

Laparoscopic cholecystectomy for severe acute cholecystitis. A meta-analysis of results

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Abstract

Objective The aim of this review was to evaluate surgical outcomes of laparoscopic cholecystectomy for gangrenous and empyematous acute cholecystitis defined as severe acute cholecystitis.

Background It is not known to what extent surgical outcomes of laparoscopic cholecystectomy for severe acute cholecystitis differ from those for the nonsevere acute form, making it questionable whether urgent laparoscopic cholecystectomy is the best approach even in severe acute cases.

Methods Literature searches were conducted to identify: (1) comparative studies which reported laparoscopic surgical outcomes separately for severe acute and nonsevere acute cholecystitis; (2) studies comparing such an approach with open cholecystectomy, subtotal laparoscopic cholecystectomy or cholecystostomy in severe acute cholecystitis. Results were pooled by standard meta-analytic techniques.

Results Seven studies with a total of 1,408 patients undergoing laparoscopic cholecystectomy were found. The risks of conversion (RR 3.2, 95% CI 2.5 to 4.2) and overall postoperative complications (RR 1.6, 95% CI 1.2–2.2) were significantly higher in severe acute cholecystitis with respect to the nonsevere acute forms. However, no difference was detected as regards to local postoperative complications. No studies comparing open cholecystectomy or cholecystostomy with urgent laparoscopy were found.

Conclusion A lower feasibility of laparoscopic cholecystectomy has been found for severe cholecystitis. A lower threshold of conversion is recommended since this may allow to reduce local postoperative complications. Literature data lack valuable comparative studies with other treatment modalities, which therefore need to be investigated.

Keywords Cholecystectomy · Statistical · Technical · Complications

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The most important innovation in the surgical treatment of acute gallstone cholecystitis (AGC) concerns timing [1]. Urgent cholecystectomy is recommended on the basis of randomized clinical trials (RCTs) [2–6] and a meta-analysis [7], since failure of initial conservative treatment has been reported in up to 32% of cases and early cholecystectomy has been proved to reduce total hospital stay. Moreover the laparoscopic approach is considered preferable [1], even if no major differences between laparoscopy and laparotomy have been reported when the outcomes evaluation was blind [8].

However, the rate of gangrenous and empyematous cholecystitis has not been specified exactly in most RCTs. In prospective studies higher conversion and morbidity

rates have been reported when gangrenous cholecystitis or empyema of the gallbladder were approached by laparoscopy [9–12]. Moreover treatment modalities other than laparoscopic cholecystectomy have also been considered, such as cholecystostomy or subtotal cholecystectomy [13–21].

Both gangrenous and empyematous cholecystitis can be defined as severe cholecystitis since, as reported, they are the expression of a worsening of the inflammatory process and bacterial colonization with a possible life-threatening evolution if not treated [22]. To what extent severe acute cholecystitis has a different surgical outcome compared with nonsevere acute cholecystitis is therefore questionable. A relevant difference would make it necessary to verify if laparoscopic cholecystectomy is the best approach even in cases of severe acute cholecystitis by way of comparative studies with other treatment modalities. As a result the problems of preoperative diagnosis would need to be further investigated. Gangrenous and empyematous acute cholecystitis would also need to be reported separately in studies on acute cholecystitis.

This study is a review of literature, specifically selecting reports that compared surgical outcomes of laparoscopic cholecystectomy in severe and nonsevere acute cholecystitis, and reports that compared different therapeutical approaches for severe acute cholecystitis with a meta-analysis of results.

Materials and methods

Literature searches

A literature data review was conducted by a researcher and an epidemiologist using the MEDLINE database. The research was constructed by combining subject headings and text words relating to the treatment of severe acute cholecystitis using Ovid syntax from 1966 to January 2006. No limit was introduced except for animal studies. Literature searches were completed by consulting the Cochrane Library, online indexes of evidence-based medicine (EBM) specialized journals such as the American College of Physicians (ACP) journal and the British medical journal (BMJ), and hand searching by reviewing all the references of the articles found. Unpublished studies or data from presentations to congress were not taken into account.

