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REVIEW ARTICLE

Laparoscopic or open cholecystectomy in cirrhosis: a systematic review of outcomes and meta-analysis of randomized trials

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Abstract

Background: Cholecystectomy is associated with increased risks in patients with cirrhosis. The well-established advantages of laparoscopic surgery may be offset by the increased risk for complications relating particularly to portal hypertension and coagulopathy.

Methods: A systematic search was undertaken to identify studies comparing open cholecystectomy (OC) and laparoscopic cholecystectomy (LC) in patients with cirrhosis. A meta-analysis was performed of the available randomized controlled trials (RCTs).

Results: Forty-four studies were analysed. These included a total of 2005 patients with cirrhosis who underwent laparoscopic (n = 1756) or open (n = 249) cholecystectomy, with mortality rates of 0.74% and 2.00%, respectively. A meta-analysis of three RCTs involving a total of 220 patients was conducted. There was a reduction in the overall incidences of postoperative complications and infectious complications and a shorter length of hospital stay in LC. However, frequencies of postoperative hepatic insufficiency did not differ significantly.

Conclusions: There are few RCTs comparing OC and LC in patients with cirrhosis. These studies are small, heterogeneous in design and include almost exclusively patients with Child–Pugh class A and B disease. However, LC appears to be associated with shorter operative time, reduced complication rates and reduced length of hospital stay.

Keywords

cirrhosis < liver, surgery < cholelithiasis, outcomes < gallbladder

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Introduction

Prevalences of gallstones in patients with cirrhosis are estimated at 29–46%[1,2] and thus are three times as high as those in patients without cirrhosis.[3,4] In the non-cirrhotic population, laparoscopic cholecystectomy (LC) appears to have substantial advantages over conventional open cholecystectomy (OC) in terms of hospital stay and convalescence, but not in mortality, complications and operative time.[5] However, in the era prior to LC, reported post-operative mortality in patients with cirrhosis undergoing OC was 7.5–25.5%[6–9] and patients with the most advanced liver disease were at the greatest risk. Perhaps for this reason, the 1992 National Institutes of Health (NIH) consensus statement on LC confirmed that patients with end-stage cirrhosis of the liver with portal hypertension were not candidates for LC. The first study to specifically report outcomes of LC in the presence of cirrhosis was published in 1993,[10] since when many case series and a few case–control studies of this group of patients have emerged. Indeed, a meta-analysis was published in 2003.[11] Since then, the literature on the topic has further expanded to include randomized controlled trials (RCTs). This aim of this study was to systematically review the current literature on LC in cirrhosis and to determine whether there is indeed evidence to substantiate the contention that OC should be used preferentially in the presence of cirrhosis.

This study was presented at the Third Biennial Congress of the Asian Pacific Hepatopancreatobiliary Association, 27–30 September 2011, Melbourne, Victoria.

Materials and methods

Literature search strategy

Searches were conducted of PubMed, the MEDLINE database from 1950 to the 25th week of 2011 and the EMBASE database from January 1980 to the 25th week of 2011. The OVID search engine (Version OvidSP_UI03.02.04.102; Ovid Technologies, Inc., New York, NY, USA) was used. The MESH/EmTree heading 'liver cirrhosis' yielded 63 980 hits in MEDLINE and 83 677 hits in EMBASE, and the search term 'liver cirrhosis' yielded 81 315 hits in PubMed. The MESH/EmTree heading 'cholecystectomy' yielded 22 175 hits in MEDLINE and 28 624 hits in EMBASE, and the search term 'cholecystectomy' yielded 27 705 hits in PubMed. The results of these searches were combined in each database to yield 246 articles in MEDLINE, 365 articles in EMBASE and 414 articles in PubMed.

