Original Article

Role of laparoscopic cholecystectomy in the management of chronic right upper quadrant pain due to biliary dyskinesia: a systematic review and meta-analysis

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Background: The objective of this study was to evaluate the surgical outcomes and feasibility of performing laparoscopic cholecystectomy (LC) in patients with longstanding right upper quadrant pain secondary to biliary dyskinesia.

Methods: A systematic review of the literature including published randomized, controlled trials, non-randomized trials and comparative trials of any type, reporting outcomes of LC in the management of chronic right upper quadrant pain in patients with biliary dyskinesia, using the principles of meta-analysis on RevMan 5.3 statistical software, was undertaken.

Results: Thirteen studies including 740 patients evaluating the symptomatic improvement following LC in patients with biliary dyskinesia presenting as chronic right upper quadrant pain were included. There were 542 patients in LC group and 198 patients in Non-LC group. Successful complete resolution of symptoms was more likely to be achieved in LC group [risk ratio (RR), 0.21; 95% confidence interval (CI), 0.09–0.50, P=0.0005]. In addition, the risk of failure to resolve symptoms (risk ratio, 0.15; 95% CI, 0.05–0.39, P=0.0001) was lower in LC group.

Conclusions: LC may be considered as an acceptable surgical intervention in patients with biliary dyskinesia presenting with chronic right upper quadrant pain. Currently there is insufficient evidence to recommend the routine use of LC in every patient with biliary dyskinesia. Paucity of high power randomised, controlled trials is the major reason for this lack of evidence which should be addressed soon and until then current study may be used to provide the basis for offering LC in selected group of patients.

Keywords: Laparoscopic; cholecystectomy; gallbladder; RUQ pain; biliary dyskinesia

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Introduction

Biliary dyskinesia is a gallbladder motility disorder associated in majority of patients with right upper quadrant abdominal pain (1,2). This pain mimics biliary colic except the patients do not have gallstones on abdominal ultrasonography or magnetic resonance cholangiopancreatography, or other conditions that could usually cause pain in this area such as peptic ulcer disease, pancreatitis and colonic diverticular disease (2). The cholescintigraphy has been used to aid in the diagnosis of biliary dyskinesia (3,4), favouring it when gallbladder ejection fraction is low (traditionally <35%) (5). Biliary dyskinesia is a less clearly defined term (6). The am-

biguity in diagnosing this condition, a lack of consistency in its management, and the background of its significant presence in the community (up to 21% in females); all these make it an issue that burdens both economy and health-care resources (7). Laparoscopic cholecystectomy (LC) has been performed for biliary dyskinesia with varying degrees of success. Several studies have reported significant improvement of symptoms in patients undergoing cholecystectomy than those who did not (8-10). This review is an attempt to answer several questions related to the surgical management of biliary dyskinesia.

The objective of this study is to evaluate the surgical outcomes and feasibility of performing LC in patients with longstanding right upper quadrant pain due to biliary dyskinesia.

Methods

Data sources and search strategy

A search of customary medical electronic databases such as MEDLINE, EMBASE, and Cochrane Library for randomized, controlled trials and other comparative studies was conducted. The medical subject headings (MeSH) search terms reported in the Medline library relevant to the target subject were used to select relevant studies. These included "acalculous biliary pain", "biliary dyskinesia", "cholescintigraphy", "functional gallbladder disorders", "laparoscopic cholecystectomy" and "right upper quadrant pain". The limitations for language, gender, age, sample size and place of study origin were removed from the search engine. Boolean operators (AND, OR, NOT) were used to narrow and widen the resulting outcomes of search results. The published titles from the search results were screened appropriately and their inclusion or exclusion was determined according to the predefined criteria. In addition, the reference list from the selected articles was also scrutinized as a further search tool to find additional trials.

Study selection

For inclusion in the meta-analysis, a study had to meet the following criteria: (I) a randomised, or non-randomised, controlled trial; (II) comparison between LC and non-cholecystectomy group (NLC); (III) the reported follow-up to evaluate the resolution of symptoms following intervention. All trials, case reports, reviews and abstracts with inadequate data or not meeting the above-mentioned inclusion criteria were excluded from the study.

