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A Meta-Analysis of the use of Intraoperative Cholangiography; Time to revisit our approach to Cholecystectomy?

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Abstract

Background

Despite some evidence of improved survival with intraoperative cholangiography (IOC) during cholecystectomy, debate has raged about its benefit, due in part to its questionable benefit, time and resources required to complete.

Methods

A PROSPERO-registered (ID CRD42018102154) meta-analysis following PRISMA guidelines using PubMed, Scopus, Web of Science and Cochrane library from 2003 to 2018 was undertaken including search strategy "intraoperative AND cholangiogra* AND cholecystectomy". Articles scoring ≥ 16 for comparative and ≥ 10 for non-comparative using the Methodological Index for Non-Randomised Studies (MINORS) criteria were included. A dichotomous random effects meta-analysis using the Mantel-Haenszel method performed on Review Manager Version 5.3 was carried out.

Results.

Of 2,059 articles reviewed, 62 met criteria for final analysis. The mean rate of IOC was 38.8% (range 1.6-96.4%).There was greater detection of bile duct stones during cholecystectomy with routine IOC compared with selective IOC (OR= 3.28, CI= 2.80-3.86, p-value <0.001). While bile duct injury (BDI) during cholecystectomy was less with IOC (0.39%) than without IOC (0.43%), it wasn't statistically significant (OR=0.88, CI=0.65-1.19, p-value= 0.41). Readmission following cholecystectomy with IOC was 3.0% compared to 3.5% without IOC (OR= 0.91, CI= 0.78-1.06, p-value= 0.23).

Conclusion

The use of IOC still has its place in cholecystectomy based on the detection of choledocholithiasis, and the potential reduction of unfavourable outcomes associated with

common bile duct stones. This meta-analysis, the first to review IOC use, identified a marked variation in cholangiography use. Retrospective studies limit the ability to critically define association between IOC use and bile duct injury.

Introduction

There have been many paradigm shifts in cholecystectomy techniques since Carl Langenbuch reported the first cholecystectomy in 1882, and Mirizzi subsequently described cholangiography in 1932.[1, 2] Coupled with this have been significant changes in the management of choledocholithiasis, suggesting an increased trend toward bile duct clearance intraoperatively.[3, 4] In general, 3-12% of patients undergoing cholecystectomy have associated common bile duct stone,[5, 6] and this is increased in those undergoing emergency surgery.[7] The impact of common bile duct stones is not clearly understood, confounded by variable rates of stone passage and adverse sequelae.[8, 9] It has been suggested that failure to remove CBD stones has an unfavourable outcome in 25%, which is halved by clearance of the CBD stone.[8]

Elderly patients with untreated CBS stone have a higher incidence of gallstone related complications.[10] Historically, surgeons have striven to detect common bile duct stone and anatomical abnormalities during cholecystectomy by using intraoperative cholangiography (IOC) as part of a perceived better surgical practice. Its use is decreasing,[11] performed in a variable fashion from routinely to never. The reason for this variance probably relates to the time required, difficulty of the procedure, especially in acute cholecystitis, and having a clear algorithm for detected CBD stones. The value of IOC is certainly in question, spurred by improved pre-operative MRCP and widespread access to endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP) and fluorescence cholangiography.[12]

The aim of the current meta-analysis was to evaluate the variability in performance and potential impact of intraoperative cholangiography.

Materials and Methods

Search strategy and study eligibility

A meta-analysis of all published articles was conducted at Letterkenny University Hospital Ireland, in June 2018, using the electronic databases Pub Med, Scopus, Web of Science and the Cochrane Library for a 15 year period from January 2003 to June 2018. Additionally, a manual troll of trial registries and reference lists for grey literature was undertaken. The reproducible search strategy “intraoperative AND cholangiogra* AND cholecystectomy” was used across all four databases to include all relevant papers.

Eligibility assessment and Data extraction

The primary outcome was to assess the variability, and potential impact on surgical outcomes following the use intraoperative cholangiography during cholecystectomy. Secondary outcomes were to identify factors that contributed to any variability.

The methods of analysis and inclusion criteria were specified in advance to avoid selection bias and documented in a protocol, registered with the International Prospective Register of Systematic Reviews (CRD42018102154) on the 23/07/2018. This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Studies were included in the meta-analysis if the following criteria were met: either open or laparoscopic cholecystectomy, elective or emergency, where the use and findings of intraoperative cholangiography were reported and full articles were available in English. Studies based on paediatric or pregnant patients were not included. Reviews, meta-analyses, case reports, errata, letters, protocols, surveys, studies that did not report key outcomes, and those whose data was inadequate for interpretation via meta-analysis, were not included in this meta-analysis.

Eligibility assessment was performed independently in a blinded standardised manner by two reviewers and disagreements between reviewers were resolved by discussion (ED, CM).

The descriptive and quantitative data from the screened studies was extracted by two reviewers (ED, MC) and compared to ensure data extraction was complete. Data was collected using a data extraction sheet with pre-specified criteria, which were further refined after pilot testing of randomly chosen studies.

