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REVIEW ARTICLE

Outcome of early cholecystectomy compared to percutaneous drainage of gallbladder and delayed cholecystectomy for patients with acute cholecystitis: systematic review and meta-analysis

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Abstract

Background: Compare outcomes of early laparoscopic cholecystectomy (ELC) and percutaneous trans-hepatic drainage of gallbladder (PTGBD) as an initial intervention for AC and to compare operative outcomes of ELC and delayed laparoscopic cholecystectomy (DLC).

Methods: English-language studies published until December 2020 were searched. Randomised controlled trials (RCTs) and observational studies compared EC and PTGBD with delayed cholecystectomy for patients presented with acute cholecystitis were considered. Main outcomes were mortality, conversion to open, complications and length of hospital stay.

Results: Out of 1347 records, 14 studies were included. 205,361 (94.7%) patients had EC and 11,565 (5.3%) patients had PTGBD as an initial intervention for AC. Mortality was higher in PTGBD; HR, 95% CI: [3.68 (2.13, 6.38)]. In contrast, complication rate was significantly higher in EC group (47%) vs PTGBD group (8.7%) in patients admitted to ICU; P-value = 0.011. Patients who had ELC were at higher risk of post-operative complications compared to DLC; RR [95% CI]: 2.88 [1.78, 4.65]. Risk of bile duct injury was six folds more in ELC; RR [95% CI]: 6.07 [1.67, 21.99].

Conclusion: ELC may be a preferred treatment option over PTGBD in AC. However, patient and disease specific factors should be considered to avoid unfavourable outcomes with ELC.

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Introduction

Acute cholecystitis (AC) is the most common complication of gallstone disease with about 12% of gallstone patients can develop AC in their lifetime.[1] Complications of AC, such as gangrene, gallbladder perforation and emphysematous AC, can happen in 7.2–26% of patients with AC.[2,3] Severe sepsis resulting in organ dysfunction and a need for organ support is a possible consequence of severe disease.[4]

Cholecystectomy is the definitive treatment for symptomatic gallstone disease aiming to eliminate or reduce biliary pain and it also reduces risk of complications such as recurrence of AC, common bile duct stones or gallstone pancreatitis.[5] Moreover, early cholecystectomy for AC is associated with less gallstone disease related hospital admissions and less total treatment cost even in elderly patients.[6]

For uncomplicated AC in low risk surgical patient, early laparoscopic cholecystectomy (ELC) is the recommended treatment option.[7,8] Management can be difficult in complicated AC or in high risk surgical patients not responding to conservative treatment and percutaneous transhepatic gallbladder drainage (PTGBD) is an option to avoid possible high risk surgery.[7,8] However, PTGBD is not a definitive treatment and is associated with more unfavourable long-term outcomes such as total hospital stay and recurrent admissions.[9–11]

There is an agreement between Tokyo guidelines (TG) 2018, National Institute for Health and Care Excellence (NICE), Association of Upper Gastrointestinal surgery of Great Britain and Ireland (AUGIS) and World Society of Emergency Surgery (WSES) 2020 guidelines that ELC should be offered to AC patients as first option whenever the risk of surgical intervention deemed acceptable.[7,8,12,13] In TG 2018 and WSES guidelines, PTGBD is an alternative option if the surgical treatment is considered high risk and expected to be associated with more unfavourable outcomes compared with PTGBD. However, there is discrepancy in criteria to select ELC or PTGBD and most of recommendations were based on low-quality evidence.[14]

The aim of this review is to compare outcomes of ELC and PTGBD as an initial intervention for AC and to compare operative outcomes of ELC and post PTGBD delayed laparoscopic cholecystectomy (DLC). Predictors of selecting PTGBD over ELC in practise are also studied. This allows comparing early cholecystectomy vs PTGBD followed by DLC as two management pathways for patients admitted with AC.

Methods

This review was prepared in line with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement. This systematic review was registered to PROSPERO (registration number: CRD42021262443).

English-language studies published between 1946 and December 2020 were searched.

Randomised controlled trials (RCTs) and observational studies compared early cholecystectomy (EC) and percutaneous transhepatic drainage of gallbladder (PTGBD) with delayed cholecystectomy for patients presented with acute cholecystitis were initially considered. Systematic reviews were excluded but considered in discussion. Only studies with target population of patients acutely presented with acute cholecystitis (AC) were included. Patients who presented with AC and did not require any intervention at index admission, whether PTGBD or EC were excluded. Main outcomes were mortality, conversion to open, complications and length of hospital stay.

Electronic database search was conducted in Ovid Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Review (CDSR). The search was conducted by a senior information specialist from the library department of the Royal College of Surgeons of England and was executed on the 17th of December 2020. Patient Intervention Control Outcome (PICO) framework was used to guide the search (Supplementary Table 1). Full electronic search strategy is shown in Supplementary Tables 2a–c.

Two independent blinded reviewers performed the abstract screening. Any conflicts were resolved by a third reviewer to produce the final list of studies eligible for full-text review. Full text review carried out by one reviewer and results were checked by a senior researcher.

Data from individual studies were extracted by two independent blinded researchers on Excel spread sheet and checked by another independent researcher to confirm adequacy and accuracy of data extracted. Data included individual study details, demographic data, type of treatment, disease characteristics and outcomes in both treatment arms. Follow up period from each study were also noted. Observational studies were classified according to Mathes and Pieper criteria.[15] The revised Cochrane risk-of-bias tool for RCTs (RoB2 Tool) was used to assess risk of bias in RCTs and Joanna Briggs Institute (JBI) assessment tool used to assess observational studies.[16,17] For JBI appraisal tool, overall risk of bias of specific study was decided based on how many questions were answered with yes, no or unclear. The study will be of low concern of bias if there is unfavourable answer to one question or less, some concern if 2 to 3 questions and high concern if 4 or more questions.

Statistical analysis

Count, percentages, and ratios were used to represent non-continuous variables and median (range) was used to represent continuous data as stated in each individual study. Range of mean values was used to represent continuous variable across studies that could not be combined. Meta-analysis of categorical variables such as post-operative complications, were represented by risk ratios (RR) (hazard ratio (HR) for mortality) and 95% confidence interval (CI). Continuous variables such as age were represented by mean difference (MD) and 95% CI.

Meta-analysis was conducted using RevMan (Review Manager) software version 5.4 if allows. I^2 and Tau^2 tests were performed to assess heterogeneity. If $I^2 > 50\%$, significant heterogeneity will be considered and Mantel–Haenszel (M–H) random effect model to be employed.[18]

Chi-square test was used to compare the studies reporting number of high-risk surgical patients and/or patients with complicated AC who had PTGBD compared to the rest of studies. A P-value of less than 0.05 was taken as statistically significant.

Handling of confounding factors

Patients and disease characteristics were highlighted and compared in EC vs PTGBD and ELC vs DLC comparisons.

Operational definitions

EC: early cholecystectomy performed at the index admission for AC.

ELC: early laparoscopic cholecystectomy.

PTGBD: Percutaneous transhepatic gallbladder drainage.

DLC: Delayed laparoscopic cholecystectomy performed after PTGBD.

Post PTGBD-DLC: DLC after PTGBD.

