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Intraoperative Cholangiography in Laparoscopic Cholecystectomy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background/Objectives: Routine intraoperative cholangiography (IOC) for laparoscopic cholecystectomy (LC) remains controversial. The primary outcomes of this meta-analysis were detection rates of choledocholithiasis, bile duct injuries (BDI), and missed stones in LCs.

Methods: A systematic literature search was conducted for the time period January 1, 1990 to July 31, 2022. Some studies reported LCs with conversion to open therefore subgroup analysis in BDI rates was performed for studies which included LCs with and without conversion to open. Studies including primary open cholecystectomies were excluded. I^2 statistics were used for heterogeneity analysis.

Results: Fourteen studies involving 440659 patients were included. In studies comparing routine and selective IOC policies in LC, 61.1% of patients underwent routine IOC; 38.9% underwent selective IOC. In studies comparing IOC to no IOC in LC, 17.3% of patients had IOC; 82.7% did not. Between the selective and routine IOC groups there was no difference in choledocholithiasis detection rate (odds ratio [OR] = 1.33, p = 0.20, 95% confidence interval [CI] = 0.86 – 2.04), no difference in the rate of missed stones (OR = 1.59, p = 0.58; 95% CI = 0.31 – 8.29), and no difference in BDI rates in selective compared to routine IOC (OR = 0.92, p = 0.92; 95% CI = 0.20 – 4.22). There was no difference in the BDI detection rates in LC with and without IOC (OR = 1.12, p = 0.77; 95% CI = 0.52 – 2.38).

Conclusion: This is the largest meta-analysis on this topic to date. There was no statistically significant difference in choledocholithiasis detection, missed stones, or BDI rates in the analyzed groups.

Key Words: Bile duct injury, Choledocholithiasis, Intraoperative cholangiography, Laparoscopic cholecystectomy, Routine and selective.

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is the gold standard for management for patients with symptomatic gallstones.[1–4] The addition of an intraoperative cholangiography (IOC), either routine or selective, is used to detect choledocholithiasis, which is found in approximately 8% – 15%.[5] Furthermore, IOC has also been justified to delineate biliary tract anatomy and the early detection of bile duct injury (BDI).

The proponents of routine IOC argue that all patients should be screened for CBD stones and BDI, as early detection can drastically improve patient morbidity and mortality.[6,7] Proponents of selective IOC use it only in patients at high risk of choledocholithiasis, based on a variety of criteria such as a history of pancreatitis, jaundice, abnormal liver function tests, or biliary dilatation on imaging.[8,9] The precise criteria for the use of selective IOC continues to be controversial and based on institution and surgeon preference.

The arguments against the routine use include the increased intraoperative time required, high false positive rates requiring unnecessary additional interventions like endoscopic retrograde cholangiopancreatography, a failure rate of 3% – 17%, and increased costs with resource utilization.[1,7,10] Furthermore, there are the risks relating to ionising radiation exposure to patients and operating theater personnel.[11]

The aim of this study was to evaluate efficacy of IOC in LC by systematically evaluating and synthesizing the evidence from the literature. This study investigated both the comparison of routine IOC to selective IOC in patients undergoing LC as well as analyzing the LC outcomes in patients without the use of IOC. The primary outcomes of interest were choledocholithiasis detection, missed stones, and the rate of BDI.

METHODS

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12] criteria were adapted (**Figure 1**). A comprehensive electronic literature search of Ovid MEDLINE, PubMed, EMBASE, and Cochrane Library was conducted for the dates January 1, 2000 – July 31, 2022. A grey literature search was conducted using the GoogleScholar search engine. A manual search of relevant journals and bibliographies of potential articles was performed for additional references. The search was completed independently by authors CH and SA.

The keywords used included the Medical Subheading (MeSH): laparoscopic cholecystectomy, cholecystectomy, cholangiography, per-operative cholangiography, routine, and selective. These terms were used in [MeSH] format for searching the Cochrane Library. For all other databases, the search was conducted by combining similar terms using the Boolean operator "OR" and terms were grouped using the Boolean operator "AND" to find appropriate results.

