REVIEWS

What surgical approach would provide better outcomes in children and adolescents undergoing cholecystectomy? Results of a systematic review and meta-analysis

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Abstract

Background: There is a lack of evidence on the surgical approach for children and adolescents undergoing cholecystectomy. Therefore, the aim of this systematic review is to compare the safety and efficacy of minimally invasive cholecystectomy to open cholecystectomy in children and/or adolescents.

Main body: A search was conducted on MEDLINE, PubMed, Cochrane and Embase from inception to October 2018. We included comparative studies investigating outcomes following robotic-assisted, laparoscopic and/or open cholecystectomy in children and/or adolescents. The outcomes of interest included post-operative complication rate, operation time, length of hospital stay, post-operative pain and conversion to open procedure. The Newcastle-Ottawa Scale was used to assess the risk of bias. Meta-analysis was performed using random-effect models. Twenty-one studies were included involving 927 children and/or adolescents. All, but one, compared outcomes between laparoscopic versus open cholecystectomy. The great majority of the included studies presented a low risk of bias. Patients undergoing laparoscopic cholecystectomy had less post-operative complications (RR: 0.57; 95%CI 0.35 to 0.94), reduced length of hospital stay (MD − 3.73; 95%CI − 4.88 to − 2.59), but longer operative time (MD 26.61; 95%CI 9.35 to 43.86) when compared to open cholecystectomy. The average conversion from laparoscopic to open cholecystectomy was 7% across studies.

Conclusions: The current evidence suggested that laparoscopic cholecystectomy in children and/or adolescents is safe resulting in lower rates of postoperative complications and length of stay, but longer operative times, when compared to the open approach.

PROSPERO registration: CRD42017067641

Level of evidence: Level III

Keywords: Cholecystectomy, Children, Minimally invasive surgery, Systematic review, Outcomes

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Background

Gallstone disease (cholelithiasis/choledocolithiasis/biliary colic) is relatively uncommon in paediatric patients, but when present is often attributed to haemolytic disease or prematurity [1]. Acute cholecystitis can also be acalculous in nature, stimulated by a recent viral illness or by chronic disease [2]. Rising childhood obesity has dramatically increased the incidence of paediatric gallstone disease globally [1]. The management of acute cholecystitis or biliary colic is often by surgical removal of the gallbladder (cholecystectomy) either through an open or laparoscopic approach. Minimally invasive surgery has become the standard approach for most thoracic, abdominal and pelvic procedures in adults and children [3]. Consequently, cholecystectomy for gallstone disease or biliary dyskinesia is being performed with rising frequency in children and has evolved from open to a minimally invasive approach [4].

Some of the main advantages of minimally invasive surgery, when compared to open surgery, is reduced postoperative pain, improved cosmesis and quicker recovery [3]. These advantages are particularly important in paediatric patients in whom scars enlarge with growth and the advantages of minimal incisions are more obvious [4]. For this reason, a rapid shift towards laparoscopic cholecystectomies occurred despite a lack of high-quality randomised trials, investigating the effectiveness of minimally invasive surgery over conventional open surgery [4].

In the adult population, there is some evidence suggesting that patients undergoing a laparoscopic cholecystectomy have equivalent mortality rates, postoperative complications and operation times when compared to open cholecystectomy [5]. Similarly, no difference in outcomes was found in a systematic review investigating the effectiveness of robotic versus laparoscopic cholecystectomy in adults [6]. Interestingly, in the elderly population, the laparoscopic approach provides better morbidity and mortality outcomes when compared to open cholecystectomy [7].

Currently, no study has systematically reviewed the literature to investigate the safety and effectiveness of minimally invasive cholecystectomy compared to open surgery in the paediatric population. Therefore, the aim of this systematic review and meta-analysis is to compare the safety and efficacy of minimally invasive (robotic-assisted or laparoscopic) cholecystectomy to open cholecystectomy in children and adolescents.

Main text

Protocol and registration

The protocol of this systematic review was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [8] and registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO 2017 CRD42017067641), available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=67641.