Study selection

Study evaluation was performed by two of the reviewers (JML and PDT). Articles were selected on the basis of three levels of screening[12] summarized in Fig. 1. Studies were included regardless of publication status, date of publication and number of participants. Studies published in languages other than English[13–15] were translated and the data extracted. Where similar data from the same institution were published on more than one occasion,[10,16,17] data from the most relevant publication were analysed. In many of the case series of OC prior to the widespread availability of endoscopic retrograde cholangiopancreatography (ERCP), many patients underwent concomitant open procedures, particularly bile duct exploration and drainage.[6,8,18–22] Because the morbidity associated with these additional open procedures might potentially bias comparison with surgery in the laparoscopic era (in which concomitant laparoscopic bile duct exploration was almost never performed), the aforementioned studies were excluded from analysis.

Data extraction

Each of these 44 articles were independently reviewed by two of the authors (JML and PDT), who separately extracted data on the following categories: dates over which the study was conducted; numbers of patients in the OC and LC groups; age and sex of the patients studied; causes of liver disease; severity of cirrhosis;[23] indication(s) for cholecystectomy; mortality; morbidity; rate of

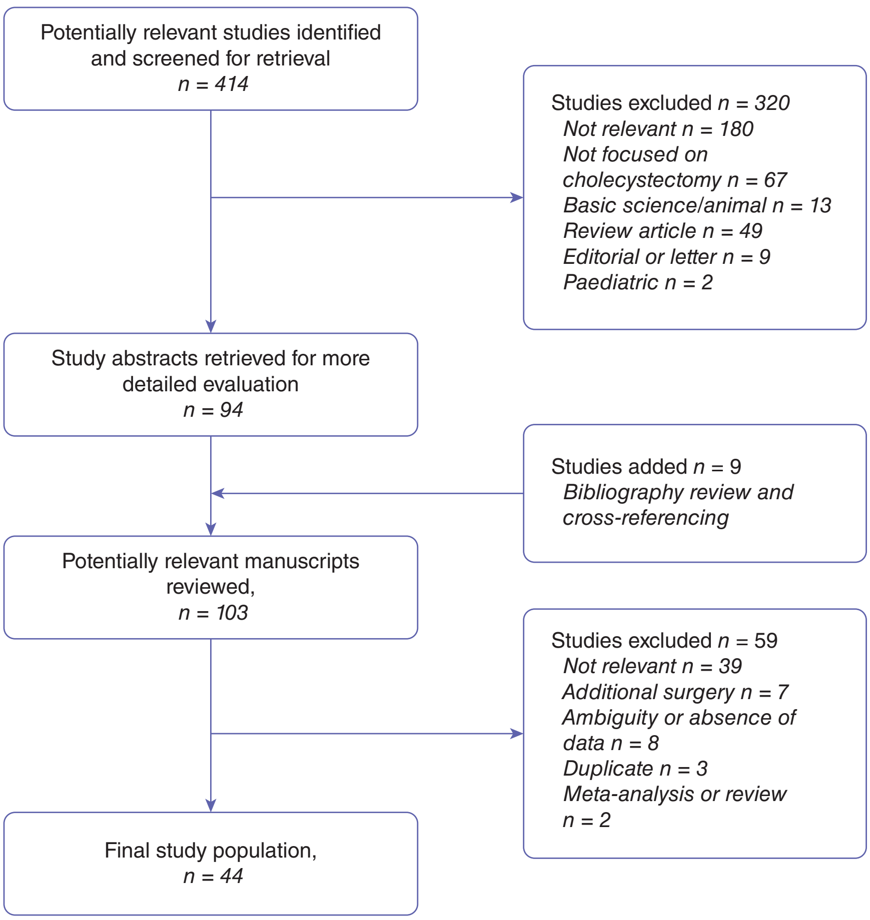


Figure 1 Flow chart showing the search strategy used to identify studies

conversion to LC; operation times; blood loss; transfusion requirements, and length of hospital stay (LoS). The extracted data were then crosschecked by the two authors to rule out discrepancy. In the event of disagreement, data were extracted by a third reviewer (VWTL).

