STRATEGIES FOR IMPROVED BILIARY INTERVENTIONS

Kovács Norbert M.D.

Ph.D. thesis

Szeged, Hungary

2024

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Szeged, Hungary

2024

Scientific metrics

Publications related to the subject of the thesis (number of publications: 2, cumulative impact factor: 6.1):

I. **Kovács, N.,** Németh, D., Földi, M., Nagy, B., Bunduc, S., Hegyi, P., Bajor, J., Müller, E., K., Vincze, Á., Erőss, B., Ábrahám, Sz. Selective intraoperative cholangiography should be considered over routine intraoperative cholangiography during cholecystectomy: a systematic review and meta-analysis. Surgical Endoscopy, 2022, 36.10: 7126-7139. (D1, IF: 3.1)

II. **Kovács, N.,** Pécsi, D., Sipos, Z., Farkas, N., Földi, M., Hegyi, P., Bajor, J., Erőss, B., Márta, K., Mikó, A., Rakonczay Jr, Z., Sarlós, P., Ábrahám, Sz., Vincze, Á. Suprapapillary Biliary Stents Have Longer Patency Times than Transpapillary Stents—A Systematic Review and Meta-Analysis. Journal of Clinical Medicine, 2023, 12.3: 898. (Q1, IF: 3)

Publications not related to the subject of the thesis (number of publications: 5, cumulative impact factor: 19.7)

I. Müller, K. E., Dohos, D., **Kovács, N.** *et al.* (2022). Immune response to influenza and pneumococcal vaccines in adults with inflammatory bowel disease: A systematic review and meta-analysis of 1429 patients. Vaccine, 40(13), 2076-2086. (Q1, IF: 5.5)

II. Weninger, V., Agócs, G., **Kovács, N.** *et al.* (2024). Hyaluronate acid plus platelet-rich plasma is superior to steroids for pain relief less than 6 months using injection therapy of partial rotator cuff tears: A systematic review and network meta-analysis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. (D1, IF: 4.7)

III. de Jonge, R., Máté, M., **Kovács, N.** *et al.* (2024). Nonoperative Treatment as an Option for Isolated Anterior Cruciate Ligament Injury: A Systematic Review and Meta-analysis. Orthopaedic Journal of Sports Medicine, 12(4), 23259671241239665. (D1, IF: 2.6)

IV. Hergár, L., **Kovács, N.**, Agócs, G. *et al.* (2024). No evidence for the superiority of 3 T MRI over 1.5 T MRI for diagnosing wrist ligamentous lesions: a systematic review and meta-analysis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. (D1, IF: 4.7)

V. Kocsis, K., Stubnya, B., **Kovács, N.** *et al.* (2024). Diagnostic accuracy of ultrasonography in acute lateral ankle ligament injury: A systematic review and meta-analysis. Injury, 55, 111730. (Q1, IF: 2.2)

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LIST OF ABBREVIATION

ASGE	American Society of Gastrointestinal Endoscopy
BDI	Bile duct injury
CBD	Common bile duct
CI	Confidence interval
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EST	Endoscopic sphincterotomy
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
IOC	Intraoperative cholangiography
IQR	Interquartile ranges
LC	Laparoscopic cholecystectomy
MBDI	Major bile duct injury
MINORS	Methodological Index for Non-Randomized Studies
OR	Odds ratio
PEP	Post-ERCP pancreatitis
RCT	Randomized clinical trial
RR	Relative risk
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
SEMS	Self-expandable metallic stent
SO	Sphincter of Oddi
SPS	Suprapapillary stent
TPS	Transpapillary stent
WMD	Weighted mean difference

I. GENERAL INTRODUCTION AND AIMS

Biliary interventions play a pivotal role in improving the quality of life for patients facing various biliary tract disorders. These interventions encompass a range of minimally invasive or intraoperatively done procedures (e.g. intraoperative cholangiography (IOC), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound), aimed at diagnosing and treating conditions affecting the bile ducts and gallbladder.

Endoscopic biliary interventions provide minimally invasive alternatives to traditional surgical approaches, yet they are highly effective in managing biliary disorders. Through ongoing advancements in technology and technique, these procedures continue to evolve, providing patients with safer, more effective treatment options and ultimately improving their quality of life. Despite the progress in biliary interventions, determining the optimal approach for each patient remains a challenge. Several research, guidelines and recommendations have been made, but in some cases their conclusions are not unanimous [1-5]. This underlines the importance of future high-quality research to compare the effectiveness of different interventions, to identify factors influencing outcomes, and to refine treatment protocols. Through clinical trials, observational studies, and meta-analyses, researchers strive to elucidate the most effective strategies for achieving optimal patient outcomes. Our team has tried to clarify certain controversial issues regarding IOC and biliary stent implantation.

II. INTRODUCTION

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Since the introduction of laparoscopy, laparoscopic cholecystectomy (LC) has emerged as the "gold standard" for treating cholecystolithiasis, offering clear benefits over open cholecystectomy. These benefits include reduced postoperative morbidity, mortality, and length of hospital stay, along with a lower incidence of complications like pneumonia and wound infections [6]. Despite these, LC carries inherent risks, among which bile duct injury (BDI) is a major concern. The consequences of BDI are severe, contributing to increased postoperative mortality, morbidity, and reduced quality of life [7, 8]. Consequently, numerous guidelines and meta-analyses have attempted to offer recommendations for preventing BDI [1, 3-5, 9-17]. Among the interventions studied, IOC has garnered significant attention [18].

The origins of IOC trace back to the beginning of the 20th century when the first reports of delineating the biliary anatomy by bismuth and petrolatum, later with lipiodol solution were published [19]. The technique evolved over time, and it was used to detect fistulas, strictures, and obstructions of the bile ducts [20, 21]. Initially, the IOCs were performed using static films, the procedure took 20-30 minutes to capture 3-4 images and it often required repetition [22]. Nowadays, the necessary time for IOC is ranges from 4.3-18 minutes [4].

To perform IOC, the critical view of safety must first be obtained, which involves identifying the cystic duct and cystic artery [23, 24]. Once this is established, the hepatocystic triangle - formed by the cystic duct, the common hepatic duct, and the inferior edge of the liver – is carefully dissected, [25] and gallbladder is manipulated to provide a clear view of cystic duct. A small transverse incision is then made in the cystic duct (or rarely, in the common bile duct (CBD)), allowing for the insertion of a cholangiocatheter, which is secured in place using a clip or a specialized tool, such as an Olsen or Kumar cholangiograsper. Finally, the C-arm X-ray machine is positioned over the right upper quadrant, and contrast media is introduced to visualize the biliary tree in real-time [23] (Figure A1).

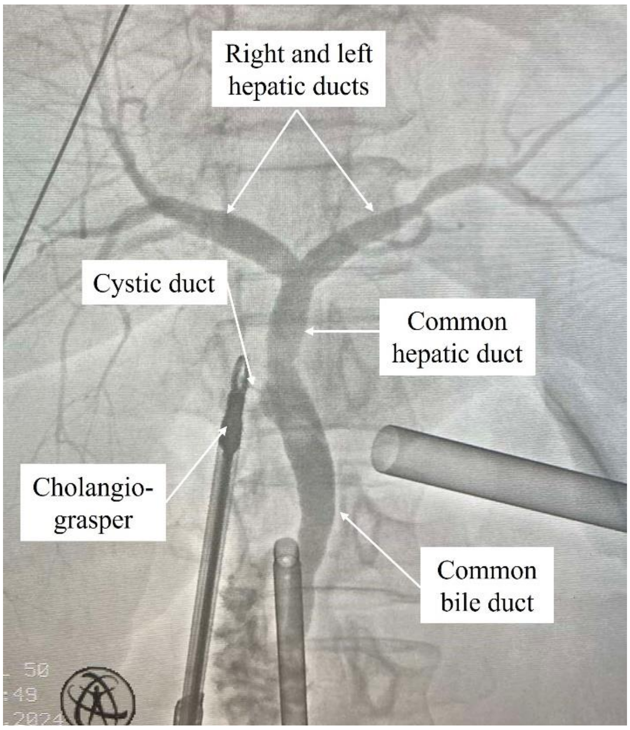


Figure A1 Intraoperative cholangiography.

Credit: Szabolcs Ábrahám, M.D., Ph.D.

The purpose of IOC is to assist surgeons identifying any abnormalities or obstructions in the bile ducts, guiding their decisions on the appropriate surgical approach and subsequent step. However, the role of IOC in preventing BDI and detecting CBD stones remains unclear. While many experts acknowledge the value of IOC in clinical practice, the absence of solid consensus among specialists persists due to the presence of conflicting evidence in the literature [15-17, 26-30]. The extent to which IOC should be used is still debated.

There are three primary approaches to IOC during cholecystectomy. Some recommend performing IOC routinely. In this case, it is done at every cholecystectomy. Others recommend omitting it completely, and a third group advocates for selective IOC, used only in specific clinical scenarios, such as unclear biliary anatomy or suspected CBD stone.

Proponents of routine IOC argue that it mitigates the risk of BDI by clarifying ambiguous or abnormal biliary anatomy and aids the intraoperative detection and treatment of BDI [14, 26, 31], potentially reducing postoperative complications. Previous studies have shown that identifying and managing BDI during surgery can improve morbidity and mortality rates [12, 28, 32]. Additionally, routine IOC can detect previously asymptomatic CBD stones, which might otherwise be missed [14, 26, 31].

On the other hand, opponents of routine IOC state that it is time-consuming, exposes both staff and patients to radiation [26] and may lead to unnecessary interventions. They point out that BDI is relatively rare, with an incidence of 0.3% to 0.5%, and routine IOC increases the detection of asymptomatic bile duct stones, most of which do not become symptomatic postoperatively [33]. In the case of biliary stones, they advocate for a wait-and-see approach [34], suggesting that asymptomatic ones should not be treated endoscopically unless they cause symptoms, as studies have shown that the rate of biliary complications with a wait-and-see approach ranges from 0% to 25.3% over follow-up periods of 30 days to 4.8 years [34-39]. Furthermore, studies indicate that ERCP may result in worse outcomes compared to a wait-and-see strategy [35]. Some guidelines recommend endoscopic management of asymptomatic CBD stones [40, 41], citing the potential risk of complications such as obstructive jaundice, acute cholangitis, and biliary pancreatitis [35]. ERCP is the preferred treatment, despite its associated risk, including post-ERCP pancreatitis (PEP), cholangitis, bleeding, and perforation, with complication rates ranging from 4.0% to 15.9% [42, 43].

A third perspective supports selective IOC, arguing that most CBD stones can be identified preoperatively and the incidence of BDI during cholecystectomy is low [44, 45]. Therefore, they believe IOC may not be necessary except in cases where CBD stones are suspected or when patients are deemed as high risk for BDI.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Until the late 1970s, surgical bypass procedures such as cholecystojejunostomy, choledochojejunostomy, and hepaticojejunostomy were the only method for biliary drainage in patients with unresectable pancreatic cancer or cholangiocarcinoma [46]. The introduction of

ERCP-guided biliary stenting by Soehendra and Reynders-Frederix [47], marked a significant shift in the management of biliary obstruction. Since then, various stents have been developed, and ERCP-guided stent placement has gradually become the preferred method for managing biliary obstruction.

Endoscopic biliary stent placement is now widely recognized as a minimally invasive intervention, particularly for patients with benign biliary strictures [48] and as a palliative therapy for malignancies causing biliary obstruction, aiming to alleviate symptoms and enhance quality of life [49]. While percutaneous stent placement remains an alternative, it is generally considered inferior to the endoscopic method [50], but still inevitable in some cases. Additionally, endoscopic ultrasonography has shown promising results, especially in cases where ERCP is unsuccessful [51], though it is less widely available. When comparing endoscopic stent placement to biliary bypass surgery as palliative treatments for patients with malignant strictures, both approaches result in similar mortality and readmission rates [52]. However, endoscopic treatment is generally more patient-friendly.

The primary concerns in the endoscopic management of biliary obstruction are stent occlusion and duration of stent patency. Despite advances in stent technology, no stent has been developed with permanent patency. The exact mechanism behind stent occlusion remain unclear, though several factors are believed to contribute, including stent diameter, material composition, the presence of side holes, bacterial adherence to the stent surface, and the accumulation of dietary fibers within the stent lumen [53-58].

Previous publications tried to answer this question by exploring different aspects of endobiliary stents and identifying methods to prolong stent function. For instance, self-expanding metal stents (SEMS) have shown superior patency to the conventional plastic stents [49], but they are more expensive and can be difficult to remove [59-62]. Another publication found that large-boar stents not only have longer function time, but also have lower rates of cholangitis [63]. In addition, some experiments have explored the use of special coatings, such as polyurethane, silver nanoparticles or hydrophobin, to prevent biofilm formation in stents [64-66], as well as the incorporation of anti-reflux valves to inhibit duodenobiliary reflux [67].

Another factor that could potentially increase the longevity of endobiliary stents is their positioning. The conventional technique for biliary stent insertion involves transpapillary stent (TPS) placement (Figure B1A), where the stent traverses the papilla and the sphincter of Oddi (SO), with the distal end extending into the duodenum. This positioning eases stent extraction and theoretically reduces the risk of proximal migration [57]. An alternative method is suprapapillary stent (SPS) placement, where the distal end of the stent is positioned above the SO within the common bile duct (CBD), leaving the major papilla intact (Figure B1).

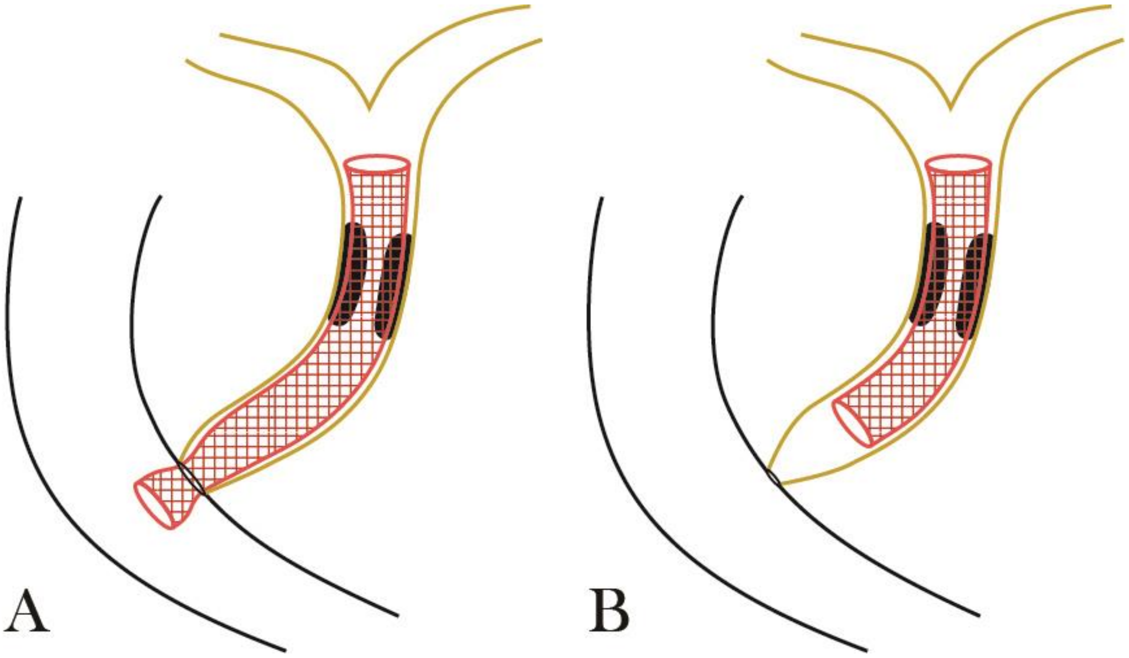


Figure B1 Positions of different endobiliary stents. A: transpapillary suprapapillary position. B: suprapapillary position. Basis for illustration: Pécsi, D., & Vincze, Á. (2020). Are suprapapillary biliary stents superior to transpapillary biliary stents? Digestive Diseases and Sciences, 65, 925-927.

