Systematic review

Meta-analysis comparing early *versus* delayed laparoscopic cholecystectomy for acute cholecystitis

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Background: **Previous studies comparing early laparoscopic cholecystectomy (ELC) with delayed laparoscopic cholecystectomy (DLC) for acute cholecystitis were incomplete. A meta-analysis was undertaken to compare the cost-effectiveness, quality of life, safety and effectiveness of ELC *versus* DLC.**

Methods: **PubMed, Embase, the Cochrane Library and Web of Science were searched for randomized clinical trials (RCTs) that compared ELC (performed within 7 days of symptom onset) with DLC (undertaken at least 1 week after symptoms had subsided) for acute cholecystitis.**

Results: **Sixteen studies reporting on 15 RCTs comprising 1625 patients were included. Compared with DLC, ELC was associated with lower hospital costs, fewer work days lost (mean difference (MD) −11·07 (95 per cent c.i. −16·21 to −5·94) days; $P < 0·001$), higher patient satisfaction and quality of life, lower risk of wound infection (relative risk 0·65, 95 per cent c.i. 0·47 to 0·91; $P = 0·01$) and shorter hospital stay (MD −3·38 (−4·23 to −2·52) days; $P < 0·001$), but a longer duration of operation (MD 11·12 (4·57 to 17·67) min; $P < 0·001$). There were no significant differences between the two groups in mortality, bile duct injury, bile leakage, conversion to open cholecystectomy or overall complications.**

Conclusion: **For patients with acute cholecystitis, ELC appears as safe and effective as DLC. ELC might be associated with lower hospital costs, fewer work days lost, and greater patient satisfaction.**

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Introduction

Acute cholecystitis is a potentially life-threatening complication, which affects more than 20 million Americans annually and leads to direct costs of over US $6·3 billion (€5·6 billion; exchange rate 16 June 2015)[1]. Laparoscopic cholecystectomy is the optimal treatment for acute cholecystitis, and approximately 917 000 operations are performed each year in the USA, and more than 50 000 in England[2–10]. However, the optimal timing of laparoscopic cholecystectomy for acute cholecystitis is debatable[11,12]. Previous systemic reviews[13–19] have shown that early laparoscopic cholecystectomy (ELC) is as safe as delayed laparoscopic cholecystectomy (DLC). Furthermore, ELC for acute cholecystitis is associated with a shorter hospital stay. However, these incomplete analyses often paid little attention to hospital costs, work days lost and quality of life, which may confound and underestimate the differences[13–19]. Recently, new randomized clinical trials (RCTs) comparing ELC with DLC have been published. An updated meta-analysis was therefore conducted to compare the safety and efficacy of ELC *versus* DLC for patients with acute cholecystitis, including data on costs, work days lost and quality of life.

Methods

The study was designed in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*[20] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting meta-analyses[21].

Literature search

The PubMed, Embase, Cochrane Library and Web of Science databases were searched from inception to 1 October 2014. The electronic searches were performed using exploded medical subject headings, and the appropriate

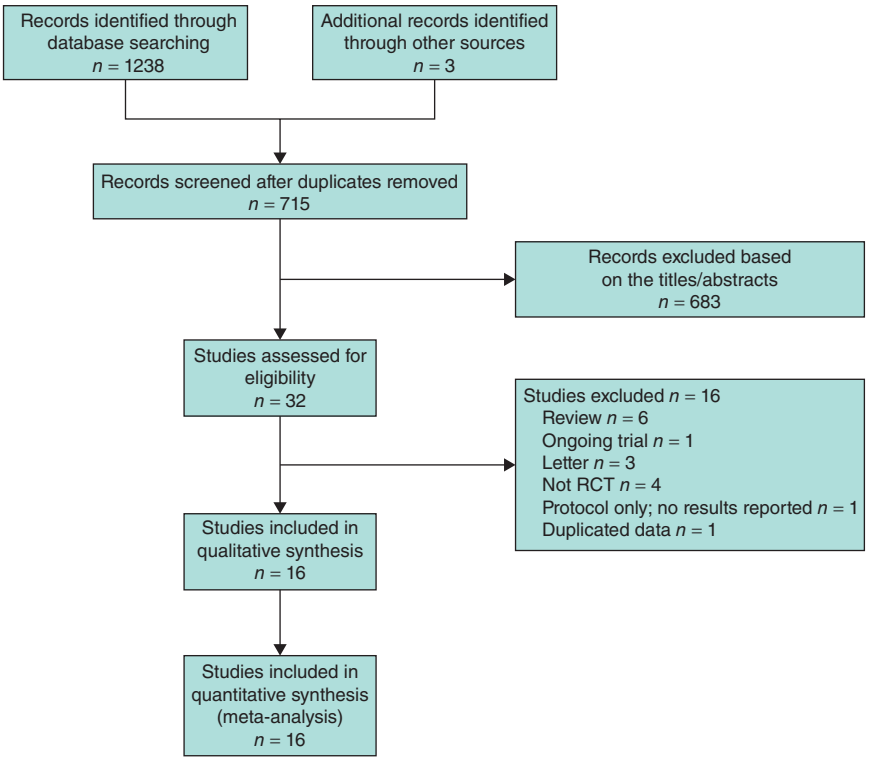

Fig. 1 PRISMA flow diagram showing selection of articles for meta-analysis. RCT, randomized clinical trial

