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Original research

Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis

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HIGHLIGHTS

- Acute cholecystitis should be attempted by laparoscopy at first.
- Post-operative morbidity, mortality and hospital stay are reduced by laparoscopic cholecystectomy.
- Severe hemorrhage rate is not influenced by the operative technique.

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ABSTRACT

Introduction: Laparoscopic cholecystectomy (LC) has become a popular alternative to open cholecystectomy (OC) in the treatment of acute cholecystitis (AC). Laparoscopic cholecystectomy (LC) is now considered the gold standard of therapy for symptomatic cholelithiasis and chronic cholecystitis. However no definitive data on its use in AC has been published. CIAO and CIAOW studies demonstrated 48.7% of AC were still operated with the open technique. The aim of the present meta-analysis is to compare OC and LC in AC.
Material and methods: A systematic-review with meta-analysis and meta-regression of trials comparing open vs. laparoscopic cholecystectomy in patients with AC was performed. Electronic searches were performed using Medline, Embase, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR) and CINAHL.
Results: Ten trials have been included with a total of 1248 patients: 677 in the LC and 697 into the OC groups. The post-operative morbidity rate was half with LC (OR = 0.46). The post-operative wound infection and pneumonia rates were reduced by LC (OR 0.54 and 0.51 respectively). The post-operative mortality rate was reduced by LC (OR = 0.2). The mean postoperative hospital stay was significantly shortened in the LC group (MD = −4.74 days). There were no significant differences in the bile leakage rate, intraoperative blood loss and operative times.
Conclusions: In acute cholecystitis, post-operative morbidity, mortality and hospital stay were reduced by laparoscopic cholecystectomy. Moreover pneumonia and wound infection rate were reduced by LC. Severe hemorrhage and bile leakage rates were not influenced by the technique. Cholecystectomy in acute cholecystitis should be attempted laparoscopically first.

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1. Introduction

There have been significant paradigm shifts in the treatment of AC and management of complex acute biliary problems in the past few years. These changes include earlier surgery and index admission cholecystectomy [1–3].

Actually there are considerable data favoring early surgery instead of delayed cholecystectomy [1,3]. Papi and Gurusamy published prospective studies and meta-analysis supporting respectively either open or laparoscopic surgery in the acute phase. Hospital stay was reduced when surgery was performed early and the complication rate was the same [1,3]. Moreover, approximately 15–20% of patients who underwent delayed procedures in the randomized trials had persistent or recurrent symptoms requiring intervention before their planned operation [1–12].

Accepting early surgery for AC and moving to technical aspects, laparoscopic should be compared to open surgery. While laparoscopic cholecystectomy (LC) has become the approach of choice for elective cholecystectomy, 48.7% of acute cholecystitis are nowadays still operated with the open technique. To our knowledge there are no meta-analysis comparing these techniques in AC. Some authors consider the presence of inflammation, edema, and necrosis as unfavorable conditions for safe dissection. As a consequence, the suspected increased rate of complications leads numerous surgeons, in the laparoscopic era to postpone cholecystectomy after resolution of acute inflammation.

In 2013 a new edition of the Tokyo Guidelines (TG 2013) has been produced with the aim to define the best surgical treatment for AC according to the grade of severity, the timing, and the procedure [54,55]. AC has been classified as mild, moderate and severe based principally on the grade of inflammation of the gallbladder rather than on the patients' conditions. This classification, mainly coming from committee agreement, leads to different treatment options for the three grades of AC and into each class. In general, the literature, including the TG 2013 in some aspects, shows concerns about supposedly higher morbidity rates in LC performed as an emergency procedure [14–16] and the higher conversion rate to open procedure during the acute phase [51,52].

No data of high grade evidence on hospitalization, morbidity and mortality comparison between LC and OC in AC have been produced. No systematic review or meta-analysis have been published on which is the better treatment between LC and OC for AC.

The aim of the present study is to systematically review and analyze the published data comparing LC and OC in AC in terms of morbidity, mortality, length of hospital stay, operative times and severe intraoperative hemorrhage.

2. Material and method

2.1. Literature search strategy

Electronic searches were performed using Medline, Embase (1988–May 2014), PubMed (January 1980–May 2014), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR) and CINAHL from (1966–2014). The search terms were: “acute cholecystitis”, “laparoscopy”, “open” combined with AND/OR. Research included also all the MeshTerms. No search restrictions were imposed. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Review articles were also obtained to determine other possible studies. Duplicate published trials with accumulating numbers of patients or increased lengths of follow-up, were considered only in the last or at least in the more complete version.