Inclusion criteria

This review included comparative studies (e.g. randomised controlled trials [RCTs], cohort studies) reporting the safety and efficacy of minimally invasive (robotic or laparoscopic) compared to open procedures (cholecystectomies). Eligible studies met the following criteria: (i) reported on children and adolescents (≤ 18 years old) of any gender; (ii) performed a cholecystectomy; and (iii) reported at least one outcome measure including complication rate, operation time, length of hospital stay, pain and conversion to open procedure. No language or publication restrictions were employed, with translations attempted for all non-English published studies. Case series reporting on a sample < 5 and abstracts published in conference proceedings were excluded.

Search strategy

A comprehensive electronic search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) (via OVID) and PubMed (www.ncbi.nlm.nih.gov/pubmed) databases was conducted from their earliest records to October 2018. Recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org/chapter_6/6_4_2_structure_of_a_search_strategy.htm) were used to develop the search strategy. Combined terms, medical subject headings and keywords were used to create a highly sensitive search strategy in order to identify potential studies. Additional citation tracking of the included studies was also conducted.

Data extraction process

Initially, one reviewer (KW) screened each citation by title and abstract to identify potentially eligible studies for inclusion. Any studies whereby the eligibility remained unclear were included as a potentially eligible study. The full text for each potentially eligible article was obtained and assessed by two independent reviewers (CT, KW or DS) to determine whether the study inclusion criteria had been met. Any disagreements between the two reviewers were resolved by discussion. For all excluded full-text articles, the main reason for exclusion was identified. Two independent review authors (CT, DS and KW) extracted data from the included studies using a pre-constructed data extraction form, which was initially tested for comprehensiveness and ease. Study information, participant baseline characteristics, intervention, control and outcome data were extracted and collated. Where more than one publication for a study was found, data was extracted from the most comprehensive publication. Discrepancies in data

extracted by the reviewers were resolved by discussion with a senior review author (DY, AJ or CS).

Risk of bias assessment

The risk of bias in included studies was assessed by two independent review authors (CT, KW or DS). Disagreements were resolved by discussion with a senior review author (DY, AJ or CS). The methodological quality of the included studies was appraised by the Newcastle-Ottawa Scale (NOS). The NOS tool consists of a checklist of eight items specifically designed for non-RCTs reporting on the selection (4 items), comparability (1 item) and outcome (3 items). Methodological quality was not regarded as an inclusion criterion.

Statistical analysis

Meta-analyses were performed with data being pooled using random effects models. Dichotomous data were expressed as relative risks and 95% confidence intervals, while continuous data were expressed as mean differences and 95% confidence intervals. Forest plots were utilized to visualize the data, and the statistical heterogeneity of the included studies was assessed using the I^2

test. Comprehensive Meta-Analysis (CMA) software was used for all analyses. Patient information, risk of bias, types of complications and conversion of procedures are presented descriptively.

Results

Selection of studies

The initial search on four medical databases identified 3912 articles after duplicates were removed. Of these, 376 full-text articles were reviewed for eligibility, with 23 of these meeting the eligibility criteria and included in this review. Most of the full-text articles were excluded due to reporting on a sample > 18 years old (n = 199) or not having a comparison group (n = 120). The complete flow diagram of included articles can be found in Fig. 1. Of the 23 included studies, 4 presented data from two different cohorts [9–12]; therefore, this review synthesises the results of 21 unique studies.

