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Review Article

Timing of laparoscopic cholecystectomy after endoscopic retrograde cholangiopancreatography in cholelithiasis patients: A systematic review and meta-analysis

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There are many variations and unclear definitions of the appropriate timing of laparoscopic cholecystectomy (LC) after endoscopic retrograde cholangiopancreatography (ERCP), and there is still a lack of consistency about the appropriate timing. Inappropriate timing can be associated with serious comorbidity and can affect the patients. This meta-analysis was conducted to assess the operative outcomes and morbidity to provide a benefit to the patients based on the best timing of LC after ERCP. Randomized controlled trials (RCTs) and retrospective studies were identified from the PubMed and Scopus databases from inception to July 2021. A meta-analysis was performed to estimate the treatment effects on operative outcomes and morbidity. Four RCTs and four retrospective studies met our inclusion criteria. A meta-analysis indicated that patients who received LC after ERCP on the same day or within 72 hours had about 0.354 days shorter length of hospital stay with a shorter operative time of about 0.111–1.835 minutes and a lower risk of complications around 37%–73%. Our evidence suggests that the appropriate timing of LC after ERCP is either the same day or within 72 hours for treating cholelithiasis patients based on the severity of disease.

Key Words: Laparoscopic cholecystectomy; Cholelithiasis; Endoscopic retrograde cholangiopancreatography; Meta-analysis

INTRODUCTION

Cholelithiasis is the most common disease requiring hepatobiliary tract surgery, and 5% to 20% of the population is affected by this disease. Approximately 15% to 20% of patients with gallstones (GS) have concomitant common bile duct stones (CBDS) [1].

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About 55% of patients with CBDS develop symptoms along with complications [2]. Many different treatments have been performed to treat patients with CBDS depending on the patient's health status, clinician consideration of the clinician, time of diagnosis, healthcare facilities, and socioeconomic status of the patient [3].

Currently, the standard recommendation for treatment of CBDS is laparoscopic cholecystectomy (LC) with endoscopic retrograde cholangiopancreatography (ERCP) for removing the stones [4-6]. This intervention can perform an ERCP and followed by LC at different times based on the clinician's experience and technical availability. There are many variations and unclear definitions of the appropriate timing of LC after ERCP, and there is still a lack of consistency about the appropriate timing, ranging from 1 day to 2 months [7-9]. Previous evidence from 2 randomized controlled trials (RCTs) [10,11] showed statistically significant differences in terms of a longer length of hospital stay (LOS), operative time (OT), and cost, which ranged from 1 day to 8 days, 66.00 minutes to 83.00 minutes, and 2,760.61 USD to 6,559.52 USD, respectively. On the other hand, two other RCTs [4,12] found no difference in these outcomes.

Moreover, an inappropriate time interval may lead to serious morbidities, such as inflammation, injury to the adjacent organ, such as the duodenum or biliary system [13,14]. However, two studies [4,15] suggested that LC should be performed 72 hours in advance since it might decrease the cost, injury to the biliary system, and remission rate. However, we do not have enough information, and previous evidence is still inconclusive about the significant effect on the operative and morbidity outcomes in terms of the appropriate definition of early and late LC after ERCP.

Therefore, we conducted a systematic review (SR) and meta-analysis (MA) to assess both the operative outcomes (LOS and OT) and morbidity (overall complications) in early and late LC after ERCP to provide a benefit to the patients based on the best timing of LC after ERCP.

MATERIALS AND METHODS

SR and MA were conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines with the following PROSPERO number: CRD42021252737.

Literature and search strategy

The studies were included according to PICO as follows: P; CBDS, cholelithiasis, and choledocholithiasis, I and C; endoscopic retrograde cholangiopancreatography, ERCP, laparoscopic cholecystectomy, and LC, O; LOS, OT, and complications. The studies were identified from 2 major databases PubMed and Scopus from inception to July 2021, and they were limited to comparative studies, studies published in English, and human studies.