All citations found via electronic search were independently reviewed sequentially. Two authors (CH and SA)

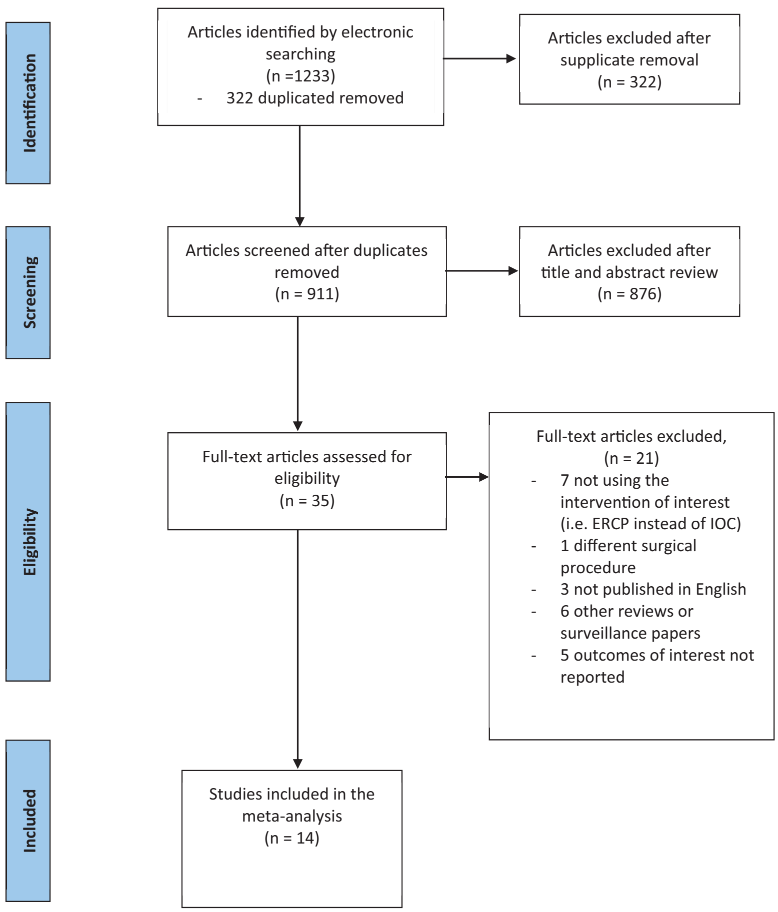

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing selection of article review.

independently screened the abstract and title articles for potential inclusion. Shortlisted articles were then screened by full-text review for inclusion or exclusion based on selection criteria. Discrepancies in paper selection were resolved through group consensus and discussion with a third author (SG).

Inclusion and Exclusion Criteria

Randomized controlled trials (RCTs), controlled clinical trials (CCTs), retrospective and prospective cohort studies that compared IOC procedures in adults were included, namely: selective compared to routine IOC and use of IOC compared to no IOC for LC. We excluded: non-English studies, reviews (systematic and narrative), theses, editorials, case reports, case series containing < 30 patients, epidemiological studies, surveillance studies, economic evaluations, and conference proceedings. Studies including primary open cholecystectomies were excluded due to the risk of bias relating to the increased complexity or difficulties relating to these procedures.[13,14] However studies investigating LCs that had some cases converted to open were included.

Quality Assessment for Included Studies

The studies were assessed independently by three authors (CH, SA, and RS) for quality using the Methodological Index for Non-Randomized Studies (MINORS).[15] This assessment involved scoring all studies from 0 to 2 against 12 items. Tallied scores can range from 0 reflecting a low-quality study to 24 for a high-quality study. Any disparities in scores were resolved through discussion with a fourth author (SG) and group consensus.

Outcome Measures

The primary outcome of this study was to assess the difference in choledocholithiasis detection rates between routine and selective IOC groups. Successful IOC was used as the denominator in this analysis. Secondary outcomes were the incidence missed choledocholithiasis found on follow-up and the rate of BDI in routine compared to selective IOC policies and in LC with IOC compared to those without IOC, the denominator was all those allocated to each group.

Data Analysis

All statistical analysis was performed using Review Manager Software, Version 5.4.1 (The Cochrane Collaboration, Oxford, UK). Pooled analysis was performed comparing routine and selective IOC policies and IOC compared to no IOC policies to calculate the odds ratio (OR) and 95% confidence interval (CI). When analyzing BDI rates, subgroup analysis was performed with papers with LC only and papers reporting LC with some cases converted to open to acknowledge there may be bias relating to the increased complexity of these procedures. I^2 statistics with *P*-value set to $P < 0.10$ for significance, were utilized to assess heterogeneity. I^2 scores > 50% denoted significant heterogeneity. When the heterogeneity test was statistically significant, a random effects model was used; which assumes variation in treatment effects between studies, and estimates a more conservative overall treatment effect with wider confidence intervals. Where heterogeneity was not significant, a fixed effects model was used. Potential publication bias was evaluated using funnel plots; asymmetry within the plot implies that the results were subject to bias (**Figure 2**). Forest plots were created to demonstrate the pooled ORs and corresponding 95% CIs. *P*-values < 0.05 were considered statistically significant.

