

Meta-analysis of laparoscopic vs open cholecystectomy in elderly patients

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dom-effects model was applied to synthesize outcome data.

RESULTS: Out of a total of 337 records, thirteen articles (2 randomized and 11 observational studies) reporting on the outcome of 101559 patients (48195 in the laparoscopic and 53364 in the open treatment group, respectively) were identified. Odds ratios (OR) were constantly in favor of laparoscopic surgery, in terms of mortality (1.0% vs 4.4%, OR = 0.24, 95%CI: 0.17-0.35, $P < 0.00001$), morbidity (11.5% vs 21.3%, OR = 0.44, 95%CI: 0.33-0.59, $P < 0.00001$), cardiac (0.6% vs 1.2%, OR = 0.55, 95%CI: 0.38-0.80, $P = 0.002$) and respiratory complications (2.8% vs 5.0%, OR = 0.55, 95%CI: 0.51-0.60, $P < 0.00001$). Critical analysis of solid study data, demonstrated a trend towards improved outcomes for the laparoscopic concept, when adjusted for age and co-morbid diseases.

CONCLUSION: Further high-quality evidence is necessary to draw definite conclusions, although best-available evidence supports the selective use of laparoscopy in this patient population.

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Abstract

AIM: To investigate the comparative effect of laparoscopic and open cholecystectomy in elderly patients.

METHODS: Laparoscopic cholecystectomy has induced a revolution in the treatment of gallbladder disease. Nevertheless, surgeons have been reluctant to implement the concepts of minimally invasive surgery in older patients. A systematic review of Medline was embarked on, up to June 2013. Studies which provided outcome data on patients aged 65 years or older, subjected to laparoscopic or open cholecystectomy were considered. Mortality, morbidity, cardiac and pulmonary complications were the outcome measures of treatment effect. The methodological quality of selected studies was appraised using valid assessment tools. The ran-

Key words: Laparoscopic; Open cholecystectomy; Surgery; Elderly; Older; Geriatric; Complications; Mortality; Morbidity

Core tip: This systematic review and meta-analysis investigates the comparative effect of laparoscopic and open cholecystectomy in elderly patients. Critical analysis of solid study data, demonstrated a trend towards improved outcomes for the laparoscopic concept, when adjusted for age and co-morbid diseases. Current data do not definitively support the use of laparoscopic or open cholecystectomy on older patients. Further high-quality evidence is necessary to draw definite conclusions, although best-available evidence supports the elective use of laparoscopy in this patient population.

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INTRODUCTION

Laparoscopic surgery has induced a tremendous revolution in the treatment of gallbladder disease. Surgery has been traditionally considered the last therapeutic resort for symptomatic cholelithiasis before the advent of laparoscopy, whereas lithotripsy and cholecystostomy have been commonly favored as less invasive alternatives^[1]. In the era of minimally invasive surgery, indications for surgery have become more liberal, resulting in an enormous rise in the number of laparoscopic cholecystectomies performed annually^[2]. The laparoscopic procedure has been shown to offer the advantages of decreased pain, shorter convalescence, reduced operative stress and limited inflammatory response^[3].

Despite these merits, the surgical community has been reluctant to implement the laparoscopic approach in the elderly population. Data from population-based studies suggest that 21% to 55% of geriatric patients in the United States are still subjected to open cholecystectomy^[4-7]. These figures largely derive from as-treated analyses, however they reflect a defensive operative position against this patient population, which commonly presents with acute or chronic recurrent cholecystitis, gallbladder empyema or hydrops. Although the role of laparoscopy in the treatment of a wide spectrum of gallbladder pathology has been well established^[8,9], this conservative surgical trend suggest that the outcomes of laparoscopic cholecystectomy in the geriatric patient population have been inadequately defined.

The present paper is a systematic review of current literature, aiming at identifying comparative evidence between laparoscopic and open cholecystectomy in the elderly. Operative results are approached statistically, using valid meta-analytical models. A critical discussion of results attempts to determine the strengths and limitations of available data, in order to evaluate the quality of evidence and identify areas of future research.

MATERIALS AND METHODS

Two investigators established the study protocol, which defined the objectives of the study, the search and abstracting design, inclusion and exclusion criteria and methodology of analysis. The protocol conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement^[10], and the Meta-analysis Of Observational Studies in Epidemiology guidelines^[11]. This study is part of a project investigating the comparative effect of various laparoscopic procedures in geriatric

patients.