Complicated acute cholecystitis: Tokyo classification of Grade II or more AC[19] or Presence of systemic sepsis, empyema, gangrene, perforation, abscess, or gallbladder (GB) wall thickness $\geq$ 4 mm.

Grade II acute cholecystitis: AC that fulfils any one of the following criteria: elevated white blood cell count (>18,000/ mm^3), palpable tender mass in the right upper abdominal quadrant, duration of complaints >72 h, or marked local inflammation (pericholecystic abscess, gangrenous cholecystitis, hepatic abscess, biliary peritonitis, emphysematous cholecystitis).[19]

Major complications: Clavien–Dindo classification (CD)[20] of 3 or more or presence of intra-abdominal abscess, pneumonia, myocardial infarction or pulmonary embolism within 30 days after randomisation or recurrent biliary disease or need for reintervention within one year.

BDI: Bile duct injury. This term also included bile leak or biloma.

Patient's morbidity and risk evaluation systems

- **APACHE II:** Acute physiology assessment and chronic health evaluation II.[21]
- **ASA:** The American Society of Anaesthesiologists classification.[22]
- **SOI:** Severity of illness scoring system.[23]

High risk surgical patient is defined as a patient who meets any of these criteria: APACHE II score of 7 or more, SOI score of 3 or more, ASA score of 3 or more or admission to intensive care unit (ICU).

Results

Study selection process is demonstrated on the PRISMA diagram (Fig. 1). 1347 records were identified on the initial search after excluding 646 duplicates. 21 studies were eligible for full text review. Of which, 7 studies were excluded for either not fulfilling the study question criteria or no comparison performed to produce a final list of 14 studies. 2 studies were randomised controlled trials and 12 were observational studies. Risk of bias assessment for RCTs has shown some concern for one study[10] and high concern for the other study[24] (Supplementary Table 3). Six observational studies were identified to have high concerns of bias (Supplementary Tables 4a, b and Table 1).[4,6,11,25–27]

Out from 14 studies, 205,361 (94.7%) patients had early cholecystectomy and 11,565 (5.3%) patients had PTGBD as an initial intervention for acute cholecystitis. In 13 studies, laparoscopic intervention was the initial approach in 10,253 (85.7%) patients undergoing early cholecystectomy.[4,10,11,24–33] From 2276 patients had PTGBD, 1618 (71.1%) patients had subsequent cholecystectomy as reported from 10 studies.[24–33]

Timing of early cholecystectomy (EC)

Timing of early cholecystectomy was not specified in seven studies.[4,6,11,26,27,30,33] On the remaining seven studies, there was a high variation, and range of time interval from hospital admission to surgery was from 24 h to 7 days.[10,24,25,28,29,31,32] Two studies specified at least 72 h from the onset of symptoms as an inclusion criteria.[24,30] Mean duration of symptoms before intervention ranged from 2.25 to 7.4 days in four studies.[10,26,30,31] (Table 1).

Time interval between PTGBD and delayed cholecystectomy

A considerable variability was present across studies. From nine studies, time interval ranged from 3 to 802 days.[10,24,25,28–33] (Table 1).

Patients and disease characteristics and predictors of PTGBD

Mean age ranged from 49.65 to 80 years in 13 studies.[4,6,10,24–33] There was no significant age difference between PTGBD and EC groups; MD, 95% CI: [0.97 (−2.29, 4.22)]. 101,741 (47.3%) patients were males and male gender was not a risk factor for PTGBD; RR, 95% CI: [0.97 (0.87, 1.07)].[4,6,10,11,24,25,27–33] Body mass index (BMI) was statistically higher in patients had EC in four studies; MD, 95% CI: [−0.43 (−0.67, −0.19)].[10,28,29,32] Mean ASA score ranged from 1.24 to 4.06 in eight studies and tended to be higher in PTGBD group; MD,95% CI: [0.29 (0.00, 0.59)].[10,24–27,29–31] (Supplementary Fig. 1).

Four studies included only high risk surgical patients according to different scoring systems (Table 1).[4,10,11,29] In those four studies, incidence of PTGBD (21.6%) was significantly higher than the rest of studies (4.7%); P-value <0.00001. Six studies included only patients with complicated acute cholecystitis[4,24–26,29,32] and the PTGBD incidence (46.9%) was significantly higher than the rest of studies (5.2%); P-value <0.00001. Two studies included 128 high risk surgical patients admitted with complicated AC[4,29] and PTGBD was significantly more commonly performed (47.7%) compared to studies included only high risk surgical patients with uncomplicated AC (21.2%); P-value <0.00001.[10,11] However, there was no statistical significance between high-risk surgical patients with complicated AC and patients with only complicated AC; P-value = 0.88 (Supplementary Table 5).

Patients with diabetes mellitus [RR, 95% CI (1.6 (1.3,1.98))],[4,6,10,26–29,32,33] cardiovascular disease [RR, 95% CI (1.78 (1.75,1.81))],[4,6,10,26–29,32,33] respiratory disease [RR, 95% CI (1.57 (1.08, 2.28))],[4,6,10,24,26–29,32] cerebrovascular disease [RR, 95% CI (1.72 (1.27, 2.33))],[25,28,29,32,33] chronic kidney disease [RR, 95% CI (2.21, (1.33,3.67))],[4,6,10,27–29,32] and liver disease [RR, 95% CI (1.63 (1.25, 2.13))][27–29,32] were at higher risk to have PTGBD rather than EC (Supplementary Fig. 2a, b).

Body temperature at admission was higher in PTGBD group but this was not statistically significant; MD, 95% CI [0.37 (−0.06, 0.81)].[24,31,33] There was no difference between PTGBD and EC groups regarding duration of symptoms prior to