Study selection

RCTs and observational studies published in English that met the following criteria were selected:

- Studies in adult patients who underwent ERCP for GS and CBDS,
- Comparison between the timing of ERCP followed by LC as early and late operations.
- Reporting of at least 1 of the following outcomes of interest: LOS, OT, and overall complications.

Two reviewers independently selected the studies by screening the titles and abstracts. Disagreement, if any, was resolved by consensus or adjudicated by a third reviewer.

Interventions and outcomes of interest

Interventions were as follows: early LC after ERCP was defined as LC performed after ERCP on the same day or within 24 hours to 72 hours, and late LC after ERCP was defined as LC performed 72 hours to 2 months after ERCP.

Outcomes were as follows: 1) LOS was defined as the time from the first admission to discharge from the hospital, 2) OT was defined as the time from the start of the operation to completion of the operation, and 3) overall complications included any of the following: wound infection, bile leakage, intra-abdominal abscess, pancreatitis, bleeding, and ileus.

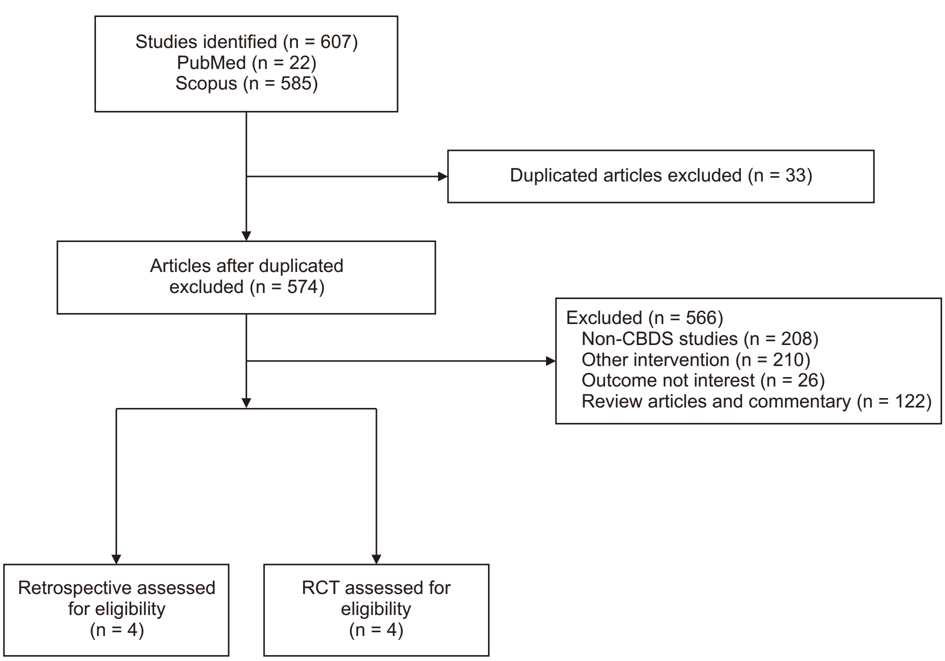

Fig. 1. Flow diagram for selection of studies. CBDS, concomitant common bile duct stones; RCT, randomized controlled trial.