2.2. Selection criteria

Studies which have been judged eligible for this systematic review and consequent meta-analysis were those in which patients with AC were included (Table 1). The diagnosis of AC was based on the finding of acute right upper quadrant tenderness and ultrasonographic evidence of acute cholecystitis (presence of gallstones with thickened and edematous gallbladder wall, positive Murphy's sign and peri-cholecystic fluid collections); or acute right quadrant tenderness, ultra-sonographic confirmation of gallstones, and one or more of the following: temperature above 38 °C and/or leukocytosis greater than 10 × 10/l and/or C-reactive protein level greater than 10 mg/l) No language restrictions were applied. Eligibility for study inclusion into the meta-analysis and study quality assessment were performed independently by two authors (FeCo, MP). The study data were extracted onto standard forms independently by two authors (FeCo, MP). Discrepancies between the two investigators were resolved by discussion. The final results were reviewed by other investigators (LA, FaCa, GL).

The primary outcome measures for the meta-analysis were morbidity and mortality. Secondary outcomes were: operative times, intraoperative blood loss of more than 500 ml and hospitalization length. Also conversion rate and bile duct injuries were evaluated and results on these two issues were reviewed although it was impossible to perform a meta-analysis on these data.

2.3. Assessment of risk of bias

There is a potential risk of overestimating the beneficial treatment effects of RCT with a resultant risk of bias. The risk of bias was assessed comprehensively according to the guidelines of The Cochrane Collaboration [17] and six items were considered relevant (Table 2): 1) whether the method of allocation was truly random; 2) whether there was proper allocation concealment; 3) whether the groups were similar at baseline; 4) whether the eligibility criteria were documented; 5) whether loss to follow-up in each treatment arm was specified; 6) whether intention-to-treat analysis was conducted. Therefore the evaluation of the quality level of the study was conducted as follows: positive answer to at least six questions was required for a trial to be rated as high quality. With a positive answer to five or four questions the study was considered to be of fair quality. With a positive answer to three or fewer questions the study was registered as low quality. When studies did not report adequate information to determine the above-mentioned assessment criteria, an attempt to obtain direct additional data from the investigators was made.

Data quality of non-randomized studies was assessed using the Methodological index for non-randomized studies (MINORS) [18] (Table 3). By considering 12 items (8 for non-comparative + 4 for comparative studies) the total score was calculated by summing the values attributed as follows: 0 (not reported), 1 (reported but inadequate), 2 (reported and adequate). Global ideal score for non-comparative studies was 16 and for comparative ones was 24.

2.4. Statistical analysis

Data from the individual eligible studies were entered into a spread-sheet for further analysis. Review Manager (RevMan) (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) [50] was used to perform the statistical analysis. Pooled odds ratios (OR) were calculated for discrete variables. Mean Difference (MD) were calculated for continuous variables. The fixed-effects and random-effects models were used to calculate the outcomes [19,20]. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified

Table 1
Summary of the included studies.

	Study (ref.) year	Number of patients (tot:1248)	Study period	Laparoscopic cholecystectomy (tot: 677)	Open cholecystectomy (tot: 697)	Study characteristics
1	Kiviluoto (13) 1998[a]	63	1995–1996	31	32	Prospective randomized
2	Johansson (21) 2005[a]	70	2002–2004	35	35	Prospective randomized
3	Boo (22) 2007[a]	33	2004	18	15	Prospective randomized
4	Chau (23) 2002	73	1994–1999	31	42	Retrospective
5	Pessaux (24) 2001	139	1992–1999	50	89	Prospective non-randomized
6	Glavic (29) 2001	209	1994–1998	94	115	Retrospective
7	Araujo-Texeira (25) 1999	200	1991–1997	100	100	Prospective non-randomized
8	Eldar (28) 1997	243	1992–1993	146	97	Retrospective with hystorical control-group
9	Catena (23) 2012[a]	144	2008–2010	72	72	Prospective randomized
10	Unger (27) 1993	200	1989–1991	100	100	Retrospective

[a] Randomized controlled studies.

Table 2
Quality assessment of randomized trials.

	Study (ref.) year	Randomization	Allocation concealment	Homogeneous baseline characteristic	Eligibility criteria	Loss to follow-up and drop-out described	Intention-to-treat analysis	Study quality
1	Kiviluoto (13) 1998	Yes	Yes	Yes	Yes	Yes	Yes	High
2	Boo (22) 2007	Yes	Yes	Yes	Yes	nr	Yes	High
3	Johansson (21) 2005	Yes	Yes	Yes	Yes	Yes	Yes	High
4	Catena (23) 2012	Yes	Yes	Yes	Yes	Yes	Yes	High

using the I^2 inconsistency test. Whenever it was possible, results were evaluated either considering all the included studies or considering only the randomized trials. Meta-regression was performed to assess the effect of quality of the study and the year of publication.

3. Results

651 papers met the potential review criteria. There were ten trials (4 randomized controlled trials, 2 prospective non-randomized and 4 retrospective trials) [13,21–29] (publication dates 1993–2012) (Fig. 1) (Table 1). There were 1248 patients (677 received LC and 697 received OC) (Table 1).

