Timing of early laparoscopic cholecystectomy for acute calculous cholecystitis: a meta-analysis of randomized clinical trials.

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Abstract

Background Early cholecystectomy for acute cholecystitis is reported in the literature to be performed up to 96 hours of admission or up to 1 week of the onset of symptoms. Based on the natural history of acute cholecystitis such timing may have missed some potential benefits that could have been expected by performing cholecystectomy in an earlier phase of the disease. The study aimed to explore the hypothesis that an immediate cholecystectomy performed within 24 hours of admission could reduce post-operative complications when compared with delayed cholecystectomy.

Methods The literature search was conducted based on the Patient Intervention Comparison Outcome Study (PICOS) strategy. Randomized trials comparing post-operative complications at different timings of cholecystectomy for acute cholecystitis were included. The main outcome was the post-operative complication rate. Studies were grouped based on the timing of cholecystectomy which was defined immediate when performed within 24 hours of admission, early when performed up to 96 hours of admission and delayed when surgery was elective after medical treatment. Pooled data of studies comparing post-operative complications after immediate versus delayed and early versus delayed cholecystectomy were analysed within a sub-group analysis. The literature search finding allowed the performance of a second analysis in which immediate cholecystectomy did not refer to a cholecystectomy performed within 24 hours of admission but within 72 hours of the onset of symptoms.

Results Immediate cholecystectomy performed within 24 hours of admission did not prove to reduce post-operative complications with relative risk (RR) 1.89 and its 95% confidence interval (CI) [0.76; 4.71]. When the timing was based on the onset of symptoms, immediate cholecystectomy performed within 72 hours of the onset of symptoms was found to reduce post-operative complications compared to delayed cholecystectomy with RR 0.57 [95% CI: 0.37;0.89].

Conclusion The present study did not confirm the hypothesis that immediate cholecystectomy performed within 24 hours of admission may reduce post- operative complications. However, the finding of studies in which timing referred not to admission but to the onset of symptoms, allows to favour immediate cholecystectomy if performed within 72 hours of the onset of symptoms.

Background

Laparoscopic cholecystectomy is considered the treatment of choice for acute cholecystitis [1,2]. Regarding timing, the current literature has reported trials comparing early versus delayed cholecystectomy, but the definition of early cholecystectomy has been heterogeneous, including interventions within 24, 48 and 72 and even up to 96 hours of admission or up to 1 week following the onset of symptoms [3-10]. Moreover, meta-analyses based on studies that adopted such heterogeneous definitions of early cholecystectomy did not find any differences in morbidity between early and delayed cholecystectomy [3-11].

Based on the general pathology timing, [12,13] with some reports confirming the same timing for acute cholecystitis [14-16], it seems legitimate to question the role of the inclusion of patients with symptoms lasting more than 72 hours in the early group within the trials comparing early versus delayed cholecystectomy. Although all patients with acute cholecystitis are expected to suffer local and systemic inflammatory processes within 72 hours of the onset of symptoms, local and systemic changes are unpredictable for each patient after this delay. Therefore, it can be hypothesized that, after this delay, any comparison with delayed cholecystectomy would be flawed. The longer the delay before an early cholecystectomy is, the more likely patients within early and delayed cholecystectomy groups may have overlying clinical and pathological conditions related to gallbladder inflammation and therefore an overlying risk of complications. As a consequence, better results in terms of postoperative complications could be expected with surgery performed as early as possible, that is, for patients admitted for acute cholecystitis, immediately after hospitalization.

This review aimed to explore the hypothesis that, in patients with acute cholecystitis, immediate cholecystectomy performed within 24 hours of admission could reduce post-operative complications when compared with delayed cholecystectomy.

Methods

Protocol and registration

A protocol reporting the methods of the meta-analysis was published [17] and registered on the PROSPERO database with number: CRD42020149600. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

Data sources

Two authors independently conducted a literature search, according to the Patient Intervention Comparison Outcome Study (PICOS) strategy. Subject headings and text words were used to identify randomized studies that included patients with acute cholecystitis submitted to laparoscopic cholecystectomy at different timings, and reported post-operative complications (Table 1). Neither date limits nor language limits were imposed.

Table 1: Detailed search strategy on the databases.

Database	Search strategy	Found articles
PubMed	((((((((cholecystitis[MeSH Terms]) OR acute cholecystitis[MeSH Terms]) OR cholecystitis, acute[MeSH Terms])) AND ((((laparoscop*) OR celioscop*) OR coelioscop*) OR peritoneoscop*)) AND ((cholecystectomy) OR cholecystectomies)) AND (((((immediate) OR early) OR urgent) OR delayed) OR timing)) AND (((morbidit*) OR complication*) OR post-operative)) AND random*	66
Cochrane Library	acute cholecystitis and cholecystectomy and randomized (publication type)	99
Embase	acute AND cholecystitis AND cholecystectomy AND [article]/lim AND [randomized controlled trial]/lim	107
ClinicalTrials.gov	acute cholecystitis and cholecystectomy and interventional studies and (terminated or completed)	14
PakiMedNet	acute cholecystitis randomized	8

The literature search was conducted on PubMed and completed by consulting the Cochrane Library, Embase, ClinicalTrials.gov and by reviewing the references of the found reviews and meta-analyses. Based on the reviews findings, the search was extended to Google Scholar and PakiMedNet database. Unpublished studies and data from presentations to Congress were not considered.

