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The optimal timing of laparoscopic cholecystectomy in patients with mild gallstone pancreatitis

A meta-analysis

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Abstract

Background: The optimal timing of laparoscopic cholecystectomy (LC) in patients with mild acute gallstone pancreatitis (MAGP) is controversial. The aim of this study was to systematically evaluate and compare the safety and efficacy of early laparoscopic cholecystectomy (ELC) and delayed laparoscopic cholecystectomy (DLC) in patients with MAGP.

Methods: A strict search was conducted of the electronic databases, including PubMed, MEDLINE Embase, the ISI Web of Science, and Cochrane Library for all relevant English literature and RevMan5.3 software for statistical analysis was used.

Results: A total of 19 studies comprising 2639 patients were included. There was no significant difference in intraoperative complications [risk ratio (RR) = 1.46; 95% confidence interval (CI) = 0.88–2.41; $P = .14$)], postoperative complications (RR = 0.81; 95% CI = 0.58–1.14; $P = .23$), rate of conversion to open cholecystectomy (RR = 1.00; 95% CI = 0.75–1.33; $P = .99$), operative time (MD = 1.60; 95% CI = −1.36–4.56; $P = .29$), and rate of readmission (RR = 0.63; 95% CI = 0.19–2.10; $P = .45$) between the ELC and DLC groups. However, the ELC group was significantly correlated with lower length of hospital stay (MD = −2.01; 95% CI = −3.15 to −0.87; $P = .0006$), fewer gallstone-related events rates (RR = 0.17; 95% CI = 0.07–0.44; $P = .0003$), and lower endoscopic retrograde cholangiopancreatography (ERCP) usage (RR = 0.83; 95% CI = 0.71–0.97; $P = .02$) compared with the DLC group.

Conclusion: Early laparoscopic cholecystectomy is safe and effective for patients with MAGP, but the indications and contraindications must be strictly controlled.

Abbreviations: CI = confidence interval, DLC = delayed laparoscopic cholecystectomy, ELC = early laparoscopic cholecystectomy, ERCP = endoscopic retrograde cholangiopancreatography, LC = laparoscopic cholecystectomy, MAGP = mild acute gallstone pancreatitis, MD = mean difference, NOS = Newcastle–Ottawa Scale, RR = risk ratio.

Keywords: gallstone, laparoscopic cholecystectomy, meta-analysis, pancreatitis

1. Introduction

Acute pancreatitis is one of the common acute abdomen in surgery. Gallbladder stones are the main pathogenic factor. Gallstone pancreatitis accounts for more than 50% of all pancreatitis cases and shows an increasing trend at present.[1]

Currently, laparoscopic cholecystectomy is the preferred method for treating acute gallstone pancreatitis and reducing its recurrence.[2] For patients with acute severe pancreatitis, since there is a higher risk of complications with early surgical intervention, surgery is often performed after the inflammation has subsided.[3] For patients with MAGP, current international guidelines support the use of "early" laparoscopic cholecystectomy. However, there is a lack of consensus regarding the definition of "early" in each guide. Diversification of early definitions may lead to bias in conclusions. The International Association of Pancreatology recommends cholecystectomy during the same admission.[4] While the American Gastroenterological Association suggests that LC should be performed within the period of hospital admission and not beyond 2 to 4 weeks after discharge.[5] In addition, some guidelines fail to advice on the timing of cholecystectomy for acute biliary pancreatitis.[6]

The timing of surgery is focused on the safety and effectiveness of surgery. It is generally believed that acute mild pancreatitis should be treated with conservative symptomatic support treatment for 2 to 4 weeks or even longer before undergoing a cholecystectomy. Delaying surgery provides time for a detailed examination, finding the cause, avoiding unnecessary biliary

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F-pZ, KW, X-qT have contributed equally to this work.

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exploration, avoiding early surgery that might aggravate the pancreatitis, and is conducive to recovery from acute pancreatitis. Since the adhesion from abdominal inflammation is relieved, surgical risk is reduced and operative complications and the rate of conversion to laparotomy are decreased.[7] However, many studies show that conservative treatments only relieve symptoms and not the underlying cause of pancreatitis. Some patients with delayed surgery have recurrence during the wait for surgery, which aggravates the economic burden of patients.[8–9] In addition, studies have shown that early surgery does not increase patient complications or hospital stay, and the perioperative period is safe.[10]

Therefore, we conducted this updated meta-analysis to compare the safety and efficacy between early laparoscopic cholecystectomy (ELC) and delayed laparoscopic cholecystectomy (DLC) in patients with mild gallstone pancreatitis to guide clinical decision-making.

2. Methods

2.1. Data sources and search strategy

A comprehensive search of MEDLINE, EMBASE, PubMed, Cochrane, and the ISI Web of Science databases from inception to March 2019 was performed by 2 investigators. "cholecystectomy" and "pancreatitis" MeSH terms were used and combined with free-text words. In addition, the references of eligible studies, pertinent reviews, and meta-analyses in this field were screened.

2.2. Inclusion and exclusion criteria

In this study, we defined ELC as same admission or laparoscopic cholecystectomy performed within 2 weeks after admission. The control group was defined as DLC. Mild pancreatitis was defined by the presence of Ranson score < 3 or according to Atlanta classification.

