



# 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

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## ABSTRACT

**Introduction** Cholecystectomy is a standard treatment in the management of symptomatic gallstone disease. Current literature has contradicting views on the cost-effectiveness of different cholecystectomy treatments. We have conducted a systematic reappraisal of literature concerning the cost-effectiveness of cholecystectomy in management of gallstone disease.

**Methods** We systematically searched for economic evaluation studies from PubMed, Embase and Scopus for eligible studies from inception up to July 2020. We pooled the incremental net benefit (INB) with a 95% CI using a random-effects model. We assessed the heterogeneity using the Cochrane-Q test,  $I^2$  statistic. We have used the modified economic evaluation bias (ECOBias) checklist for quality assessment of the selected studies. We assessed the possibility of publication bias using a funnel plot and Egger's test.

**Results** We have selected 28 studies for systematic review from a search that retrieved 8710 studies. Among them, seven studies were eligible for meta-analysis, all from high-income countries (HIC). Studies mainly reported comparisons between surgical treatments, but non-surgical gallstone disease management studies were limited. The early laparoscopic cholecystectomy (ELC) was significantly more cost-effective compared with the delayed laparoscopic cholecystectomy (DLC) with an INB of US\$1221 (US\$187 to US\$2255) but with high heterogeneity ( $I^2=73.32\%$ ). The subgroup and sensitivity analysis also supported that ELC is the most cost-effective option for managing gallstone disease or cholecystitis.

**Conclusion** ELC is more cost-effective than DLC in the treatment of gallstone disease or cholecystitis in HICs. There was insufficient literature on comparison with other treatment options, such as conservative management and limited evidence from other economies.

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## INTRODUCTION

Gallstones constitute one of the most common and expensive gastrointestinal

disorders and cause significant epidemiological and economic burdens worldwide. Approximately 20% of people with gallstones experience symptoms requiring medical attention or surgery, while the remaining 80% remain asymptomatic for many years.<sup>1</sup> Treatment options for cholecystitis include surgical (cholecystectomy-open and laparoscopic) or conservative management. The treatment of gallstone disease is expensive and often engenders substantial economic and social burdens if symptoms or complications occur. The healthcare system in the USA alone reported treatment costs as US\$6.5 billion per year.<sup>2</sup>

The optimal timing and the treatment choice for cholecystectomy in patients with acute cholecystitis have always been contentious.<sup>3</sup> In earlier days, several weeks of hospital stay and an initial intense medical management were the norm before an open cholecystectomy (OC).<sup>4</sup> Introducing early cholecystectomy (open or laparoscopic) reduced the overall treatment duration considerably.<sup>3</sup> Performing early surgery for cholecystitis has the advantage of reducing hospital stay and circumvents the risk of emergency surgery in the wake of a non-resolved or recurrent issue.<sup>4</sup>

Delayed laparoscopic cholecystectomy (DLC) and OC require multiple hospital visits considering 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.<sup>5</sup> 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.<sup>4</sup> Studies have confirmed that ELC also

reduces treatment costs significantly.<sup>6–8</sup> However, uncertainty still prevailed around the ELC as the standard of care, conceivably due to fear of complication. The unpredictability in health outcomes and costs makes comparison of the overall cost-effectiveness of ELC over DLC debatable as well as imperative.<sup>7</sup>

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 interventions and comparators in terms of the monetary cost and a generic measure of health gain.<sup>9</sup> Concurrently, even the reported cost-effectiveness studies depict conflicting results, as some studies have reported ELC as cost-effective (CE).<sup>7 10 11</sup> In contrast, some others<sup>12 13</sup> concluded it was only cost saving and not CE. 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 and 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-laparoscopic Cholecystectomy (LC)) compared with a comparator intervention (delayed/open- LC, conservative management). Therefore, the results could provide appropriate information to choose the most CE method.