Studies selection

Studies were included in the current analysis only if they were randomized trials comparing different timings of cholecystectomy, in which the criteria for the diagnosis of acute cholecystitis, the population study, timings for surgery and data on post-operative complications were reported.

Studies were excluded if the timing was defined using imprecise language without an exact numerical timing for the intervention, the population study was not defined, any clinically relevant categories of patients were excluded or patients with diseases other than acute cholecystitis were included.

Data collection

Data were independently collected by two authors and reported in a pre-prepared sheet. The main outcome was the post-operative complication rate. The hypothesis, that immediate laparoscopic cholecystectomy could reduce post-operative complications when compared to delayed cholecystectomy while classical early cholecystectomy may not, was explored by pooling data on post-operative complications of studies that compared immediate versus delayed and early versus delayed cholecystectomy within a sub-group analysis.

For this purpose, cholecystectomy was considered immediate when performed within 24 hours of admission, early when performed up to 96 hours of admission and delayed when surgery was elective

after medical treatment during the same admission or during a second scheduled admission.

The findings of studies that reported data on cholecystectomy performed within 72 hours of the onset of symptoms, more suitable for the initial hypothesis, prompted a minor deviation in the protocol. As a result, a second analysis was performed in which immediate cholecystectomy did no more refer to a cholecystectomy performed within 24 hours of admission but within 72 hours of the onset of symptoms and early cholecystectomy to a cholecystectomy performed up to 1 week following the onset of symptoms.

Three other secondary outcomes were registered: bile duct injury, conversion and mortality.

Risk of bias in individual studies

Two authors independently assessed the risk of bias. The quality assessment focused on the risk of bias arising from the randomization process, allocation concealment, blinding, missing outcome data, the measurement of the outcome and selective reporting. Three different levels of risk (low, uncertain and high) were incorporated according to the findings of the risk of bias assessment.

Statistical methods

Since studies were all randomized and selected based on defined criteria, neither clinical nor methodological heterogeneities were expected. The relative risk (RR) and its 95% confidence interval (95% CI) were calculated adopting a fixed-effect model [19]. Heterogeneity was estimated with the I^2 statistic, was excluded when $I^2 < 25\%$, considered moderate up to 50% and high when $I^2 > 50\%$ [20,21]. A chi-squared test for subgroup differences was performed. The level of significance was set at 0.05. The meta-analysis was conducted using ReviewManager (RevMan) software (version 5.3) [22].

Risk of bias across studies

The quality of evidence was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [23]. The five domains that can lower the certainty of a body of evidence were considered as follows: risk of bias, inconsistency across studies, indirectness of studies, imprecision of studies and publication bias. The rating up of the evidence was considered in case of a large effect. Publication bias was explored with a funnel plot by using the asymmetry of trial size against treatment effect to assess this bias [24,25].

Sensitivity analysis

The fixed-effect model was compared to the random-effects model using the DerSimonian Laird method [26]. No included studies reported early timing later than 72 hours, the planned sensitivity analysis comparing early cholecystectomy within 72 hours of admission and delayed cholecystectomy was therefore not feasible. An analysis was performed by excluding studies, the inclusion of which required a discussion. The role of excluded studies because of incomplete information about the exact timing of

cholecystectomy or methodological aspect of the research was explored by including each of them in the immediate or delayed group according to the indicated or best estimate of the cholecystectomy timing.

Results

Study selection

As reported in Figure 1, there were 294 studies found from the five databases, with another 14 articles from other sources. After reading the titles and abstracts and eliminating duplicates, 35 articles were selected for full-text reading, of which 15 were included in the analysis [15,16,27-39].

Study characteristics

In total, three studies compared immediate cholecystectomy performed within 24 hours of admission to delayed cholecystectomy [27-29] and six studies reported a comparison between early and delayed cholecystectomy, with early timing within 48 and 72 hours of admission [15,30-34]. However, the studies that compared immediate to delayed cholecystectomy included in the immediate group, patients with symptoms persisting up to 1 week [27] or up to 96 hours [28], while in one study, it was not possible to assess the exact timing related to the onset of symptoms [29]. Moreover, six additional studies were found that compared immediate cholecystectomy, performed within 72 hours of the onset of symptoms, to delayed cholecystectomy [16,35-39]. The inclusion among these studies of one study in which patients were randomized to be operated on before and after 72 hours of the onset of symptoms required discussion [36]. As all patients received medical treatment, the timing of 72 hours after the onset of symptoms was considered to be delayed. The characteristics and the results of the studies reporting data on immediate versus delayed cholecystectomy are summarized in Table 2.