The inclusion criteria were as follows:

1. patients with mild gallstone pancreatitis according to a clear MAGP severity scoring system;
2. trials comparing the clinical indicators between ELC and DLC;
3. studies that provided adequate and extracted clinical outcome data;
4. original high-quality English articles.

The exclusion criteria were:

1. conference abstracts, expert opinion, review articles, case reports, editorials, and letters to the editor;
2. articles that included patients with severe and/or other origins of pancreatitis; and
3. articles that lack clinical outcome data and unable to get full text.

2.3. Data extraction

The following information was captured using data abstraction forms: first author, year, country and journal of publication, number of patients, study design, criteria of MAGP, definition of ELC and DLC, clinical outcomes including the rate of conversion to open cholecystectomy (COC), rate of complications, rate of gallstone-related events, rate of readmission, rate of endoscopic retrograde cholangiopancreatography (ERCP) usage, operative time (OT), and length of stay (LOS). To reduce inaccuracy in the extracted outcome indicator, this work was performed by 2 independent investigators.

2.4. Quality assessment

A total of 19 studies were included. The quality evaluation of the literature was assessed using the Newcastle–Ottawa Scale.[11] The scoring criteria are based on the following 3 sections: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome. The highest score is 9 points. The higher scores reflect a better methodological quality. This work was performed independently by 2 investigators. Disagreements were resolved through discussion or third party ruling.

2.5. Statistical analyses

Meta-analysis was performed using Review Manager5.3 software (Cochrane Collaboration, Copenhagen, Denmark). The risk ratio (RR) and the mean difference (MD) was used for the count data and the measurement data, respectively and the 95% confidence interval (CI) represented the combined statistics. Statistical heterogeneity between trials was evaluated by the Chi-Squared test. When there was no statistically significant heterogeneity ($P > .05$, $I^2 < 50\%$), the fixed-effect model was applied for the meta-analysis, otherwise, the random-effect model was selected. The risk ratio (RR) and 95% CI were used to evaluate clinical efficacy. The consolidated result was an average RR and 95% CI weighted according to the standard error of the RR of the trial. $P < .05$ was considered a statistically significant difference. Funnel plots were used to assess the publication bias.

2.6. Ethics declarations

Ethics approval and consent to participate are not applicable for meta-analysis.

3. Results

3.1. Study characteristics

The PRISMA flow diagram of the study selection process is shown in Figure 1. A total of 3297 articles were identified after a comprehensive search of the database. 1445 articles were left after duplicate removal. Upon further reading of the title and abstract, eventually 42 articles tentatively qualified. Three studies that were conference abstracts were excluded. Of the remaining 39 articles, 4 did not specify the MAGP criteria, 3 involved severe pancreatitis, 9 studies showed that the surgical procedure was not only LC, and 4 lacked clinical outcomes to extract data and were all therefore excluded. Ultimately, 19 eligible studies, 5 randomized controlled trials [RCTs],[10,12–15] and 14 retrospective studies[16–29] comprising a total of 2639 patients, were considered eligible for the meta-analysis. Characteristics of included studies and literature quality scores are summarized in Table 1.

3.2. Meta-analysis

3.2.1. Complications. Data regarding complications were provided in 19 studies, comprising 2639 patients. There was no significant difference in intraoperative complications (RR = 1.46; 95% CI = 0.88–2.41; $P = .14$; Fig. 2) and postoperative complications (RR = 0.81; 95% CI = 0.58–1.14; $P = .23$; Fig. 3)