Eligibility criteria

Prospective and retrospective studies which provided outcome data on patients aged 65 years or older, who were subjected to either laparoscopic or open cholecystectomy were considered for inclusion. Studies reporting on at least one of the outcome measures were included. Articles not containing distinct data for patients 65 years or older, or not reporting on any of the outcome measures were discarded.

Outcome measures

Mortality was the primary outcome measure of treatment effect. Secondary outcome measures included cardiac complications, pulmonary complications, and overall morbidity.

Search strategy and study selection

The literature search was performed in collaboration with a clinical librarian. The database of the National Library of Medicine (Medline, provider PubMed) was searched without date restrictions. Limits were applied with regard to age (65+ years), language (English, German), and text availability (abstract available). The terms laparoscopy, laparotomy, open, conventional, aged, elderly, older, sexagenarian, septuagenarian, octogenarian, nonagenarian, postoperative complication, morbidity, death, and mortality were combined using the Boolean operators AND or OR. The search strategy protocol is available upon request. Date of the last screening was June 11, 2013. Titles and abstracts were scrutinized to identify potentially eligible articles. The full texts of studies considered to contain data predetermined by the protocol were obtained. First-level and second level screening was performed by two independent authors in an unblinded manner (Antoniou SA, Antoniou GA). Disagreements were resolved by discussion.

Data collection

An electronic database based on the Cochrane Consumers and Communication Review Group's data extraction template was pilot-tested on the three most recent studies and refined accordingly. Data were collected on study characteristics, name of first author, year of publication, patient recruitment period, study design, total number of patients, number of patients in the laparoscopic and the open arm, age limit, mean or median age of the study population, standard deviation or range, method of analysis (intention to treat/as treated) and the outcome measures as outlined above. Cardiac complications were considered the following: myocardial infarction, myocardial ischemia, arrhythmia, cardiac failure, or the terms "cardiovascular complications or morbidity". Respiratory complications were considered atelectasia, pneumonia, adult respiratory distress syndrome, pleural effusion, or the terms "respiratory or pulmonary failure", "respiratory or pulmonary insufficiency", or "pulmonary morbidity".

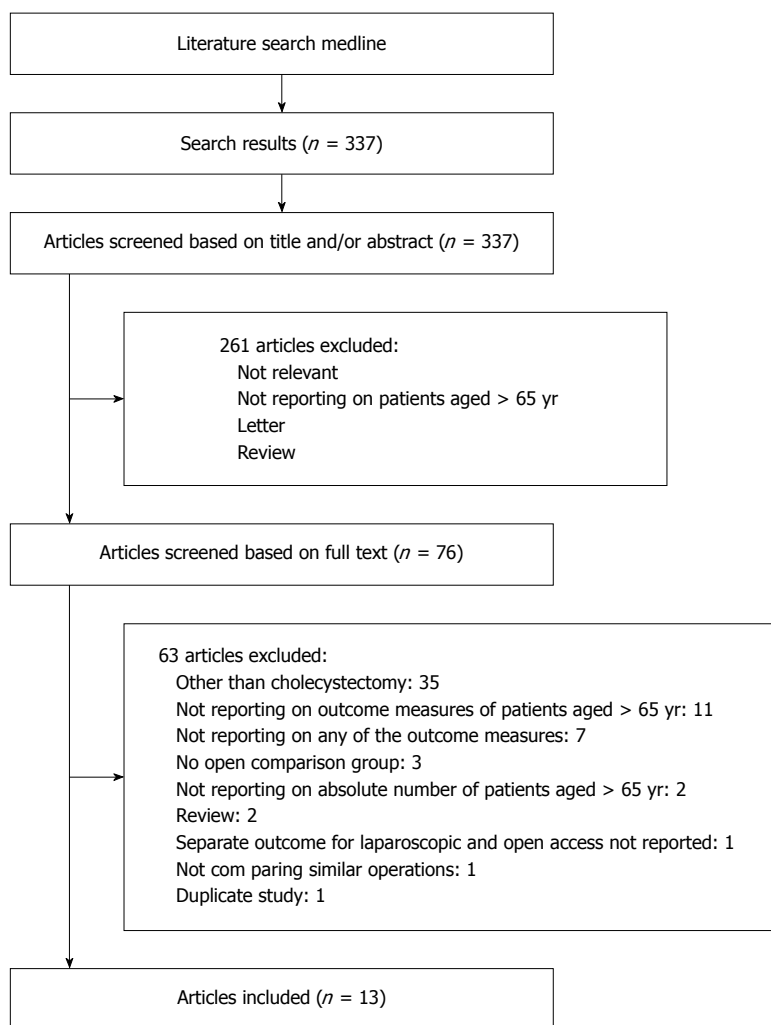


Figure 1 Search history and selection of studies.