Studies reporting the total number of cholecystectomies carried out with and without attempted IOC were analysed to assess the variability in IOC use across different studies. The mean rate of IOC was defined as the total number of successful cholangiographies completed as a percentage of the number of cholecystectomies carried out. As the use of IOC depends on the policy of a surgeon or hospital, randomized trials where participants were randomly allocated to treatment groups were not used in analysis of the rate of IOC use during cholecystectomy but were included for analysis of other outcomes. Studies that did not report the total number of cholecystectomies performed with IOC and without a planned IOC during the study period were also not used for the analysis of rate.

Analysis of the rate under a selective and routine policy of IOC use was also carried out. An additional analysis of multi-centre studies (representing more than two institutions) only was performed to analyse the variation in the use of IOC across different countries, with studies from a same country grouped together.

Data was extracted from studies that reported a routine or selective policy of IOC to evaluate the detection of common bile duct stones, incidence of bile duct injury, conversion rates and intraoperative complication rates under each policy. The rates of each outcome were calculated as a percentage of the total cholecystectomies carried out.

The impact of intraoperative cholangiography on biliary injury and readmission rate was investigated by analysis of studies reporting outcomes with and without the use of intraoperative cholangiography.

Quality assessment

The Methodological Index for Non-Randomised Studies (MINORS) criteria,[14] was used for quality assessment of comparative and non-comparative surgical studies using a 3-point scale (0 not reported, 1 reported but inadequate, 2 reported and adequate) on eight items for non-comparative studies and 12 items for comparative studies. The ideal global score for non-comparative and comparative studies was chosen at 16 and 24, respectively. All collated studies including randomised controlled trials were marked against the MINORS criteria to assess the studies with the best methodologies to include in the final analysis. Although the criteria were designed for non-randomised studies, randomised control trials were also marked using the criteria because they are the gold standard of original published research and were used in validating the MINORS criteria. Three reviewers performed quality assessment independently in a blinded standardised manner and disagreements between reviewers were resolved by discussion between the review authors (ED, MC, JC), and if an agreement could not be reached then by a fourth reviewer (LF). The studies with a MINORS score of ≥16 out of 24 for comparative and ≥10 out of 16 for non-comparative were included in the final analysis.

Statistical Analysis

A dichotomous meta-analysis using the Mantel-Haenszel method was used to analyse the data .[15] The results were presented as pooled odds ratios with 95% confidence interval (CI) in a forest plot performed on Review Manager (RevMan) Version 5.3. Statistical significance was defined as $p < 0.05$. Statistical heterogeneity was measured using I^2 scores calculated using Review Manager. A random effects model was used when the I^2 statistic reached over

50%, otherwise a fixed effects model would be used. Any levels of substantial heterogeneity were explored in conjunction with the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 with an I^2 statistic of 0%- 40% representing little heterogeneity between studies, 30%-60% moderate heterogeneity, 50%-90% substantial heterogeneity and 75%-100% considerable heterogeneity.[15] Chi-square testing was used to examine differences in proportions, and a 2-way contingency table analysis was used to calculate relevant odds ratios.

Results

This study reviewed 2,059 articles of which 90 were potentially suitable. After applying the MINORS cut off score, 62 were included for meta-analysis as shown in the PRISMA flow chart, Figure 1.

The rate of IOC use during cholecystectomy

The rate of intraoperative cholangiography use during cholecystectomy was analysed across 56 studies (n= 4,221,311). Six studies were not included because the total number of cholecystectomies with and without planned IOC was not reported, or the use of IOC was randomised to an intervention and control group. The mean rate of IOC use during cholecystectomy was 38.8% (range 1.6% to 96.4%). There was marked variation in the use of IOC with studies reporting data from 19 countries (Figure 2). The mean operating time for IOC across four studies was 11 minutes (range 6-15 min).[16, 17, 18, 19]

When analysing 20 multicenter studies (96% of which were based on American and Swedish studies), the mean rate of IOC use was 38.5% (CI=38.5-38.6), range 12 to 88%. [6, 8, 11, 20-36] The use of IOC from 11 multicenter studies carried out in the USA[11, 20-29] revealed a mean rate of 33.2% (CI= 33.1-33.3) compared to a mean rate of 69.5% (CI= 69.4-69.6) from four multicenter Swedish studies.[6, 8, 30, 31]

Comparing routine and selective policies of IOC

A selective policy of IOC use was adopted in 14 studies with a mean IOC usage of 16.7% (2.8-36.9%) in 12,064 patients.[18, 19, 34, 37-47] Additionally, 14 studies adopted a policy of routine IOC with a mean average usage of 88.3% (63.5-99.2%) in 25,072 patients.[17, 19, 34, 37, 42, 48-56]

Eleven studies (n=10,466) reported the incidence of common bile duct stones on routine IOC with a mean of 11.8%, ranging from 2.8% to 18.9%.[19, 34, 37, 38, 50-56] Eight studies (n=4,556) reported the incidence of common bile duct stones on selective IOC with a mean of 3.9%, range 0.7% to 12.8%.[18, 19, 34, 37-39, 44, 45] A routine IOC policy significantly increased the rate of CBD stone detection (OR= 3.28, CI= 2.80-3.86, p-value <0.001).

Five studies (n=116,726) [19, 34, 37, 38, 57] reported findings of bile duct injury from routine and selective policies of intraoperative cholangiography use (Figure 3). The average incidence of bile duct injury using a routine policy of IOC was 0.22%, compared with 0.27% for a selective approach (OR= 0.81, CI=0.57-1.15, p-value= 0.23).