Study outcomes

The main outcomes analysed were the total numbers of patients with cirrhosis undergoing OC and LC and the total number of postoperative deaths in each group. When reported, the patients' Child–Pugh[23] status, age, sex and indication for surgery were recorded. Mortality was described with respect to Child–Pugh status when data were provided. All studies, irrespective of design, were included for these outcomes. Total postoperative complication rate, postoperative infectious complication rate, postoperative hepatic insufficiency and LoS were recorded for each study, but a meta-analysis was performed only for the RCTs. The total rate of postoperative complications was a composite outcome measure of complications including pneumonia, wound infection, urinary tract infection, intra-abdominal abscess and peritonitis. The rate of postoperative hepatic insufficiency referred to a composite of the reported incidences of episodes of unspecified liver failure, ascites and encephalopathy. Because not all outcomes were universally reported in each study, when the proportional frequency of an outcome was reported, the denominator was altered according to the number of patients in the studies reporting that outcome (i.e. the population at risk).

Statistical methods

Because of the heterogeneity of the studies selected and the fact that most of them lacked a control group, no meta-analysis could be carried out on the case series and case–control studies. Hence, a descriptive analysis based on the patient pool comprising all of the patients in each of the OC and LC groups was performed. For the RCTs only, meta-analyses were performed using Revman 5.0 (Version 5.0.25 for Mac OS X; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).[24] For dichotomous outcomes, the odds ratio (OR) was calculated with a 95% confidence interval (CI) using the Mantel–Haenszel (M–H) method. For continuous outcomes, the mean difference (MD) and 95% CI were calculated. A random effects model was used. The heterogeneity of study results was assessed using the chi-squared test and the I^2 statistic of inconsistency. Statistically significant heterogeneity was defined as a *P*-value of <0.1 or an I^2 statistic >50%.[25]

Study quality

The studies were assessed using the Oxford Centre for Evidence-Based Medicine Level of Evidence Scale.[26] The studies included in the analysis constituted Level 3b or Level 4 evidence, with the exception of the three RCTs, which constituted Level 1b evidence (Table 1).

Results

Description of studies

The studies included in the systematic review are summarized in Table 1. Forty-four studies were included in the analysis.[7,13,15,16,22,27–65] These included three RCTs comparing open and laparoscopic surgery in cirrhosis,[47,52,56] three case–control studies[22,29,37] and 38 case series.[7,13,15,16,27,28,30–36,38–46,48–51,53–55,57–65] Two RCTs comparing outcomes of conventional LC and LC performed using the harmonic scalpel in cirrhotic patients were included.[28,57] Only the outcomes of conventional LC from these studies were analysed. Main outcome measures are summarized in Table 2.

Patient characteristics

The systematic review included data pertaining to 2005 patients with cirrhosis undergoing laparoscopic (n = 1756) and open (n = 249) cholecystectomy. Data pertaining to the demographics, severity of chronic liver disease, proportion of patients with acute cholecystitis and conversion rate are summarized in Table 2.

Mortality and complications

Mortality rates in LC and OC were 0.74% and 2.00%, respectively (Table 2). All the deaths in the OC cohort were contributed from a single study,[7] which did not report Child–Pugh status. Studies of LC in which mortality was stratified according to Child–Pugh status were analysed, including data pertaining to 1328 patients among whom six deaths were reported. Four of these patients had Child–Pugh class C status and the remaining two had Child–Pugh class A and class B status, respectively. Rates of overall complications, infectious complications and postoperative hepatic insufficiency in the LC and OC groups are summarized in Table 2.

Meta-analysis of RCTs

Outcomes for a total of 220 patients reported in the RCTs were subjected to meta-analysis. No instances of mortality were recorded in any RCT. There were reductions in the overall incidence of postoperative complications (OR 0.25, 95% CI 0.07–0.88) (Fig. 2a) and in the incidence of infectious complications in LC (OR 0.23, 95% CI 0.10–0.56) (Fig. 2b), but the frequency of postoperative hepatic insufficiency did not differ significantly between LC and OC (OR 0.53, 95% CI 0.12–2.32) (Fig. 2c). Length of hospital stay was substantially shorter in patients undergoing LC (MD − 3.31, 95% CI − 4.46 to − 2.16) (Fig. 2d). Statistically significant heterogeneity was observed in the analyses of rates of all postoperative complications (I^2 = 75%), postoperative hepatic insufficiency (I^2 = 69%) and LoS (I^2 = 69%), but not in the infectious complications outcome (I^2 = 0%). Given the small number of studies, funnel plot analysis could not be used to explore bias.[66,67]