The suprapapillary method was first described in a dog model [68]. By preserving sphincter function, SPS placement aims to reduce stent occlusion rate, by inhibiting direct food impaction, biofilm formation, and subsequent sludge accumulation [69]. This position also minimizes the risk of bacterial contamination, and ascending infection from duodenobiliary reflux through the SO [69]. However, SPS is not suitable for all patients, particularly those with distal tumors like pancreatic or papillary cancers, making it a less universal option [70]. Currently, SPS is predominantly used in Asian centers and has not gained widespread adoption [71-73].

One of the main concerns with SPS is the risk of migration or dislocation. An early publication states that SPS might be more prone to migration [74], but a later research attributed this to the stents' higher rigidity used in the study [57] and the predominance of pancreatic cancer patients in the sample [75]. As a result, the evidence on SPS migration risk remains inconclusive. Another issue with SPS is the difficulty of removal due to its position. To overcome this, researchers have experimented with adding thread to the distal end of plastic SPS, making removal easier [72], making SPS placement more attractive. Additionally, the ease of SPS removal is often associated with endoscopic sphincterotomy (EST). In some cases, EST was done when placing an SPS to ease stent extraction and lower the burden on the major papilla to reduce the rate of PEP [69, 71, 76]. However, EST may compromises the SO's natural barrier function against duodenobiliary reflux, potentially affecting stent performance [77].

III. AIM

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Our objective was to assess the existing literature about the role of routine, selective, and omission of IOC during cholecystectomy and to compare these approaches, particularly concerning BDI and CBD stone-related complications.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

We aimed to gather all existing publications examining individuals with biliary strictures of any etiology who underwent endobiliary stent placement via ERCP and assess stent patency and other procedure-related complications associated with SPS and TPS placements.

IV. METHODS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

We reported our systematic review and meta-analysis following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [78]. The protocol has been previously registered to PROSPERO under the identifier CRD42021240405. In addition to the analyses prespecified in the protocol, we conducted an additional subgroup analysis specifically focusing on randomized control trials (RCT) and prospective studies.

Search Strategy and Eligibility Criteria

We carried out a thorough systematic literature search until October 19, 2020, across Embase, MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The search employed specific keywords, namely: cholangiogra* and "cholecystectomy". Our exploration encompassed all fields/texts in each database, except for Scopus, where we focused on the "Article title, Abstract, Keywords" fields. No filters were employed.

We employed the PICO framework to establish eligibility criteria. Articles were included if the population (P) comprised LC or a mixed population of open and LC. Three intervention (I)/comparison (C) groups were set based on available literature: IOC *vs.* no IOC, routine IOC *vs.* selective IOC, and selective IOC *vs.* no IOC. In the routine IOC group, all patients underwent cholangiography during cholecystectomy. Selective IOC was defined as if patients were chosen based on predefined criteria (clinical, laboratory, or imaging findings). Only RCTs and observational studies were deemed eligible based on study type.

Selection Strategy and Data Extraction

For the removal of duplicate entries, both through software and manual processes, we utilized Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA). Two independent authors (NK and BN) conducted the selection process in different stages, evaluating titles, abstracts, and full texts. After each stage, Cohen’s kappa coefficient was calculated to assess agreement between the researchers. Unrelated titles, abstracts, and full texts were excluded. No reports were excluded based on follow-up periods; however, we only included studies with equal or similar follow-up periods for quantitative synthesis. Grey literature was not included. Any disagreements were resolved through consensus.

Two independent authors (NK and BN) conducted the data extraction, resolving any disagreements through consensus. A standardized data collection sheet was, using Excel software (Office 365, Microsoft, Redmond, WA, USA) to gather all essential information, including the first author, publication year, study design, Digital Object Identifier (DOI), type of surgical intervention, nature of comparison (IOC *vs.* no IOC, routine IOC *vs.* selective IOC, and selective IOC *vs.* no IOC), definition of selective IOC, age and gender distribution in each group, number of patients in each comparison group, and the count of events in each group concerning primary and secondary outcomes.

Outcomes

The assessment of the groups was based on primary outcomes, including the rate of BDI and retained stone rate, as well as secondary outcomes such as readmission rate, the conversion rate from LC to open surgery, the success rate of IOC, operation time (in minutes), and length of hospital stay (in days).

BDI was defined as "any tissue damage to the biliary system resulting from surgery," while retained stones were characterized as bile duct stones overlooked during cholecystectomy and discovered postoperatively.

Subgroup Analysis

We conducted several subgroup analyses. We examined (a): studies exclusively involving laparoscopic cholecystectomy cases, (b) prospective studies, and (c) studies addressing major bile duct injury (MBDI). MBDI was defined as damage to the CBD, common hepatic duct, left or right main hepatic duct, or any bile duct injury requiring surgical repair.

Risk of Bias Assessment and Certainty of Evidence

The assessment of the risk of bias was independently done by two authors (NK and BN) using the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) [79] tool for non-randomized studies and the RoB 2 tool recommended by the Cochrane Collaboration [80] for RCTs. Any disagreements were resolved through consensus. To evaluate the potential presence of publication bias, a funnel plot and Egger’s test were employed when a sufficient number of articles allowed for it. A funnel plot was generated when at least six studies were aggregated, while Egger’s test was applied with a minimum of ten studies pooled.

The evaluation of the certainty of evidence followed the guidelines of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) workgroup recommendations [81]. Two independent authors (NK and BN) assessed each endpoint, resolving any discrepancies through consensus. We created several GRADE evidence profile tables using the GRADEpro GDT software [82], separately for each comparison group (routine *vs.* selective IOC and IOC *vs.* no IOC).

Statistical Analysis

We utilized the data synthesis methods recommended by the Cochrane Collaboration working group [83]. A meta-analysis was conducted, and the calculated effect sizes were visually presented on forest plots. For continuous outcomes, we computed weighted mean differences (WMD), while for dichotomous outcomes, we calculated relative risks (RR), both with 95% confidence intervals (CI). These measures were employed to investigate differences among the groups. Heterogeneity was assessed by Cochran's Q test and Higgins' I^2 indicator. The Q statistics were derived from the squared deviations from the pooled effect of the weighted sum of individual study effects, with the weights used in the pooling method. P-values were obtained by comparing the test statistics with a Chi-square with k-1 degrees of freedom (where k represented the number of studies). A p-value less than 0.10 indicated significant heterogeneity. The I^2 index represented the percentage of total variability across studies attributed to heterogeneity, with a rough classification based on Cochrane's handbook: not important (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) [84]. All statistical analyses were conducted using StataIC (version 16).

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Our systematic review and meta-analysis was conducted following the guidelines outlined in the PRISMA Statement [85]. The review protocol was submitted to the PROSPERO database on July 4, 2017, under registration number CRD42017069840. Deviating from the protocol, patients undergoing percutaneous transhepatic cholangiography were excluded and opted for the ROBINS-I tool for assessing study quality instead of the Methodological Index for Non-Randomized Studies (MINORS) criteria.

Search Strategy and Eligibility Criteria

We conducted a comprehensive literature search until December 20, 2020, using the electronic databases of the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE (via PubMed). The search key was the following: ("intraductal" OR "Oddi sphincter" OR "suprapapillary" OR "inside") AND "stent". No restrictions were used on the publication year or language, and all fields were searched in the databases. Grey literature, except for conference abstracts, was excluded.

Study eligibility was decided based on the predetermined PICO framework. We searched for publications investigating endobiliary stent placement via ERCP in adult patients with any benign or malignant biliary obstruction (P). The stent position had to be transpapillary (I) or suprapapillary (C), and outcomes (O) such as stent patency time, migration rate, cholangitis, pancreatitis, cholecystitis and other procedure-related complications (bleeding, perforation) were compared. Definitions of outcomes were accepted as presented in each publication. RCTs and prospective or retrospective observational studies meeting PICO criteria were considered eligible, while studies focusing on percutaneous stent placement were excluded, along with research protocols, conference abstracts, and publications lacking a control group or not reporting relevant endpoints.

Selection Strategy and Data Extraction

To examine all identified publications, we employed the EndNote X9 citation management software (Clarivate Analytics, Philadelphia, PA, USA). Following the removal of duplicates, two independent reviewers (NK and DP) evaluated study eligibility based on titles, abstracts, and full texts. Any discrepancies were resolved through consensus. Cohen's kappa coefficient was utilized after each selection step to gauge the inter-rater reliability.

For data extraction, a standardized form was designed using Excel software (Office 365, Microsoft, Redmond, WA, USA). Two independent review authors (NK and DP) conducted the data extraction, resolving any disagreements through consensus. The information extracted from each included publication encompassed details such as the first author, study design, publication date, study duration, study site, number of centers, inclusion criteria, indication for stent placement, exclusion criteria, biliary stent type, number of patients, age, gender, number of patients in each investigated group, and the number of events in each examined group concerning the investigated dichotomous endpoints. Additionally, means, standard deviations, medians, ranges, and IQR were extracted for continuous endpoints.

Risk of Bias Assessment and Certainty of Evidence

To determine the quality of the included publications, two independent review authors (NK and DP) conducted a risk of bias assessment, resolving any disagreements through consensus. The ROBINS-I tool [79] was utilized for non-randomized studies, while RCTs were assessed using the RoB 2 [80]. Both tools are recommended by the Cochrane collaboration. The robvis web app (available at https://mcguinlu.shinyapps.io/robvis/, accessed on 15 February 2022) was employed to represent the results of the risk of bias assessment visually [86]. We used Egger's test and funnel plots for outcomes with at least ten studies to evaluate the risk of publication bias. If at least six studies were available, only funnel plots were generated.

To evaluate the certainty of evidence, two independent investigators (NK and DP) followed the GRADE workgroup recommendations [81], resolving disagreements through consensus. 'Summary of findings' tables were constructed for each investigated outcome using the GRADEpro GDT software [87].

Statistical Analysis

All statistical analyses were conducted within the R environment (R Core Team (2021), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, R version 4.1.2 (1 November 2021)). For dichotomous outcomes, odds ratios (OR) were computed, and for continuous variables, WMDs were calculated, with 95% CIs. In cases where mean values or standard deviations were missing, Wan's method was applied, or the Cochrane Handbook suggestion [88] was followed, respectively. A p-value less than 0.05 denoted a statistically significant difference. The random effects model, employing the DerSimonian–Laird method [89], was utilized to calculate overall estimates. Meta-analysis results are visually presented in forest plots, with the random effects model using the restricted maximum likelihood estimator [90] to calculate heterogeneity variance (τ^2). Heterogeneity was assessed using I^2 statistics, following the Cochrane Handbook guidelines [88]. I^2 indicates the magnitude of heterogeneity ('Might not be important': 0–40%, 'Moderate': 30–60%, 'Substantial': 50–90%, and 'Considerable': 75–100%). Heterogeneity with a p-value < 0.1 was considered significant.

V. RESULTS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Systematic Search and Selection

A systematic search of the literature revealed a total of 19,863 articles. The selection procedure, along with Cohen's kappa coefficients, are comprehensively summarized in the PRISMA flowchart (Figure A2). Following the completion of the selection process, 38 eligible articles were identified [26-31, 33, 91-121] and included in the qualitative synthesis, with 32 of them included in the quantitative synthesis [26-31, 33, 91-95, 97, 99-104, 106, 107, 109, 110, 112-119, 121].

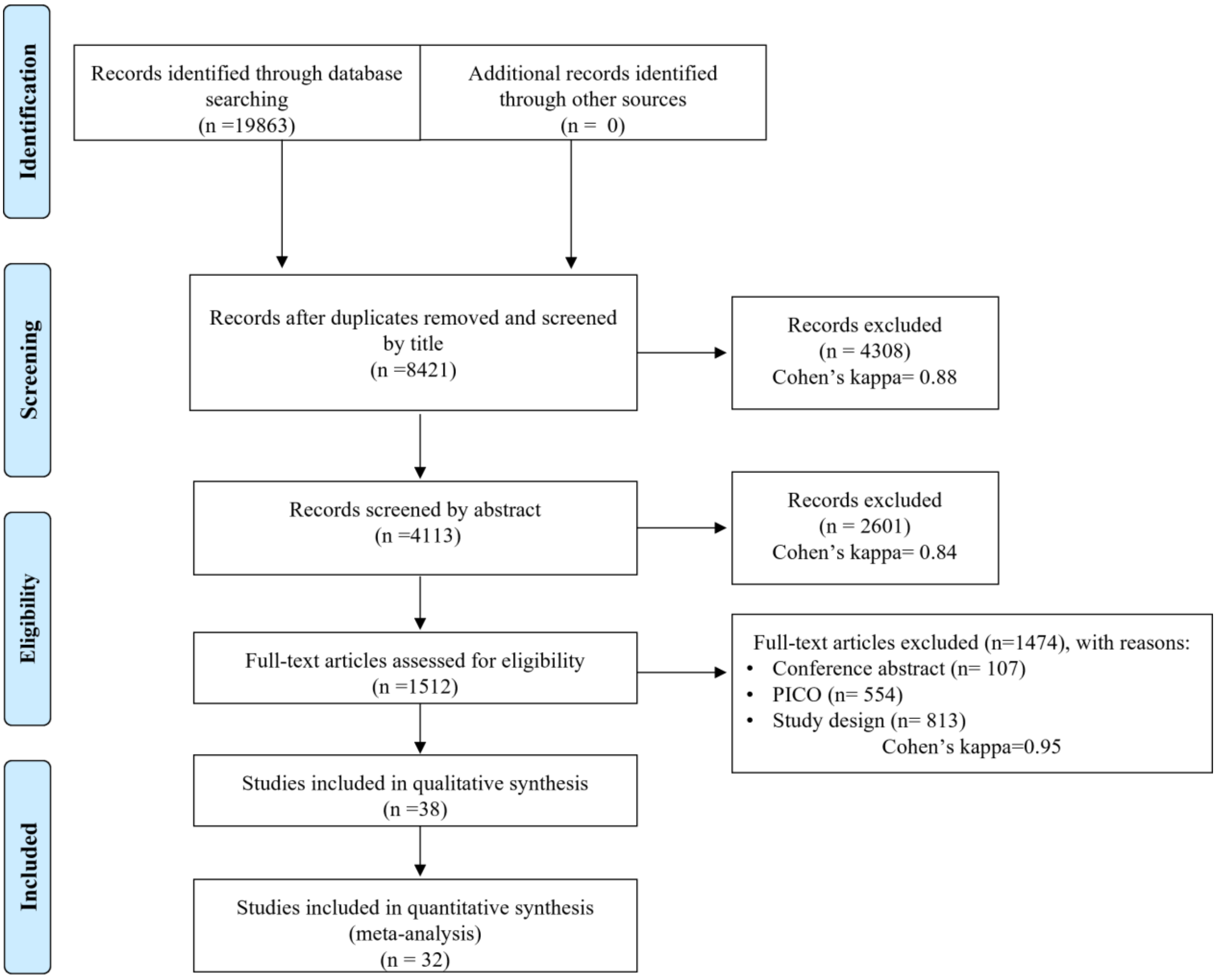


Figure A2 PRISMA flow diagram. PICO: Population, Intervention, Comparison, and Outcome