Risk of bias assessment

The risk of bias assessment for all included studies is described in full detail in Table 1. Of all the included studies, only one presented a high risk of bias in the
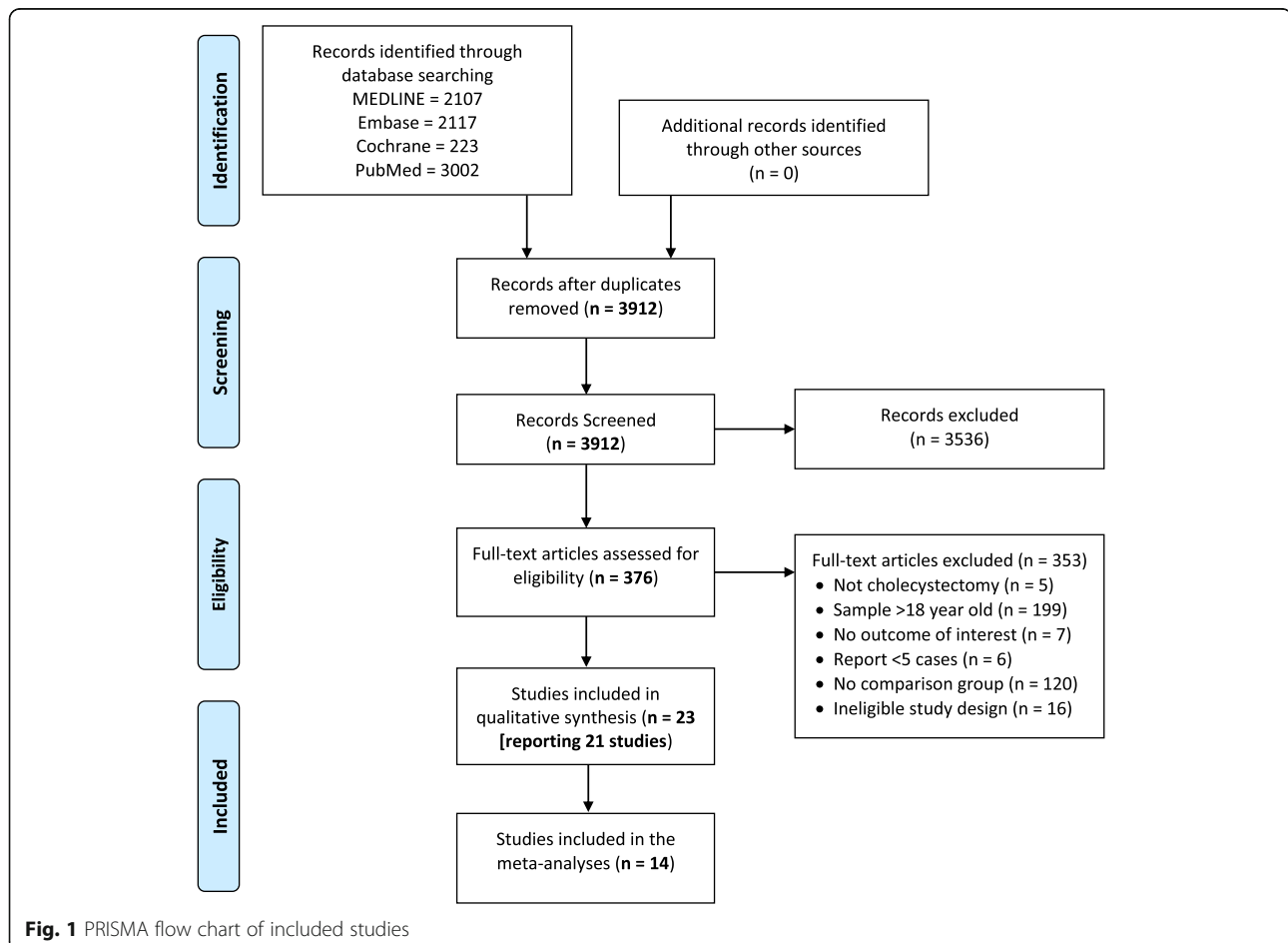

Fig. 1 PRISMA flow chart of included studies

Table 1 Newcastle-Ottawa quality assessment scale

Author, year	Selection (****)				Comparability (**)	Outcome(***)		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Ainsworth et al., 2010	*	*	*	*		*	*	*
Al-Salem et al., 1997	*	*	*	*	**	*	*	*
Al-Salem et al., 2012	*	*	*	*	**	*	*	*
Chabchoub et al., 2010	*	*	*	*	**	*	*	*
Dumont et al., 1999	*	*	*	*	**	*	*	*
Espinosa-Saavedra et al., 2014	*	*	*	*	**	*	*	*
Holcomb et al., 1993	*	*	*	*	**	*	*	*
Jawad et al., 1998	*	*	*	*	**	*	*	*
Jeanty, 2015	*	*	*	*	**	*	*	*
Kim, 1995	*	*	*	*	**	*	*	*
Lugo-Vicente et al., 1997	*	*	*	*	**	*	*	*
Luks, 1999	*	*	*	*	**	*	*	*
Mahida et al., 2015	*	*	*	*	**	*	*	*
Mehmood et al., 2010	*	*	*	*	**	*	*	*
Miltenburg et al., 2001	*	*	*	*	**	*	*	*
Parez et al., 2001	*	*	*	*	**	*	*	*
Ruangtrakool et al., 2002	*	*	*	*	**	*	*	*
Stringer et al., 2004	*	*	*	*	**	*	*	*
Tannuri et al., 2012	*	*	*	*	**	*	*	*
Ure et al., 1999	*	*	*	*	**	*	*	*
Zeman et al., 2004	*	*	*	*	**	*	*	*

Good quality: 3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain or 0 stars in comparability domain or 0 or 1 stars in outcome/exposure domain

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comparability domain [13] and one on the selection [14] (i.e. representativeness of the exposed cohort). Overall, most studies presented a low risk of bias.