Discussion

This systematic review addressed the issue of whether the preferential utilization of OC in cirrhotic patients, as suggested by the

Table 1 Summary of studies included in this systematic review

Author(s)	City of institution	Year	Study design	Participants, *n*	LC	OC	Level of evidence[a]
Angrisani *et al*.[27]	Naples	1997	RCS	31	31	0	4
Bende & Csiszar[13]	Budapest	1997	RCS	27	27	0	4
Bessa *et al*.[28]	Alexandria	2011	PCS	20	20	0	4
Bingener *et al*.[65]	San Antonio, TX	2008	RCS	99	99	0	4
Clark *et al*.[64]	Sydney, NSW	2001	RCS	25	25	0	4
Cobb *et al*.[63]	Charlotte, NC	2005	RCS	22	22	0	4
Cucinotta *et al*.[16]	Messina	2003	RCS	22	22	0	4
Curro *et al*.[62]	Messina	2005	RCS	42	42	0	4
D'Albuquerque *et al*.[61]	São Paulo, SP	1995	RCS	12	12	0	4
da Silveira[60]	Stanford, CA	2006	RCS	33	24	9	4
Delis *et al*.[59]	Miami, FL	2010	RCS	220	220	0	4
Dunnington *et al*.[58]	Tucson, AZ	1987	RCS	22	0	22	4
El Nakeeb *et al*.[57]	Mansoura	2010	PCS	60	60	0	4
El-Awadi *et al*.[56]	Mansoura	2009	RCT	110	55	55	1b
Fernandes *et al*.[55]	San Antonio, TX	2000	RCS	48	48	0	4
Fontes *et al*.[15]	Porto Alegre, RS	2002	RCS	10	10	0	4
Friel *et al*.[54]	Boston, MA	1999	RCS	30	30	0	4
Garrison *et al*.[7]	Louisville, KY	1984	RCS	29	0	29	4
Gugenheim *et al*.[53]	Nice	1996	RCS	9	9	0	4
Hamad *et al*.[52]	Assiut	2010	RCT	30	15	15	1b
Hamid *et al*.[51]	Karachi	1993	RCS	18	0	18	4
Ishikawa *et al*.[50]	Osaka	1995	RCS	4	4	0	4
Jan & Chen[49]	Chang Gung	1997	RCS	21	21	0	4
Ji *et al*.[48]	Nanjing	2004	RCS	38	38	0	4
Ji *et al*.[47]	Nanjing	2005	RCT	80	42	38	1b
Kogut *et al*.[46]	New York, NY	1985	RCS	27	0	27	4
Lacy *et al*.[45]	Barcelona	1995	RCS	11	11	0	4
Leandros *et al*.[44]	Athens	2008	RCS	34	34	0	4
Leone *et al*.[43]	Turin	2001	RCS	24	24	0	4
Mancero *et al*.[42]	São Paulo, SP	2008	RCS	30	30	0	4
Morino *et al*.[41]	Turin	2000	RCS	33	33	0	4
Nguyen *et al*.[40]	Pittsburgh, PA	2011	RCS	68	68	0	4
Palanivelu *et al*.[39]	Tamilnadu	2006	RCS	265	265	0	4
Pavlidis *et al*.[38]	Thessaloniki	2009	RCS	38	38	0	4
Poggio *et al*.[22]	Rochester, MN	2000	RCC	36	24	12	3b
Saeki *et al*.[37]	Fukuoka	1997	RCC	13	7	6	3b
Schiff *et al*.[36]	Boston, MA	2005	RCS	31	27	4	4
Shaikh & Muneer[35]	Sindh	2009	RCS	20	20	0	4
Sleeman *et al*.[34]	Miami, FL	1998	RCS	25	25	0	4
Tuech *et al*.[33]	Angers	2002	RCS	26	26	0	4
Urban *et al*.[32]	Cleveland, OH	2001	RCS	15	15	0	4
Van Landingham[31]	Temple, TX	1984	RCS	7	ND	7	4
Yeh *et al*.[30]	Taoyuan	2002	RCS	226	226	0	4
Yerdel *et al*.[29]	Ankara	1997	PCC	14	7	7	3b

[a]Oxford Centre for Evidence-Based Medicine level of evidence scale.
LC, laparoscopic cholecystectomy; OC, open cholecystectomy; RCS, retrospective case series; PCC, prospective case–control study; RCC, retrospective case–control study; RCT, randomized controlled trial; PCS, prospective case series; ND, no data.