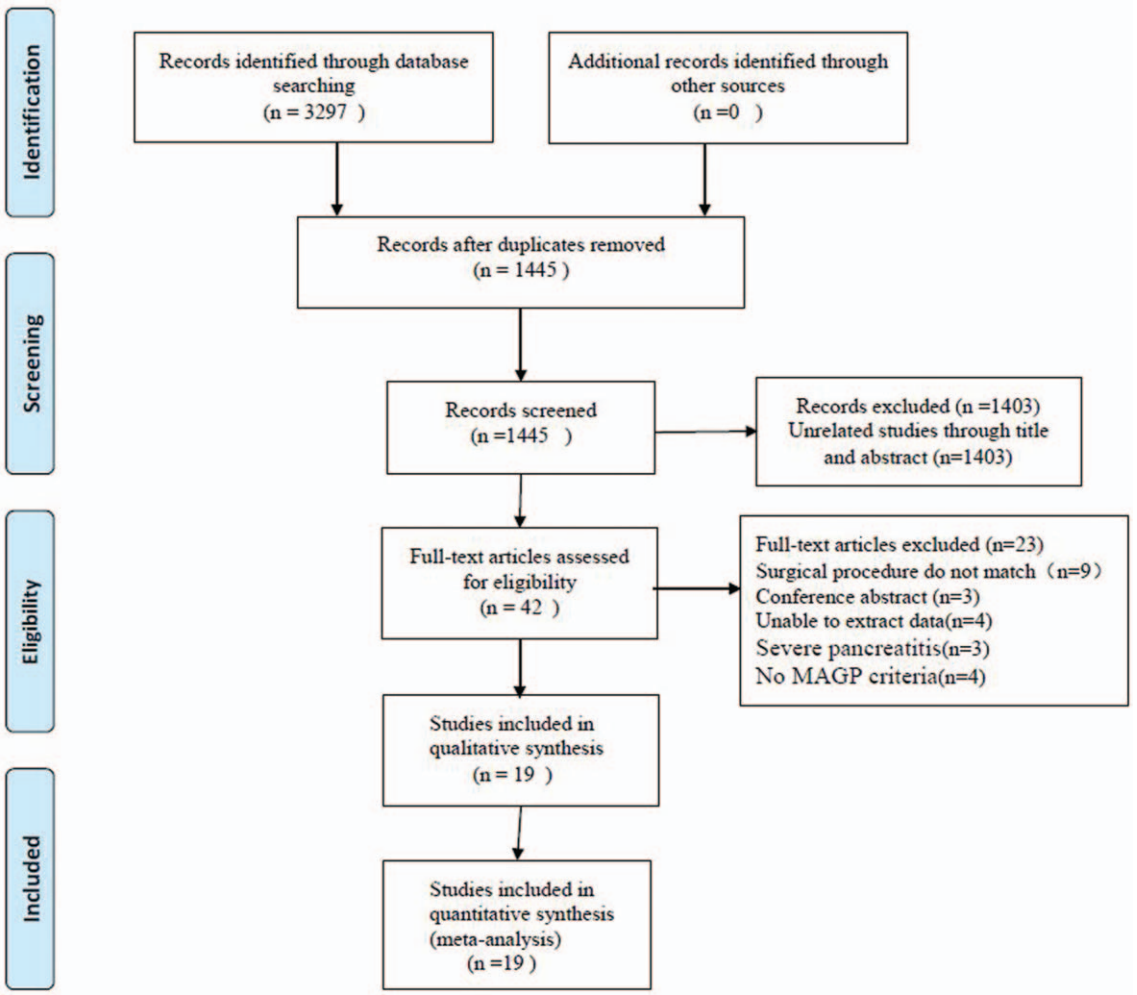

Figure 1. The PRISMA flow diagram of the study selection process.

Table 1

Main characteristics and quality scores of the included studies in the meta-analysis.

					Sample		Definition			
Study	**year**	**Country**	**design**	**Magzine**	**ELC**	**DLC**	**ELC**	**DLC**	**Criteria of MAGP**	**NOS**
Aboulian et al	2010	USA	RCT	Ann Surg	25	25	<48 hours	>48 hours	Ranson score	8
Aksoy et al	2017	Turkey	Retrospective	Asian J Surg	75	87	<72 h	4–10 weeks	Ranson score	8
Al-Qahtani et al	2014	Saudi Arabia	Retrospective	J T U med sc	267	83	Same admission	6–12 weeks	Ranson score	7
Costa et al	2015	Dutch	RCT	The Lancet	128	136	<72 hours	25–30 day	Atlanta classification	8
Falor et al	2012	USA	Retrospective	Arch Surg	117	186	<48 hours	>48 hours	Ranson score	7
Griniatsos et al	2005	UK	Retrospective	AM Surg	20	24	<2 weeks	>2 weeks	Ranson score	7
Guadagni et al	2017	Italy	Retrospective	Minerva Chir	98	218	<72 hours	>3 days	Ranson score	8
Jee et al	2016	Malaysia	RCT	Asian J Surg	38	34	Same admission	>6 weeks	Atlanta classification	8
Nebiker et al	2009	Switzerland	Retrospective	Surgery	32	67	<2 weeks	>2 weeks	Ranson score	8
Rozh Noel et al	2018	Sweden	RCT	HPB	32	34	Same admission	>6 weeks	Atlanta classification	8
Sinha et al	2008	India	Retrospective	HPB	81	26	<7 days	>6 weeks	Ranson score	8
Li et al	2012	China	Retrospective	Hepatogastroenterology	54	26	<48 hours	6–8 weeks	Ranson score	7
Zhao et al	2013	China	RCT	Surg Today	30	30	<48 hours	>48 hours	Ranson score	8
Rosing et al	2007	Torrance	Retrospective	J Am Coll Surg	43	177	<48 hours	5 days	Ranson score	7
Prabhu et al	2009	Mumbai	Retrospective	Tropical gastroenterology	9	17	Same admission	4–6 weeks	Ranson score	6
Taylor et al	2004	Bakersfield	Retrospective	AM Surg	26	20	<48 hours	>48 hours	Ranson score	7
Borreca et al	2016	Italy	Retrospective	Minerva Chir	24	55	<5 days	>6 weeks	Ranson score	8
Eğin et al	2017	Turkey	Retrospective	Ulus Travma Acil Cerrahi Derg	47	84	<2 weeks	>2 weeks	Ranson score	7
Mccullough et al	2003	Canada	Retrospective	HPB	74	90	Same admission	discharge	Ranson score	8