RESULTS

The PRISMA diagram exhibiting the different phases of the study selection is shown in **Figure 1**.[12] A total of 1,232 articles were retrieved from primary electronic searches. After removal of duplicates, 910 citations were screened using title and abstract. Forty-one articles were selected for final evaluation. Full texts of these articles were retrieved and three reviewers performed the final selection. Of these, 14 articles (four RCTs, four prospective studies, and six retrospective longitudinal studies) fulfilled the inclusion criteria.

A total of 440,659 pooled patients were included. In studies comparing routine versus selective IOC cohorts there were 3,605 (61.1%) patients and 2,294 (38.9%) patients, respectively. In studies that compared outcomes of IOC in LC, 17.3% of patients had IOC during LC (n = 75,211) and 82.7% patients had LC only (n = 359,549), with most of these patients coming from large retrospective studies.

Three of the seven papers comparing routine to selective IOC reported LCs that were converted to open. The rates of conversion were in the single figures[2,16,17] other than in Kohn's[18] paper which had a selective IOC conversion to open rate of 18%, compared to 0% among the routine IOC group. Of the seven papers that compared IOC to no IOC in LC, three papers reported rates of conversion to open ranging from 0% to 3%.[4,19,20]

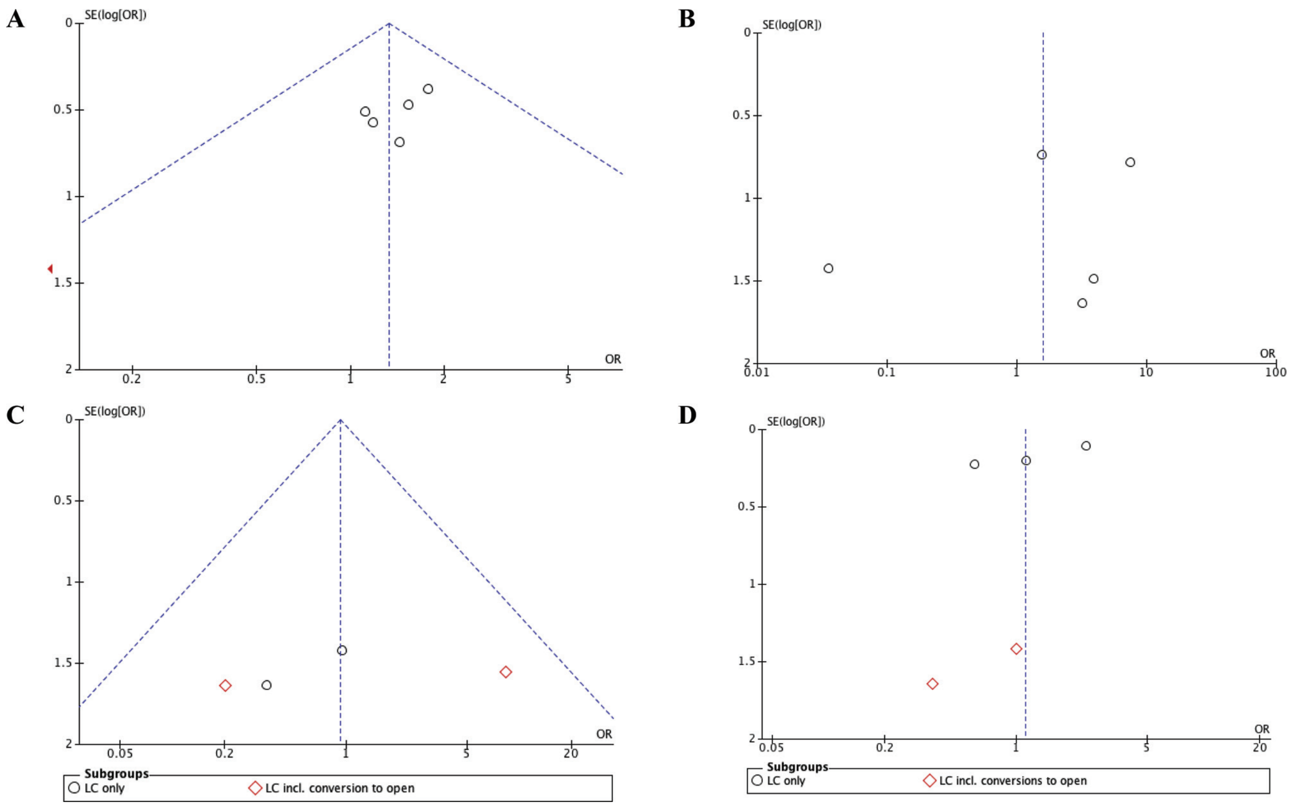

Figure 2. Funnel plots for safety outcomes with ninety-five percent confidence limits: **(A)** common bile duct stone detection in routine versus selective intraoperative cholangiography (IOC) in laparoscopic cholecystectomy **(B)** missed stones on follow-up in routine and selective intraoperative cholangiography **(C)** bile duct injury rates in routine and selective intraoperative cholangiography **(D)** bile duct injury rates in intraoperative cholangiography versus no intraoperative cholangiography.

The characteristics of included studies are summarised in **Tables 1** and **2**.

Methodological Quality of the Included Studies

There was heterogeneity among the included trials in terms of methodological quality and assessment methods. Overall, the quality of the studies scored using the MINORS criteria was good to medium (**Table 3**). The overall mean for the included trials methodological quality scores was 17.9 ± 1.7 and ranged from 15 – 21 out of 24. Half of the non-RCTs had flaws in their methodological design with a high risk of bias related to their group allocation procedure, outcome assessors, and outcome analysis. Moreover, 10 studies were limited to a single facility. In those reporting on stones on follow-up, follow-up time points varied with three having greater than 12 months and three article not specifically stating follow-up timing, but rather referred to 'stones on follow-up'.