Description of the Selected Studies

The characteristics of eligible publications are summarized across three tables. Table A1 encompasses publications investigating routine IOC *vs.* selective IOC approaches. We summarized the characteristics of the included studies investigating IOC *vs.* no IOC, and selective IOC and no IOC in the online supplementary material and the appendix of this work [122]. Eleven of the articles reported findings for both open and LC [27-30, 33, 93-95, 97, 104, 114], while 27 studies exclusively covered LC cases [26, 31, 91, 92, 96, 98-103, 105-113, 115-121]. A summary of the various indications for selective IOC is detailed in the online supplementary material and the appendix of this dissertation [122].

Study	**Study design**	**Center(s)**	**Type of procedure**	**Number of patients (routine *vs.* selective IOC) (female %, mean age ± SD)**	**Number of selective IOC (n)**	**Outcomes**	**Follow up**
Alkhaffaf *et al.* 2011	Prospective cohort	Multicentric (4) in the UK	LC	463(80%, 47.8±14.8)	-	BDI, conversion rate to open surgery, LOHS	N/A
				1159(80%, 50.2±15.7)	263		
Amott *et al.* 2005	Quasi-randomised trial	Single center in Australia	LC	148	-	BDI, retained stone rate, success rate of IOC, operation time	N/A
				155	45		
Buddingh *et al.* 2011	Retrospective cohort	Single center in the Netherlands	Cholecystectomy	435 (63.9%, 53±17)	-	BDI, conversion rate to open surgery, success rate of IOC, operation time	N/A
				421(64.4%, 53±16)	25		
Carlson *et al.* 1993	Prospective cohort	Multicentric [87] in the USA	LC	164	-	BDI, retained stone rate	A inst: 9-28 months, B inst: 16-31 months
				155	21		
Guerra-Filho *et al.* 2007	Prospective cohort	Single center in Brazil	LC	127(73.2%, 48.8)	-	Success rate of IOC	N/A
				127(74%, 47.9)	71		
Nickkholgh *et al.* 2006	Retrospective cohort	Single center in Iran	LC	1133		BDI, retained stone rate, success rate of IOC	N/A
				800	159		
Pham *et al.* 2016	Retrospective cohort	Multicentric [87] in China	LC	246 (81%, 40, range: 33-57)	-	Retained stone rate, readmission rate, operation time	30-day
				274 (76%, 44, range: 31-53)	15		
Ragulin-Coyne *et al.* 2013	Retrospective cohort	Multicentric (NIS) in USA	Cholecystectomy	13025 (66.9%, 53.5)	-	BDI, LOHS	N/A
				98790 (66%, 52.5)	N/A		

Snow *et al.* 2001	Retrospective cohort	Multicentric (4) in USA	LC	1522 487	- 139	BDI, retained stone rate, success rate of IOC	11 years

Table A1 Characteristics of included studies (routine IOC vs. selective IOC)
BDI: bile duct injury, IOC: intraoperative cholangiography, LC: laparoscopic cholecystectomy, LOHS: length of hospital stays, N/A: not available

Primary Outcomes

1. Bile Duct Injury

a. Routine IOC *vs.* Selective IOC

To compare routine IOC *vs.* selective IOC regarding BDI, we combined data from six articles involving 118,742 patients [33, 91, 92, 95, 109, 115]. Our analysis indicated that neither group exhibited a protective effect against BDI (RR = 0.91, 95% CI 0.66; 1.24), and we found that the heterogeneity is statistically not significant ($I^2 = 0.0\%$, p = 0.805) (Figure A3).

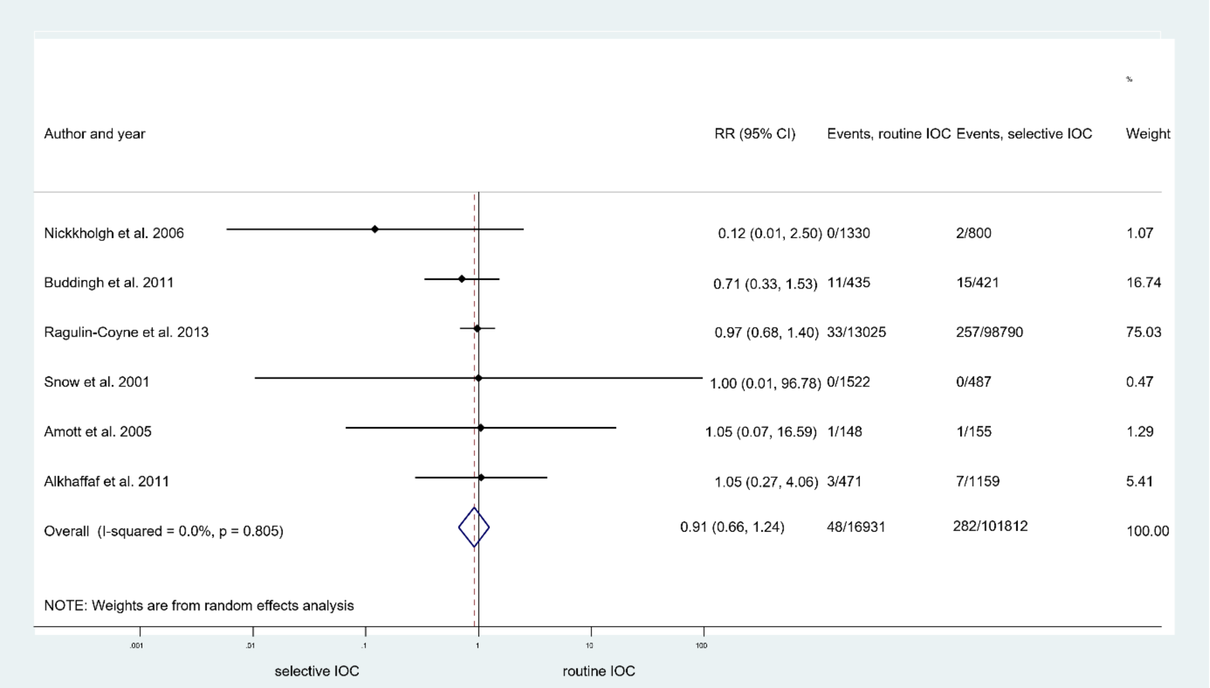


Figure A3 Forest plot comparing the risk of bile duct injury between routine IOC and selective IOC groups (population: both types of cholecystectomies). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P-value; RR: relative risk

Even after excluding articles that reported on open cholecystectomy, the absence of a protective effect against BDI persisted (RR = 0.78, 95% CI 0.25; 2.41) [91, 92, 109]. This analysis was conducted among articles with statistically not significant heterogeneity ($I^2 = 0.0\%$, p = 0.420) (Figure A4).

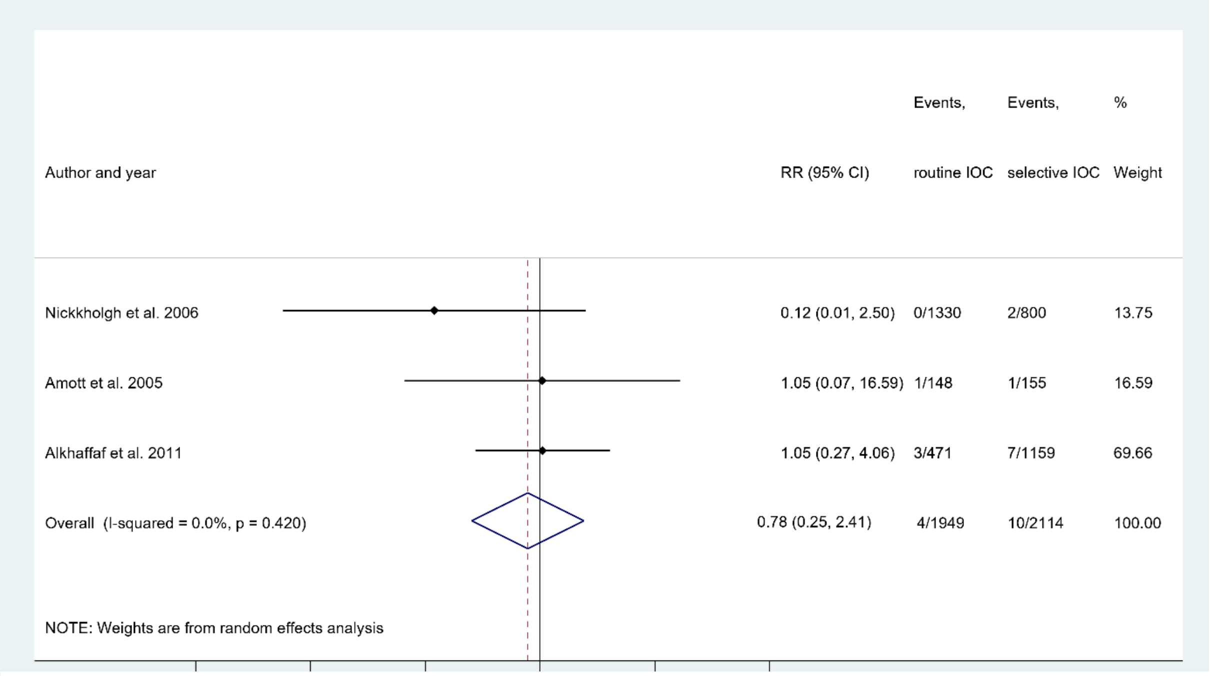


Figure A4 Forest plot comparing the risk of bile duct injury between routine IOC and selective IOC groups (population: laparoscopic cholecystectomy). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P-value; RR: relative risk

Within the same comparison, we conducted additional subgroup analyses to investigate MBDI. When exploring both open and LC cases, no significant differences were identified between the groups (RR = 0.44, 95% CI 0.11; 1.84; $I^2 = 47.7\%$, p = 0.125) (Figure A5) [33, 92, 95, 109].

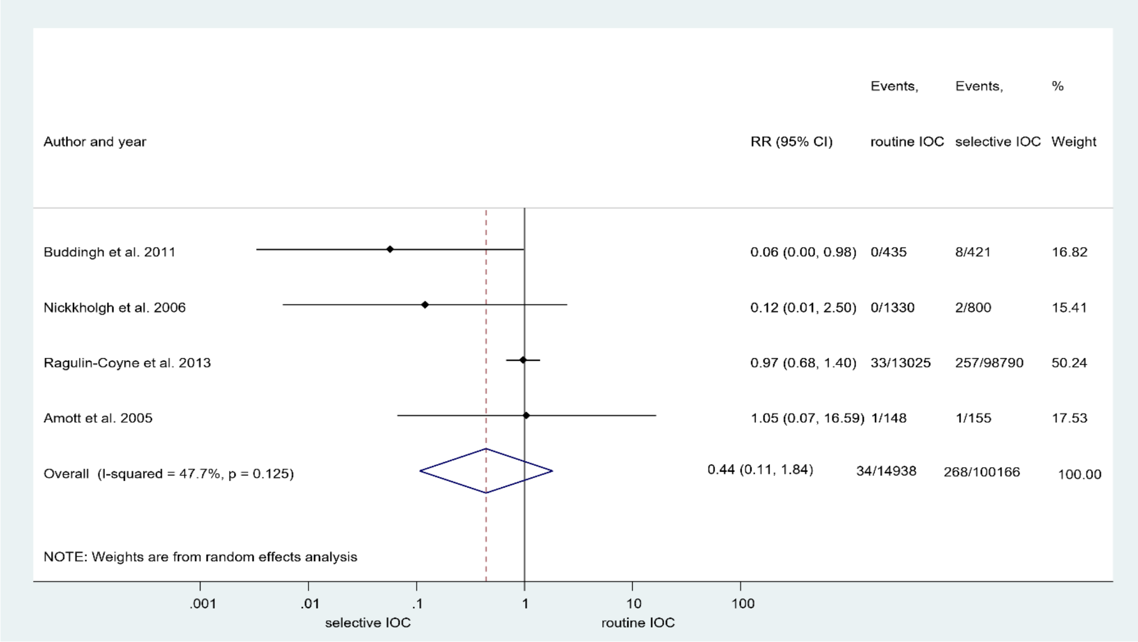


Figure A5 Forest plot comparing the risk of major bile duct injury between routine IOC and selective IOC groups (population: both types of cholecystectomies). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P-value; RR: relative risk

Similarly, no discernible difference was observed when considering only LC cases (RR = 0.39, 95% CI 0.05; 3.28; $I^2 = 7.9\%$, p = 0.297) (Figure A6) [92, 109].