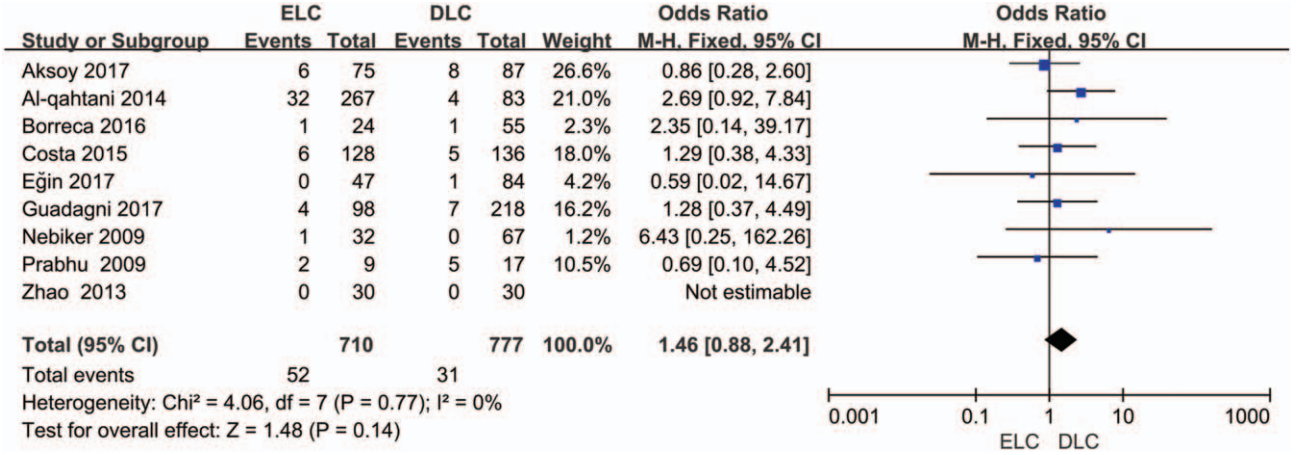

Figure 2. Forest plot of intraoperative complications comparing ELC and DLC.

between the ELC and DLC groups. According to the different criteria of MAGP and study design for postoperative complications, the subgroup analysis also showed no significant differences in the 2 subgroups (Table 2)

3.2.2. Conversion to open cholecystectomy. Nineteen studies evaluated the association between ELC and DLC groups in terms of the rate of conversion to open cholecystectomy. There was no significant difference between the 2 groups (RR = 1.00; 95% CI = 0.75–1.33; $P = .99$; Fig. 4). The subgroup analysis showed no significant differences in the 2 subgroups (Table 2).

3.2.3. Hospital length of stay. Twelve studies comprising 1867 patients evaluated the association on hospital length of stay between ELC and DLC. In comparison with the DLC group, the ELC group was significantly correlated with lower length of stay (MD = −2.01; 95% CI = −3.15 to −0.87; $P = .0006$; Fig. 5).

3.2.4. Operative time. Nine studies involving 1431 patients evaluated the association on operative time between the ELC and DLC groups. There was no significant difference between the 2 groups (MD = 1.60; 95% CI = −1.36 to 4.56; $P = .29$; Fig. 6).

3.2.5. Gallstone-related events. Ten studies involving 1646 patients evaluated the association on gallstone-related events between ELC and DLC. There was significant difference between the 2 groups (RR = 0.17; 95% CI = 0.07–0.44; $P = .0003$; Fig. 7).