Table 1. Characteristics of the included studies

Author (year)	Type of patient	Study design	Inter-vention	Country	Outcome	Period of study	No. of sub-jects	Mean age (yr)	Male (%)	Mean BMI (kg/m^2)	Mean bilirubin (μmol/L)	Mean WBC (×10^9/L)	Mean SGPT (IU)	Mean GGT (U/L)	Mean ALP (U/L)	Mean amy-lase (U/L)	Lost F/U (%)
Salman et al. (2009) [12]	CBDS	RCT	Early LC vs. late LC	Turkey	Successful LOS Complications OT	2005–2008	79	44.1	31.6	25.6	4.8	NR	NR	514	226.0	NR	NR
El Nakeeb et al. (2016) [4]	CBDS	RCT	Early LC vs. late LC	Egypt	LOS Complications OT Conversion Blood loss Recurrence	NR	110	45.4	31.8	29.6	3.3	6.9	3.3	NR	NR	127.9	0
Ali et al. (2021) [10]	CBDS	RCT	Early LC vs. late LC	Egypt	LOS Complications OT	2019–2020	40	43.5	15.1	27.2	NR	NR	NR	NR	NR	NR	0
Muham-medoğlu and Kale (2020) [11]	CBDS	RCT	Early LC vs. late LC	Turkey	LOS Cost	2017–2019	119	NR	40	NR	0.9	7.5	NR	NR	NR	51.3	0
Wild et al. (2015) [18]	CBDS	Retro-spective	Early LC vs. late LC	USA	Successful LOS Complications OT Conversion Blood loss Recurrence Cost	2010–2014	240	64.5	43.7	NR	NR	NR	NR	NR	NR	NR	NR
Passi et al. (2018) [19]	CBDS	Retro-spective	Early LC vs. late LC	USA	LOS OT Cost	2012–2016	214	49.5	28.9	29.1	NR	NR	NR	NR	NR	NR	NR
Al-Temimi et al. (2018) [20]	CBDS	Retro-spective	Early LC vs. late LC	USA	Successful LOS Complications Blood loss	2012–2014	440	50.4	35	29.9	NR	NR	NR	NR	NR	NR	NR
Aziret et al. (2019) [21]	CBDS	Retro-spective	Early LC vs. late LC	Turkey	LOS Complications OT Conversion	2015–2016	85	52.6	44.7	25.9	NR	NR	NR	NR	NR	NR	NR

ALP, alkaline phosphatase; BMI, body mass index; CBDS, common bile duct stone; F/U, follow-up; GGT, gamma-glutamyl transferase; LC, laparoscopic cholecystectomy; LOS, length of hospital stay; NR, not reported; OT, operative time; RCT, randomized controlled trial; SGPT, serum glutamate-pyruvate transaminase; USA, United States of America; WBC, white blood cell.

Data extraction and risk of bias assessments

Two reviewers (NP and PT) independently selected the studies by screening the titles and abstracts, including the full text. Also, the quality of observational studies was assessed based on the ROBINS-I tool [16] of representativeness of the studied subjects, information bias (i.e., ascertainment of the outcome and surgical technique), and confounding bias. For RCTs, the assessment was performed using established tools recommended by the Cochrane Library [17]. Each item was graded as "yes" for low risk of bias, "no" for high risk of bias, and "unclear" if there was insufficient information to judge as either low or high risk.

Statistical analysis

For continuous outcomes, the mean difference (MD) along with the variances of LOS and OT was estimated, and the risk ratio (RR) of overall complications was estimated for dichotomous outcomes. The pooled effect sizes of MD and RR were then pooled across studies.

The heterogeneity was checked using the Cochran's Q test and I^2 statistics. The model of a random-effects model or a fixed-effects which was depended on the degree of heterogeneity. If heterogeneity occurred, meta-regression with sub-group analysis was performed accordingly. Publication bias was assessed using a funnel plot and Egger test.

All analyses were performed using STATA 16. *p*-value less than 0.05 was set as the threshold for statistical significance, except for heterogeneity where $p < 0.10$ was used.

RESULTS

Six-hundred and seven studies were identified from PubMed (n = 22) and Scopus (n = 585) databases, and 33 articles were duplicates. Eight studies [4,10-12,18-21] were included; 4 RCTs [4,10-12] and 4 retrospective studies [18-21] met our inclusion criteria (Fig. 1).