## 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).<sup>14</sup> This study is part of a more extensive economic evaluation study.<sup>15</sup>

### Data sources, screening and study selection

The search was performed from inception to 1 July 2020, in PubMed, Embase and Scopus databases. We followed the Population, Intervention, Comparator, Outcome approach 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 or endoscopic management covered the comparator strategy. The possible economic outcomes included were incremental cost-effectiveness ratio (ICER), incremental net benefit (INB), quality-adjusted life-years (QALYs) gained, life years saved and costs saved.

The detailed search terms and search strategies are reported in online supplemental material 1. The total number of studies identified from the database search was

8710, including 2977 from PubMed, 3696 from Scopus and 2037 from Embase. After removing the duplicates (n=1414), 7296 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, MN and AS) for potential inclusion using the Rayyan software.<sup>16</sup> After screening, the authors (BSB, MN and AS) independently reviewed the full-text articles (n=660). The final list of studies that met the inclusion and exclusion criteria was prepared by the authors' mutual consensus (BS, MN and AS).

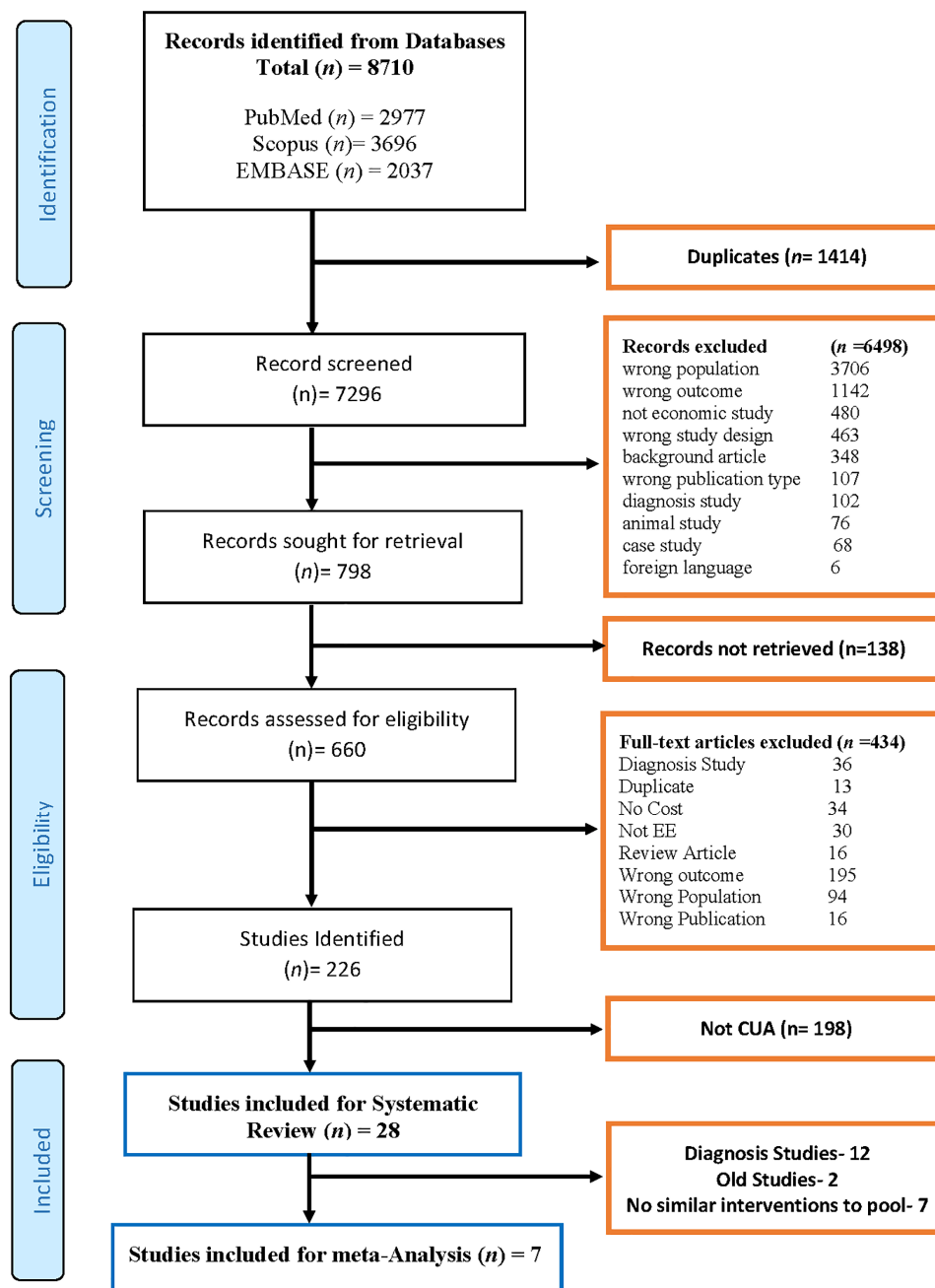
All full economic evaluation studies with a study population of cholelithiasis or cholecystitis that compared the costs and consequences of intervention with a comparator in terms of QALYs, ICERs or INBs were included in the study. Studies other than cost–utility analysis (CUA), reviews, letters, editorials, abstracts, books, reports, grey literature and methodological articles were excluded from the study. We identified 28 studies for systematic review based on these inclusion–exclusion criteria, and the data were extracted from these papers using a data extraction form. The PRISMA flow chart of the screening process is appended as [figure 1](#).