Quality assessment

Randomized trials were subjected to methodological quality assessment according to the Cochrane Collaboration's Tool for assessing risk of bias^[12]. This tool considers the sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, inadequately reported or missing outcome data, selective outcome reporting, and other potential threats to validity.

The quality of observational studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for case control studies or cohort studies (as applicable)^[13]. This tool evaluates three main methodological elements of case-control studies: selection methods (adequate case definition, representativeness of the cases, appropriate selection and definition of controls), comparability of cases and controls on the basis of the design or analysis, and assessment of exposure (ascertainment of exposure, non-response rate). The scale uses a star system, with a maximum of nine stars; studies achieving ≥ 6 stars were considered to be of higher quality.

Statistical analysis

Individual study odds ratios (ORs) and 95%CI were calculated from event numbers extracted from each study

before data pooling. In calculation of the OR, the total number of patients assigned in each group was used as the denominator. Summary estimates of ORs were obtained with a random effects model according to DerSimonian and Laird^[14]. Heterogeneity was assessed using the I^2 statistic, a method expressing the percentage of variation across studies. I^2 values between 0% and 25% suggest low level, values above 25% suggest moderate level, and values above 75% suggest high level of heterogeneity. Publication bias was assessed visually evaluating the symmetry of funnel plots. Statistical analysis was performed using RevMan (Review Manager 5.2, The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical expertise was available and it was provided by one of the study authors (Antoniou GA).

RESULTS

Search results

A total of 337 records were identified by the primary search of the electronic database. The first level screening identified 76 potentially eligible articles. Full text review excluded 63 articles. Thirteen articles fulfilled the

Table 1 Study characteristics

Ref.	Year	Study design	Period	Patients (n) (lap/open)	Age	Investigated outcomes	ITT/AT	NOS
Massie <i>et al</i> ^[15]	1993	Retrospective	1990-1991	58 (33/25)	> 70	Morbidity	NR	3
Feldman <i>et al</i> ^[4]	1994	Prospective database ¹	1988-1992	2269 (1508/761)	> 65	Mortality	NR	4
Lucier <i>et al</i> ^[5]	1995	Prospective database ²	1991-1992	3907 (1769/2138)	> 65 (mean 73.9 lap, 75.4 open)	Morbidity, mortality, cardiac, respiratory	NR	3
Samkoff <i>et al</i> ^[6]	1995	Prospective database ³	1992-1993	63920 (29731/34189)	> 65	Morbidity, mortality, respiratory	NR	3
Huang <i>et al</i> ^[16]	1996	RCT	1992-1993	27 (15/12)	> 70	Morbidity, mortality, cardiac, respiratory	NA	NA
Lujan <i>et al</i> ^[17]	1998	RCT	1991-1996	264 (133/131)	> 65 [median 71 (65-87) lap, 72 (65-88) open]	Morbidity, mortality, respiratory	NR	NA
Maxwell <i>et al</i> ^[18]	1998	Prospective database ⁴	1988-1992	18500 (5034/13466)	> 80 (mean, 83.9 lap, 84.0 open)	Mortality	NR	4
Pessaux <i>et al</i> ^[19]	2001	Prospective	1992-1999	139 (50/89)	> 75 [mean 81.9 (75-98) lap, 81.9 (75-93) open]	Morbidity, mortality, cardiac, respiratory	NR	7
Fisichella <i>et al</i> ^[20]	2002	Retrospective	1995-1998	35 (24/11)	> 70 (mean 74 ± 2.4 lap, 74 ± 4.1 open)	Morbidity, mortality, cardiac, respiratory	ITT	4
Chau <i>et al</i> ^[21]	2002	Retrospective	1994-1999	73 (31/42)	> 75 (mean 79.2 ± 4.2 lap, 80.7 ± 4.6 open)	Morbidity, mortality, cardiac, respiratory	ITT	5
Moyson <i>et al</i> ^[22]	2008	Retrospective	1991-2007	100 (85/15)	> 75 [median 83 (75-94)]	Mortality, morbidity	AT	5
Leardi <i>et al</i> ^[23]	2009	Retrospective	2000-2006	341 (258/83)	> 70	Morbidity	NR	4
Tucker <i>et al</i> ^[7]	2011	Prospective database ⁵	2005-2008	11926 (9524/2402)	> 65 [median 73.0 (69-79)]	Mortality, morbidity, cardiac, respiratory	AT	4