Table 2: Characteristics of studies that reported post-operative complications in comparing immediate cholecystectomy performed within 24 hours of admission or within 72 hours of the onset of symptoms compared to delayed cholecystectomy.

Authors	Year	Patients		Timing		Inclusion criteria	Exclusion criteria	Pathology confirmation	Post-operative complications		P value
		Early	Delayed	Early	Delayed				Early	Delayed	
Lai [27]	1998	53	51	<24h from admission	6-8 weeks	Clinical Laboratory Ultrasound	CBD stone complications Previous surgery High risk for surgery Symptoms for more than 7 days	Yes	5	3	0.8
Kolla [28]	2014	20	20	<24h from admission	6-12 weeks	Clinical Laboratory Ultrasound HIDA	CBD stone complications Previous surgery High risk for surgery Symptoms for more than 96 hours	No	2	3	NR
Ozkardes [29]	2014	30	30	<24h from admission	6-8 weeks	Clinical Laboratory Ultrasound	CBD stone complications Previous surgery High risk for surgery	No	5	0	NR
Saber [30]	2014	60	60	<72h from symptoms	6-8 weeks	Clinical Laboratory Ultrasound	NR	No	6	4	NR
Rajock [31]	2016	31	31	<72h from symptoms	6-8 weeks	Clinical Laboratory Ultrasound	NR	Yes	3	8	NR
Jan [32]	2016	50	50	<72h from symptoms	>72h from symptoms Up to 7 days	Clinical Laboratory Ultrasound	CBD stone complications Previous surgery High risk for surgery Gallbladder malignancy Acalculus cholecystitis Symptoms for more than 7 days	No	1	3	NR
Arafa [33]	2019	74	74	<72h from symptoms	6-12 weeks	Clinical Laboratory Ultrasound	CBD stone complications Previous surgery High risk for surgery Free biliary perforation Pregnancy Decompensated cirrhosis No consent available	Yes	9	17	NR
Arslan Onuk [34]	2019	32	32	<72h from symptoms	>72h from symptoms Up to 6 days after initial treatment	Clinical Laboratory Ultrasound	CBD stone complications Previous surgery Perforation Sepsis Pregnancy Immunosuppression	Yes	4	9	0.12
El Kordy [35]	2019	20	20	<72h from symptoms	6-8 weeks	Clinical Laboratory Ultrasound	NR	No	4	6	NR

In total, 20 studies were excluded for the following reasons: the absence of or uncertainty about randomization [40–44], lack of reporting or uncertainty about timing [40, 45–48,52], lack of reporting or uncertainty about diagnostic criteria for acute cholecystitis [40, 44, 45, 49-51,53], limitation of the population study to the first episode and inclusion of biliary colic cases [51], the inclusion of only patients with symptoms persisting for more than 72 hours [52], exclusion of elderly patients [53], lack of reporting post-operative complications or lack of specifying whether the reported complications were primarily post-operative [40, 47, 48, 53–57], or the study reported interim results of a randomized study [58].

Risk of bias within studies

Only five studies reported a computer-generated randomization sequence allowing a low risk of allocation concealment bias [27,28,32,35,38], seven studies reported an odd-even simple randomization method [16,29,30,33,34,36,39] and three studies did not report data on randomization method [15,31,37], with, as a result, an uncertain or high risk of selection bias. None of the studies reported any blinding. While the absence of information on blinding of operators and patients could be considered to be at low risk of bias (being hardly feasible in surgical trials), the absence of blinding of the outcome assessment may be of concern and the risk should be considered as uncertain [59]. The risk of bias related to the missing outcome data, the measurement of the outcome and selective reporting was considered low as for all the studies.

Synthesis of results

The risk of post-operative complications was not significantly different after immediate cholecystectomy performed within 24 hours of admission compared to delayed cholecystectomy with RR 1.89 [95% CI 0.76; 4.71], as well as for early compared to delayed cholecystectomy with RR 1.32 [95% CI 0.82; 2.11]. Heterogeneity was moderate in both comparisons. The test for differences between sub-groups did not provide a significant result with p = 0.49 (Figure 2).

Within the second analysis, pooling data showed a statistically significant reduction in the rate of post-operative complications with RR 0.57 [95% CI 0.37; 0.89] after immediate cholecystectomy performed within 72 hours of the onset of symptoms compared to delayed cholecystectomy. No heterogeneity was found. For the sub-group comparison, eight studies comparing early with delayed cholecystectomy, the early timing of which was reported to be up to 1 week of the onset of symptoms, were selected among the included studies [15,27,28,30-34]. Pooled data from these studies did not show a significant difference between early and delayed cholecystectomy with RR 1.28 [95% CI 0.84; 1.97], heterogeneity was found to be moderate. Moreover, the comparison between the two sub-groups, immediate versus delayed and early versus delayed, showed a statistically significant difference with p = 0.01, giving strength to the results on immediate cholecystectomy (Figure 3).