The data extraction form captured general study characteristics, characteristics of the studied population, economic input parameters—cost and incremental/delta costs (C and  $\Delta C$ ), clinical effectiveness and incremental/delta effectiveness (E and  $\Delta E$ ), ICERs, INB values and their measures of dispersion (ie, SD, SE or 95% CI), and willingness-to-pay (WTP) threshold (K) as well as details of intervention and comparator outcomes data for the pooling domain. From the CE plane graph, we have extracted  $\Delta C$  and  $\Delta E$  using WebPlotDigitizer software.<sup>17</sup> The intervention of interest was early surgical removal (within 7 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, AS and SKS) 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 evaluation bias (ECOBIA) checklist.<sup>18</sup> It considers overall biases (11 items) and biases from model-specific aspects, that is, structure (4 items), data (6 items) and internal consistency (1 item). Each item was graded as yes, partly, unclear, no or not applicable (online supplemental figure 1).

### The outcome of interest

The primary outcome parameter of interest was INB, defined as,  $INB = K * \Delta E - \Delta C$ , where K was the WTP threshold,  $\Delta C$ —incremental cost (ie, the difference in costs between intervention and comparator),  $\Delta E$ —incremental effectiveness (ie, the difference in effectiveness between intervention and comparator). The positive INB favours treatment, that is, the intervention was CE. In contrast, a negative INB suggests favouring the comparator, that is, the intervention was not CE. We used INB instead of ICER as the effect measure



**Figure 1** PRISMA flow chart of selection of studies. CUA, cost–utility analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

because of limitations with ICER and the ambiguity in interpreting them.<sup>19 20</sup> 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.<sup>21</sup>

### Data preparation and statistical analysis

We followed the data preparation method and analysis as detailed in Bagepally *et al.*<sup>22</sup> In brief, to calculate the INB and its variance, mean values along with dispersions (SD, SE and 95% CI) of  $\Delta C$  and  $\Delta E$  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.<sup>19</sup>

Following the data preparation, INBs were pooled across studies stratified by low-income, lower-middle-income (LMIC), upper-middle-income and high-income countries (HICs) as per the World Bank classification. A meta-analysis was applied to pool the INBs using a random-effects model if heterogeneity was present (ie,  $I^2 \geq 25\%$  or  $Q, p < 0.1$ ). 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. Furthermore, 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 V.16.<sup>23</sup> Two-sided  $p < 0.05$  was considered statistically significant.

