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REVIEW ARTICLE

Systematic review and meta-analysis of factors which reduce the length of stay associated with elective laparoscopic cholecystectomy

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Abstract

Background: Laparoscopic cholecystectomy is a safe ambulatory procedure in appropriately selected patients; however, day case rates remain low. The objective of this systematic review and meta-analysis was to identify interventions which are effective in reducing the length of stay (LOS) or improving the day case rate for elective laparoscopic cholecystectomy.

Methods: Comparative English-language studies describing perioperative interventions applicable to elective laparoscopic cholecystectomy in adult patients and their impact on LOS or day case rate were included.

Results: Quantitative data were available for meta-analysis from 80 studies of 10,615 patients. There were an additional 17 studies included for systematic review. The included studies evaluated 14 perioperative interventions. Implementation of a formal day case care pathway was associated with a significantly shorter LOS (MD = 24.9 h, 95% CI, 18.7–31.2, $p < 0.001$) and an improved day case rate (OR = 3.5; 95% CI, 1.5–8.1, $p = 0.005$). Use of non-steroidal anti-inflammatories, dexamethasone and prophylactic antibiotics were associated with smaller reductions in LOS.

Conclusion: Care pathway implementation demonstrated a significant impact on LOS and day case rates. A limited effect was noted for smaller independent interventions. In order to achieve optimal day case targets, a greater understanding of the effective elements of a care pathway and local barriers to implementation is required.

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Introduction

Laparoscopic cholecystectomy (LC) is the standard of care in the management of symptomatic gallstone disease.^{1,2} Since its introduction, the length of stay (LOS) associated with LC has steadily reduced and it is now widely accepted as an appropriate and safe ambulatory procedure in carefully selected patients.^{2–5} Implementation of standard clinical pathways for LC have been reported to successfully reduce LOS and increase day case success.^{6–12} Day case laparoscopic cholecystectomy (DCLC) is associated with cost-savings^{3,13,14} without

increasing the risk of adverse events or readmissions.^{3,15,16} It has a high rate of patient satisfaction^{17,18} and is comparable with inpatient stay with respect to quality of life, return to work and normal activity.¹⁶ Additionally, in the current climate every effort should be made to reduce the LOS associated with elective surgery in order to minimise potential exposure to COVID-19.

Despite this, a recent study from the United Kingdom (UK) and Ireland report a DCLC rate of only 49%.¹⁹ While this has improved significantly from 6.4% in the UK in 2005,²⁰ it remains well below the 75% target, and DCLC rates are highly variable between hospitals and health systems.²¹ Patient-related factors often pose barriers to universal DCLC implementation. - DCLC is less likely to be successful in older patients, male patients, those

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with higher ASA scores, previous acute gallstone-related admissions, and preoperative endoscopic intervention¹⁹; therefore, proper patient selection is important. The most frequently cited modifiable reasons for failed discharge where DCLC was intended are uncontrolled pain, nausea, drain insertion, urinary retention, late return from theatre, and patient wishes or expectations.^{3,9,12,14,22,23} In addition to patient selection criteria, the other necessary components of a DCLC patient pathway, from an institutional and a technical surgical perspective, are not well defined in the literature.

The objective of this meta-analysis was to identify perioperative interventions which reduce the LOS or increase the day case rate associated with elective laparoscopic cholecystectomy in adult patients. A previous systematic review focused on interventions to facilitate ambulatory laparoscopic cholecystectomy,²⁴ however no meta-analysis has been performed on this subject.

Materials and methods

Search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.²⁵ PubMed, PubMed Central, Medline, Embase, and Cochrane databases were searched using a Boolean search algorithm for articles published up to January 2019. Original comparable studies were included if they examined the effects of any clinical intervention during adult inpatients' trajectories for elective LC (Fig. 1). Exclusion criteria were papers where data were unavailable or uninterpretable and authors were uncontactable, and papers in languages other than English. Ethical approval and written

consent were not required for this systematic review and meta-analysis.