In 25 studies (n=71,191 patients) who reported successful IOC completion, the mean success rate was 95% (range 66% to 99%).[5, 6, 16-19, 34, 37-44, 48-53, 55, 56, 59, 60] Successful completion of IOC was significantly greater with a routine IOC policy (95.2 %) compared to a selective policy (90.6%) (OR= 2.09, CI=1.73-2.51, p-value <0.001).

Comparing bile duct injury and readmission rate with and without the use of IOC

The incidence of bile duct injury during cholecystectomy with and without the use of IOC was assessed across 10 studies (n= 3,160,760 patients) as shown in Figure 4.[6, 11,20, 21, 25, 30, 31, 36, 61, 62] The total number of cholecystectomy patients with intraoperative cholangiography performed was 1,266,275 and the incidence of bile duct injury was 0.39%. The total number of patients undergoing cholecystectomy without cholangiography was 1,894,485 and the incidence of bile duct injury was 0.43%. Although IOC is potentially weakly associated with a lower incidence of bile duct injury, this effect is not significant (OR=0.88, CI=0.65-1.19, p-value= 0.41). There was also considerable heterogeneity reported (I^2 = 97%).

Four studies reported a readmission rate following cholecystectomy both with and without the use of intraoperative cholangiography (Figure 5). [11, 61, 28, 29] The total number of patients undergoing cholecystectomy with IOC was 105,908, with an average readmission rate of 3.0%. The total number of patients undergoing cholecystectomy without IOC was 569,871, with an average readmission rate of 3.46%. IOC is not significantly associated with a decrease in readmissions (OR= 0.91, CI= 0.78-1.06, p-value= 0.23, I^2 =88%).

Discussion

This meta-analysis reviewed over 2000 publications identifying a wide variation in the performance of IOC, with variable detection of choledocholithiasis. Previously, there have been many studies of IOC but the current meta-analysis is one of the first to assess the impact of the variable use of IOC during cholecystectomy.

Surgeons opting for the routine use of IOC feel it aids detection of common bile duct stones, and promotes surgical skills that facilitate cystic duct cannulation and transcystic single stage bile duct exploration, which is a safe and efficacious treatment option in the management of choledocholithiasis.[63, 64] In addition, it has been suggested that IOC is an effective tool for effectively reducing bile duct injury but this has been the subject of major debate and the controversy remains.[20, 27] With the advent of other imaging like ERCP and magnetic resonance cholangiopancreatography (MRCP), the role of IOC has been challenged even further, with many surgeons opting for a selective policy of IOC use or not at all.[46, 65]

Different approaches have been advocated in the management of CBD stones from laparoscopic single stage CBD clearance (LCBDC), to single and dual stage LCBDC with intra-operative ERCP.[66, 67] In their meta-analysis, Pan and colleagues found that LCBDC during LC has superior outcomes to a pre-operative ERCP sphincterotomy followed by laparoscopic cholecystectomy (LC), and should be considered as optimal treatment choice for CBD stones.[67] Mohseni et al, in a recent retrospective study of over 200 patients undergoing simultaneous intra-operative ERCP with LC, found this approach was associated with few complications.[68]

A key approach to single stage, or operative clearance, requires IOC to be performed even in cases with pre-operative MRCP. In a recent multicentre study of approaches to cholecystitis in fit patients undergoing a therapeutic sequence for the management of choledocholithiasis, 80% of the 25 centres reported that they favoured a staged approach with upfront ERCP followed by cholecystectomy (either during the same admission or, more commonly, at an interval). A minority of survey respondents favoured simultaneous cholecystectomy and either operative CBD exploration (4 of 25, 16%) or rendezvous intraoperative ERCP (5 of 25, 20%) as a one-stage procedure.[69] Our study identified that IOC was performed in over one third of patients (38.8%) undergoing cholecystectomy. This rate increased in Swedish and Australian cohorts compared to the US. In Australia, the Royal Australasian College of Surgeons report a 90% median use of IOC during cholecystectomy in their Surgical Variance Report 2017.[70] A very recent multinational prospective evaluation of cholecystectomy outcomes in 504 patients in 16 countries found the IOC rate was 13% and pre-operative ERCP rate was 16%.[71] These variations in IOC are truly remarkable, hard to explain scientifically and must in part be based on emotive learning by the surgeons involved.

Surgical opinion regarding the appropriate indications for the selective use of IOC varied considerably, contributing to the range of selective IOC rates recorded (2.8-36.9%). Some studies reported high volume surgeons and high volume hospitals were more likely to perform IOC.[21, 27, 35] Overall, this data was limited in the literature and not appropriate for statistical analysis.

Selective IOC based on preoperative indications is supportive as an alternative to routine IOC for the detection of choledocholithiasis.[39, 72] A selective policy of IOC use results in an IOC rate of 16.7% compared to 88.3% in the routine policy institutions. The success of routine IOC is limited by occluded, friable or very short cystic ducts, and the required lead lined operating rooms.