The mean reported conversion rate was 20.87% (range 9.5–35.5). Only one study (25) reported common bile duct injuries with 1 injury for each group among 200 cholecystectomies. The other 3 studies [13,23,27] reported no bile duct injuries.

3.1. Quality of trials

There was good agreement between the reviewers (FeCo and MP) on the eligibility and quality of the studies. Tables 2 and 3 demonstrates the quality of the 10 included studies [13,21–29].

In all four RCTs [13,21–23], the method of allocation concealment was adequate; randomization was performed on a central site and transmitted to treatment providers by telephone, fax or sealed opaque envelopes. The baseline features were similar between treatment groups in the 4 RCTs. All RCTs specified the eligibility criteria for patients to be enrolled. All RCTs but two [13,22] specified the numbers lost to follow-up in each of the treatment group. All RCTs [13,21–23] analyzed the data on an intention-to-treat (ITT) basis, whereby the participants were analyzed in the groups to which they were initially randomized. Blinding after allocation was impossible because of the nature of the trials.

All prospective and retrospective non-randomized studies had good MINORS scores (Table 3) [24–29].

All eleven trials were considered to be at an acceptable risk of bias in the important domains (Tables 2 and 3).

3.2. Morbidity

Nine studies reported morbidity [13,21–28], of them four were randomized [13,21–23], 2 prospective non-randomized [24,25] and 3 retrospective [26–28]. 613 patients were treated with OC and 605 with LC (Fig. 2). There was no significant difference in heterogeneity among the studies. With fixed effects model, the pooled post-operative morbidity rate was favorable to LC (OR = 0.46, 95% CI = 0.34–0.61).

Meta-regression performed according to the quality score of the studies resulted not to be statistically significant.

3.3. Mortality

Four studies reported mortality rates which were different from zero [24–26,29]. Of these studies, 2 were prospective non-randomized [24,25] and 2 retrospective [26,29]. The remaining

Table 3
Quality assessment of non-randomized trials: Items are scored as follows: 0 (not reported), 1 (reported but inadequate), 2 (reported and adequate). Global ideal score for non-comparative studies is 16 and for comparative ones is 24.

Study (ref.) year	Quality evaluation criteria								Additional criteria in comparative studies				
	Clear stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to the study aim	Unbiased assessment of study end-point	Appropriate follow-up period	Loss to follow-up less than 5%	Prospective calculation of the study size	Adequate control group	Contemporary groups	Baseline equivalence	Adequate statistical analysis	Total
1 Chau (26) 2002	2	2	0	2	2	2	2	0	2	1	2	2	19
2 Pessaux (24) 2001	2	2	2	2	2	2	2	0	2	2	2	2	22
3 Glavic (29) 2001	2	2	0	2	2	2	2	0	2	1	2	2	19
4 Araujo-Texeira (25) 1999	2	2	2	2	2	2	2	0	2	2	1	2	21
5 Eldar (28) 1997	2	2	0	2	2	2	2	0	2	1	2	2	19
6 Unger (27) 1993	2	2	0	2	2	2	2	0	2	1	2	2	19

studies reported no mortality among the operated patients. 346 patients were treated with OC and 275 with LC (Fig. 3). There was no significant difference in heterogeneity among the studies. With fixed effects model, the pooled mortality was favorable to LC (OR = 0.20, 95% CI = 0.04–0.89).

3.4. Operative time

Three studies reported the mean operating time with a standard deviation [13,22,26]. Of these studies, two were randomized [13,22] and 1 retrospective [26]. 88 patients were treated with OC and 81 with LC (Fig. 4). There was significant difference in heterogeneity among the studies. With random effects model, there was no significant difference in the operative times. Meta-regression performed according to the year of publication showed significant difference ($p = 0.03$). The analysis showed that the difference in the mean operative time was progressively in favor of LC from 1998 to 2007.

3.5. Post-operative length of hospital stay

Two studies reported the post-operative length of hospital stay with standard deviation [22,25]. Of these studies, 1 was randomized [22] and 1 retrospective [25]. 115 patients were treated with OC and 118 with LC (Fig. 5). Though statistically these studies were heterogeneous, both studies were in favor of LC. With random effects model, the pooled length of hospital stay was favorable to LC (MD = −4.74 days, 95% CI = −9.05, −0.43).

3.6. Intra-operative blood loss of more than 500 ml

Two studies reported intra-operative blood loss of more than 500 ml [21,26]. Of these studies, 1 was randomized [21] and 1 retrospective [26]. 77 patients were treated with OC and 66 with LC (Fig. 6). There was no significant difference in heterogeneity between the studies. With fixed effects model, there were no significant difference between the groups in intra-operative blood loss of more than 500 ml.