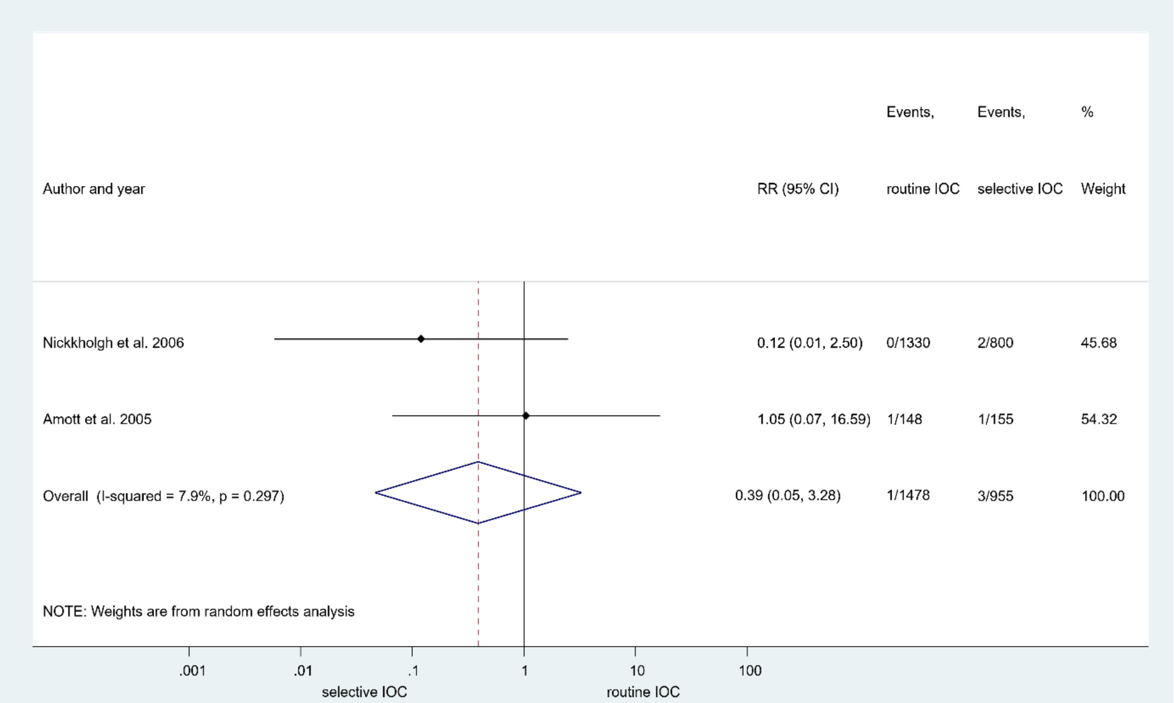


Figure A6 Forest plot comparing the risk of major bile duct injury between routine IOC and selective IOC groups (population: laparoscopic cholecystectomy). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P-value; RR: relative risk

b. IOC *vs.* no IOC

From our analysis of 14 articles involving 3,155,940 patients, the use of IOC did not demonstrate an association with a reduced risk of BDI (RR = 1.03, 95% CI 0.77; 1.37) within significantly heterogeneous publications ($I^2 = 96.5\%$, p = 0.000) (Figure A7) [26-31, 94, 97, 100, 105-107, 113, 116, 121].

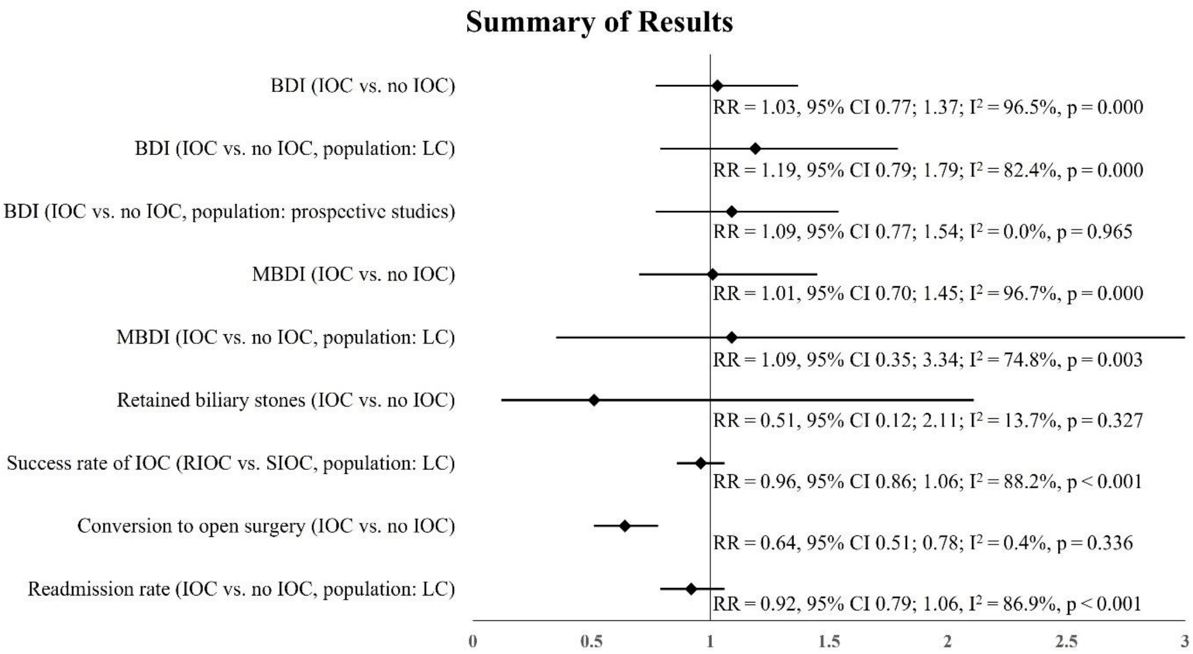


Figure A7 Summary of Results. BDI: bile duct injury; CI: confidence interval; IOC: intraoperative cholangiography; LC: laparoscopic cholecystectomy; MBDI: major bile duct injury; p: P-value; RR: relative risk; RIOC: routine intraoperative cholangiography; SIOC: selective intraoperative cholangiography

A subgroup analysis of ten studies focusing solely on LC found no significant difference between the two strategies, including a total of 706,336 patients (RR = 1.19, 95% CI 0.79; 1.79); however, substantial heterogeneity was identified ($I^2 = 82.4\%$, p = 0.000) (Figure A7) [26, 31, 97, 99, 100, 105-107, 113, 116, 121].

Three additional subgroup analyses were conducted: one exclusively with prospective studies (RR = 1.09, 95% CI 0.77; 1.54; $I^2 = 0.0\%$, p = 0.965) (Figure A7) [31, 100, 106, 116, 121], another with studies reporting on MBDI (RR = 1.01, 95% CI 0.70; 1.45; $I^2 = 96.7\%$, p = 0.000) (Figure A7) [27, 29-31, 94, 106, 113, 116, 121], and the third involving studies with MBDI in LC only (RR = 1.09, 95% CI 0.35; 3.34; $I^2 = 74.8\%$, p = 0.003) (Figure A7) [31, 99, 106, 113, 116]. None of these analyses revealed significant differences between the investigated groups.

2. Retained Biliary Stones after Cholecystectomy

In the comparison between IOC and no IOC, a synthesis of five studies involving 2,069 cases revealed no discernible difference (RR = 0.51, 95% CI 0.12; 2.11) within a one-year follow-up period. There was also no statistically significant heterogeneity detected ($I^2 = 13.7\%$, p = 0.327) (Figure A7) [31, 93, 116-118].

The examination of routine IOC *vs.* selective IOC groups in the case of this outcome was precluded due to substantial variability in follow-up periods. The findings of these articles can be accessed in the online supplementary material and the appendix of this dissertation [122].

Secondary Outcomes

1. Routine *vs.* Selective IOC

Examining the success rate of IOC during LC across four studies comparing routine IOC and selective IOC, no statistically significant difference was identified (RR = 0.96, 95% CI 0.86; 1.06; $I^2 = 88.2\%$, $p < 0.001$) (Figure A7) [92, 101, 109, 115].

In the comparison of routine and selective approaches based on operation time, the results did not reveal a statistically significant difference (WMD = 14.02, 95% CI –6.96; 35.00, $I^2 = 98.2\%$, $p < 0.001$) across three studies involving 2,445 patients. These studies exclusively focused on patients who had undergone LC (Figure A8) [91, 92, 110].

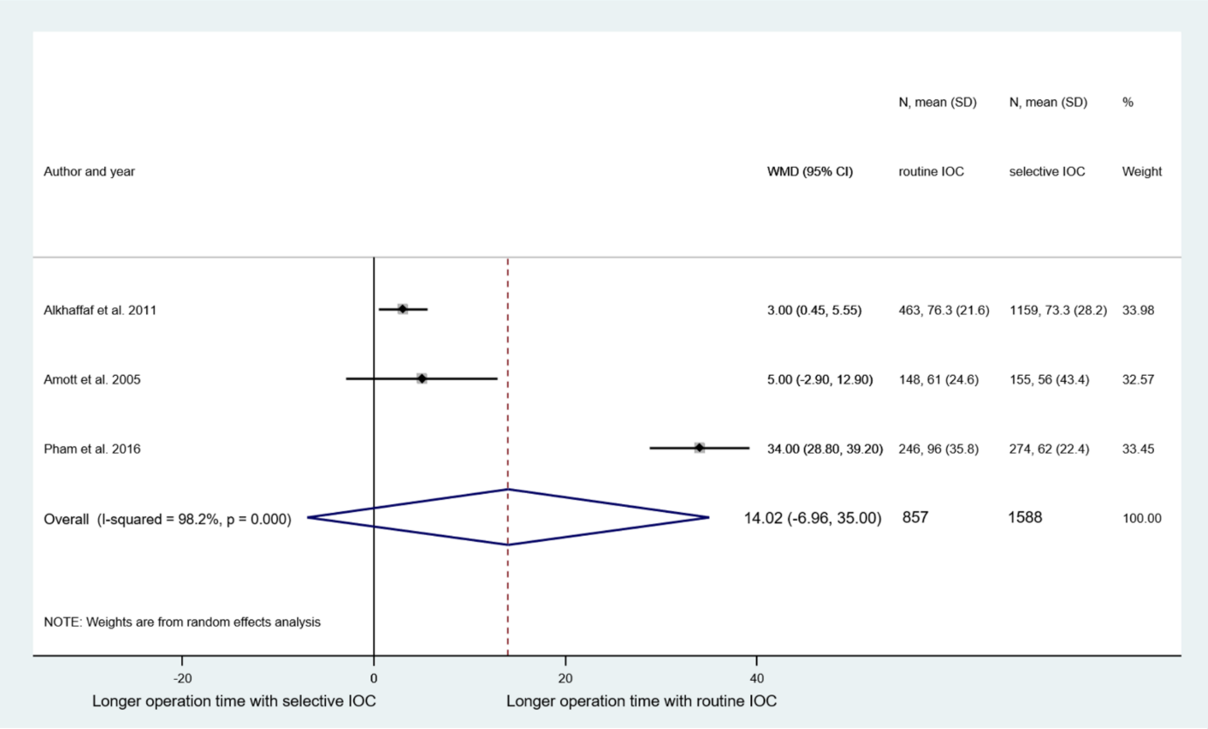


Figure A8 Forest plot comparing operation time between routine IOC and selective IOC groups (population: laparoscopic cholecystectomy). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P value; WMD: weighted mean difference

2. IOC *vs.* no IOC

In the comparison involving three studies with 10,735 patients, a significant difference was observed (RR = 0.64, 95% CI 0.51; 0.78), favoring IOC with a lower risk of conversion to open surgery compared to the no IOC group. This result did not show significant heterogeneity ($I^2 = 0.4\%$, $p = 0.336$) (Figure A7) [31, 106, 121].

The operation time took significantly longer during cholecystectomy in the IOC group (WMD = 11.25 min, 95% CI 6.57; 15.93; $I^2 = 95.9\%$, p = 0.000) (Figure A9) [31, 93, 98, 102, 106, 109, 116, 119].

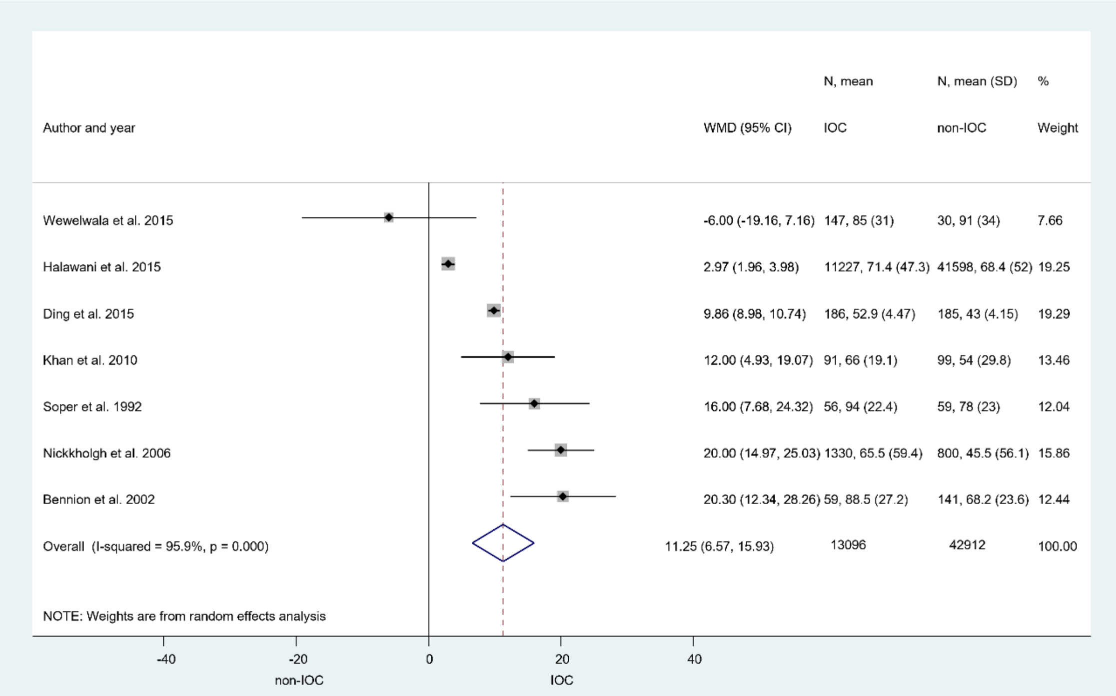


Figure A9 Forest plot comparing operation time between IOC and no IOC groups (population: laparoscopic cholecystectomy). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P value; WMD: weighted mean difference

Investigating readmission rates following LC, comparing groups with and without IOC within a 30-day follow-up period, no statistically significant difference was detected (RR = 0.92, 95% CI 0.79; 1.06, $I^2 = 86.9\%$, $p < 0.001$) (Figure A7) [26, 102, 112, 116].

Likewise, when examining groups with and without IOC in terms of length of hospital stay, no statistically significant differences were observed (WMD = -0.03, 95% CI –0.26; 0.20; I2 = 98.3%, $p < 0.001$) (Figure A10) [26, 31, 93, 103, 104, 114, 116, 119]. The findings remained consistent when examining studies that reported on cases of LC only (WMD = 0.04, 95% CI –0.12; 0.19; I2 = 90.0%, $p < 0.001$) (See in the online supplementary material and in the appendix of this dissertation [122]) [31, 103, 116, 119].