## RESULTS

We retrieved 8710 potentially relevant studies through our search. Twenty-eight studies were eligible for the systematic review, as shown in the PRISMA flow diagram (figure 1). Of the identified 28 studies, 12 were diagnostic,<sup>24–35</sup> and the remaining 16 were therapeutic. Only 7 out of the 16 therapeutic studies were included in the meta-analysis.<sup>8 11–13 36–38</sup> The remaining nine studies were excluded because two<sup>39 40</sup> of them were conducted before the year 2000 and had considerable variation in their cost data; and seven had no similar intervention comparator duos to pool (table 1).

Based on analytical approach and design, 78.57% (N=22) studies were model-based, and the remaining 21.43% (N=6) studies were primary economic evaluations.<sup>10 13 28 40–42</sup> The model-based techniques used in these studies were decision tree (N=19, 67.86%) and Markov model (N=3, 10.71%).<sup>7 8 39</sup> 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,<sup>24 29 42 43</sup> and the remaining three studies did not mention the study perspective.<sup>13 35 44</sup>

The time horizons used in these studies vary from 1 year to a lifetime. The majority of the studies used a 1-year time horizon (N=13, 46.43%), followed by 5 years (N=5, 17.86%). Two studies each used 2-year and 3-year time horizons,<sup>11 43–45</sup> and only one study used lifetime horizons.<sup>27</sup> Five studies failed to mention a time horizon, and three were from before the year 2000.<sup>10 24 30 35 40</sup>

All the diagnostic studies evaluating the effectiveness of endoscopic retrograde cholangiopancreatography and endoscopic ultrasound over MR cholangiopancreatography (MRCP) reported MRCP as the dominant strategy, either as CE or by providing more QALYs compared with the alternatives. The initial diagnosis with MRCP was reported as the most CE option, with the highest monetary net benefit.<sup>30–34</sup>

Among the three therapeutic studies<sup>7 8 44</sup> that compared conservative management with surgery (LC), two studies reported that early detection and treatment of cholecystitis is cost saving and that ELC was less expensive and provided greater QALY gains compared with DLC and watchful waiting. Both these studies confirmed that DLC was the most expensive treatment and implied the need for early treatment.<sup>7 8</sup> In contrast, the study conducted by Parmar *et al* reported that observation was the most CE approach.<sup>44</sup> 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.<sup>10 39 40</sup> Contrastingly,

Teerawattananon and Mugford found that LC was not CE compared with OC.<sup>43</sup>

## Risk of bias assessment

The ECOBIAS checklist shows that best current practice was chosen as a comparator for most of the studies, and all the comparators have been described in adequate detail. Studies also reported a clear presentation of the data used in the model, provided sufficient detail on the costs, applied recommended discount rates and outwardly disclosed details of funding received. Bias related to 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 (see online supplemental figure 1).

## Pooled INBs of early versus DLC

The INBs of ELC vs DLC varied across the seven studies,<sup>8 11–13 36–38</sup> with high heterogeneity ( $I^2=73.32$ ) and a pooled INB of US\$1221 (US\$187 to US\$2255) (figure 2). The calculated overall INB and 95% CI values of the selected studies favour the intervention; infers that ELC is CE compared with the DLC in HICs. We found that the meta-analysis results are dominated by two studies<sup>11 12</sup> with 48% weightage each. We further conducted sensitivity analysis by omitting each of these studies one after the other, the results indicated these are source of heterogeneity but still ELC is CE; On omitting Kerwat *et al*, study the pooled INB US\$1798 (US\$1442 to US\$2154,  $I^2=0$ ),<sup>11</sup> while on omitting Morris *et al*, the pooled INB US\$588 (US\$232 to US\$944,  $I^2=0$ ).<sup>12</sup> However, on sensitivity analysis by omitting both the studies reduced the heterogeneity (US\$2146 (US\$–3427 to 7719),  $I^2=0$ ), but the statistical significance of ELC being CE is lost.

Examination of the evidence of publication bias on the funnel plot 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 (online supplemental figure 2). To distinguish between publication bias or other causes would be a challenge due to high between-study heterogeneity.