An initial search of the above databases was used to identify the interventions to be included and subsequent additional searches for each intervention using Boolean algorithms were carried out on Pubmed. All search terms used are available as [Supplementary file \(appendix I\)](#). The initial search was designed to be as broad as possible to identify interventions published in relation to elective LC. The citations from the initial search were reviewed to create a list of interventions which are relevant to common clinical practice in laparoscopic cholecystectomy and may be modified by surgical teams. The interventions included appear in Fig. 1. Subsequent searches were conducted using Boolean search terms related to each intervention separately. A manual search of reference lists and published review papers were also conducted to ensure optimal identification of relevant publications. All search results were compiled in a reference manager database (Endnote, Version X7, Thompson Reuters, New York, NY). Duplicates were removed automatically and then by hand.

Data extraction

Two independent reviewers (J.R. and E.O'C.) applied the inclusion and exclusion criteria (Fig. 1) to retrieve citations, the abstracts were reviewed, and full-text articles were selected. Reviewers extracted data from the full-text articles and applied exclusion criteria; discrepancies were agreed by consensus. For each study, data on baseline characteristics (journal, year published, country, study period, total number of patients, sex, study methodology, and definition of perioperative intervention) were extracted. Where drug classes were used and grouped

<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Original publication (reviews, opinions, letters, protocols and conference proceedings excluded) • Comparative studies involving patients undergoing elective laparoscopic cholecystectomy with any of the following peri-operative interventions: Ambulatory pathway implementation, pre-operative education, perioperative nutrition/fluid management/analgesia/anti-emetics/steroids, prophylactic antibiotics, low-pressure/warmed pneumoperitoneum, regional/local anaesthesia, and prophylactic drain insertion • Outcome measure is reported as day case versus inpatient stay OR overall length of stay <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Papers in languages other than English • Papers where data were unavailable or uninterpretable and authors uncontactable • Papers with interventions specific to Anaesthesiology* • Papers with surgical techniques as the intervention • Studies in children under 16
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Figure 1 Study inclusion and exclusion criteria. *Refers to interventions which are delivered specifically by the Anaesthesiologist, e.g. administration of parenteral or intrathecal anaesthesia, pressor management intraoperatively, etc

together for meta-analysis, the specific dosages and drugs used in each study are available in the [Supplementary file](#).

Authors were contacted if data were not available or interpretable. Where median and range were presented, the methods described by Hozo and colleagues^{26,27} were followed to derive mean and standard deviation (SD). Where means were presented without SD, but p values were available, the average of the two SDs was imputed.²⁸ Study methodological quality and risk of bias were assessed by applying the MINORS criteria for observational studies²⁹ and the Jadad score for randomized controlled trials (RCTs).³⁰ This information is available in the [Supplementary tables provided in the appendix](#).

Statistical analysis

Data were analysed using RevMan software (Review Manager, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Statistical expertise was available to the authors. Studies were included for meta-analysis if three or more existed which reported the LOS or day case rate for the same comparator. Mean LOS was compared between studies using the mean difference calculated using the inverse variance method in a fixed effects model. Mean length of stay was measured in hours for the purpose of analysis. Day case rate was compared between studies using the odds ratio calculated using the Mantel-Haenszel technique in a fixed effect model. An objective measure of heterogeneity was obtained by calculation of the I^2 statistic from the Cochran Q test; an I^2 value greater than 50% was taken to denote significant heterogeneity between studies. Where statistical heterogeneity existed in the analysis a random effects model was employed. Forest plots were included in the text where statistical significance was achieved; all forest plots for non-significant meta-analyses are included in the [Supplementary file](#).

Results

Literature search

The literature search revealed 1173 publications, and a further 135 were identified from hand searches and bibliographic sources ([Fig. 2](#)). Following exclusion of duplicates and abstract review, 216 studies were subject to full text review. Quantitative data were available for meta-analysis from 80 studies. There were an additional 17 studies included for systematic review. Details for all 97 included studies have been provided in a [Supplementary file](#). The included studies evaluated 14 peri-operative interventions. In the 80 studies suitable for meta-analysis, the mean LOS for 10,615 patients was 61.2 h, with a 41.1% day case rate where reported. The LOS and day case rates of perioperative interventions are summarised in [Table 1](#). The forest plots for non-significant meta-analyses have been provided in the [Supplementary file](#).