Table 2 Summary of outcome measures for laparoscopic and open cholecystectomy in cirrhosis

Outcome	Laparoscopic cholecystectomy	Open cholecystectomy
Number of patients	1756	249
Mortality rate, % (deaths/number at risk)	0.8% (13/1623)	2.0% (5/249)
Stratified mortality[a] (A/B/C)	4/1/1	ND
Mean age ± SE, years	52.6 ± 1.2	50.2 ± 3.2
Sex, male/female	804/759	103/67
Severity of liver disease[a], Child–Pugh class A/B/C	915/260/19	117/50/7
Indication for surgery, % AC (number AC/number at risk)	19.6% (283/1442)	28.8% (19/66)
Conversion rate, % (conversion/number at risk)	5.8% (98/1698)	ND
Overall complications, % (events/number at risk)	17.6% (304/1729)	47.7% (103/216)
Infectious complications, % (events/number at risk)	5.9% (100/1729)	19.9% (43/216)
Postoperative hepatic insufficiency, % (events/number at risk)	7.7% (133/1729)	18.1% (39/216)

[a]Child–Pugh status stratified as A/B/C.
SE, standard error; AC, acute cholecystitis; ND, no data.

1992 NIH consensus statement,[68] has an impact on surgical outcomes. There are few data pertaining to patients with Child–Pugh class C cirrhosis; however, the review and meta-analysis shows that for patients of Child–Pugh class A or B status, LC appears to be associated with reduced complication rates, shorter operative time and reduced LoS. In 1982 Aranha *et al.* described a 25.5% mortality rate in patients with cirrhosis undergoing cholecystectomy.[9] During the dissemination of LC technique, concern about the safety of the procedure in cirrhosis was coloured by such data from the era of open surgery. Certainly, patients with chronic liver disease are at increased risk for mortality when undergoing abdominal surgery.[69–71] Cholecystectomy in particular may be more hazardous in cirrhosis because of haemorrhage related to portal hypertension, coagulopathy and thrombocytopenia. In addition, the reduced compliance of the fibrotic liver may make the retraction and exposure of Calot's triangle more difficult laparoscopically.[72] It was therefore posited that the benefits of laparoscopic surgery in terms of postoperative recovery[5] would be offset by the greater risk for complications associated with the lesser degree of tactile control[73] and three-dimensional feedback.[74]

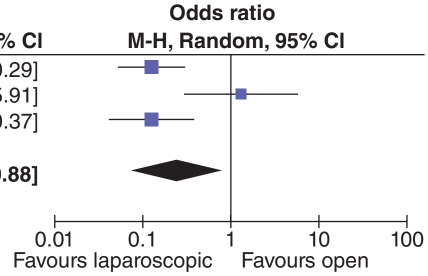
The quality of the evidence comparing the outcomes of LC and OC is poor. The majority of the data are derived from case series; only three small RCTs have been published. In this systematic review, the data from all studies were pooled as if the combined findings were derived from a single sample, but statistical analyses were not applied. The application of any formal meta-analytic methods, particularly simple pooling, to observational studies is associated with a significant risk for error and for biased conclusions, but it does provide an indication of real-world outcomes.[75] Given that combining data by meta-analytic methods is preferable,[76] only data from the RCTs were combined. However, it must be acknowledged that the RCTs included in this review each include a small number of patients and, indeed, heterogeneity is evident in meta-analytic statistical measures (I^2 statistic). This heterogeneity is probably attributable to differences in the patient samples (such as in the severity of liver disease and the proportion of patients with acute cholecystitis), interventions (use of subtotal cholecystectomy and conversion to OC), outcome assessments and reporting quality. Despite the aforementioned caveats, it appears that LC offers the cirrhotic patient a similar advantage over OC in terms of LoS as it does the non-cirrhotic patient.[5] In contradistinction to the non-cirrhotic population undergoing cholecystectomy, this meta-analysis suggests that overall complications and infectious complications may be fewer in LC than in OC in cirrhosis.