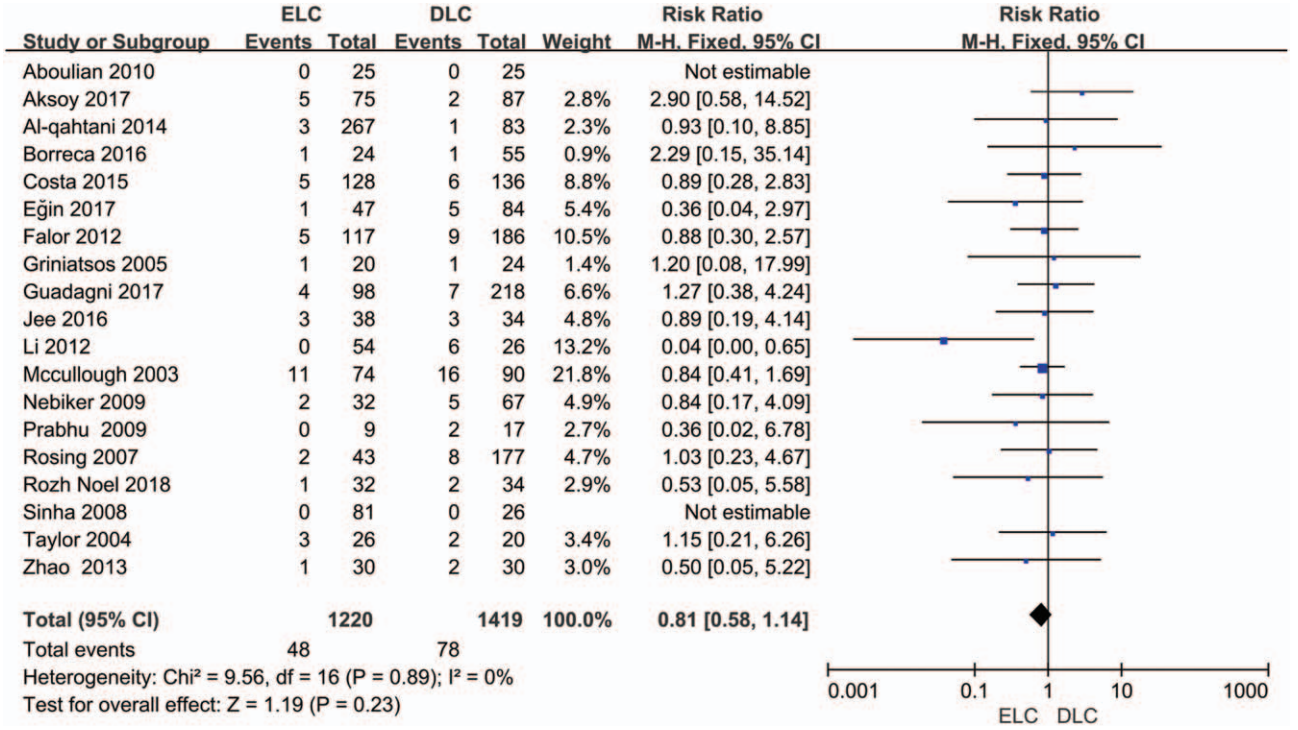

Figure 3. Forest plot of postoperative complications comparing ELC and DLC.

Table 2

Pooled hazard ratios (HRs) for outcome according to subgroup analyses.

Outcome subgroup	No. of studies	No. of patients	Effects model	HR (95% CI)	*P* value	Heterogeneity I^2 (%)	Heterogeneity pH
Postoperative complications							
Criteriaof MAGP							
Ranson score	16	2237	Fixed	0.81 [0.56, 1.18]	.27	0	0.74
Atlanta classification	3	402	Fixed	0.83 [0.35, 1.95]	.66	0	0.92
Study design							
RCT	5	512	Fixed	0.77 [0.35, 1.73]	.53	0	0.96
Retrospective	14	2127	Fixed	0.84 [0.58, 1.21]	.35	0	0.71
COC							
Criteriaof MAGP							
Ranson score	14	2237	Fixed	0.98 [0.72, 1.34]	.92	26	0.18
Atlanta classification	3	402	Fixed	1.09 [0.48, 2.50]	.83	0	0.91
Study design							
RCT	5	512	Fixed	0.92 [0.43, 1.96]	.83	0	0.77
Retrospective	14	2127	Fixed	1.01 [0.74, 1.39]	.93	26	0.19

COC = conversion to open, MAGP = mild actue gallstone pancreatitis, RCT = Randomized controlled trial.

3.2.6. Re-admission. Nine studies comprising 1726 patients analyzed the rate of readmission between the ELC and the DLC group. There was no significant difference between the 2 groups (RR = 0.63; 95% CI = 0.19–2.10; *P* = .45; Fig. 8).

3.2.7. ERCP usage rate. Seventeen studies comprising 2433 patients evaluated the ERCP usage rate between the 2 groups. In comparison with the DLC group, the rate of ERCP usage during perioperative period was significantly lower in the ELC group (RR = 0.83; 95% CI = 0.71–0.97; *P* = .02; Fig. 9).

4. Discussion

Different surgical timings have an impact on the surgical procedure, related complications, and prognosis of patients with MAGP. Laparoscopic cholecystectomy is a decisive treatment for patients with MAGP; however, no consensus has yet been reached for an optimal timing. Our results of this meta-analysis show that for patients with mild acute gallstone pancreatitis, early laparoscopic cholecystectomy is safe and effective and can shorten hospital stays, decrease the incidence of gallstone-related