Care pathway implementation

Implementation of a dedicated care pathway for patients undergoing elective LC was examined in 10 non-randomized

studies.^{6–12,14,31,32} Implementation of a care pathway was associated with a significantly shorter mean LOS (MD 24.9 h; 95% CI, 18.7–31.2; $p < 0.001$; [Fig. 3a](#)) and an improved day case rate (OR, 3.5; 95% CI, 1.5–8.1; $p = 0.005$; [Fig. 3b](#)).

Preoperative carbohydrate loading

The delivery of preoperative carbohydrate loading in the form of supplement drinks was examined in seven RCTs^{33–39} and no difference was found in either mean LOS ($p = 0.970$) or day case rate between those receiving carbohydrate loading and those fasting or receiving a placebo.

Pneumoperitoneum pressure

The effect of reduced pneumoperitoneum pressure was examined in six RCTs^{40–45} and no difference was found in the mean LOS between patients undergoing surgery with a pressure of ≤ 10 mmHg compared to those undergoing surgery with pressure of 10–15 mmHg ($p = 0.080$).

Preoperative non-steroidal anti-inflammatory drugs (NSAIDs)

The effect of preoperative NSAIDs was examined in six RCTs.^{46–51} There was a significant reduction in mean LOS in patients receiving NSAIDs compared to placebo (MD 1.7 h; 95% CI, 1.0–2.4; $p < 0.001$; [Fig. 3c](#)). A subgroup analysis of studies specifically involving COX2 inhibitors also demonstrated a significant difference in mean LOS (MD 2.8 h; 95% CI, 0.7–4.9; $p = 0.008$; [Fig. 3d](#)).^{47–50}

Preoperative anti-emetics

The effect of preoperative dexamethasone was examined in eight RCTs,^{52–59} with a mean reduction in LOS by 1.4 h noted amongst patients receiving dexamethasone compared with placebo (95% CI 0.2–2.6; $p = 0.020$; [Fig. 3e](#)). No difference in LOS was noted in six RCTs^{60–65} comparing preoperative ondansetron with placebo ($p = 0.080$).

Prophylactic intra-operative antibiotics

The effect of prophylactic antibiotics was examined in 11 RCTs and one comparative study.^{66–77} Patients who received antibiotics before skin incision had a marginally shorter hospital stay, by 0.6 h, than those who received no antibiotics ($p = 0.020$, [Fig. 3f](#)).

Local/regional anaesthesia

The effect of incisional local anaesthesia (LA) was examined in four RCTs,^{78–81} which did not lead to a reduction in LOS compared with placebo ($p = 0.200$). The effect of intraperitoneal LA was examined in 12 studies,^{81–92} which demonstrated no change in LOS ($p = 0.200$) or day case rates ($p = 0.110$). A total of five studies^{81,93–96} were found examining the effect of combined intraperitoneal and incisional LA and this likewise did not show a significant reduction ($p = 0.060$). Three studies^{97–99} examined