The principal goal of IOC is CBD stone detection and this meta-analysis identified that routine IOC will detect more than threefold the number of CBD stones as selective IOC, with an average incidence of CBD stones during routine IOC reported as 12% compared to 4% on selective IOC (OR= 3.28, CI= 2.80-3.86, p-value <0.001). Up to 50% of CBD stones will pass spontaneously and for this reason, some have argued for an expectant strategy based on spontaneous clearance rates of CBD stone.[5, 73]. The sequelae of persistent untreated stones are becoming clearer with an increase in adverse outcomes if the stones are not removed.[10, 74] However, these additional stones found on routine IOC may indeed be important, potentially causing further complications, recurrent cholangitis, pancreatitis and readmission, as well as possibly contributing to a post cholecystectomy syndrome.[75, 76] Recently, Hakuta et al. revealed the cumulative incidence of biliary complications related to asymptomatic stones picked up on incidental imaging was 6.1% at 1 year, 11% at 3 years, and 17% at 5 years.[9] Möller et al., found that among patients in whom no measures taken intraoperatively or planned postoperatively (representing natural course), the risk for unfavourable outcomes ranged from 15.9% to 35.9% depending on stone size, in a cohort of patients diagnosed with CBD stones using IOC.[8] Unfavourable outcome was defined as known incomplete clearance of bile ducts with any symptoms or complications related to bile duct stones within 30 days after cholecystectomy. This study also reported 14.9% of patients diagnosed with CBD stones using IOC required postoperative ERCP for CBD stone clearance. Their data from the Swedish GallRiks Registry is one of the largest analyses reported and provides a cautionary note to those who disregard the importance of CBD stones diagnosed at the time of cholecystectomy.

Many now feel that MRCP will replace the use of IOC, and almost one third of UK patients have a pre-operative MRI. This was a stimulus for the Sunflower study, assessing the clinical effectiveness and cost-effectiveness of an expectant management versus preoperative imaging with MRCP in patients with symptomatic gallstones undergoing laparoscopic cholecystectomy, at low or moderate risk of CBD stones.[77] Pre-operative MRCP without IOC has been shown previously to be an effective and safe strategy in the treatment of gallstones, with an acceptable rate of retained CBD stones and BDI.[46]

In patients with gallstone pancreatitis, intraoperative imaging modalities such as IOC or laparoscopic ultrasound (LUS) are important in ensuring that patients are not at risk of subsequent pancreatitis due to retained CBD stones.[78] The main benefit of IOC and LUS over MRCP is its ability to enable CBD imaging at the time of laparoscopic cholecystectomy. IOC has been reported to exhibit a higher diagnostic accuracy at detecting choledocholithiasis compared with MRCP (98% vs. 85),[79] while Richard et al. concluded that there was no place for preoperative MRCP in patients with suspected choledocholithiasis due to the unacceptably elevated rate of false negative results compared with IOC.[80] Thacoor et al. similarly concluded that patients presenting with acute gallstone pancreatitis can be safely and successfully managed with laparoscopic cholecystectomy and IOC, without requiring a preoperative MRCP.[81]

In a randomised controlled trial, Lehrskov found fluorescent cholangiography was not inferior to IOC in detecting the cystic junction with the CBD. This study was very selective including 120 of a potential cohort of 1889 patients with 60 in each arm in a single surgeon study over three years.[12]

The role of laparoscopic ultrasound (LUS) in identifying biliary anatomy and preventing CBD injury is not well defined. LUS and IOC have similar success in visualising the biliary anatomy but it is not widely available and requires significant experience. [82, 83]

There is evidence to support the routine use of IOC in the prevention, diagnosis and management of bile duct injury.[17, 34, 84] During the transitioning period from open to laparoscopic cholecystectomy, a previous meta-analysis conveyed the effective role of routine IOC in the prevention of bile duct injury.[85] Since then, surgical approach to cholecystectomy has changed with the introduction of the critical view of safety technique. It is has been suggested that implementation of a critical view of safety (CVS) could replace routine IOC, but this may reduce the detection rate of choledocholithiasis.[45] In many cases of severe cholecystitis the CVS is not visible, and IOC may be difficult in those patients. In their retrospective study, 57/477 had IOC, and 15/57 had choledocholithiasis. One must assume therefore that the incidence of missed CBD stones must have been significant. Other authors have argued that the two together provide optimal patient outcome.[38] In a recent consensus conference on prevention of bile duct injury during cholecystectomy, Brunt and colleagues recommended the use of IOC among surgeons to mitigate the risk of BDI.[86] In our study, although routine IOC was shown to reduce bile duct injury in the majority of studies, it was an insignificant association. The definition of BDI in these included studies was lacking. For example, Törnqvist includes all forms of bile leakage and cystic duct leakage post cholecystectomy when reporting BDI rate of over 1.3%.[6]

Bile duct injury occurs in 0.3% of cholecystectomies, which results in 2500 injuries per annum in the US alone, with resultant 8.8-fold increase in mortality and a common cause for litigation. [87, 88] The numbers to power a RCT to finally answer the question whether IOC reduces the rate of BDI at cholecystectomy would be near impossible.[89] For this reason, the best available evidence comes from large-scale retrospective analyses. However, these analyses are limited in their interpretation. Three retrospective studies reporting the smallest percentage use of IOC during cholecystectomy are also the three studies reporting an association of increased BDI with IOC.[11, 25, 36] The recent recommendation by the Prevention of Bile Duct Injury Consensus Work Group, for the liberal use of IOC in acute hot gallbladder surgery could skew a potential association of IOC with a higher incidence of BDI as these cases are more prone to CBD injury.[86] Additionally, using IOC as a diagnostic tool after an injury has occurred makes the interpretation of the value of IOC uncertain on retrospective analysis.