A total of 10 studies reported data on biliary injury [15,27,28,30-34,36,38], but only four were from the immediate cholecystectomy sub-groups [27,28, 36,38]. When considering immediate cholecystectomy performed within 24 hours of admission compared to delayed cholecystectomy [27,28], the RR was not estimable because one study reported no biliary injury [27] and one reported only one case in the immediate cholecystectomy group [28]. When considering immediate cholecystectomy performed within 72 hours of the onset of symptoms [36,38], no significant difference was found with RR 0.23 [95% CI 0.04; 1.34].

All included studies reported data on conversion. No significant difference was found when comparing immediate cholecystectomy performed within 24 hours to delayed cholecystectomy with RR 1.38 [95% CI 0.75; 2.54], while immediate cholecystectomy performed within 72 hours of the onset of symptoms appeared to significantly reduce the rate of conversion compared to delayed cholecystectomy with RR 0.53 [95% CI 0.32; 0.89].

Reported mortality was very low and data were not sufficient to perform a meta-analysis on this variable.

Sensitivity analysis

The sensitivity analysis performed by applying the random-effects model revealed similar results compared to the fixed-effect model, for both the definitions of immediate cholecystectomy respectively within 24 hours of admission and within 72 hours of onset of symptom. For the former, RR of immediate versus delayed cholecystectomy was 1.61 [95% CI 0.44; 5.85], RR of early versus delayed cholecystectomy was 1.36 [95% CI 0.73; 2.55] and p = 0.02 for the sub-group comparison. For the latter,

RR of immediate versus delayed cholecystectomy was 0.58 [95% CI 0.37; 0.90], RR of early versus delayed cholecystectomy was 1.27 [95% CI 0.78; 2.06] and p = 0.82 for the sub-group comparison.

According to the literature finding, no other sensitivity analysis was feasible for comparisons based on immediate cholecystectomy performed within 24 hours of admission. The two further planned sensitivity analysis were therefore limited to the comparisons based on immediate cholecystectomy performed within 72 hours of the onset symptoms. By excluding the study, which was a matter of discussion [36], sensitivity analysis confirmed the results on the risk of post-operative complications with RR of immediate versus delayed cholecystectomy of 0.59 [95% CI 0.38; 0.92], RR of early versus delayed cholecystectomy of 1.28 [95% CI 0.84; 1.97] and p = 0.01 for the sub-group comparison.

When investigating the effect of the inclusion of studies that had been omitted because of incomplete information regarding the exact timing of cholecystectomy, the absence of reported criteria for the diagnosis of acute cholecystitis, or other methodological aspects of the studies, the sensitivity analysis confirmed the results of the main comparison with RR of immediate versus delayed cholecystectomy of 0.57 [95% CI 0.37; 0.89], RR of early versus delayed cholecystectomy of 1.09 [95% CI 0.82; 1.44] and p = 0.02 for the sub-group comparison.

Quality of evidence

As the present meta-analysis only included randomized studies, the level of evidence should first be high according to the GRADE rule. The only domain that should be considered in rating down the quality of evidence has been the potential risk of bias. None of the dedicated domains could allow the level of evidence to be rated up. The risk of bias involved not only the method of randomization, allocation concealment and blinding but also the lack of pathological confirmation of a diagnosis of acute cholecystitis. While non-acute cholecystitis is expected at the time of surgery in the delayed group, an unknown rate of non-acute cases may be included in the immediate group because of a diagnostic error that may lead to an overestimation of the benefit of an immediate cholecystectomy.

A large magnitude of the effect was not found, the dose-response gradient was not applicable and no potential residual confounders would decrease the magnitude of the effect. The funnel plot shown in Figure 4 illustrates the low risk for potential publication bias in this study. Overall, the quality of evidence of this meta-analysis should be considered moderate.

Discussion

The present review did not confirm the hypothesis that immediate cholecystectomy performed within 24 hours of admission may influence post-operative complications, but the result is based on studies that included, in the immediate cholecystectomy group, patients with late presentation suffering symptoms for more than 72 hours. The additional analysis however found that post-operative complications were reduced when immediate cholecystectomy was performed within 72 hours of the onset of symptoms when compared to delayed cholecystectomy.