Given that conversion to OC is always an option, LC in cirrhosis should be at least as safe as *ab initio* open surgery provided that the surgeon who starts the procedure laparoscopically has a range of safe options available if problems arise intraoperatively. Commonly discussed options include laparoscopic subtotal[39,77–79] and partial[80] cholecystectomy, which have been used successfully to circumvent the hazards associated with dissection in the cirrhotic liver bed and around the porta hepatis. Other options include laparoscopic cholecystostomy[81] and percutaneous transhepatic cholecystostomy.[82,83] Ultimately, conversion to an open procedure remains a fall-back option when safe dissection, visualization of anatomy or control of haemorrhage become impossible laparoscopically. In this review, conversion from LC represented a reasonably frequently used option and occurred in about 5% of procedures. Although an increase in morbidity may be associated with the occasional conversion to open surgery compared with cases completed laparoscopically,[84] it seems intuitive that this morbidity will be lower than that caused by a policy of universal OC *ab initio*, provided that minimal complications arise in the preliminary laparoscopic dissection.

In the current analysis, the mortality rates reported for both LC and OC are substantially lower than those reported for OC in the 1980s. This probably reflects improvements in patient selection and critical care, better treatment of liver failure (particularly liver transplantation), and the availability of a variety of non-surgical

Study or subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds ratio M-H, Random, 95% CI
El-Awadi *et al.* 2009	12	55	38	55	37.4%	0.12 [0.05, 0.29]
Hamad *et al.* 2010	6	15	5	15	27.9%	1.33 [0.30, 5.91]
Ji *et al.* 2005	7	42	23	38	34.7%	0.13 [0.05, 0.37]
Total (95% CI)		**112**		**108**	**100.0%**	**0.25 [0.07, 0.88]**
Total events	25		66			

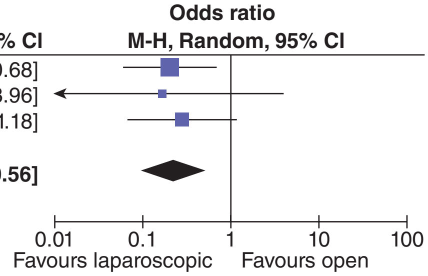
Heterogeneity: Tau^2 = 0.94; Chi^2 = 8.01, d.f. = 2 (P = 0.02); I^2 = 75%
Test for overall effect: Z = 2.16 (P = 0.03)



(a)

Study or subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds ratio M-H, Random, 95% CI
El-Awadi *et al.* 2009	4	55	15	55	54.3%	0.21 [0.06, 0.68]
Hamad *et al.* 2010	0	15	2	15	7.7%	0.17 [0.01, 3.96]
Ji *et al.* 2005	3	42	8	38	37.9%	0.29 [0.07, 1.18]
Total (95% CI)		**112**		**108**	**100.0%**	**0.23 [0.10, 0.56]**
Total events	7		25			

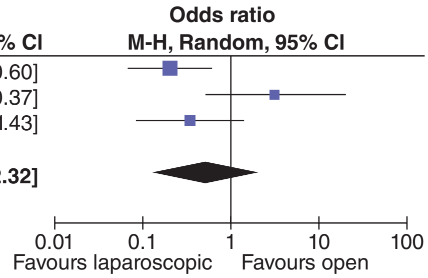
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.15, d.f. = 2 (P = 0.93); I^2 = 0%
Test for overall effect: Z = 3.29 (P = 0.001)



(b)