corresponding terms including 'cholecystitis', 'cholecystectomy' and 'random*'. The searches were limited to human subjects and no language restriction was imposed. The references of relevant reviews and included studies were also checked manually to identify additional potentially eligible studies.

Study selection

Two investigators executed the literature search independently, removed the duplicate records, screened the titles and abstracts for relevance, and tagged the articles as included, excluded or requiring further assessment. Published RCTs meeting the following criteria were included: adult patients with acute cholecystitis; ELC performed within 7 days of the onset of symptoms; DLC performed at least 1 week after initial conservative treatment; and reporting one or more of the outcomes described below.

Data extraction and outcome measures

The following information was extracted from each study: first author, year of publication, number of patients, patient characteristics, study design, definition of ELC and DLC, and outcomes.

The outcomes were duration of operation, length of hospital stay, wound infection, bile duct injury, bile leakage, conversion to open surgery, overall complications and mortality, cost-effectiveness (hospital cost and number of work days lost) and quality of life. Hospital stay in the delayed group comprised the combined length of stay for the admission at presentation and readmission for DLC. Extracted data were entered into a pregenerated standard Microsoft® Excel (Microsoft Corporation, Redmond, Washington, USA) file. Data extraction was performed by one author and then checked by another. Any disagreement was resolved by discussion and consensus.

Assessment for risk of bias

The Cochrane risk of bias tool was used to appraise risk of bias[22]. Two investigators independently reviewed all studies and graded the risk as 'high', 'low' or 'unclear' in the following categories: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and baseline imbalance. Trials with a high risk of bias for any one or more key domains were considered to be at high risk of bias, whereas trials with a low risk of bias for all key domains were considered to be

Table 1 Characteristics of randomized clinical trials included in the meta-analysis

Reference	Country	No. of patients (ELC/DLC)	Mean age (years)	Men (%)	Definition of ELC	Definition of DLC	Article type
Lai *et al.*[31] (1998)	China	104 (53/51)	55·9	36·5	Within 24 h of randomization	6–8 weeks after acute episode subsided	Full text
Lo *et al.*[32] (1998)	China	86 (45/41)	58·4	55	As soon as possible within 72 h of admission	Following 8–12 weeks of discharge after conservative treatment	Full text
Dávila *et al.*[33] (1999)	Spain	63 (27/36)	56	29	Within 4 days of diagnosis	2 months later	Full text
Khan[34] (2002)	Pakistan	43 (22/21)	57·4	35	Within 7 days of onset	2–4 months after acute episode subsided	Full text
Johansson *et al.*[35,36]* (2003, 2004)	Sweden	145 (74/71)	56·3	40	Within 48 h after randomization but no later than 7 days after onset of symptoms	Following 6–8 weeks of discharge after conservative treatment	Full text
Kolla *et al.*[37] (2004)	India	40 (20/20)	40·1	20	Within 24 h of randomization	6–12 weeks after acute inflammation subsided	Full text
Macafee *et al.*[38] (2009)	UK	72 (36/36)	52·5	35	Within 72 h of recruitment	Following 3 months of discharge after conservative treatment	Full text
Yadav *et al.*[39] (2009)	Nepal	50 (25/25)	41·5	24	As soon as possible	Following 6–8 weeks of discharge after complete relief of symptoms	Full text
Mare *et al.*[40] (2012)	Switzerland	54 (27/27)	n.r.	n.r.	Immediately after diagnosis	At least 6 weeks after initial diagnosis	Abstract†
Verma *et al.*[41] (2013)	India	60 (30/30)	32·3	10	Within 72 h of onset of symptoms	After 6–8 weeks	Full text
Faizi *et al.*[42] (2013)	Pakistan	50 (25/25)	41·5	48	Within 72 h of onset of symptoms	At least 5 weeks after acute inflammation resolved	Full text
Gul *et al.*[43] (2013)	India	60 (30/30)	39·1	20	Within 72 h of admission	Following 6–12 weeks of discharge as soon as acute attack subsided	Full text
Gutt *et al.*[44] (2013)	Germany	618 (304/314)	56·2	41·3	Within 24 h of hospital admission	On days 7–45	Full text
Saber and Hokkam[45] (2014)	Egypt	120 (61/59)	n.r.	n.r.	Within 72 h of admission	Following 6–8 weeks of discharge after complete relief of symptoms	Full text
Ozkardeş *et al.*[46] (2014)	Turkey	60 (30/30)	58·7	38	Within 24 h of admission	Following 6–8 weeks of discharge after conservative treatment	Full text

*Outcome of this trial published in two separate papers[35,36]. †Conference abstract that provided sufficient data for this meta-analysis. ELC, early laparoscopic cholecystectomy; DLC, delayed laparoscopic cholecystectomy; n.r., not reported.

at low risk of bias. Otherwise they were considered to be at unclear risk of bias. All discrepancies were resolved by consensus.