Characteristics of the included studies

The information on the characteristics of these 8 studies [4,10-12,18-21] is described in Table 1. Among them, 4 RCTs [4,10-12] and 4 retrospective studies [18-21] had an overall mean patient age ranging from 43 to 45 years and from 49 to 64 years, respectively. The percentage of males ranged from

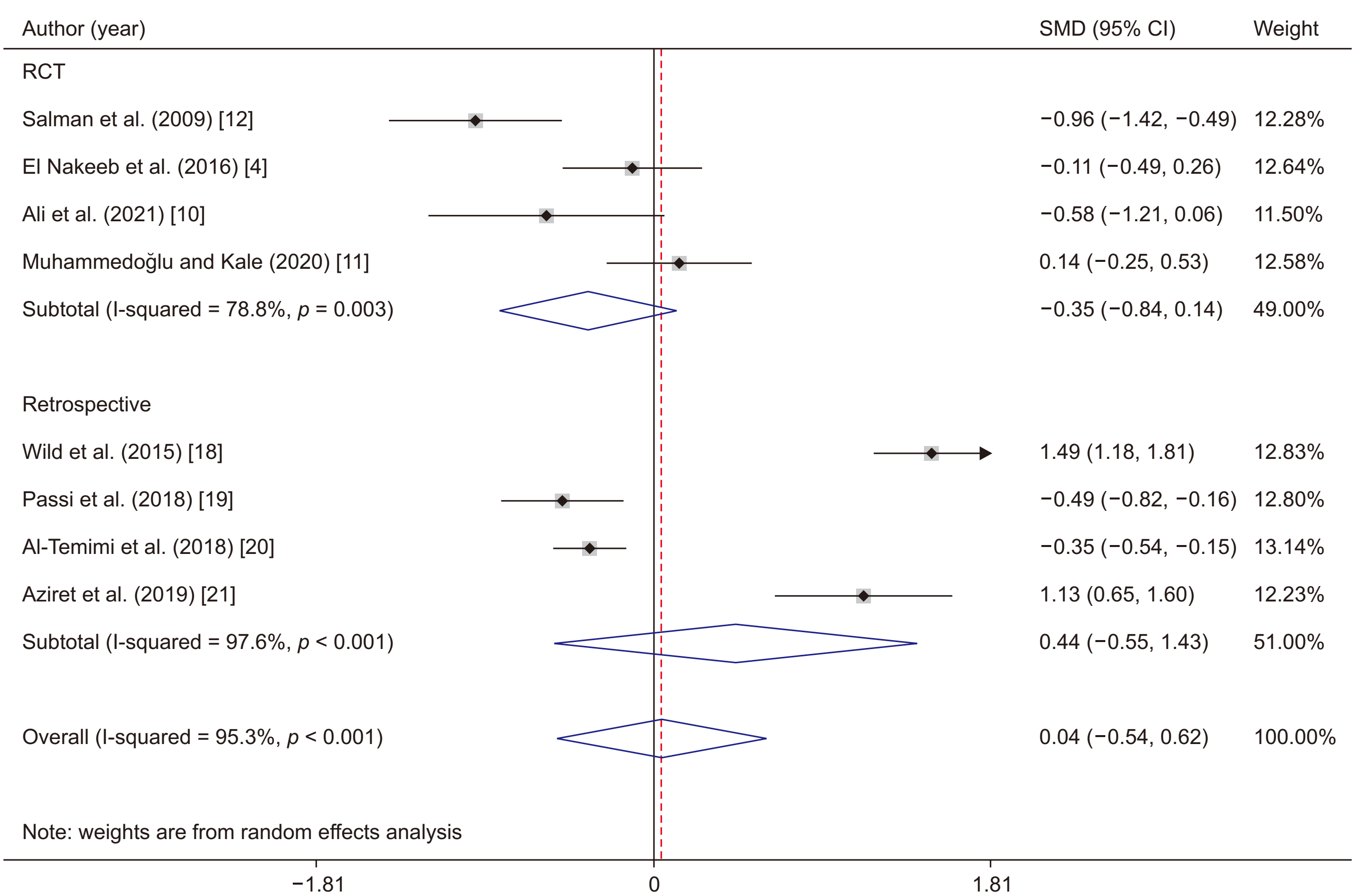

Fig. 2. Pooled effect sizes of length of hospital stay in early laparoscopic cholecystectomy (LC) and late LC by the design. RCT, randomized controlled trial; SMD, standard mean different.

15% to 45% in all included studies. All these studies included only patients with CBDS who underwent ERCP.