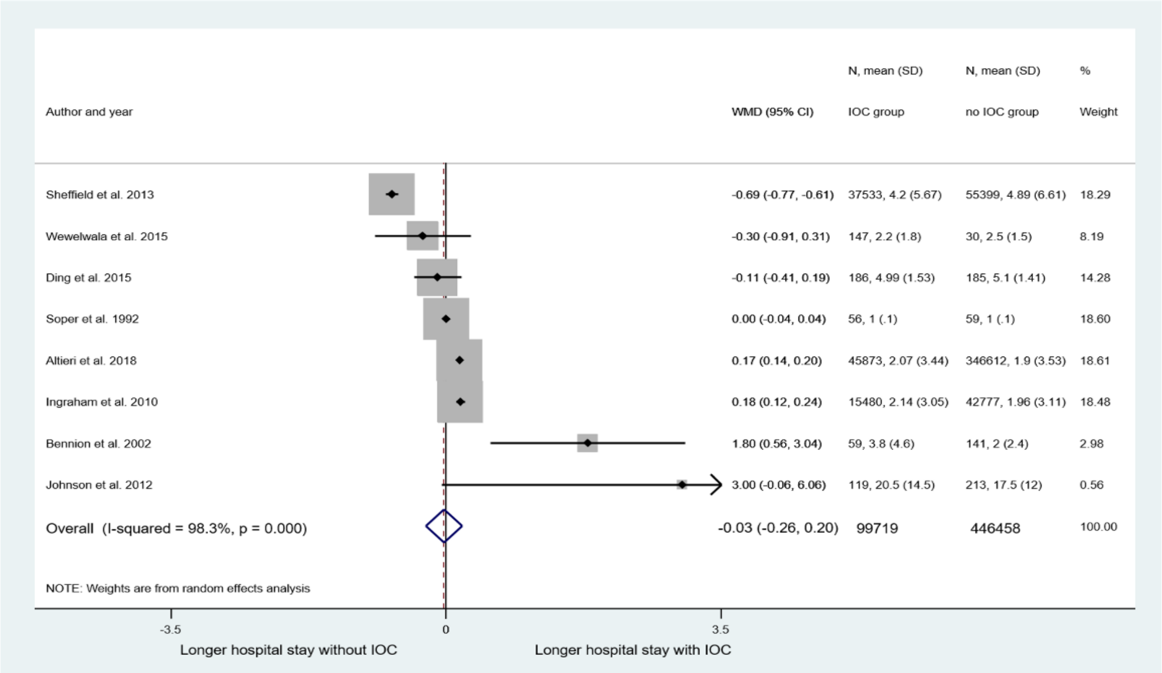


Figure A10 Forest plot comparing length of hospital stay between IOC and no IOC groups (population: both types of cholecystectomies). CI: confidence interval; I-squared: I^2; IOC: intraoperative cholangiography; p: P-value; WMD: weighted mean difference

Qualitative Synthesis

In our qualitative synthesis, we incorporated the following outcomes: BDI, MBDI (routine IOC *vs.* selective IOC: one publication [96]; IOC *vs.* no IOC: one publication [105]), retained stone rate (routine IOC *vs.* selective IOC: five studies [92, 96, 109, 110, 115]; IOC *vs.* no IOC: one publication [98]; selective IOC *vs.* no IOC: three studies [108, 111, 120]), readmission rate (IOC *vs.* no IOC: four studies [93, 106, 117, 118]), conversion rate to open surgery (routine IOC *vs.* selective IOC: two studies [91, 95]), success rate of IOC (routine IOC *vs.* selective IOC: one study [95]), operation time (routine IOC *vs.* selective IOC: one study [95]; IOC *vs.* no IOC: one study [98]), and length of hospital stay (IOC *vs.* no IOC: one study [117]; routine IOC *vs.* selective IOC: three studies [33, 91, 110]). The online supplementary material and the appendix of this dissertation provide a summary of studies exclusively included in the qualitative synthesis [122].

Risk of Bias Assessment and Certainty of Evidence

The majority of the investigated articles were judged to carry a serious risk of bias due to the presence of uncontrolled confounding factors. Three articles were excluded from the quantitative synthesis due to a critical risk of bias [96, 98, 105]. A summary of the risk of bias assessment is available in the online supplementary data and in the appendix of this dissertation [122].

Upon visually assessing funnel plots, a substantial risk of publication bias was observed in cases of MBDI when the population included both types of cholecystectomy and when exclusively LCs were performed, as well as in studies reporting on retained biliary stones after cholecystectomy, operation time (population consisted of LC, comparison: IOC *vs.* no IOC), and length of hospital stay (population consisted of both types of cholecystectomy; comparison: IOC *vs.* no IOC). Comprehensive results on publication bias, funnel plots, and Egger's tests are detailed in the online supplementary data and in the appendix of this dissertation [122].

Every analyzed outcome was appraised as having a very low level of evidence. The study designs included, the presence of uncontrolled confounding factors, and the substantial heterogeneity significantly impacted the quality of evidence. The GRADE evidence profile tables are presented in the online supplementary material and the appendix of this dissertation [122].

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Systematic Search and Selection

From a total of 3912 records yielded through our search, 13 publications were deemed eligible. The qualitative synthesis included thirteen articles [56, 57, 62, 71-74, 123-128] while quantitative synthesis incorporated twelve [56, 57, 62, 71-74, 123-126, 128]. The rationale for excluding publications at the full-text level is elaborated in the online supplementary material and the appendix of this dissertation [129]. A concise overview of the selection process is presented in the PRISMA flow diagram (Figure B2).

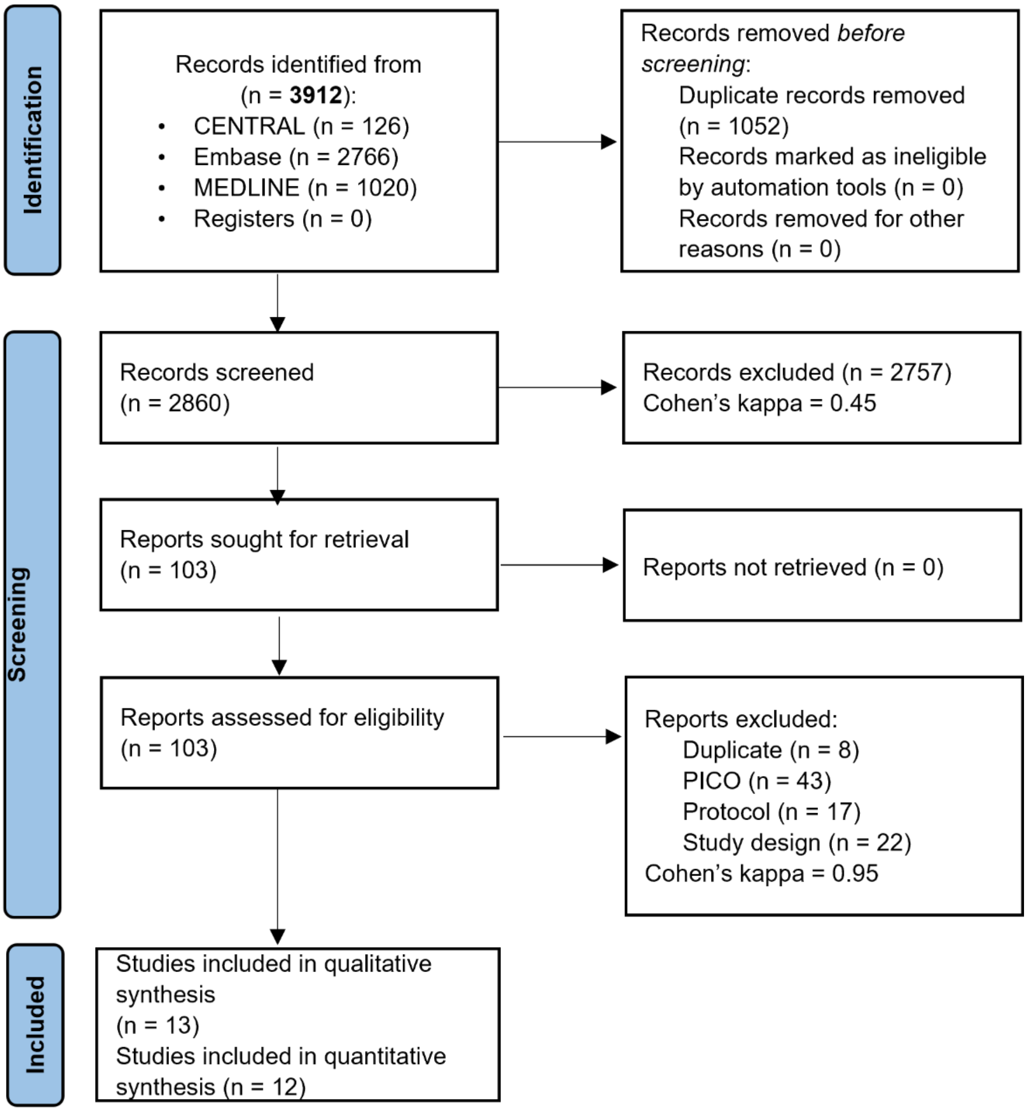


Figure B2 PRISMA 2020 flow diagram. PICO: Population, Intervention, Comparison, and Outcome

Description of the Selected Studies

The literature search yielded three prospective studies [57, 71, 74] and ten retrospective studies [56, 62, 72, 73, 123-128]. Among these, only two studies were RCTs [71, 74]. Four of the included publications were in the form of abstracts [71, 126-128]. The eligible articles, published between 1992 and 2019, were predominantly from Asia [56, 57, 62, 71-73, 125, 127], North America had two publications [123, 124], and Europe had one [74]. Two of the publications had multicentric design [71, 124], while the others were single-center [56, 57, 62, 72-74, 123, 125, 127]. In some cases, information regarding this aspect was not available [126, 128]. Among the included publications, 12 exclusively analyzed malignant etiologies [56, 57, 62, 71-74, 124-128], while only one study considered both benign and malignant etiologies of biliary obstruction [123]. Table B1 provides detailed characteristics of the included articles.

Author, year, country, number of centers	**Study design**	**Time of enrolment**	**N^0 of patients (age, N^0 of females)**	**Indication(s) for stent placement**	**Stent type (TPS *vs.* SPS)**	**EST (TPS, SPS)**	**Outcome(s)**
Brijbassie *et al* 2015, USA, 1 center	Retrospective case series	2006 - 2009	195 patients (mean age 67.1±12.2 years, 75)	Benign and malignant biliary strictures	metal (FCSEMS) *vs.* metal (FCSEMS)	yes, partial	Stent patency, post-ERCP cholangitis
Cho *et al.* 2013 (abstract), Japan, 6 centers	Prospective, randomized trial	2010 - 2012	84 patients (mean age 72±12.5, N/A)	Unresectable malignant biliary obstruction	metal (CSEMS) *vs.* metal (CSEMS)	yes, no	Stent patency, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis, other procedure-related complications: bleeding, cholecystitis
Cosgrove *et al.* 2017, USA, 3 centers	Retrospective cohort	2007 - 2013	172 patients (mean age 66.5±14.18, 66)	Unresectable malignant hilar biliary strictures of any etiology	bilateral metal (SEMS) *vs.* bilateral metal (SEMS)	yes, based on the endoscopist's decision (108, 5)	Stent patency, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis, other procedure-related complications: bleeding, perforation
Inatomi *et al*. 2011, Japan, 1 center	Retrospective cohort	2007 - 2011	42 patients (67.5±12.2 years, 20)	Unresectable malignant hilar biliary obstruction	plastic + metal (uncovered) *vs.* plastic (threaded)	only in metal stents	Stent patency, stent dislocation, other procedure-related complications: bleeding, perforation
Kobayashi *et al*. 2015, Japan, 1 center	Retrospective cohort	2006 - 2011	57 patients (median age 71 (56-86), 12)	Primary biliary duct cancer	plastic *vs.* plastic	yes (3,3)	Stent patency, stent occlusion, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis, other procedure-related complications: bleeding, biliary and pancreatic fistula, liver abscess
Kubota *et al.* 2015, Japan, 1 center	Retrospective cohort	2012 - 2015	40 patients (mean age 70, 13)	Primary biliary duct cancer	plastic *vs.* threaded plastic	yes (multiple TPS)	Stent patency, stent occlusion, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis
Lee *et al.* 2018 (abstract), N/A	Retrospective cohort	2015 - 2017	56 (N/A, N/A)	Obstructive jaundice due to resectable extrahepatic malignant biliary obstruction	plastic *vs.* metal (FCSEMS)	N/A	Stent occlusion, stent dislocation
Pedersen *et al.* 1998, Denmark, 1 center	Prospective, randomized trial	1992 - 1996	34 patients (median age 73.5 (IQR: 67-80), 21)	Malignant biliary obstruction	plastic *vs.* plastic	No	Stent patency, stent occlusion, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis, other procedure related complications: bleeding, cholecystitis, perforation
Shin *et al.* 2020, Korea, 1 center	Retrospective cohort	2005 - 2015	73 patients (median age 75 (49-90), 36)	Hilar cholangiocarcinoma	metal (SEMS) *vs.* metal (SEMS)	Yes (all)	Stent patency, stent occlusion, post-ERCP cholangitis, post-ERCP pancreatitis, procedure-related complications: cholecystitis
Takada *et al.* 2020, Japan, 1 center	Retrospective cohort	2014 - 2016	73 patients (median age 69 (52-86), 38)	Unresectable distal malignant biliary obstruction	metal (SEMS: covered+ uncovered) *vs.* metal (SEMS: covered+uncovered)	yes (12,10)	Stent patency, stent occlusion, stent dislocation, other procedure-related complication: cholecystitis, liver abscess, liver hematoma

Taniguchi *et al.* 2020 (abstract), Japan, 1 center	Retrospective cohort	2016 - 2019	96 patients (N/A, N/A)	Nonhilar, extrahepatic, malignant biliary stricture	metal (covered) *vs.* metal (covered)	N/A	Stent patency, stent occlusion
Uchida *et al.* 2005, Japan, 1 center	Prospective, non-randomized	1999 - 2003	32 patients (mean age 75 (56-92), 15)	Unresectable and previously untreated malignant biliary obstruction	plastic *vs.* plastic	No	Stent patency, stent occlusion, stent dislocation, post-ERCP pancreatitis, post-ERCP cholangitis, other procedure-related complications: bleeding, cholecystitis, perforation
Yamaguchi *et al.* 2019 (abstract), N/A	Retrospective cohort	2008 - 2018	74 patients (N/A, N/A)	Unresectable malignant hilar or middle bile duct obstruction	plastic *vs.* plastic	N/A	Stent patency, stent dislocation, post-ERCP cholangitis, post-ERCP pancreatitis, other procedure-related complication: bleeding, cholecystitis

Table B1 Characteristics of included studies

ERCP: endoscopic retrograde cholangio-pancreatography, EST: endoscopic sphincterotomy, N/A: not available, SEMS: self-expandable metallic stent, SPS: suprapapillary stent, TPS: transpapillary stent

Outcomes:

1. Stent Patency

The analysis of stent patency time involved 11 studies encompassing 875 patients [56, 57, 62, 71-74, 123-125, 128]. Significantly longer stent patency time was observed in the SPS group (WMD = 50.23 days, 95% CI: 8.56; 91.89; p = 0.018; I^2 = 77%, p < 0.001) (Figure B3).