Common Bile Duct Stone Detection Incidence

Rates of common bile duct (CBD) stone detection rates were evaluated in six of the included studies. As the heterogeneity was low to moderate, ($p = 0.20$, $I^2 = 31\%$), a fixed effects model was used for statistical analysis. As demonstrated in **Figure 3**, there was no statistically significant difference in choledocholithiasis detection rates in successful IOC between the routine and selective groups, though there was a trend towards higher CBD stone detection rate in the selective group ($OR = 1.33$, $P = 0.20$, 95% $CI = 0.86 – 2.04$). Additionally, the false positive rate of IOC differed among the studies ranging from 0% to 5.5%.[2,16]

Missed Choledocholithiasis on Follow-up

Six studies reported rates of missed stones on follow-up. There was no difference between routine and selective IOC policies and missed stones ($OR = 1.59$, $P = 0.58$;

Table 1.
Summary of Included Studies – Laparoscopic Cholecystectomy with and without Intraoperative Cholangiography (IOC)

Author, Year Country, Type of study	Study Design	Study period	Use of IOC	% BDI With or Without IOC	IOC vs. No IOC	Number of patients	LC converted to open	Patient demographics	Outcome: BDI
Altieri, 2017, USA[21]	Retrospective analysis	2000 – 2014	13.30%	With IOC: 0.25%	IOC	43688	Nil	NR	108/43688
				Without IOC: 0.10%	No IOC	327860	Nil	NR	343/327860
Ding, 2015, China[4]	Randomized trial	2012 – 2014	49.87%	With IOC: 0.54%	IOC	182	4/182	Mean age = 58.22 ± 8.41 years	1/182
				Without IOC:0.54%	No IOC	182	3/182	Mean age = 57.43 ± 7.15 years	1/182
Flum, 2001, USA[40]	Retrospective study	1991 – 1998	63.71%	With IOC : 0.20%	IOC	19514	Nil	NR	39/19514
				Without IOC: 0.33%	No IOC	11116	Nil	NR	37/11116
Giger, 2011, Switzerland[41]	Retrospective analysis of prospectively collected database	1995 – 2005	36.60%	With IOC: 0.34%	IOC	11642	Nil	Mean age 54.4 ± 15.9 years. M:F 10:22	40/11642
				Without IOC: 0.3%	No IOC	20196	Nil		61/20196
Khan, 2011, UK[19]	Randomized trial	2003 – 2007	47.89%	With IOC: 0%	IOC	91	0/91	Mean age = 59 years, M:F ratio = 15:76	0/91
				Without IOC: 1%	No IOC	99	1/99	Mean age = 53 years, M:F ratio = 1:3	1/99
Soper, 1992, USA[42]	Randomized trial	1991 – 1992	48.70%	With IOC: 0%	IOC	56	nil	Mean age = 48 ± 2 years, M:F ratio = 1:3	0/56
				Without IOC: 0%	No IOC	59	nil	Mean age = 51 ± 2 years, M:F ratio = 27:73	0/59
Verma, 2016, Australia[20]	Prospective study	2013 – 2014	50.7%	With IOC: 0%	IOC	38	2/75 (not defined which group)	M:F ratio = 3:7	0/38
				Without IOC: 0%	No IOC	37			0/37