RCTs and retrospective studies compared early LC vs late LC after ERCP, and the latest study period was from 2019 to 2020 in a RCT [10] performed in Egypt. RCTs [4,10-12] also reported the value of bilirubin, white blood cell, serum glutamate-pyruvate transaminase, gamma-glutamyl transferase, alkaline phosphatase, and amylase, without the proportion of loss to follow-up (Table 1).

Risk of bias assessment

Risk of bias assessment was performed (Supplementary Fig. 1A). The 4 RCTs [4,10-12] were considered at high risk of bias for blinding the participants and blinding of outcome assessment (detection bias), and at low risk of bias for random sequence generation and allocation concealment (selection bias). About 100% of RCTs were at low risk of bias for selective reporting (reporting bias) and incomplete outcome data (attrition bias). All RCTs showed a high risk of bias since the participants who received the treatment could not be blinded. The four retrospective studies [18-21] were considered at low risk of bias for the study population, study attrition, and outcome measure. About 50% of these studies were considered at high risk of bias for prognostic factor measurement, confounding factors, and statistical analysis and presentation. But the overall results for the risk of bias considered high risk and low risk were equally biased (Supplementary Fig. 1B).

Outcomes of interest

Length of hospital stay

All RCTs (n = 4) [4,10-12] with 348 patients compared the MD of LOS between early LC versus late LC after ERCP. The pooled treatment comparison estimated and indicated that early LC had about 0.354 (–0.845, 0.136) days shorter LOS than late LC, but the difference was not statistically significant. In contrast, the four retrospective studies [18-21] with 979 patients indicated that the MD of LOS in the early LC group was longer than that in the late LC group at about 0.438 days (–0.553, 1.428) (Fig. 2). The heterogeneity of pooled estimated data was high in RCTs and retrospective studies at 78.8% and 97.6%, respectively. The results of meta-regression to explore the sources of heterogeneity suggested that age (coefficient, –5.438; tau^2, 0.192; p = 0.013) and gender (coefficient, –2.389; tau^2, 0.265; p = 0.029) were the sources of heterogeneity.

There was no evidence of publication bias by Egger test and funnel plots in RCTs (coefficient, –6.098; SE, 5.570; p = 0.388) and retrospective studies (coefficient, 10.792; SE, 10.172; p = 0.400) (Supplementary Fig. 2).