¹Connecticut Health Information and Management Exchange; ²Medicare database Indiana; ³8-State Medicare Database; ⁴Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project-3; ⁵American College of Surgeons Quality Insurance Program ACS NSQIP. ITT: Intention-to-treat; NOS: None otherwise specified; NA: Not available; NR: Not reported; AT: As treated analysis.

Table 2 Study outcomes

Ref.	Conversion	Mortality	Morbidity	Cardiac	Respiratory
Massie <i>et al</i> ^[15]	NR	NR	4/33 lap 19/66 open	NR	NR
Feldman <i>et al</i> ^[4]	NR	7/1508 lap 11/761 open	NR	NR	NR
Lucier <i>et al</i> ^[5]	NR	16/1769 lap 116/2138 open	200/1769 lap 354/2138 open	17/1769 lap 26/2138 open	25/1769 lap 64/2138 open
Samkoff <i>et al</i> ^[6]	NR	252/29731 lap 1523/34189 open	3428/29731 lap 7361/34189 open	NR	871/29731 lap 1751/34189 open
Huang <i>et al</i> ^[16]	0 / 15 (0%)	0/15 lap 0/12 open	0/15 lap 3/12 open	0/15 lap 0/12 open	0/15 lap 1/12 open
Lujan <i>et al</i> ^[17]	11/113 (9.7%)	0/133 lap 1/131 open	18/133 lap 29/131 open	NR	0/133 lap 5/131 open
Maxwell <i>et al</i> ^[18]	NR	91/5034 lap 593/13466 open	NR	NR	NR
Pessaux ^[19]	16/50 (32%)	0/50 lap 4/89 open	9/50 lap 19/89 open	0/50 lap 2/89 lap	1/50 lap 2/89 open
Fisichella <i>et al</i> ^[20]	2/24 (8.3%)	0/24 lap 0/11 open	3/24 lap 6/11 open	0/24 lap 0/11 open	0/24 lap 0/11 open
Chau <i>et al</i> ^[21]	11/31 (35.5%)	0/31 lap 3/42 open	4/31 lap 17/42 open	0/31 lap 4/42 open	1/31 lap 6/42 open
Moyson <i>et al</i> ^[22]	12/85 (14.1%)	3/73 lap 5/27 open	19/73 lap 14/15 open	NR	NR
Leardi <i>et al</i> ^[23]	16/158 (10.1%)	NR	12/258 lap 14/83 open	NR	NR
Tucker <i>et al</i> ^[7]	728/9529 (7.6%)	67/9524 lap 65/2402 open	NR	48/9524 lap 26/2402 open	76/9524 lap 87/2402 open

NR: Not reported.

selection criteria and were included in the analysis^[4-7,15-23]. Figure 1 summarizes the search history.

Study characteristics

Two randomized studies and 11 observational studies were identified (Table 1). The study population consisted of 101559 patients; 48195 in the laparoscopic treatment group and 53364 in the open treatment group. Eleven articles reported on mortality rates, 10 reported on overall morbidity, 6 reported on cardiac complications and 8 reported on respiratory complications (Table 2). The two randomized trials were of poor quality, because they did not provide adequate information to permit judgment on any of the quality parameters (quality assessment of randomized trials available upon request). Only one observational study achieved a NOS score of 6 or more; sensitivity analysis of quality reports could thus not be undertaken. Age, American Society of Anesthesiologists (ASA) score and/or cardiopulmonary co-morbidities were similar in both treatment arms in 3 studies only; a planned sensitivity analysis including these data was thus not performed.