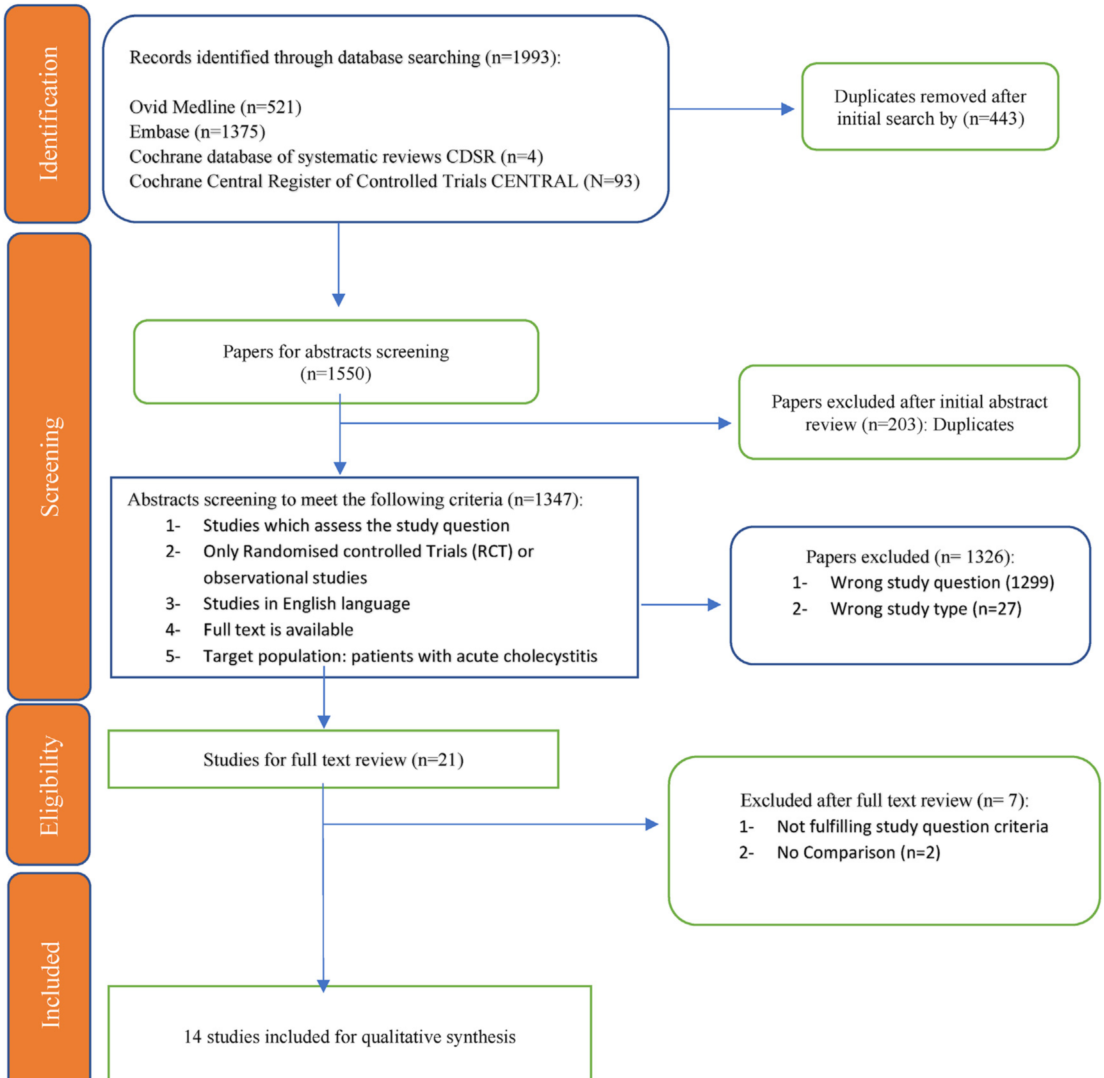


Figure 1 PRISMA diagram

intervention; MD, 95% CI [−0.04 (−0.19, 0.11)][10,26,30,31] (Supplementary Fig. 3).

C-reactive protein (CRP) was significantly higher in patients underwent PTGBD; MD, 95% CI [3.37 (2.71, 4.03)].[10,24,25,28,30,32,33] However, there was no difference in white blood count (WBC) between both groups; MD, 95% CI [0.74 (−0.32, 1.8)][24−26,29−33] (Supplementary Fig. 4).

Liver functions tests (LFTs) did not show significant difference between both groups for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin with MD, 95% CI: 7.44 (−9.40, 24.27), 3.62 (−10.14, 17.38), 28.35 (4.05, 52.65) and 0.30 (−0.08, 0.67), respectively from two studies[26,32] (Supplementary Fig. 5).

Albumin level was lower in PTGBD group but this was not significant; MD, 95% CI: −2.81 (−6.88, 1.26).[29,32] APACHE II scoring system did not show considerable difference in three studies; MD, 95% CI: 0.53 (−0.62, 1.68)[10,26,33] (Supplementary Fig. 6).

Outcomes of PTGBD vs EC

Patients who had PTGBD were at more than three times risk of mortality compared to EC group; HR, 95% CI: [3.68 (2.13, 6.38)] (Supplementary Fig. 7).[4,6,10,11,26,27] For patients aged 65 years or older, overall post-procedural complications were significantly higher in patients who had PTGBD (30.6%) compared to patients who had EC (15.2%); P-value <0.0001.[6] Likewise, in high risk surgical patients, PTGBD group had about three folds complications rate (13.3%) compared to EC group patients who had laparoscopic approach (4.9%); P-value<0.05.[11] In contrast, complication rate was significantly higher in EC group (47%) vs 8.7% in PTGBD group in patients

Table 1 Study details

Study and year	Risk of bias	Design	Inclusion/exclusion criteria	Early cholecystectomy	Timing/definition of EC	DLC + PTGBD	Timing of LC after PTGBD	Outcome domains
Choi *et al.* 2012[25]	High concerns	Retrospective cohort	Included only patients with diagnosis of complicated AC based on clinical, imaging and peri-operative findings. **Excluded** patients with cholangitis based on ERCP or MRCP	63	LC within 72 h from admission	40	Average 7.9 days – minimum 5 days	Operative time, development of complications, LOS
El-Gendi *et al.* 2017[24]	High concerns	Randomised controlled trial	Patients with grade II acute cholecystitis and presented >72 h after onset of symptoms. **Excluded** patients admitted to ICU, pregnancy and a calcular cholecystitis	75	Within 24 h	75	6 weeks	Conversion to open, complications, mortality, post-operative LOS
Endo *et al.* 2017[28]	Low concerns	International multicentre Retrospective cohort	Diagnosis of AC in patients aged 18 years or more	2947 1921 (67.4%) had primary laparoscopic approach	Within median interval of 3 days (70% had cholecystectomy by day 3)	1239 had cholecystectomy following PTGBD 531 had PTGBD alone	Median interval of 22 days (range: 1–802 days) **Mean ± SD** 39.9 ± 76.4 days	Post-operative bile leak, major BDI, conversion to open, overall morbidity, operative time, LOS and post-operative complications
Hall *et al.* 2018[11]	High concerns	Multicentre, retrospective cohort	Included high risk surgical patients based of SOI scoring system. Included only patients scored 3 or 4	7879 7221 (91.6%) had primary laparoscopic approach	Not specified	1682 (PTGBD only)	Not specified	LOS, cost, mortality, complications
Huang *et al.* 2007[26]	High concerns	Retrospective cohort	Included patients with GB perforation secondary to AC. **Excluded** patients younger than 14 years old and patients with traumatic GB perforation	16 (OC)	Not specified	17 (PTGBD) – 6 had elective OC	Not specified	Mortality, LOS, complications
Jia *et al.* 2018[29]	Some concerns	Retrospective cohort	Included patients with clinical and radiological evidence of AC associated with severe systemic disease and ASA score of 3 or more. **Excluded** patients with CBD stones or cholangitis.	48	Within 1 day	38	3–5 days	Operative time and complications, conversion to open, post-operative complications, LOS, mortality
Karakayali *et al.* 2014[30]	Low concerns	Prospective cohort	Only included low risk surgical patients with ASA score of 1 or 2 presented with symptoms for 72 h or more and not responded to medical treatment for at least 48 h due to AC	48	Not specified	43	4–8 weeks	Conversion to open, intraoperative bleeding, post-operative complications, LOS
Kim *et al.* 2011[31]	Some concerns	Retrospective cohort	Included patients with AC who had initial medical treatment for 12–24 h. **Excluded** asymptomatic patients, known chronic cholecystitis, gallbladder polyps	147	mean time interval 42.2 h from admission	97 had PTGBD – 94 (97%) had DLC	(DLC <7 days after PTGBD) Mean time interval 188.4 h	Operative time, conversion to open, complications, mortality, LOS