The quality of evidence was rated as moderate because of the finding of a potential risk of selection bias. The risk was due to the method of randomization, allocation concealment and blinding, as well as a lack of pathological confirmation of the diagnosis of acute cholecystitis. However, among the studies on immediate cholecystectomy, only one did not report data on the randomization process [38] and four reported a simple randomization method with an uncertain or high allocation concealment risk [16,29,36,39]. Globally, the level of risk related to the absence of blinding of operators and patients was considered being low while that related to the absence of blinding of the outcome assessment was uncertain [59]. Although the combined clinical, laboratory and imaging criteria for acute cholecystitis have a low risk of diagnostic error [1], without a pathological confirmation of the diagnosis, which was reported in only four studies [16,27,37,38], the inclusion of non-acute cases studies could not be excluded [2]. Randomization would equally distribute these patients in both arms. But, while all patients are expected to be non-acute in the delayed group, a percentage of non-acute cases in the immediate group may be the cause of an overestimation of the effect of immediate cholecystectomy because non-acute cases are expected to suffer fewer post-operative complications.

The general applicability of the results of the present review may appear limited by the exclusion criteria reported in six of the studies on immediate cholecystectomy [16,27-29,36,38]. Some reported exclusion criteria, such as patients with sepsis, severe cholecystitis with organ failure, perforation, or those at high surgical risk because of medical illness, were mandatory for ethical reasons. Nevertheless, only the complications related to biliary migration in the common bile duct, the previous surgery reported in the six studies [16,27-29,36,38] and pregnancy reported in one study [16] should be considered a limitation when assessing the external validity of the studies.

The results focused on the safety of immediate cholecystectomy by analysing post-operative complications as the main outcome. This is the main parameter concerning morbidity that may change the course of the disease. Overall morbidity would have been a better parameter for the evaluation of the timing of cholecystectomy, but it may include when reported, intra-operative complications and complications while awaiting cholecystectomy. However, intra-operative complications do not substantially change the course of a patient's history unless they require conversion or involve bile duct injury. Both have been analysed as secondary outcomes in the present review, with the finding that immediate cholecystectomy performed within 72 hours of admission reduced conversion compared to delayed cholecystectomy, while no significant differences were found in instances of bile duct injury. Moreover, complications while awaiting cholecystectomy that should also be primarily considered in delayed cholecystectomy are rarely reported. At the contrary, the failure rate of conservative treatments and re-admission for the recurrence of symptoms of acute cholecystitis in the delayed cholecystectomy group while awaiting cholecystectomy was reported in several studies to be up to 33% and 33.3% of cases, respectively [15,27,28,30,31,33-35,37,45,49,50,51].

The present meta-analysis focused on post-operative complications and was based on a double comparison, immediate versus delayed and early versus delayed cholecystectomy. The failure to

demonstrate a reduction in post-operative complications after immediate cholecystectomy performed within 24 hours of admission compared to delayed cholecystectomy may be explained by the inclusion of patients with late presentation who suffered symptoms for more than 72 hours. Although the inclusion of such patients did not corroborate the initial hypothesis based on the natural history of acute cholecystitis, it reproduces what commonly occurs in surgical practice.

Conclusions

Immediate cholecystectomy performed within 24 hours of admission has not proved to reduce post-operative complications compared to delayed cholecystectomy. However, the finding of studies in which immediate timing did not refer to admission but to the onset of symptoms allowed to better explore the initial hypothesis. The analysis of the results permitted the conclusion that immediate cholecystectomy should be preferred to delayed cholecystectomy when feasible within 72 hours of the onset of symptoms. Once symptoms have persisted for more than 72 hours at the time of a feasible surgery, others risk factor than the risk of post-operative complications should be considered when deciding the timing of cholecystectomy. Finally, in future research, criteria for the early or delayed timing of cholecystectomy should focus on the onset of symptoms rather than on the time of admission.

Abbreviations

PICOS: Patient Intervention Comparison Outcome Study

RR: Relative Risk

CI: Confidence Interval

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

Declarations

Ethics approval and consent to participate

Not applicable

Ethical approval was not be required for this systematic review and meta-analysis, as only a secondary analysis of data already available in scientific databases were conducted.

Consent for publication

Not applicable

The manuscript does not contain data from any person.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GB conceived the systematic review and meta-analysis, developed the search and data collection strategy, designed and wrote the protocol and participated in the assessment of the quality of the studies and risk of bias assessment, statistical analyses, the interpretation of findings, assessment of the quality of evidence and the drafting of the manuscript. SK contributed to the development of the review protocol and participated in the literature search and the selection of the studies. MS participated in the literature search and the selection of studies. MP contributed to the development of the review protocol, data collection and the assessment of the quality of the studies, as well as the risk of bias assessment and revision of the manuscript. NA participated in data collection, statistical analyses, the interpretation of findings, the assessment of the quality of evidence and the revision of the manuscript. LA provided critical revision of the manuscript. YK acted as an arbitrator in cases of disagreement between two authors and provided critical revision of the manuscript. All authors read, provided feedback and approved the final version of the protocol and all authors read, provided feedback and approved the final version of the manuscript.

