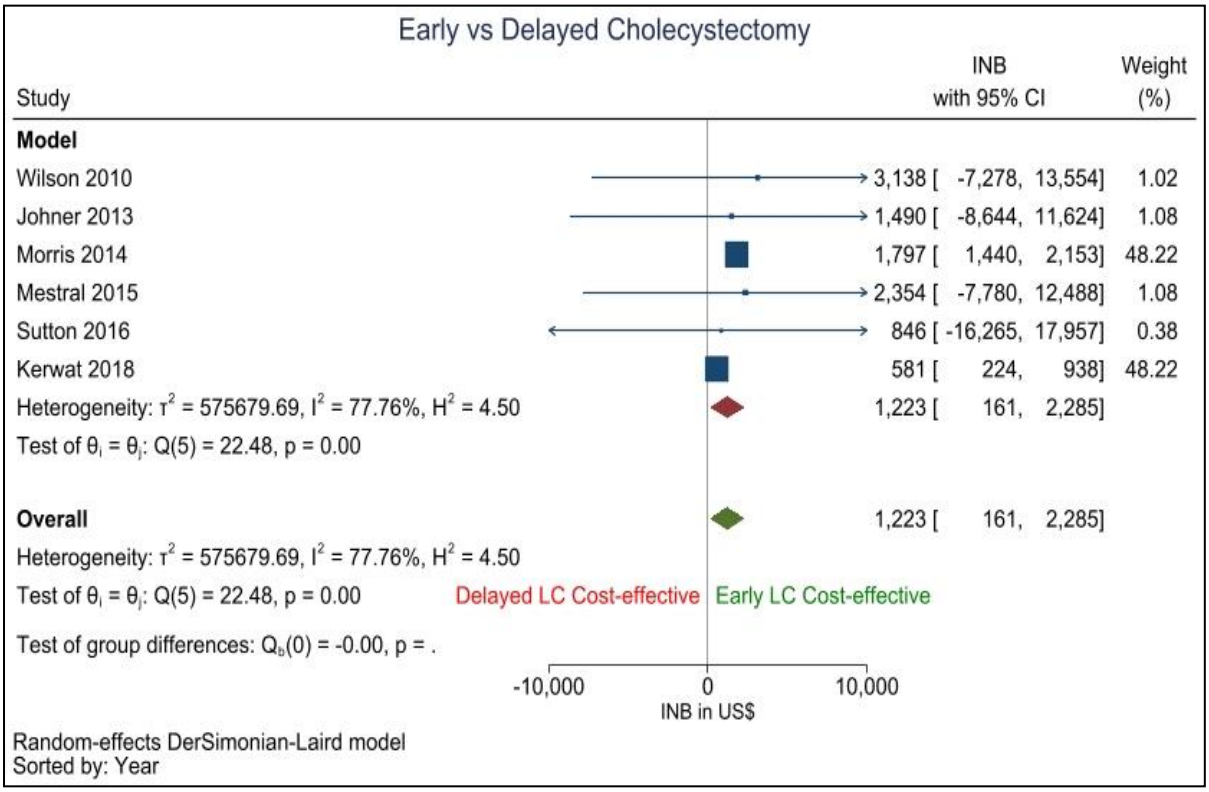



**Figure 3.1.6 Sensitivity analysis of Pooled INBs based on Analytical Design of the study**

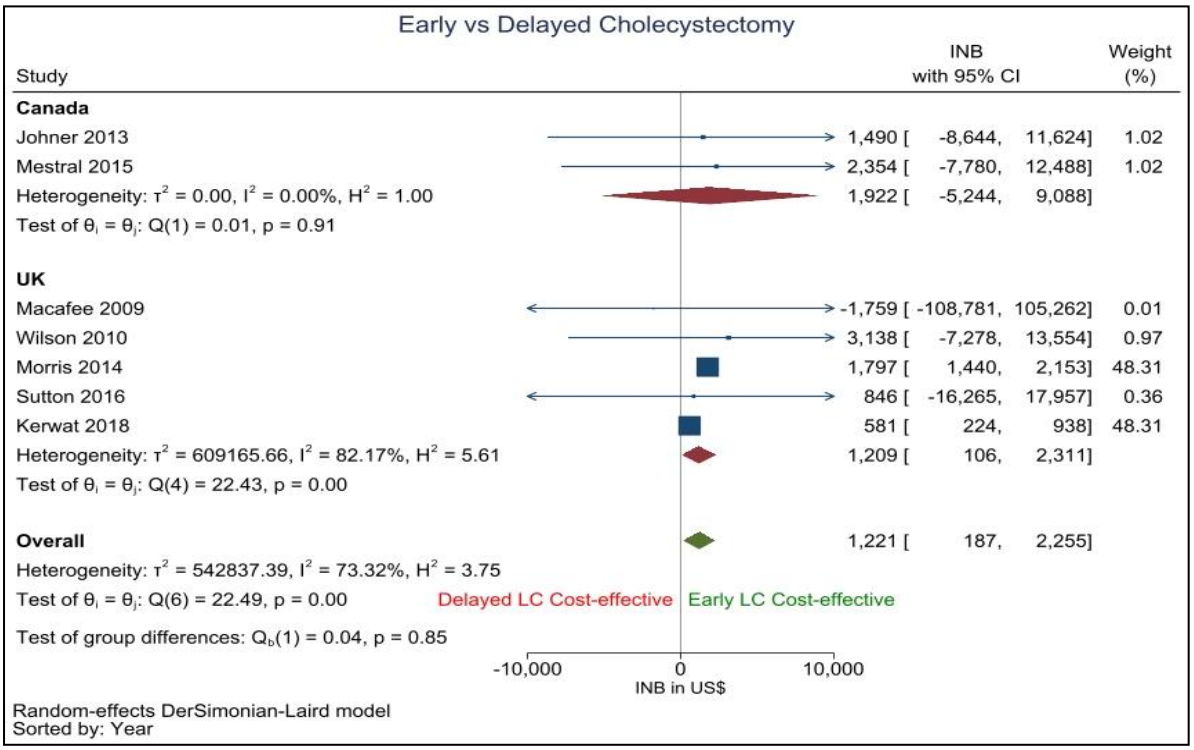



**Figure 3.1.7 Forest plot for subgroup analysis of country wise Pooled INBs**

All the selected studies except Macafee, 2009 followed the payer's perspective. The pooled INB values from the sensitivity analysis of all these studies, excluding the societal perspective (Macafee, 2009) with a 95% CI, was $1 221 (161 to 2,285) (Figure 3.1.8), also depicts that ELC was dominant over DLC.

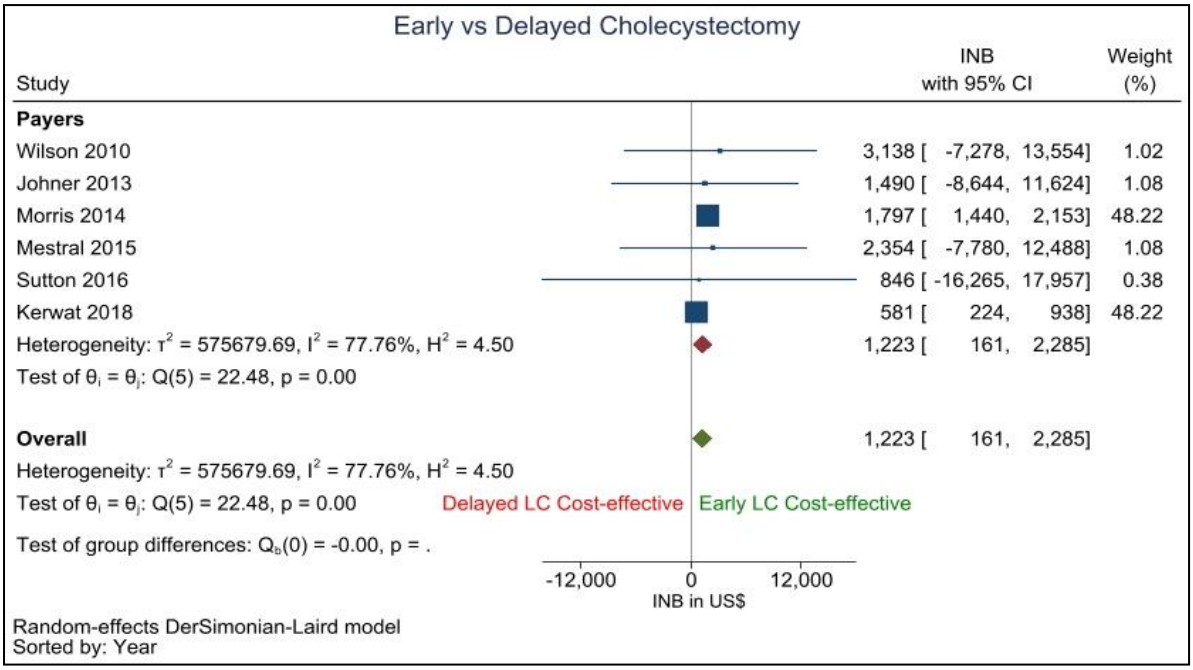



**Figure 3.1.8 Sensitivity analysis of Pooled INBs based on study perspective**

### 3.1.4 Discussion

We conducted a systematic review and meta-analysis of various treatment options for gallstone diseases. On meta-analysis of cost-effective evidences, the ELC was significantly cost-effective than DLC. Subgroup, as well as sensitivity analysis, strengthened the robustness of this finding. However, limited studies across different settings and lifetime horizon warrant the need for primary economic evaluation studies to fill the knowledge gap.

The subgroup analysis revealed that ELC was cost-effective compared to DLC from the payer’s perspective. However, only one study reported non-cost effectiveness from a societal

perspective, thus postulating unpredictability in the overall cost-effectiveness of the ELC with societal perspectives. Similarly, ELC was cost-effective in studies from Canada but not from the UK; both are high-income countries (HICs) also point out the high heterogeneity across available studies. Also, studies are limited in terms of different economies, mainly from LMICs, societal perspectives, and over a longer time horizon.

Many retrospectives [167, 168] and prospective studies [169] reported ELC as the best treatment of choice for patients with acute cholecystitis. Updated Tokyo guidelines made ELC mandatory for patients with mild cholecystitis and DLC for moderate or severe cholecystitis patients [170]. Overlapping meta-analysis had reported discordant results and conclusions. A systematic review of meta-analyses by Song et al. (2016) suggested ELC as the standard treatment option and indicated a non-significant difference in mortality and complications, with a significant reduction in hospitalisation and improvement of the quality of life when comparing with DLC [171]. Recent meta-analyses also suggested ELC as safe and effective against DLC for acute cholecystitis within seven days from the presentation [43]. ELC should be preferred to DLC when feasible within 72 hours of the onset of symptoms [172]. World Society of Emergency Surgery (WSES) Guidelines in 2020 suggested ELC as the standard of care whenever possible [173].

Previous RCTs had reported quality improvements and cost savings through the same-day surgery (ELC) over a pre-operative admission [152, 133]. Model-based CUAs have reported ELC as the optimal management for uncomplicated gallstones and less expensive and with more significant QALY gains than DLC or watchful waiting [135, 149, 138]. However, reported studies are mostly incongruous and clustered around the specific geography- HICs. Further, it depends on the different study conditions and perspectives. Some studies have reported conflicting results primarily because of different analytical perspectives or different

healthcare contexts [174]. Although early detection and treatment is clinically an effective strategy, synthesized economic evidence was limited. The present meta-analysis of cost-effectiveness evidence fills the knowledge gap in this regard.

The majority of the studies included in the analysis reported ELC as cost-effective and superior to DLC except for two [158, 155]. Full economic evaluation studies in people with gallstones or cholecystitis assessing the cost-utility effectiveness of cholecystectomy compared with other managements, especially conservative management, were largely limited.

Our study has several limitations. Most of the selected studies were from HIC, either UK or Canada, limiting the extension of results to other countries, especially the (Lower middle-income countries) LMIC. We had only one study with a societal perspective, and studies with indirect cost would provide a real-world comparison scenario. Hence, synthesized findings have limited generalisability while extrapolating the results to all the other health care contexts. The inadequacy of similar studies to be pooled for the INB values for intervention and comparators only permitted us, with seven studies, to perform the meta-analysis. Lack of peer-reviewed published literature curtailed the idea of meta-analysis with the conservative gallstone disease management.

### 3.1.5 Conclusion

The synthesised results showed that ELC as a cost-effective option compared to DLC. There is a need to generate comparative economic evidences between surgical and conservative management as well as other aspects of gallstone disease management, such as endoscopic approaches as well as diagnostic aspects.

## 3.2 COST MINIMISATION ANALYSIS OF GALL STONES MANAGEMENT-SYSTEMATIC REVIEW

### 3.2.1 Introduction

Gallbladder diseases are costly, costing healthcare systems throughout the world roughly 6.5 billion dollars every year [10]. The availability of competing technology and techniques for diagnosing and treating gallstones are manifold. Different procedures are used to treat common bile duct stones (CBDs; however, the best treatment depends on the patient's satisfaction, the quantity and size of stones, and the surgeon's laparoscopic experience[175]. The most crucial issue to answer for treating CBD stones is the appropriate treatment modality under the given circumstances [175]. Cost-minimization analysis explains the determination of the least costly interventions among alternatives with demonstrably equivalent clinical effectiveness. However, there was limited evidence on cost-minimization analysis of gall stone management in the literature. [176-179]. Therefore, this study systematically examines the cost of cholecystitis or cholelithiasis treatment to determine which treatment is the least expensive among alternative approaches.

### 3.2.2 Methods

We followed the preferred reporting items for systematic review and meta-analysis (PRISMA) protocol, and the protocol was registered at PROSPERO CRD42020194052.

**Data Sources, Screening, and Study Selection**

The systematic search was performed using the PICO approach (population, intervention, comparator, outcome) to construct the search words. The chosen population were individuals aged >18 years diagnosed with Cholelithiasis or Cholecystitis. All surgical or conservative management of gall stones or cholecystitis were included. The comparison can be any alternative management with (within) the above intervention. The possible economic outcome

is cost reported from cost minimisation analysis. The detailed search terms and search strategies were reported in Appendix Table 3.1.1. The details on screening and study selection refer to section 3.1.2. The data were extracted from the selected articles using a data extraction form. The data were extracted on the following domains; characteristics of the studied population, sample size, country of origin of those studies, economic model input parameters (Study perspective, time horizon, currency), and details of intervention and comparator with their cost for pooling domain. The data for the pooling domain shows the details of both measures of central tendency and dispersion data for total costs. All the data pooling work has been prepared using Microsoft Excel version 2019. The quality (risk of bias) of selected studies were assessed using the CHEERS checklist [180]

### 3.2.3 RESULTS

We retrieved 8,709 potentially relevant studies, out of which three studies were eligible for the systematic review, as shown in the PRISMA flow diagram (Figure 3.1.2, Table 3.2.1). Of the identified studies, one was a multi-centre study while the others were single-centre studies. [178]. Two studies were model-based (clinical decision), and one study was done alongside RCT. All studies adopted the societal perspective. Three studies [181, 177, 176] compared laparoscopic cholecystectomy (LC), open cholecystectomy (OC), small-incision cholecystectomy (SIC), and Mini lap cholecystectomy (MC). LC reported $424,235, MC and OC reported ($631,449, $896,569) proved LC is saving the cost [181]. Similar result was found in [176] [177]. In contrast, when cost of LC is compared with SILC, from both a hospital and societal perspective, small-incision cholecystectomy appears to be the preferred operational approach over laparoscopic cholecystectomy [176].

**Risk of bias assessment:**

According to the CHEERS checklist, the best current practice was selected to compare most of the research. All of the comparators were adequately explained. The studies also included a clear presentation of the data employed in the model, sufficient cost detail, and external disclosure of the financing received. Because all of the studies were designed to find the least expensive management in terms of money, there was no bias linked to quality-of-life weights (utilities) in any of them. Because most of the research did not employ a time horizon, there was much bias. Practically in all studies, limited scope bias is more likely.

**Table-3.2.1 Characteristics of the study**

| Author, Year | Country | Setting | Study perspective | Target population | Intervention | Comparator | Findings | Remarks |
|---|---|---|---|---|---|---|---|---|
| HH Bailey 2005 | West Indies | Hospital | Hospital, Societal | Gall stones CBD stones | LC | OC, MC | LC = $424,235 MC= $631,449 OC = $896,569 | LC is cost savings |
| Ulf Berggren 1996 | Sweden | Hospital | Societal | Gall stone | LC | OC, open choledocho lithectomy. | LC = 3,671 SEK OCL= 4,767 SEK OC= 4,388 SEK | LC is cost savings |
| Frederik Keus 2009 | Netherland | Hospital | Hospital, Societal | Symptomatic cholecystolithiasis | LC | SIC | LC = 439,463 £ SIC = 400,404 £ | SIC is cost savings |

### 3.2.4 DISCUSSION

We conducted a systematic review of CMA studies with various available managements for gall stone disease. Considering similar effectiveness of existing interventions for gallstone, evidence-based recommendations of the least expensive and cost-saving interventions are vital. The available individual studies report that LC is a safe and effective treatment for acute cholecystitis. Percutaneous cholecystostomy followed by LC (PCLC) was safer and less expensive in patients with underlying comorbidities [16]. From the societal and hospital perspective, LC and MC were expended similar costs. In terms of the number of hospital days, LC will prove a cost-cutting technique for hospitals. This study has several limitations. Most selected studies were from high-income countries (HIC), either Europe or the USA, limiting study findings to other countries. We synthesised only three studies; which compared surgical interventions; the lack of peer-reviewed published literature curtailed the idea of meta-analysis with gallstone disease management. For some patients, the surgical risk-benefit profile may favour non-surgical or conservative treatment [23]. However, there is a lack of evidence to support.

### 3.2.5 CONCLUSION

Since only three primary studies, more quality cost minisation studies are essential to arrive at any valid conclusion.

## 3.3 SYSTEMATIC REVIEW OF COSTING STUDIES IN GALLSTONE DISEASE

### 3.3.1 Introduction

Cholecystectomy is the standard treatment for symptomatic gallstones [182]. Since the natural history of silent gallstones is not very well documented, a conclusive treatment regimen for such patients is often not recommended [182]. A nationwide survey of persons aged 65 to 79 years found that they underwent more open surgical procedures, thus incurring higher costs [183]. Studies have shown that LC reduces morbidity and hospital costs against the conservative approach [63]. Furthermore, laparoscopic cholecystectomy (LC) is cost-effective than open cholecystectomy (OC) and increases the patients' quality of life (QOL) [184]. Economic evaluations and RCTs conducted in different geographical areas recommend early laparoscopic cholecystectomy (ELC), which reduces hospital stays and costs [185] and is less expensive with potential cost savings compared with delayed laparoscopic cholecystectomy (DLC) [186, 138]. Regardless of varying patient charges for surgery across countries, e.g., the USA, the patient cost is twice that of Canada for gallstone treatment [187].