Table 1 (*continued*)

Study and year	Risk of bias	Design	Inclusion/exclusion criteria	Early cholecystectomy	Timing/definition of EC	DLC + PTGBD	Timing of LC after PTGBD	Outcome domains
			or malignancy on permanent treatment					
La Greca *et al.* 2017[27]	High concerns	Retrospective cohort	Included patients admitted with AC based on clinical and radiological criteria	556	During index admission	90 (13 of them had subsequent LC)	Not specified	Mortality, LOS, Clavien–Dindo classification of post-operative morbidity
Lee *et al.* 2017[32]	Some concerns	Retrospective cohort	Included patients underwent LC for moderate to severe AC according to TG13. **Excluded** patients with a history of upper abdominal surgery or ERCP for CBD stones.	41	36 had LC within 24 h/3 had LC 1-3d/2 had LC > 7d	44	mean 30 days after PTGBD	Operative time, conversion to open, post-operative complications. Evaluated predictors of prolonged operative time in PTGBD + LC group
Loozen *et al.* 2018 (CHOCOLATE trial)[10]	Some concerns	Multicentre Randomised controlled Trial	Included adults with calculous cholecystitis and a high surgical risk defined by APACHE II of 7 or more Excluded patients with APACHE II score of 15 or more	66 (2 patients did not have LC: one needed ERCP and one had hyponatremia)	Within 24 h of randomisation time interval from the onset of symptoms: median (IQR): 3 (2–3) days	68 randomised to PTGBD. PTGBD was left for 3 weeks then checked by cholangiogram. Further treatment was left to the discretion of treating clinician	3 weeks	**Primary end points**: death within one year and major complications. (Major complications defined as presence of intra-abdominal abscess, pneumonia, myocardial infarction or pulmonary embolism within 30 days after randomisation or recurrent biliary disease or need for reintervention within one year). **Secondary end points**: individual components of primary outcome, minor complications and difficulty of cholecystectomy (as scored by a visual analogue from 1 to 10)
Melloul *et al.* 2011[4]	High concerns	Retrospective cohort	Patients with sepsis related to acute calculous/ acalculous cholecystitis admitted to ICU. Excluded patients with additional cholangitis or pancreatitis	19 Only 10 (52.6%) had primary laparoscopic approach.	Not specified	23 (PTGBD)	Not specified	90 days mortality, overall, minor and major complication rates, LOS in hospital and in ICU
Ni *et al.* 2015[33]	Some concerns	Retrospective case-control	Patients diagnosed with acute cholecystitis and underwent LC or PTGBD. Excluded patients had open surgery, history of previous upper abdominal surgery, CBD stones, complications of other acute abdominal condition	33	Not specified	26 (64 patients did not have PTGBD-36 – had PTGBD alone)	Within 1 year	Remission of symptoms, operative time, intra-operative blood loss, conversion to open, LOS

(*continued on next page*)

Table 1 (*continued*)

Study and year	Risk of bias	Design	Inclusion/exclusion criteria	Early cholecystectomy	Timing/definition of EC	DLC + PTGBD	Timing of LC after PTGBD	Outcome domains
Schlottmann *et al.* 2018[6]	High concerns	Retrospective national cohort	Included 65 years or older patients admitted with a primary diagnosis of acute cholecystitis who underwent either cholecystectomy of PTGBD during index hospitalisation	193,399	Not specified	7516 had PTGBD	Not specified	Post-procedural complications, mortality, LOS and total cost

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; LC, laparoscopic cholecystectomy; LOS, length of hospital stay; ICU, intensive care unit; GB, gallbladder; OC, open cholecystectomy; TG13, Tokyo Guidelines 2013; CBD, common bile duct.

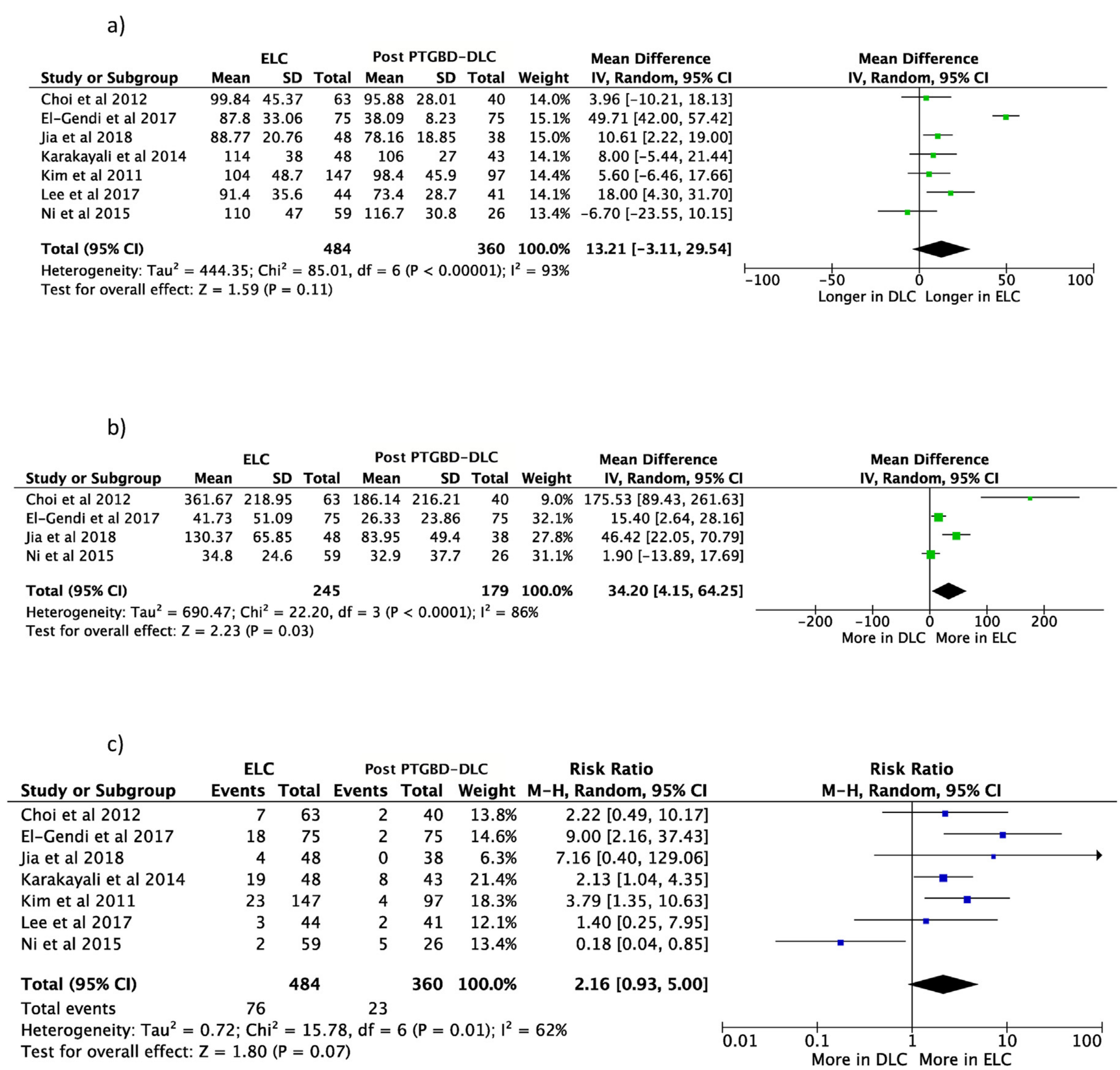


Figure 2 Intra-operative outcomes (ELC vs post PTGBD-DLC); a) operative time, b) blood loss(ml), c) risk of conversion to open

admitted to intensive care unit (ICU) for sepsis related to AC; P-value = 0.011.[4]