Statistical analysis

Relative risks (RRs) with 95 per cent c.i. were estimated for dichotomous outcomes, and mean differences (MDs) with 95 per cent c.i. for continuous outcomes. When mean values were not available for continuous data, median values were used for evaluation[23]. The results were considered statistically significant at the $P < 0{\cdot}050$ level if the 95 per cent c.i. did not include 1·00. A random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I^2 statistic; a value of 0 per cent indicated no heterogeneity and over 50 per cent indicated significant heterogeneity. Results were considered as statistically significant if $P < 0{\cdot}050$. Funnel plots were created to determine the presence of publication bias[24]. All statistical analyses were done using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Table 2 Risk of bias in individual studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline imbalance
Lai *et al.*[31]	+	+	?	–	+	+	+
Lo *et al.*[32]	+	+	?	?	+	+	+
Dávila *et al.*[33]	?	?	?	?	–	?	?
Khan[34]	?	?	?	?	?	+	+
Johansson *et al.*[35,36]	+	+	?	?	+	+	+
Kolla *et al.*[37]	+	+	?	–	+	+	+
Macafee *et al.*[38]	+	+	?	–	+	–	+
Yadav *et al.*[39]	?	?	?	?	?	–	+
Mare *et al.*[40]	?	?	?	?	+	+	?
Verma *et al.*[41]	+	?	?	?	–	+	+
Faizi *et al.*[42]	+	?	?	?	–	+	?
Gul *et al.*[43]	+	+	?	?	?	+	?
Gutt *et al.*[44]	+	+	?	?	+	+	+
Saber and Hokkam[45]	+	+	?	?	+	–	+
Ozkardeş *et al.*[46]	?	?	?	?	+	+	+

+, Low risk of bias; –, high risk of bias; ?, unclear risk of bias.

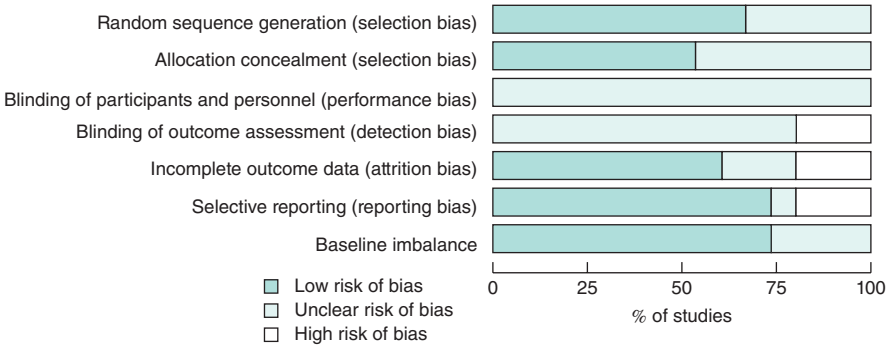

Fig. 2 Summary of risks of bias of included studies

Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors owing to sparse data and repetitive testing of cumulative data[25–27]. Thus, sensitivity analysis with trial sequential analysis was performed in case the data were too sparse to draw firm conclusions. Trial sequential analysis is comparable to interim analysis in a single trial, and the trial sequential monitoring boundary can be applied to meta-analysis to determine whether the *P* value is small enough to show the anticipated effect and whether the trial should be terminated early[25–28]. If the trial sequential analysis boundary or the futility zone is crossed, more trials are unnecessary[26,29,30].

Trial sequential analysis was applied with the required sample size calculated based on an α error of 0·05, a β error of 0·20 (power 80 per cent), and an anticipated intervention effect of 20 per cent RR reduction. For binary outcomes, a control event proportion was obtained from the result of the meta-analysis. For continuous outcomes, the variance was estimated empirically, using a minimal clinically relevant difference of 15 min for duration of operation and 1 day for length of hospital stay. The analyses were done with trial sequential analysis version 0.9 beta (www.ctu.dk/tsa)[29,30].

Results

The selection of articles for meta-analysis is summarized in *Fig. 1*. Some 16 studies[31–46] (reporting 15 RCTs) with a total of 1625 patients (ELC 809, DLC 816) were included in the meta-analysis. Study characteristics are presented in *Table 1*. All studies were published between 1998 and 2014, and the sample size ranged from 40 to 618. The trial by Gutt and colleagues[44] was a multicentre study; all other studies were from a single centre.