Study or subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds ratio M-H, Random, 95% CI
El-Awadi *et al.* 2009	5	55	18	55	38.7%	0.21 [0.07, 0.60]
Hamad *et al.* 2010	5	15	2	15	27.9%	3.25 [0.52, 20.37]
Ji *et al.* 2005	3	42	7	38	33.5%	0.34 [0.08, 1.43]
Total (95% CI)		**112**		**108**	**100.0%**	**0.53 [0.12, 2.32]**
Total events	7		25			

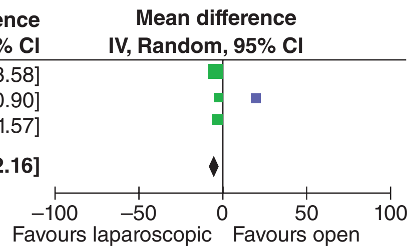
Heterogeneity: Tau^2 = 1.18; Chi^2 = 6.53, d.f. = 2 (P = 0.04); I^2 = 69%
Test for overall effect: Z = 0.85 (P = 0.40)



(c)

Study or subgroup	Laparoscopic Mean	Laparoscopic SD	Laparoscopic Total	Open Mean	Open SD	Open Total	Weight	Mean difference IV, Random, 95% CI
El-Awadi *et al.* 2009	1.87	1.11	55	6	1.74	55	43.9%	–4.13 [–4.68, –3.58]
Hamad *et al.* 2010	2.1	2.1	15	4.5	2.1	15	26.6%	–2.40 [–3.90, –0.90]
Ji *et al.* 2005	4.6	2.4	42	7.5	3.5	38	29.5%	–2.90 [–4.23, –1.57]
Total (95% CI)			**112**			**108**	**100.0%**	**–3.31 [–4.46, –2.16]**

Heterogeneity: Tau^2 = 0.70; Chi^2 = 6.50, d.f. = 2 (P = 0.04); I^2 = 69%
Test for overall effect: Z = 5.65 (P < 0.00001)



(d)

Figure 2 Forest plots illustrating meta-analyses of outcomes in patients with cirrhosis undergoing cholecystectomy by laparoscopic or open surgery. Outcomes analysed were: (a) total postoperative complications, (b) infectious complications, (c) postoperative hepatic insufficiency and (d) length of hospital stay. M–H, Mantel–Haenszel test; 95% CI, 95% confidence interval

options (such as percutaneous cholecystostomy and ERCP) for the high-risk cirrhotic patient. There are relatively few data about the outcome of cholecystectomy in Child–Pugh class C cirrhosis as only 26 patients with this disease class were included in this review, but this group was over-represented amongst the mortalities. Although mortality rates as high as 25% were reported for OC in cirrhosis as recently as the 1980s,[9] this analysis of the literature found no reports of death in OC in the cirrhotic population during the era of LC. Clearly, therefore, the dramatic reduction in mortality in cholecystectomy in cirrhosis after LC became commonplace was not associated with the introduction of minimally invasive surgery, but, rather, with other changes in the assessment and management of both chronic liver disease and gallstones. Previously, a considerable proportion of patients with significant jaundice underwent OC and, subsequently, open bile duct exploration and drainage procedures. Often these explorations were not therapeutic as the jaundice was presumably related to the decompensation of chronic liver disease and not obstruction.[6,8,18–22] This type of scenario has become uncommon since the accuracy of imaging[85,86] and efficacy of endoscopic intervention[87,88] have improved and percutaneous biliary interventions have become available.[83,89,90] More generally, the death rate from chronic liver disease has changed substantially coincident with the introduction of LC.[91,92] Moreover, a significant proportion of the change in mortality in patients with chronic liver disease undergoing surgery is likely to be attributable to the widespread introduction of liver transplantation in the mid-1980s[93] and the impact this has had on techniques for managing liver failure and portal hypertension. The greatest danger of mortality in cholecystectomy refers to patients with decompensated liver disease. The most critical factors in avoiding death are, therefore, appropriate diagnosis and treatment of the underlying chronic liver disease, judicious selection of patients for surgery and use of non-surgical temporization measures for patients in whom the level of risk prohibits operative procedures.

Conflicts of interest

None declared.

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