Abbreviations: LC, Laparoscopic Cholecystectomy; IOC, Intraoperative Cholangiography; BDI, bile duct injury; CBD, common bile duct; M: F ratio, male to female ratio; NR, not reported; RCT, Randomized controlled trial; UK, United Kingdom; USA, United States of America.
Results are reported as mean (standard deviation) or as a fraction.

Table 2.
Summary of Included Studies – Routine and Selective Intraoperative Cholangiography (IOC) Use in Laparoscopic Cholecystectomy

Author, Year of publication, country	Study Design	Study period	Policy of IOC	Incidence of BDI with and without IOC	IOC policy	Number of patients	Conversions to open	Patient demographics	Outcomes: BDI	Outcomes: CBD stone detection incidence	Outcomes: Missed stones
Amott, 2005, Australia[43]	Prospective Randomized study	1995 – 2002	Routine and Selective	Routine: 0.68%	Routine	148	nil	NR	1/148	12/94	3/152
				Selective 0.65%	Selective	155	nil	NR	1/155	5/34	5/163
Carlson, 1993, USA[44]	Prospective study	Not stated	Routine and Selective	Routine: 0.61%	Routine	164	nil	NR	1/164	NR	0/164
				Selective: 0%	Selective	155	nil	NR	0/155	NR	1/155
Guerra-Filho, 2007, Brazil[17]	Prospective study	1992 – 1994	Routine and selective	Not recorded	Routine	127	nil	Mean age = 48.8 (13 – 83) years, M:F ratio = 1:3 approximately	NR	11/102	NR
					Selective	127	nil	Mean age = 47.9 (12 – 91) years, M:F ratio = 1:3 approximately	NR	7/59	NR
Kohn, 2004, USA[18]	Retrospective study	1999 – 2000	Routine and Selective	Not recorded	Routine	38	0/38	Mean age = 49 years, M:F ratio = 12:27	NR	5/38	0/38
					Selective	112	20/112	Mean age = 47 years, M:F ratio = 43:69	NR	5/28	5/112
Ladosci, 1997, England[16]	Randomized trial	1991 – 1993	Routine and Selective	Routine: 0.36% Selective: 0%	Routine	276	19/276	Mean age = 48.1 ± 16.4 years, M:F ratio = 24.6:73.6	1/276	13/187	0/276
					Selective	458	15/458	Mean age = 49 ± 16.3 years, M:F ratio = 1:3 approximately	0/458	8/78	0/458
Nickkholgh, 2006, Iran[2]	Retrospective study	1992 – 2001	Routine and Selective	Routine: 0% Selective: 0.25%	Routine	1330	61 total, not described which group	NR	0/1330	37/1330	2/1330
					Selective	800		NR	2/800	9/159	9/800
Snow, 2001, USA[45]	Retrospective study	1989 – 1998	Routine and Selective	0% both	Routine	1522	nil	NR	0/1522	136/1517	42/1522
					Selective	139	nil	NR	0/487	0/138	0/487

Abbreviations: IOC, Intraoperative Cholangiography; BDI, bile duct injury; CBD, common bile duct.