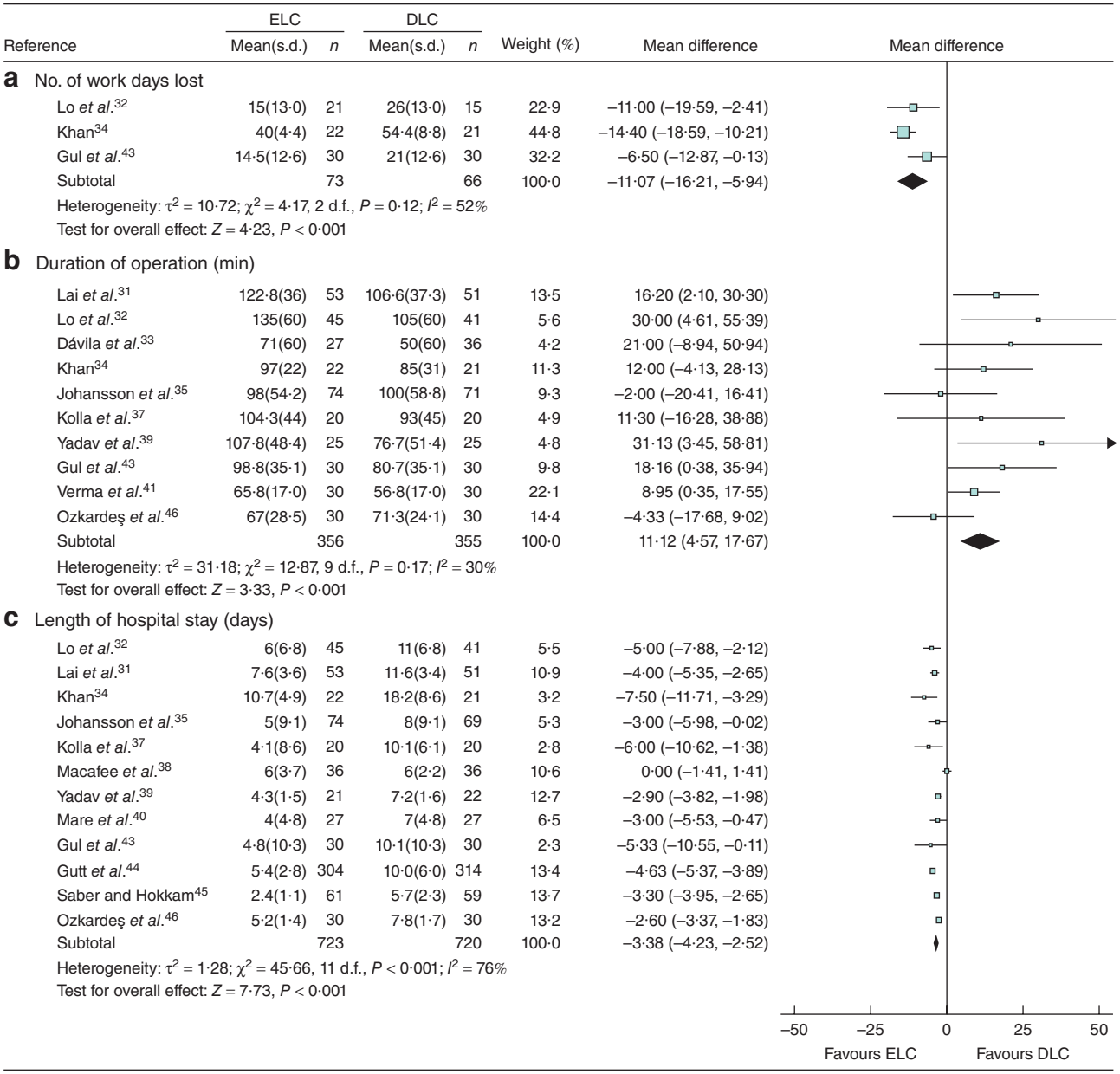

Fig. 3 Forest plots comparing **a** work days lost, **b** duration of operation and **c** length of hospital stay in early laparoscopic cholecystectomy (ELC) and delayed laparoscopic cholecystectomy (DLC) groups. An inverse-variance random-effects model was used. Mean differences are shown with 95 per cent c.i.

Risk of bias

Details of risk of bias for each RCT are shown in *Table 2*, with a summary in *Fig. 2*. Randomized sequence generation and allocation concealment were conducted adequately in most studies[31,32,35,37,38,43–45]. Because it is impossible to blind the participants and surgeons who performed the surgery, all outcomes were at unclear risk of bias for this domain.