Data extraction

Two independent reviewers (S Rehman and MS Sajid), using a predefined meta-analysis form, extracted data from each study which resulted in a high and satisfactory inter-observer agreement. The documented variables in the pre-defined meta-analysis profroma were the name of the authors, the title of the study, the journal in which the study was published, the country and year of the study, intervention regimen, no-intervention regimen, the length of the therapy, testing sample size (with sex differentiation if applicable), the number of patients receiving each regimen within the group, the number of patients who succeeded and failed the allocated treatment, the patient compliance rate in each group, the number of patients reporting complications and the number of patients with absence of complications in each arm. Third reviewer (KK Singh) confirmed the data and all three reviewers discussed the results and, if discrepancies were present, a consensus was reached.

Data synthesis and statistical analysis

The software package RevMan 5.3 (11,12), provided by the Cochrane Collaboration, was used for the statistical analysis to achieve a combined outcome. The risk ratio (RR) with a 95 per cent confidence interval (CI) was calculated for binary data, and the standardised mean difference (SMD) with a 95 per cent CI was calculated in case of continuous data variables. The random-effects model (13-15) was used to calculate the outcomes of variables. Heterogeneity was explored using the chi^2 test, with significance set at $P<0.05$, and was quantified (16) using I^2, with a maximum value of 30 per cent identifying low heterogeneity, up to 66% suggesting moderate heterogeneity and more than 66% suggesting significant heterogeneity (17). The Mantel-Haenszel method was used for the calculation of RR under the random effect models (18). In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either the treatment or control group, according to the method recommended by Deeks *et al.* (18). If the standard deviation was not available then it was calculated according to the guidelines of the Cochrane Collaboration (19). This process involved assumptions that both groups had the same variance, which may not have

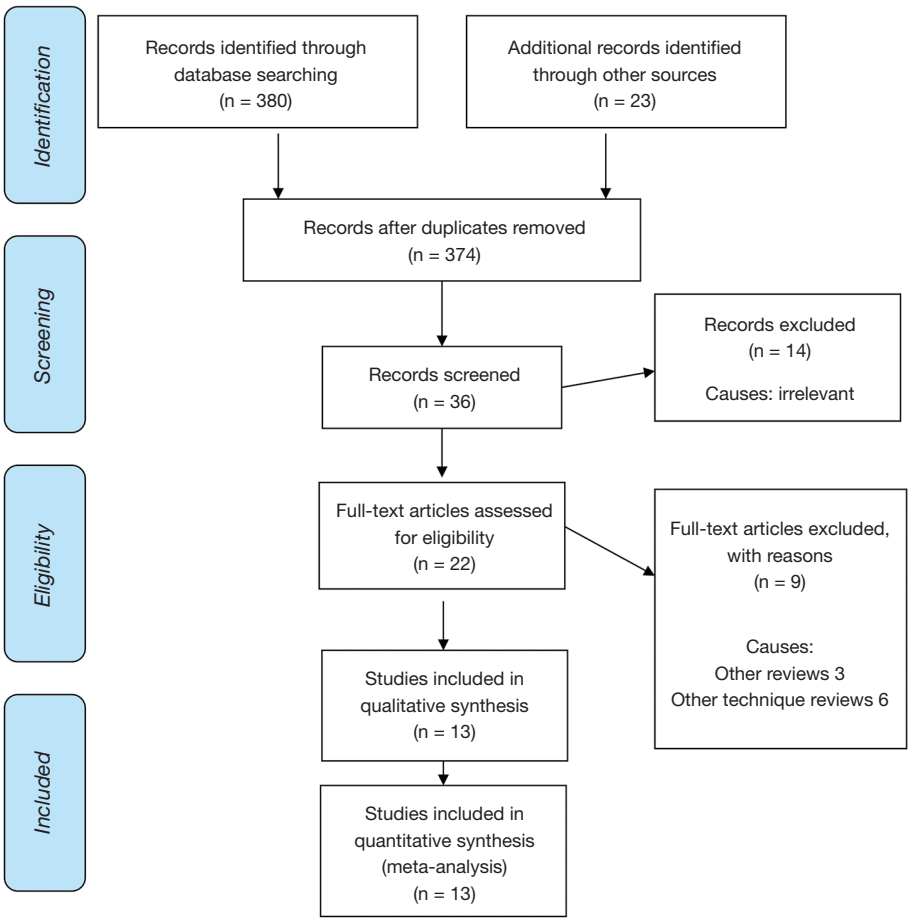

Figure 1 PRISMA flow diagram.