The few attempts drawn on the systematic research for the cost-effectiveness of gall stone management [188-195] recommend different management [196, 147], which can lead to complex decision-making. No studies have systemically reviewed the costs of surgical management for cholelithiasis. We systematically reviewed the reported costs of definitive management (surgical treatments) of cholecystitis or cholelithiasis. This review would identify the primary sources of costs in the management of gallstone disease.

### 3.3.2 Methods

We conducted a systematic published literature search in PubMed, Scopus, and Embase databases. We followed the preferred reporting items for systematic review and meta-analysis protocol and was registered the protocol at PROSPERO (CRD42020194052).

#### 3.3.2.1 Selection criteria

The popular PICO approach (population, intervention, comparator, and outcome) was employed to construct the search words. The PICO criteria followed are,

**Population (P)** - Individuals aged >18 years diagnosed with cholelithiasis or Cholecystitis.

**Intervention (I)** - Surgical management of gall stones or cholecystitis, including but not limited to Cholecystectomy - Open Cholecystectomy, Laparoscopic Cholecystectomy, Single Incision cholecystectomy, Mini laparoscopic cholecystectomy, Mini-laparotomy Cholecystectomy, Robotic Surgery.

Comparator(s)/control (C) – Any comparator

**Outcome (O)** - The measures of cost related to cholecystectomy. Cost estimates included unit costs and assumptions used to estimate those costs and/or total costs for implementing the intervention(s).

#### 3.3.2.2 Search of publications

We searched the following electronic databases on 1st July 2020 in PubMed, Embase, and Scopus. We used both controlled vocabulary and text words for synonyms terminology with titles and abstracts to develop search strategies. The search strategy contained the following

three concepts, “Gall stones,” “management,” “cost,” linked with the AND operator (Appendix table- 3.2.1). The total number of studies identified from the three databases were 8,710, including 2,977 from PubMed, 3696 from Scopus, and 2037 from Embase. After removing the duplicates (n=1,414), 7295 studies were selected for an initial title and abstract screening. The searches were restricted to studies conducted in humans. All the citations found through searching the databases were uploaded to Rayyan software, a cloud-based platform for screening citations data [45].

#### 3.3.2.3 Screening and selection of study articles

Based on the inclusion and exclusion criteria, two reviewers independently screened methodically all titles and abstracts of the studies listed from the three electronic databases. If agreement cannot be reached on including an article in the full-text screening, a third reviewer was consulted, and a consensus was reached. Once the title and abstract screening stage are complete, two reviewers obtained and screened the full texts of all potentially eligible papers, and decisions were made on whether they should be included or excluded. After identifying the eligible studies, the reference lists of the included papers were screened by the two reviewers for additional studies that meet the inclusion criteria. The final list of studies was prepared on reviewers’ mutual consensus (Figure 3.3.1).

#### 3.3.2.4 Criteria for selection of articles

We included an article in this systematic review if it fulfilled the following inclusion criteria; If the study reported costs related to gall stones management and the included study population comprised individuals aged 18 or above with cholelithiasis/cholecystitis. We included all articles published in English or translatable to English from peer-reviewed journals. We

excluded an article from the systematic review if it came under any of the Exclusion criteria; if the patients were undergoing any other surgery along with gall stone management. We also excluded duplicates, reviews, letters, editorials, perspectives, abstracts, and methodological articles.

#### 3.3.2.5 Data extraction & Management

We extracted the data from the finally selected articles using a predesigned data extraction form. Two reviewers independently extracted data on the following domains; characteristics of the studied population, sample size, country of origin of those studies, economic model input parameters (Study perspective, time horizon, currency), and details of intervention with their cost for pooling domain. We captured the details of measures of central tendency and measures of dispersion [i.e., standard deviation (SD), standard error (SE), or 95% confidence interval (CI)] for various costs parameters such as surgical cost, inpatient care, operating room cost, instrument/equipment, cost of the procedure, anaesthesia, X-ray/radiology, lab investigation, pathology, medical supplies, drugs, outpatient care, inpatient care, Overhead cost and staffs cost. Similarly, direct non-medical cost and indirect cost with any measures of dispersion were extracted. All the data capturing and preparation were done using Microsoft Excel 2019.

We extracted all the reported costs, including direct medical, direct non-medical, indirect, and fixed and variable costs related to gall stone management across studies conducted in different years and countries. We extracted the mean, standard deviation, median and interquartile ranges or the range of the reported cost. The median and IQR or range has been converted to mean using Luo et al. [197] and standard deviation based on the Shi et al. [198]. To ensure cost comparability among the included articles, we adjusted the costs to PPP-adjusted 2019 US

dollars. As per IMF data, the reported costs were adjusted to 2019 costs using a country-specific consumer price index, then to PPP-adjusted US dollars.

#### 3.3.2.6 Risk of Bias (Quality) Assessment

The quality of the selected publications was assessed using the NIH quality assessment tool for the cohort study, case-control, and cross-sectional studies; ROB-2 was used for RCTs [199] [46] (Appendix 3.3.1).

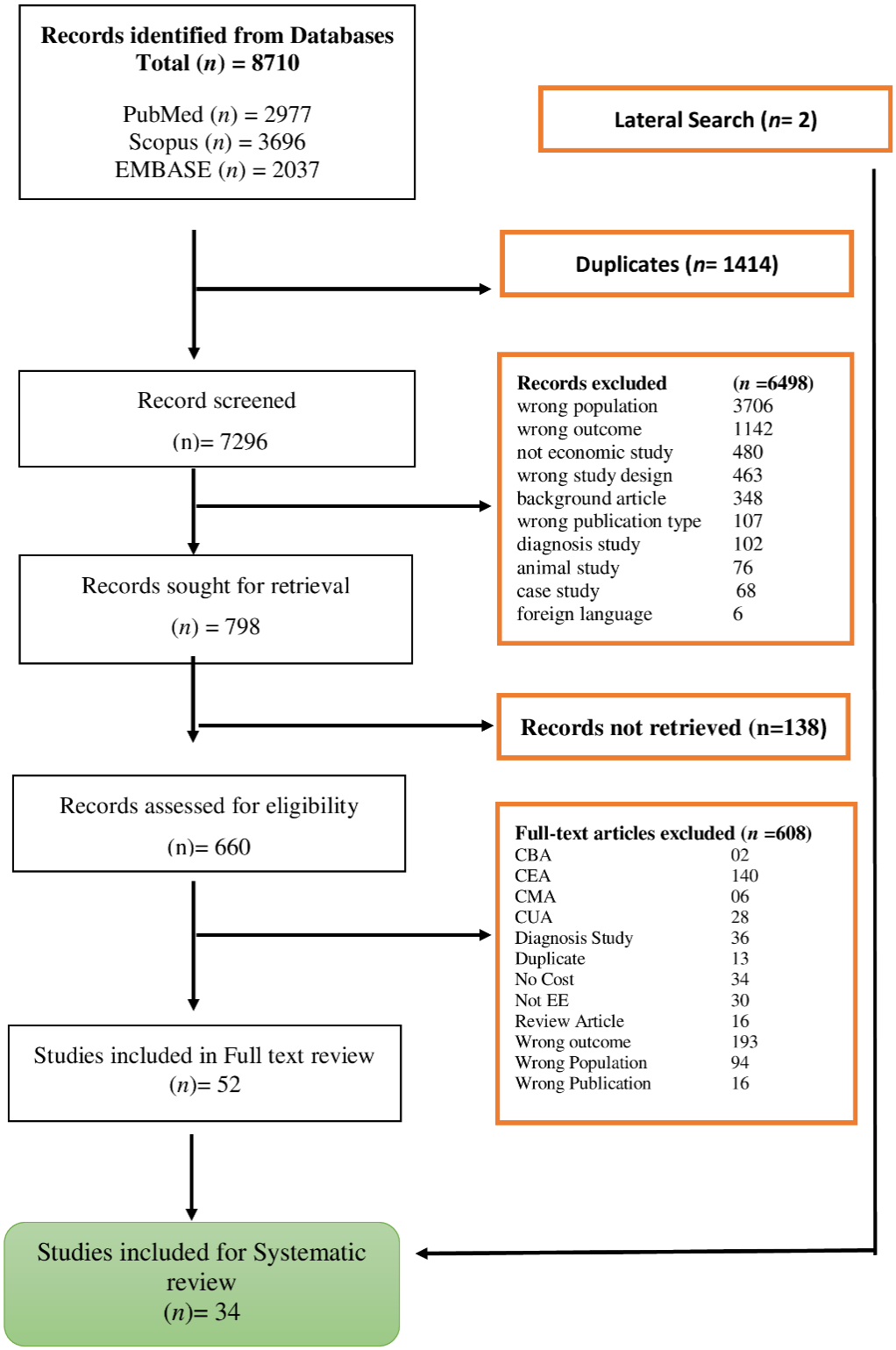



**Figure 3.3.1 Prisma diagram of study selection**

### 3.3.3 Results

#### 3.3.3.1 Characteristics of the included articles

We retrieved 8,710 articles through initial searches from the databases. We included 34 articles for the systematic review, as shown in the PRISMA flow diagram (Figure 3.3.1). Most of the included articles reported a higher number of females. The sample size among the included studies ranged from 11 to 518,665. Among the 34 identified costing studies, most of the studies (N=24) analysed the cost of LC and, N=7 studies analysed the cost of the OC. Almost all the studies analysed the cost from the payers, health care provider, or a third-party payer's perspective; one study each, reported a patient perspective and societal perspective.

Variable costs are reported in the included studies under the following categories: operating room (OR), supplies, anaesthesiology, drugs, radiology, and laboratory costs. The Fixed costs reported included fixed salaries and hospital infrastructure, i.e., buildings, machines, robots, non-disposable instruments, and other non-disposable hospital property. Fixed costs did not differ from one procedure to another in the same hospital setting. Direct medical costs reported included the total cost of hospitalisation, including the hospital cost, operation costs, and related medical costs. Direct non-medical costs reported included travel expenses and the cost of food and accommodation. Loss of income by patients and caregivers commensurate the majority of the indirect cost. The included studies and the collected reported costs are shown in Table 3.3.1. Out of the included studies, only eleven were assessed as good quality, as shown in Appendix Table- 3.3.1.

#### 3.3.3.2 Cost analysis of cholecystectomy

The cost of cholecystectomy for inpatients reported varied significantly across the studies (N=8), from as low as $1,017 reported from India [200] to as high as $24,755 [201] reported from Medicare inpatient claims in the USA. The lowest cost reported for a cholecystectomy is 112$ from Vietnam [202] from a patient's perspective for outpatients. Gender-based differences in the management of cholecystitis have been reported with higher costs among men at $17,283 compared to women at $13,820 [203]. If the patients had comorbidity, cholecystectomy may get complicated and necessitate extended hospital stays, leading to higher costs [31] [32], implying that indirect cost magnifies the difference between the operations.[204] Bile duct injury (BDI) is an uncommon but significant complication of cholecystectomy, which increases the hospital costs and length of stay; a study reported $26,409 per inpatient and $5,327 for outpatients with BDI compared to $1,017 without BDI [200]. Readmission costs were reported at $937 for each episode of readmission, nearly the same as the cost of open cholecystectomy (OC) reported in the same study [205].

#### 3.3.3.3 Cost analysis of laparoscopic management

LC quickly emerged as an alternative to OC [206] in patients with acute cholelithiasis [207]. All the studies reported the cost of LC (N=26) except [204, 208], which included only direct medical costs in their analyses. Majority of the studies which reported the cost of LC are from higher-income countries (HIC), especially from the United States, which suggests a lacuna of evidence from LMIC or UMC. The lowest cost for LC was from India, which compared the cost for ELC and DLC, reported $414, and $962 for ELC and DLC, respectively. The higher difference in cost has been contributed by the cost of conservative and operative treatment

included in DLC [209]. The reported cost did not specify whether it included direct non-medical or indirect costs. Bieder et al. [210] reported the cost of LC as $1,948 ± 428 in the USA, which is the lowest reported cost from any HIC. However, the study has included only variable costs and did not consider the fixed costs such as salaries, hospital infrastructure and instrumental costs.

Interestingly, the highest cost for LC was reported from the USA by Beck et al. [211], estimated at $19,711 ± 4644. However, the cost of LC reported from the societal perspective was much lower ($7082) [212]. The cost of conversion from LC to OC was reported at $12,420 [207] in the USA. Hospital price estimates [213] from 22 hospitals across the USA reported that the cost of LC varied from $20,445 ± 33,198 to $21,648 ± 32,538. It is noteworthy that the highest price estimate reported from the study was almost twice the Medicare reimbursement in the USA during the year of reporting. Fleisher et al. reported the cost of outpatient LC as $3,542, which is lower than the LC costs reported across the literature [214]. An RCT of day-care versus overnight stay reported that the mean direct medical cost per patient in the day-care group ($6,382) was lower than that in the overnight group ($7020.74) [215]. LMICs and MICs, including Asian countries such as India, Pakistan, and China, reported lower costs than the HIC's [205, 216-219, 209]. Traverso et al. reported that 60% of the hospital costs occurred in the operation room. Disposable laparoscopic equipment accounted for 17% of the total hospital costs and 28% of the OR costs. [220]. Healthcare institutions' financial costs due to readmissions in patients waiting for gall bladder disease surgery is very high; hence, early laparoscopic cholecystectomy plays a crucial role in minimising the cost [205].

#### 3.3.3.4 Cost analysis of Open Cholecystectomy

Cost for OC was reported by seven studies. The lowest reported cost for OC was $957.2 from Pakistan [205]. Reported cost for OC varies across HICs; a study from Canada reported $4,051, while a higher cost of $9,817 ± 972 was reported from the USA [174].

#### 3.3.3.5 Cost analysis of Single Incision Laparoscopic Surgery (SILC)

The cost of a SILC was reported as $2,214 in the UK [221]. The cost of SILC reported is higher than the cost of LC; both highest ($20,537 ± 11,194) [211] and the lowest cost, $16,950 ± 619, were reported by studies from the USA [222]. A significant difference among the cost variables also was found when SILCs were converted to LCs. The cost of converting SILC to LC was higher at $20,580 ± 1,589, as reported by Love et al. [222]

#### 3.3.3.6 Cost analysis of Mini-laparoscopic Surgery (MLC)

MLC is a newer procedure that can be routinely used for elective cholecystectomy and decreases the overall cost. The mean cost for an MLC procedure was reported as $2,497 ± 2,636 without considering the cost of mini-laparoscopic instruments [208].

#### 3.3.3.7 Cost analysis of Robotic surgery

The reported cost of robotic surgery is much lower than the cost of LC for a hospital that already has the necessary infrastructure for robotic surgery, with the lowest reported cost at $1,448 ± 187 from the USA [210]. The lower cost was mainly driven by cutting down on supplies and, to a lesser extent, of operation room time primarily because the patients were outpatients. The highest procedure cost for robotic surgery was $10,861 ± 84, reported from

Pakistan [223]. The total cost of installation of the robotic platform was not considered in either of these studies. However, the annual maintenance charges were included in the latter

**Table 3.3.1 Included Studies and reported costs**

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| Dua,2013 | 2005 | USA | Country | Retrospective cross-sectional analysis | | Chole | 15,023.51 | NR | NR | NR | NR |
| Stey,2015 | 2013 | USA | Hospital | Retrospective analysis | >65 | Chole | 24,755.00 | NR | NR | NR | NR |
| Tran,2019 (a) | 2017 | Vietnam | Patients | cross sectional | | Chole | 992.38±698.35 | 151.65±206.71 | NR | 124±110.24 | 1,258.85±781.12 |
| Tran,2019 (b) | 2017 | Vietnam | Patients | cross sectional | | Chole - Outpatient | 60.18±99.71 | 21.59±29.41 | NR | 13.77±18.36 | 94±112.12 |
| George,2020 | 2015 | USA | Health care provider | Retrospective analysis | 49.00± 18.88 | Chole | 12,467±14,660.51 | NR | NR | NR | NR |
| Board.2000 | 1996 | Australia | Health care provider | Sequential controlled trial, prospectively before and after | | Chole | 7,515.12 | NR | NR | NR | NR |
| Kuy,2011 (a) | 2006 | USA | Health care provider | Retrospective cross-sectional analysis | 56.7±4.3 | Chole | 14,808.27 | NR | NR | NR | NR |
| Kuy,2011 (b) | 2006 | USA | Health care provider | Retrospective cross-sectional analysis | 7.31.9 ±4 | Chole | 17,728.07 | NR | NR | NR | NR |
| Kuy,2011 (c) | 2006 | USA | Health | Retrospective | 84.5±3 | Chole | 21,611.83 | NR | NR | NR | NR |

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| | | | care provider | cross-sectional analysis | .8 | | | | | | |
| Obrien,2019 (a) | 2018 | USA | Health care provider | Retrospective, observational study | 55.7±18.2 | Chole | 13,474.82 | NR | NR | NR | NR |
| Obrien,2019 (b) | 2018 | USA | Health care provider | Retrospective, observational study | | Chole-Outpatient | 4,716.95 | NR | NR | NR | NR |
| Kapoor,2011 | 2007 | India | | Retrospective review | 45.12±36.70 | Chole | 1,016.69 | NR | NR | NR | NR |
| Waqas,2014 | 2012 | Pakistan | Hospital | Multi-centre prospective descriptive survey | 43±8.8 | OC | 957.12 | NR | NR | NR | NR |
| Hsu,2010 (a) | 2004 | China | Health care provider | Retrospective review | 62.59±14.88 | OC | 3,693.11±2169.26 | NR | NR | NR | NR |
| Demco,1997 (a) | 1993 | Canada | Health care provider | Retrospective review | | OC | 4,050.46 | NR | NR | NR | NR |
| Demco,1997 (b) | 1993 | USA | Health care provider | Retrospective review | | OC | 7,404.89 | NR | NR | NR | NR |
| Anderson,1991 (a) | 1990 | USA | Health care provider | Prospective study | 37±5.4 | OC | 9,816.65±972.20 | NR | NR | NR | NR |
| Hardy,1994 | 1991 | Austr | Health | observational | 50.5±0 | OC | NR | NR | 4,851 | 3,008.47 | 7,860.24 |

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| (a) | | alia | care provider | study | .10 | | | | .77 | | |
| Jones,2011 (b) | 2009 | UK | Health care provider | Retrospective review | | OC | 7,110.78 | NR | NR | NR | NR |
| Peters,1990 (b) | 1988 | USA | | Prospective cohort | | OC | 9,188.52±2,135.56 | NR | NR | NR | NR |
| Beck,2013 (a) | 2012 | USA | Health care provider | Retrospective review | | SILC | 20,536.81±1,1194 | NR | NR | NR | NR |
| Love,2011 (a) | 2010 | USA | Health care provider | Retrospective review | | SILC | 16,950.32±618.98 | NR | NR | NR | NR |
| Beck,2013 (b) | 2012 | USA | Health care provider | Retrospective review | | MILC | 19,710.94±4,6440.02 | NR | NR | NR | NR |
| Calvert,2000 (b) | 1998 | UK | providers perspective | Retrospective analysis, results from RCT | | Mini LC | 2,213.60 | NR | NR | NR | NR |
| Bedeir,2015 (a) | 2014 | USA | Health care provider | Retrospective review | | RSSC - Outpatient | 1,447.46±186.79 | NR | NR | NR | NR |
| Ghanzanfar,2019 | 2011 | Pakistan | Public sector | Retrospective review | 42.1±13.4 | RRSC | NR | NR | NR | NR | 10,861.44±83.95 |
| Ure,1995 | 1992 | Germ | Societal | Prospective | 51.67± | LC | 3,329.21 | 1,420.60 | 4,649 | 2,432.34 | 7,082.15 |