Characteristics of included studies

A total of 927 unique children and/or adolescents were reported on the included 21 articles [9, 10, 13–31] with the majority of the included studies comparing outcomes between laparoscopic versus open cholecystectomy (20/21). A single study compared outcomes of robotic cholecystectomy and laparoscopic cholecystectomy [23]. The study sample sizes ranged from 10 [19] to 221 [29] patients with the mean age ranging from 0.4 [19] to 14.8 [21] years, with a female predominance (Table 2).

Laparoscopic versus open cholecystectomy
Post-operative in-hospital complication rate

A total of 16 studies investigated post-operative in-hospital complications following laparoscopic or open cholecystectomy. Of these, 7 studies reported no postoperative complication following laparoscopic (n = 125) or open cholecystectomy (n = 43) [13, 14, 16, 18, 19, 24, 28]. The pooled results of 7 studies (n = 523) [9, 10, 21, 25–27, 29] demonstrated that patients undergoing laparoscopic cholecystectomy were less likely to develop postoperative complications when compared to patients who underwent open cholecystectomy (RR: 0.57; 95%CI: 0.35 to 0.94) (Fig. 2). Two of the included studies (n = 43) [15, 17] reported one postoperative complication each (i.e. wall infection and lung infection), although they have not assigned this to any procedure (e.g. laparoscopic or open cholecystectomy).

Operative time

Operative time was investigated in 9 studies. The pooled operative time of 7 studies (n = 299) [9, 10, 18, 20, 22, 25, 30] demonstrated that open cholecystectomy had a significantly lower duration when compared with laparoscopic cholecystectomy (MD: 26.61 min; 95%CI 9.35 to 43.86) (Fig. 3).

Holcomb et al. [14] reported that the mean operative time was 110 min for open cholecystectomy and 106 min for the laparoscopic procedure (p value not reported), whereas Lugo-Vicente et al. [21] reported a significant shorter operative time for laparoscopic cholecystectomy when compared to open cholecystectomy (94 versus 138 min, respectively; p = 0.03).

Length of hospital stay

All 17 studies that investigated the length of hospital stay demonstrated that patients that underwent laparoscopic surgery have a shorter stay when compared to open cholecystectomy patients [9, 10, 13, 14, 16–18, 20–

22, 25–31]. Our meta-analysis including 574 patients showed that children who underwent open cholecystectomy stayed approximately 4 days longer than children who underwent laparoscopic cholecystectomy (MD – 3.73 days; 95%CI – 4.88 to – 2.59) (Fig. 4) [9, 10, 13, 17, 18, 20, 22, 27–30].

Post-operative pain

Only two studies investigated postoperative pain outcomes following laparoscopic and open cholecystectomy [21, 25]. Lugo-Vicente et al. [21] reported the number of days patients required pain medication. Patients undergoing laparoscopic cholecystectomy had a significantly shorter duration for requiring pain medication than the open cholecystectomy group (0.7 versus 1.4 days respectively, p < 0.001). Milternburg et al. [25] reported that patients that underwent open cholecystectomy required more postoperative analgesia compared with patients who underwent laparoscopic cholecystectomy (morphine 0.7 mg/kg versus 1.5 mg/kg), although the difference between groups was not significant.

Conversion to open cholecystectomy

Twelve studies report on conversion rates from laparoscopic to open cholecystectomy (n = 479) [9, 10, 13, 19–21, 25–29, 31]. Conversion rates ranged from 0% [20, 28] to 25% [19], whereas the average across all studies was 7%.