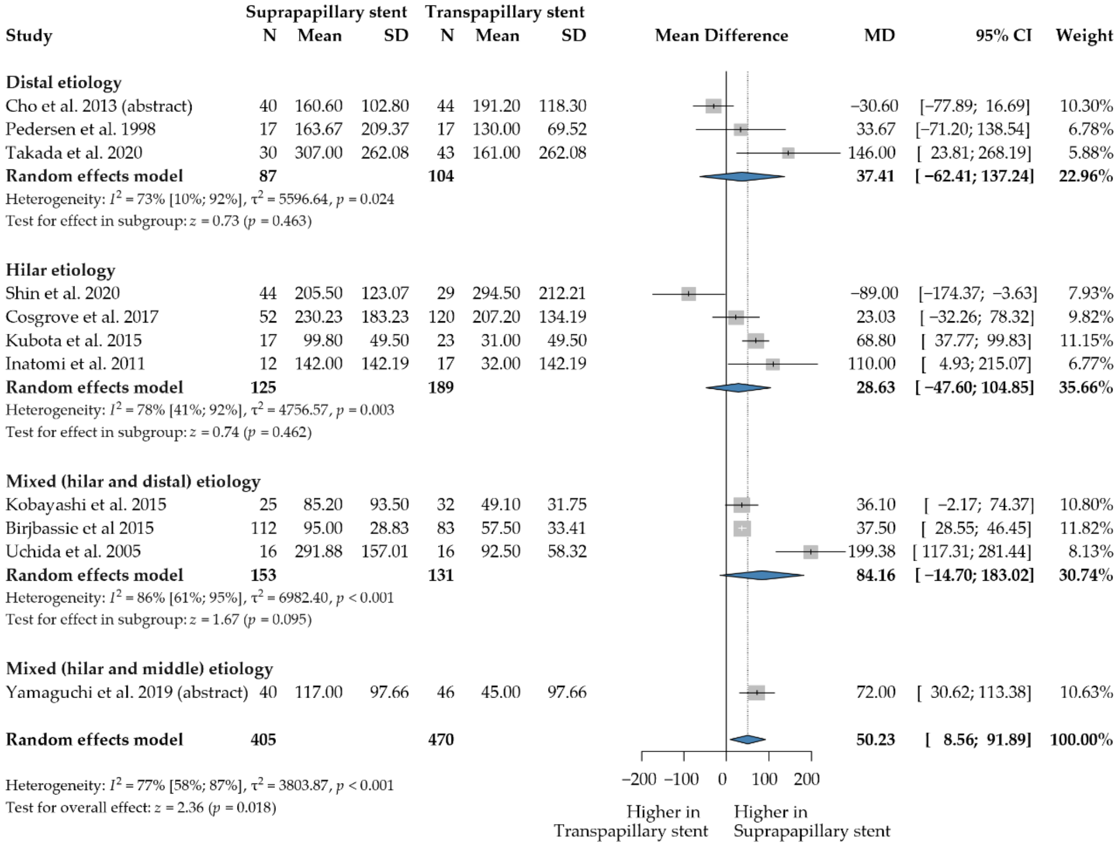


Figure B3 Forest plot comparing the stent patency time between suprapapillary and transpapillary stents. Unit of measurement: days. CI: confidence interval; MD: mean difference; p: P-value; SD: standard deviation

The same result was found when focusing solely on full-text reports addressing malignant indications (WMD = 62.30 days, 95% CI: 4.39, 120.21; p = 0.035; I^2 = 76.0%, p < 0.001) [56, 57, 62, 72-74, 124, 125] (See in the online supplementary material and in the appendix of this dissertation [129]).

We conducted separate analyses for stent patency times in SPS and TPS positions, considering metal and plastic stents. Five studies involving 597 patients utilized SEMS [56, 71, 73, 123]. No significant difference was observed between SPS and TPS positions (WMD = 10.85 days, 95% CI: −48.23, 69.94; p = 0.719; I^2 = 79%, p < 0.001) (See in the online supplementary material and in the appendix of this dissertation [129]). When exclusively focusing on malignant indications, similar results were obtained, with no significant differences found (WMD = 3.98, 95% CI: −79.63; 87.59; p = 0.926; I^2 = 74%, p = 0.009) (See in the online supplementary material and in the appendix of this dissertation [129]) [56, 71, 73, 124].

In the plastic stent subgroup, six publications with a total of 278 patients were included [57, 62, 72, 74, 125, 128]. SPS plastic stents exhibited a significantly longer stent patency time (WMD = 80.49 days, 95% CI: 37.57, 123.40, p < 0.001; I^2 = 63%, p = 0.019) (See in the online supplementary material and in the appendix of this dissertation [129]).

2. Stent Migration

Analyzing seven articles encompassing 376 patients [56, 57, 71, 72, 74, 125, 130], no significant difference was observed in terms of stent migration between the two techniques (OR: 0.67, 95% CI: 0.17, 2.72; p = 0.577; I^2 = 58%, p = 0.027) (Figure B4). Only one publication indicated a significant increase in stent migration with SPS placement compared to TPS [74], while all other studies demonstrated no significant differences in this aspect.

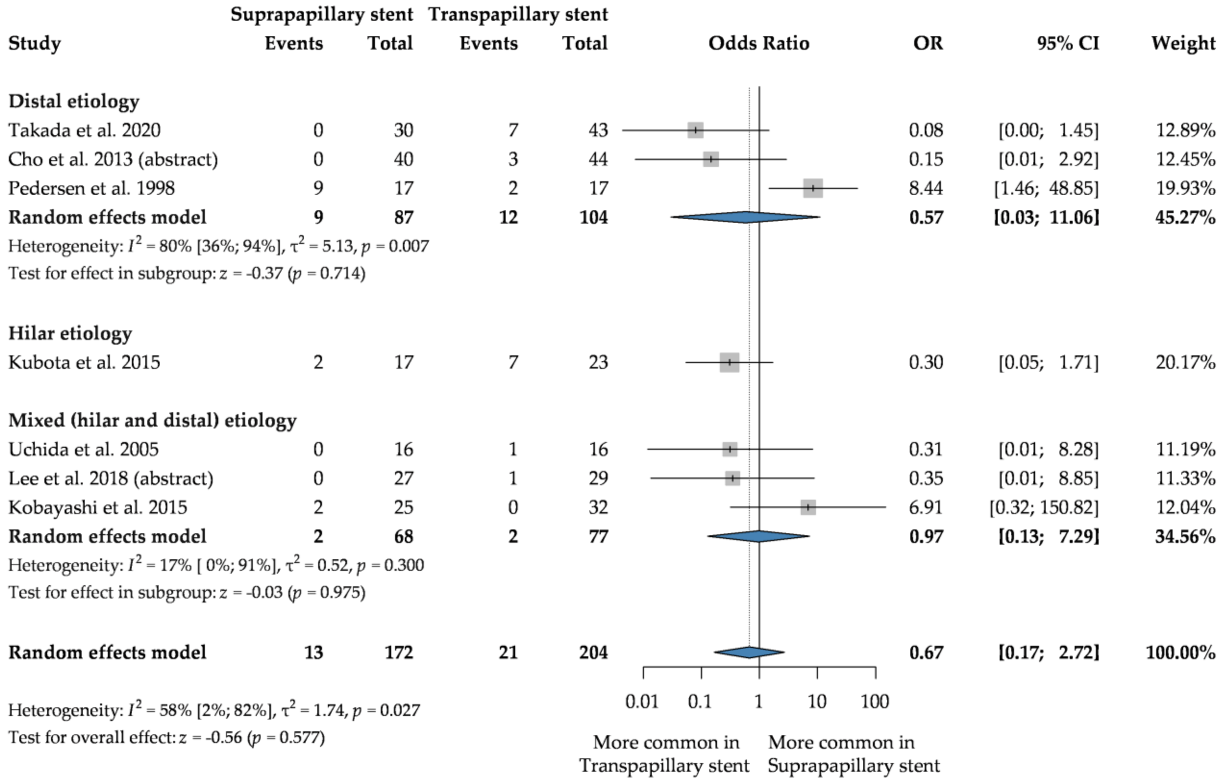


Figure B4 Forest plot comparing stent migration rate between suprapapillary and transpapillary stents. CI: confidence interval; OR: odds ratio, p: P-value

The subgroup analysis focusing on plastic stent placement, involving four publications and 163 patients [57, 72, 74, 125], revealed also no significant difference between the two techniques (OR: 1.57, 95% CI: 0.25, 9.83; p = 0.627; I^2 = 66%, p = 0.032) (See in the online supplementary material and in the appendix of this dissertation [129]).

3. Cholangitis

Data on cholangitis rates from six studies involving a total of 598 patients were included in our analysis [71, 73, 74, 123-125]. Among these, only one publication indicated that SPS placement led to significantly lower cholangitis rates than the transpapillary method [125]. The rest of the articles indicated comparable rates of this complication in both groups. The overall rate of cholangitis exhibited similarity between the two investigated groups (OR: 0.52, 95% CI: 0.25, 1.09; p = 0.082; I^2 = 16%, p = 0.309) (Figure B5).

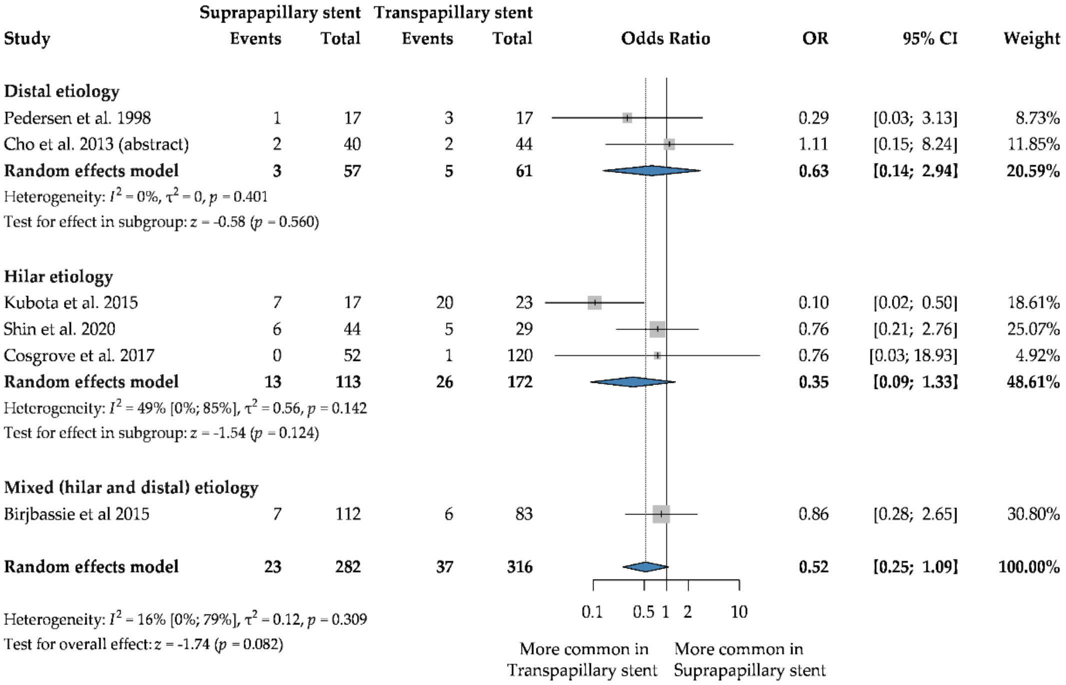
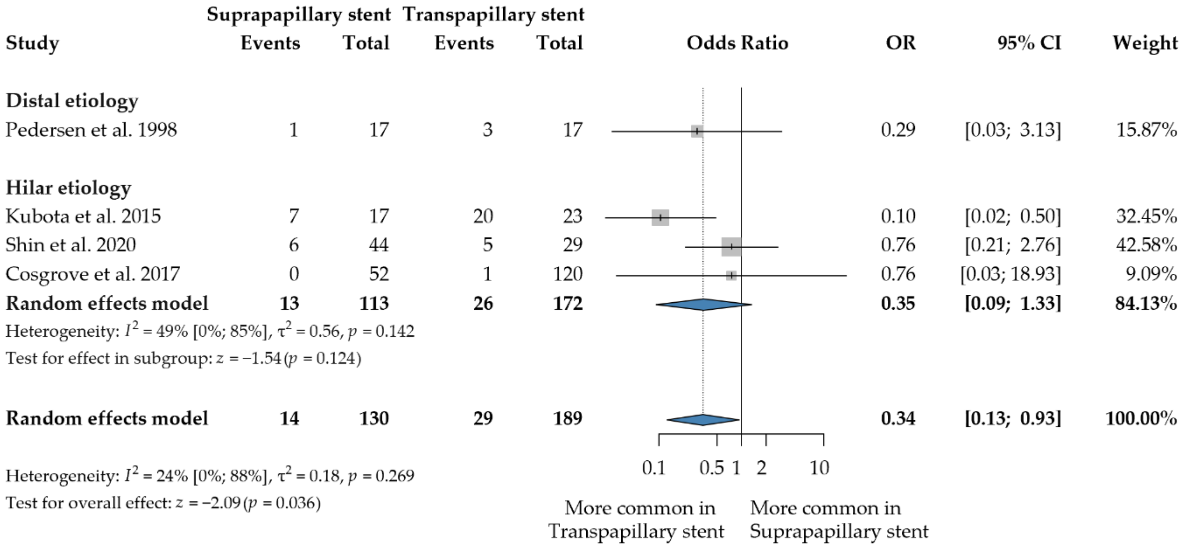


Figure B5 Forest plot comparing cholangitis rate between suprapapillary and transpapillary stents. CI: confidence interval; OR: odds ratio; p: P-value

Notably, there is a distinct trend toward lower cholangitis rates with the SPS position. Additionally, when specifically analyzing full texts that exclusively focused on malignant indications, there was a significantly lower risk of cholangitis with SPS (OR: 0.34, 95% CI: 0.13, 0.93; p = 0.036; I^2 = 24%, p = 0.269) (Figure B6) [73, 74, 124, 125].