3.7. Wound infection

Seven studies reported data on wound infections [21–24,26,28,29] and three of them were randomized [21–23]. 468 patients were treated with OC and 443 with LC (Fig. 7). There was no significant difference in heterogeneity among the studies. With the random effect model there were a significant reduction in wound infection rate in the laparoscopic group (OR = 0.54, 95% CI = 0.31–0.95).

3.8. Pneumonia

Seven studies reported data on pneumonia [13,21–24,26,28] and four of them were randomized [13,21–23]. 384 patients were treated with OC and 381 with LC (Fig. 8). There was no significant difference in heterogeneity among the studies. With the random effect model there were a reduction in pneumonia during the post-operative course with the laparoscopic approach (OR = 0.51, 95% CI = 0.25–1.01).

3.9. Bile leakage

Four studies reported data on bile leakage [23,26,28,29] and only one was randomized [23]. 326 patients were treated with OC and 343 with LC (Fig. 9). There was no significant difference in heterogeneity among the studies. With the random effect model

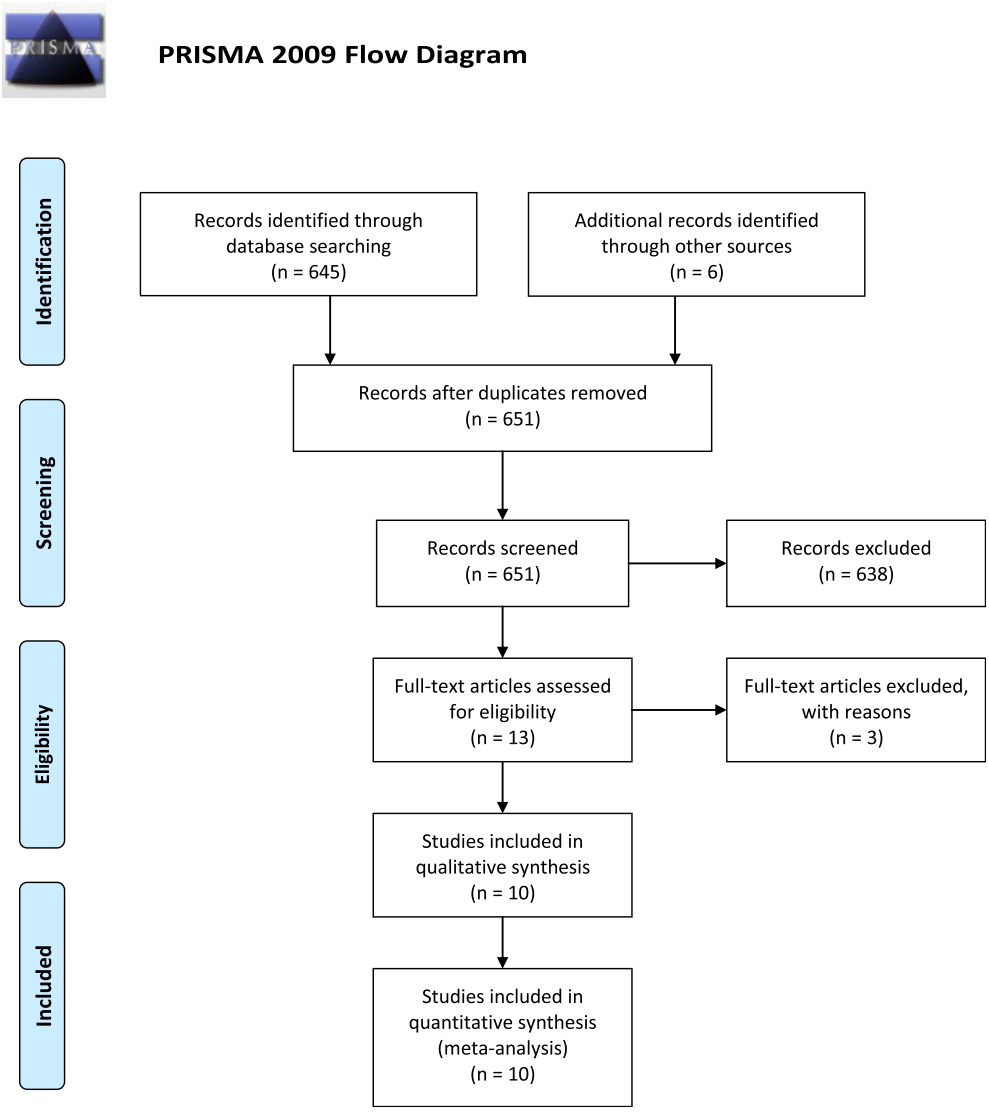

Fig. 1. Prisma flow diagram.

there were no significant differences in bile leakage between the two groups (OR = 1.26, 95% CI = 0.34–4.62).

4. Discussion

Every year, 1–4% of patients with gallstones will develop gallstone-related complications, such as AC [30].