Publication selection

Two reviewers, a consultant and a fellowship from the surgical department, carried out the first selection on the basis of title and abstract, if present, to identify studies that

clearly reported results of surgical treatment of severe acute cholecystitis.

A second selection was completed by thoroughly reading the articles; a mother-language translator was required for publications in an unknown language. Studies were included in the review only if: gallstone cholecystitis was the main topic; a complete description of the treatment was reported; results were referred, for severe acute forms only to gangrenous, empyematous or perforated cholecystitis; final diagnosis was confirmed intraoperatively and/or by histological examination; a comparison was feasible between severe acute and nonsevere acute cholecystitis or between different treatment modalities for severe acute cholecystitis.

Exclusion criteria were as follows: not original articles; age limitation such as infant or elderly; limitation to alithiasic cholecystitis; nonconsecutive series; occasional reports with fewer than 10 patients; previous reports from the same institution including only the more recent or more-appropriate results; the lack of a clear description of the study method or study design such as randomized trials, comparative nonrandomized or case series, reported results not made on an intention to treat; the lack of data on conversion or morbidity; or the lack of data on inclusion and/or exclusion of patients from the study.

Database searches yielded a total of 283 articles, out of which 34 were selected on the basis of the title or the abstract. Hand searching of references of selected articles led us to retrieve nine further studies of possible interest. Thus, 43 publications were selected for detailed assessment. These were 29 cases series on laparoscopic surgery, one randomized and two nonrandomized comparative studies on open versus laparoscopic cholecystectomy, one randomized and one nonrandomized comparative study and nine case series on treatments other than laparoscopic cholecystectomy.

However, of these 43 publications 36 had to be excluded, because they either lacked specific data on severe acute cholecystitis [12, 23–29], included forms other than gangrenous or empyematous cholecystitis [30, 31], failed to describe patient selection [32–35], reported on fewer than 10 patients [14, 36–39], contained no comparison on severe acute cholecystitis versus nonsevere acute cholecystitis [40–46] or results not referred to histological findings [13, 15–17, 47–50]. One study was a double publication [11]. A randomized study [51] comparing open and laparoscopic cholecystectomy lacked specific data on severe acute cholecystitis and was therefore not selected for the review.

Finally, we included seven cases series that had compared results of laparoscopic cholecystectomy for severe acute cholecystitis and nonsevere acute cholecystitis (Table 1).

Table 1 Studies characteristics

Citation	Study design patients exclusion	Quality score
Cox MR [9]	Prospective consecutive series	3
Singer JA [25]	Retrospective consecutive series	2
Lo CM [53]	Retrospective consecutive series	2
Eldar S [10]	Prospective consecutive series	8
Merriam LT [54]	Retrospective series 10 patients excluded as a result of surgeon preferences	4
Navez B [55]	Retrospective consecutive series	3
Gharaibeh KI [56]	Retrospective consecutive series	3

Publications analysis

The quality of observational studies was scored according to the following criteria: definition of study's objectives (1 point if reported; 0 points if not), statistical method described (1 point if reported; 0 points if not or not correct), measures of outcomes (1 point if clearly reported; 0 points if data had to be calculated), possible bias in the inclusion/exclusion criteria (1 point if not present; 0 points if present), differences in the population of the compared groups (1 point if reported without differences except for American Society of Anesthesiologists (ASA) score, gender and age; 0 points if not reported or reported with some differences other than those related to ASA score, age and gender), different types of treatment beside the investigated one (1 point if reported without differences in the groups; 0 point if not), different technical skills in the same series or different experience of operators (1 point if reported without differences in the groups; 0 points if not) and eventual commercial interest, related to techniques performed only through certain devices (1 point if no commercial devices were cited in the text; 0 points if they were). The total score therefore ranged between 0 to 8.

Data collection and control for confounding

Feasibility and safety of laparoscopic cholecystectomy in severe acute cholecystitis in comparison with the nonsevere acute form was evaluated through meta-analysis of these results.