Study	Suprapapillary stent Events	Suprapapillary stent Total	Transpapillary stent Events	Transpapillary stent Total	OR	95% CI	Weight
Distal etiology							
Pedersen et al. 1998	1	17	3	17	0.29	[0.03; 3.13]	15.87%
Hilar etiology							
Kubota et al. 2015	7	17	20	23	0.10	[0.02; 0.50]	32.45%
Shin et al. 2020	6	44	5	29	0.76	[0.21; 2.76]	42.58%
Cosgrove et al. 2017	0	52	1	120	0.76	[0.03; 18.93]	9.09%
Random effects model	**13**	**113**	**26**	**172**	**0.35**	**[0.09; 1.33]**	**84.13%**
Random effects model	**14**	**130**	**29**	**189**	**0.34**	**[0.13; 0.93]**	**100.00%**

Hilar etiology subgroup: Heterogeneity: $I^2 = 49\%$ [0%; 85%], $\tau^2 = 0.56$, $p = 0.142$
Test for effect in subgroup: $z = -1.54$ ($p = 0.124$)

Overall: Heterogeneity: $I^2 = 24\%$ [0%; 88%], $\tau^2 = 0.18$, $p = 0.269$
Test for overall effect: $z = -2.09$ ($p = 0.036$)

Figure B2 Forest plot comparing cholangitis rate between suprapapillary and transpapillary stents including full texts with malignant indications. CI: confidence interval; OR: odds ratio, p: P-value

In the subgroup of metal stents, there was no difference in cholangitis between SPS and TPS positions (OR: 0.85, 95% CI: 0.40, 1.81; p = 0.665; I^2 = 0.0%, p = 0.992) (See in the online supplementary material and the appendix of this dissertation [129]) [71, 73, 123, 124]. Similarly, when exclusively considering malignant indications, no significant difference was found (OR = 0.84, 95% CI: 0.30; 2.34; p = 0.753; I^2 = %, p = 0.951) (See in the online supplementary material and in the appendix of this dissertation [129]) [71, 73, 124].

4. Pancreatitis

Data on the rate of pancreatitis were available from five articles, encompassing a total of 426 patients [71-73, 124, 125]. Our analysis revealed a comparable rate of pancreatitis between the groups (OR: 0.38, 95% CI: 0.11, 1.28; p = 0.120; I^2 = 0.0%, p = 0.425) (Figure B7).

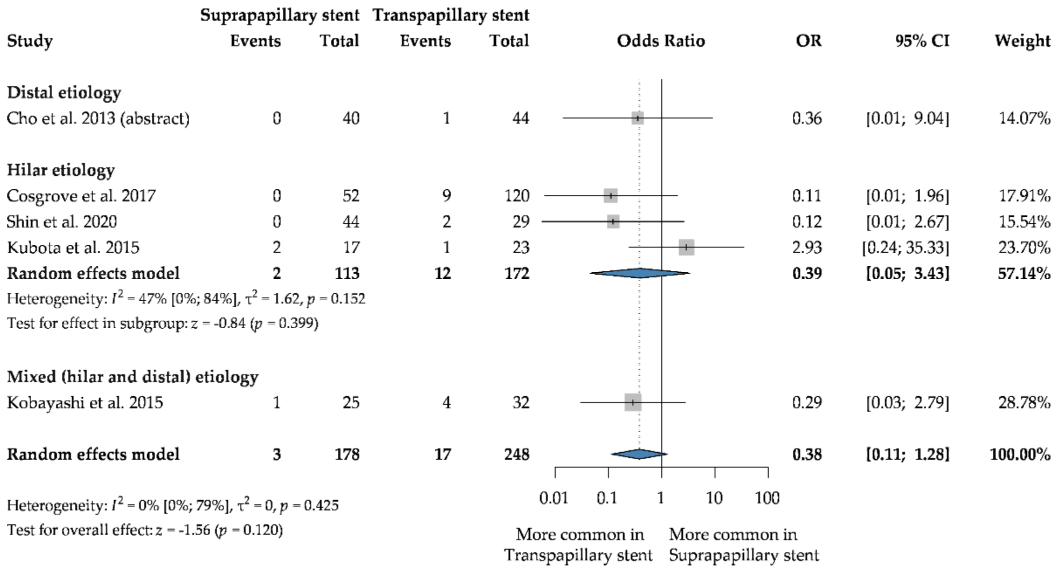


Figure B7 Forest plot comparing pancreatitis rate between suprapapillary and transpapillary stents. CI: confidence interval; OR: odds ratio; p: P-value

Following a sensitivity analysis that excluded the study reported solely as an abstract [71], the same result persisted (OR: 0.38, 95% CI: 0.08, 1.66; p = 0.197;I^2 = 22%, p = 0.277) (See in the online supplementary material and the appendix of this dissertation [129]). In the subgroup of metal stents, the suprapapillary method exhibited a significantly lower rate of pancreatitis (OR: 0.16, 95% CI: 0.03, 0.95; p = 0.043; I^2 = 0.0%, p = 0.850) (Figure B8) [71, 73, 124].

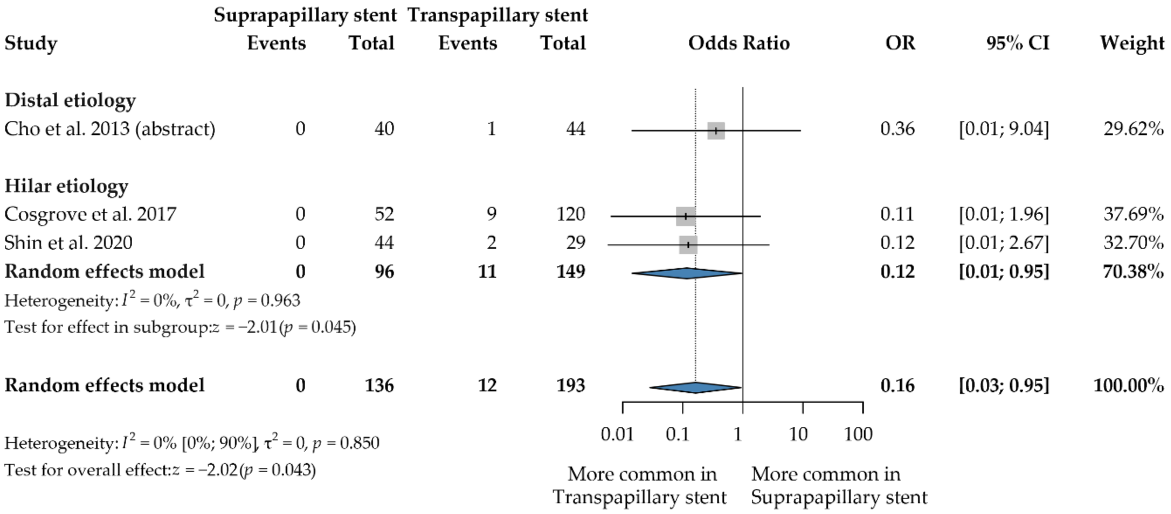


Figure B8 Forest plot comparing pancreatitis rate between suprapapillary and transpapillary metal stents. CI: confidence interval; OR: odds ratio, p: P-value

5. Cholecystitis

Three articles, with a combined total of 230 patients explored the occurrence of cholecystitis in the context of metal stents [56, 71, 73]. Our results revealed comparable rates of cholecystitis in both groups (OR: 1.41, 95% CI: 0.28, 7.15; p = 0.677; I^2 = 0%, p = 0.455) (Figure B9).

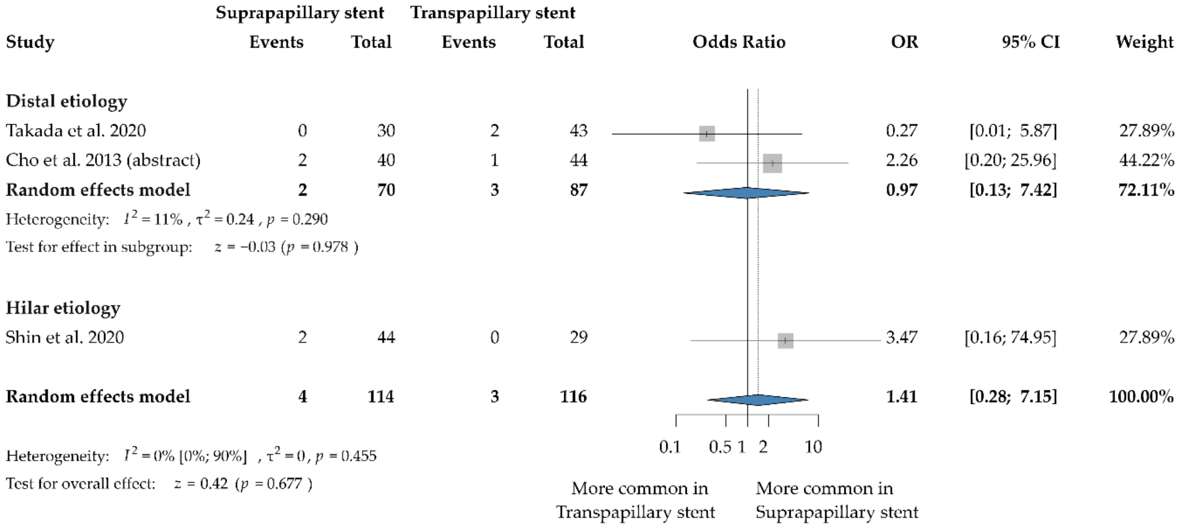


Figure B9 Forest plot comparing cholecystitis rate between suprapapillary and transpapillary metal stents. CI: confidence interval; OR: odds ratio; p: P-value

6. Other Complications

Rates of bleeding were detailed in seven studies [57, 62, 71, 72, 74, 124, 128], primarily linked to EST. One bleeding complication was reported in the SPS group [72] and two in the TPS group [124]. Three perforations were documented, with two in the TPS group and one in the SPS group [124]. Procedure-related complications, endoscopic sphincterotomy, and survival rates are summarized in the online supplementary material and in the appendix of this dissertation [129].

Risk of Bias Assessment and Certainty of Evidence

We evaluated the quality of each included publication utilized in the quantitative synthesis. Detailed results at the study and domain levels for each outcome can be found in the supplementary material (See in the online supplementary material and in the appendix of this dissertation [129]). In the eligible non-randomized publications [56, 57, 62, 72, 73, 123-128], the risks of bias at pre-, at-, and post-intervention levels were predominantly deemed as low, not counting the domains of "bias due to confounding" and "bias in the selection of reported results," where we identified serious and moderate risks in most studies, respectively. The overall risk of bias was mainly assessed as serious.

In the case of two eligible RCTs [71, 74], we identified "some concerns" in the "randomization process" domain in one study [71], and we also identified some concerns in the "selection of the reported result" domain in both publications [71, 74]. The overall risk of bias was deemed at "some concerns".

For stent patency time, we conducted Egger's test which revealed no evidence of publication bias ($p = 0.591$). Funnel plots were generated for patency (subgroup of plastic stents), stent migration, and cholangitis. Upon visual inspection, publication bias was suspected in the cases of stent migration and cholangitis. The funnel plot for each outcome is available in the supplementary material (See in the online supplementary material and in the appendix of this dissertation [129]).

The evaluated endpoint was judged to have a low to very low level of evidence. The quality of evidence was significantly influenced by factors such as the study design, the presence of a substantial risk of bias, potential inconsistency rooted in heterogeneity, and a notable risk of imprecision. The summary of findings tables can be found in the online supplementary material and in the appendix of this dissertation [129].

VI. DISCUSSION

In our research, we presented new strategies for improving biliary interventions. We expect our results to help integrate these aspects of biliary interventions into day-to-day practice and stimulate further research in these topics.

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Bile Duct Injury

Cholecystectomy treats various gallbladder-related issues such as gallstones and inflammation [131]. Cholecystectomy carries risks, one of the most significant being BDI. BDI can lead to complications such as biloma, intraabdominal abscess, infection, and sepsis, and in severe cases, death [132]. IOC provides real-time imaging of the biliary tree, allowing surgeons to prevent and identify BDI [17, 133]. However, the correct execution and interpretation of IOC require trained and experienced surgeon [134].

Our findings suggest that routine IOC does not provide a significant protective effect against BDI compared to selective IOC. Additionally, performing IOC does not offer a clear advantage over omitting it entirely, suggesting that a selective approach may be more judicious. We believe the key question is whether IOC should be performed routinely during every cholecystectomy or selectively based on different indications.

There is a consensus on the relevance of IOC in surgical practice for detecting CBD stones and diagnosing and preventing BDI. However, recommendations vary due to lingering doubts about the extent to which IOC should be used in everyday practice [15-17]. A recent meta-analysis suggests routine IOC’s protective effect against BDI over the selective approach, offering additional benefits such as cost-effectiveness, reduced postoperative complications, and shorter hospital stays [17]. This study also raises the educational role of the IOC for surgeons training, helping them to understand complex biliary anatomy [17]. Similarly, a meta-analysis from 2021 supports routine IOC for its potential to reduce BDI risk and increase cost-effectiveness [13]. However, these conclusions should be interpreted cautiously due to discrepancies in how the population was defined in some cases. Participants marked as selective IOC patients appear as patients "without IOC" in most analyzed studies [30, 97, 99, 100, 114, 135], which can affect the validity of the conclusions. Despite these issues, several surgical associations, including those in France and Sweden, recommend systematic IOC to reduce BDI risk [136, 137].

In contrast, several meta-analyses and large-scale observational studies question the protective effect of routine IOC compared to the selective approach [15, 16, 138]. The 2018 Tokyo guideline for the surgical management of acute cholecystitis state that IOC is optional due to mixed results and a lack of conclusive evidence [139]. An Australian study showed a 31.8% increase in IOC but only a 7.0% rise in cholecystectomies, with minimal change in BDI rates, suggesting that routine IOC may not be necessary to prevent BDIs [138]. Ragulin-Coyne et al. published a study in 2013 involving 111,815 patients, also concluded that routine IOC does not reduce BDI rates but increases costs [33].

The differing conclusions on this topic may be due to variations in study design, the patient enrollment method, the potential presence of biases and confounding factors, and the statistical methodologies applied. For instance, Sheffield et al. believe that the correlation between IOC and common BDI may stem from unmeasured confounding variables [114], and differences in baseline characteristics between comparator groups. They argue that the association between IOC and BDI depends heavily on the statistical methodology used [114]. While standard risk adjustment techniques indicated an association between IOC omission and BDI, this association became statistically insignificant when instrumental variable methods were employed. Another issue in the debate over the IOC use is the reliance on large databases studies comparing IOC and no IOC that often lack precise definitions of BDI [26, 27, 29, 30, 99, 107, 113], leading to the use of proxy, or indirect definitions that may introduce confounding factors [27].