Outcomes

Pooled results showed that ELC was associated with a significantly increased duration of operation (MD 11·12

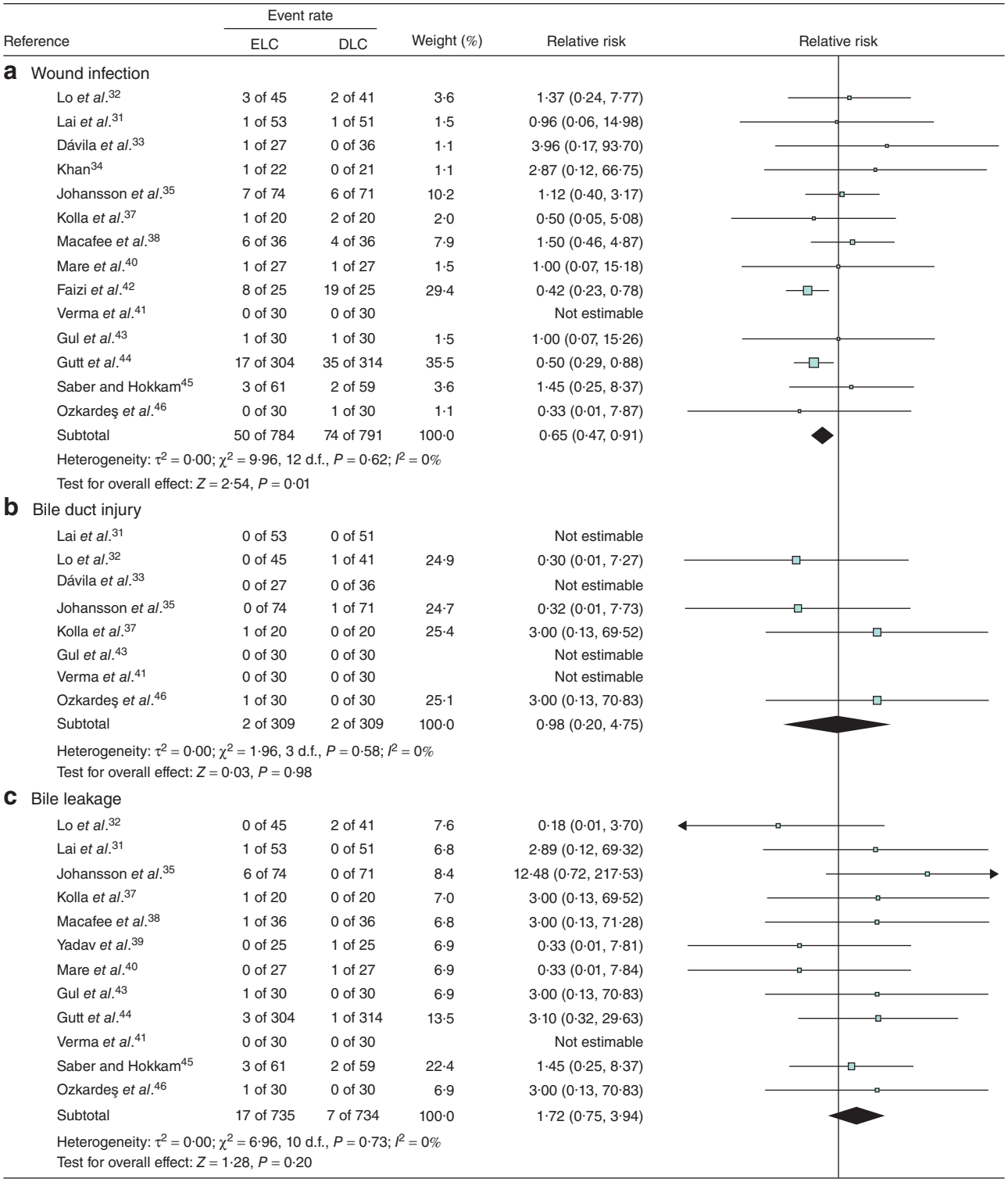

Fig. 4 Forest plots comparing **a** wound infection, **b** bile duct injury, **c** bile leakage, **d** conversion to open surgery and **e** overall complications in early laparoscopic cholecystectomy (ELC) and delayed laparoscopic cholecystectomy (DLC) groups. A Mantel–Haenszel random-effects model was used. Relative risks are shown with 95 per cent c.i. *Figure 4* continued on next page.