This meta-analysis was hampered by considerable statistical heterogeneity reported in the analysis of bile duct injury (p-value< 0.0001, I^2 =97%) and readmission rate (p-value< 0.0001, I^2 =88%) (Figure 4 and 5). Clinical diversity relating to the differences associated with the participants, interventions and outcomes, as well as methodological diversity, contribute to the statistical heterogeneity reported. Furthermore, IOC use extended widely, from routine, selective, to no use at all. A subgroup analysis of the three more routine policies allowed a reduction of I^2 statistic to 64%, with all three reporting a significant protective effect. [6, 30, 31] The remaining five retrospective studies adopting a more selective IOC use, reported an I^2 statistic of 99% when grouped together, revealing an inconclusive effect of the relationship of IOC and BDI. [11, 20, 21, 61, 62] Further investigation of the participants analysed in each of these studies revealed a difference in the average age, with two studies reporting outcomes only from patients aged above 66 and differences involving the indication for cholecystectomy. [21, 25] Of the 10 studies analysed, two were prospective randomized trials reporting outcomes from a small number of patients and therefore a much smaller number of events [61, 62] while the remaining 8 were large retrospective studies using regional or national databases of registered cholecystectomies.[6, 11, 20, 21, 25, 30, 31, 36]

Recent new practice guidelines aimed at prevention of CBD injury make reference to an unpublished meta-analsyis of 8 studies showing the use of IOC was associated with increased intraoperative recognition of CBD injury compared to those without IOC (OR 2.92, 95% CI 1.55-5.68, p=0.014). [86]

Readmission rate assessed across four studies revealed an insignificant association, with IOC (3%) lower than without IOC (3.5%) (p =0.23).[11, 61, 28, 29] Recently McIntyre et al, in a meta-analysis on readmission rate following LC, suggested that IOC might reduce readmission rate.[90] The differences in study design explain part of heterogeneity represented. However, differences in the clinical definition of readmission also existed. Readmission rate was defined according to 30 days[11, 28, 29] or one year.[61] The readmissions were defined in most cases as any referral or readmission to a hospital or clinic, whether they were related to the primary operation or not, usually not defined. One author appropriately defined readmission as being related to the primary operation however, which is a more accurate definition but likely to record a smaller number of events.[28]

There were some limitations to our study due to a lack of reported data on intra-operative complication and conversion rates related to both routine and selective policies of IOC and use of papers in English only. This meta- analysis was not tasked with assessment of the actual skill set required to undertake IOC and its potential benefit in facilitating transcystic CBD stone clearance.

Where routine IOC is planned, the success of the procedure is high (95%) and with a short time to complete (11 min). An important aspect of IOC is the ability of the general surgeon to interpret the results. Interpretation of anatomy was recently described in a study by Chehade that reported 95% of IOCs adequately demonstrated biliary anatomy. Aberrant right sectoral ducts were identified in 15.2% of the complete IOCs, and 2.6% demonstrated left sectoral or confluence anomalies. Only 20.4% of these were reported intraoperatively. [91] Regarding the detection of CBD stones, the combined sensitivity and specificity of IOC in the detection of CBD stones is reported as 0.87 (95% CI: 0.83–0.89) and 0.98 (95% CI: 0.98–0.98) respectively. [78]

We believe that IOC has benefits even in an era of increasing availability of MRCP. Other imaging techniques of the biliary tree will not provide a portal for stone removal. The effectiveness of LCBDE- LC varies between studies, with a recent series by Ballou et al. reporting a success rate of completion and stone clearance of 66%,[92] while others have reported success rates of 80-98.5%.[93-95] With increasing use of one stage bile duct clearance, either with or without intra-operative ERCP, ability to cannulate the cystic duct is becoming increasingly important. IOC should be more widely and consistently used.

Conclusion

The use of IOC still has its place in cholecystectomy based on the detection of choledocholithiasis, and the potential reduction of unfavourable outcomes associated with common bile duct stones.

Figure 1: Identification, review and selection of articles included in the meta-analysis, shown by PRISMA Flow Chart