been true, and variance was either estimated from the range or from the p-value. The estimate of the difference between both techniques was pooled, depending upon the effect weights in results, determined by each trial estimated variance. A forest plot was used for the graphical display of the results. The square around the estimate stood for the accuracy of the estimation (sample size), and the horizontal line represented the 95% CI. The methodological quality of the included randomised trials was initially assessed using the published guidelines of Jadad *et al.* and Chalmers *et al.* (20,21). Based on the quality of the included trials, the strength and summary of the evidence was further evaluated by GradePro® (22), a tool provided by the Cochrane Collaboration.

Endpoints

Complete resolution of symptoms was analysed as the primary endpoint in this study. Secondary endpoints included partial resolution and no-resolution of symptoms.

Results

The PRISMA flow chart to explain the literature search strategy and trial selection is given in *Figure 1*. Thirteen studies (two randomised, controlled trials and 11 comparative studies) (23-35) recruiting 740 patients were retrieved from the search of medical electronic databases. There were 542 patients in the LC group and 198 patients in the NLC group. The characteristics of the included trials are given in *Table S1*.

Methodological quality of included studies

According to Jadad *et al.* and Chalmers *et al.* (17,18), the quality of two included randomised trials was good due to

Laparoscopic cholecystectomy compared to no-cholecystectomy for biliary dyskinesia

Patient or population: patients with biliary dyskinesia
Settings: hospitalized patients
Intervention: Laparoscopic cholecystectomy
Comparison: no-cholecystectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence(GRADE)	Comments
	Assumed risk	Corresponding risk				
	No-cholecystectomy	Laparoscopic cholecystectomy				
Complete symptoms resolution Risk ratio Follow-up: 6-63 months	Study population		RR 0.21 (0.09 to 0.5)	740 (13 studies)	⊕⊖⊖⊖ very low	
	914 per 1000	192 per 1000 (82 to 457)				
	Moderate					
	1000 per 1000	210 per 1000 (90 to 500)				
Partial symptoms resolution risk ratio Follow-up: 6-63 months	Study population		RR 0.66 (0.33 to 1.32)	740 (13 studies)	⊕⊖⊖⊖ very low	
	338 per 1000	223 per 1000 (112 to 447)				
	Moderate					
	400 per 1000	264 per 1000 (132 to 528)				
No symptoms resolution Risk ratio Follow-up: 6-63 months	Study population		RR 0.15 (0.05 to 0.39)	740 (13 studies)	⊕⊖⊖⊖ very low	
	520 per 1000	78 per 1000 (26 to 203)				
	Moderate					
	333 per 1000	50 per 1000 (17 to 130)				

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 2 GradePro summary of evidence.

the satisfactory utilization of randomization techniques. In addition, there was adequate reporting of power calculation, allocation concealment and intention-to-treat analysis. The quality of retrospective and prospective comparative trials was moderate based upon their review as per Scottish Intercollegiate Guidelines Network (SIGN). Based on the quality of included studies, the strength and summary of evidence analysed on GradePro® (22) is given in *Figure 2* which is expected to be of low quality due to paucity of high powered randomised, controlled trials.