Synthesis of outcome

Mortality was 1.0% for the laparoscopic approach and 4.4% for the open approach (OR = 0.24, 95%CI: 0.17-0.35, $P < 0.00001$). High level of heterogeneity ($I^2 = 79\%$) and publication bias was evident (Figures 2A).

Morbidity rates were 11.5% and 21.3%, respectively (OR = 0.44, 95%CI: 0.33-0.59, $P < 0.00001$). Moderate heterogeneity existed ($I^2 = 67\%$), and strong evidence of publication bias (Figure 2B).

Cardiac complications occurred in 0.6% and 1.2% of the laparoscopic and the open patient population, respectively (OR = 0.55, 95%CI: 0.38-0.80, $P = 0.002$). Heterogeneity across studies was not evident ($I^2 = 0\%$) and the possibility for publication bias was low (Figures 2C).

Respiratory complications were registered in 2.8% and 5.0% of the laparoscopic and the open treatment arm, respectively (OR = 0.55, 95%CI: 0.51-0.60, $P < 0.00001$). There was no evidence of heterogeneity across studies ($I^2 = 0\%$) or publication bias (Figure 2D).

DISCUSSION

Comparative evidence on the application of laparoscopic cholecystectomy in elderly patients is not adequately robust to support or refute its routine use, according to analysis of currently available evidence. Although the effect sizes are indicative of a benefit for the laparoscopic approach, there are several shortcomings of the provided data, which need to be taken into account, before definite conclusions can be reached.

A significant limitation is introduced by the variety of criteria for inclusion among reports. Although eight of 13 studies predefined inclusion and exclusion criteria, which provides some homogeneity of the study population, selection bias regarding the stage of acute chole-

cystitis, the presence of sepsis, and co-morbid diseases cannot be eliminated. The open surgical approach may thus have been preferred more often in cases of complicated gallbladder disease or in the presence of significant co-morbidity. The spectrum of inclusion criteria and surgical trends is reflected in the moderate-to-high level of heterogeneity of the variables mortality and morbidity. Morbidity data from two available randomized studies, which provide homogeneity of patients and randomization of procedures, were in favor of laparoscopic cholecystectomy^[16,17]. Acute cholecystitis as inclusion criterion provided relative homogeneity of the study populations of three studies^[19,21,22], which all favored the laparoscopic approach. Similarly, when symptomatic cholecystolithiasis was considered as inclusion criterion, the results favored laparoscopic cholecystectomy^[16,17,20].

The majority of studies were of poor methodological quality, which may bias the results in favor of either approach. The study by Pessaux *et al.*^[19] was of high methodological quality, achieving seven of 8 NOS stars. The authors prospectively included 139 patients with acute cholecystitis over a 7-year period. They found a constant trend in favor of the laparoscopic arm considering the outcome measures of this analysis, although statistical significance was not reached. Three studies, which included patients with similar ASA score and/or cardiopulmonary disease^[16,19,21], all demonstrated reduced mortality, morbidity, and incidence of cardiac and respiratory complications.

Opposite to the above limitations of this analysis, its strengths allow for a rational interpretation of the results. The large number of patients, the variety of reports and the time of publication, ranging from the early years of laparoscopic cholecystectomy until recently, allow multifaceted representation of surgical trends. Based on the present published and anecdotal data, it cannot be overstated, that open surgery is being a persisting surgical practice in acute biliary operations of the geriatric patient population. Emerging evidence suggests decreased inflammatory response both in acute and elective laparoscopic cases as compared to open surgery^[24-26], which might adversely affect pulmonary function^[27]. This association becomes more important in the elderly, where functional reserves are decreased, and frequent co-morbidities make postoperative rehabilitation more complex^[28].

The role of percutaneous cholecystostomy in poor operative candidates may not be disregarded. With this treatment option, both life expectancy and co-morbid diseases need to be taken into account, because definite surgical treatment due to recurrent disease is necessary in a significant proportion of these patients^[29,30], whereas subsequent laparoscopic cholecystectomy is accompanied by acceptable technical success^[31,32], although difficulties may be encountered due to distorted anatomy.