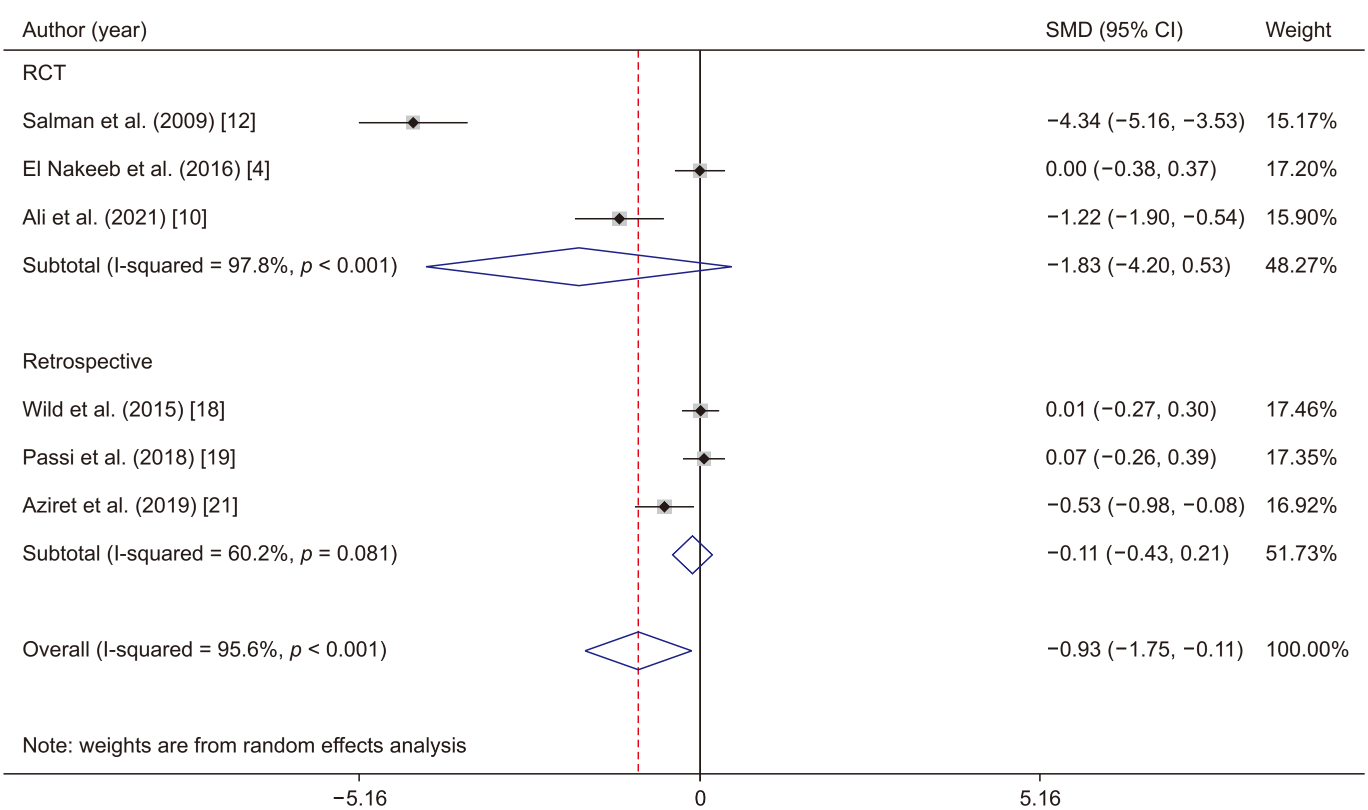

Fig. 3. Pooled effect sizes of the operative time in early laparoscopic cholecystectomy (LC) and late LC by the design. RCT, randomized controlled trial; SMD, standard mean different.

Operative time

Three RCTs [4,10,12] with 114 patients and 3 retrospective studies [18,19,21] with 397 patients compared the MD of OT between early LC and late LC after ERCP. The results of pooled estimated data in RCTs and retrospective studies indicated that OT in early LC was shorter than that in late LC after ERCP at about 1.835 minutes (–4.199, 0.530) and 0.111 minutes (–0.428, 0.207), respectively, and statistical significance was not reached (Fig. 3). In addition, the heterogeneity was high in RCTs and retrospective studies at 97.80% and 60.20%, respectively. Sensitivity analysis was not performed due to the number of studies.

The evidence of publication bias was not found in RCTs (coefficient, –15.127; SE, 6.771; $p = 0.268$) and retrospective studies (coefficient, –6.586; SE, 2.753; $p = 0.252$) (Supplementary Fig. 3).

Overall complications

Data from 3 RCTs [4,10,12] with 114 patients were used to compare the relative treatment effects between 2 interventions, early LC and late LC. The pooled incidence of overall complications was 0.269 (0.067, 1.073) lower in early LC than in late LC, but the difference was not statistically significant (Fig. 4). Three retrospective studies [18,20,21] (n = 394) also suggested a lower incidence rate of overall complications at about 0.719 (0.421, 1.228), which was not statistically significant. The degree of heterogeneity did not occur in RCTs and retrospective studies.

In this part of overall complications, evidence of publication bias by Egger test and funnel plot was not found in RCTs and retrospective studies (Supplementary Fig. 4).

DISCUSSION

We conducted a SR and MA to assess the operative outcomes (LOS and OT) and morbidity (complications) in early LC and late LC after ERCP to explore the optimal period for performing LC after ERCP. The Updated Tokyo Guidelines 2018 for the management of acute cholangitis and cholecystitis [22], which are standardized for the diagnosis and treatment of patients with acute cholangitis and cholecystitis, suggested that there was no appropriate timing to perform LC after ERCP. The question of optimal timing and the results of post-intervention are still not consistent with previous evidence. Therefore, we considered and determined the feasibility of the approach that can be the standard strategy for the best timing and efficacy in patients with cholelithiasis.