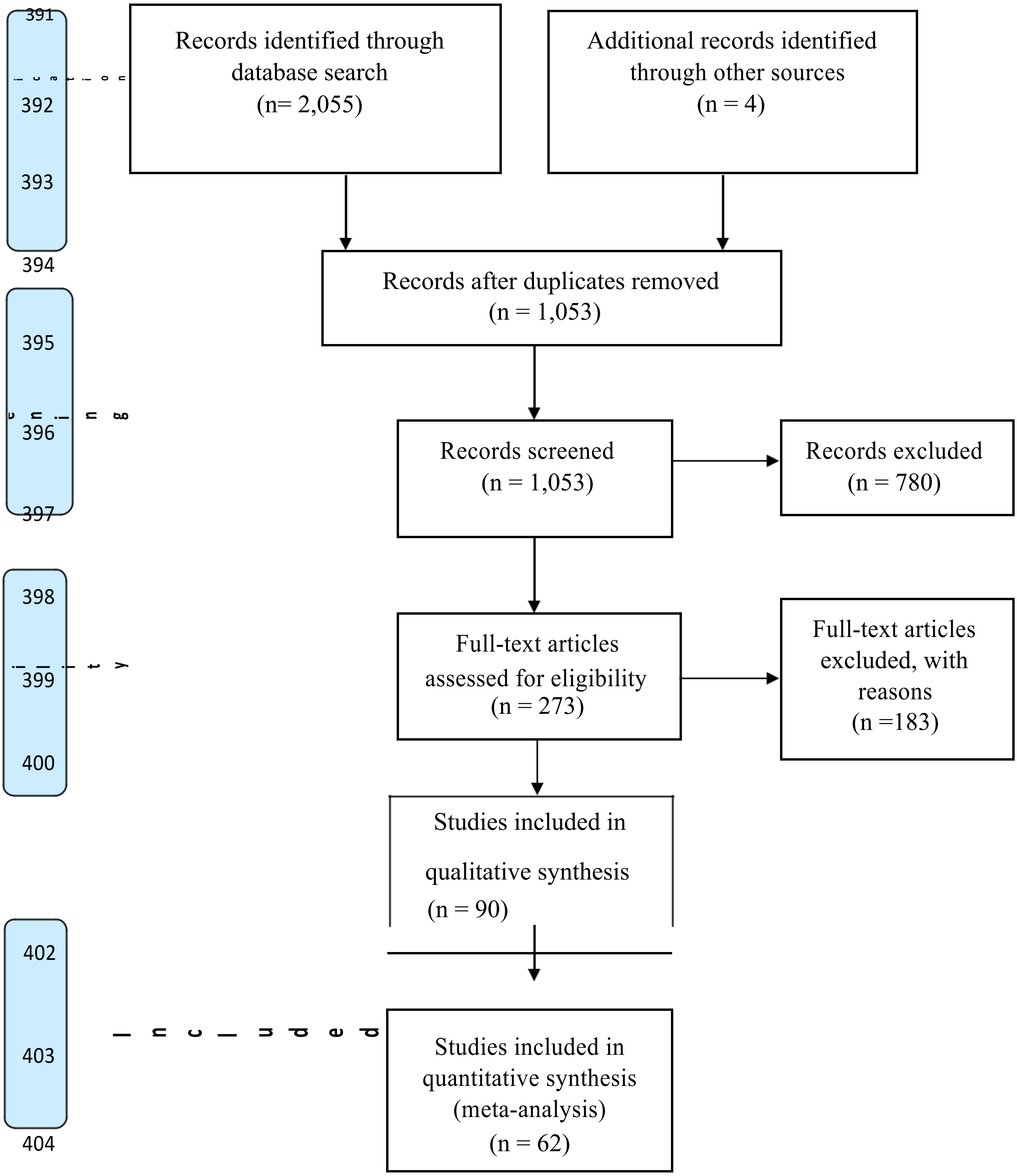


Figure 2: The rate of IOC during cholecystectomy, reported from 56 studies.