Robotic cholecystectomy versus laparoscopic cholecystectomy

One study compared robotic (n = 46) versus laparoscopic cholecystectomy (n = not reported) [23]. No outcomes were reported for post-operative complication rates, operative time, post-operative pain and conversion rates. The median length of hospital stay between patients that underwent robotic or laparoscopic cholecystectomy was equivalent (1 versus 1 day, respectively; p = 0.92).

Conclusions
Statement of principal findings

This systematic review and meta-analysis identified 21 unique comparative studies reporting on 927 children and/or adolescents that underwent a cholecystectomy. Twenty studies compared outcomes following laparoscopic and open cholecystectomies, and only one study compared robotic-assisted with laparoscopic cholecystectomy. No randomised controlled trial or studies comparing robotic-assisted versus open cholecystectomy was identified.

The results of this systematic review and meta-analysis indicate that children and/or adolescents undergoing a laparoscopic cholecystectomy had a lower post-operative

Table 2 Characteristics of included studies

| Author, year	Country	Study period	Indication	Mean age, years (SD)	Gender, male (%)	Procedure 1 (*N*)	Procedure 2 (*N*)
Ainsworth et al., 2010	Denmark	2000–2009	Recurrent abdominal pain and cholelithiasis	5.3 (2.94)	3 (23%)	Laparoscopic (9)	Open (4)
Al-Salem et al., 1997	Saudi Arabia	1989–1995	Sickle cell with cholelithiasis	14.7 (1.08)	17 (34%)	Laparoscopic (21)	Open (29)
Al-Salem et al., 2012	Saudi Arabia	1995–2009	Sickle cell anaemia with biliary colic/dyspepsia	11.4 (0.96)	47 (54%)	Laparoscopic (52)	Open (35)
Chabchoub et al., 2010	Tunisia	1979–2008	Cholelithiasis	7.8 (1.86)	9 (47%)	Laparoscopic (6)	Open (7)
Dumont et al., 1999	USA	1993–1997	Chronic abdominal pain	13.3 (2.21)	7 (17%)	Laparoscopic (40)	Open (2)
Espinosa-Saavedra et al., 2014	Mexico City	2006–2012	Biliary lithiasis	12.5 (1.17)	10 (33%)	Laparoscopic (18)	Open (12)
Holcomb et al., 1993	USA	Not reported	Not reported	Not reported	Not reported	Laparoscopic (22)	Open (7)
Jawad et al., 1998	Saudi Arabia	1990–1996	Symptomatic cholelithiasis	8.77 (2.97)	5 (28%)	Laparoscopic (11)	Open (7)
Jeanty et al., 2015	USA	1997–2013	Cholelithiasis	0.4 (0.25)	4 (40%)	Laparoscopic (8)	Open (2)
Kim et al., 1995	Canada	1990–1993	Non-haemolytic cholelithiasis	9.76 (2.41)	21 (44%)	Laparoscopic (27)	Open (21)
Lugo-Vicente et al., 1997	Puerto Rico	1990–1995	Cholelithiasis or dyskinesia	14.8 (1.1)	20 (24%)	Laparoscopic (59)	Open (24)
Luks et al., 1999	USA	1995–1998	Not reported	Not reported	Not reported	Laparoscopic (33)	Open (3)
Mahida et al., 2015	USA	2008–2013	Not reported	Not reported	Not reported	Robotic (46)	Not reported
Mehmood et al., 2010	Pakistan	1988–2008	Cholelithiasis and/or choledocholithiasis	Not reported	Not reported	Laparoscopic (7)	Open (9)
Miltenburg et al., 2001	USA	1991–1996	Cholelithiasis	12.0 (0.78)	11 (27%)	Laparoscopic (20)	Open (20)
Parez et al., 2001	France	1982–1998	Cholelithiasis	10.8 (1.11)	13 (50%)	Laparoscopic (9)	Open (17)
Ruangtrakool et al., 2002	Thailand	1992–2000	Cholelithiasis	9.85 (4.83)	6 (38%)	Laparoscopic (8)	Open (8)
Stringer et al., 2004	United Kingdom	1994–2003	Cholelithiasis	11.66 (1.28)	15 (43%)	Laparoscopic (23)	Mini-open (12)
Tannuri et al., 2012	Brazil	1994–2011	Cholelithiasis	10.2 (3.75)	104 (47%)	Laparoscopic (204)	Open (17)
Ure et al., 1999	Germany	1988–1997	Cholelithiasis	9.9 (1.27)	Not reported	Laparoscopic (10)	Open (10)
Zeman et al., 2004	Czech Republic	1998–2003	Symptomatic cholelithiasis	12.5 (1.2)	10 (21%)	Laparoscopic (39)	Open (9)
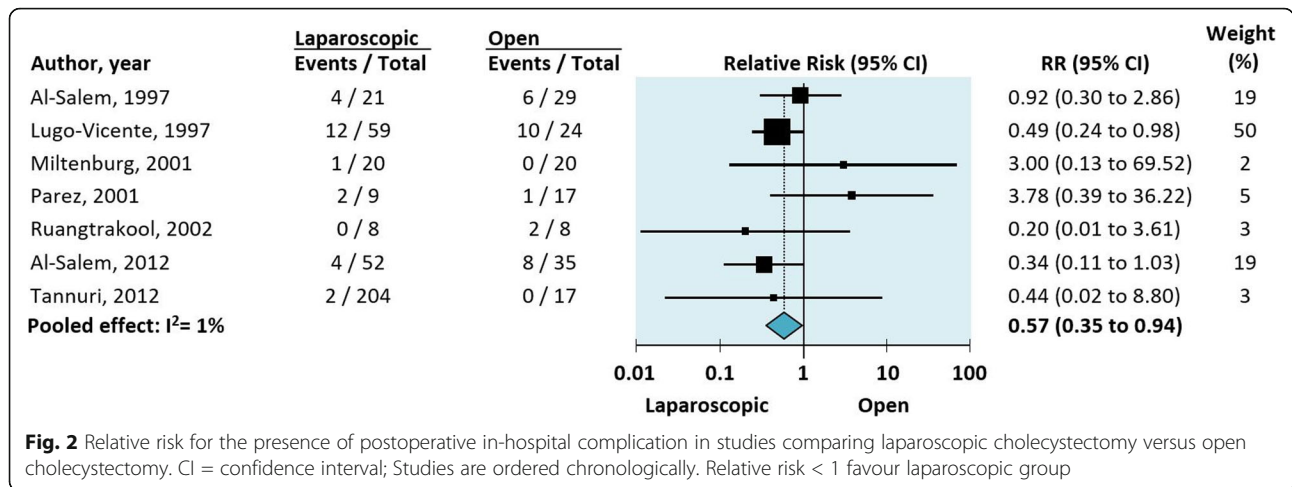
Fig. 2 Relative risk for the presence of postoperative in-hospital complication in studies comparing laparoscopic cholecystectomy versus open cholecystectomy. CI = confidence interval; Studies are ordered chronologically. Relative risk < 1 favour laparoscopic group