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| | | any | | study | 11.67 | | | | .81 | | |
| Hsu,2010 (b) | 2004 | China | Health care provider | Retrospective analysis | 53.14± 15.18 | LC | 2,148±556.70 | NR | NR | NR | NR |
| Menezes,2016 | 2014 | Brazil | Health care provider | Retrospective review | 39.15± 12.16 | LC | 3,611.81±1072.21 | NR | NR | NR | NR |
| Prigoff,2016 | 2014 | USA | Third party payer | Prospective study | 53.19 | LC | 15,468.08 | NR | NR | NR | NR |
| Hardy,1994 (b) | 1991 | Australia | Health care provider | observational study | 43±0.10 | LC | NR | NR | 3,754.69 | 2,327.70 | 6,082.39 |
| Bedeir,2015 (b) | 2014 | USA | Health care provider | Retrospective review | | LC - Outpatient | 1,948.31±427.51 | NR | NR | NR | NR |
| Love,2011 (b) | 2010 | USA | Health care provider | Retrospective review | | LC | 18,067.52±1,283.67 | NR | NR | NR | NR |
| Koo,1996 | 1995 | USA | Health care provider | Retrospective review | 51±16.5 | LC | 6,512.78 | NR | NR | NR | NR |
| Traverso,1995 | 1994 | USA | Health care provider | Retrospective review | | LC | 4,294.63±1,431.54 | NR | NR | NR | NR |
| Demco,1997 (c) | 1993 | Canada | Health care | Retrospective review | | LC | 2,587.34 | NR | NR | NR | NR |

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| | | | provider | | | | | | | | |
| Demco,1997 (d) | 1993 | USA | Health care provider | Retrospective review | | LC | 5,347.78 | NR | NR | NR | NR |
| Fleisher,1999 (a) | 1995 | USA | providers perspective | Open-label observational trial | 46±13 | LC | 7,110.04 | NR | NR | NR | NR |
| Fleisher,1999 (b) | 1995 | USA | providers perspective | Open-label observational trial | 46±13 | LC-outpatient | 3,541.60 | NR | NR | NR | NR |
| Johansson,2006 (a) | 2004 | Sweden | Health care provider | RCT | | LC-day care | 6,381.55 | NR | NR | NR | NR |
| Johansson,2006 (b) | 2004 | Sweden | Health care provider | RCT | | LC-overnight | 7,020.74 | NR | NR | NR | NR |
| Calvert,2000 (a) | 1998 | UK | providers perspective | Retrospective analysis, results single blind prospective RCT | | LC | 3,107.94 | NR | NR | NR | NR |
| Anderson,1991 (b) | 1990 | USA | Health care provider | Retrospective review | 45±4.4 | LC | 7,964.14±580.89 | NR | NR | NR | NR |
| Orlando,1996 | 1993 | USA | Health | Retrospective | | | 5,245.74 | NR | NR | NR | NR |

| First author, year | Year of costing | Country | Study perspective | Analytical approach | Mean age | Surgical Procedure | Cost $ * | | | | Total cost $ * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | DMC | DNMC | DC | IDC | |
| | | | care provider | review | | | | | | | |
| Chatterjee,2015 | 2011 | India | Health care provider | Retrospective review | | LC | 2,038.40 | NR | NR | NR | NR |
| Bhargava,2016 (a) | 2016 | India | Health care provider | Prospective and randomized study | 42.4 | LC-DLC | NR | NR | NR | NR | 961.63 |
| Bhargava,2016 (b) | 2016 | India | Health care provider | Prospective and randomized study | 43.1 | LC-ELC | NR | NR | NR | NR | 413.57 |
| Jones,2011 (a) | 2009 | UK | Health care provider | Retrospective review | 45.3±15.1 | LC | 4,910.61 | NR | NR | NR | NR |
| Peters,1990 (a) | 1990 | USA | | Prospective analysis | | LC. | 7,083.05±1,966.43 | NR | NR | NR | NR |

*CPI converted cost in US $ NR- Not reported, Chole-cholecystectomy

### 3.3.4 Discussion

The cost of cholecystectomy for inpatients reported varied significantly across the studies, based on perspective, gender, preexisting comorbidity, and complication occurrence. Readmission and conversion to OC and waiting for surgery were among the major cause of increased costs in LC surgeries. The reported cost varies based on the country's economy, with HIC reporting a higher cost for all surgical procedures, whereas the LMIC reported a reduced cost for the same procedures. OC is costlier than LC, and among LC, ELC is less costly than DLC. Outpatient LC is less costly than the inpatient LC, and the newer procedures, SILC and MILC, incur a higher cost than the traditional LC. The reported cost of robotic surgery is for outpatients and the calculated from a setting with an already established robotic department, so considering the low cost reported may lead to ambiguity.

Even though LC mandates laparoscopic instruments and requires skilled surgeons, it is more economical than OC because of the markedly shorter hospital stay reported in earlier studies [181]. Similar results were reported in a population-based cohort study [217] and outpatients as well. [214], moreover, LC can be performed as a day-case procedure with a similar acceptance among patients as an overnight stay. [224] Kuy et al. showed that the cost of cholecystectomy increases with age [183]. Elderly patients undergoing inpatient cholecystectomies may have impairments such as advanced complex diseases, multiple comorbidities, which worsens the outcomes requiring a longer time from admission to surgery leading to prolonged hospital stays. Interestingly, the severity of illness nor comorbidity was not always a consistent predictor of hospital costs or lengths of stay [225]. An increase in operative time always leads to an increased cost of any procedure under question. Women have better clinical and economic outcomes than age-matched men in cholecystitis and cholecystectomy. Performing early LC may reduce costs by preventing recurrent emergency

admissions by the patients. [226]. Despite the growing acceptance of LC, most effective savings can be achieved only by shortening the hospital stay and the time of inability to work [212] and reducing the extended preoperative stay, which leads to an increased cost. Studies have focused on hospital costs for gallstone diseases (GSDs), and none of the studies investigated the household expenditure for the GSD treatment [202]. Cost-effective management of gallstones is possible by adopting strategies to limit the length of stay, with discharge possible on the day of surgery for many patients. [227]

Implausibly LC has a significant cosmetic advantage over OC, but newer procedures such as SILC and MLC claim even better cosmetic results than traditional LC; hence, single-incision surgeries are becoming more prevalent. The cost of SILC does not differ much from that of LC when standard materials were used. For surgeons, the experience with MILC allows for an easier transition to a single-incision cholecystectomy compared with other single-incision procedures.

Studies included in the review merely converted their monetary value to the United States Dollars (US$) at the exchange rate of the year of analysis. Most of the studies often covered participants who have undergone surgery across years; without considering the inflation factor. Thus, the effect of inflation over the study period is often not considered. Studies often provided a cost for a cost year which was often the final year of data collection. We have tried to account for inflation from the reported year of reference used.

The limitations of this study also include the fact that most of the studies included have used retrospective data. Costs used in the study may be estimates because no absolute cost figures are often available. After all, unit costs and base prices for equipment are proprietary information. The cost to a specific facility varies based on contract negotiations. Also, a

hospital's profit depends on variable payer formulas for reimbursement. These must be factored in by the facility when determining OR cost and charges. These totals will be unique to each institution, influenced by the payer mix and contracts in place. Therefore, looking at the results from a single lens may not be meaningful or universally applicable.

Almost all the studies included only direct cost of medical management, including expenses incurred for pre-admission OPD visits, hospitalisation for operation, investigations, procedures and medicines. Studies that included post-operative follow-up visits have not perspicuously stated whether they have considered the cost of follow-up visits in the calculation of the final cost. Only a few studies reported non-medical costs that covered the expenses incurred on travel and transportation (for patients and attendants) from their home to the hospital, accommodation and food for attendants accompanying the patient. The included studies failed to account for any social costs, such as loss of workdays. It can be argued that there is an inherent nature of difficulty in capturing such information.

### 3.3.5 Conclusion

In conclusion, that early laparoscopic cholecystectomy is less costly than open cholecystectomy/delayed cholecystectomy. Emergency presentation and repeat admissions result in higher inpatient costs. Therefore, reduced delay to elective surgery through active participation by primary care needs to be encouraged, along with early laparoscopic cholecystectomy in acute cholecystitis. Also, in the future, the robotic platform may provide a safe and cost-effective alternative to laparoscopic procedures in a setting with a robot-existing model. Intensive investments in surgical services for cholecystectomy in LMICs can provide more affordable service, and can save more lives as well as promote economic growth for the country.

# CHAPTER 4

# COST-EFFECTIVENESS OF CHOLECYSTECTOMY COMPARED WITH CONSERVATIVE MANAGEMENT IN PEOPLE PRESENTING WITH UNCOMPLICATED SYMPTOMATIC GALLSTONES (BILIARY PAIN) OR CHOLECYSTITIS IN INDIA

## 4.1 INTRODUCTION

Cholelithiasis/cholecystitis is one of the expensive diseases imposing a significant burden on the healthcare systems worldwide [10]. In India, the risk of gallbladder diseases is high [14]. Although mostly gallstone disease is asymptomatic and requires no treatment, certain risk factors drive the progression from asymptomatic to symptomatic disease with or without complications and make it imperative to treat [5]. With the advent of laparoscopic cholecystectomy, it has become the most preferred treatment for cholelithiasis/cholecystitis, which has proven effective yet seems costly. Conservative management, which involves pain and symptom management, has also shown effectiveness towards cholelithiasis and cholecystitis and carries a low risk of complications and is considered an alternative to surgery in the clinical practice [23]. The prevalence of gallstones was found to be in the range of 6-20% in the adult Indian population [6] [1] [7], which poses a significant economic burden on the healthcare systems. Therefore, determining cost-effective management options for gallstones for implementation into the Indian health care system is critical. This substantiates the importance of conducting health technology assessment to determine the cost-effectiveness of cholecystectomy compared with conservative management in people presenting with uncomplicated symptomatic gallstones (biliary pain) or cholecystitis.

## 4.2 METHODS

The project proposal was presented to Institutional Human Ethics Committee of ICMR-National Institute of Epidemiology and exemption was sought before study initiation.

### 4.2.1 PICO

We conducted a cost-utility analysis (CUA) using the decision-analytic Markov model to calculate and compare the costs and QALY of cholecystectomy with conservative management in patients with gallstones.

***Problem/Population:*** Patient aged 30 years with symptomatic uncomplicated gallstones (Cholelithiasis)/acute cholecystitis (Cholecystitis) will enter the model. Since the prevalence of gallstones is low at early ages and becomes more common beyond 30 years in the Indian population. [228].

***Intervention:*** The intervention included surgical removal of the gallbladder through the laparoscopic method; early laparoscopic cholecystectomy (ELC), where surgery is performed within 72 hours of hospitalization or seven days from symptom onset and delayed laparoscopic cholecystectomy (DLC), where patients undergo surgery after 6-12 weeks after initial symptomatic management [229].

***Comparator:*** The comparator is conservative management where patients with gallstones are symptomatically managed using analgesics, antibiotics, diet, and lifestyle changes.

***Outcome:*** Quality-adjusted life-years (QALYs) gained and incremental cost-effectiveness ratio (ICER)

***Time Horizon:*** Lifetime horizon

***Perspective:*** Health system perspective

***Discounting:*** All future costs and consequences were discounted at 3% as per WHO guidelines along with sensitivity analysis with 0 to 6% per annum.

***Willingness to pay (WTP) threshold:*** We applied Gross Domestic Product (GDP) per capita based on WHO guideline for willingness to pay threshold, and considered ICER of less than one GDP per capita as highly cost-effective, one-to-three GDP/capita as cost-effective, and more than three GDP/capita as not cost-effective [230]. Thus, India's 2020 GDP per capita of INR ₹ 97,265 has been considered the cost-effectiveness threshold value per QALY gained [231].

### 4.2.2 Data collection methodology (For Clinical parameters)

The data on transition rates/probabilities for the input parameters of the model were collected through systematic review and meta-analysis or from published literature based on a hierarchy of evidence, including

(i) systematic review and meta-analysis (SRMA) of randomized controlled trials (RCTs)

(ii) RCTs

(iii) SRMA of observational studies

(iv) Clinical trials, and

(v) Observational studies

The data on probabilities of surgical complications were obtained through systematic review and meta-analysis of proportions reported in RCTs which has been presented in Chapter 2.1

### 4.2.3 Estimation of Costs and health outcomes

#### 4.2.3.1 Cost data

Direct medical costs (DMC) of treatment, including cholecystectomy and conservative management, costs of managing surgical complications and recurrent gallstone-related symptoms, monitoring costs such as cost of outpatient visits were considered. Cost of early cholecystectomy was obtained by taking the mean of the costs from Pradhan Mantri Jan Arogya Yojana (PMJAY), Central Government Health Scheme (CGHS) Chennai (National Accreditation Board for Hospitals - NABH and non-NABH), Pradhan Mantri Rashtriya Swasthya Suraksha Mission (PMRSSM), Chief minister's health insurance scheme, Tamil Nadu and Private hospital's rate. The cost of conservative management was obtained from Bhargava et al 2016, a prospective RCT conducted in India [209]. The cost of delayed cholecystectomy was obtained as the sum of early cholecystectomy and conservative management. Costs of bile duct injury were obtained from Vinay K Kapoor et al 2011 [200]. The cost of other surgical complications was considered from PMJAY, CGHS Chennai (NABH and non-NABH), PMRSSM, and Chief minister's health insurance scheme Tamil Nadu or mean cost was obtained if the cost is available from more than one source [232-234]. The cost of outpatient visits was taken from National Health System Cost Database for India developed by the Post Graduate Institute of Medical Education and Research (PGIMER) [235]. All the costs were adjusted using the consumer price index (2020) and reported in Indian National Rupees (INR). The cost data are provided in Table 4.1

#### 4.2.3.2 Utility data

Health state utilities used in the model were obtained through meta-analysis detailed in Chapter 2.2 or from published literature. The details of utility data are provided in Table 4.1

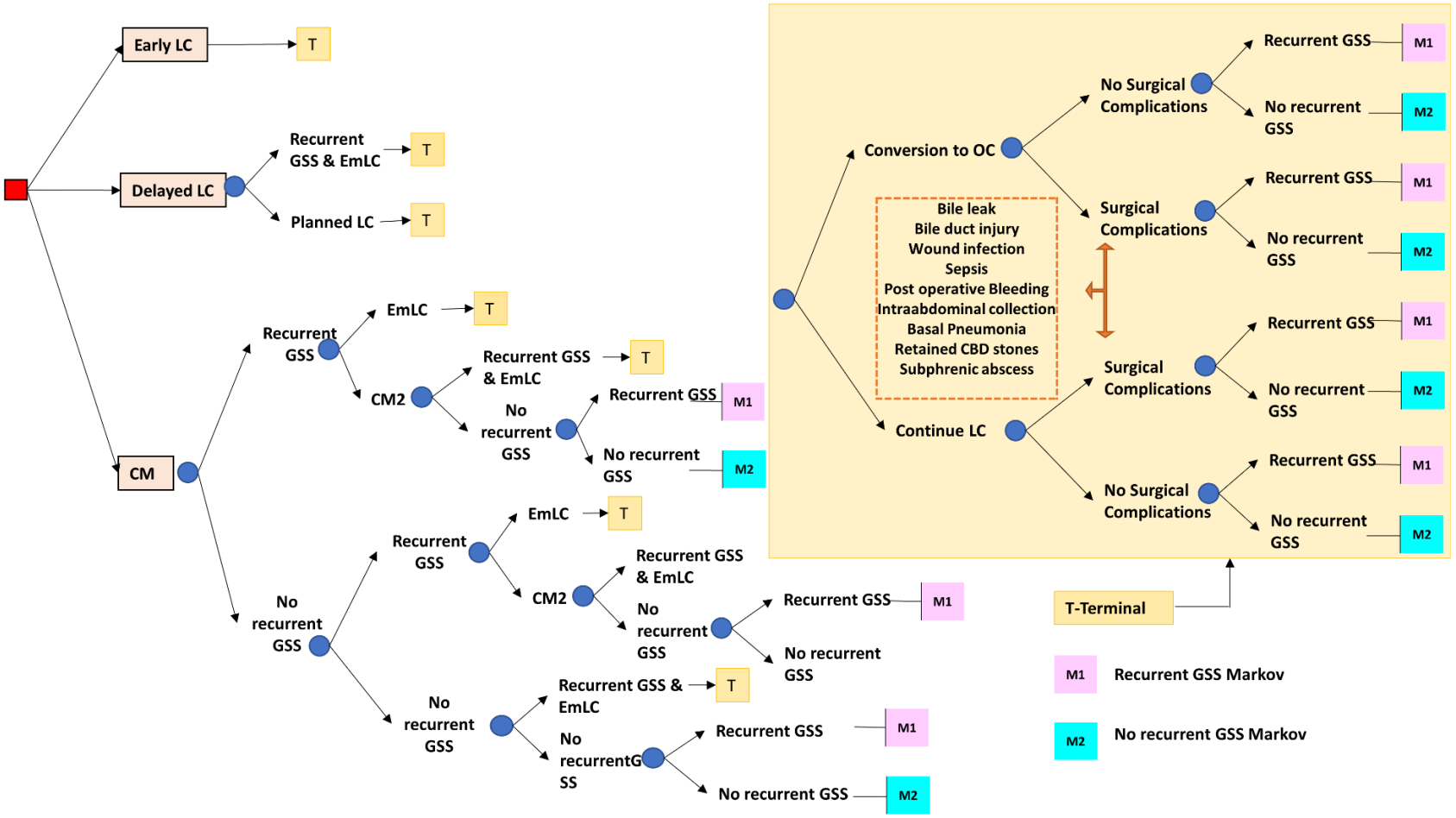
### 4.2.4 Conceptual Framework for decision tree/Markov model

#### 4.2.4.1 Decision tree

In the decision tree (Figure 4.1), the interventions include ELC, DLC, and CM compared to each other. Individual aged 30 years with symptomatic uncomplicated gallstones/acute cholecystitis enter the model through ELC, DLC, or CM arm. In the ELC arm, the individual will undergo ELC within 72 hours of hospitalization. In case of difficulties in surgery (calot's triangle, adhesion, bile duct injury), it could get converted to open cholecystectomy (EOC). Also, during the surgery, individual may have surgical complications. In the DLC arm, the individual will initially be treated symptomatically and later undergoes laparoscopic cholecystectomy after 6-12 weeks. With the failure of initial symptomatic treatment, individuals may undergo emergency laparoscopic cholecystectomy (EmLC). During the surgery, if required, laparoscopy may be converted to open surgery. During the surgery, individuals could develop surgical complications.