Conversion rates were calculated as the primary end point for the evaluation of feasibility of laparoscopic cholecystectomy, and overall postoperative morbidity was calculated as the primary end point for safety. Data on local complications, defined as abdominal complications, were also recorded when available as well as data on bile duct injury and on mortality.

Results were extracted and grouped into two categories. Only cases of gangrenous (necrosis of the parietal wall of the gallbladder), empyematous (pus in gallbladder contents and/or phlegmon of the parietal wall) or perforated cholecystitis were included as severe acute cholecystitis, while all other types of inflammation (e.g., edematous), mucocele or hydrops were included as nonsevere acute cholecystitis. Emphysematous cholecystitis was excluded since this condition is reported only in limited series and is mainly alithiasic. The total number of patients, the proportion of severe acute cholecystitis, and the empyematous/gangrenous ratio of severe acute cholecystitis were also taken into account. Data were extracted using a data extraction form and was cross-checked by a second reviewer.

Associated systemic diseases may be the main confounders for postoperative morbidity. However a correlation between general comorbidities such as cardiovascular diseases or diabetes and the severity of cholecystitis has been reported, while the most severe associated diseases do not allow surgical treatment. Therefore extraction of data on postoperative complications may be a source of bias; extraction from subgroups of patients comparable on the basis of the ASA would be attempted. Local complications were recorded since a closer correlation with severity of cholecystitis rather than with the systemic associated diseases may be hypothesized.

Retained common bile duct stone has also been included among possible postoperative morbidity since this complication does not directly depend on the severity of cholecystitis but rather on technical difficulties in severe acute cases that may prevent performance of an intraoperative cholangiogram with a retained common bile duct stone as a result. Timing of surgery or previous treatment for bilio-pancreatic diseases may not be taken into account since the aim of the research is an evaluation of outcomes limited to confirmed diagnosis by intraoperative or histological findings of an empyematous or gangrenous cholecystitis. Authors were not contacted for eventually lacking information.

Statistical methods

Although the primary studies were expected to differ in their design, data were extracted from cohort studies that compare patients with severe acute cholecystitis and those with nonsevere acute cholecystitis. Relative risk (RR) and risk difference (RD) were therefore calculated for conversion and for overall and local postoperative complications.

Since studies were expected to be heterogeneous a priori, a random effects model rather than a fixed effect model was used in the evaluation of the results. Therefore pooling

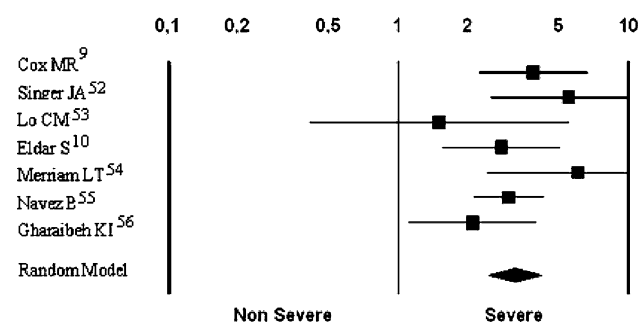
Table 2 Details of included studies

Citation	Total patients	Mean Age	F/M ratio	Severe cases (%)	No. of conversions (%)		Overall post-operative morbidity (%)	
					Severe	Nonsevere	Severe	Nonsevere
Cox MR [9]	98	57	1.2	28 (28.6)	20 (71.4)	13 (18.6)	NR	NR
Singer JA [52]	68	54.7	1.7	24 (35.3)	18 (75)	6 (13.6)	2 (8.3)	5 (11.4)
Lo CM [53]	70	60	1.5	28 (40)	4 (14.3)	4 (9.5)	NR	NR
Eldar S [10]	215	54.5	1.4	99 (46)	31 (31.3)	13 (11.2)	21 (21.2)	16 (13.8)
Merriam LT [54]	144	45.4	2.5	23 (16)	8 (34.8)	7 (5.8)	0 (0)	5 (4.1)
Navez B [55]	609	60.8	1.4	254 (41.7)	82 (32.3)	38 (10.7)	51 (20.1)	40 (11.3)
Gharaibeh KI [56]	204	38	1.5	13 (6.4)	6 (46.2)	42 (22)	NR	NR
Total	1,408			469/1408	169/469	123/939	74/400	66/636

Studies are ordered chronologically

NR: not reported

F/M: female-to-male ratio

**Fig. 1** Forest plot on relative risk of conversion

of results was done using the DerSimonian Laird method [57]. The level of statistical significance was set to 5%. Accordingly, confidence intervals (CI) were calculated at 95%. Homogeneity was evaluated with the I^2 statistic, which may be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and is intrinsically independent of the number of studies. When $I^2 < 30\%$ there is little concern about statistical heterogeneity [58, 59].