complication rate and length of hospital stay when compared to open cholecystectomy, although had a longer operative time. There is limited evidence in relation to post-operative pain outcomes or the comparison between robotic-assisted versus laparoscopic or open cholecystectomy. Conversion rates between laparoscopic and open cholecystectomy varied between studies, with an overall conversion rate of 7%.

Strengths and weaknesses of the study

To our knowledge, this is the first systematic review and meta-analysis to compare outcomes between surgical approaches for cholecystectomy in children and/or adolescents. Some of the strengths of this review include the robust design and transparency, with a pre-specified research question and registered protocol as a priori in PROSPERO. In addition, we use a highly sensitive search strategy developed by an experienced librarian to identify studies comparing outcomes following cholecystectomy. Some of the limitations of this review include the limited number of studies found in the literature, especially on

robotic-assisted cholecystectomy and the absence of randomised controlled trials. In addition, although all patients underwent cholecystectomy, the indications for surgery varied and included symptomatic cholelithiasis, choledocholithiasis or biliary dyskinesia which were often investigated in those with sickle cell anaemia, biliary dyspepsia or otherwise not specified. This may have introduced a level of heterogeneity within the investigated samples, and therefore, caution should be taken when interpreting the results. Furthermore, a subgroup analysis was not performed due to the small number of studies identified in the literature.