The development of an evidence-based treatment protocol which considers factors as patient's age, co-morbidities, the present of complicated gallbladder disease

A

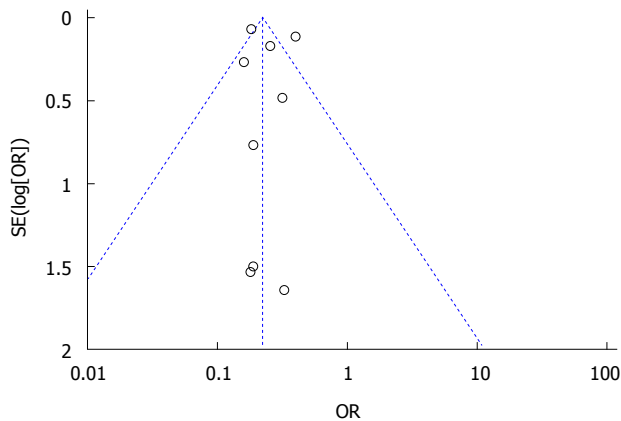
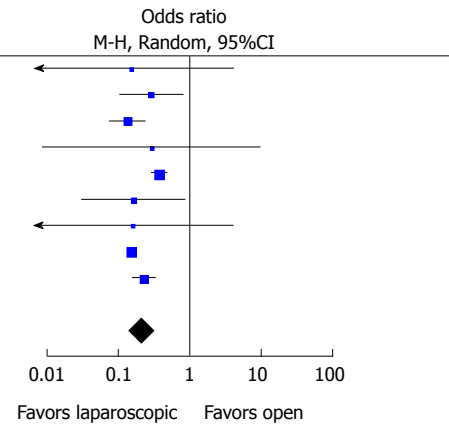
Study or subgroup	Laparoscopic		Open		Weight	Odds ratio M-H, Random, 95%CI
	Events	Total	Events	Total		
Chau CH 2002	0	31	3	42	1.5%	0.18 [0.01, 3.60]
Feldman MG 1994	7	1508	11	761	9.4%	0.32 [0.12, 0.82]
Lucier MR 1995	16	1769	116	2138	16.3%	0.16 [0.09, 0.27]
Lujan JA 1998	0	133	1	131	1.3%	0.33 [0.01, 8.07]
Maxwell JG 1998	91	5034	593	13466	22.0%	0.40 [0.32, 0.50]
Moyson J 2008	3	73	5	27	4.9%	0.19 [0.04, 0.85]
Pessaux P 2001	0	50	4	89	1.5%	0.19 [0.01, 3.57]
Samkoff JS 1995	252	29731	1523	34184	23.2%	0.18 [0.16, 0.21]
Tucker JJ 2011	67	9524	65	2402	19.9%	0.25 [0.18, 0.36]

Total (95%CI) 47853 53240 100.0% 0.24 [0.17, 0.35]

Total events 436 2321

Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 37.33$, $df = 8$ ($P < 0.0001$); $I^2 = 79\%$

Test for overall effect: $Z = 7.42$ ($P < 0.00001$)



B

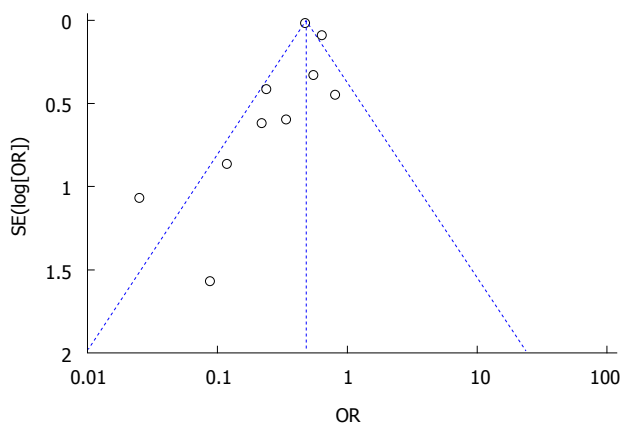
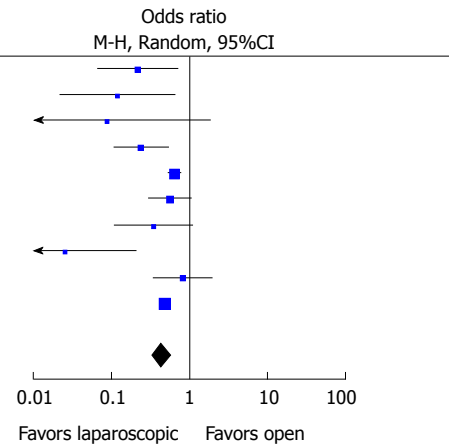
Study or subgroup	Laparoscopic		Open		Weight	Odds ratio M-H, Random, 95%CI
	Events	Total	Events	Total		
Chau CH 2002	4	31	17	42	4.6%	0.22 [0.06, 0.74]
Fischella PN 2002	3	24	6	11	2.6%	0.12 [0.02, 0.65]
Huang SM 1996	0	15	3	12	0.8%	0.09 [0.00, 1.89]
Leardi S 2009	12	258	14	83	8.7%	0.24 [0.11, 0.54]
Lucier MR 1995	200	1769	354	2138	26.9%	0.64 [0.53, 0.77]
Lujan JA 1998	18	133	29	131	11.8%	0.55 [0.29, 1.05]
Massie MT 1993	4	33	19	66	4.9%	0.34 [0.11, 1.10]
Moyson J 2008	19	73	14	15	1.7%	0.03 [0.00, 0.20]
Pessaux P 2001	9	50	19	89	7.8%	0.81 [0.33, 1.95]
Samkoff JS 1995	3428	29731	7361	34189	30.1%	0.47 [0.45, 0.50]