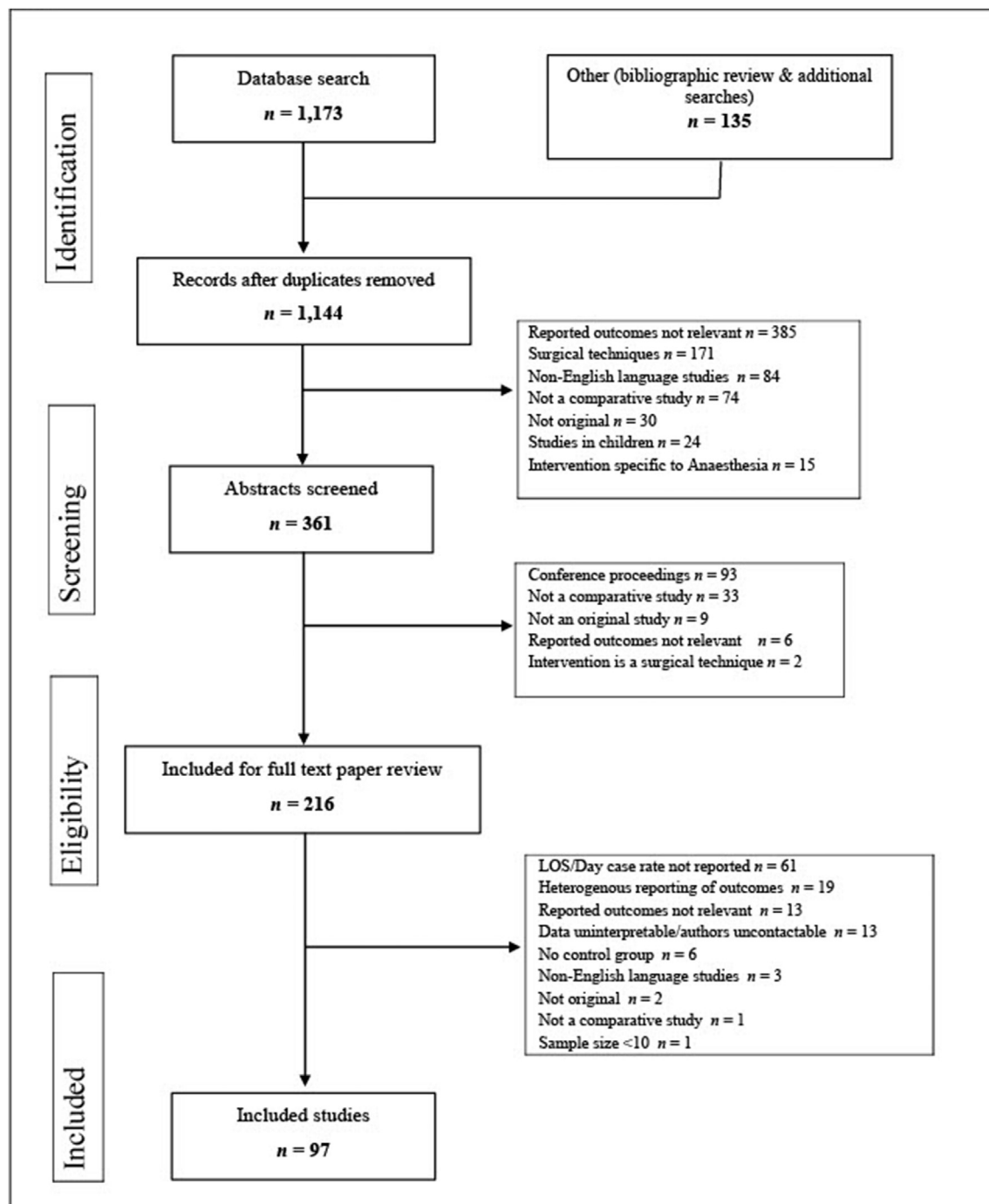


Figure 2 PRISMA diagram showing selection of articles for review

the effect of intraoperative transversus abdominis plane (TAP) blocks versus no TAP blocks and systematic review found no difference in LOS or day case rate.

Prophylactic drain insertion

A total of eight studies^{100–107} were found which reported on the effects of routine prophylactic drain insertion and found no

significant difference in mean LOS between those receiving drainage and those with no drain insertion ($p = 0.080$). Two RCTs revealed that drain insertion significantly increased the likelihood of admissions in excess of 48 h.^{108,109} These studies were not suitable for meta-analysis as there were not enough studies reporting this LOS outcome ($>/<48$ h) in relation to drain insertion.

Table 1 Meta-analyses of perioperative interventions to reduce the length of stay (LOS) or increase the day case rate in patients undergoing laparoscopic cholecystectomy

Intervention	Outcome	Studies (n)	Participants (n)	Effect (95% CI) ^a	p value
Care pathway	LOS	5	962	24.9 (18.7–31.2)	<0.001 ^b
Care pathway	Day case rate	6	2321	OR 3.5 (1.5–8.1)	0.005 ^b
Carbohydrate supplement	LOS	5	307	0.0 (–2.7 to 2.8)	0.97
Reduced pressure pneumoperitoneum	LOS	6	1001	4.2 (–0.4 to 8.9)	0.08
Preoperative non-steroidal anti-inflammatory drugs	LOS	6	447	1.7 (1.0–2.4)	<0.001 ^b
Antiemetic					
Dexamethasone	LOS	8	1053	1.4 (0.2–2.6)	0.02 ^b
Ondansetron	LOS	6	395	0.8 (–0.1 to 1.7)	0.08
Antibiotics	LOS	12	3410	0.6 (0.1–1.2)	0.02 ^b
Local anaesthesia (LA)					
Incisional LA	LOS	4	382	9.4 (–5.0 to 23.8)	0.2
Intraperitoneal LA	LOS	8	784	1.19 (–0.6 to 3.0)	0.2
Intraperitoneal LA	Day case rate	4	308	OR 1.8 (0.9–3.6)	0.11
Combined incisional and intraperitoneal LA	LOS	5	360	2.7 (–0.1 to 5.5)	0.06
Drain insertion	LOS	8	1629	11.97 (–1.5 to 25.5)	0.08

^a Units of effect size for length of stay are reported as hours. Effect size for day case rate is reported as odds ratios (OR).