Subgroup analysis of the time horizon used for the study also indicates that ELC was significantly CE compared with DLC for 1-year and 5-year time frames. The pooled INBs of studies with 1-year and 5-year time horizon with 95% CI values was US\$1797 (US\$1441 to US\$2154) and US\$583 (US\$227 to US\$940), respectively (online supplemental figure 3). 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 US\$1223 (US\$161 to US\$2285) (online supplemental figure 4).

The countrywise pooled INB statistic from the subgroup analysis revealed that intervention was not CE in Canada (US\$1922 (–US\$5244 to US\$9088)), and there was no

**Table 1** Characteristics of studies included in the systematic review

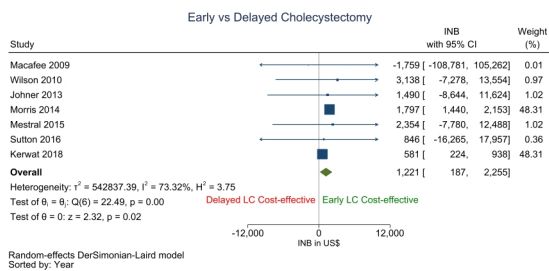
Author, year	Country	Setting	Study perspective	Target population	Time horizon (Year)	Discount rate (%)	Intervention	Comparator	Findings
Weinstein <i>et al</i> <sup>24</sup> 1990	USA	Risk group	Societal	Biliary colic, non-calcified gallstones	NA	5	Elective Chole	Ursodiol with surgery	Not Cost effective
Bass <i>et al</i> <sup>25</sup> 1991	USA	Others	Payers	Bile duct stones with gallstones	5	No	ESWL	Surgery	NA
Bass <i>et al</i> <sup>39</sup> 1993	USA	Others	Payers	Acute/chronic biliary pain	5	5	LC	OC	Dominant
Cook <i>et al</i> <sup>40</sup> 1994	Australia	Others	Payers	Underwent cholecystectomy	NA	No	LC, OC	LC, ESWL	LC dominant
Gregor <i>et al</i> <sup>30</sup> 1996	Canada	Others	Third Party Payers	CBD patients	NA	5	ERCP	No ERCP	ERCP dominant
Teerawattananon <i>et al</i> <sup>43</sup> 2005	Thailand	Country	Societal	Gallstone pancreatitis, bile duct stones	3	3.5	LC	OC	Not cost-effective
Howard <i>et al</i> <sup>34</sup> 2006	Australia	NA	Health System	Post cholecystectomy patients with biliary obstruction	1	No	MRCP	ERCP	Dominant
Vergel <i>et al</i> <sup>32</sup> 2006	UK	Risk group	Healthcare provider	CBD patients with biliary obstruction	1	No	MRCP	ERCP	Dominant
Poulose <i>et al</i> <sup>26</sup> 2007	USA	Others	Payers	symptomatic Cholelithiasis and incidental CDL at the time of LC	1	No	LCBDE	ERCP	Dominant
Keränen <i>et al</i> <sup>41</sup> 2007	Finland	Hospital	Healthcare Provider	Bile duct stone, diagnosed with cholelithiasis	1	No	From home to operation	Ward	Dominant
Macafee <i>et al</i> <sup>13</sup> 2009	UK	Hospital	Societal	Acute Biliary Cholic	1	No	Early LC	Delayed LC	ELC cost-saving
Wilson <i>et al</i> <sup>37</sup> 2010	UK	Country	Payers	Gallstone pancreatitis, cholecystitis	1	No	Emergency LC	Delayed LC	ELC dominant
Dageforde <i>et al</i> <sup>29</sup> 2012	USA	Others	Societal	Underwent cholecystectomy	1	3	Early HBS	Late HBS,	Dominant
Gurusamy <i>et al</i> <sup>45</sup> 2012	UK	Country	Payers	gall bladder stones with CBD stones	3	3.5	IOES	POES	Dominant
Johner <i>et al</i> <sup>38</sup> 2013	Canada	Others	Healthcare Provider	Acute cholecystitis	1	No	Early LC	Delayed LC	Dominant
Parmar <i>et al</i> <sup>44</sup> 2014	USA	NA	NA	bile duct stones/cholelithiasis	2	No	CM	Elective LC	CM cost-effective
Morris <i>et al</i> <sup>12</sup> 2014	UK	Others	UK NHS	LC for Mild, acute gallstone pancreatitis	1	No	Early LC	Late LC	ELC cost saving
Brazzelli <i>et al</i> <sup>7</sup> 2014	UK	NA	UK NHS	symptomatic uncomplicated gallstone, cholecystitis	5	3.5	Surgery (LC)	CM	LC cost-effective
Morris <i>et al</i> <sup>31</sup> 2015	UK	NA	UK NHS	CBD stone patients	1	No	EUS, MRCP	ERCP	MRCP cost-effective