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Figures

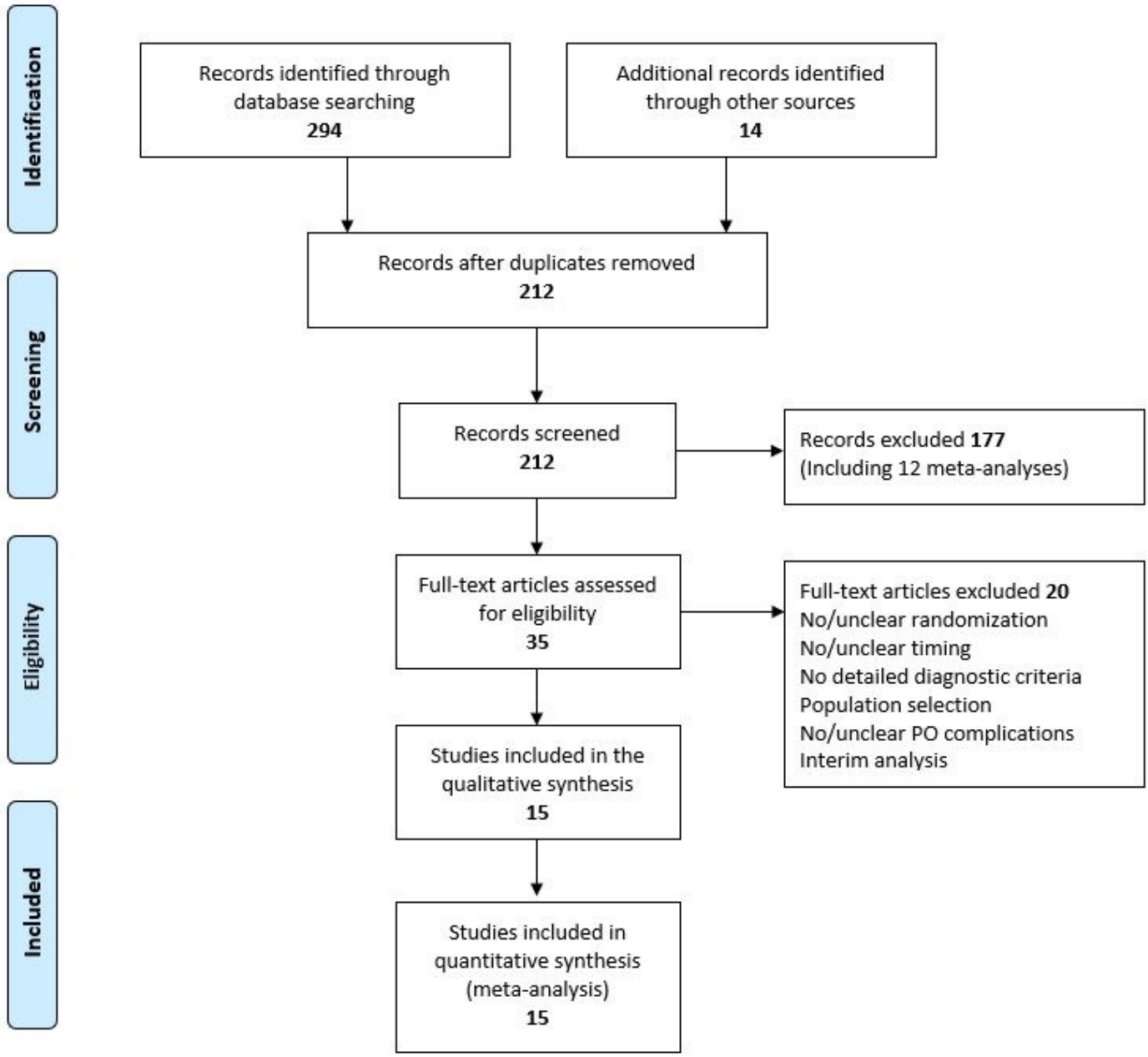

Figure 1

Literature search flow chart.