^b Indicates statistical significance.

Preoperative education

Three studies^{110–112} were identified examining the effect of intensive versus standard preoperative education and none found differences in LOS or day case rate. This intervention was not amenable to meta-analysis as there were not enough studies for inclusion in either LOS or day case rate.

Perioperative fluid management

One RCT¹¹³ found a significant improvement in day case rate in patients who received a liberal intraoperative intravenous fluid regimen, however, a further four RCTs^{114–117} found no significant difference in mean LOS. None of these studies were amenable to meta-analysis due to heterogenous reporting of LOS outcomes.

Warmed pneumoperitoneum

Mean LOS was reported in two RCTs comparing warmed, humidified pneumoperitoneum with standard pneumoperitoneum^{118,119} and no significant difference in mean LOS was noted in either study. This intervention was not amenable to meta-analysis as it did not meet the number of studies required for inclusion.

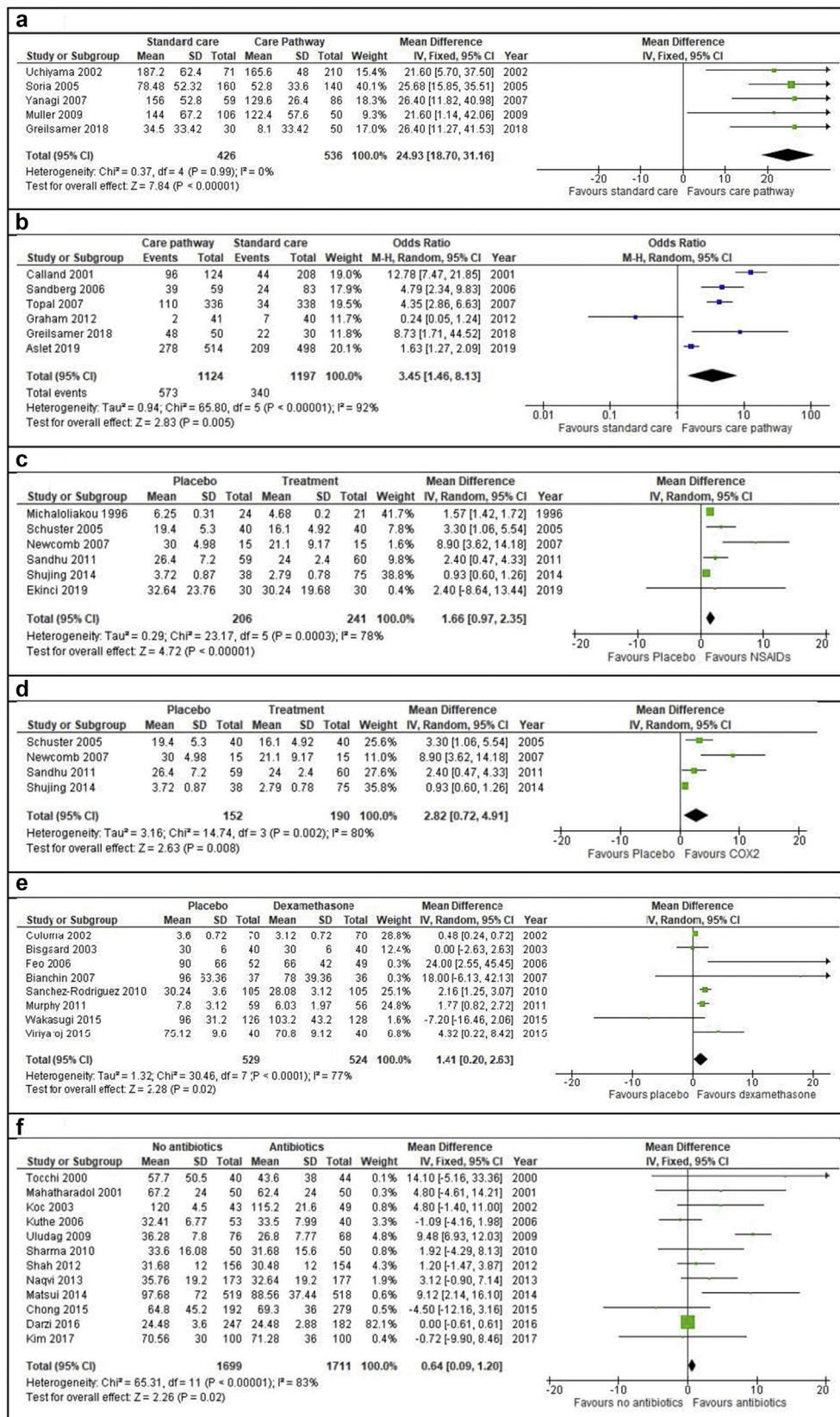
Country and time period

Mean LOS was noted to be significantly longer in Japanese studies than the rest of the world (130.17 vs 44.22 h; $p = 0.001$). There was no difference in mean LOS between studies published before or after 2010 (52.11 vs 50.47 h; $p = 0.850$). A table of studies by country and year has been provided in the [supplementary results file](#).

Discussion

This review was designed to examine the evidence base for clinical interventions that have the potential to reduce LOS following LC. DCLC is associated with cost-savings^{3,13,14} and a high rate of patient satisfaction.^{17,18} In addition to this, shorter hospital stays lead to reduced healthcare associated infections¹²⁰ and are likely to lead to reduce waiting list times due to better utilisation of resources. The 80 studies included in this meta-analysis, related to 10,615 LC patients who had a mean LOS of 61.2 h and a 41.1% day case rate. A total of 14 interventions were examined, of which only four were found to influence length of stay or likelihood of successful management as a day case: implementation of a dedicated care pathway, preoperative antibiotics, preoperative NSAIDs, and the antiemetic dexamethasone. Each of these demonstrated a statistically significant reduction in mean LOS. The largest effect size was seen with care pathway implementation, which led to a mean reduction in LOS of 24.9 h and a day case rate of 51.0%, compared with 27.9% for those treated prior to pathway implementation. The majority of the remaining interventions, used in isolation, did not lead to a reduction in LOS. Even among the three individual interventions with a significant difference, the change was of limited clinical importance, reducing LOS by 0.6–2.8 h. The reduction in LOS associated with the delivery of preoperative antibiotics is likely spurious. This is supported by the fact that antibiotics were only found to reduce LOS by 0.6 h, which is minimal.