There was no significant difference in complications rate between PTGBD and open approach EC in patients admitted with GB perforation secondary to AC; 64.7% and 50%, respectively.[26]

Seven (7.7%) patients from PTGBD group compared to 23 (4.1%) patients from EC group had major complication but this was not significant in one study.[27] Loozen *et al.*, a multicentre RCT (CHOCOLATE trial), compared 1-year mortality and major complications between patients who had ELC and PTGBD for AC.[10] The risk of major complications was about five times less in ELC group (12%) compared to PTGBD group (65%); RR (95% CI): 0.19 (0.10–0.37), P value <0.001.[10] Moreover, ELC had about 10 folds less risk of having recurrent biliary disease and 10 folds less risk of need for surgical intervention within one year of randomisation; RR (95% CI): 0.09 (0.03–0.27) and 0.10 (0.03–0.30), P-values: <0.001, respectively.[10]

Total number (range per patient) of visits to the emergency department was significantly higher in PTGBD vs ELC group within one year from intervention; 56 (0–5) vs 7 (0–1), P value <0.001, respectively.[10]

Patients who had PTGBD needed to stay longer in ICU compared with patients receiving EC but this was not statistically significant; Mean (range): 10.5 (2–71) vs 3[2–31] days, respectively; P value = 0.17.[4]

Outcomes of ELC vs post PTGBD-DLC

- Characteristics of both groups:

Eight studies compared outcomes of ELC and post PTGBD-DLC.[24,25,28–33] Laparoscopic approach was the main primary approach in the majority of patients (Table 1). 3458 (67.7%) patients had ELC, and 1653 (32.3%) patients had post PTGBD-DLC. Patients were nearly 4 years younger in ELC group; MD (95% CI): −3.72 [−7.14, −0.30].[24,25,28–33] Less males were in the ELC compared to post PTGBD-DLC groups; RR (95% CI); 0.95 [0.90, 0.99].[24,25,28–33] serum CRP tended to be lower in the ELC; MD (95% CI): −3.37 [−4.03, −2.72].[24,25,28,30,32,33] Body mass index (BMI) was higher in the ELC group; MD (95% CI): 0.45 [0.20, 0.69].[28,29,32] Patients with DM, hypertension, cardiovascular disease, cerebrovascular disease or liver disease are less likely to have ELC; RR (95% CI): 0.69 [0.61, 0.77],[24,25,28,29,32,33] 0.83 [0.73, 0.94],[24,25,28,29,33] 0.51 [0.41, 0.65],[24,25,28,29,32,33] 0.58 [0.43, 0.79][25,28,29,32,33] and 0.65 [0.49, 0.87],[28,29,32] respectively. Duration of symptoms was longer in ELC group, but this was not significant; MD (95% CI): 0.37 [−0.07, 0.81] days.[30,31]

- Intra-operative outcomes:

Operative time was about 13 min longer in ELC but this was not significant; MD (95% CI): 13.21 (−3.11, 29.54) min.[24,25,29–33] ELC group had significantly more intra-operative blood loss than post PTGBD-DLC group; MD (95% CI): 34.2 (4.15, 64.25) ml.[24,25,29,33] Patients underwent ELC were at about two times risk of open conversion of laparoscopic cholecystectomy compared to post PTGBD-DLC group but this was not statistically significant; RR (95% CI): 2.16 [0.93, 5.00] (Fig. 2).[24,25,29–33] No patient had subtotal cholecystectomy in post PTGBD-DLC group compared to 13 (17.3%) patients in the ELC group; P value <0.001.[24]

- Post-operative outcomes:

There was no difference in mortality between the two groups; HR (95% CI): 1.30 [0.60, 2.83].[28,29] Patients had ELC are at about three times risk of post-operative complications compared to those had post PTGBD-DLC; RR [95% CI]: 2.88 [1.78, 4.65].[24,25,29–31] Risk of bile leak or bile duct injury (BDI) was six folds more in ELC; RR [95% CI]: 6.07 [1.67, 21.99].[24,25,29,30] Similarly, ELC group were at higher risk of developing sub-hepatic collection but this was not significant; RR [95% CI]: 2.62 [0.83, 8.34].[24,25,30] Likewise, risk of wound site complications was higher in ELC but not statistically significant; RR [95% CI]: 1.73 [0.65, 4.58].[24,29,30,32] (Fig. 3).

Patients from ELC group were likely to stay one day more in the hospital post-operatively compared to patients had post PTGBD-DLC; MD [95% CI]: 1.09 [0.52, 1.66].[29–32] However, ELC patients are likely to stay about six days less than post PTGBD-DLC patients in total; MD [95% CI]: −6.60 [−10.10, −3.09].[25,29,31–33] (Fig. 4).

- Outcomes in complicated AC:

From four studies, operative time was longer in ELC than post PTGBD-DLC but this was not statistically significant; MD [95% CI] 20.9 [−2.19,43.99] min.[24,25,29,32] Intra-operative blood loss was significantly more in ELC group; MD [95% CI] 56.57 [8.82, 104.32] ml.[24,25,29] Open conversion was about 4 times higher in ELC; RR [95% CI] 4.29 [1.91, 9.63][24,25,29,32] (Supplementary Fig. 8).

Post-operative hospital stay was longer in ELC but it was not statistically significant; MD [95% CI] 0.47 [−0.34, 1.27].[29,32] Post-operative complications did not show statistical significance but was about 3 times higher in ELC; RR [95% CI] 2.93 [0.82, 10.47].[24,25,29] BDI was 7 times higher in ELC compared with post PTGBD-DLC; RR [95% CI] 7.07 [1.38, 36.21].[24,25,29] There was no significant difference regarding risk of subhepatic collection or wound site complications; RR [95% CI] 2.56 [0.14, 46.36][24,25] and 1.71 [0.59, 4.99],[24,29,32] respectively (Supplementary Fig. 9).

Mortality was only reported in one study included high risk surgical patients with complicated AC with one mortality in ELC group (2%), but no mortality recorded in post PTGBD-DLC group.