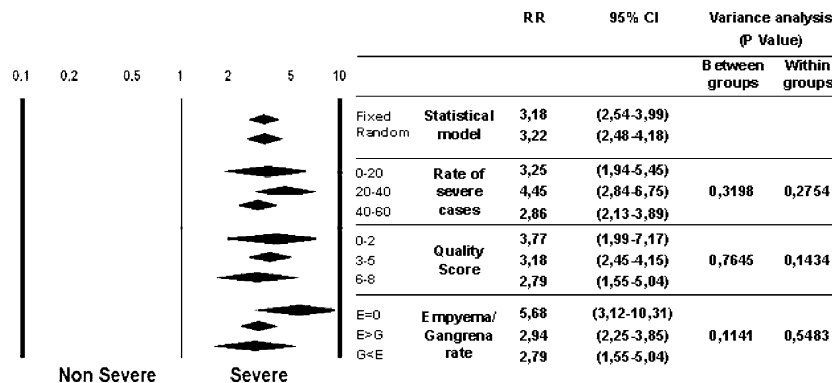
Sensitivity analyses were performed by comparing fixed and random effects models and by dividing studies

according to the quality score of the study, and the relative number of cases of severe acute cholecystitis. As the gangrenous form may lead to different results than the empyematous one, sensitivity analysis for selection bias was completed by a comparison based on the ratio of empyematous to gangrenous cases.

Review Manager (Version 4.1)® and STATA® software were used for the statistical analysis.

Results

All included studies reported data on conversion in a total of 1,408 patients, of which 469 had severe acute cholecystitis and 939 had nonsevere acute cholecystitis (Table 2). The summary RR for conversion in severe acute cholecystitis versus nonsevere acute cholecystitis was 3.22 (95% CI 2.48–4.18) according to the random effects model (Fig. 1). No heterogeneity was found ($I^2 = 18.9\%$). The summary RD for conversion was 0.3 (95% CI 0.17–0.42), however heterogeneity was found with $I^2 = 79.5\%$. None of the sensitivity analyses based on RR resulted in the identification of possible confounding variables (Fig. 2).

Fig. 2 Sensitivity analyses for relative risk of conversion

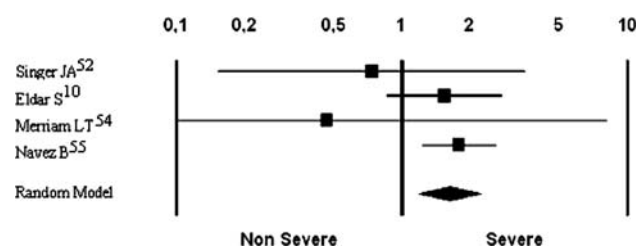


Fig. 3 Forest plot on relative risk of overall postoperative complications

Four of the seven case series contained data on complications in a total of 1,036 patients and reported them separately for severe acute and nonsevere acute cases in 400 and 636 patients, respectively (Table 2). The summary RR for overall complications was 1.61 (95% CI 1.17–2.21) according to the random effects model (Fig. 3). Again no heterogeneity was found ($I^2 = 0\%$). The summary RD for complications was 0.03 (95% CI -0.04 – 0.11), however heterogeneity was found with $I^2 = 74.8\%$. Sensitivity analysis based on RR failed to show any influence of study quality or patient sample on overall results (Fig. 4). However extraction of data from subgroups of patients comparable on the basis of associated systemic diseases have not been possible since such data were not clearly reported in the retrieved studies.