Total (95%CI) 32117 36776 100.0% 0.44 [0.33, 0.59]

Total events 3697 7836

Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 27.43$, $df = 9$ ($P = 0.001$); $I^2 = 67\%$

Test for overall effect: $Z = 5.63$ ($P < 0.00001$)



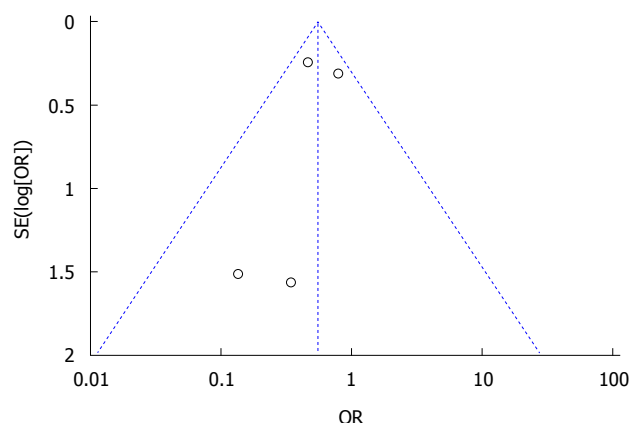
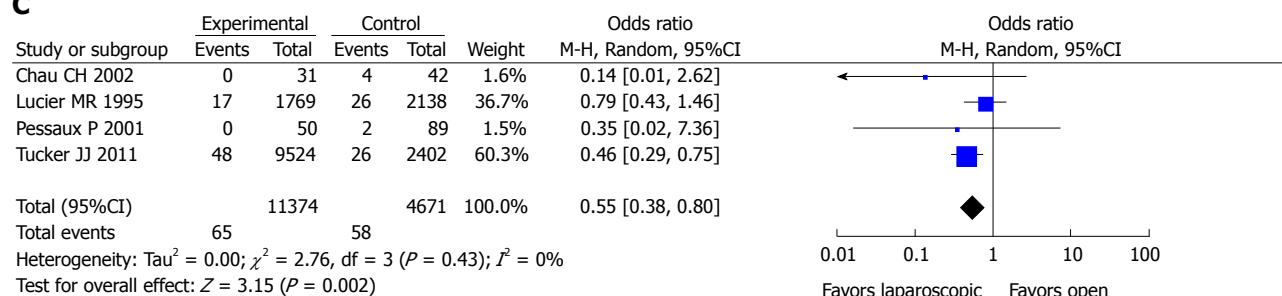
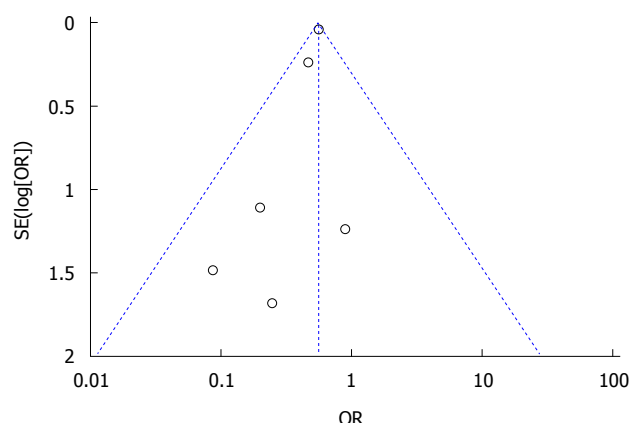
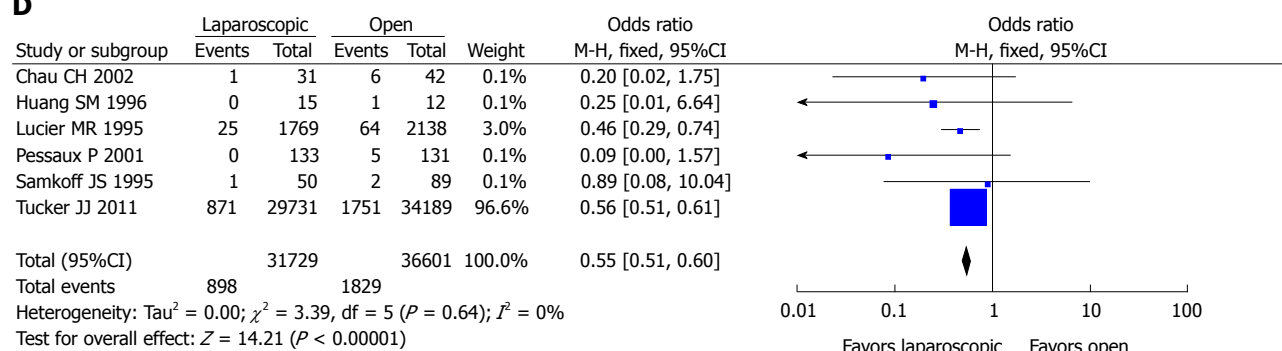
C