Continued

Table 1 Continued

Author, year	Country	Setting	Study perspective	Target population	Time horizon (Year)	Discount rate (%)	Intervention	Comparator	Findings
Oliver <i>et al</i> <sup>33</sup> 2015	USA	Others	Healthcare provider	Biliary stricture without mass	5	3	ERCP	EUS, Surgery	EUS cost-effective
Javid <i>et al</i> <sup>10</sup> 2016	Iran	Hospital	Healthcare Provider	Undergone cholecystectomy	NA	No	LC	OC	Cost-effective
de Mestral <i>et al</i> <sup>6</sup> 2016	Canada	Hospital	Third-party payer	Cholecystitis	5	5	Delayed LC	Early LC	ELC cost-saving
Sun <i>et al</i> <sup>35</sup> 2016	USA	Others	NA	Intermediate bile duct stones	NA	No	IOUS, IOCP	EM	IOUS dominant
Sutton <i>et al</i> <sup>36</sup> 2016	UK	NA	Payers	Bile duct stones with gallstones	1	No	Delayed LC	Early LC	ELC dominant
Rosenmüller <i>et al</i> <sup>42</sup> 2017	Sweden	Others	Societal	Acute emergency gallstone pancreatitis bile duct stones	1	No	LC	SIOC	SIOC cost saving
Kang <i>et al</i> <sup>27</sup> 2017	USA	Country	US health system	Symptomatic bile duct stones with gallstones	Lifetime	3	MRCP	ASGE	Cost-effective
Rystedt <i>et al</i> <sup>28</sup> 2017	Sweden	Country	Payers	Symptomatic bile duct stones with gallstones	10	3	Routine IOCP	On demand IOCP	Not cost-effective
Kerwat <i>et al</i> <sup>11</sup> 2018	UK	Country	Payers	Acute bile duct stones with gallstones	2	No	Early LC	Delayed LC	ELC cost-effective

ASGE, American Society for Gastrointestinal Endoscopy; CBD, Common bile duct; CDL, choledocholithiasis; ELC, early laparoscopic cholecystectomy; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, Extracorporeal Shock Wave Lithotripsy; HBS, Hepatobiliary surgeon; IOCP, Intra operative Cholangiography; IOUS, Intraoperative ultrasonography; LC, laparoscopic cholecystectomy; LCBDE, Laparoscopic common bile duct Exploration; MRCP, MR cholangiopancreatography; NA, not available; OC, open cholecystectomy; SIOC, Single Incision open cholecystectomy.



**Figure 2** Comparison of incremental net benefit between early and delayed cholecystectomy. INB, incremental net benefit; LC, laparoscopic cholecystectomy.

heterogeneity between these studies ( $I^2=0$ ). Conversely, ELC was CE in the UK with a positive pooled INB of US\$1209 (US\$106 to US\$2311) but with substantial heterogeneity ( $I^2=82.17\%$ ) (online supplemental figure 5). 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.

All the selected studies followed the payer's perspective, except Macafee *et al*<sup>13</sup> which followed a societal perspective. The pooled INB values from the sensitivity analysis of all these studies, excluding the Macafee *et al* with a 95% CI, was US\$1221 (US\$161 to US\$2285) (online supplemental figure 6), depicts that ELC is CE over DLC.