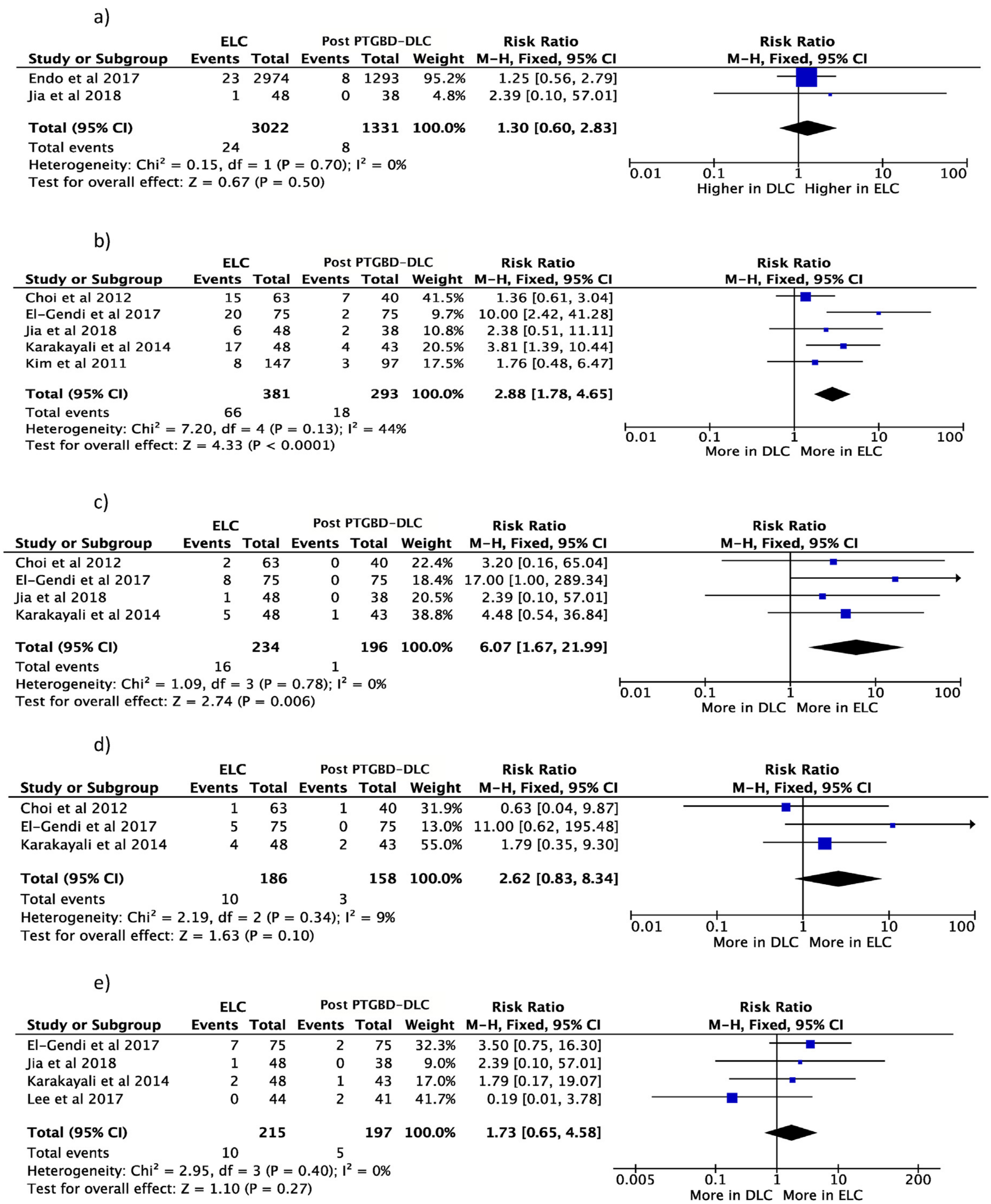


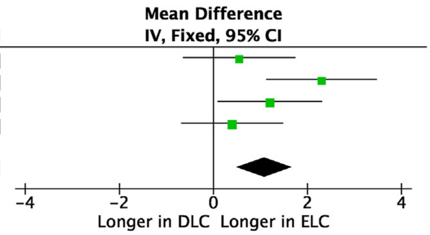
Figure 3 Post-operative outcomes (ELC vs post PTGBD-DLC); a) mortality, b) post-operative complications, c) bile duct injury, d) sub-hepatic collection, e) wound site complications

Discussion

In this review, about 94.7% patients with AC had EC which constitutes a much higher proportion of patients compared to United Kingdom (UK) practise.[34–36] We compared outcomes of the initial intervention with either ELC or PTGBD for patients with AC. Operative outcomes of ELC vs post PTGBD-DLC were also compared. This is in order to assess the two pathways of management. Predictors of performing PTGBD in practise were a)

Study or Subgroup	ELC Mean	ELC SD	ELC Total	Post PTGBD-DLC Mean	Post PTGBD-DLC SD	Post PTGBD-DLC Total	Weight	Mean Difference IV, Fixed, 95% CI
Jia et al 2018	9.65	2.8	48	9.1	2.81	38	22.7%	0.55 [−0.64, 1.74]
Karakayali et al 2014	5.3	3.3	48	3	2.4	43	23.4%	2.30 [1.12, 3.48]
Kim et al 2011	6.5	4.2	147	5.3	4.4	97	26.4%	1.20 [0.09, 2.31]
Lee et al 2017	5.4	2.5	44	5	2.6	41	27.5%	0.40 [−0.69, 1.49]
Total (95% CI)			**287**			**219**	**100.0%**	**1.09 [0.52, 1.66]**

Heterogeneity: $Chi^2 = 6.43$, df = 3 (P = 0.09); $I^2 = 53\%$
Test for overall effect: Z = 3.75 (P = 0.0002)



b)

Study or Subgroup	ELC Mean	ELC SD	ELC Total	Post PTGBD-DLC Mean	Post PTGBD-DLC SD	Post PTGBD-DLC Total	Weight	Mean Difference IV, Random, 95% CI
Choi et al 2012	12.92	5.63	63	20.08	7.33	40	19.1%	−7.16 [−9.82, −4.50]
Jia et al 2018	9.65	2.8	48	13.05	2.61	38	20.9%	−3.40 [−4.55, −2.25]
Kim et al 2011	9	4.5	147	10.7	5.4	97	20.8%	−1.70 [−3.00, −0.40]
Lee et al 2017	6.3	3.5	44	17.3	7.9	41	19.1%	−11.00 [−13.63, −8.37]
Ni et al 2015	8.2	3.9	59	18.5	4.5	26	20.0%	−10.30 [−12.30, −8.30]
Total (95% CI)			**361**			**242**	**100.0%**	**−6.60 [−10.10, −3.09]**

Heterogeneity: $Tau^2 = 14.92$; $Chi^2 = 81.01$, df = 4 (P < 0.00001); $I^2 = 95\%$
Test for overall effect: Z = 3.69 (P = 0.0002)

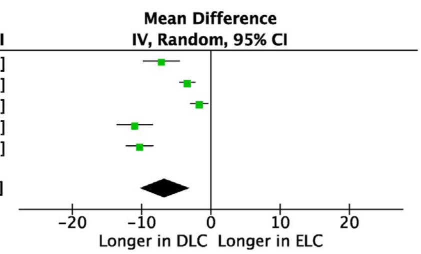


Figure 4 Length of hospital stay (ELC vs post PTGBD-DLC); a) post-operative hospital stay, b) total hospital stay

also studied and this helped to detect potential confounding factors which can affect the interpretation of significant difference in the outcomes between PTGBD and ELC groups. Patients underwent PTGBD had more co-existing diseases such as diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic kidney disease or liver disease. Serum CRP was the only laboratory marker to be significantly higher in PTGBD group. ASA grade and body temperature at admission tended to be higher in PTGBD group but were not statistically significant. There was no difference regarding duration of symptoms or LFTs. 21.6% of high-risk surgical patients and 46.9% of patients with complicated AC had PTGBD and this was significantly higher from the rest of studies (P < 0.00001).