Table 3.
Methodological Index for Non-Randomized Studies Assessment of Bias

MINORS items	Altieri 2017[21]	Amott, 2005[42]	Carlson, 1993[44]	Ding, 2015[4]	Flum 2001[40]	Giger 2011[41]	Guerra-Filho 2007[17]	Khan, 2011[19]	Kohn, 2004[18]	Ladocsi, 1997[16]	Nickkholgh, 2005[2]	Snow 2000[45]	Soper, 1992[42]	Verma, 2016[20]
1. A clearly stated aim	2	2	2	2	2	2	2	1	1	1	1	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	1	2	2	2	1	1	2	2	2	2	2	2	2	2
4. Endpoints appropriate to aim	1	2	2	2	1	2	1	2	2	2	2	2	2	1
5. Unbiased assessment of the study endpoint	2	1	2	2	1	2	2	2	2	2	2	2	2	2
6. Appropriate follow-up period	1	2	2	2	0	1	0	2	2	2	2	1	1	2
7. Loss to follow up less than 5%	0	1	2	1	0	0	2	2	2	2	2	2	0	2
8. Prospective calculation of the study size	2	1	1	1	2	2	1	1	1	1	1	0	1	1
9. An adequate control group	2	2	2	2	2	2	2	2	2	2	2	2	2	2
10. Contemporary groups	2	2	1	2	1	2	1	2	2	2	0	1	2	1
11. Baseline equivalence of groups	2	0	0	2	1	0	1	1	2	2	1	0	1	0
12. Adequate statistical analyses	2	0	0	0	2	2	0	0	0	1	0	0	0	0
TOTAL SCORE	19	17	18	20	15	18	16	19	20	21	17	16	17	17

MINORS, Methodological Index for Non-Randomized Studies.

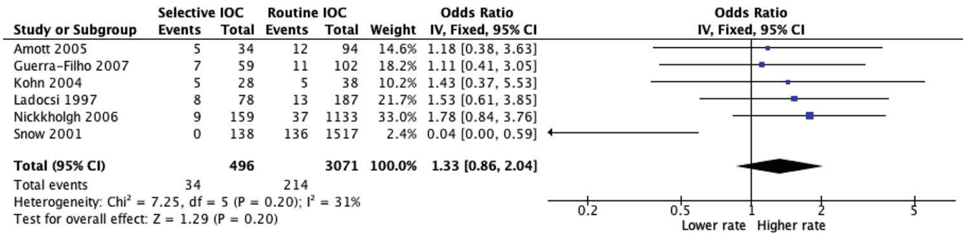

Figure 3. Meta-analysis of choledocholithiasis detection rates between routine versus selective intraoperative cholangiography (IOC) in laparoscopic cholecystectomy.

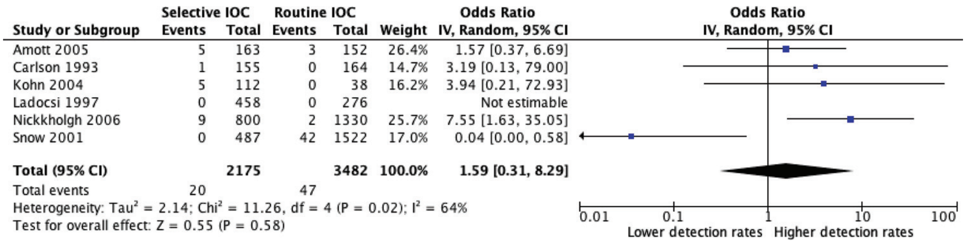

Figure 4. Meta-analysis of missed choledocholithiasis between routine and selective intraoperative cholangiography.

95% CI = 0.31 – 8.29). Due to heterogeneity (P = 0.02, I^2 = 64%), a random effects model was used. The meta-analysis for missed stones on follow-up is illustrated in **Figure 4**.

Bile Duct Injury

A total of five studies included data comparing BDI rates between routine and selective IOC use in LCs. Subgroup analyses were performed to account for potential bias between studies which included some LCs converted to open and those that were purely LCs. However, as demonstrated in **Figure 5**, there was no statistically significant result in each group or combined (OR = 0.92, P = 0.92; 95% CI = 0.20 – 4.22).

In comparing IOC to no IOC use in LC, the meta-analysis found no significant difference in the BDI detection rates (OR = 1.12, P = 0.77; 95% CI = 0.52 – 2.38). Similarly, there was no significant finding in each subgroup or combined for the rates of BDI. As there was significant heterogeneity