## DISCUSSION

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

The subgroup analysis revealed that ELC was CE compared with 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 CE in studies from Canada but not from the UK; both are HICs, and this points out the high heterogeneity across available studies. Studies are limited in terms of different economies, mainly from LMICs, societal perspectives, and longer time horizons. Sensitivity analysis identified both Kerwat *et al* and Morris *et al* are the sources of heterogeneity, even though both of them had precise estimates or shorter 95% CI. Since, Kerwat *et al* is in scenario 5 and we used the variance from Morris *et al* (most similar study), hence, possibly the Morris *et al* study is the main source of heterogeneity. Further the study population of Morris *et al* study is mild acute gallstone disease with pancreatitis, which may be the reason for heterogeneity, while most of the other studies were with only gallstone disease.

Many retrospectives<sup>46 47</sup> and prospective studies<sup>48</sup> 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.<sup>49</sup> Overlapping meta-analysis has reported discordant results and conclusions. A systematic review of meta-analyses by Song *et al* 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 in quality of life when compared with DLC.<sup>50</sup> Recent meta-analyses also suggested ELC as safe and effective against DLC for acute cholecystitis within 7 days from presentation<sup>51</sup>; also, ELC should be preferred to DLC when feasible within 72 hours of the onset of symptoms.<sup>52</sup> In 2020, the World Society of Emergency Surgery recommended that ELC should be the standard of care whenever possible.<sup>53</sup>

Previous Randomised control trials have reported quality improvements and cost savings through same-day surgery (ELC) over preoperative admission.<sup>6 41</sup> Model-based CUAs have reported ELC as the optimal management for uncomplicated gallstones and less expensive, with more significant QALY gains than DLC or watchful waiting.<sup>8 11 38</sup> However, reported studies are mostly incongruous and clustered around the specific geography of HICs. Furthermore, 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.<sup>54</sup> Although early detection and treatment is clinically an effective strategy, synthesised 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 CE and superior to DLC, except for two studies.<sup>43 44</sup> Full economic evaluation studies in people with gallstones or cholecystitis comparing the cost-utility effectiveness of cholecystectomy to other treatments, especially conservative management, were largely limited.

Our study has several limitations. Most of the selected studies were from HICs, either the UK or Canada, limiting results to other countries, especially the LMICs. We had only one study with a societal perspective, and studies with indirect cost would provide a real-world comparison scenario. Hence, synthesised findings have limited generalisability when extrapolating the results to all other healthcare contexts. The inadequacy of similar studies to be pooled for the INB values for intervention and comparators only permitted us to perform the meta-analysis with seven studies. Due to a lack of peer-reviewed published literature, the idea of meta-analysis with the conservative gallstone disease management was curtailed. Further, due to limited information in the primary literature, sensitivity and subgroup analysis to explore comorbidity-related costs, gender differences, patient's age, etc could not be performed.

Future research from various economies, primarily LMICs, societal perspectives and longer time horizons are needed. Future research should be context-specific, include primary economic evaluations based on well-conducted clinical trials that provide a more accurate estimate of costs and benefits. Furthermore, timely cost-effectiveness evaluations of such interventions, will facilitate the incorporation of such health economic evidence into clinical practise. Thereby reducing barriers and overall poor uptake of economic evidence outside of health technology assessment and may positively influence the adoption and resource allocations for those interventions for greater societal benefit.

## Conclusion

The synthesised results from the available studies showed ELC is a CE option compared with DLC in the treatment of gallstone disease or cholecystitis in HICs. There is a need to generate comparative economic evidence between surgical and conservative management as well as other aspects of gallstone disease management, such as endoscopic approaches and diagnostic aspects.

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**Contributors** BBS: guarantor, conceptualisation, data curation, formal analysis, investigation, methodology, software, original draft, review and editing. SKS: data curation, formal analysis, original draft. AS: conceptualisation, data curation, formal analysis, original draft. MN: data curation, review and editing.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as online supplemental information.

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