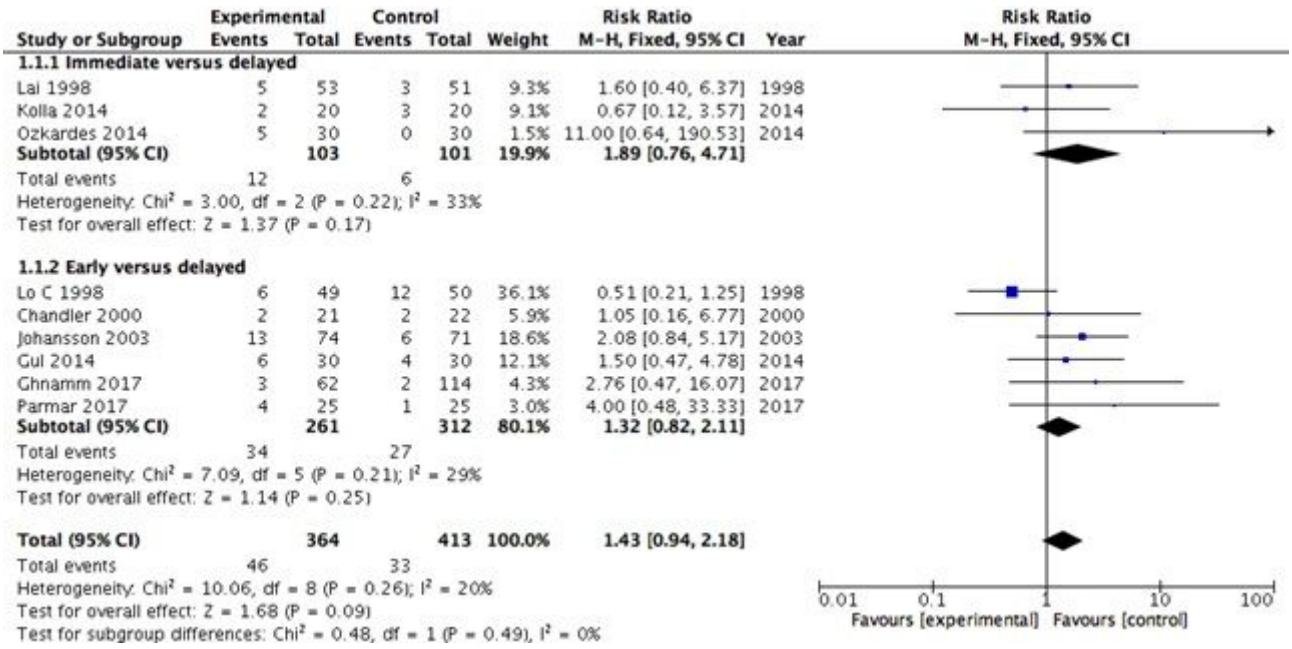

Figure 2

Sub-group comparison on post-operative complications based on timing related to time from admission with immediate cholecystectomy performed within 24 hours of admission, early cholecystectomy later than 24 hours and up to 96 hours of admission, delayed cholecystectomy performed after non-operative management.