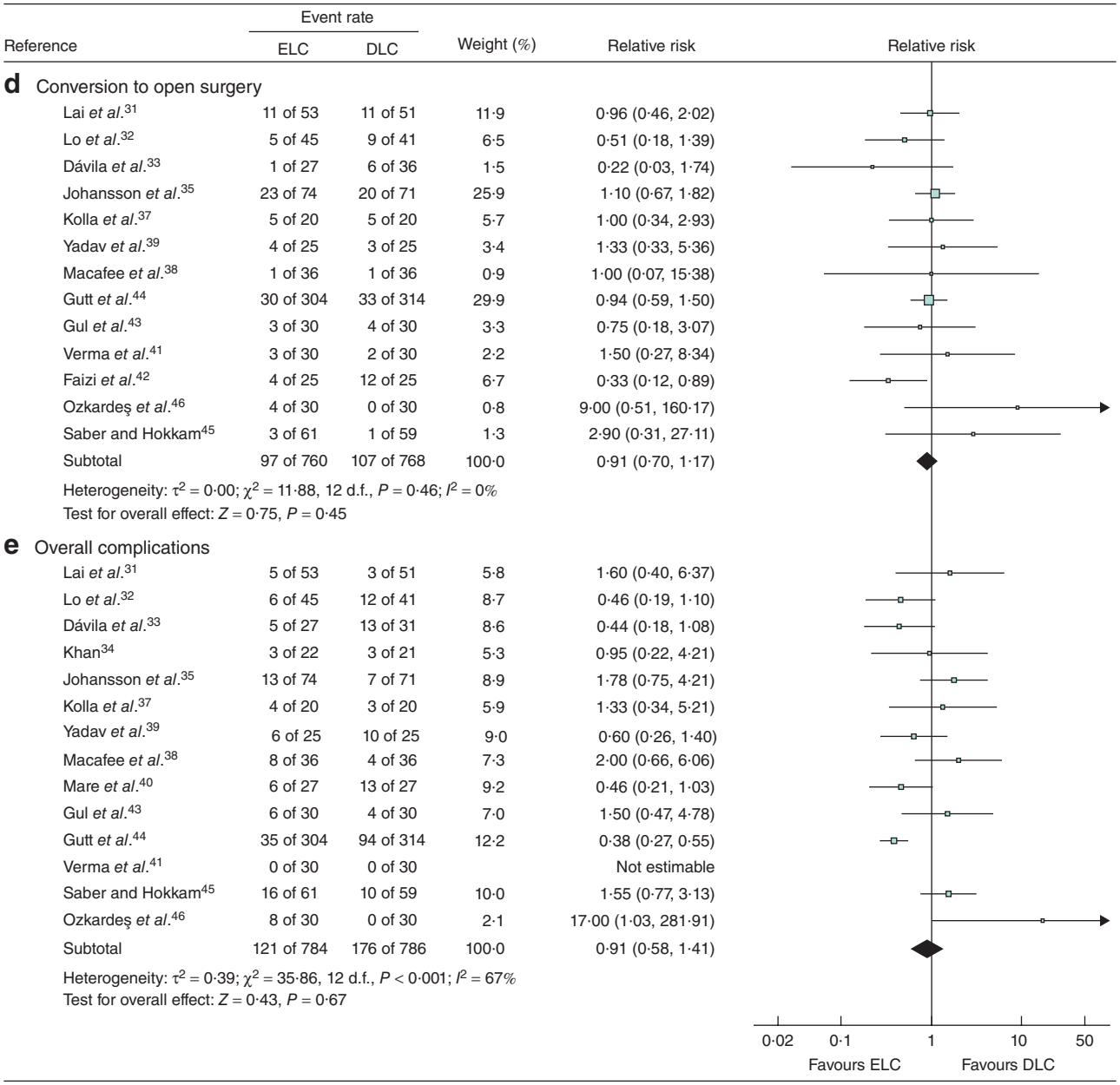

Fig. 4 Continued

(95 per cent c.i. 4·57 to 17·67) min; $P < 0{\cdot}001$) ($I^2 = 30$ per cent), but reduced length of hospital stay (MD −3·38 (−4·23 to −2·52) days; $P < 0{\cdot}001$) ($I^2 = 76$ per cent) (*Fig. 3*).

For duration of operation and hospital stay, the accumulative Z-curve crossed the trial sequential analysis boundary, which suggested that the differences were unlikely to result from chance, and further studies are unlikely to change the conclusion (*Fig. S1*, supporting information).

Compared with DLC, ELC was associated with a lower risk of wound infection (RR 0·65, 95 per cent c.i. 0·47 to 0·91; $P = 0{\cdot}01$) ($I^2 = 0$ per cent), whereas there was no significant difference in bile duct injury or other complications (*Fig. 4*). Only Gutt and colleagues[44] provided data on mortality, which was 0·3 per cent in both groups (ELC, 1 of 304; DLC, 1 of 314).