In the CM arm, individuals undergoing symptomatic treatment either respond to treatment and become symptoms-free or continue to experience symptoms. Symptomatic individuals will undergo emergency laparoscopic cholecystectomy or continue conservative management. Individuals who became symptom-free could develop recurrent symptoms and may undergo emergency laparoscopic cholecystectomy. In the post-surgical period, persons may or may not exhibit gallstone symptoms (GSS). Persons who show symptoms will enter into the Markov model 1 for recurrent GSS, and those who do not show symptoms will enter the Markov model 2 for no recurrent GSS.

The cost and utility of emergency laparoscopic cholecystectomy were considered for the symptomatic persons when conservative management failed.

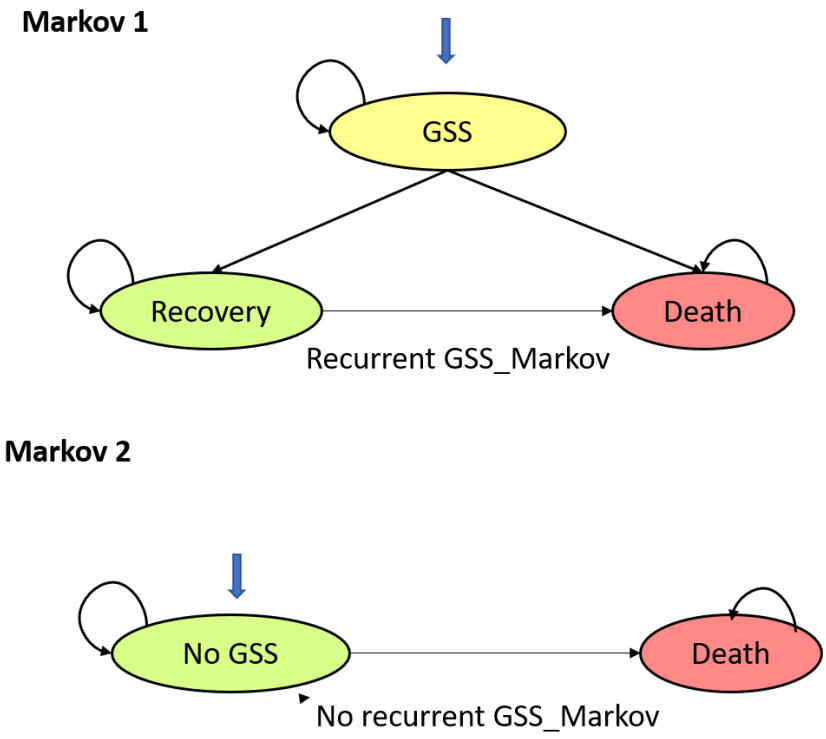



LC-Laparoscopic cholecystectomy; EmLC- Emergency laparoscopic cholecystectomy; OC- Open Cholecystectomy; CM-Conservative Management; GSS-Gallstone symptoms

**Figure 4.1 Schematic representation of Decision tree**

#### 4.2.4.2 Markov Model

Markov model 1 for recurrent GSS includes three health states, including symptoms (recurrence of pain), recovery (becomes symptom-free) and death. Individuals who develop recurrent GSS post-ELC/DLC/CM treatment enter the model at the symptom state. Individuals with symptoms either undergo recovery or death. Recovered individuals could also die due to age-specific all-cause mortality. Probability of developing gallbladder cancer was considered in individuals entering the markov model following CM who did not undergo surgery. From published literature, we observed no gallstone-related mortality; hence the probability of gallstone-related mortality is considered zero. Markov model 2 for no recurrent GSS includes two health states such as No GSS and Death. In this model, individuals with no recurrent symptoms undergo death as per age-specific all-cause mortality (Figure 4.2).




GSS-Gallstone symptoms

**Figure 4.2 Schematic representation of Markov model**

#### 4.2.4.3 Model Assumptions

- The proportion of common surgical complications, including wound infection, bile leak, bile duct injury, post-operative bleeding, intraabdominal collection, subphrenic abscess, sepsis, pneumonia, or chest infection, were estimated using meta-analysis. The difference between the sum of the above individual complications and total surgical complications (as reported in individual studies) is calculated as other complications. Other complications were considered as rare events for which utility of pain and cost is assumed as zero.

- Post-surgical complications were assumed to lasts for two months. So, the utility of corresponding surgical complications was considered for two months. The utility post-cholecystectomy estimated through meta-analysis was considered for the remaining ten months in the decision tree.

- Utility of intra-abdominal collection was not available; hence we used the utility of pain.

- We used the surgical complications rates of open cholecystectomy for the LC converted to open.

- In recurrent GSS, only biliary colic/pain was assumed to recur in post-cholecystectomy or conservative management.

- The probability of recurrent GSS after cholecystectomy was assumed to be the same in all types of cholecystectomies (including EOC, ELC, EmOC, EmLC, DOC, DLC)

- In the CM arm, after initial symptom free with CM, an individual may have three more prospects of getting symptomatic in the model.

- Individuals with no recurrence of gallstones after 3 times were assumed to remain symptom-free for their lifetime. Only age-specific mortality was considered in the Markov model 2 for no recurrent GSS.

- Persons who do not show recurrent GSS within one year were assumed to be symptom-free for their lifetime.

- It was assumed that patients experiencing recurrent GSS have three outpatient visits and are managed with analgesics (twice a day) and proton-pump inhibitors (twice a day) as per the expert opinion. Costs & utilities were calculated accordingly.

- The probability of recovery from recurrent GSS was assumed to be the same for ELC and DLC.

- We assumed gallbladder cancer (GBC) to occur only among the individuals treated with CM without surgery

- In an RCT with a follow-up duration of 14 years, no deaths were documented due to gallstone disease. Hence, gallstone-related mortality was assumed to be zero in the Markov model, and only age-specific mortality was considered [228].

### 4.2.5 Cost-effectiveness Analysis

The total cost and total QALYs gained for each of the interventions were calculated for a lifetime. Total cost was calculated as the sum of the cost of the intervention (ELC, DLC, or CM), cost of treating surgical complications, and costs of managing recurring biliary pain. Total QALYs include the sum of QALYs of all health states, including post-surgical complications and no surgical complications in the decision tree, recurrent pain, and no recurrent pain in Markov. Incremental cost/QALY is the difference in the total cost/QALY between the interventions. ICER is obtained by taking the ratio of incremental cost and incremental QALY.

$$ICER = \frac{Cost\ of\ intervention - Cost\ of\ comparator}{QALY of\ intervention - QALY\ of\ comparator}$$

### 4.2.6 Sensitivity analysis

The robustness of the model was assessed using sensitivity analysis, including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA)

#### 4.2.6.1 One Way Sensitivity Analysis (OWSA)

In one-way sensitivity analysis, 95% CI values for utility values and 25% upper/lower values for the other model input parameters were used and reported as tornado diagrams.

#### 4.2.6.2 Probabilistic Sensitivity Analysis (PSA)

PSA was performed with 5000 Monte Carlo simulations based on its data distribution. Transitional probabilities and utilities were simulated using beta distribution, whereas costs were simulated using Gamma distribution. Results are reported as Cost-effectiveness (CE) plane and Cost-effectiveness Acceptability Curve (CEAC).

### 4.2.7 Scenario Analysis

An RCT that compared the effectiveness of cholecystectomy and conservative management has reported that no surgeries took place in the conservative management group beyond five years [4]. Therefore, we conducted a scenario analysis for a 5-year time horizon in our model, and the ICER was calculated. We also conducted a scenario analysis with varying proportion (10-100%) of individuals undergoing open cholecystectomy.

### 4.2.8 What If Analysis

We conducted a What if analysis, to determine the cost of ELC and DLC at which the ICER exceeds the cost-effectiveness threshold.

### 4.2.9 Budget Impact Analysis

The budget impact analysis was carried out as per the Indian guidelines for BIA from a health system perspective for a time horizon of 5 years. The costs were calculated by the decision-analytic Markov model. The eligible population for cholecystectomy was estimated using a top-down approach (Figure 4.3).

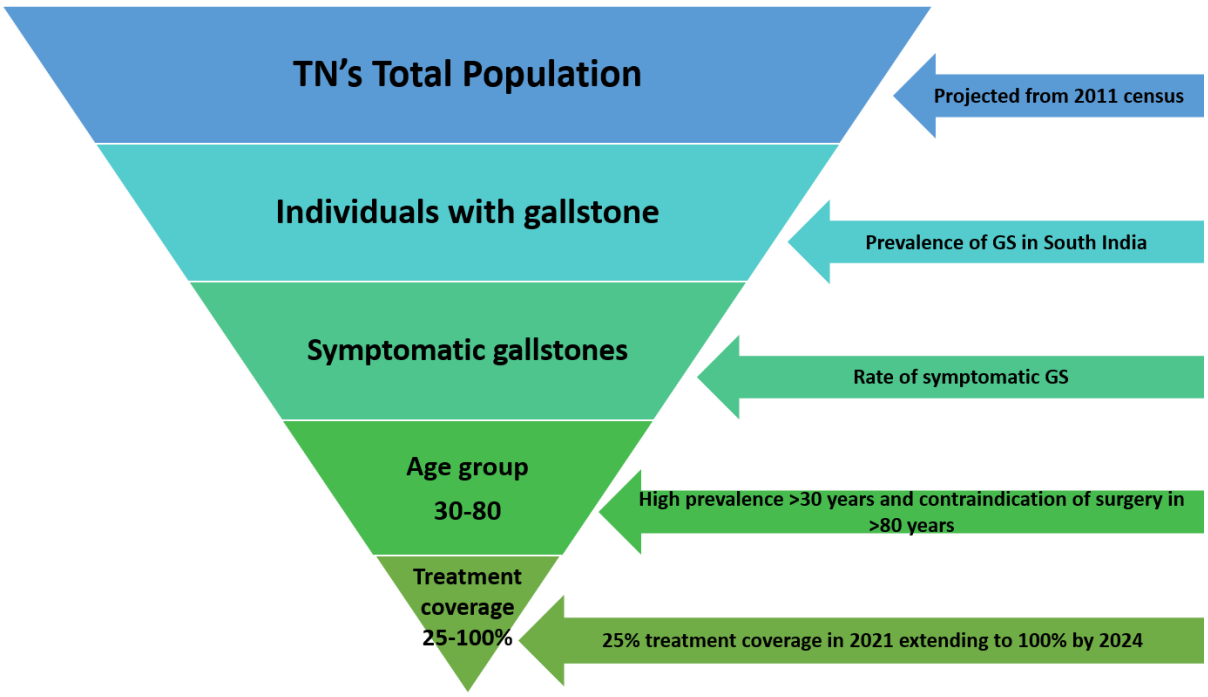



**Figure 4.3 Estimation of the eligible population for treatment using a top-down approach**

Tamil Nadu's (TN) 2021 health budget was considered for analysis. The budget required for offering cholecystectomy for the eligible population was estimated as given below.

$$B = N * (C_{dt} + C_{y1})$$

where,

B= Budget required for offering cholecystectomy to the eligible population

N= Eligible population estimated using a top-down approach

$C_{dt}$= Total cost of intervention from decision tree (dt)

$C_{My1}$= Cost of managing recurrent GSS in the first year from markov (M)

No discount was applied. The health budget was projected based on a 5% annual increase in the health expenditure, and the estimated budget for cholecystectomy was projected using population annual growth rate [236] and incidence of gallstones until 2025 [237].

**Table 4.1 Input parameters used in the model**

| Parameter | Mean (SE) | Distribution | Source |
|---|---|---|---|
| Probability of conversion to OC(P_EOC) | 0.11(0.02) | Beta | Meta-analysis |
| Probability of Surgical Complications with EOC(P_EOC_SC) | 0.15(0.02) | Beta | Meta-analysis |
| Probability of Surgical Complications with ELC(P_ELC_SC) | 0.13(0.02) | Beta | Meta-analysis |
| (P_D_GSS_Em LC) | 0.13(0.03) | Beta | Meta-analysis |
| Probability of Surgical Complications with DOC(P_EMOC_SC) | 0.34(0.03) | Beta | [238] |
| Probability of Surgical Complications with DLC(P_EMLC_SC) | 0.15(0.01) | Beta | Meta-analysis |
| Probability of conversion to OC with DLC(P_DOC) | 0.11(0.02) | Beta | Meta-analysis |
| Probability of Surgical Complications with DOC(P_DOC_SC) | 0.20(0.04) | Beta | Meta-analysis |
| Probability of Surgical Complications with DLC(P_DLC_SC) | 0.14(0.03) | Beta | Meta-analysis |
| Probability of no GS Symptoms post CM1 at index admission (P_CM1_Index_No GSS) | 0.86(0.03) | Beta | [23] |
| Probability of no GS Symptoms post CM1 at follow-up (P_CM1_F_No GSS) | 0.44(0.03) | Beta | [25] |
| Probability of getting symptomic & Emergency LC following CM1(P_CM_GSS_Em LC) | 0.39(0.11) | Beta | [89] |
| Probability of GS Symptoms post CM2(P_CM2_GSS_Em LC) | 0.2(0.05) | Beta | [23] |
| Probability of Recovery with ELC(P_Recovery_C) | 0.06(0.00) | Beta | Meta-analysis |
| Probability of Recovery with CM(P_Recovery_CM) | 0.05(0.00) | Beta | Meta-analysis |
| Probability of mortality due to GS disease(P_Death_GS) | 0 | Beta | [4] [26] |
| Incidence of gallbladder cancer | 0.000076 (0.0000076) | Beta | [239] |
| Utility of recovery post-cholecystectomy (U_Post surgery) | 0.92(0.010) | Beta | [128] |
| Utility of ERC (PU__Bile leak) | 0.76(0.02) | Beta | [162] |
| utility of Post-operative BDI (U__CBD injury) | 0.75(0.05) | Beta | [240] |
| Utility of wound infection (U__Wound infection) | 0.53(0.07) | Beta | [241] |
| utility of Sepsis(U__Sepsis) | 0.47(0.05) | Beta | [242] |
| Utility of post-operative bleeding(U__Post_op_Bleeding) | 0.747 (0.02) | Beta | [243] |

| Parameter | Mean (SE) | Distribution | Source |
|---|---|---|---|
| U of Intraabdominal collection (U__Intraabdominal collection) | 0.88(0.01) | Beta | [243] |
| Utility of Pneumonia (U__Basal Pneumonia) | 0.61(0.03) | Beta | [244] |
| Utility of CBD stones (U__Retained CBD stones) | 0.88(0.01) | Beta | [166] |
| utility of abscess (U__Subphrenic abcess) | 0.64(0.06) | Beta | [242] |
| Utility of Pain(u_pain) | 0.88(0.01) | Beta | [51] |
| Utility of recovery post-cholecystectomy (U_Recovery) | 0.93(0.01) | Beta | Meta-anlaysis |
| Utility of_Galbladder cancer | 0.4 (0.26) | Bete | [245] |
| Utility of_death | 0 | Beta | |
| Cost of early laparoscopic cholecystectomy(C_ELC) (in INR) | 32877.17(3432.32) | Gamma | [232] |
| Cost of delayed laparoscopic cholecystectomy(C_DLC) (in INR) | 44532.72(4453.27) | Gamma | [209] |
| Cost of conservative management (C_CM) (in INR) | 12377.51(85.81) | Gamma | [209] |
| Cost of Bile leak (C__Bile leak) (in INR) | 32073.06 (2169.59) | Gamma | [246] |
| Cost of treating Bile duct injury (C__CBD injury) (in INR) | 229569.37 (57392.34) | Gamma | [247] |
| Cost of Wound infection (C__Wound infection) (in INR) | 5203.33(559.02) | Gamma | [232-234] |
| Cost of Sepsis(C__Sepsis) (in INR) | 15750(5809.48) | Gamma | [232] |
| Cost of Post_op_Bleeding (C__Post_op_Bleeding) (in INR) | 7617.50(515.24) | Gamma | [246] |
| Cost of Intraabdominal collection (C__Intraabdominal collection) (in INR) | 7617.50(515.24) | Gamma | [246] |
| Cost of Basal Pneumonia (C__Basal Pneumonia) (in INR) | 15750.00(5809.48) | Gamma | [232] |
| Cost of Retained CBD stones (C__Retained CBD stones) (in INR) | 74930.50(5068.83) | Gamma | [246] |
| Cost of Subphrenic abcess(C__Subphrenic abcess) (in INR) | 13000.00(1300.00) | Gamma | [248] |
| Cost of managing recurrent (c_symptoms) (in INR) | 1551.141655.55(155.14) | Gamma | [235] |
| Cost of GBC treatment (in INR) | 510000 (51000) | Gamma | [249] |

## 4.3 RESULTS

### 4.3.1 Cost-effectiveness analysis

Based on a probabilistic approach, from the health system perspective, we assessed the cost-effectiveness of ELC versus DLC, ELC vs. CM, and DLC vs. CM (Table 4.2). In the base-case analysis, the total cost of ELC, DLC, and CM were ₹38,883, ₹50,884, and ₹48,782, respectively. ELC, compared to DLC, incurred an additional cost of -₹12,001 for the 0.0002 QALYs gained. ICER was -₹6,43,89,441, which is less than one GDP per capita and is cost-saving. ELC and DLC, compared to CM, incurred an additional cost of -₹10,948 and ₹1,054 for the 0.032 QALYs gained. The ICER was -₹3,42,758 for ELC compared to CM, showing ELC is cost-saving. The ICER was ₹33,183 for DLC compared to CM, which is less than one GDP per capita, suggesting DLC is cost-effective compared to conservative management.

**Table 4.2 Base-case Results**

| | **ELC vs DLC** | | **ELC vs CM** | | **DLC vs CM** | |
|---|---|---|---|---|---|---|
| | **ELC** | **DLC** | **ELC** | **CM** | **DLC** | **CM** |
| Cost | ₹ 38,883 | ₹ 50,884 | ₹ 38,883 | ₹ 49,001 | ₹ 50,884 | ₹ 49,001 |
| QALY | 17.1448 | 17.1446 | 17.1448 | 17.1122 | 17.1446 | 17.1122 |
| Net benefit | ₹16,28,704 | ₹16,16,684 | ₹16,28,704 | ₹16,15,416 | ₹16,16,684 | ₹ 16,15,416 |
| Incremental Cost | -₹ 12,001 | | -₹ 10,118 | | ₹ 1,884 | |
| Incremental QALY | 0.0002 | | 0.033 | | 0.032 | |
| INB | 12019.56 | | 13287.81 | | 1268.25 | |
| ICER | -₹ 6,43,89,441 | | -₹ 3,10,429 | | ₹ 58,129 | |

### 4.3.2 OWSA

#### 4.3.2.1 ELC vs. DLC

In ELC vs. DLC, ICER was most sensitive to variation in the probability of total surgical complications and wound infection among all the input parameters. ICER was also sensitive to variation in the cost of DLC, showing up to ±93% change in ICER, followed by the cost of

ELC showing 68% change. Other parameters that influence ICER includes the probability of conversion to OC in DLC, wound infection in ELC, EmLC, and DOC, sepsis in DLC, bile leak in ELC, basal pneumonia in ELC and DLC, the utility of sepsis, wound infection, pain, CBD injury, bile leak, and post-cholecystectomy upto 75% change in ICER (Figure 4.4).