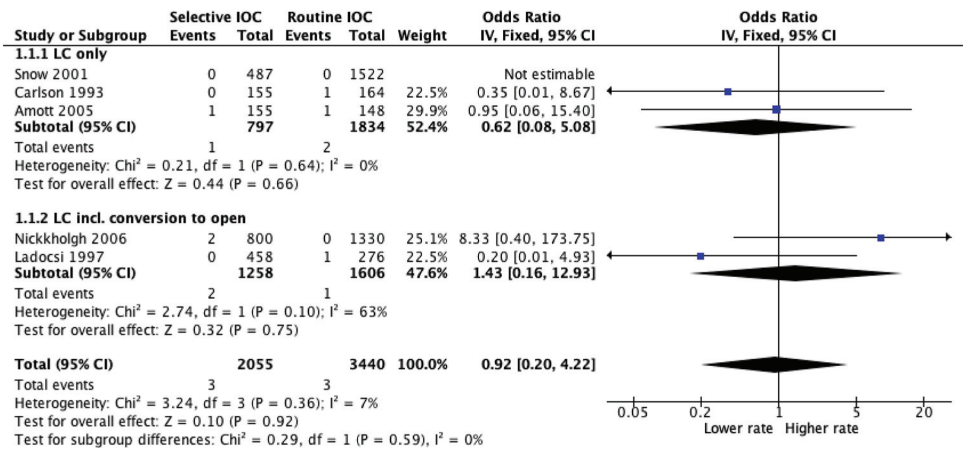

Figure 5. Meta-analysis of bile duct injury rates between routine and selective intraoperative cholangiography.

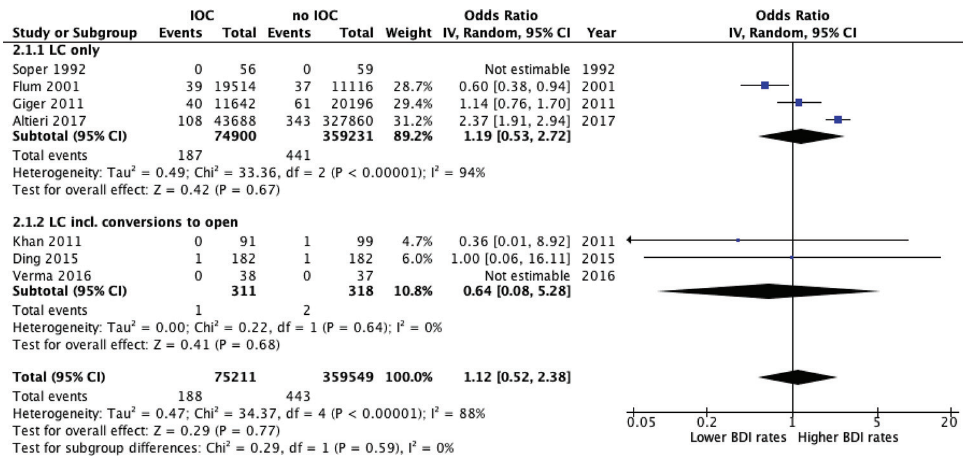

Figure 6. Meta-analysis of bile duct injury rates between laparoscopic cholecystectomy with intraoperative cholangiography versus without intraoperative cholangiography.

(I^2 = 88%, P < 0.00001) a random effects model was employed (**Figure 6**).

DISCUSSION

This is the largest systematic review and meta-analysis to look at choledocholithiasis, missed stones, and BDI detection rates in laparoscopic cholecystectomies. There were no statistically significant findings in any outcome comparison group and there was significant heterogeneity within the studies. Essentially, larger, more robust studies are required to support IOC policy application one way or another.

Despite minimal evidence for the selective or routine application of IOC, there remain strong surgical cultures of routine and selective IOC worldwide. In 2014 – 2015, IOC was performed in 81% of LC cases in Australia[1] whereas, in the United States of America the trend is towards selective IOC with only 10% to 12% of LCs in New York needed an IOC.[21] Even within Australia, there are differences between IOC rates in the public and private healthcare systems; in the private sector, surgeons used IOC at the lower rate of 75%[22] in LC compared to 81% in the public hospital system. Additionally, this report found that 60% of surgeons billed an IOC for some patients, this may be a reflection that 60% of surgeons in the private sector perform IOCs selectively in Australia.[22] An additional factor is that studies report that surgeons with a high-volume caseload, operating in high volume hospitals are more likely to perform IOC.[23–25]

Indeed, the updated 2018 Tokyo Guidelines for surgical management of acute cholecystitis state that "there is no evidence for the value of intraoperative cholangiography"[14] and due to insufficient evidence and mixed results,[25–28] the guidelines suggest that IOC is optional.[14] The findings of this meta-analysis are in line with these sentiments as there was no statistically significant difference in the rates of CBD stone detection, rates of missed stones, or BDI between the groups.