Our study comprised two interventions of surgical techniques, including early LC (on the same day or within 24 hours to 72 hours after ERCP) and late LC (after 72 hours to 2 months after ERCP). Our results suggested that early LC may perform

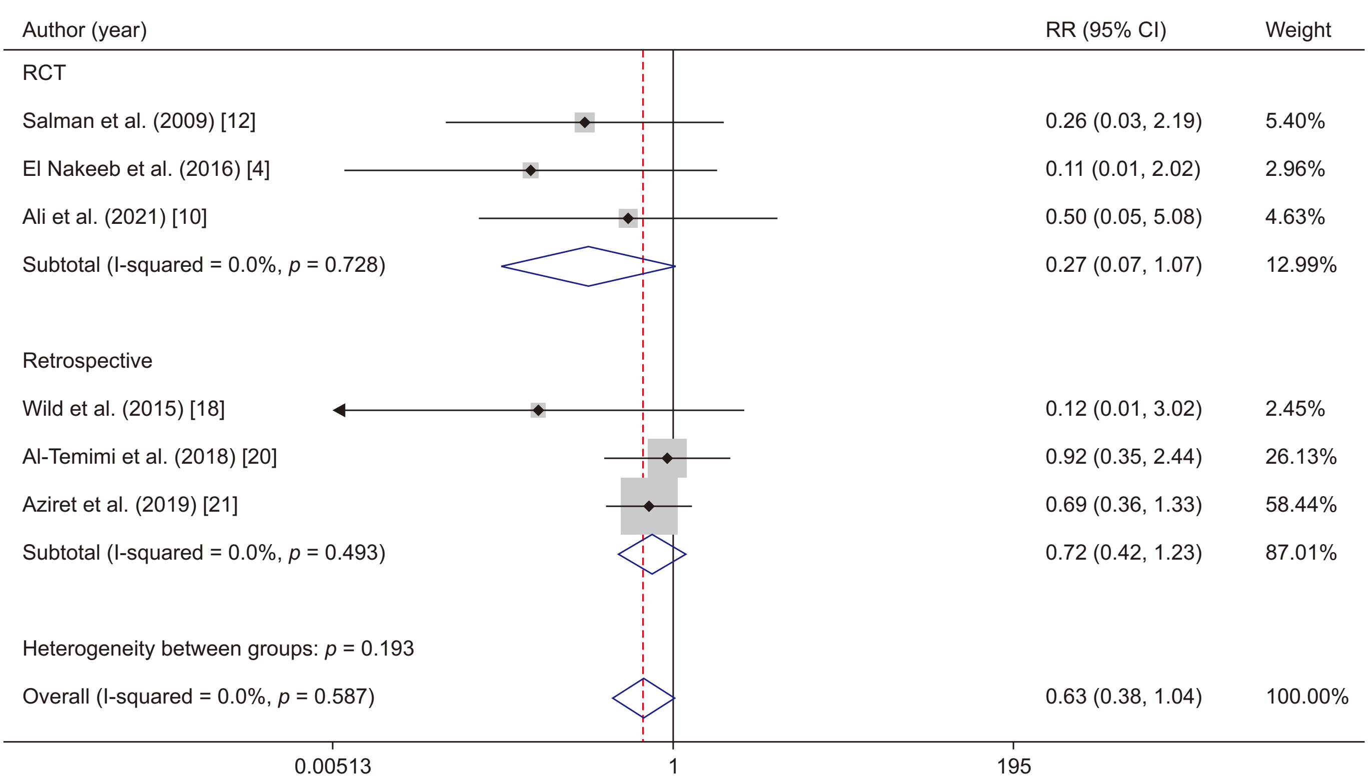

Fig. 4. Pooled effect sizes of complications in early laparoscopic cholecystectomy (LC) and late LC by the design. RCT, randomized controlled trial; RR, risk ratio.

better than late LC after ERCP in all outcomes including a shorter LOS, lesser OT, and lower risk of overall postoperative complications.