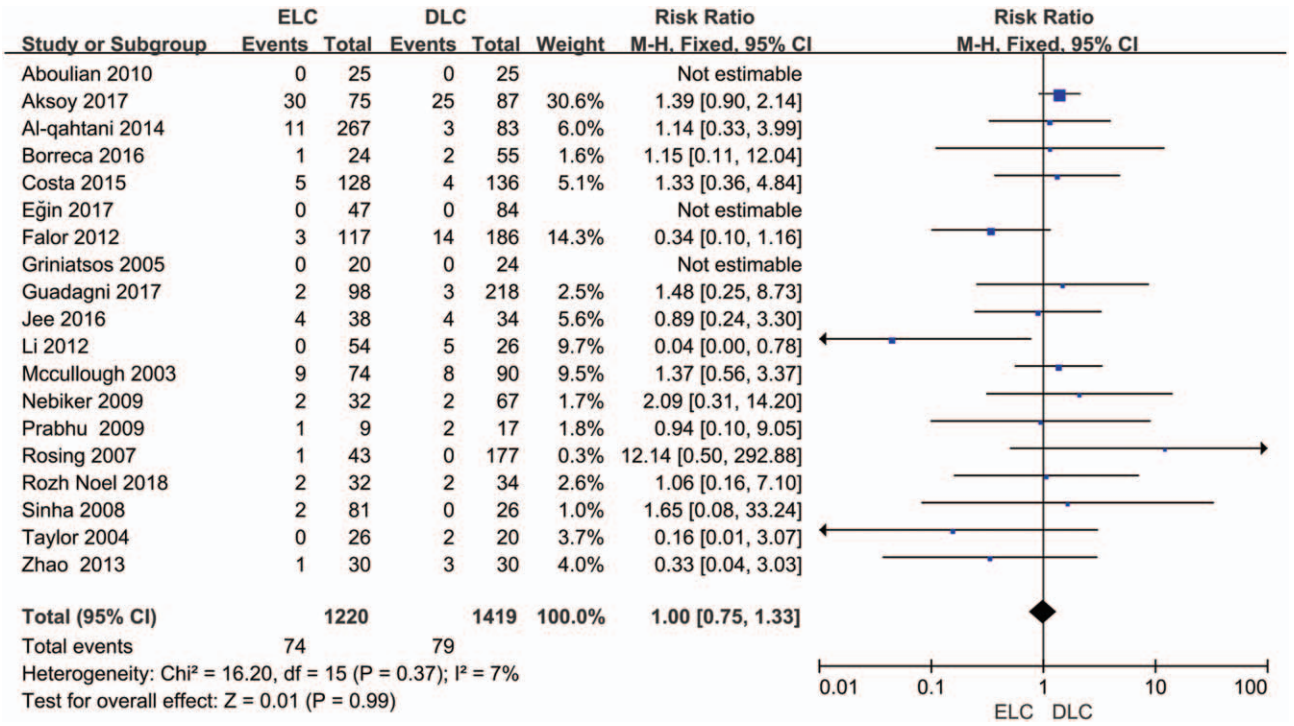

Figure 4. Forest plot of conversion to open cholecystectomy comparing ELC and DLC.

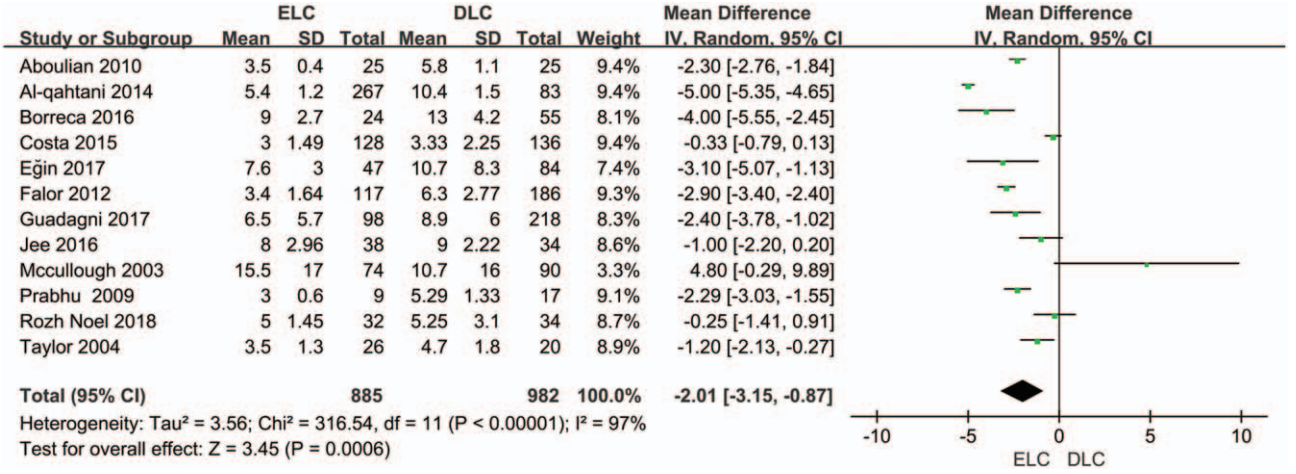

Figure 5. Forest plot of hospital length of stay comparing ELC and DLC.

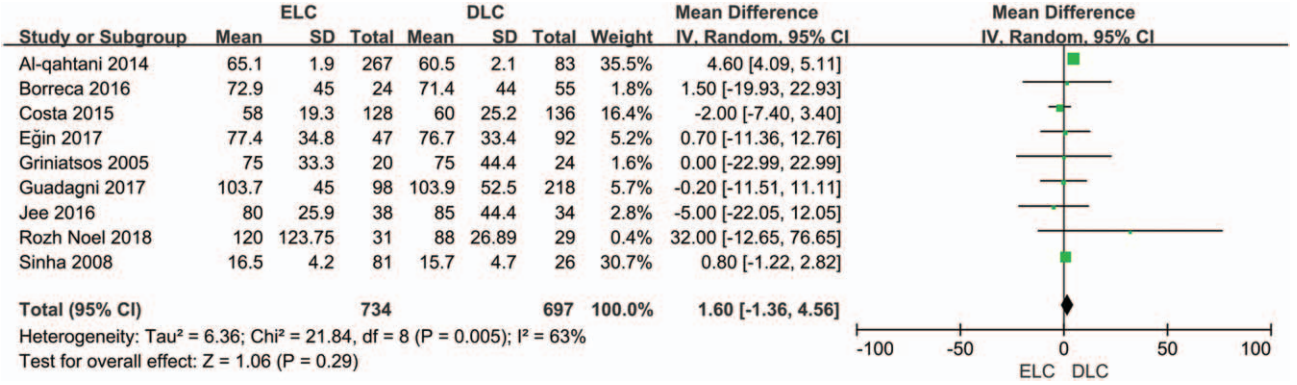

Figure 6. Forest plot of operative time comparing ELC and DLC.

events, and reduce the overall usage of ERCP during the course of the disease without increasing postoperative complications, conversion to open cholecystectomy, re-admission, and operation time.