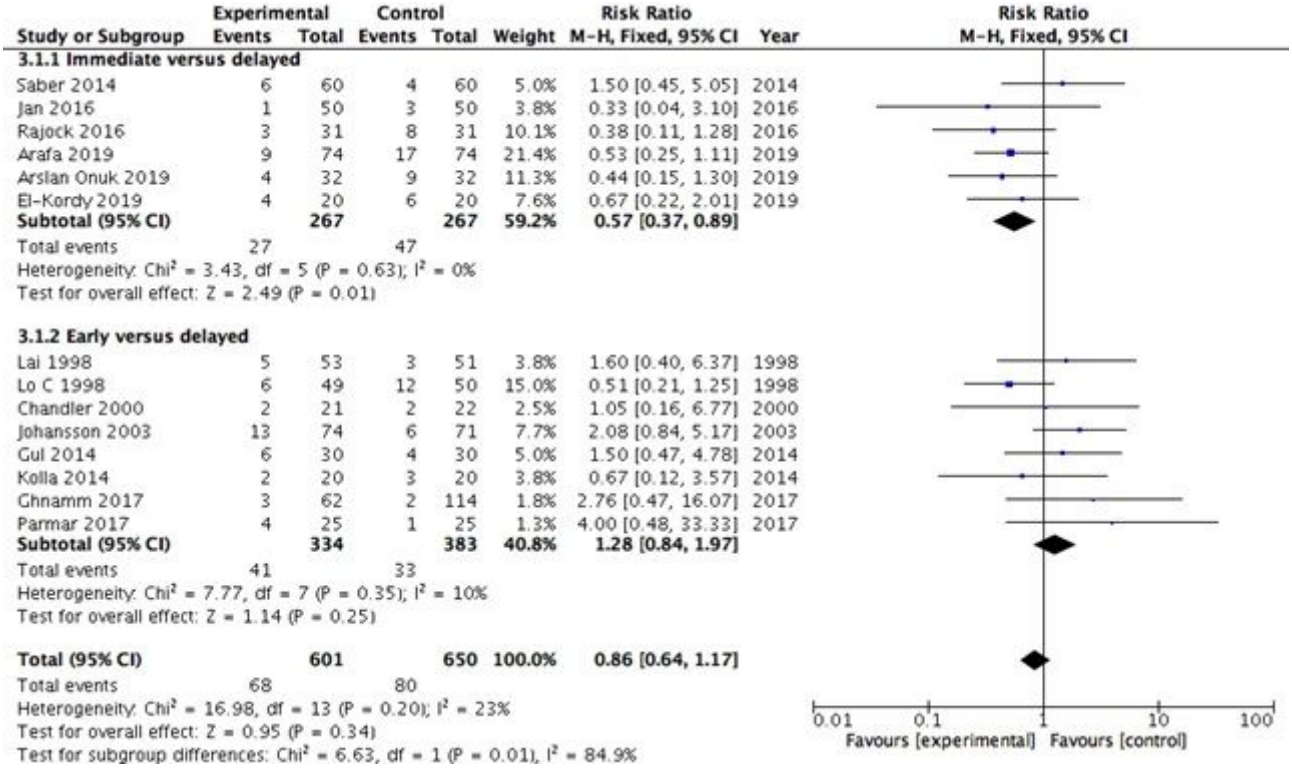

Figure 3

Sub-group comparison on post-operative complications based on timing related to time from the onset of symptoms with immediate cholecystectomy performed within 72 hours of the onset of symptoms, early cholecystectomy after 72 hours and up to 1 week of the onset of symptoms, delayed cholecystectomy performed after non-operative management.

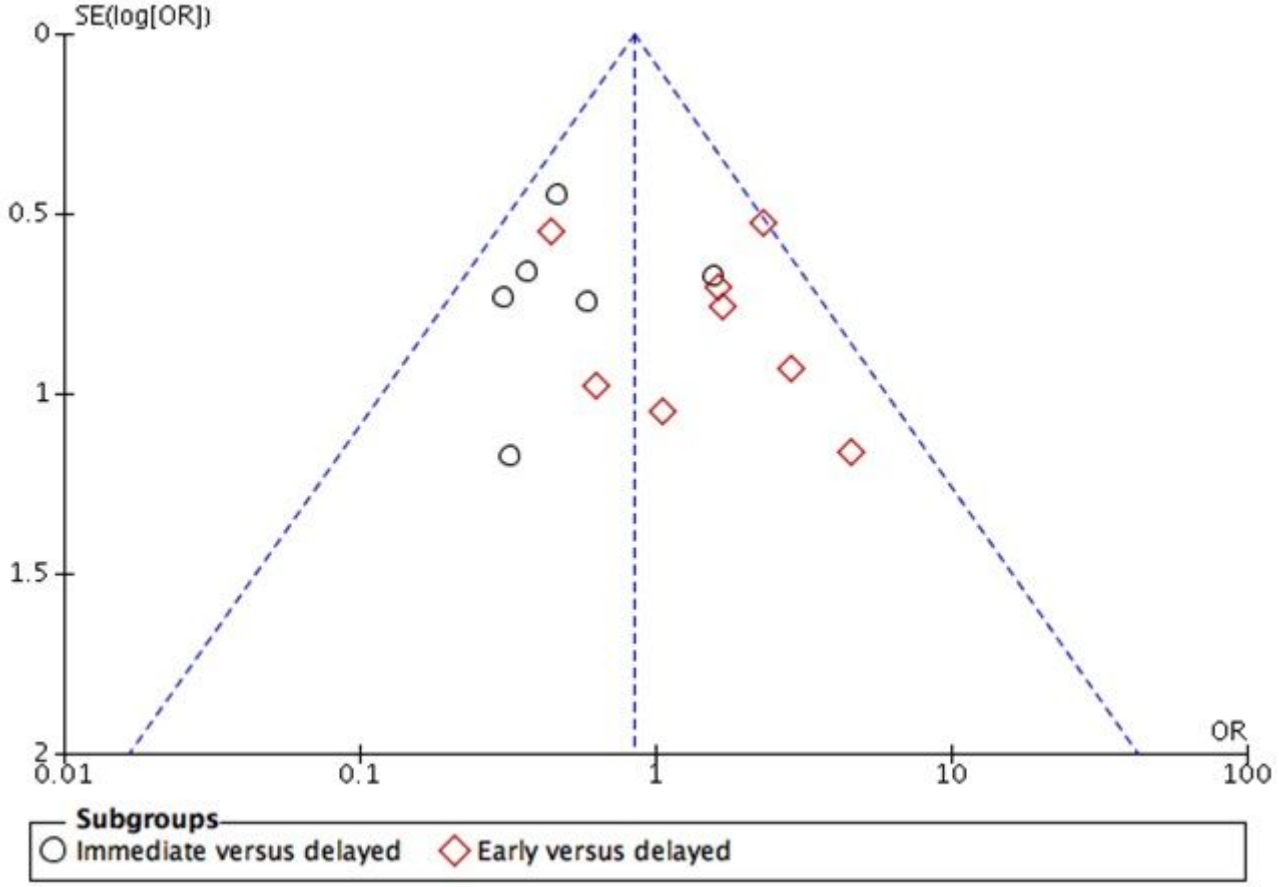

Figure 4

Funnel plot assessing the risk for potential publication bias.

Supplementary Files

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- PRISMAchecklist.doc
- PROSPEROregistration.pdf
- Protocol.pdf