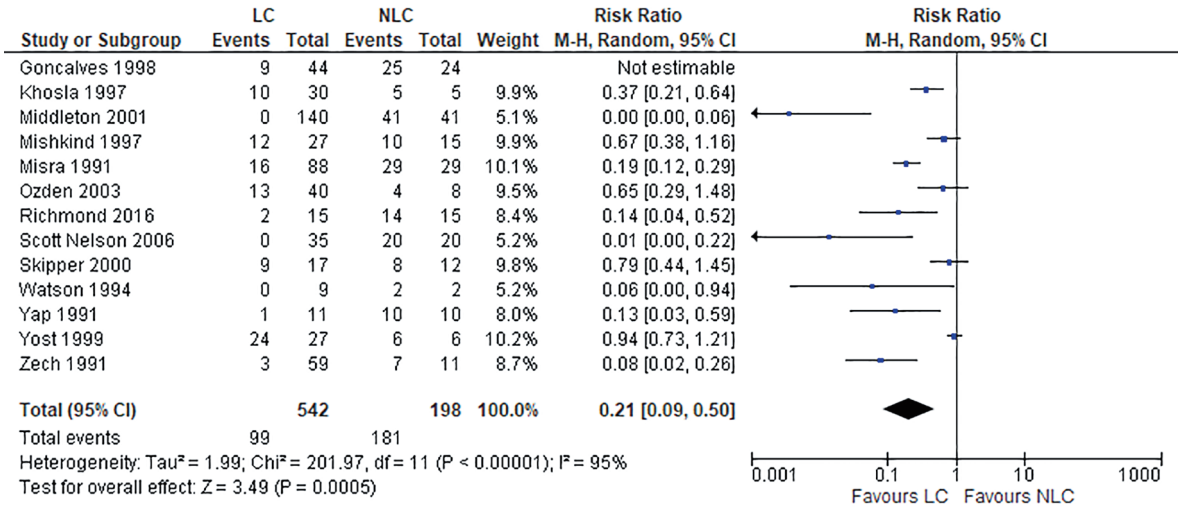

Figure 3 Forest plot for complete symptomatic resolution following laparoscopic cholecystectomy versus no cholecystectomy. Risk ratios are shown with 95 per cent confidence intervals.

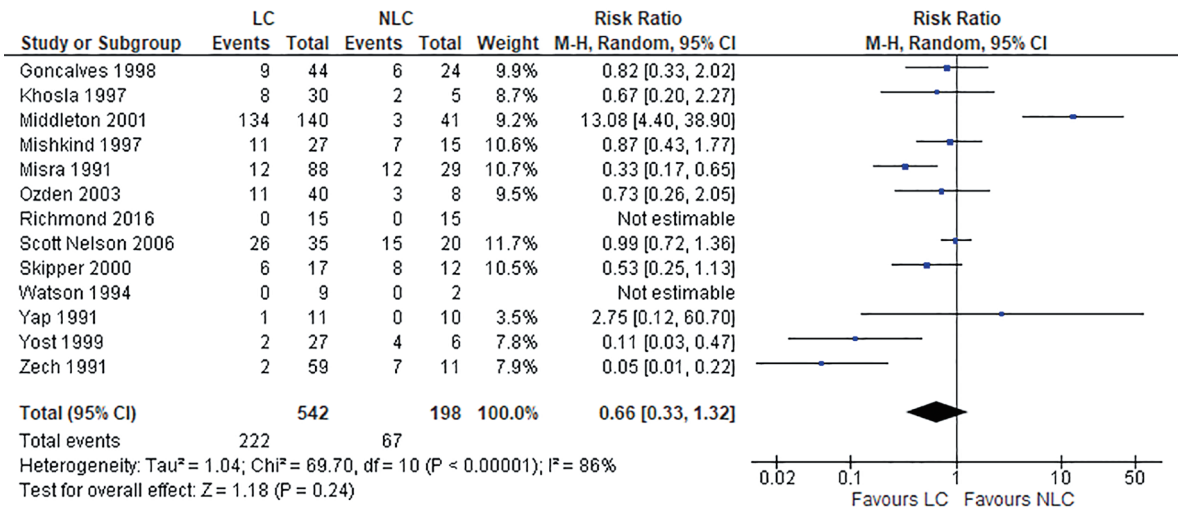

Figure 4 Forest plot for partial symptomatic resolution following laparoscopic cholecystectomy versus no cholecystectomy. Risk ratios are shown with 95 per cent confidence intervals.

Complete resolution of symptoms

There was significant heterogeneity (Tau^2 =1.99, Chi^2 =201.97, df =11, P<0.00001: I^2 =95%) among trials. In the random effects model analysis (RR, 0.21; 95% CI, 0.09, 0.50; z =3.49; P=0.0005. *Figure 3*), complete resolution was more likely in LC group compared to NLC group.