D


Figure 2 Forest plot of the odds ratio and funnel plot for the outcome. A: Mortality; B: Morbidity; C: Cardiac complications; D: Respiratory complications.

and previous operations is considered essential. Current data are inadequate to support routine use of laparoscopic cholecystectomy in elderly patients, although best

available evidence demonstrates a constant trend in favor of the laparoscopic approach in terms of mortality, morbidity, cardiac and respiratory complications in selected

cases.

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The authors are grateful to Ms. Aggeliki Zachou, clinical librarian, for her kind and continuous support.

COMMENTS

Background

Laparoscopic cholecystectomy has been established as the gold standard therapy for gallbladder disease. Population-based data suggest that elderly patients are more frequently subjected to open than laparoscopic cholecystectomy. The comparative treatment effect of these two approaches in elderly patients has been inadequately defined.

Research frontiers

Minimally invasive treatment modalities, such as percutaneous cholecystostomy and lithotripsy or definite surgical therapy by means of open cholecystectomy appear to be preferred by a significant proportion of surgeons. The well-defined beneficial comparative effects of laparoscopic over open surgery, such as minimization of trauma and inflammatory response, shorter convalescence and reduced respiratory compromise, may apply stronger to this frail patient population.

Innovations and breakthroughs

Early clinical evidence has suggested positive results for elderly patients in a variety of laparoscopic procedures. These data are fragmentary and mostly lack significant power. Due to the low morbidity and mortality of laparoscopic and open cholecystectomy, significant differences in treatment effects are often not detected. Cardiac and pulmonary morbidity are of paramount importance in elderly patients; the low incidence of these complications may result in underestimation of their association with the laparoscopic or the open treatment. Furthermore, concerns have been raised regarding the effect of pneumoperitoneum in elderly patients.

Applications

Best available evidence suggests lower mortality, overall morbidity, cardiac and pulmonary complications in elderly patients subjected to laparoscopic as compared to open cholecystectomy. For the application of laparoscopic cholecystectomy in elderly patients, co-existing factors, such as co-morbidities, the presence of complicated gallbladder disease and previous operations need to be taken into account.

Terminology

Laparoscopic cholecystectomy: The surgical procedure of removing the gallbladder by laparoscopy, that is, application of pneumoperitoneum and introduction of special instruments into the abdomen; pneumoperitoneum: Refers to the application of CO₂ gas into the peritoneal cavity, in order to perform a laparoscopic procedure.

Peer review

This is a generally well-written, scientifically sound and well-researched article. It includes a large number of patients in the included articles.

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