Oddi sphincter edema and spasm caused by incarceration or stone discharge of gallstones results in bile and pancreatic juice excretion, which leads to ectopic activation of pancreatic enzymes and self-digestion that causes inflammation of the

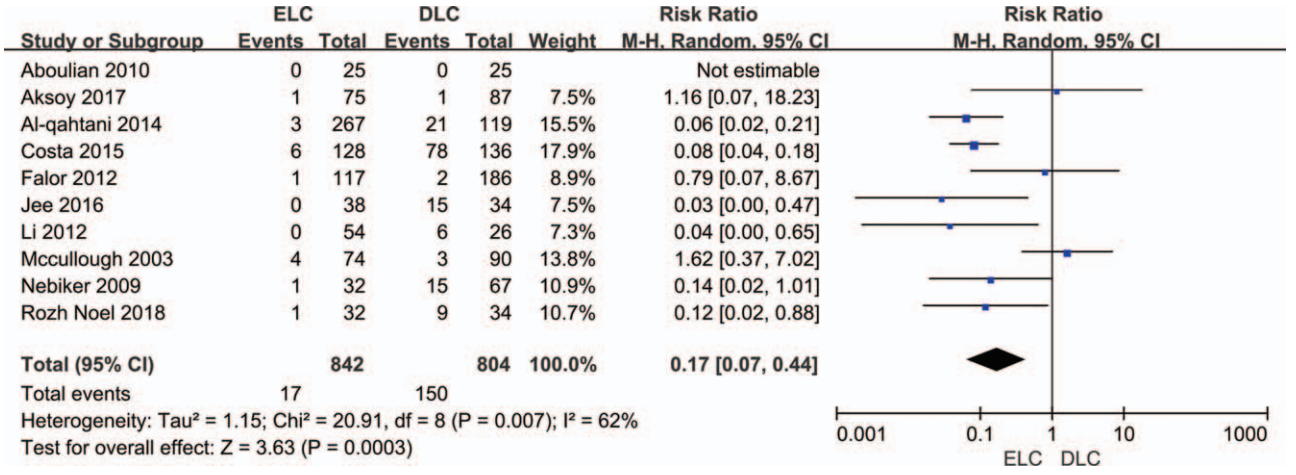

Figure 7. Forest plot of gallstone-related events comparing ELC and DLC.

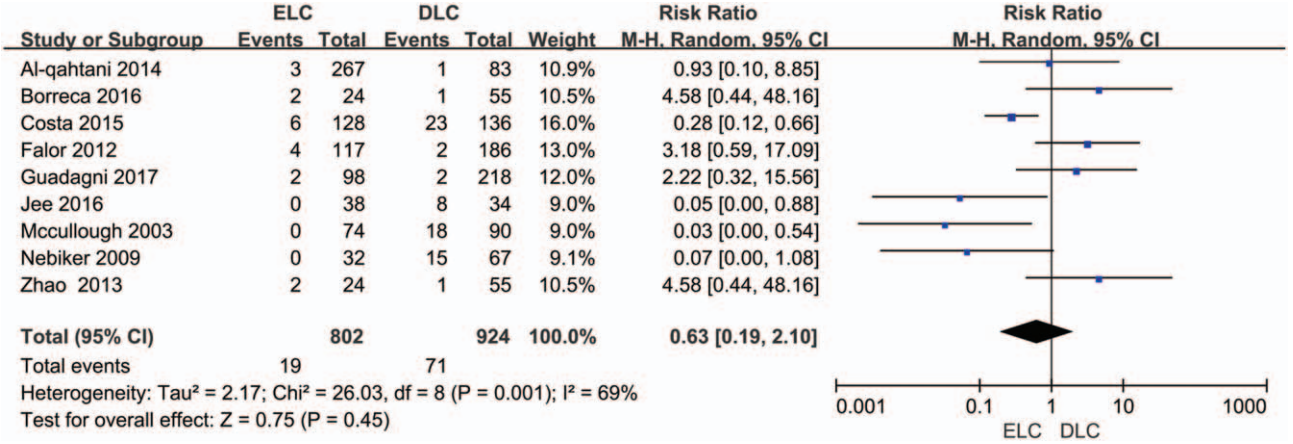

Figure 8. Forest plot of the incidence of re-admission comparing ELC and DLC.

pancreas, which in turn causes systemic inflammatory lesions.[30] For clinically experienced surgeons, the difficulty of surgery is similar, irrespective of the timing. This is due to the following reasons.

1. *Anatomical variation*: Surgical difficulty or intraoperative conversion to open surgery will be affected by anatomical variation, which is an independent factor and is not related to the timing of surgery.[31] Therefore, ERCP before surgery is necessary because it can visually display the internal lesions and anatomical structures of the pancreaticobiliary system. It can determine the preoperative biliary calculi and can also clarify the anatomical relationship of the cystic duct, common hepatic duct, hepatic duct, and common bile duct, which helps the physician to identify the biliary anatomy of the patient and reduce the intraoperative injury rate.
2. *Degree of abdominal adhesion*: The main criterion for the adhesion around the gallbladder is the thickness of the gallbladder wall, which is the main reason for the high rate of intraoperative laparotomy.[32]

Research has shown that when the wall thickness of the gallbladder is <0.5 cm and there is no stone incarceration, the gallbladder has no adhesion or only membranous adhesion to the surrounding tissue, this does not increase the difficulty of surgery and the chance of conversion to open laparotomy. When the wall thickness of the gallbladder is ≥ 0.5 cm, the inflammation is greater.[33] In the case of acute inflammation the Calot triangle is congestion, edema, and surgical separation is easier at this time; in subacute or chronic inflammation cases, the Calot triangle fiber connective tissue is significantly thickened, due to which the Calot triangle is often unclear and difficult to separate, leading to an