A number of factors were not independently associated with reduced LOS in this meta-analysis. The provision of preoperative education, which played a role in several of the care pathways^{7–10,31}



and which is generally considered mandatory to achieve same day discharge²⁰ did not lead to a reduced LOS in the studies included. Unfortunately, only three studies reported LOS outcomes with respect to this intervention, each of insufficient power to detect a difference.^{110,112} Equally unexpectedly, the insertion of prophylactic drainage was not associated with increased LOS. Avoidance of unnecessary drain insertion is generally recommended⁵ and the authors hypothesise that the similar LOS observed among drained and undrained patients relates to study protocols designed to compare endpoints such as pain, development of collections, and drain outputs, at standard timepoints.

LOS is a challenging outcome measure, subject to both incentives and perverse incentives that may be financial or organisational.¹²¹ The definition of a day case varies between departments, institutions and health systems ranging from just a few hours to 23.¹²² Accuracy of LOS reporting is difficult to assess or internally validate. The authors assume for this meta-analysis that in each system the same problems arise in a constant way, such that the measure of mean difference between groups then most accurately represents a valid unit, which varies by the intervention studied. The current study excluded papers which did not report LOS, resulting in exclusion of a large amount of good quality studies evaluating specific interventions. A further potential weakness is that many included studies were underpowered to identify changes in LOS, as it was often a secondary outcome. Interestingly, many studies had longer than average postoperative stays, possibly suggesting that investigators evaluating a new intervention exercised caution in discharging trial subjects or kept patients in hospital to capture data at specific timepoints. Japanese studies were found to have a significantly longer overall LOS than other countries, however the difference in LOS seen with each intervention should not have changed despite this finding. For example, regarding the care pathway intervention, despite the fact that patients involved in studies from Japan had longer overall LOS, there was still a significant reduction seen between those who were involved in a care pathway and those who were not. The available literature was heterogenous in terms of reporting of outcomes and interventions delivered. A further challenge is the potential publication bias where studies with negative results could be under-reported.