Despite the lack of convincing evidence on the matter, The Australian Medicare Benefits Schedule Review Taskforce Report for General Surgery from 2019 states that it is 'best practice to perform an intraoperative cholangiogram at the time of cholecystectomy' and that 'performing a cholangiogram is incentivised' at time of LC, with a higher fee attributed.[29] An Australian study of The Medicare Benefits Scheme that analyzed trends of IOC, cholecystectomy, and BDI repair between January 1, 2001 and December 31, 2019 revealed a 31.8% increase in IOCs performed despite only a 7.0% increase in cholecystectomies.[30] Additionally, there was a minimal change in the number of BDIs and thereby claimed that use of routine IOC to prevent or minimise BDI was unwarranted.[30]

A factor which may confound the results is that with routine cholangiography, the surgeon becomes more experienced and is more likely to perform it well and safely.[31] Surgeons who do not perform IOC routinely may find the procedure difficult and consequently this may increase the potential for injury and misinterpretation.[32] Furthermore, with the global trend of rising obesity, the technical challenge of IOC performance is amplified. Additionally, when there is a positive IOC finding in LC, there is a developing trend towards performing an LCBDE during LC rather than postoperative like endoscopic retrograde cholangiopancreatography. This is because additional anesthesia is not required and complications such as pancreatitis, cholangitis, and duodenal perforation are avoided.[33] This is relevant because the skills associated with IOC provide an excellent foundation for LCBDE and therefore with routine application of IOC one may develop confidence in performing LCBDE.[33]

The arguments regarding increased operative time may be mitigated with the fact with routine performance of IOC the staff may be more adept with the set-up of the IOC equipment and shorter IOC procedure length compared to those who perform IOC occasionally. One large Swedish analysis found that for surgeons and teams performing IOC routinely, the procedure length is on average 12 min compared to 25 min for selective IOC.[34] Additionally, while the cost of performing IOC during every LC may be higher in the immediate term, an economic analysis found that the cost to the healthcare system of missed BDI and stones with resultant readmission, further imaging, and return to operating theater in those without IOC during LC is far higher.[35]

The detection of CBD stones is one of the primary reasons for IOC in cholecystectomies.[36] However, there was no difference between intraoperative choledocholithiasis detection rates between routine and selective IOC. Additionally, there was no difference in the rates of missed stones between the two groups, suggesting that there is no greater benefit in performing routine IOC in the hopes of detecting more potentially troublesome choledocholithiasis.

In total, 11 of the 14 included studies were RCTs and were of good quality (MINORS score >16). The remaining three articles consisted of one prospective and two retrospective studies and were of moderate to poor quality. Furthermore, each of the studies greatly varied in methodologies and only four were multicenter studies. To account for the heterogeneity of the data, random effects models were employed where appropriate. There are limitations in the methodology and the completeness of the retrieved literature in this review. Inclusion of the nonrandomized longitudinal studies may have introduced selection and recall bias. Only papers published in English were included which might have introduced a reference bias.

This is the largest meta-analysis investigating laparoscopic cholecystectomies and the use of IOC in detection of choledocholithiasis and BDI. Previous meta-analyses have included primary open-cholecystectomies,[35,37] pediatric populations,[13,35,37,38] misclassified routine and selective IOC when indeed they were papers comparing IOC to no IOC,[35,36,38] had much smaller populations,[39] and/or had narrower timeframes.[37] Our results, therefore, provide the most comprehensive analysis to date to address the role of IOC during laparoscopic cholecystectomy with an all-inclusive timeframe and specific, well-defined inclusion criteria.

CONCLUSION

This study is the largest to investigate choledocholithiasis and BDI detection rates in IOC in LC. Despite surgical cultures and incentives to perform IOC routinely, this study supports that there is no strong evidence to suggest that intraoperative choledocholithiasis detection, missed stones, and BDI detection rates are lower with either routine or selective IOC. Due to significant heterogeneity in the analyses and, with large patient numbers from retrospective studies and a lack of large multicenter trials, no definitive conclusions about how IOC should be used can be drawn from this study. To add to the literature and to support routine IOC use one way or another, a large multicenter RCT with robust methodology is needed. Additionally, an outcome analysis should be performed based on clinical signs and biochemical markers in those who had routine and selective IOC in LC to inform a standard algorithm on who benefits most from an IOC during LC.

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