Data on local complications were extractable from three studies in a total of 427 patients, of which 146 had severe acute cholecystitis and 281 had nonsevere acute cholecystitis. Results failed to show a difference with a summary RR of 1.16 (95% CI 0.59–2.26) and summary RD of -0.01 (95% CI -0.06 – 0.04) according to the random model, and no heterogeneity ($I^2 = 0\%$). Due to the small number of study no sensitivity analysis was performed.

Bile duct injury was reported in only one study. No significant difference was found between gangrenous, empyematous, and oedematous cholecystitis with rates of 1.06% (1/94), 1.26% (2/160) and 0.28% (1/355), respectively. Zero mortality was reported in five studies, whereas two studies described mortality rates of 0.7 and 1%,

respectively, but without further details on mortality according to disease severity.

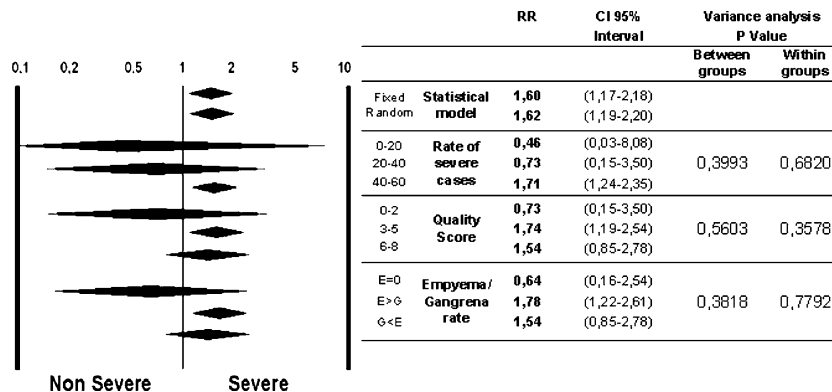
Discussion

The aim of this study was to evaluate surgical outcomes of laparoscopic cholecystectomy for severe acute cholecystitis such as gangrenous cholecystitis or gallbladder empyema. Different surgical outcomes between severe acute cholecystitis and nonsevere acute cholecystitis were found, favoring the latter. This results seem intuitive but such a difference has never been evaluated by a quantitative nor qualitative analysis. The literature research failed moreover to retrieve valuable studies that compared different surgical approaches for the severe form of acute cholecystitis.

Factors associated with severe acute cholecystitis have been reported to be age, male gender, cardiovascular associated disease, diabetes, and delayed surgery [10–12, 43]. Different population studies may explain the wide range of acute severe cholecystitis reported in consecutive clinical series, lying from 6 to 50% of total acute cholecystitis [9, 10, 53, 56, 60]. An estimation from the studies selected for this review using a weighted average of the ratios of each of the studies indicated that severe acute cholecystitis constitutes 27.6% of total acute cholecystitis cases. Increasing population age and more frequent association with systemic diseases in older patients will play a role in maintaining such a high incidence; not only may associated diseases such as cardiovascular disorder or diabetes be risk factors for developing severe acute cholecystitis, but they may also lead to delayed surgery with further risks as a result. This makes the question relevant and, to our knowledge, this is the first review on such a topic.

The heterogeneity of the studies on severe acute cholecystitis, both in their design and results, made it difficult to draw conclusive consideration. A meta-analysis of results based on a review of the literature would prove more valuable. In the present study a meta-analysis of

Fig. 4 Sensitivity analyses for relative risk of overall postoperative complications



observational studies has therefore been performed to answer the question on surgical outcomes of laparoscopic cholecystectomy for severe acute cholecystitis. Since there is no clear consensus on the method for quality assessment of observational studies [62], and since the aim of the present study was a comparison between two different surgical outcomes rather than two surgical procedures, our own quality assessment criteria adapted for the purpose have been used. Surgical outcomes in severe and nonsevere acute cholecystitis were therefore registered, and relative and absolute risks were calculated using a random effects model since studies were expected to be heterogeneous. The number needed to treat (NNT) and number needed to harm (NNH) were not calculated since a comparison was not being made between two different procedures but between two different forms of disease. Lack of heterogeneity for RR on conversion and overall postoperative complications, and the lack of identification of possible confounding variables in the sensitivity analysis make the results of the present review valuable. The present study suffers from some limits since authors were not contacted, unpublished data or data from oral presentation at congresses were not considered, and no quantitative assessment of publication bias was performed. Most publications report some results on gangrenous or empyematous cholecystitis, although structured comparative analysis are very rare.