The findings of this paper can be used to improve outcomes associated with DCLC, but first it is necessary to establish which interventions are central to an effective day case pathway. This is

difficult for a number of reasons. Firstly, the studies involving care pathways varied widely in their approach to elective surgery. A number of them specified admission prior to the day of surgery, retained patients for a number of days postoperatively, and referred to removal of routine drains. While the care pathway protocols may have reduced LOS, some of their elements or outcomes may have lost their relevance to contemporary surgery. The significant impact of care pathway implementation on shortening LOS in this meta-analysis may be attributed to the cumulative effect of multiple factors with smaller individual effects. For example, a number of factors are common to the studied care pathways including NSAID use, opiate minimisation, multimodal antiemetics, and combined skin and peritoneal local anaesthesia. It remains unclear whether the interventions themselves lead to the benefit observed when a care pathway is implemented, or whether the improved team dynamics and multi-disciplinary collaboration characteristic of care pathway implementation¹²³ is responsible. Additionally, some of the pathway components were poorly described. Three papers did not describe the pathway sufficiently to be able to replicate it.^{8,14,31} Lastly, none of the studies included were randomised, and all involved study of outcomes pre- and post-implementation of care pathways. Non-randomized designs are subject to many potential biases including the Hawthorne effect, recall bias and publication bias. Such potential biases could influence the effect on LOS from clinical pathways.

Evaluation of the studied care pathways provides some insight into the methods for introduction, but very little information on the barriers that exist to their implementation. Many health systems have defined care pathways for day case laparoscopic cholecystectomy, including guidance provided locally by the Irish National Clinical Programme for Surgery.¹²⁴ In spite of the availability of such a care pathway, Irish day case rates continue to fall below expected targets of 60%.¹²⁵ In addition, even among hospitals of similar characteristics, utilisation of day case laparoscopic cholecystectomy is widely variable, with rates of 0%–95.8% reported across Irish hospitals in 2019.¹²⁵ It is clear that a defined care pathway is necessary but not sufficient to effect change in LOS¹²⁶; equal attention to factors relating to implementation is required. Attention to the context, planning and structures necessary for successful day case surgery implementation are also important but generally less emphasised by surgeons.¹²⁷ Inclusion of implementation outcomes alongside intervention outcomes would greatly enhance the reproducibility

Figure 3 a – Meta-analysis of mean length of stay for dedicated care pathway implementation for laparoscopic cholecystectomy versus standard care pathway implementation. b – Meta-analysis of day case rate for dedicated care pathway implementation for LC versus standard care pathway implementation. c – Meta-analysis of mean length of stay in patients who received preoperative non-steroidal anti-inflammatory drugs (NSAIDs) during laparoscopic cholecystectomy versus those who received no NSAIDs or a placebo. d – Subgroup analysis of mean length of stay for those who received COX2 inhibitors versus no COX2 inhibitors or placebo. e – Mean length of stay for preoperative dexamethasone versus no dexamethasone or placebo. f – Meta-analysis of mean length of stay for patients who received prophylactic antibiotics during laparoscopic cholecystectomy versus those who received no antibiotics

of surgical literature. It is apparent that further research regarding care pathway components is unlikely to increase the effectiveness of care pathways. Rather, understanding methods of care pathway implementation is necessary to facilitate effective pathway use.

Implementing a care pathway which incorporates a range of perioperative interventions is more likely to lead to a significant reduction in LOS and increase in day case rate than any single intervention, although there has yet to be an RCT demonstrating this. Very few interventions in isolation have an effect on LOS after elective LC, and the effect size of such isolated interventions is small. Future studies should focus to a greater extent on the contextual and organisational factors associated with successful implementation of short-stay LC pathways instead of on the individual components of the care pathway.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.hpb.2020.08.012>.