For bile duct injury and other complications, the accumulative Z-curve did not cross the conventional

Table 3 Meta-analyses of early *versus* delayed laparoscopic cholecystectomy

	Lau *et al.*[14] (2006)	Siddiqui *et al.*[15] (2008)	Gurusamy *et al.*[16] (2010)	Gurusamy *et al.*[19] (2013)	Zhou *et al.*[18] (2014)	Present study
No. of RCTs	4	4	5	6	7	15
No. of participants	504	375	451	488	1106	1625
Search strategy until (year)	2004	2006	2008	2012	2013	2014
Definition of early	Within 72 h after diagnosis	Within 7 days of onset of symptoms	Within 7 days of onset of symptoms	Within 7 days of onset of symptoms	Within 7 days of onset of symptoms	Within 7 days of onset of symptoms
Definition of delayed	6–10 weeks later	6 weeks after admission	At least 6 weeks after index attack of acute cholecystitis	At least 6 weeks after index attack of acute cholecystitis	At least 1 week after initial conservative treatment	At least 1 week after initial conservative treatment
Outcomes						
Hospital cost	n.r.	n.r.	n.r.	n.r.	n.r.	ELC less than DLC
No. of work days lost	n.r.	n.r.	MD −11·00 (−19·61, −2·39)	MD −11·00 (−19·61, −2·39)	n.r.	MD −11·07 (−16·21, −5·94)
Quality of life	n.r.	n.r.	Not completed	n.r.	n.r.	ELC better than DLC
Trial sequential analysis	n.r.	n.r.	n.r.	Confirmed hospital stay	n.r.	Confirmed duration of operation, hospital stay
Mortality	n.r.	n.r.	No death	No death	No difference	No difference
Wound infection	n.r.	n.r.	n.r.	n.r.	n.r.	RR 0·65 (0·47, 0·91)
Bile duct injury	n.r.	OR 0·68 (0·13, 3·49)	RR 0·64 (0·15, 2·65)	OR 0·49 (0·05, 4·72)	OR 0·49 (0·05, 4·72)	RR 0·98 (0·20, 4·75)
Bile leakage	OR 2·22 (0·64, 7·72)	OR 2·42 (0·76, 7·74)	RR 5·50 (0·98, 30·83)	n.r.	n.r.	RR 1·72 (0·75, 3·94)
Conversion to open surgery	OR 0·56 (0·24, 1·33)	OR 0·92 (0·57, 1·48)	RR 0·88 (0·62, 1·25)	RR 0·89 (0·63, 1·25)	RR 0·91 (0·69, 1·20)	RR 0·91 (0·70, 1·17)
Overall complications	OR 0·97 (0·59, 1·61)	OR 1·07 (0·60, 1·92)	n.r.	n.r.	n.r.	RR 0·91 (0·58, 1·41)
Duration of operation (min)	MD 0·13 (−0·59, 0·84)	MD 0·412 (0·15, 0·68)	MD −1·33 (−3·25, 0·59)	MD −1·22 (−3·07, 0·64)	MD 15·31 (1·09, 29·53)	MD 11·12 (4·57, 17·67)
Hospital stay (days)	MD −1·14 (−1·58, −0·70)	MD 0·91 (0·63, 1·18)	MD −4·12 (−5·22, −3·03)	MD −4·12 (−5·22, −3·03)	MD −4·12 (−5·22, −3·03)	MD −3·38 (−4·23, −2·52)

Values in parentheses are 95 percent c.i. RCT, randomized clinical trial; n.r., not reported; ELC, early laparoscopic cholecystectomy; DLC, delayed laparoscopic cholecystectomy; MD, mean difference; OR, odds ratio; RR, relative risk.

boundary or the trial sequential analysis boundary. Trial sequential analyses suggested that the present meta-analysis was underpowered to draw firm conclusions (*Fig. S2*, supporting information).

Hospital costs and work days lost

Three studies[38,44,46] included hospital costs. Gutt and colleagues[44] demonstrated that total hospital cost was significantly lower in the ELC group (mean €2919 *versus* €4262 in DLC group; $P < 0{\cdot}001$), which was in agreement with the findings of Ozkardeş and co-workers[46] (mean(s.d.) Turkish lira (TRY) 2500·97(755·27) for ELC *versus* TRY 3713·47(517·33) for DLC; $P = 0{\cdot}03$) (€815(246) *versus* €1210(169); exchange rate 16 June 2014). Macafee *et al.*[38] reported similar costs for both groups (mean(s.d.) £4589(1715) for ELC *versus* £4671(2243) for DLC; $P = 0{\cdot}999$) (€6382(2385) *versus* €6497(3120)). Meta-analysis was not performed because there was considerable heterogeneity.

Three studies[32,34,44] included data for work days lost. ELC was associated with fewer work days lost than DLC (MD −11·07 (95 per cent c.i. −16·21 to −5·94) days; $P < 0{\cdot}001$), and there was moderate heterogeneity ($I^2 = 52$ per cent) (*Fig. 3*).