The overall mortality was 3 folds higher in PTGBD group in six studies, but this can be partly or totally attributed to confounding factors like higher incidence of co-existing medical diseases in patients had PTGBD. However, there was no difference in mortality in CHOCOLATE trial where both groups' characteristics were comparable, supporting the role of co-existing diseases in affecting mortality. Post-procedural complications were 3 times higher in high-risk surgical patients underwent PTGBD compared to ELC in one study with high concerns of bias and this also can be explained by significant confounding factors.[11] In contrary to this, in patients needed admission to ICU, total number of complications was significantly higher in EC group (47%) than PTGBD group (8.7%); P-value: 0.011. Likewise, incidence of major complications in EC group (21%) was significantly higher than PTGBD group where no patient had major complications; P-value: 0.03 for patients admitted to ICU.[4] These findings support that PTGBD can be superior than EC in significantly high risk surgical patients admitted to ICU. However, in CHOCOLATE trial, which included high-risk surgical patients, incidence of major complications in 1-year time was significantly lower in ELC group (12%) compared to 65% in PTGBD group; RR (95% CI): 0.19 (0.1, 0.37); P-value<0.001.[10] Worthy to mention, ELC procedures were performed by experienced surgeons performing more than 100 laparoscopic procedures, yearly and this may explain more favourable outcomes in CHOCOLATE trial.

In comparing ELC and post PTGBD-DLC, meta-analysis has shown significantly higher risk of more blood loss, BDI (6 times higher risk), post-operative complications and longer post-operative hospital stay in ELC group. On the other side, post PTGBD-DLC is associated with longer total hospital stay but no significant difference in open conversion rate or mortality between both groups. El-Gendi *et al.*, which is the second RCT in this review but of high concerns of bias, reported overall more favourable results in post PTGBD-DLC group but similar mortality between the two groups.[24]

In this review, another meta-analysis comparing ELC and post PTGBD-DLC in complicated AC showed ELC is associated with about 4 times higher risk of open conversion and 7 times risk of BDI. Total hospital stay was longer in post PTGBD-DLC group but there was no difference in overall complications and post-operative hospital stay.

Huang *et al.*, is another systematic review which compared outcomes of ELC and DLC and reported similar results.[37] Operative and post-operative outcomes of ELC and DLC were only compared. There was no description of patient characteristics or severity of AC.

This review has some limitations. The majority of included studies were retrospective observational studies. Seven studies were assessed as having high risk of bias. Several potential confounding factors could not be stratified for each outcome. Data could not be pooled from all studies because some studies used different grouping systems. Laparoscopic approach was not the primary approach for EC in 14.3% of patients from 13 studies and this confounding factor can affect estimating outcomes and could not be controlled.

PTGBD provides a quick approach to drain the gallbladder and control sepsis in high-risk surgical patients. However, there is no high-quality study which has proven superiority of PTGBD over ELC.[38,39] Adding to this, CHOCOLATE trial, included in this review, is the first RCT to compare ELC and PTGBD in high-risk surgical patients and results were in favour of ELC for this cohort of patients. Therefore, PTGBD should be reserved for those patients with considerably high risk of mortality from surgical intervention such as patients admitted to ICU with organ failure.

While laparoscopic cholecystectomy is the definitive recommended treatment of complicated gallstone disease,[7,8] it may not be the best initial treatment option during the acute attack of complicated cholecystitis or in high risk patients and trial with conservative treatment should be considered first. However, ELC for AC should be the preferred intervention over PTGBD and DLC if operative risks of both pathways were comparable in any particular patient.[1,7]

In TG 2018, ELC can be performed in all grades of AC, including severe (grade III) AC.[8] The evidence in this review supports this for patients not needing ICU admission. Endo *et al.* is the largest good quality international multicentric cohort study included in this review compared outcomes of ELC and post PTGBD-DLC in severe AC and concluded mortality is similar in both groups in the absence of predictive factors of mortality such as BMI < 20.[28] TG 2018, recommended PTGBD in grade II AC if failed medical treatment even in a fit patient which is not supported with strong evidence. In this review, ELC in complicated AC is associated with higher risk of open conversion and BDI. However, this did not result in significantly longer post-operative stay which may indicate minimal bile collection or leak not requiring prolonged hospital stay nor surgical intervention. In contrary, total hospital stay was significantly longer in post PTGBD-DLC group. Therefore, ELC should be considered in complicated AC patients with acceptable surgical risks as long as experienced surgeon and high level post-operative care are available. TG2018 safe steps in laparoscopic cholecystectomy should be followed in those cases.[40] Delay in definitive treatment of complicated gallstone disease can expose patients to more complications, re-intervention and increase costs of treatment.[10,36]

In conclusion, ELC may be a preferred treatment option over PTGBD in AC. However, patient and disease specific factors should be considered to avoid unfavourable outcomes with ELC. Within the constraints of comparing emergency with elective procedure, ELC is associated with less total hospital stay but more intra-operative blood loss and post-operative complications compared to DLC following PTGBD. Future high-quality studies are needed to assess different management strategies in high-risk surgical patients with complicated AC.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Kimura Y, Takada T, Kawarada Y, Nimura Y, Hirata K, Sekimoto M *et al*. (2007) Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 14:15–26, 2007/01/30.
2. Hunt DR, Chu FC. (2000 Jun) Gangrenous cholecystitis in the laparoscopic era. *Aust N Z J Surg* 70:428–430.
3. Tokunaga Y, Nakayama N, Ishikawa Y, Nishitai R, Irie A, Kaganoi J *et al*. (1997 Jun) Surgical risks of acute cholecystitis in elderly. *Hepatogastroenterology* 44:671–676.
4. Melloul E, Denys A, Demartines N, Calmes JM, Schafer M. (2011 Apr) Percutaneous drainage versus emergency cholecystectomy for the treatment of acute cholecystitis in critically ill patients: does it matter? *World J Surg* 35:826–833.
5. Gutt C, Schläfer S, Lammert F. (2020 Feb 28) The treatment of gallstone disease. *Dtsch Arztebl Int* 117:148–158.
6. Schlottmann F, Gaber C, Strassle PD, Patti MG, Charles AG. (2019) Cholecystectomy Vs. cholecystostomy for the management of acute cholecystitis in elderly patients. *J Gastrointest Surg* 23:503–509.
7. Pisano M, Allievi N, Gurusamy K, Borzellino G, Cimbanassi S, Boerna D *et al*. (2020 Nov) 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. *WJES* 15:61.
8. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I *et al*. (2018 Jan) Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. *J Hepatobiliary Pancreat Sci* 25:55–72.
9. Sanaiha Y, Juo Y-Y, Rudasill SE, Jaman R, Sareh S, de Virgilio C *et al*. (2020 Jul) Percutaneous cholecystostomy for grade III acute cholecystitis is associated with worse outcomes. *Am J Surg* 220:197–202.
10. Loozen CS, van Santvoort HC, van Duijvendijk P, Besselink MG, Gouma DJ, Nieuwenhuijzen GA *et al*. (2018 Oct) Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute

cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial. *BMJ* 363:k3965.
11. Hall BR, Armijo PR, Krause C, Burnett T, Oleynikov D. (2018) Emergent cholecystectomy is superior to percutaneous cholecystostomy tube placement in critically ill patients with emergent calculous cholecystitis. *Am J Surg* 216:116–119.
12. Warttig S, Ward S, Rogers G. (2014 Oct 30) Diagnosis and management of gallstone disease: summary of NICE guidance. *BMJ* 349:g6241.
13. AUGIS (2015). Pathway for the management of acute gallstone diseases. Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. http://www.augis.org.
14. Jeon HW, Jung KU, Lee MY, Hong HP, Shin JH, Lee SR. (2020) Surgical outcomes of percutaneous transhepatic gallbladder drainage in acute cholecystitis grade II patients according to time of surgery [Internet] *Asian J Surg* 4. Available from: https://www.sciencedirect.com/science/article/pii/S1015958420302554?via%3Dihub.
15. Mathes T, Pieper D. (2017 Jul 17) Clarifying the distinction between case series and cohort studies in systematic reviews of comparative studies: potential impact on body of evidence and workload. *BMC Med Res Methodol* 17:107.
16. Sterne J, Savović J, Page M, Elbers R, Blencowe N, Boutron I, *et al*. eds. (2019) *RoB 2: a revised tool for assessing risk of bias in randomised trials*. BMJ.
17. Aromataris E, Munn Z, eds. (2020) *JBI manual for evidence synthesis*. JBI. Available from: https://synthesismanual.jbi.global/.
18. Barili F, Parolari A, Kappetein PA, Freemantle N. (2018 Sep 1) Statistical primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg* 27:317–321.
19. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G *et al*. (2018 Jan) Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 25:41–54.
20. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al*. (2009 Aug) The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 250:187–196.
21. Hansted AK, Møller MH, Møller AM, Vester-Andersen M. (2020 Feb) Apache II score validation in emergency abdominal surgery. A post hoc analysis of the InCare trial. *Acta Anaesthesiol Scand* 64:180–187.
22. Irlbeck T, Zwißler B, Bauer A. (2017 Jan) ASA classification : transition in the course of time and depiction in the literature. *Anaesthesist* 66:5–10.
23. Keegan MT, Gajic O, Afessa B. (2011 Jan) Severity of illness scoring systems in the intensive care unit. *Crit Care Med* 39:163–169.
24. El-Gendi A, El-Shafei M, Emara D. (2017) Emergency versus delayed cholecystectomy after percutaneous transhepatic gallbladder drainage in grade II acute cholecystitis patients. *J Gastrointest Surg* 21:284–293.
25. Choi JW, Park SH, Choi SY, Kim HS, Kim TH. (2012 Nov) Comparison of clinical result between early laparoscopic cholecystectomy and delayed laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage for patients with complicated acute cholecystitis. *Korean J Hepatobiliary Pancreat Surg* 16:147–153.
26. Huang CC, Lo HC, Tzeng YM, Huang HH, Chen JD, Kao WF *et al*. (2007 Dec) Percutaneous transhepatic gall bladder drainage: a better initial therapeutic choice for patients with gall bladder perforation in the emergency department. *Emerg Med J* 24:836–840.
27. La Greca A, Di Grezia M, Magalini S, Di Giorgio A, Lodoli C, Di Flumeri G *et al*. (2017 Oct) Comparison of cholecystectomy and percutaneous cholecystostomy in acute cholecystitis: results of a retrospective study. *Eur Rev Med Pharmacol Sci* 21:4668–4674.
28. Endo I, Takada T, Hwang TL, Akazawa K, Mori R, Miura F *et al*. (2017 Jun) Optimal treatment strategy for acute cholecystitis based on predictive factors: Japan-Taiwan multicenter cohort study. *J Hepatobiliary Pancreat Sci* 24:346–361.
29. Jia B, Liu K, Tan L, Jin Z, Liu Y. (2018 Mar) Percutaneous transhepatic gallbladder drainage combined with laparoscopic cholecystectomy versus emergency laparoscopic cholecystectomy in acute complicated cholecystitis: comparison of curative efficacy. *Am Surg* 84:438–442.
30. Karakayali FY, Akdur A, Kirnap M, Harman A, Ekici Y, Moray G. (2014 Jun) Emergency cholecystectomy vs percutaneous cholecystostomy plus delayed cholecystectomy for patients with acute cholecystitis. *Hepatobiliary Pancreat Dis Int* 13:316–322.
31. Kim IG, Kim JS, Jeon JY, Jung JP, Chon SE, Kim HJ *et al*. (2011 Dec) Percutaneous transhepatic gallbladder drainage changes emergency laparoscopic cholecystectomy to an elective operation in patients with acute cholecystitis. *J Laparoendosc Adv Surg Tech A* 21:941–946.
32. Lee R, Ha H, Han YS, Kwon HJ, Ryeom H, Chun JM. (2017 Nov) Percutaneous transhepatic gallbladder drainage followed by elective laparoscopic cholecystectomy for patients with moderate to severe acute cholecystitis. *Medicine* 96:e8533.
33. Ni Q, Chen D, Xu R, Shang D. (2015 Aug) The efficacy of percutaneous transhepatic gallbladder drainage on acute cholecystitis in high-risk elderly patients based on the Tokyo guidelines. *Medicine* 94:e1442.
34. CholeS Study Group WMRC. (2016 Nov 1) Population-based cohort study of outcomes following cholecystectomy for benign gallbladder diseases. *Br J Surg* 103:1704–1715.
35. Stephens TJ, Bamber JR, Beckingham IJ, Duncan E, Quiney NF, Abercrombie JF *et al*. (2019 Aug 23) Understanding the influences on successful quality improvement in emergency general surgery: learning from the RCS Chole-QuIC project. *Implement Sci* 14, 84–84.
36. Imtiaz M, Prakash S, Iqbal S, Fernandes R, Shah A, Shrestha AK *et al*. (2022 Mar) 'Hot gall bladder service' by emergency general surgeons: is this safe and feasible? *J Minim Access Surg* 18:45–50.
37. Huang SZ, Chen HQ, Liao WX, Zhou WY, Chen JH, Li WC *et al*. (2020) Comparison of emergency cholecystectomy and delayed cholecystectomy after percutaneous transhepatic gallbladder drainage in patients with acute cholecystitis: a systematic review and meta-analysis [Internet] *Updates Surg* 13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8005400/.
38. Mizumoto H, Takara K, Suzuki Y, Matsutani S, Tsuchiya Y, Ohto M. (1992 Jan) Treatment of acute cholecystitis by direct-puncture bile aspiration with ultrasound-image control. *Nihon Shokakibyo Gakkai Zasshi* 89:61–67.
39. Tsuyuguchi T, Takada T, Kawarada Y, Nimura Y, Wada K, Nagino M *et al*. (2007) Techniques of biliary drainage for acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 14:46–51.
40. Wakabayashi G, Iwashita Y, Hibi T, Takada T, Strasberg SM, Asbun HJ *et al*. (2018 Jan) Tokyo guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 25:73–86.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.04.010.