Partial resolution of symptoms

There was significant heterogeneity (Tau^2 =1.04, Chi^2 =69.70, df =10, P<0.00001: I^2 =86%) among included studies. In the random effects model analysis (RR, 0.66; 95% CI, 0.33, 1.32; z =1.18; P=0.24. *Figure 4*), there was no statistically significant difference between two groups.

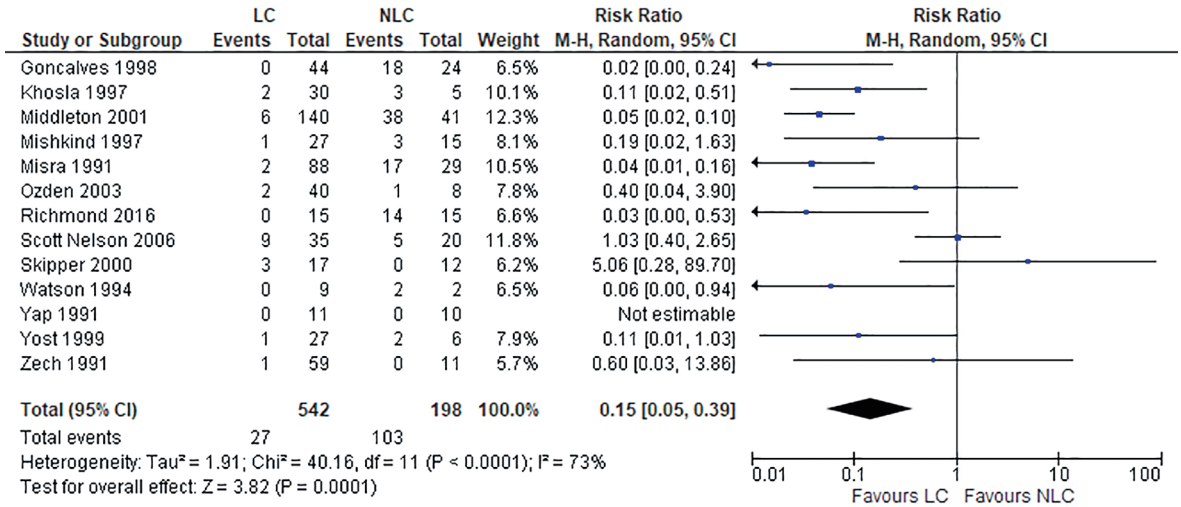

Figure 5 Forest plot for no symptomatic resolution following laparoscopic cholecystectomy versus no cholecystectomy. Risk ratios are shown with 95 per cent confidence intervals.

No resolution of symptoms

There was significant heterogeneity (Tau^2 =1.91, Chi^2 =40.16, df =11, P<0.0001: I^2 =73%) among included trials. In the random effects model analysis (RR, 0.15; 95% CI, 0.05, 0.39; z =3.82; P=0.0001: *Figure 5*), the risk of failure to resolve symptoms was lower in LC group.

Discussion

LC may be considered as an acceptable surgical intervention in patients with biliary dyskinesia presenting with chronic right upper quadrant pain. Currently there is insufficient evidence to recommend the routine use of LC in every patient with biliary dyskinesia. Paucity of high power randomised, controlled trials is the major reason for this lack of the evidence which should be addressed sooner and until then current study may be used to provide basis for offering the LC in the selected group of patients.

Our understanding of biliary dyskinesia has improved recently, partly because of the efforts to define it more clearly (3). It is now believed to be a gallbladder motility disorder hence the understanding that decreased emptying on cholescintigraphy supports the diagnosis (25,36). This dysmotility disorder of the gallbladder has been associated with multiple intrinsic and extrinsic factors influencing gallbladder function such as gallbladder neuronal problems, diabetes mellitus, liver cirrhosis and chronic gallbladder inflammation etc. (34). Various studies have reported that the gallbladder histology in these patients showed chronic inflammation (25). Despite this knowledge and an expanding horizon on its aetio-pathogenesis, patients with biliary dyskinesia represent an exhausted group of patients who have been withstanding with this biliary colic type pain despite multiple health-care encounters and an array of blood and radiological investigations (36).