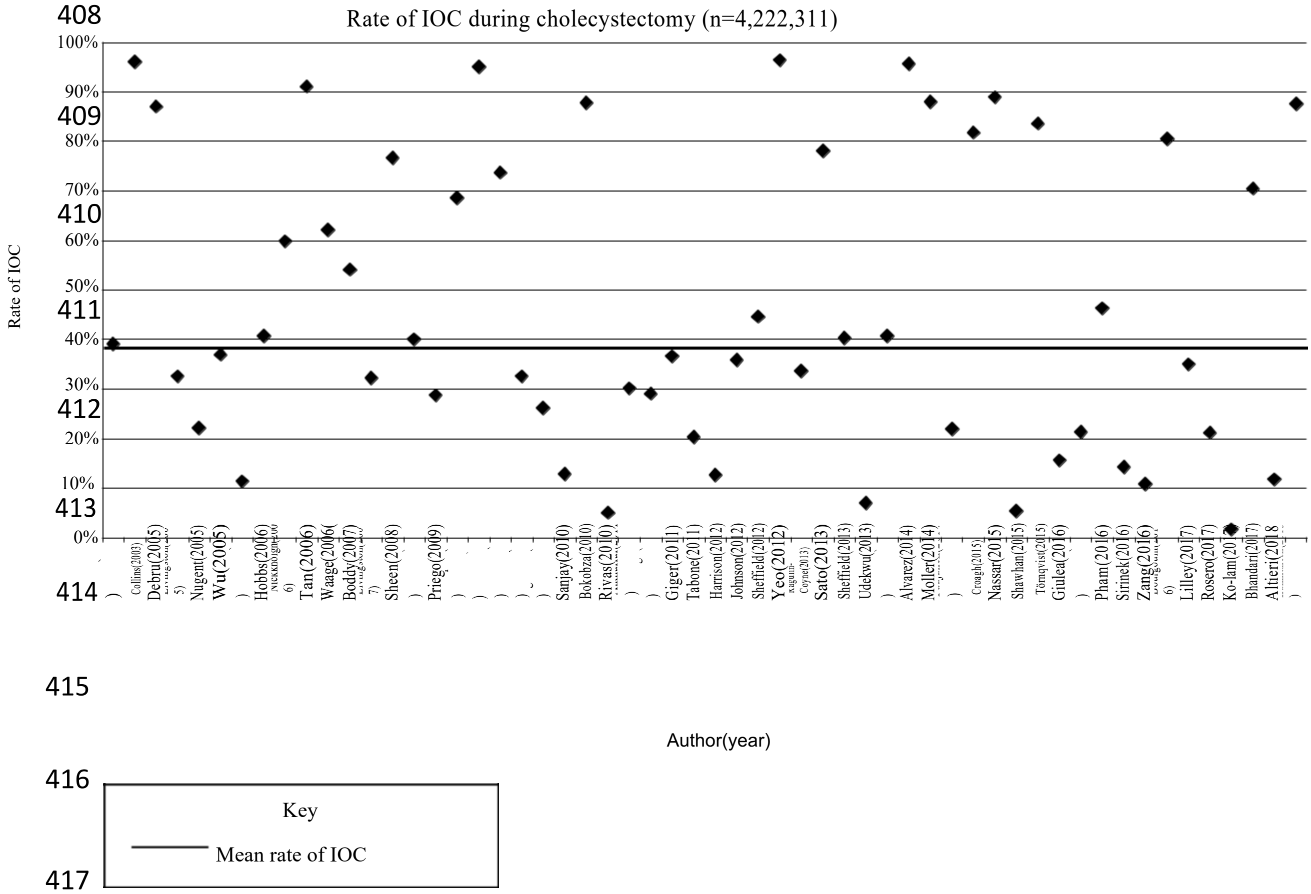


Figure 3: The rate of biliary injury during cholecystectomy with routine IOC versus selective IOC.

Study or Subgroup	Routine Events	Routine Total	Selective Events	Selective Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alkhaffaf (2011)	0	463	4	1159	3.4%	0.28 [0.01, 5.16]
Amott (2005)	1	148	1	155	1.3%	1.05 [0.06, 16.90]
Buddingh (2011)	0	435	8	421	11.5%	0.06 [0.00, 0.97]
Nickkholgh (2006)	0	1330	2	800	4.1%	0.12 [0.01, 2.50]
Ragulin-Coyne (2012)	33	13025	258	98790	79.7%	0.97 [0.67, 1.39]
Total (95% CI)		**15401**		**101325**	**100.0%**	**0.81 [0.57, 1.15]**
Total events	34		273			

Heterogeneity: Chi² = 6.41, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 1.20 (P = 0.23)

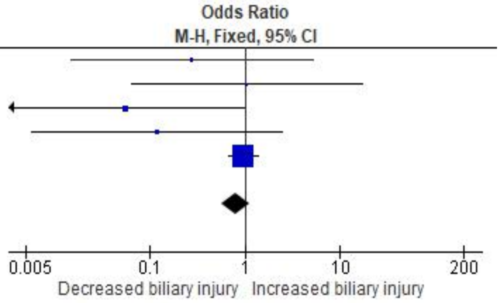


Figure 4: The rate of biliary injury during cholecystectomy with IOC versus without IOC.

Study or Subgroup	With IOC Events	With IOC Total	Without IOC Events	Without IOC Total	Weight	Odds Ratio M-H, Random, 95% CI
Altieri(2018)	108	43688	451	371548	12.2%	2.04 [1.65, 2.52]
Ding(2015)	1	182	1	182	1.1%	1.00 [0.06, 16.11]
Flum(2003)	2380	613706	5531	956655	13.0%	0.67 [0.64, 0.70]
Giger(2011)	40	11642	61	20196	10.5%	1.14 [0.76, 1.70]
Khan(2011)	0	91	1	99	0.8%	0.36 [0.01, 8.92]
Lilley(2017)	643	165471	786	306896	12.8%	1.52 [1.37, 1.69]
Sheffield(2013)	79	37533	201	55399	11.8%	0.58 [0.45, 0.75]
Tornqvist (2015)	580	42346	164	8308	12.4%	0.69 [0.58, 0.82]
Tornqvist(2009)	780	256714	606	117328	12.8%	0.59 [0.53, 0.65]
Waage(2006)	333	94902	280	57874	12.5%	0.72 [0.62, 0.85]
Total (95% CI)		**1266275**		**1894485**	**100.0%**	**0.88 [0.65, 1.19]**
Total events	4944		8082			

Heterogeneity: Tau² = 0.18; Chi² = 313.28, df = 9 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.82 (P = 0.41)

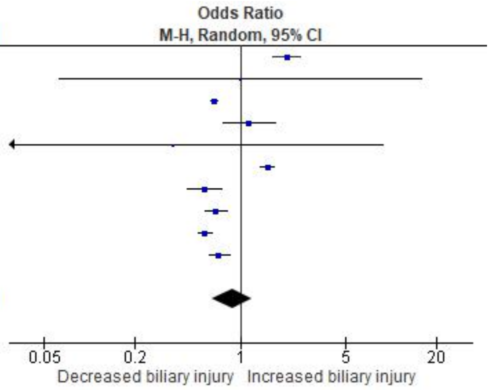
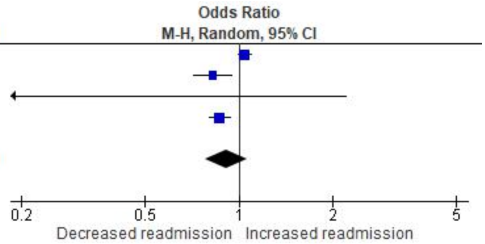


Figure 5: The rate of readmission following cholecystectomy with IOC versus without IOC.