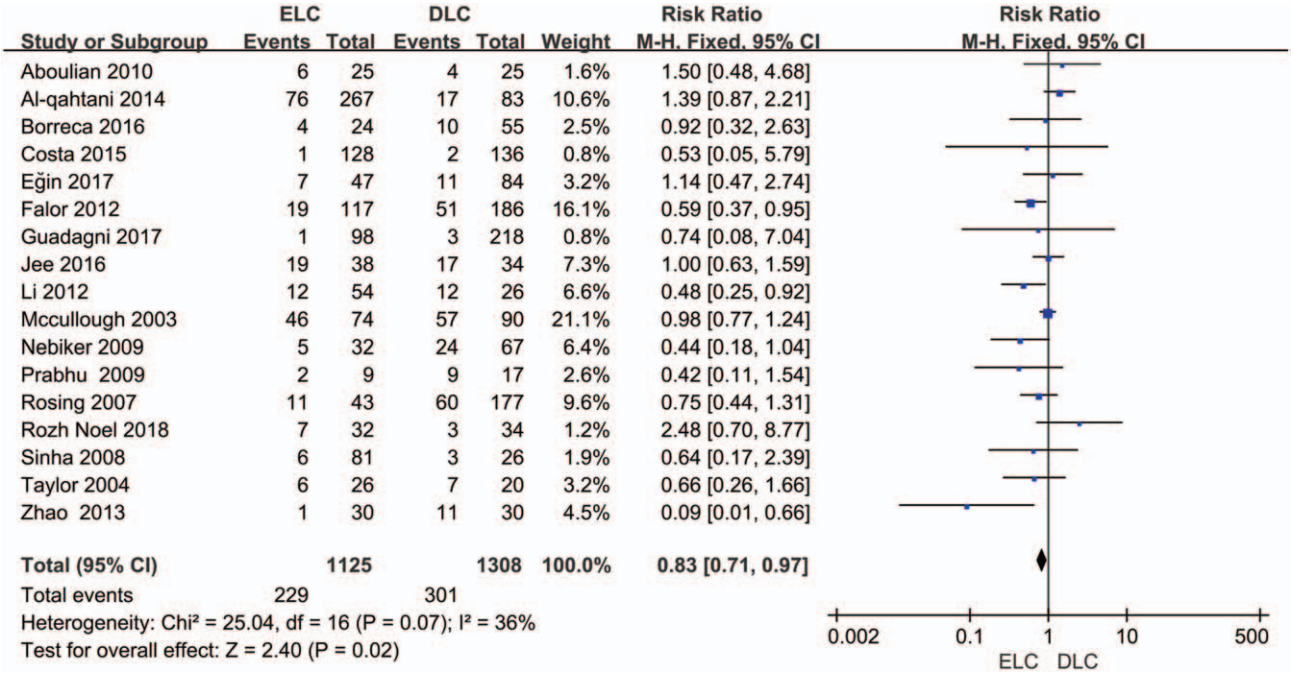

Figure 9. Forest plot of t the incidence of ERCP comparing ELC and DLC.

increased chance of conversion to open surgery and postoperative complications.[34] Clinical practice has shown that in the early stage of acute inflammation, especially within 72 hours, the gallbladder triangle is often edematous and hyperemic, with no obvious fibrosis. ELC did not increase the difficulty of surgery. On the contrary, with readmission surgery, dissection is sometimes more difficult.[16,21]

Conservative treatment of internal medicine is only symptomatic treatment and does not eradicate the cause of pancreatitis, so there is a risk of recurrence while waiting for surgery. Studies have shown that 20.0% to 60.0% of patients suffered gallstone related events such as recurrence of cholecystitis, pancreatitis, and biliary colic during the waiting phase.[35] Repeated invisible disease increases patient LOS and chance of ERCP.

We understand that under acute conditions, surgery within 72 hours of onset is less difficult, and the separation still has obvious anatomical boundaries. With the progression of time, operational difficulty may increase. However, careful dissection, patience, and critical recognition of the anatomy can result in safe completion of most LC procedures. Moreover, we defined the node with 72 hours as an early group and conducted a meta-analysis of the included literature. The results showed that the early surgery group did not experience increased postoperative complications[12,14–16,18,20–23,25,27–28] (RR = 0.86; 95% CI = 0.56–1.32; $P = .49$) and conversion to open surgery[12,14–16,18,20–23,25,27] (RR = 0.84; 95% CI = 0.37–1.91; $P = .68$) compared with delayed surgery.

This meta-analysis has several limitations. First, in the included literature, Ranson scores were mostly used, and Yeung et al reported that the APACHE-II score was more predictive of the degree of inflammation in pancreatitis compared to the Ranson score within 48 hours. Second, most of the literature contains non-randomized controlled trials. Results from more randomized controlled trials are required to support this study. Additionally, only published English articles were included. Therefore, the summary statistics obtained may not approximate the true average.

In summary, for patients with mild acute gallstone pancreatitis, early laparoscopic cholecystectomy is safe and effective during the first admission, but the indications and contraindications must be strictly controlled. These results need to be further confirmed by higher quality randomized controlled studies.

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Writing – review & editing: Fu-ping Zhong.

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