A few prospective randomized studies from the pre-laparoscopic era showed the superiority of early versus delayed OC for AC in hospital stay and time to full recuperation [3,30–32]. Many authors remained rather skeptical as whether the information acquired from open surgery could be applied to laparoscopic surgery in AC [14–16,30]. Some published data have shown a trend toward an increased rate of urgent (44%) and same-admission (23%) LC for patients admitted with AC [31]. Several meta-analyses are clearly in favor of early (within 1 week of symptom onset) LC, which seems safe and feasible [1,3,10,12,32,53]. A meta-analysis failed to show any difference for patients operated within 4 or 7 days after symptomatic onset [32]. If on one hand the exact time-point of LC in AC remains a matter of great debate, on the other hand no data of high level evidence on comparison between OC and LC in AC exist. LC in AC is supposed to increase morbidity because of the difficulty to perform laparoscopy in such a complicated operating field. Potentially serious complications [14,16] and high conversion rates [33–35] have usually been the main arguments for postponing early LC in the setting of AC [30] The same factors are still debated on LC.

The present meta-analysis demonstrated that the overall morbidity rate was reduced with LC in AC when the intervention was performed in the same admission. Subgroup analysis of different complications showed pneumonia and wound infection were reduced by the use of laparoscopy. It seems that the bile leakage rate had no relation with the technique. These outcomes have been investigated either evaluating all the included studies, or evaluating only the randomized trials. The supposed acute or chronic inflammation-linked tissue modification had for years suggested to increase the risk of severe bleeding when AC were treated with LC. The reported intra-operative hemorrhage rate of more than 500 ml showed that severe bleeding in AC treated either by LC or OC was not significantly different.

The operative time analysis was not significantly different. The two different techniques were equivalent in operative times. The supposed increase in difficulty of dissection in AC when treated with LC could not be confirmed using operative times. The outcome was investigated either evaluating all the included studies, or

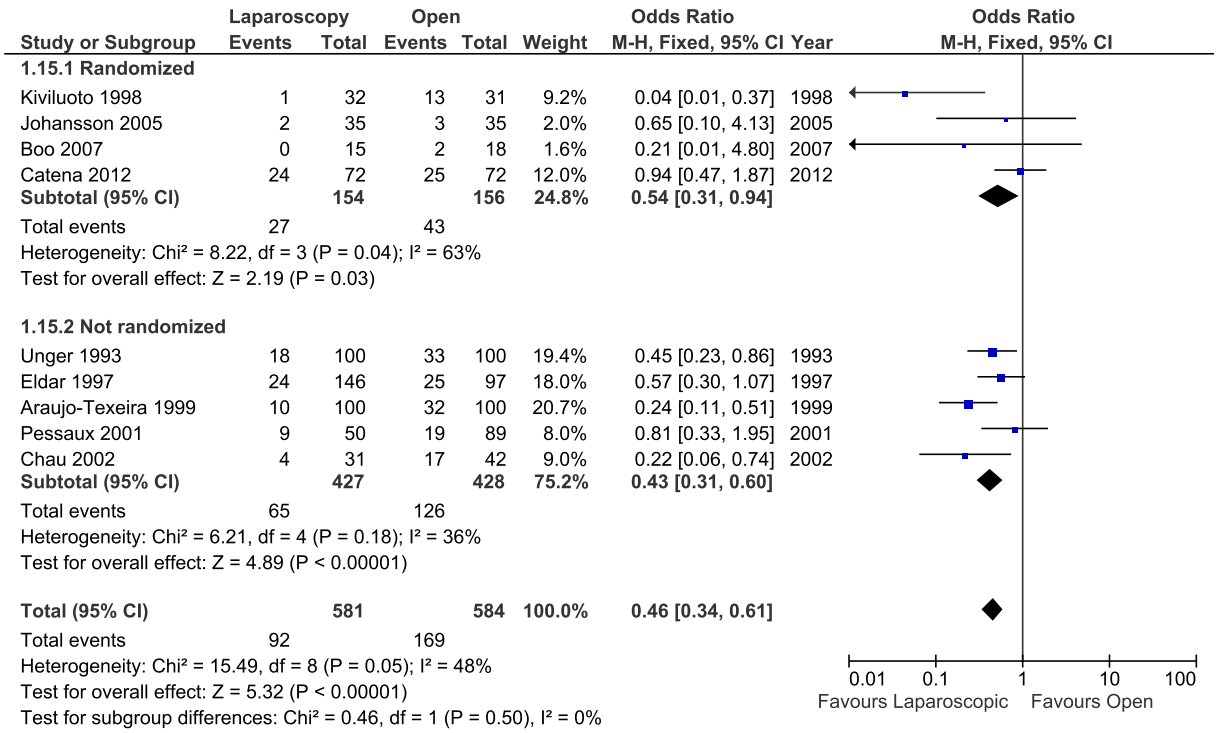

Fig. 2. Morbidity.