Current study has shown that LC may result in significant symptomatic improvement in patients with biliary dyskinesia. This is supported by several other reported studies (9,37-40). With much improved safety profile than of open cholecystectomy, LC these days can be a considerable option for the management of symptomatic biliary dyskinesia. The data is lacking as to which of these patients will benefit the most from LC (37). Some published literature suggests that reproduction of characteristic biliary colic type pain and low ejection fraction on cholescintigraphy is a good indicator of symptomatic improvement after LC (39,41).

There are several limitations of this study. Combined analysis of randomised and non-randomised studies is not an ideal way of achieving high quality evidence but due to the paucity of decent number of randomised trials, authors decided to include all types of studies to achieve relatively better evidence. Significant heterogeneity among included studies may be due to the diverse inclusion and exclusion criteria. Other potential sources of heterogeneity and biased outcome include the varying protocols of performing cholescintigraphy, lack of an agreed definition

of biliary dyskinesia and lack of standard technique of LC in reported/included studies. The future implication of this study is to consider running a major multicentre randomised, controlled trial with agreed definition and diagnostic pathway of biliary dyskinesia, and a standard post-operative tool to accurately measure the symptomatic relief in patients after LC (42). Until then the current study may be used as baseline evidence to offer LC in a group of symptomatic patients with biliary dyskinesia.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Characteristics of included studies

Characteristics	Goncalves (LC/NLC)	Khosla (LC/NLC)	Middleton (LC/NLC)	Mishkind (LC/NLC)	Misra (LC/NLC)	Ozden (LC/NLC)	Richmond (LC/NLC)	Scott Nelson (LC/NLC)	Skipper (LC/NLC)	Watson (LC/NLC)	Yap (LC/NLC)	Yost (LC/NLC)	Zech (LC/NLC)
Year	1998	1997	2001	1997	1991	2003	2016	2006	2000	1991	1991	1999	1991
Country	USA	USA	UK	USA	USA	USA	USA	USA	USA	Australia	Australia	USA	USA
Type of study	Prospective comparative	Retrospective comparative	Prospective comparative	Retrospective comparative	Prospective	Retrospective comparative	RCT	Retrospective	Retrospective comparative	Retrospective comparative	RCT	Retrospective comparative	Prospective comparative
Participants	44/24	30/5	140/41	27/15	88/29	40/8	15/15	35/20	17/12	9/2	11/10	27/6	59/11
Mean age (y)	48	37	NR	46.8	48	45.6 50.4	43	NA	43	43	31	47	36
Gender (F)	74%	88%	76%	66%	79%	80%	69%		82%	80%	83%	66%	84%
Diagnostic criteria*	GBEF <35%	GBEF <35%	GBEF ≤35%	GBEF <35%	GBEF <35%	GBEF ≤35%	GBEF <38%	GBEF <35%	GBEF <35%	GBEF <50%	GBEF <40%	GBEF <35%	GBEF <50%
Procedure LC/OC 2 port/4 port	LC	LC	LC in 69% of patients	NR	NR	LC	LC	LC	LC	NR	OC	LC	NR
Duration of follow up (months)	32	6 - 36	18-63	13-15	22	36	12	24	11	1-3	34	1-54	NR
Primary outcome	Complete symptomatic resolution	Asymptomatic	Complete or significant improvement of symptoms	Symptoms gone/not pain improved/not	Complete symptomatic resolution	Clinical remission	SF-8 questionnaire	Symptomatic resolution	Complete symptomatic resolution	Cured	Nil symptoms	Significant improvement	Symptomatic improvement
Secondary outcome	Partial symptomatic resolution	Partial improvement or no change	NR	NR	Partial or no symptomatic resolution	0-2, no-slight improvement	Nil	NA	Partial or no symptomatic improvement	Better, same, worse symptoms	Improved or same symptoms	Partial or minimal improvement	Nil

*, on the basis of dynamic biliary scanning. LC, laparoscopic cholecystectomy; OC, open cholecystectomy; NR, not recorded; GBEF, gallbladder ejection fraction.