Comparison with other studies

No previous systematic review and meta-analysis focusing on childhood and/or adolescent cholecystectomy were identified [5, 32]. Therefore, the results of this review were compared to systematic reviews and randomised controlled trials that included the adult population. None of the included studies reported any deaths following cholecystectomy. In the adult
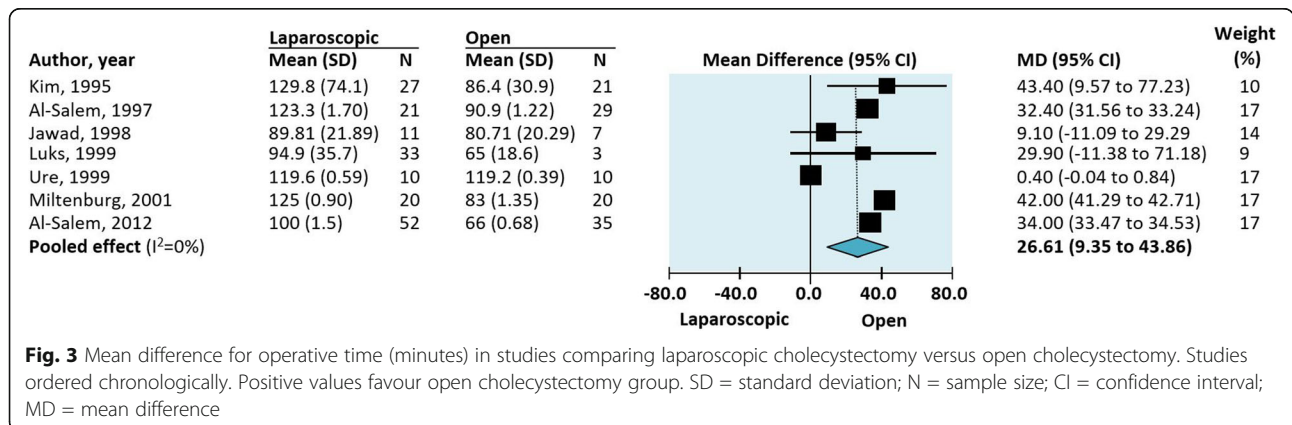

Fig. 3 Mean difference for operative time (minutes) in studies comparing laparoscopic cholecystectomy versus open cholecystectomy. Studies ordered chronologically. Positive values favour open cholecystectomy group. SD = standard deviation; N = sample size; CI = confidence interval; MD = mean difference

Fig. 4 Mean difference for the length of hospital stay (days) in studies comparing laparoscopic cholecystectomy versus open cholecystectomy. Studies ordered chronologically. Negative values favour laparoscopic cholecystectomy group. SD = standard deviation; N = sample size; CI = confidence interval; MD = mean difference
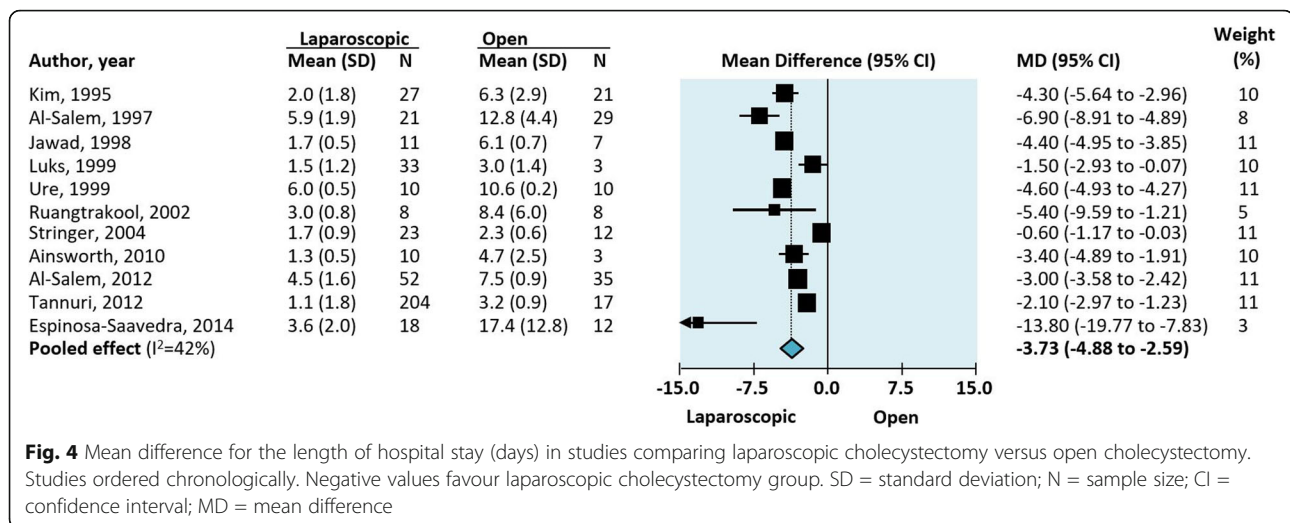
population, the mortality rate is low, with no significant differences between open (< 1%) and laparoscopic procedures (0%) [5]. Although our systematic review demonstrated a similar advantage to the adult population in terms of post-operative complication rates, where laparoscopy surgery was superior to open cholecystectomy, when a subgroup analysis in the adult population was performed including only high-quality trials, no significant differences were found between laparoscopic and open cholecystectomy [5]. Whether this same trend is observed in children and/or adolescents is currently unknown, due to the paucity of age-specific randomised controlled trials.