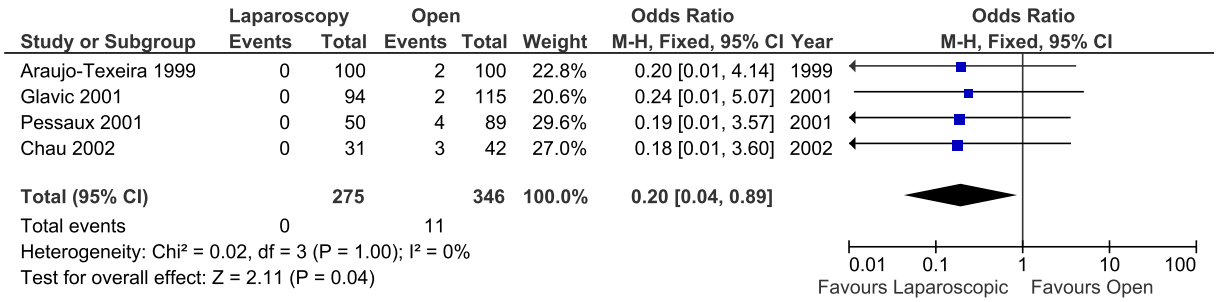

Fig. 3. Mortality.

evaluating only the randomized trials.

Although cholecystectomy has a relatively low operative mortality of 0.4–0.6% [36,37] post-operative mortality is associated with emergency admission, co-morbid cardiorespiratory disease, and advanced age [38]. The present analysis showed the positive impact on mortality of LC in AC. In fact mortality rate was reduced by laparoscopic procedures.

The rate of conversion to OC is believed to be higher when LC is performed for AC than for uncomplicated cholelithiasis, and this is true whether the operation is performed in the acute phase [43] or after a delay [41]. Conversion rates ranging from under 5%–30% have been reported. The predictors of the need for conversion include a duration of symptoms of more than a range of 72–96 h [44,45], a white-cell count of more than 18,000 cells/sqmm at the time of presentation [44,48,49] and an age over 60 years [44,46,47]. In the present study the average conversion rate was of 20.87% but without a high rate of bile duct injuries. There were no report on the time frame between onset of symptoms and intervention in the studies. However all the patients were operated for AC during the same admission. The time frame during which the included studies

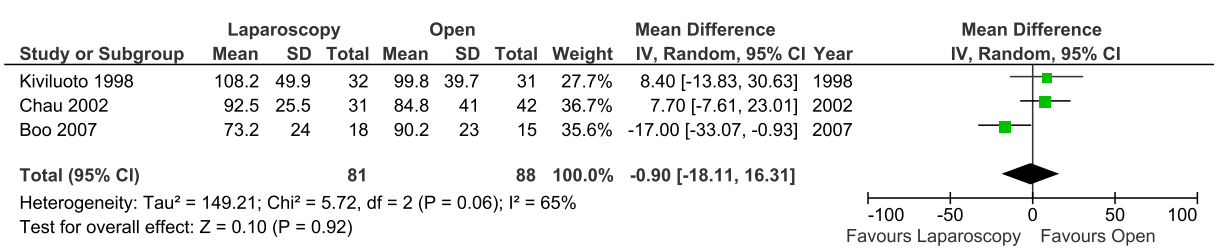

Fig. 4. Operating time.

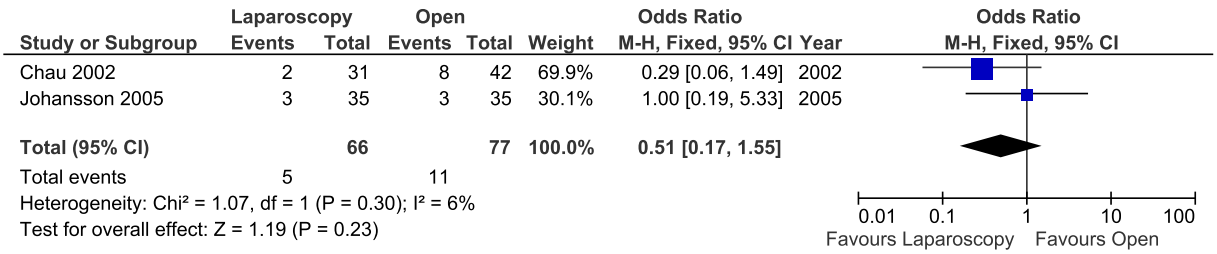

Fig. 5. Post-operative length of stay.