Regarding the feasibility of laparoscopic cholecystectomy we can conclude that a threefold higher conversion rate is to be expected when a severe acute cholecystitis is approached by laparoscopy. This result does not seem to be affected by the quality of analysis, the experience of the surgeons or the quality of the studies since the sensitivity analysis did not find confounding variables.

As expected, overall postoperative complications were also higher for severe acute cholecystitis. An analysis based on subgroups of patients comparable on the basis of associated systemic diseases has not been possible since such results were not reported in the included studies. Therefore it is not possible to verify to what extent such an analysis would be able to reduce the bias of the associated systemic diseases. Complications of acute cholecystitis are mainly due to the presence of an inflammatory process acting through mediators with possible complications on distant organs with impaired function due to comorbidities, especially when necrotic tissue or purulent collection are present. Urgent intervention is therefore advocated to avoid worsening of clinical conditions and the risk of ongoing sepsis and death. However surgical intervention may play an additional role in complications, and an increase in overall complications and mortality have been reported in patients scored ASA III/IV and with gangrenous cholecystitis [12, 61, 63]. Use of cholecystostomy may be

indicated in such cases to delay cholecystectomy until local and systemic signs of the inflammatory process have disappeared, as documented by clinical series on such a topic either for severe acute cholecystitis or for critically ill patients with every form of cholecystitis [15, 16, 18–20, 50].

Although subtotal cholecystectomy and percutaneous preoperative cholecystostomy have been reported as possible alternatives to reduce conversion and overall postoperative complications in severe acute cholecystitis [13, 14, 16, 18, 19, 45] our literature research failed to retrieve valuable comparative studies with such procedures.

Postoperative local complications were evaluated since they are defined as complications arising from the site of intervention and are supposed to be related more closely to the severity of cholecystitis. In a report on open cholecystectomy, gallbladder empyema was significantly associated with a higher rate of local complications when compared with nonempyematous acute cholecystitis [64]. In the technically more demanding laparoscopic cholecystectomy for severe acute cholecystitis a higher rate of local complications was expected too. Surprisingly our research did not show such a difference. However data on local complications were limited since only three of the included studies reported the differences in local and systemic complications between severe and nonsevere acute cholecystitis. Moreover local complications during laparoscopic cholecystectomy may be influenced by conversion. The clue is: if and when to convert, until which point surgical expertise would be more appropriate in laparoscopy rather than in laparotomy. Pooling conversion rates from the three studies reporting data on local complications highlighted a higher relative risk for conversion up to 4.16 (95% CI 2.49–6.96, $I^2 = 30\%$). A higher conversion rate without an increase in local complications for severe acute cholecystitis may therefore be explained by a lower threshold for conversion in severe acute cases. A more prudent attitude rather than a true limitation of the laparoscopic procedure may be hypothesized to explain the retrieved lower feasibility of laparoscopic cholecystectomy for severe acute cholecystitis.

Conclusions

We can therefore conclude that laparoscopic cholecystectomy may be considered an acceptable indication even in cases of severe acute cholecystitis. However, a threefold of conversion rate has to be taken into account, a significant higher overall postoperative complication rate has been observed, although this result may be confounded by associated systemic diseases and no increase in local postoperative complications was retrieved. Therefore when

diagnosis is made during laparoscopic cholecystectomy a lower threshold of conversion has to be encouraged since it may lead to reduced local complications.

Due to the different surgical outcomes, other treatment modalities for severe acute cholecystitis need to be assessed since literature research failed to retrieve valuable comparative studies. A more-precise preoperative diagnosis would also be assessed and severe acute cholecystitis would need to be reported separately in studies on acute cholecystitis.

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