The operative time of laparoscopic surgery was longer when compared to open cholecystectomy (almost 30 min shorter in the open group). This may be explained by the initial of the learning curve to the laparoscopic approach and the additional time required to assemble the laparoscopic equipment during surgery. Most of the included studies had a small sample size (only 4/20 presenting a sample > 50 patients) with most samples presenting retrospective data extracted from medical records of large hospitals. Consequently, it is important to consider that a large number of surgeons would be performing a small number of surgeries, augmenting the effect of the initial learning curve on their operative time [33]. Whereas in the adult population, previous trials have demonstrated no difference in operative times between laparoscopic and open cholecystectomy possibly due to the higher frequency of cholecystectomies to improve the learning curve [32]. Another factor that could explain this difference between the young and adult population is that most high-quality trials (observed only in the adult population) required surgeons to be proficient in the procedure before they start delivering the intervention.

In our systematic review, our meta-analysis demonstrated that patients undergoing laparoscopic surgery have a significant shorter length of hospital stay when compared to an open procedure. It is well documented that minimally invasive surgical procedures result in shorter hospitalisation. Other studies that have investigated the effectiveness of laparoscopic versus open cholecystectomy have similar results, with a reduction in hospital duration by 3 days in patients that underwent laparoscopic cholecystectomy [5, 32].

Post-operative pain was only reported in two studies and was assessed based on the number of days patients required pain medication. This lack of evidence was also observed in systematic reviews in the adult population [5]. The mean reported conversion rate (laparoscopic to open cholecystectomy) in the current study was 7% (range 0 to 25%) and seems considerably lower when compared with the adult population where the conversion rate ranges from 10 to 36% [32].

Meaning of the study and future directions
Although this systematic review and meta-analysis found that laparoscopic cholecystectomy significantly reduces post-operative complication rates and length of hospital stay when compared to open cholecystectomy, the lack of high-quality randomised controlled trials prevent strong endorsement, and therefore, caution should be taken when interpreting these results. It is apparent that laparoscopic cholecystectomy is safe for the children and/or adolescent population, with no deaths reported and an acceptable post-operative complication and conversion rate. The fast uptake of robotic-assisted surgery, observed in other surgical specialities, must be embedded in clinical trials investigating the effectiveness over laparoscopic and open cholecystectomy. Furthermore, further studies should investigate if age would influence surgical outcomes and

other patient-reported outcomes. Other variables, such as endoscopic retrograde cholangiopancreatography and their potential influence on the length of hospital stay, should also be investigated.

This systematic review and meta-analysis indicate that laparoscopic cholecystectomy is likely to reduce post-operative complication rates and length of hospital stay, despite a longer operative time compared to an open cholecystectomy. There limited evidence that laparo-scopic cholecystectomy reduces pain when compared to open surgery. Whether minimally invasive surgery re-sults in better surgical and patient-reported outcomes over open cholecystectomy is unknown due to the lim-ited evidence to date.

Abbreviations
CENTRAL: Cochrane Central Register of Controlled Trials; CMA: Comprehensive meta-analysis; MD: Mean difference; NOS: Newcastle-Ottawa Scale; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; PROSPERO: International Prospective Register of Systematic Reviews; RCTs: Randomised controlled trials; RR: Relative risk

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