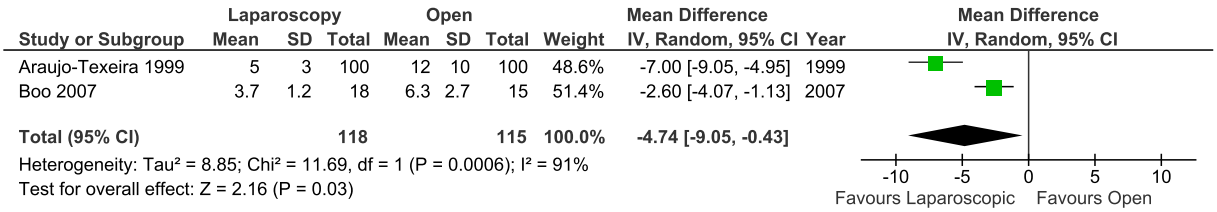

Fig. 6. Intraoperative blood-loss of more than 500 ml.

were comprised warrants a homogeneous distribution of patients, techniques and surgeons' capability through the years. In the first years the rate of conversion was higher probably because of the inexperience in managing AC with LC. Recent studies suffered on the contrary. This is confirmed by the meta-regression performed according to the year of publication, showing a significant trend in reduction of operative times through the years.

The analysis of post-operative hospital stay showed reduced hospitalization times in patients treated with LC. The mean difference was 4.1 days less than in OC. The improved pain and recovery times in LC has already been demonstrated in LC in the elective setting.

As the trend in resources distribution showed reduction in the health care systems across Europe and North America, cost-effectiveness becomes nearly as important as overall patient safety [30]. A cost-utility analysis comparing early versus delayed LC for AC suggests that early LC is not only less expensive but also results in better quality of life when compared to delayed LC [39]. The present analysis confirmed the improvement of resource usage if AC was treated with LC. In fact LC reduced the morbidity and mortality rates and the post-operative hospital stay without increasing the operative times and the severe hemorrhage rates. A recently published worldwide epidemiological study investigating intra-abdominal infections showed that the most frequently performed procedure to treat AC was OC in 48.7% of patients. LC was performed in 36.7% of cases. In the remaining cases (14.6%), conservative treatment methods (percutaneous drainage, non-operative treatment) were alternatively employed. These data enforce the necessity of the role of the present study to define a more appropriate surgical technique in treating AC [56].

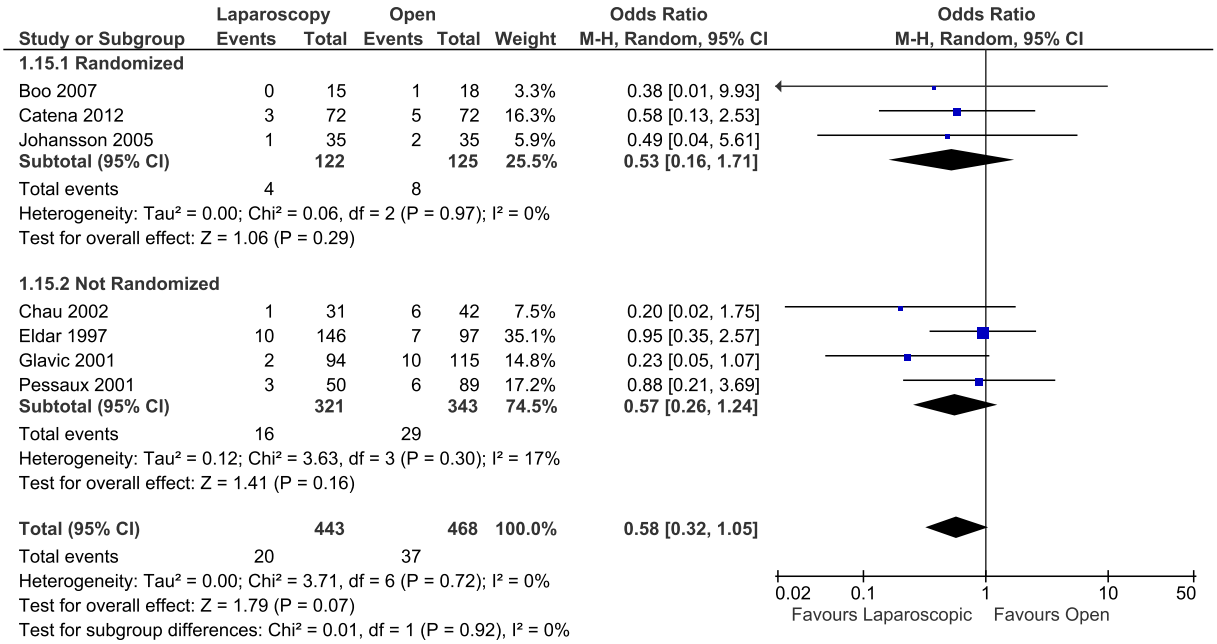

Fig. 7. Wound infection.