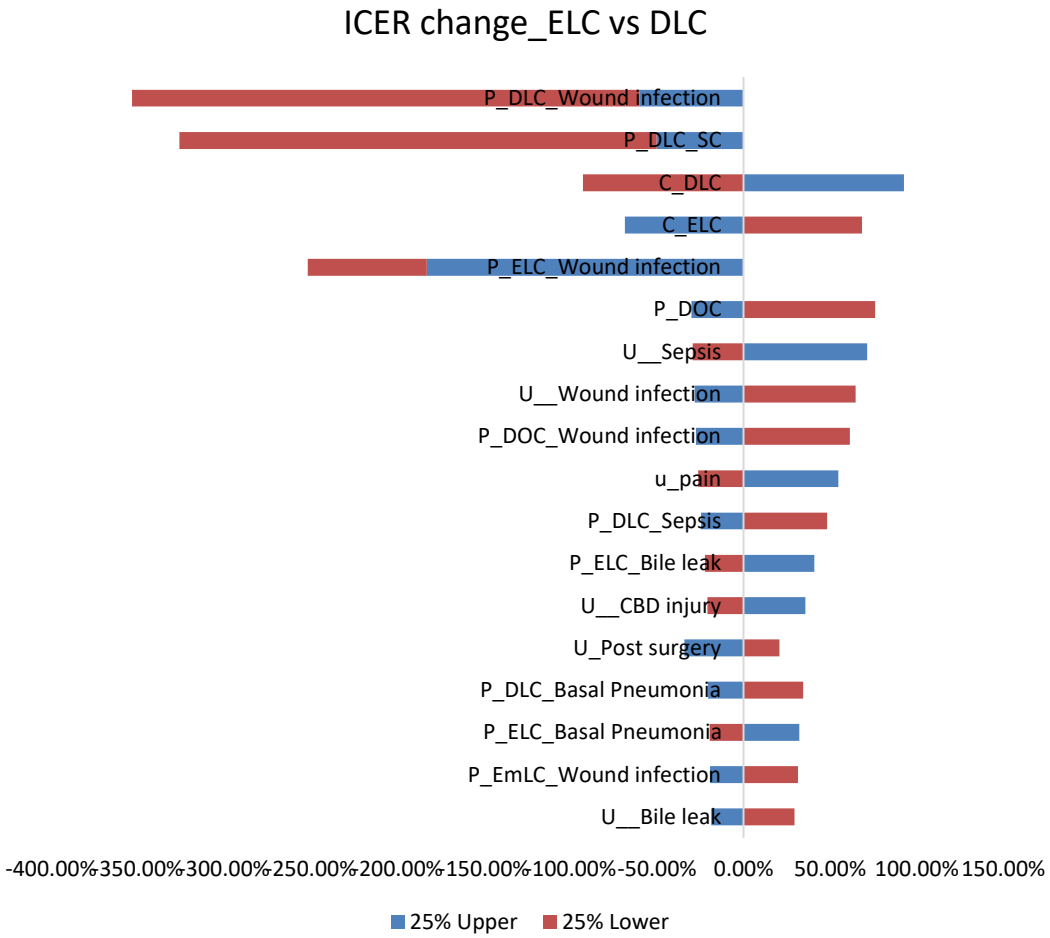



**Figure 4.4 One-way sensitivity analysis for ELC vs. DLC**

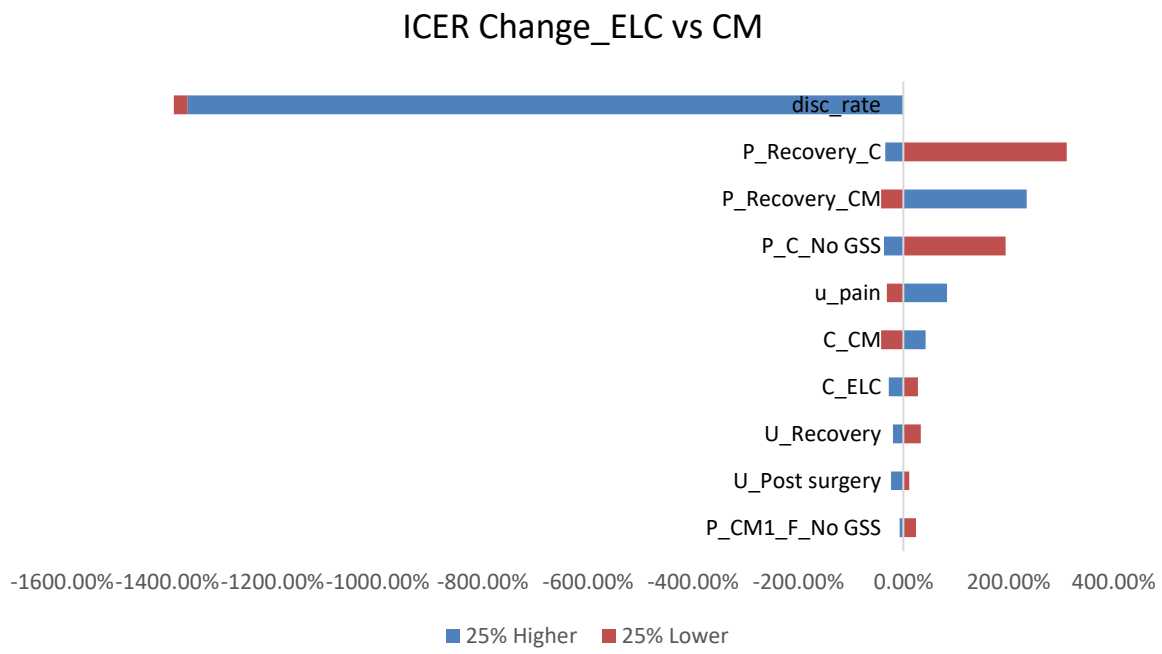
One-way sensitivity analysis was conducted using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of the specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter

### 4.3.2.2 ELC vs. CM

In ELC vs. CM, ICER was most sensitive to variation when 6% discount rate was used followed by probability of recovery from recurrent GSS and probability of being symptom-

free after cholecystectomy, showing up to 400% change in ICER. Variation in parameters such as the utility of pain, cost of CM and ELC, the utility of recovery, probability of being symptom-free after CM showed a 25-85% change in ICER. Other parameters that influenced ICER include the probability of undergoing emergency LC with conservative management, surgical complications in EmLC, cost of bile leak, and cost of managing recurrent symptoms with less than 25% change in ICER (Figure 4.5).

**Figure 4.5 One-way sensitivity analysis for ELC vs. CM**




One-way sensitivity analysis was conducted by using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of a specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter

### 4.3.2.3 DLC vs. CM

In DLC vs. CM, sensitivity of ICER to variation in the cost of DLC, discount rate, probability of recovery from recurrent symptoms, and probability of being symptom-free after DLC/CM shows a change in the ICER between 500-2000% followed by cost of ELC and CM which

changes 492% and 384% respectively. Variation in utility of pain shows a change of 86% in ICER and the other parameters that influence the ICER with less than 50% change include the probability of CM's success in index admission, the utility of recovery, probability of surgical complications in EmLC, cost of bile leak, utility post-cholecystectomy, and cost of managing recurrent symptoms (Figure 4.6).

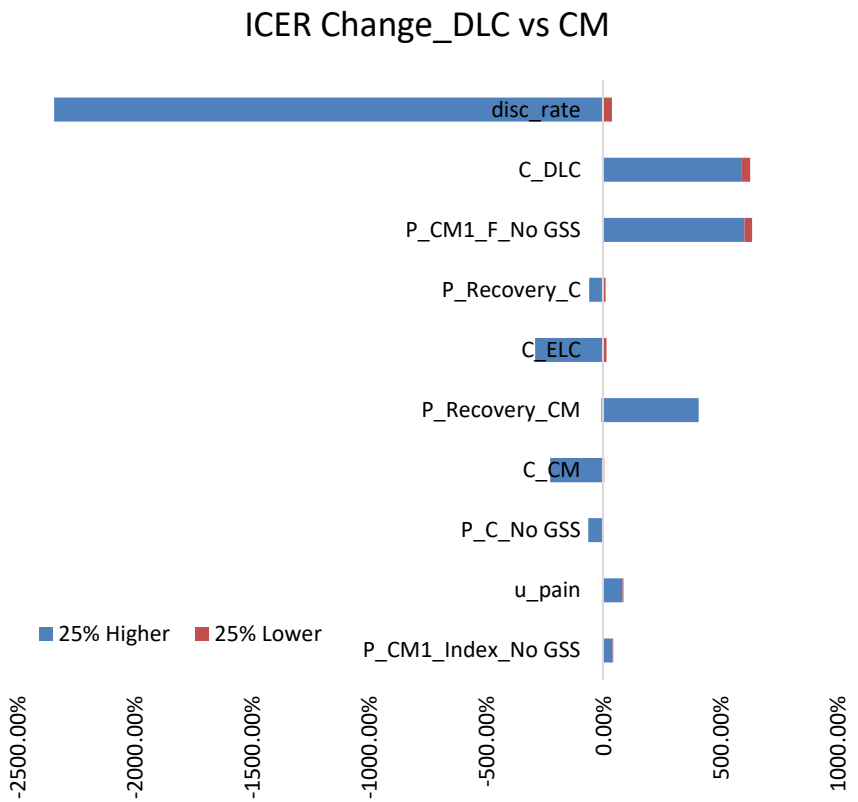



**Figure 4.6 One-way sensitivity analysis for DLC vs. CM**

One-way sensitivity analysis was conducted by using 25% higher and lower values of all the transitional probabilities, cost, and utility values. The red bars show the effect on the ICER of applying the lower limit (-25%) of a specific parameter, while the blue bars show the effect on the ICER of applying the upper limit (+25%) of the specific parameter

### 4.3.3 PSA

***ELC vs. DLC***

PSA performed with 5000 Monte Carlo simulations for ELC vs. DLC showed that a majority (nearly 50%) of the ICER points were distributed in the lower-right quadrant of the CE-plane, suggesting that ELC is cost-saving than DLC. A few points were observed in all the other quadrants indicating some level of uncertainty. However, the mean stochastic ICER is -₹6,22,41,435.3 (95%CI -₹29,48,85,350 to ₹26,77,11,501) which is in line with the base case result (Figure 4.7). In the cost-effectiveness acceptability curve (CEAC), considering a upto a ceiling ratio of INR 5,00,000 per life-year gained, the probability that ELC is cost-effective compared to DLC was 0.99 (Figure 4.8).

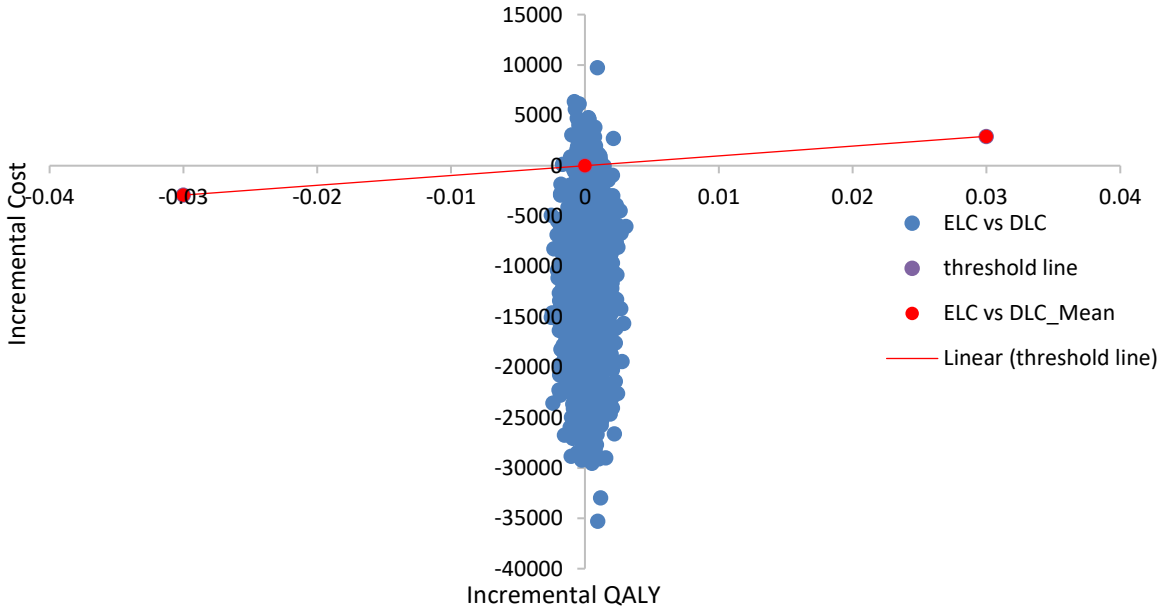



**Figure 4.7 Probabilistic sensitivity analysis showing CE-plane for ELC vs. DLC**

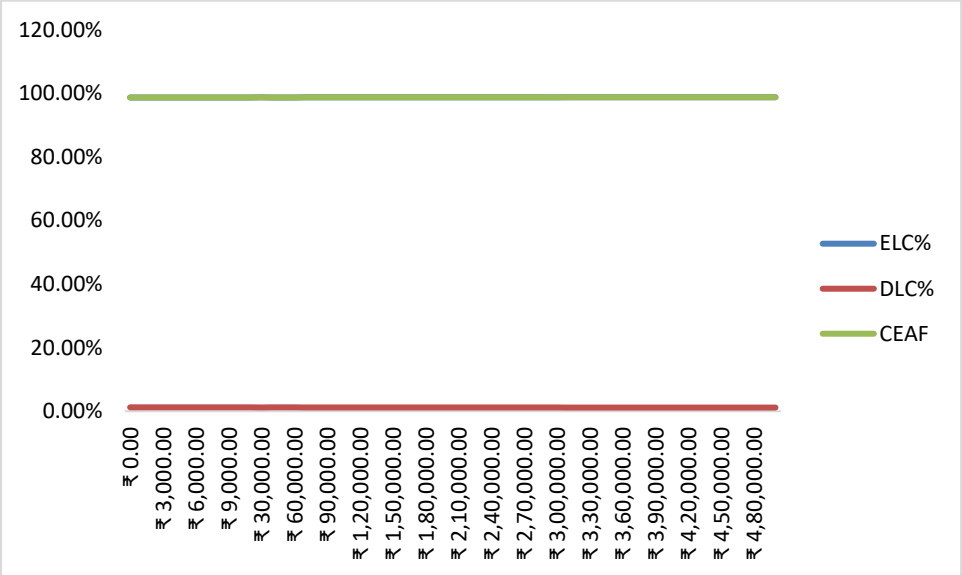



**Figure 4.8 Cost-effectiveness acceptability curve for ELC vs. DLC**

***ELC vs. CM***

For ELC vs. CM, 99.9% of the simulated points were distributed in the lower-right quadrant of the CE-plane within the WTP threshold, indicating ELC is cost-saving compared to CM, which confirms no uncertainty concerning cost-saving of ELC compared to CM. The mean stochastic ICER is -₹3,13,054 (-₹8,77,797 to -₹1,55,120), close to the base case ICER (Figure 4.9). In the cost-effectiveness acceptability curve (CEAC), considering up to a ceiling ratio of INR 5,00,000 per life-year gained, the probability that ELC is cost-effective compared to CM was 1 (Figure 4.10).

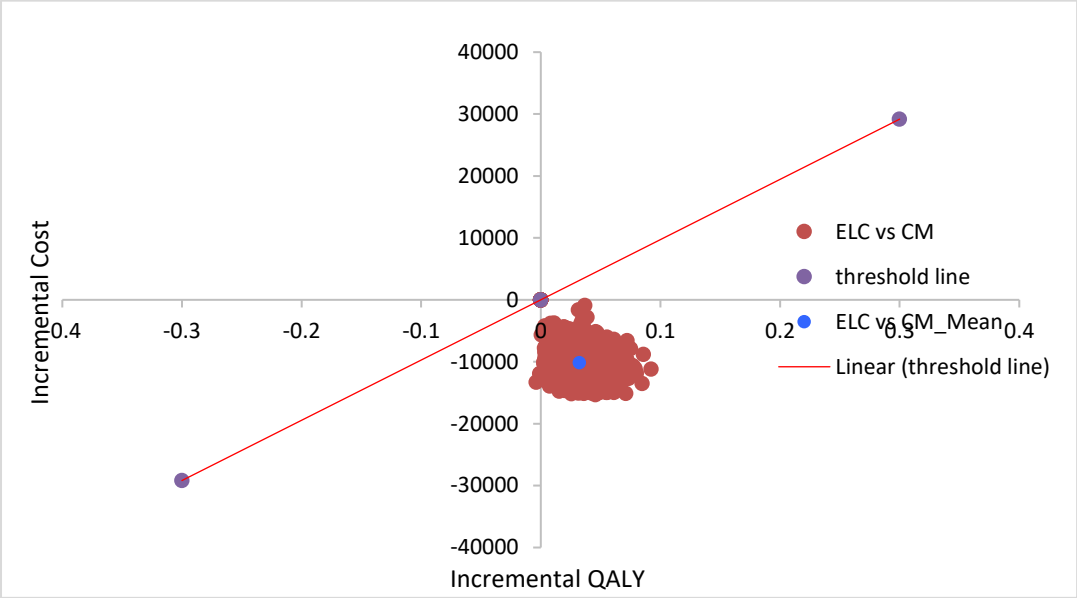



**Figure 4.9 Probabilistic sensitivity analysis showing CE-plane for ELC vs. CM**

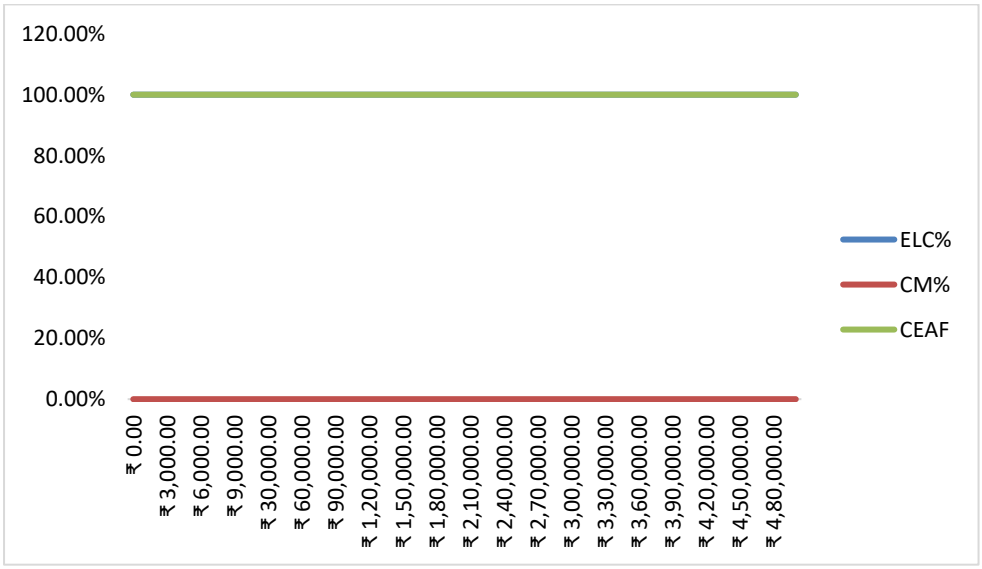



**Figure 4.10 Cost-effectiveness acceptability curve for ELC vs. CM**

***DLC vs. CM***

In DLC vs. CM, 50% of the ICER plots were distributed within the WTP threshold, among which approximately 25% were in the lower-right quadrant, indicating DLC is cost-saving

similar to the base-case result, whereas 25% of the plots were distributed in the lower right quadrant of the plane indicating DLC to be cost-effective. However, 50% of the ICERs were distributed above the threshold, indicating some uncertainty. The mean stochastic ICER is ₹64,822 (-₹311435 to ₹5,86,896), similar to the base-case ICER (Figure 4.11). In the cost-effectiveness acceptability curve (CEAC), considering upto a ceiling ratio of INR 5,00,000 per life-year gained, the probability that DLC is cost-effective compared to CM is 0.58 (Figure 4.12).