Patient satisfaction and quality of life

The overall rate of satisfaction was higher for patients who underwent ELC than for those in the DLC group[45]. Johansson and colleagues[36] reported ELC to be associated with a more favourable gastrointestinal symptom score at 1 month after surgery, whereas there were no significant differences at 3 and 6 months. Macafee *et al.*[38] reported significantly lower visual analogue scale scores in the ELC group compared with the DLC

group, but both treatments resulted in rapid recovery.

Publication bias

Publication bias is summarized by means of funnel plots (*Fig. S3*, supporting information). For dichotomous outcomes, funnel plots were symmetrical, whereas the plots for continuous parameters were not.

Discussion

The present study suggests that ELC is associated with a lower risk of wound infection, shorter hospital stay, better cost-effectiveness, and higher patient satisfaction and quality of life. Several meta-analyses[13–19] on outcome after ELC *versus* DLC have been published previously (*Table 3*). Hospital costs have not been assessed in previous reviews. Of the three RCTs that reported costs, two[44,46] suggested that ELC could lower the healthcare cost, whereas Macafee and colleagues[38] found no difference between ELC and DLC. However, recent observational studies that analysed actual hospital costs, and some cost–utility studies have confirmed that ELC could significantly reduce expenditure and should be the preferred strategy from this perspective[47–50].

One of the most consistent findings in this meta-analysis concerned work days lost. On average, participants in the DLC group lost 11 more days from work than those who underwent ELC, mainly because of the two separate hospital admissions. ELC thus contributes to an earlier return to work and provides maximal economic gain.

Information on patient satisfaction and quality of life could be informative for clinical decision-making. Even though different methodologies were used to estimate quality of life and patient satisfaction, the conclusions were consistent. Patients treated with DLC were found to experience recurrent gastrointestinal symptoms frequently, take anti-inflammatory drugs, and may have unresolved or recurrent cholecystitis before the delayed operation. In a population-based study assessing the risk of recurrence in patients with a first episode of acute cholecystitis discharged without cholecystectomy, the incidence of gallstone-related events was 14 per cent at 6 weeks, 19 per cent at 12 weeks and 29 per cent at 1 year. There was an increased risk in younger patients and this was associated with decreased quality of life, reinforcing the value of ELC[51].

The risk of wound infection was lower in the ELC group. A retrospective study[52] also found that the risk of postoperative infections increased with the length of delay to surgery. Bile duct injury is the most feared complication of laparoscopic cholecystectomy, and may lead to morbidity and reinterventions. The trial sequential analysis indicated that additional RCTs would still be subject to limited data and only large-scale population-based studies may address this unresolved issue[19,53]. Recently, a study[54] with sufficient power to detect the difference in bile duct injury showed a significantly lower rate of bile duct injuries for ELC compared with DLC (0·3 *versus* 0·5 per cent; RR 0·53, 95 per cent c.i. 0·31 to 0·90; $P = 0·025$).

This meta-analysis has several limitations. First, limited data were available on costs of ELC and DLC, and quality of life after ELC *versus* DLC has not been well studied. Second, several trials in this review had high risks of bias, and the benefits and harms of ELC or DLC may have been overestimated. Third, substantial heterogeneity across studies was observed. The heterogeneity for duration of operation can perhaps be explained by the technical advances in recent years, different surgical practice between hospitals and/or differences in level of surgical expertise. Heterogeneity of hospital stay and work days lost was also observed. Finally, 11 of the 15 eligible RCTs included in the meta-analysis had relatively modest sample sizes (fewer than 100 patients), and overestimation of the treatment effect is more likely than in larger studies.

Further studies focusing on the following aspects are needed. The definition of ELC varied from 0 to 7 days according to the study protocols, and the optimal timing of ELC remains unclear. Several studies have explored the timing of ELC during the admission for acute cholecystitis. All reported that, even at an early stage, delaying laparoscopic cholecystectomy was associated with more complications, higher mortality and higher costs, and thus immediate cholecystectomy is preferred[52,55,56]. Interestingly, another retrospective study[57] suggested that night-time laparoscopic cholecystectomy was associated with an increased risk of conversion to open surgery compared with procedures carried out during the day, whereas hospital stay and complication rates were similar in the two groups. These findings suggest that ELC should be performed as soon as possible, but preferably during the day. On the other hand, another study[58] suggested that patients undergoing emergency laparoscopic cholecystectomy for acute cholecystitis suffered the highest conversion and complication rates, whereas elective surgery was superior. However, elective laparoscopic cholecystectomy was not defined clearly and was performed mostly in a specialized hospital, which may

have introduced bias. The experience and operation technique of the surgeon may also differ and influence the results[13,31,32,35,37,38,46].

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Trial sequential analysis of continuous outcomes (Word document)

Fig. S2 Trial sequential analysis of dichotomous outcomes (Word document)

Fig. S3 Funnel plots of publication bias (Word document)