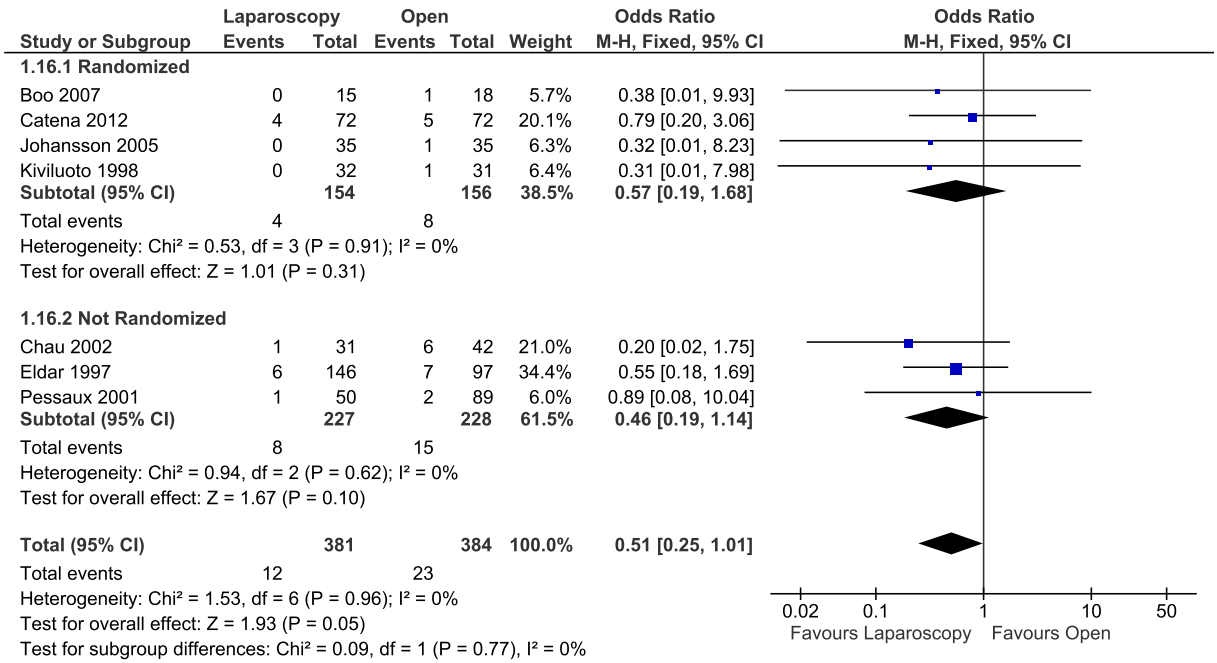

Fig. 8. Pneumonia.

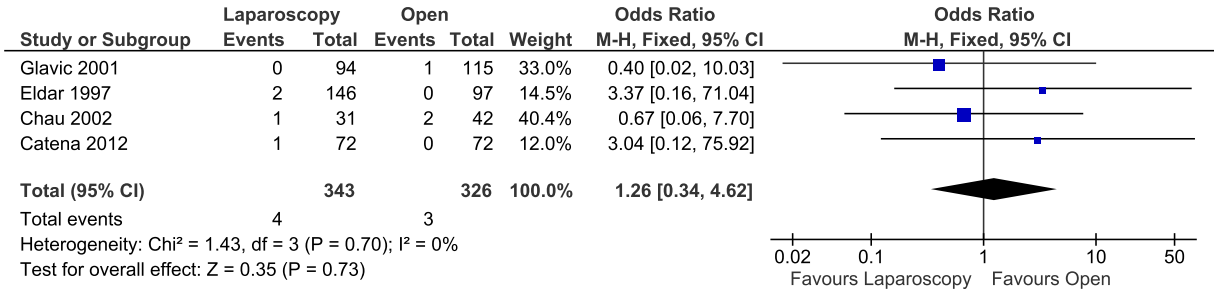

Fig. 9. Bile leakage.

In the literature, indications on the treatment of AC with LC were reported only in selected cases. In fact the Tokyo guidelines provide recommendations for management depending on the severity of AC [40]. Early LC is recommended in mild AC. Early or delayed cholecystectomy may be selected for moderate AC but, early LC should be performed only by highly experienced surgeons and promptly terminated by conversion to OC if operative conditions make anatomical identification difficult. In patients with severe AC, initial conservative management with antibiotics is recommended, with the use of percutaneous cholecystostomy as needed; surgery should be reserved for patients in whom this treatment fails [41]. Our suggestion is to revise the Tokyo guidelines in order to assess the risk in relation to the patient's condition and not only to the AC severity [42]. The indication for cholecystectomy, either laparoscopic or open, should be based on patient-related factors in the guidelines [42].

5. Conclusion

In acute cholecystitis post-operative morbidity, mortality and hospital stay are reduced by laparoscopic cholecystectomy. Moreover pneumonia and wound infection rate are reduced by laparoscopy. A positive trend exists in operating time favoring laparoscopy, however more studies are necessary. Severe hemorrhage and bile leakage rate are not influenced by the technique. Cholecystectomy in acute cholecystitis should be attempted by laparoscopy at first.

Conflicts of interest

None.

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