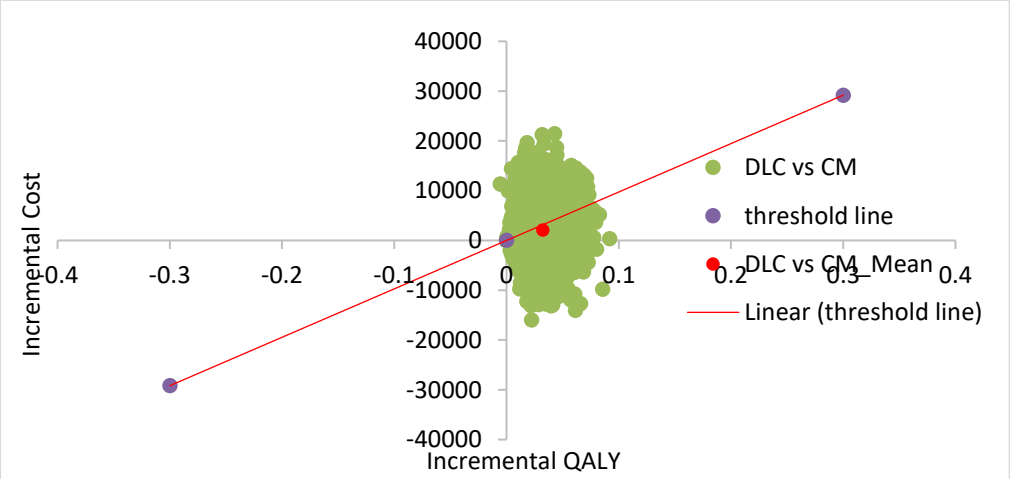



**Figure 4.11 Probabilistic sensitivity analysis showing CE-plane for DLC vs. CM**

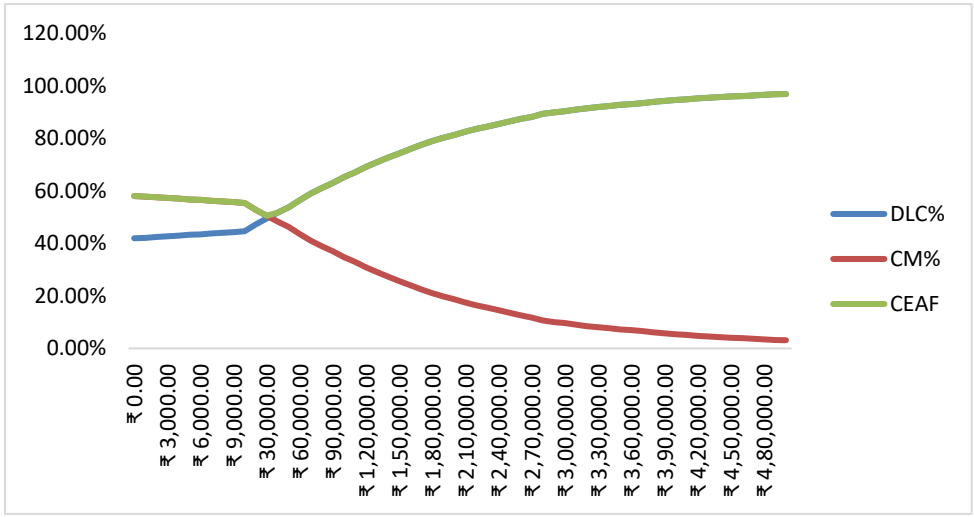



**Figure 4.12 Cost-effectiveness acceptability curve for DLC vs. CM**

### 4.3.4 Scenario Analysis- 5-year Time Horizon

We considered a 5-year time horizon in our model as a scenario and conducted the cost-effectiveness analysis. The total cost, QALY and Net benefit, incremental cost, QALY and Net benefit and the ICER for 5-year time horizon are summarized in Table 4.3.

**Table 4.3 Base-case results for a 5-year time horizon**

| | **ELC vs DLC** | | **ELC vs CM** | | **DLC vs CM** | |
|---|---|---|---|---|---|---|
| | **ELC** | **DLC** | **ELC** | **CM** | **DLC** | **CM** |
| Cost | ₹ 35,612 | ₹ 47,614 | ₹ 35,612 | ₹ 44,751 | ₹ 47,614 | ₹ 44,751 |
| QALY | 4.3008 | 4.3006 | 4.3008 | 4.2941 | 4.3006 | 4.2941 |
| Net benefit | ₹3,82,706 | ₹3,70,686 | ₹3,82,706 | ₹3,72,908 | ₹3,70,686 | ₹3,72,908 |
| Incremental Cost | -₹ 12,001 | | -₹ 9,139 | | ₹ 2,862 | |
| Incremental QALY | 0.0002 | | 0.0068 | | 0.0066 | |
| Incremental Net benefit | 12019.56 | | 9797.54 | | -2222.03 | |
| ICER | -₹ 6,43,89,441 | | -₹ 13,50,538 | | ₹ 4,34,918 | |

### 4.3.5 Scenario Analysis- For varying proportions of individuals undergoing open cholecystectomy

We have conducted a scenario analysis with varying proportions of individuals undergoing open and laparoscopic cholecystectomy. Even with 100% of the cohort undergoing open cholecystectomy, the cost-effectiveness results remain the same. . Thus, irrespective of Laparoscopic or Open cholecystectomy, Early surgery is cost-saving compared Delayed surgery and Conservative management The ICERS of scenario analysis are presented in Table 4.4.

**Table 4.4 ICERs with varying proportions of individuals undergoing OC**

| Proportion undergoing OC | Proportion undergoing LC | EC vs DC_ICER | EC vs CM_ICER | DC vs CM_ICER |
|---|---|---|---|---|
| 10% | 90% | -₹ 7,43,10,279 | -₹ 3,09,832 | ₹ 58,624 |
| 20% | 80% | -₹ 3,10,05,257 | -₹ 3,16,791 | ₹ 52,106 |
| 30% | 70% | -₹ 1,96,72,830 | -₹ 3,23,674 | ₹ 45,569 |
| 40% | 60% | -₹ 1,44,51,367 | -₹ 3,30,482 | ₹ 39,013 |
| 50% | 50% | -₹ 1,14,47,611 | -₹ 3,37,216 | ₹ 32,437 |
| 60% | 40% | -₹ 94,96,165 | -₹ 3,43,879 | ₹ 25,842 |
| 70% | 30% | -₹ 81,26,468 | -₹ 3,50,469 | ₹ 19,227 |
| 80% | 20% | -₹ 71,12,127 | -₹ 3,56,990 | ₹ 12,592 |
| 90% | 10% | -₹ 63,30,730 | -₹ 3,63,442 | ₹ 5,938 |
| 100% | 0% | -₹ 57,10,298 | -₹ 3,69,826 | -₹ 737 |

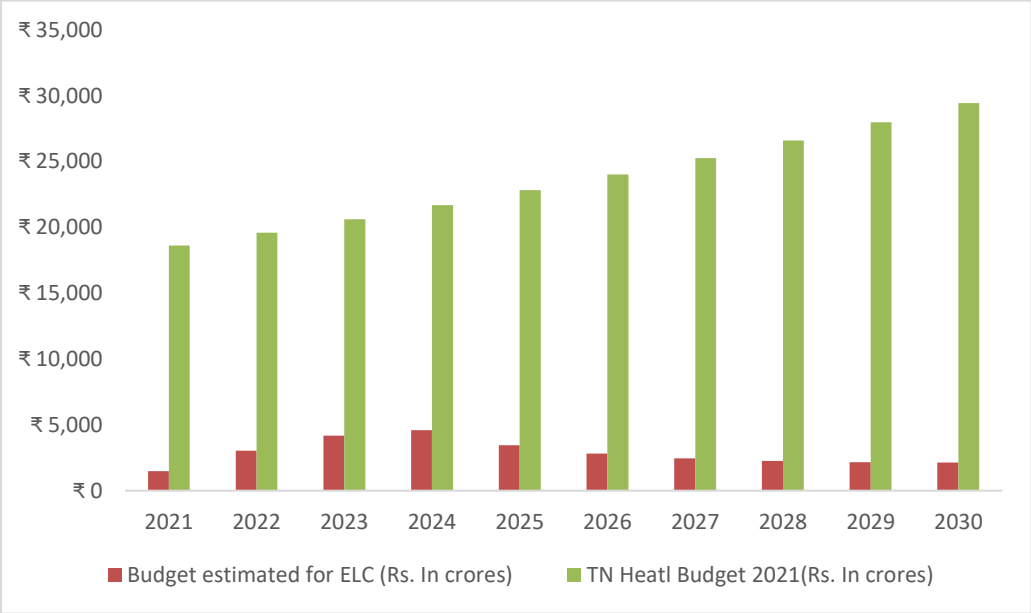
### 4.3.6 What if Analysis

We have conducted a What if analysis to determine the cost of ELC and DLC at which the ICER exceeds the cost-effectiveness threshold. With the cost of ELC as ₹91078 and the cost of DLC as ₹52105, the ICER exceeds the three times GDP per capita making ELC and DLC not cost-effective than conservative management.

### 4.3.7 Budget Impact Analysis

The prevalence of gallstone disease in South India is 4.87% which estimates the total gallstone cases to be 40.6 lakh in Tamil Nadu in 2021 [250]. Based on a gallstone incidence of 0.63% [237], there would be 5.25 lakhs new cases annually for the Tamil Nadu population of 8.3 crores approximately, a projected 2021 estimate from the 2011 census. A population-based survey in North India has demonstrated 88% of patients with gallstones to be symptomatic [6]. Further, considering a population greater than 30 years (as the prevalence of gallstone is more common beyond 30 years) and eliminating population older than 80 years (as surgery could be contraindicated in the elderly) results in 17 lakhs eligible patients for surgery in the year 2021.

Considering an annual incremental increase in treatment coverage of 25% of eligible patients. The estimated budget for early cholecystectomy was ₹1,488 crores for 2021. This is 7.9% of Tamil Nadu's 2021 health budget (₹18,632 crores) and reaches 21.23% of the projected health budget with full (100%) coverage in 2024. However, the budget requirement reduces in the following years to cover the entire eligible patients. The estimated budget would start declining gradually from the fifth year as only the annual new cases would require treatment. For the State of Tamil Nadu, early cholecystectomy for gallstone patients could save ₹384 crores for the year 2021 (₹8,847 per patient) with 25% treatment coverage, and cost-savings could increase up to ₹1,165 crores by the year 2024 with 100% treatment coverage as compared to conservative management. Further, suppose cholecystectomy is carried within 72 hours of admission for symptomatic gallstones instead of delayed cholecystectomy (carried out in 6-12 weeks after initial symptoms). In that case, the cost-savings (₹12,001 per patient) could amount to ₹520 crores by 2021 and up to ₹1,591 crores by 2024. The projected health budget and the estimated budget of Tamil Nadu for early laparoscopic cholecystectomy for all the eligible population is shown for ten years in Figure 4.13. State-wise additional budget required (in percentage) to offer ELC to all the eligible population for 2021-2024 is presented in Figure 4.14.




ELC-Early Laparoscopic Cholecystectomy; TN-Tamil Nadu, *Numbers mentioned in Crores.

**Figure 4.13 Budget Impact Analysis for the TN State Government**

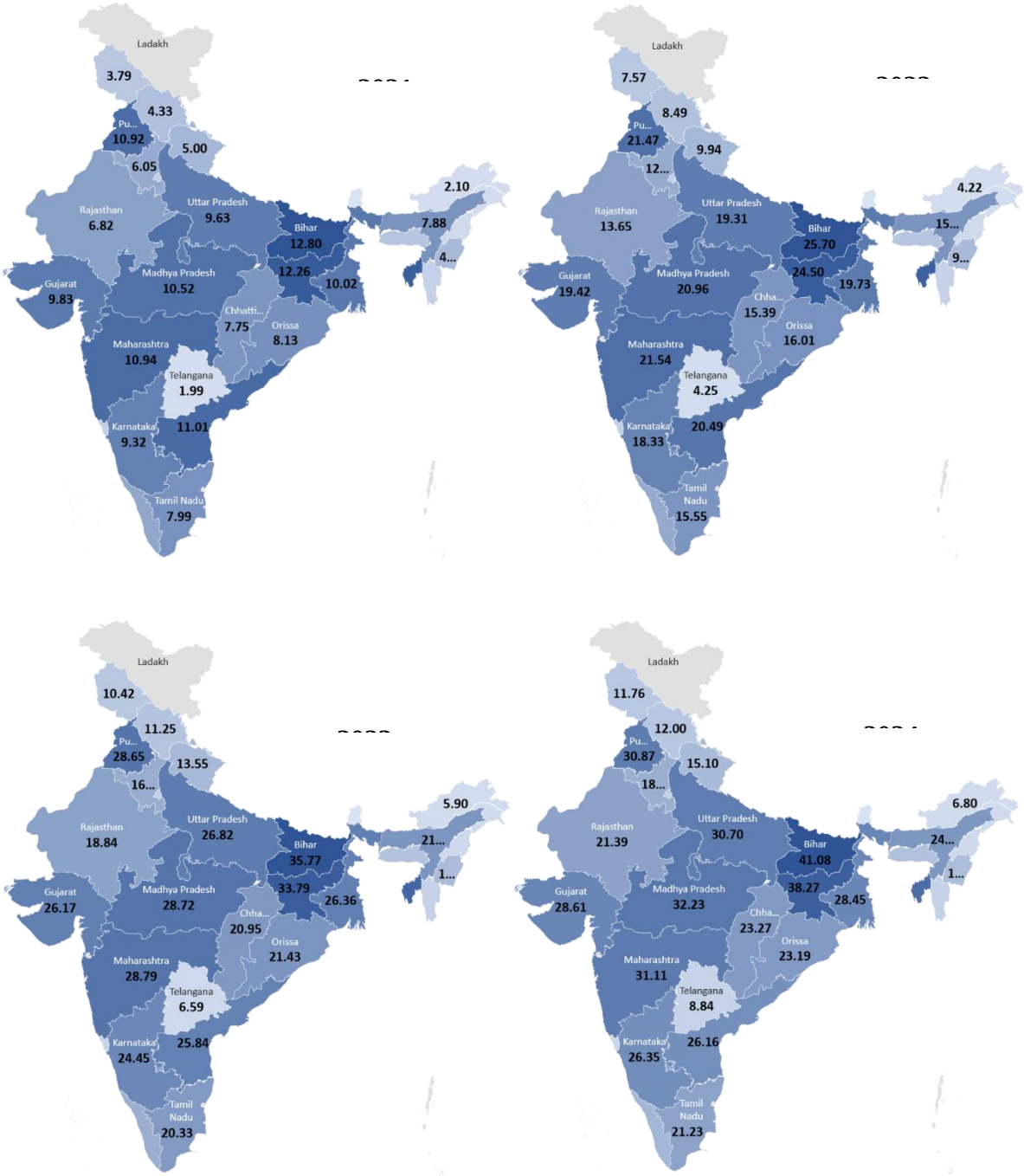



**Figure 4.14 State-wise estimated additional budget (in percentage) to offer ELC to all the eligible population for 2021-2024**

## 4.4 DISCUSSION

We evaluated the cost-effectiveness of cholecystectomy with conservative management in individuals with uncomplicated gallstone or acute cholecystitis in the Indian context from the health system perspective. We compared ELC, DLC, and CM treatment strategies of gallstone disease in the cost-effectiveness analysis. We observed that ELC is dominant or cost-saving compared to DLC and CM, while DLC is cost-effective compared to CM.

Comparing ELC and DLC, the incremental cost is -₹12,001, which suggests that DLC is expensive. Still, DLC is similar to ELC in effectiveness as the observed incremental QALY is very minimal. Hence, ELC has slightly higher effectiveness than DLC but at a much lower cost. Sensitivity analysis revealed that if the probability of surgical complications, mainly wound infection, is 25% lower in DLC or 25% higher in ELC, then ELC tends to lose its cost-effectiveness. However, while considering the same rate of surgical complications in both ELC and DLC, ELC is cost-saving. Thus, higher clinical effectiveness of ELC over DLC depends mainly on the rate of surgical complications. The cost of DLC is another important parameter that influences the cost-effectiveness of ELC. With a 25% reduction in DLC costs, ELC was still cost-saving, although ICER increased by 14 times. However, PSA also revealed a minimal difference between stochastic mean ICER and base-case ICER with wide confidence intervals. Thus, the findings suggest that ELC is cost-saving to DLC in the Indian context. Previous cost-effectiveness studies conducted in other high-income country settings have also shown that ELC is cost-saving than DLC [33], [34], [35], [36], except one study which reported DLC is cost-effective [37].