Although the outcome of LOS indicated that early LC had a shorter LOS than late LC at about 0.35 days, retrospective studies did not differ in terms of LOS. These findings were consistent with previous studies, in which LC was performed after ERCP on the same day or within 24 hours to 72 hours with a shorter LOS [10-12,18-20] but they are in contrast to some studies, which found longer LOS or no difference in LOS [4,21]. However, most previous evidence [4,10,12,21] suggested a shorter OT for early LC than late LC. According to the supportive evidence of OTs, our results also showed a shorter OT in the patients who received LC after ERCP on the same day or within 24 hours to 72 hours. We considered that the outcomes of LOS and OT in the early LC group might be due to the fact that the patients received LC and ERCP from the same experienced surgeon with the same learning curve in a short period. Conversely, a longer LOS and OT in patients who received LC at more than 72 hours after ERCP might have been due to the fact that the techniques were performed by different surgeons with different learning curves [11,23]. For instance, among these outcomes, results might have originated from complicated disease or disease progression during the time period of waiting for LC after 72 hours, which might also be associated with a longer LOS and OT.

Our finding of complications in the early LC group showed a lower rate of complications ranging from 37% to 73% than that in the late LC group. Most of the previous findings [10,12,18,20,21] were consistent with our study in terms of fewer complications in the early LC group ranging from 0% to 10%. In contrast, 1 RCT [4] and 1 retrospective study [19] found no difference between the 2 time periods for performing LC after ERCP. Undoubtedly, the severity of the disease was dependent on the time associated with the level of inflammation in the gall bladder and bile duct. In addition, the operative complications were also directly associated with long OT; especially, bleeding was the most important complication that should be a cause of concern [10,15,24].

Moreover, Ali et al. [10] assessed the range of operative difficulty in early and late LC by using the Nassar scale, the scale used for reporting the operative difficulty and severity of the disease. According to the information, about 85% of early LC cases reported the lowest grade but only 30% of cases in the late LC group reported difficulty. Therefore, operative difficulty should be associated with all outcomes of interest.

Although a standard of care for cholelithiasis patients was surgical management as a clinical practice guideline. Based on our recommendation, LC should be performed after ERCP on the same day or within 24 hours to 72 hours as a strategy of care for cholelithiasis patients depending on the clinician's and patient's judgment and discussion based on the results from computed tomography to confirm CBDS.

Our study has several strengths. This is the first SR with MA that has assessed both operative outcomes i.e., LOS with OT and overall complications for cholelithiasis patients by comparing the timing of early and late LC performed after ERCP. Related RCTs and retrospective studies from inception were also included and analyzed separately based on the design of study to decrease the effects of selection bias and confounding factors from observational studies.

However, a few limitations could not be avoided. First, the definition of timing for performing LC after ERCP (i.e., the same day, before 72 hours, or after 72 hours) and outcomes (i.e., LOS, OT, and complications) were defined in a different manner across studies, as shown in the part of heterogeneity, which might have an effect on the clinical efficacy and generalizability. Second, a few included studies had a variety of reported outcomes that could affect the power of the test and also be linked to the validity of outcomes of interest. Thus, further study should be conducted to determine a consistent definition of timing and outcomes, and also to determine the definition of study subjects with adequate power either in an original study or meta-analysis.

In conclusion, our evidence suggests that appropriate timing of LC after ERCP is either the same day or within 72 hours for treating cholelithiasis patients depending on the severity of disease for achieving a reduced LOS, OT, and complications. Further large-scale study with a consistent definition of timing, outcomes, and study subjects should be conducted.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.22-040.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: All authors. Data curation: NP. Methodology: NP, WS, PT. Visualization: All authors. Writing - original draft: All authors. Writing - review & editing: All authors.

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