Study or Subgroup	With IOC Events	With IOC Total	Without IOC Events	Without IOC Total	Weight	Odds Ratio M-H, Random, 95% CI
Altieri(2018)	2045	45873	14843	346612	36.2%	1.04 [0.99, 1.09]
Halawani(2016)	249	11227	1113	41598	28.9%	0.83 [0.72, 0.95]
Khan(2011)	0	90	4	99	0.3%	0.12 [0.01, 2.21]
Rosero(2017)	883	48718	3780	181562	34.6%	0.87 [0.81, 0.93]
Total (95% CI)		**105908**		**569871**	**100.0%**	**0.91 [0.78, 1.06]**
Total events	3177		19740			

Heterogeneity: Tau² = 0.02; Chi² = 24.82, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 1.20 (P = 0.23)



Author contribution

Eoin Donnellan: Conceptualisation, Methodology, Formal analysis, Investigation, Project administration, Writing - Review & Editing. **Jonathan Coulter**: Validation, Formal analysis. **Cherian Mathew**: Investigation, Validation, Data curation. **Michelle Choynowski**: Methodology, Formal analysis. **Louise Flanagan**: Validation **Magda Bucholc**: Methodology, Formal analysis **Alison Johnston**: Conceptualisation, Methodology, Funding acquisition, Writing - Review & Editing. **Michael Sugrue**: Conceptualisation, Supervision, Funding acquisition, Writing - Review & Editing

Conflict of interest

None

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Table 1. Characteristics of studies reporting outcomes from a routine or selective policy of IOC use

Study ID	**Year**	**Study design**	**Study Period**	**Policy of IOC**	**Incidence of common bile duct stones detected by IOC**	**Incidence of bile duct injury with routine and selective IOC**
Amott et al.	2005	Prospective randomized study	1995-2002	Routine and selective	Routine: 8.1% Selective: 3.2%	Routine: 0.68% Selective: 0.65%
Wu et al.	2005	Prospective study	1988-2000	Selective	9.2%	-
Nickkholgh et al.	2006	Retrospective study	1992-2001	Routine and Selective	Routine:2.8% Selective:1.1%	Routine:0% Selective: 0.25%
Horwood et al.	2010	Prospective study	2004-2008	Selective	12.8%	-
Sanjay et al.	2010	Retrospective study	2004-2007	Selective	3.4%	-
Alkhaffaf et al.	2011	Comparison study using data collected from a prospective database.	2005-2007	Routine and selective	Routine:7.8% Selective: 0.7%	Routine: 0% Selective: 0.35%
Buddingh et al.	2011	Retrospective study	2004-2009	Routine and selective	Routine: 4.8% Selective:1.0%	Routine:0% Selective:1.9%
Giulea et al.	2016	Retrospective study	2013-2014	Selective	6.1%	-
Nassar et al.	2015	Prospective study	1992-2014	Routine	18.9%	-
Photi et al.	2017	Retrospective study	2013-2015	Routine	10.1%	-
Tan et al.	2006	Prospective study	2004	Routine	5.9%	-
Videhult et al.	2008	Prospective study	2003-2005	Routine	11.4%	-
Ragulin-Coyne et al.	2012	Retrospective study	2004-2009	Routine and Selective	-	Routine:0.25% Selective:0.26%
Sheen et al.	2007	Prospective study	1999-2006	Routine	7%	-
Iranmanesh et al.	2018	Retrospective study of a prospective database	2013-2015	Routine	6.6%	-
Yeo et al.	2011	Prospective study	2009-2010	Routine	9.1%	-

LC=laparoscopic cholecystectomy

Table 2. Characteristics of studies reporting outcomes with and without the use of IOC

Study ID	Year Published	Study design	Study period	Use of IOC	Incidence of BDI with and without IOC	Readmission rate with and without IOC
Altieri et al.	2018	Retrospective analysis	2000-2014	11.7%	With: 0.25% Without: 0.12%	With: 4.5% Without: 4.3%
Ding et al.	2015	Randomized trial	2012-2014	Patients equally randomized to 2 treatment groups: LC and IOC, Routine LC.	With: 0.54% Without:0.54%	-
Flum et al.	2003	Retrospective study	1992-1999	39.1%	With: 0.39% Without:0.58%	-
Giger et al.	2011	Retrospective analysis of a prospectively collected database	1995-2005	36.6%	With:0.34% Without:0.3%	-
Khan et al.	2011	Randomized trial	2003-2007	Patients equally randomized to 2 treatment groups: LC with IOC, LC only	With: 0% Without: 1%	With: 0% Without: 4%
Halawani et al.	2016	Retrospective study	2012-2013	21.3%	-	With: 2.2% Without: 2.7%
Lilley et al.	2017	Retrospective study	2005-2010	35%	With: 0.39% Without: 0.26%	-
Rosero et al.	2017	Retrospective study	2009-2011	21.1%	-	With:1.8% Without: 2.1%
Sheffield et al.	2013	Retrospective study	2001-2009	40.4%	With:0.21% Without:0.36%	-
Törnqvist et al.	2009	Retrospective study	1965-2005	68.6%	With: 0.3% Without:0.52%	-
Törnqvist et al.	2015	Retrospective study	2005-2010	83.6%	With:1.37% Without:1.97%	-
Waage et al.	2006	Retrospective study	1987-2001	62.1%	With: 0.35% Without: 0.48%	-

LC- laparoscopic cholecystectomy