Similarly, ELC was cost-saving when compared to CM. The probability of recovery from recurrent symptoms after ELC or CM minimally varied the ICER, as shown in OWSA. However, ELC remained cost-saving in all the OWSA. Thus, the results were robust and did

not change with variation in any of the input parameters, which was also denoted in PSA. Similar observations were also reported in a study from UK [31]. While considering the cost and QALYs from the decision tree with a one-year time horizon alone, CM gained slightly more QALYs than ELC/DLC and was cost-effective. Indicating that if one considers the immediate costs and effects, the CM may appear cost-effective. Still, considering the life-long post-treatment sequelae, CM incurs more costs for lesser QALY gains due to recurrence of GSS. In an RCT that compared the effectiveness of cholecystectomy and conservative management, it has been reported that no surgeries took place in the conservative management group beyond five years [4]. So, we considered a 5-year time horizon in our model as a scenario, which showed ELC was still cost-saving compared to CM.

We also assessed the cost-effectiveness of DLC with CM, which revealed that DLC is cost-effective. In sensitivity analysis, the ICER was most sensitive to variation in the cost of DLC and probability of recovery from recurrent GSS. With 25% higher costs of DLC, DLC was not cost-effective compared to CM. Similarly, DLC was not cost-effective when the probability of recovery decreases in DLC or increases in CM by 25%. In scenario analysis with 5-year time horizon, DLC was not cost-effective. In PSA, even though the stochastic mean of 5000 simulations showed that DLC is cost-saving, about 50% of simulation points were present above the threshold in the CE-plane, indicating results are sensitive to changes in the input parameters.

Existing CUAs indicate that cholecystectomy is more effective and less costly than CM. The main reason is that more people in the CM group require surgery, which reduces the cost-effectiveness of conservative management [31]. Similarly, we observed that 66% of individuals in CM underwent emergency cholecystectomy subsequently due to recurrence of GSS. We considered that individuals who became symptom-free with initial CM could have three more prospects of becoming symptomatic within one year in the decision tree. If the

chances of getting recurrent GSS decreases, then CM could be cost-saving. Thus, it is evident that the effectiveness of CM depends on the recurrence of GSS.

Tamil Nadu currently follows the Chief minister's health insurance scheme (CMHIS). The scheme covers the population with an annual income of 72,000 rupees. The Govt pays the premium to a public insurance company and covers various health conditions, including gall stone disease treatment. Under the scheme, the gallstone treatment is covered free of charge to the patients in the selected hospitals. The insurance company will reimburse the treatment costs to the hospitals. We have considered the costs of reimbursement while calculating the costs while estimating the budget impact. We have calculated the budget impact by assuming an annual 25% incremental increase in treatment of the eligible patients who require cholecystectomy. For 2021, an additional budgetary allocation of ~8 % would be required to treat 25% of the eligible patients. All the eligible patients would be covered by 2024 with a requirement of 21% additional budgetary allocation. However, the estimated budget required for early cholecystectomy would decline from the sixth year as the number of gallstone cases would substantially reduce with full treatment coverage.

The study has several limitations. The study is limited mainly due to the lack of high-quality evidence from the Indian context. In addition, we had to rely on secondary data for all of the model input parameters generated from other countries/scenarios. The transitional probabilities, such as the probability of recurrent GSS and recovery from recurrent GSS are from two RCTs conducted in Norway [89, 42]. However, in CUAs, when the local data is scarce, it may be permissible to use available information from other settings. Secondly, most of the utility scores used in this model were obtained from older studies and from other countries, not necessarily estimated using EQ-5D, which indicates the lack of EQ-5D utility data, particularly in the Indian setting. However, most of the input parameters used in our

economic model have been obtained through systematic review and meta-analysis, which may increase the reliability of the data. Lastly, we have adopted a health system perspective in our study. In India, the health expenses are borne by the individuals through out-of-pocket expenditure. Since, limited availability of data on out-of-pocket spending, indirect medical costs, and loss of wages, other perspectives could be explored. In BIA, the incidence of gallstones reported elsewhere has been used as local evidence was not available; therefore, the estimates may not be very accurate.

## 4.5 CONCLUSION

The gallstone diseases represent a substantial financial burden on the Indian healthcare system, and it is imperative to find a cost-effective intervention. Cholecystectomy for symptomatic cholelithiasis is cost-effective, when assessed by cost per QALY. The ELC is cost-saving compared to DLC or CM, and DLC is cost-effective than CM. Thus, ELC could be a preferable option to the others treatment options of gallstone disease management. The findings may assist policymakers in prioritizing the gallstone treatments to include in the public health system.

# RECOMMENDATIONS

- Laparoscopic cholecystectomy may be a preferable option unless deemed necessary in cases of the complicated gallbladder. Since laparoscopic cholecystectomy is less costly than open cholecystectomy due to lesser hospitalization costs.
- Early laparoscopic cholecystectomy (within 72 hours of admission or seven days from symptom onset) may be a preferred treatment option for uncomplicated cholelithiasis and acute cholecystitis. However, we cannot completely rule out conservative management due to limited literature on the long-term effectiveness of conservative management.
- We recommend, an incremental increase in treatment coverage for eligible patients to have a minimal budgetary impact.
- There is a need to develop standard treatment guidelines, to consider the conservative management for gallstone disease.
- There is a need to generate high-quality evidence on this topic in the Indian context; in terms of the clinical effectiveness of conservative management, health-related quality of life for gallstone disease.

# POLICY IMPLICATIONS

- Cholecystectomy (open or laparoscopic) is cost-effective than conservative management for symptomatic uncomplicated gallstone disease (biliary colic) and acute cholecystitis.
- Early cholecystectomy is cost-effective than conservative management/delayed cholecystectomy for symptomatic uncomplicated gallstone disease
- Early cholecystectomy is cost-effective for acute cholecystitis than conservative management/delayed cholecystectomy. However, it may require a clinical decision regarding the timing of surgery, whether early or delayed surgery with initial symptomatic management followed by cholecystectomy (6-12 weeks later), considering the possible intraoperative complications in early surgery.
- More evidences are needed on conservative management's effectiveness for symptomatic uncomplicated gallstone disease and acute cholecystitis

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# LIST OF PUBLICATIONS

Bagepally BS, Haridoss M, Sasidharan A, Jagadeesh KV, Oswal NK. Systematic review and meta-analysis of gallstone disease treatment outcomes in early cholecystectomy versus conservative management/delayed cholecystectomy. BMJ Open Gastroenterol. 2021 Jul;8(1):e000675. doi: 10.1136/bmjgast-2021-000675. PMID: 34261757; PMCID: PMC8280848.

# APPENDICES

**Systematic review and meta-analysis of Gallstone-disease treatment outcomes in early cholecystectomy versus conservative management/delayed cholecystectomy**

**Appendix 2.1.1 PRISMA Checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Yes, 8 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | NA (For report) |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Yes, 9 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Yes, 9 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Yes, 9 PROSPERO ID: 2020 CRD42020192612 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Yes, 9-10 |

| | | | |
|---|---|---|---|
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Yes, 10 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Yes, 142 & Appendix 2.1.2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Yes, 10 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Yes, 10-11 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Yes, 10-11 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Yes, 11 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Yes, 11 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | Yes, 11-12 |

| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Yes 13 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Yes, 12 |
| **RESULTS** | | | |

| | | | |
|---|---|---|---|
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Yes, 14<br>Figure 2.1.1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Yes, 14-16<br>Table 2.1.1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Yes, 20<br>Figure 2.1.2 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Yes, 24-38<br>Figure 2.1.6 & 2.1.15, |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Yes, 24-38<br>Figure 2.1.6 & 2.1.15, |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Figure 2.1.5, 2.1.9, 2.1.12, 2.1.14 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Table 2.1.2, 2.1.3, 2.1.4<br>Figure 2.1.3, 2.1.4, 2.1.7, 2.1.8, 2.1.10, 2.1.11, 2.1.13 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Yes, 39 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Yes, 41 |

| | | | |
|---|---|---|---|
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Yes, 41 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | NA |

**Appendix 2.1.2 Search terms and no. of hits in PubMed**

| PICOS | Pubmed Search terms | Hits (on date 16th July 2020) |
|---|---|---|
| P | "gall bladder" OR gallbladder OR cholecystitis OR cholelithiasis OR gallstone OR “gall stone” OR “gall stones” OR cholecystolithiasis OR "bile duct stone" OR “common bile duct” OR CBD OR "biliary disease" OR "biliary tract disease" OR cholec* OR “gallbladder inflammation” | 151,737 |
| I | cholecystectomy OR "gallbladder removal" OR "gallbladder excision" OR ("surgical removal" AND ("gall bladder" OR gallbladder)) OR ("surgical excision" AND ("gall bladder" OR gallbladder)) OR "restrictive strategy" OR cholecystostomy OR "biliary tract surgery" OR "bile duct operation" OR "bile duct surgery" OR "bile tract surgery" OR "biliary surgery" OR "biliary tract operation" OR "biliary tract reoperation" OR "biliary tract surgery" OR "biliary tract surgical procedures" OR "gall bladder surgery" OR "gallbladder operation" OR "gallbladder surgery" OR sphincterotomy | 55,069 |
| C | “conservative treatment” OR “conservative management” OR “conservative therapy” OR “nonoperative treatment” OR “nonsurgical treatment” OR 'organ sparing treatment' OR ‘'organ sparing treatments' OR supportive OR non-invasive OR non-surgical OR non-operative OR "wait and watch" OR "wait and see" OR watchful-waiting OR "usual care" | 10,190,039 |
| S | "randomized controlled trial" [pt] OR "controlled clinical trial" [pt] OR randomized [tiab] OR placebo [tiab] OR "drug therapy" [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] | 4,809,100 |
| PICS | PICS | 1742 |
| Additional search with new search terms | (Lithotripsy OR dissolution OR "ursodeoxycholic acid" OR "endoscopic retrograde cholangiopancreatography" OR "Percutaneous cholecystolithotomy" OR "methyl tert-butyl ether" OR ursodiol)) NOT PICS | 130 |
| | Updated search as on 12th January 2021 | 74 |
| | Total | 1945 |

**Appendix 2.1.3 Search terms and no. of hits in Embase**

| PICOS | EMBASE Search terms | Hits (on date 16th July 2020) |
|---|---|---|
| P | ‘gall bladder'/exp OR 'gall bladder' OR 'gallbladder'/exp OR gallbladder OR 'cholecystitis'/exp OR cholecystitis OR 'cholelithiasis'/exp OR cholelithiasis OR 'gallstone'/exp OR gallstone OR 'gall'/exp OR gall OR 'cholecystolithiasis'/exp OR cholecystolithiasis OR 'calculi'/exp OR calculi OR 'choledocholithiasis'/exp OR choledocholithiasis OR 'bile duct stone'/exp OR 'bile duct stone' OR 'cbd stone' OR 'biliary disease'/exp OR 'biliary disease' OR 'biliary tract disease'/exp OR 'biliary tract disease' OR “gallbladder inflammation” | 356,517 |
| I | cholecystectomy OR 'gallbladder removal' OR 'gallbladder excision' OR ('surgical removal' AND ('gall bladder' OR gallbladder)) OR ('surgical excision' AND ('gall bladder' OR gallbladder)) OR 'restrictive strategy' OR cholecystostomy OR 'biliary tract surgery'/exp OR 'bile duct operation' OR 'bile duct surgery' OR 'bile tract surgery' OR 'biliary surgery' OR 'biliary tract operation' OR 'biliary tract reoperation' OR 'biliary tract surgery' OR 'biliary tract surgical procedures' OR 'gall bladder surgery' OR 'gallbladder operation' OR 'gallbladder surgery' OR 'sphincterotomy, transhepatic' OR 'surgery, biliary tract' | 89,610 |
| C | 'conservative management' OR 'conservative therapy' OR 'conservative treatment' OR 'nonoperative treatment' OR 'nonsurgical treatment' OR 'organ sparing treatment' OR 'organ sparing treatments' OR 'treatment, conservative' OR analges* OR 'non-steroid anti-inflammatory' OR 'non-steroidal anti-inflammatory' OR nsaid OR 'anti inflammatory' OR antinflammatory OR antibiotic* OR supportive OR 'non invasive' OR 'non surgical' OR 'non operative' OR 'wait and watch' OR 'wait and see' OR 'watchful waiting' OR 'usual care' | 1,783,181 |
| S | trial OR trail OR blind OR rct OR randomization OR randomisation OR randomized OR randomised OR placebo OR 'randomized control trial' OR 'randomized controlled trial' OR 'randomized controlled trail' OR 'randomized control trail' OR 'controlled clinical trial' OR randomly OR groups OR 'randomised controlled study' OR 'randomized controlled study' | 5,139,403 |
| PICS | | 1646 |

**Appendix 2.1.4 Search terms and no. of hits in Scopus**

| PICOS | **SCOPUS Search terms** | **Hits (on 16th July 2020)** |
|---|---|---|
| **P** | ALL(“gallbladder" OR gallbladder OR cholecystitis OR cholecystitis OR cholelithiasis OR cholelithiasis OR "gallstone" OR gallstone OR cholecystolithiasis OR calculi OR choledocholithiasis OR choledocholithiasis OR "bile duct stone" OR "cbd stone" OR "biliary disease" OR "biliary tract disease" OR “Gallbladder inflammation” ) | **630,221** |
| **I** | ALL ( cholecystectomy OR "gallbladder removal" OR "gallbladder excision" OR ( "surgical removal" AND ( "gall bladder" OR gallbladder ) ) OR ( "surgical excision" AND ( "gall bladder" OR gallbladder ) ) OR "restrictive strategy" OR cholecystostomy OR "biliary tract operation" OR "biliary tract reoperation" OR "biliary tract surgical procedures" OR "gallbladder operation" OR sphincterotomy OR surger* AND (gall OR biliar*) ) | **283,560** |
| **C** | ALL conservative OR observatio* OR analgesi* OR (nonsteroid AND anti-inflammatory) OR "non-steroidal anti inflammatory" OR nsaid OR anti inflammatory OR antinflammatory OR anti-infective OR anti bacterial OR supportive OR non invasive OR noninvasive OR non surgical OR nonsurgical OR non operative OR nonoperative OR "wait and watch" OR "wait and see" OR watchful-waiting OR "usual care" ) | **9,204,582** |
| **S** | ALL ( trial OR trail OR blind OR rct OR randomization OR randomisation OR randomized OR randomised OR placebo OR 'randomized control trial' OR 'randomized controlled trial' OR 'randomized controlled trail' OR 'randomized control trail' OR 'controlled clinical trial' OR randomly OR groups OR 'randomised controlled study' OR 'randomized controlled study' ) | **1,184,853** |
| **PICS** | Limited only to journal | **2.903** |

**Health-related quality of life among patients with gallstone disease: A systematic review and meta-analysis of Euroqol (EQ-5D) utility scores**

**Appendix 2.2.1 PRISMA Checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Yes, 42 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | NA |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Yes, 43 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Yes, 43 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Yes, 43 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Yes, 43 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Yes, 43 |

| | | | |
|---|---|---|---|
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Yes, appendix 2.2.1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Yes, 44 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Yes, 44 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Yes, 44 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Yes, 44 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Yes, 50-54 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | Yes, 50-54 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Yes Table 2.2.2, 2.2.3, & 2.2.4 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | No |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Yes, Fig 2.2.1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 2.2.1 |

| | | | |
|---|---|---|---|
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Yes, 44 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Yes, 50-54 Figure 2.2.2 to 2.2.7 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Yes, 50-54 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | No |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | No |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Yes, 55 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Yes, 55 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Yes, 56 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | No |

**Appendix 2.2.1 Search terms used in PubMed using PICO method**

| **Database: PubMed Date: Feb-2021** | **Search words** | **Number of records** |
|---|---|---|
| **P(Population)** | Gallstone OR "Gall stone" Cholelithiasis OR Cholecystitis OR Gallbladder OR "Gall bladder" OR Cholecystolithiasis OR Choledocholithiasis OR "bile duct stone" OR "cbd stone" OR "biliary disease" OR "biliary tract disease" OR cholangitis OR "gallstone pancreatitis" OR "biliary pancreatitis" OR cholecystectomy OR ("surgical removal" AND ("gall bladder" OR gallbladder)) OR ("surgical excision" AND ("gall bladder" OR gallbladder)) OR "bile duct operation" OR "bile duct surgery" | 113,381 |
| **O(Outcome)** | Nottingham Health Profile OR Sickness Impact Profile OR GIQLI OR EQ-5D OR Euroqol OR EQ5D OR EQ5-D OR PROMS OR "patient reported outcome" OR “patient reported outcomes" OR QoL OR HRQoL OR 15D OR SF-36 OR "Short Form 36" OR "Short Form 12" OR SF-12 OR SF-6D OR "Short form 6D" OR "Short form 6 Dimension" OR "Medical outcomes study" OR “Quality of life” | 456,252 |
| **P AND O** | | 1,257 |

**Appendix 2.2.3 Search terms used in Scopus using PICO method**

| **Database: Scopus** Date: **Feb-2021** | **Search words** | Number of records |
|---|---|---|
| **P(Population)** | gallstone OR "Gall stone" OR cholelithiasis OR cholecystitis OR gallbladder OR "Gall bladder" OR cholecystolithiasis OR choledocholithiasis OR "bile duct stone" OR "cbd stone" OR "biliary disease" OR "biliary tract disease" OR cholangitis OR "gallstone pancreatitis" OR "biliary pancreatitis" OR cholecystectomy OR "bile duct operation" OR "bile duct surgery" | 304,317 |
| **O(Outcome)** | "Nottingham Health Profile" OR "Sickness Impact Profile" OR GIQLI OR EQ-5D OR Euroqol OR EQ5D OR EQ5-D OR PROMS OR "patient reported outcome" OR "patient reported outcomes" OR QoL OR HRQoL OR SF-36 OR "Short Form 36" OR "Short Form 12" OR SF-12 OR SF-6D OR "Short form 6D" OR "Short form 6 Dimension" OR "Quality of life" | 1,356,296 |
| **P AND O** | | 2652 |

**Systematic review and meta-analysis of economic evaluations in gallstone disease**
**Appendix 3.1.1 Assessment of Risk of Bias using ECOBIAS Checklist**

| Author Year<br>Issue addressed | Bass 1993 | Gurusamy 2012 | Johner 2013 | Kang 2017 | Kerwat 2018 | Parmar 2014 | Paulose 2007 | Rystedt 2017 | Sutton 2016 | Wilson 2010 | Bass 1991 | Teerawattanam 2005 | Keranen 2007 | Javid 2016 | Macafee 2009 | Mestral 2015 | Rosenmuller 2017 | Weinstein 1990 | Dageforde 2012 | Morris 2014 | Gregor 1996 | Howard 2006 | Brazzeli 2014 | Morris 2015 | Vergel 2006 | Oliver 2015 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Narrow perspective bias | P | Y | P | P | P | Y | Y | P | Y | Y | N | Y | UC | P | Y | P | Y | Y | Y | P | P | UC | Y | P | Y | P |
| Inefficient comparator bias | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Cost measurement omission bias | P | Y | P | Y | P | P | P | P | Y | Y | Y | Y | P | P | Y | P | Y | P | P | P | P | P | P | P | P | P |
| Intermittent data collection bias | UC | Y | Y | Y | Y | Y | P | UC | Y | Y | P | Y | N | P | Y | Y | Y | N | Y | Y | UC | P | Y | Y | Y | Y |
| Invalid valuation bias | P | Y | P | Y | P | P | P | P | Y | Y | P | Y | P | P | Y | Y | UC | N | Y | P | P | P | Y | P | P | P |
| Ordinal ICER bias | P | Y | UC | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | UC | UC | UC | Y | P | UC | UC | UC | UC |
| Double-counting bias | UC | P | P | P | UC | UC | P | P | P | P | UC | UC | UC | UC | UC | UC | UC | UC | P | P | UC | P | P | P | P | P |
| Inappropriate discounting bias | Y | Y | N | Y | N | N | N | Y | Y | N | N | Y | UC | N | N | Y | N | Y | Y | Y | UC | N | Y | N | N | Y |
| Limited sensitivity analysis bias§ | UC | P | P | P | UC | P | UC | UC | P | P | UC | P | P | UC | UC | P | P | P | P | P | P | UC | N | P | P | P |
| Sponsor bias | N | UC | UC | Y | UC | Y | Y | UC | UC | UC | UC | Y | UC | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | N | N |
| Reporting and dissemination bias | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | Y | Y | UC | Y | NA | Y | NA | UC | UC | UC | UC | Y | UC | UC | N |
| Structural assumptions bias | UC | Y | Y | Y | Y | N | UC | UC | Y | Y | Y | Y | NA | NA | NA | Y | NA | Y | Y | Y | UC | Y | Y | Y | Y | Y |
| No treatment comparator bias | P | Y | Y | Y | Y | P | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Wrong model bias | UC | Y | Y | Y | Y | Y | UC | UC | Y | Y | Y | Y | NA | P | NA | Y | NA | Y | Y | Y | UC | Y | Y | Y | Y | Y |
| Limited time horizon bias | P | P | P | Y | P | UC | P | P | P | P | P | N | P | P | NA | Y | NA | UC | P | P | P | UC | Y | P | Y | N |
| Bias related to data identification | P | Y | P | Y | Y | Y | P | Y | Y | Y | Y | Y | UC | UC | Y | Y | P | UC | P | P | P | P | P | P | P | P |
| Bias related to baseline data | P | Y | P | Y | Y | Y | P | UC | Y | Y | Y | Y | UC | UC | UC | UC | P | UC | P | P | Y | P | P | P | P | P |
| Bias related to treatment effects | P | Y | P | P | P | P | UC | P | Y | P | Y | Y | Y | UC | UC | UC | P | P | N | UC | Y | P | P | P | P | P |
| Bias related to quality-of-life weight (utilities) | P | Y | Y | Y | Y | Y | P | P | Y | Y | Y | Y | Y | Y | Y | Y | P | P | P | Y | Y | P | Y | Y | Y | Y |
| Non-transparent data incorporation bias | P | P | Y | P | P | Y | P | UC | Y | Y | Y | Y | N | P | Y | Y | Y | Y | P | Y | P | P | Y | Y | Y | Y |
| Limited scope bias | UC | P | P | P | UC | P | UC | UC | P | P | P | P | UC | UC | P | P | P | P | P | P | P | UC | P | P | UC | UC |
| Bias related to internal consistency | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC | UC |

NA-Not applicable, N-No, P-Partly, UC-Unclear, Y-Yes,

**Appendix 3.1.2 PRISMA Check list table**

| Section/topic | # | Checklist item | Reported on page # | | |
|---|---|---|---|---|---|
| **TITLE: SYSTEMATIC REVIEW AND META-ANALYSIS OF ECONOMIC EVALUATIONS IN GALLSTONE DISEASE** | | | **CUA** | **CMA** | **Costing** |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Yes, 57 | Yes, 75 | Yes, 79 |
| **ABSTRACT** | | | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: | NA | NA | NA |
| **INTRODUCTION** | | | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Yes, 57-58 | Yes, 75 | Yes, 79 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Yes, 58 | Yes, 75 | Yes, 79&80 |
| **METHODS** | | | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Yes, 59 | Yes, 75 | Yes, 80 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Yes, 59-60 | Yes, 77 Table 3.2.1 | Yes,79&80 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Yes, 59-60, Table 3.1.1 | Yes, 75, Table 3.1.1 | Yes, 80, |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Yes, 59 & appendix 3.1.3 | Yes, 75, Table 3.1.3 | Yes,99,appendix table 3.1.3 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Yes, 59-60 & Figure 3.1.1 | Yes, 75, Table 3.1. | Yes,80, 81, 83, figure .3.1.1, |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Yes, 60 | Yes 75-76 | Yes, 81 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Yes, 60 | Yes, 75 | Yes, 81 |

| | | | | | |
|---|---|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Yes, 60 | Yes | Yes, 82 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Yes, 61-62 | NA | Yes, 81 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | Yes, 61 | Yes, Table – 3.2.1 | Yes, 81 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Yes, 60 | Yes, Table – 3.2.1 | NA |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Yes, 61-62 | NA | NA |
| **RESULTS** | | | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Yes, 68 & Figure 3.1.1 | Yes, 76 & Figure 3.1.1 | Yes, figure .3.1.1, |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Yes, 68 & Figure 3.1.1, table 3.1.1 | Yes, 76 & Figure 3.1.1 | Yes, 83,Table 3.3.1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Yes, 68, Appendi fig 3.1.1 | Yes, 76 | Yes, 3.3.2 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Yes, 62-69, Figure 3.1.2 to 3.1.3 | Yes, 76 | NA |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Yes, 68-69 | Yes, 77 | NA |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Yes, 69, Figure 3.1.4 | | NA |

| | | | | | |
|---|---|---|---|---|---|
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Yes, 70-72. Figure 3.1.5 to 3.1.8 | NA | NA |
| **DISCUSSION** | | | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Yes, 72-74 | Yes. 78 | Yes,92, |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Yes, 74 | Yes, 78 | Yes, 93 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Yes, 74 | | Yes, 93 |
| **FUNDING** | | | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | NA | NA | NA |

**Appendix 3.1.3 Search Strategy**

| | PUBMED Search | No of Hits on 21st July 2020 |
|---|---|---|
| P | "gall bladder" OR gallbladder OR cholecystitis OR Cholelithiasis OR gallstone OR “gall stone” OR “gall stones” OR cholecystolithiasis OR "bile duct stone" OR “common bile duct” OR "biliary disease" OR "biliary tract disease" OR cholec* OR “gallbladder inflammation” OR cholecystectomy OR "gallbladder removal" OR "gallbladder excision" OR ("surgical removal" AND ("gall bladder" OR gallbladder)) OR ("surgical excision" AND ("gall bladder" OR gallbladder)) OR "restrictive strategy" OR cholecystectomy OR "biliary tract surgery" OR "bile duct operation" OR "bile duct surgery" OR "bile tract surgery" OR "biliary surgery" OR "biliary tract operation" OR "biliary tract reoperation" OR "biliary tract surgery" OR "biliary tract surgical procedures" OR "gall bladder surgery" OR "gallbladder operation" OR "gallbladder surgery" OR “Sphincterotomy” OR (“robotic” AND “cholecystectomy”) | 154,847 |
| Costs | cost OR costs OR (“Expenditure” NOT energy) OR “money” OR “finance” OR “budget” OR “payment” OR "economics"[MeSH Terms] OR price | 1,265,302 |
| Outcomes | benefi* OR “minimi*”OR “quality of life” OR “QALY” OR “quality adjusted” OR “life year” OR “life years” OR “DALY” OR “disability adjusted” OR “ICER” OR “ICERS” OR “utility” OR “benefit ratio” OR INB OR “healthy year equivalent” OR “healthy years equivalent” OR “willingness to pay” OR markov OR “decision tree” OR “decision model” OR “decision analytic” OR horizon OR “discounting” OR “discount rate” OR "inflation, economic"[MeSH Terms] OR "economics"[MeSH Terms] OR "economics pharmaceutical"[MeSH Terms] OR averted OR prevented OR | 13,202,634 |

| | | |
|---|---|---|
| | "saved" OR "cured" OR recovered OR "outcome" OR "outcomes" OR efficacy OR effectiveness | |
| | PCO | 2,977 |
| | **EMBASE Search** | **No of Hits on 21st July 2020** |
| P | cholecystitis OR Cholelithiasis OR gallstone OR 'gall stone' OR 'gall stones' OR cholecystolithiasis OR 'bile duct stone' OR 'biliary disease' OR 'biliary tract disease' OR cholec* OR 'gallbladder inflammation' OR cholecystectomy OR 'gallbladder removal' OR 'gallbladder excision' OR ('surgical removal' AND ('gall bladder' OR gallbladder)) OR ('surgical excision' AND ('gall bladder' OR gallbladder)) OR 'restrictive strategy' OR cholecystectomy OR 'biliary tract surgery' OR 'bile duct operation' OR 'bile duct surgery' OR 'bile tract surgery' OR 'biliary surgery' OR 'biliary tract operation' OR 'biliary tract reoperation' OR 'biliary tract surgery' OR 'biliary tract surgical procedures' OR 'gall bladder surgery' OR 'gallbladder operation' OR 'gallbladder surgery' OR 'Sphincterotomy' | 180,575 |
| Costs | 'cost benefit analysis'/exp OR 'cost analysis' OR 'cost benefit' OR 'cost benefit analysis' OR 'cost benefit ratio' OR 'cost-benefit analysis' OR 'cost minimization analysis'/exp OR 'cost minimization' OR 'cost minimization analysis' OR 'quality of life' OR 'QALY' OR 'quality adjusted' OR 'life year' OR 'life years' OR 'DALY' OR 'disability adjusted' OR 'ICER' OR 'ICERS' OR INB OR 'cost effectiveness analysis'/exp OR 'cost effectiveness' OR 'cost effectiveness analysis' OR 'cost effectiveness ratio' OR 'cost efficiency analysis' OR 'willingness to pay' OR 'cost utility analysis'/exp OR 'cost utility' OR 'cost utility analysis' | 833,703 |
| PC | P & C | 4,065 |

| | | |
|---|---|---|
| | P & C (restricted to journal articles + in press) | 2,037 |
| | **Scopus Search** | **No of Hits on 21st July 2020** |
| P | cholecystitis OR Cholelithiasis OR gallstone OR “gall stone” OR “gall stones” OR “cholecystolithiasis” OR “bile duct stone” OR “biliary disease” OR “biliary tract disease” OR cholec* OR “gallbladder inflammation” OR cholecystectomy OR “gallbladder removal” OR “gallbladder excision” OR cholecystectomy OR “biliary tract surgery” OR “bile duct operation” OR “bile duct surgery” OR “bile tract surgery” OR “biliary surgery” OR “biliary tract operation” OR “biliary tract reoperation” OR “biliary tract surgery” OR “gall bladder surgery” OR “gallbladder operation” OR “gallbladder surgery” OR “Sphincterotomy” | 312,298 |
| Costs | cost* OR "cost effectiv*" OR "cost utility" OR "Cost benefit" OR "Cost-Benefit" OR "Quality Adjusted Life Years" OR qaly OR ly OR "life year$" OR daly OR “disability adjusted” OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR “benefit ratio” OR ‘cost benefit’ OR ‘cost minimisation’ OR “cost effectiveness” OR “cost effectiveness ratio” OR “cost efficiency analysis” OR “cost utility” | 557,452 |
| PC | P & C | 6,678 |
| | P & C (restricted to articles + in press) | 3,696 |

**Systematic review of costing studies in gallstone disease**

**Appendix 3.3.1 Assessment of Risk of Bias using NIH Quality Assement Checklist**

| Author, Year | Components | | | | | | | | | | | | | | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Dua,2013 | Y | Y | Y | Y | N | Y | Y | CD | Y | Y | Y | Y | CD | Y | G |
| Stey,2015 | Y | Y | Y | Y | Y | CD | Y | Y | Y | CD | Y | Y | CD | Y | G |
| Tran,2019 (a) | Y | Y | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | CD | Y | G |
| Tran,2019 (b) | Y | Y | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | CD | Y | G |
| George, 2020 | Y | Y | Y | Y | Y | CD | Y | Y | Y | CD | Y | CD | Y | Y | G |
| Kuy,2011 (a) | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | CD | CD | Y | F |
| Kuy,2011 (b) | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | CD | CD | Y | F |
| Kuy,2011 (c) | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | CD | CD | Y | F |
| Obrien,2019 (a) | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | N | CD | Y | F |
| Obrien,2019 (a) | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | N | CD | Y | F |
| Kapoor,2011 | Y | Y | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | NR | Y | G |

| Author, Year | Components | | | | | | | | | | | | | | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Hsu,2010 (a) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | CD | CD | Y | G |
| Demco,1997 (a) | Y | N | N | Y | CD | Y | Y | CD | CD | NR | Y | NR | CD | Y | F |
| Demco,1997 (b) | Y | N | N | Y | CD | Y | Y | CD | CD | NR | Y | NR | CD | Y | F |
| Hardy, 1994 | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | CD | NR | Y | F |
| Jones,2011 | Y | Y | Y | Y | NR | CD | Y | CD | Y | CD | Y | NR | CD | Y | F |
| Beck,2013 (a) | Y | Y | Y | Y | Y | NR | Y | NR | Y | CD | Y | CD | CD | Y | F |
| Love,2011 (a) | Y | Y | Y | Y | Y | Y | Y | Y | CD | Y | Y | Y | CD | Y | G |
| Beck,2013 (b) | Y | Y | Y | Y | Y | NR | Y | NR | Y | CD | Y | CD | CD | Y | F |
| Bedeir,2015 (a) | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | Y | CD | Y | F |
| Ghanzanfar,2019 | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | CD | CD | Y | F |
| Hsu,2010 (b) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | CD | CD | Y | G |
| Menezes,2016 | Y | Y | Y | Y | N | CD | Y | CD | Y | N | Y | CD | CD | Y | F |
| Hardy, 1994 (b) | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | CD | NR | Y | F |
| Bedeir,2015 (b) | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | Y | CD | Y | F |

| Author, Year | Components | | | | | | | | | | | | | | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Love,2011 (b) | Y | Y | Y | Y | Y | Y | Y | Y | CD | Y | Y | Y | CD | Y | G |
| Koo,1996 | Y | Y | N | Y | Y | CD | Y | CD | Y | CD | Y | CD | N | N | F |
| Traverso,1995 | Y | Y | Y | Y | N | N | Y | CD | Y | CD | N | N | CD | CD | F |
| Demco,1997 (c) | Y | N | N | Y | CD | Y | Y | CD | CD | NR | Y | NR | CD | Y | F |
| Demco,1997 (d) | Y | N | N | Y | CD | Y | Y | CD | CD | NR | Y | NR | CD | Y | F |
| Orlando,1996 | Y | Y | Y | Y | N | CD | Y | CD | Y | CD | Y | CD | N | N | F |
| Chatterjee,2013 | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | CD | N | Y | F |
| Jones,2011 (b) | Y | Y | Y | Y | NR | CD | Y | CD | Y | CD | Y | NR | CD | Y | F |
| Board, 2000 | Y | Y | Y | Y | Y | CD | Y | CD | Y | NR | Y | NR | NR | CD | F |
| Waqas,2014 | Y | Y | Y | Y | Y | CD | Y | NR | Y | CD | Y | NR | NR | Y | F |
| Anderson,1991 (a) | Y | Y | Y | Y | N | NR | Y | NR | Y | NR | Y | CD | CD | N | F |
| Peters,1990 (b) | Y | Y | Y | Y | N | CD | Y | CD | Y | NR | Y | CD | CD | Y | F |
| Calvert,2000 (b) | Y | Y | Y | Y | N | CD | Y | CD | Y | CD | Y | NR | NR | Y | F |
| Ure,1995 | Y | Y | Y | Y | Y | CD | Y | CD | Y | CD | Y | CD | NR | Y | F |

| Author, Year | Components | | | | | | | | | | | | | | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
| Prigoff,2016 | Y | Y | Y | Y | Y | Y | Y | CD | Y | CD | Y | Y | CD | Y | G |
| Fleisher,1999 (a) | Y | Y | Y | Y | N | CD | Y | CD | Y | CD | CD | CD | CD | Y | F |
| Fleisher,1999 (b) | Y | Y | Y | Y | N | CD | Y | CD | Y | CD | CD | CD | CD | Y | F |
| Calvert,2000 (a) | Y | Y | Y | Y | N | CD | Y | CD | Y | CD | Y | NR | NR | Y | F |
| Anderson,1991 (b) | Y | Y | Y | Y | N | NR | Y | NR | Y | NR | Y | CD | CD | N | F |
| Bhargava,2016 (a) | Y | Y | Y | Y | N | Y | Y | NR | Y | NR | Y | CD | CD | Y | F |
| Bhargava,2016 (b) | Y | Y | Y | Y | N | Y | Y | NR | Y | NR | Y | CD | CD | Y | F |
| Peters,1990 (a) | Y | Y | Y | Y | N | CD | Y | CD | Y | NR | Y | CD | CD | Y | F |

CD-cannot determine; NR-Not reported; G-Good; F-Fair; Y-Yes; N-No

**Cost-Effectiveness of Cholecystectomy Compared With Conservative Management in People Presenting With Uncomplicated Symptomatic Gallstones (Biliary Pain) or Cholecystitis in India**

**Appendix 4.1 Risk of bias assessment – CHEERS Checklist**

| Section/item | Item No | Recommendation | Reported on page no/ para no |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared | page 104 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | Not applicable |
| **Introduction** | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study.<br>Present the study question and its relevance for health policy or practice decisions | page 104 |
| **Methods** | | | |
| Target populatior and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | page 105 para 2 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | Not applicable |
| Study perspectiv | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | page 105 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | page 105 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | page 105 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | page 105 |

| Section/item | Item No | Recommendation | Reported on page no/ para no |
|---|---|---|---|
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | page 105 |
| Measurement of effectiveness | 11a | Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | page 111, para 2 |
| | 11b | Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | page 106& 107 |
| Measurement and valuation of preference-based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | Not applicable |
| Estimating resources and costs | 13a | Single study-based economic evaluation Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs | Not applicable |
| | 13b | Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | page 106 |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | page 106, para 3 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show | Page109, Figure 4.1 |

| Section/item | Item No | Recommendation | Reported on page no/ para no |
|---|---|---|---|
| | | model structure is strongly recommended. | |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | page 120 & 121 |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | page 109&110 |
| **Results** | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | Table 4.1 |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | page 112,para 1, table 4.2, line 12 |
| Characterising uncertainty | 20a | Single study-based economic evaluation Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | Not applicable |
| | 20b | Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | OWSA page 115-118, figure 4.3 - 4.5<br>PSA page 118-122<br>Figure 4.6 - 4.11<br>Scenario page - 123, |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can | Not applicable |

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|---|---|---|---|
| | | be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | |
| **Discussion** | | | |
| Study findings, limitations, generalisability, and uncertainty | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Page 123 |
| **Other** | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | Not applicable |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | Not applicable |