Retained Biliary Stones after Cholecystectomy

IOC is also used to identify CBD stones intraoperatively. In Sweden, CBD stones are detected in 8.6% of elective cholecystectomies and 21% of emergency cases [140]. Other sources report that the prevalence of CBD stones during cholecystectomy is less than 5% in patients without jaundice or a dilated CBD on transabdominal ultrasound [38].

Our findings indicate that routine IOC does not significantly decrease the incidence of postoperatively-detected residual CBD stones. Current guidelines suggest using ERCP for the management of asymptomatic CBD stones due to the potential risk of complications [40, 41]. Patients with CBD stones detected during IOC and left in situ had a higher risk of needing ERCP than those who had planned perioperative removal [141]. However, some believe it should not be done for every asymptomatic stone because ERCP itself carries high risks [34]. The risk of leaving small (less than 4 mm) stones in the CBD is generally considered to carry minimal risks [141].

A 2012 meta-analysis suggests that routine IOC may lower readmission rates for retained CBD stones [14]. However, it does not recommend for routine IOC for patients who do not exhibit clinical, biochemical, or radiological sings of CBD stones [14]. Additionally, another publication found no added benefit from routine IOC, as the detection rates of choledocholithiasis and the rates of missed stones were similar between routine and selective IOC [142].

Hope et al. advocate for the liberal use of IOC in detecting CBD stones, citing its high sensitivity, specificity, and predictive accuracy [4]. They emphasize that the effectiveness of IOC depends on the operator's expertise [4]. Contrary, a 2021 retrospective study revealed that confirmation of CBD stones on ERCP, endoscopic ultrasound, or magnetic resonance cholangiopancreatography revealed a high false-positive rate (46.5%) of IOC [143], suggesting some stone may pass spontaneously [143]. Similar findings have been reported, with up to one-third of patients with an abnormal IOC having no evidence of stone on subsequent ERCP [144]. This uncertainty reflects the unclear natural history of asymptomatic CBD stones [145].

Hakuta et al. found that untreated, asymptomatic CBD stones have a cumulative incidence of biliary complications of 6.1% at one year, 11% at three years, and 17% at five years [34]. Despite this, they recommend a "wait-and-see strategy" for patients with in situ stones, rather than early endoscopic management, due to the significant risk of postprocedural complications with ERCP, especially in asymptomatic patients [34, 146]. Ragulin-Coyne et al. note that routine IOC may identify more CBD stones during surgery than the selective IOC group [33]. This increased detection leads to more ERCP and CBD explorations, contributing to a higher overall complication rate. Consequently, they advocate for selective IOC to reduce unnecessary interventions. Sheffield et al. support this view, demonstrating also that routine IOC correlates with increased rates of ERCP and CBD exploration [114].

The ASGE and ESGE endorse two similar preoperative risk stratification methods to assess the likelihood of CBD stones [2, 40]. These guidelines provide valuable tools for identifying patients who may require further investigation and management, aiding surgeons in determining the necessity of IOC.

Secondary Outcomes

We found no significant differences between routine and selective IOC regarding the success rate of IOC and operation time. However, significant differences were noted between IOC and no IOC groups in the conversion rate to open surgery and operation time. Patients who did not undergo IOC had a higher conversion rate to open surgery, often occurring during challenging laparoscopic procedures or when BDI is suspected [107]. Wolf et al. indicate an increased risk of BDI associated with the conversion from laparoscopic to open procedures [147], possibly reflecting surgeon inexperience with open cholecystectomy [148] or the overall complexity of the case [107].

Our data indicates that patients undergoing LC with IOC experienced a significantly longer operation time of nearly 13 minutes. This finding supports the contention of IOC opponents who suggest that IOC significantly prolongs the duration of LC. However, increased operative time can be mitigated as routine IOC makes staff more efficient. A previous study found that routine IOC takes 12 minutes on average, compared to 25 minutes for selective IOC [142].

In the comparison of readmission rates and length of hospital stay between IOC and no IOC groups, no significant differences were observed.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Stent Patency

To delay and prevent stent occlusion, various strategies have been explored, including the use of covered stents to impede tumor ingrowth, biofilm formation and anti-reflux valves to prevent duodenobiliary reflux [54, 67, 149, 150]. Research has shown that SPS placement may extend stent patency time by preventing sludge formation, biofilm accumulation, and preserving the sphincter of Oddi as a natural barrier against reflux. [69, 123]. Although this theory appears plausible, further direct testing is needed [151].

Our analysis showed significantly longer stent patency times in the SPS group. One of the first randomized trial suggests that SPS have shorter patency time than TPS [74]. Some publications argued that the shorter patency of SPS detected may be due to its higher migration rate, which is attributed to the greater rigidity of the stents used and the large proportion of pancreatic cancer patients in the sample [57] [75].

In subgroup analyses that included only metal stents, there was no significant difference in patency between SPS and TPS. This aligns with the previous assumption that the material properties of metal stents may counteract the advantages of SPS by preventing debris deposition and reducing occlusion rates [124]. While metal stents have longer patency than plastic ones in the TPS position, they are more expensive, often require endoscopic sphincterotomy (EST), and are difficult to remove [61, 62, 152, 153]. On the other hand, plastic stents are more affordable and easier to handle them in certain clinical scenarios, but they tend to occlude more rapidly, necessitating more frequent replacements [152]. Suprapapillary positioning could be a solution to this issue, though concerns about stent removal have been raised [74].

Solutions like attaching a nylon thread to the distal end of the stent have been proposed to facilitate removal [62, 72, 125]. In some studies, threaded SPS stents without EST showed significantly prolonged patency compared to metal stents positioned suprapapillary with EST [62]. A randomized trial by Kanno and his colleagues found no significant difference between plastic and metal stents in SPS position, suggesting suprapapillary plastic stents could be an alternative to metal stents for unresectable malignant hilar biliary obstructions [154].

The effectiveness of SPS may also be influenced by factors like the type of cancer (e.g. pancreatic cancer), the distance of the cancer and stent from the ampulla, the site of biliary obstruction, and the presence of EST [56, 75]. Theoretically, keeping the barrier function of SO and avoiding duodenobiliary reflux might increase the stent patency time. Therefore, avoiding EST in cases of SPS might lead to better outcomes [69]. Takada et al. demonstrated that SPS without EST has been associated with longer patency times [56]. However, in the TPS group, the presence or absence of EST did not significantly affect stent patency [56].

Stent Migration

One of the earliest studies suggested that stent migration occurs more frequently with SPS and recommended TPS instead [74]. This might be why it became generally accepted that SPS is more prone to migration. In this study, the distal flaps of the stents were removed in half of the patients, and the majority of the patients suffered from pancreatic cancer, a condition associated with significant axis deviation [75]. Uchida et al. noted that they used a more rigid stent type, which also could contribute to stent migration and recommended a more flexible “curved” stent to mitigate this risk [57].

Surprisingly, most studies in our analysis reported a lower incidence of SPS migration, although the results were not statistically significant. The attachment of TPS stents to two independently moving anatomical sites, the sphincter of Oddi and the tumor, may facilitate migration [125]. If we investigate stent types, the uncovered SEMS migration occurs less frequently than covered SEMS or plastic stents [155], though they are much harder to remove.

Studies have explored anti-migration measures, such as 10-Fr double-pigtail plastic stent within fully covered transpapillary SEMS [156] or employing modified fully covered SEMS (stent with saddle-shaped central portion, convex margin without flares, and thread at the distal end to facilitate retrieval) to prevent migration [157]. Mangiavillano et al. used fully covered SEMS to treat benign biliary obstructions with a low migration rate (3.3%) [158]. The stents were modified with flared ends, four ‘anchoring flaps’, and a ‘lasso’ at the proximal and distal end of the stent [158]. These innovations show promise in reducing migration rates and improving the overall effectiveness of stent placement.

Cholangitis

TPS placement has been linked to a higher risk of reflux cholangitis [159], as it may compromise the sphincter of Oddi's barrier function [124]. In contrast, SPS placement might reduce complication rates by preserving this natural defense [124]. Our results showed no significant difference in cholangitis rates between SPS and TPS groups, but a tendency toward lower rates with SPS was observed. Notably, when focusing on full-text articles with only malignant cases, SPS was associated with a significantly reduced rate of cholangitis. No significant difference was found within the subgroup analysis limited to metal stents. Some studies have found a correlation between metal stents in the TPS position and increased risk of cholangitis [159], while others did not [160]. EST combined with suprapapillary SEMS placement has been associated with an elevated risk of cholangitis [161], thus SPS placement without EST might be beneficial.

Pancreatitis

SPS placement might mitigate the risk of PEP by alleviating stress on the major duodenal papilla [69], preventing the obstruction of pancreatic juice flow into the duodenum [162].

While our analysis did not find a significant difference in PEP rates between SPS and TPS placements, a trend toward lower PEP rates in the SPS group was observed. Notably, a significantly reduced rate of pancreatitis was apparent in the subgroup analysis focusing on SEMS. Placement of a SEMS significantly heightens the risk of PEP compared to plastic stents [163]. Larger stent diameters and the mechanical obstruction posed by SEMS in the TPS position may increase PEP risk [125], this effect could be mitigated with SPS placement. EST is commonly employed to reduce the risk of PEP in TPS placement by alleviating pressure on the pancreatic duct [164], but previous meta-analyses have shown mixed results regarding its effectiveness. Some studies suggest that EST may protect against PEP [165], while others have found no significant benefit [160, 162, 166].

STRENGTH AND LIMITATIONS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Our research stands out for its comprehensive analysis, including a large number of patients and several subgroup analyses (including exclusively LC cases, MBDI, and prospective studies) to enhance the quality of evidence and ensure more exhaustive research. We placed great emphasis on comparing the routine IOC *vs.* selective IOC approaches and found several additional articles not examined [94, 96, 97, 105, 107, 113, 115, 116, 121]. However, most of the included studies were retrospective, which used data from large-scale databases with potential sources of bias and lack of control of confounding variables. Variations in-study design, patient populations, and IOC utilization contributed to statistical heterogeneity, which should be considered when interpreting our findings. Moreover, IOC is a diagnostic tool for detecting BDI in some cases, which could introduce a potential distortion effect also.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Our research provides an extensive synthesis of available data on SPS and TPS placement, with several subgroup analyses to increase the relevance of our findings. The methodology is transparent and reproducible, adhering to rigorous standards throughout the research process. However, the included studies were mostly non-randomized and non-prospective, leading to lower quality evidence. Additionally, studies published solely as abstracts were included. Confounding factors are present in the included studies, and many of which were deemed to carry a serious risk of bias. The populations across the included studies exhibit heterogeneous etiology of biliary obstruction. Some patients received additional or adjunctive therapy beyond palliative treatment, potentially influencing outcomes. Heterogeneity was substantial in pooled publications regarding stent patency time and migration. Moreover, SPS placement is feasible only in patients with intact lower bile ducts, limiting its applicability in cases such as pancreatic cancer where obstruction often occurs near the papilla. Disease progression may also render SPS placement impractical. Cases of hilar strictures requiring multiple SPS insertions may have influenced our results as well. Additionally, publication bias could not be thoroughly assessed due to the limited number of studies.

VII. CONCLUSION

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Selective IOC may be as effective as routine IOC in preventing BDI, suggesting that IOC might not be necessary in every case. Instead, a selective approach combined with preventive measures against BDI, such as ensuring a critical view of safety, adopting a fundus-first approach, utilizing a multi-port laparoscopic technique, and maintaining a low threshold for conversion to open cholecystectomy [1, 18], alongside procedures for detecting CBD stones perioperatively, such as abdominal ultrasound, endoscopic ultrasound, and magnetic resonance cholangiopancreatography [1, 2], could be a viable alternative.

A standardized indication system for selective IOC has yet to be developed. It should account for various risk factors associated with BDI (e.g., sex, age, surgeon experience, prolonged laparoscopic cholecystectomy, history of abdominal surgery, and the indication for cholecystectomy, uncertain biliary anatomy). Additionally, it should consider the potential presence of asymptomatic biliary stones based on clinical, laboratory, and imaging findings, as well as their available treatment options. Future research endeavors should establish a universally accepted indication system, guiding surgeons in determining when to perform IOC. Randomized trials are not feasible for studying BDI due to their low incidence. Consequently, there is a pressing need for high-quality prospective studies that carefully address potential biases and confounding factors.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Although our results should be interpreted cautiously, they suggest that the SPS could be a viable alternative to TPS in certain cases offering prolonged stent patency and reduced complications, albeit with a comparable migration rate. These benefits could lead to fewer interventions, enhancing patient quality of life and reducing healthcare costs. The incorporation of threads at the distal ends of both plastic and covered metal stents might facilitate their removal.

The scarcity of the available number of RCTs limits the presented evidence. Therefore, further high quality RCTs are needed to confirm these advantages effects of SPS placement. Future trials should explore the feasibility and impact of SPS across both benign and malignant etiologies. Additionally, consideration of key stent characteristics, such as material, size, and length, or insertion method (side-by-side, stent-in-stent) might be crucial as well. Future RCTs should investigate various outcomes and aspects such as insertion success rates, endoscopic revision success rates, stent removability, stent patency time, and post-procedural complication rates associated with both stent positions, the necessity and effect of EST, and the effect of prophylactic pancreas stents. Cost-effectiveness analyses would provide valuable insights for future clinical guidelines. A recent report compared the performance of suprapapillary threaded plastic and metal stents and found no significant differences between the two groups in any of the investigated endpoints [154], this could set a direction for future publications as well.

VIII. SUMMARY OF NEW FINDINGS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

To conclude,

1. The necessity of IOC in every case is not conclusive.

2. Selective IOC may be as effective as routine IOC in preventing BDI, selective IOC could serve as an alternative to routine practice.
3. The rate of BDI was comparable between IOC and no IOC groups.
4. The rate of residual CBD stones was comparable between IOC and no IOC groups.
5. The success rate of IOC and the operation time were comparable between selective and routine IOC groups.
6. A higher conversion rate to open surgery appeared in the no IOC group.
7. Significantly longer operation time was characteristic of the IOC group *vs.* no IOC group.
8. Further high-quality research is needed to establish precise criteria when to use IOC.
9. Further high-quality prospective studies that address potential biases and confounding factors are needed.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

In light of our findings,

1. SPS potentially leads to longer stent patency time.
2. SPS and TPS might have similar migration rates.
3. SPS might result in a lower rate of cholangitis compared to TPS in cases of malignant biliary obstruction.
4. Metal SPS placement might lead to lower rate of pancreatitis compared to metal TPS in cases of malignant biliary obstruction.
5. Further RCTs are necessary to strengthen the quality of evidence.

ACKNOWLEDGMENT

I would like to extend my heartfelt gratitude to my supervisor, Szabolcs Ábrahám, for his exceptional guidance, mentorship, and invaluable insights. His mentorship, constructive feedback, and belief in my abilities have been instrumental in shaping my path and fostering my development. I am genuinely grateful for the time and effort he has invested in me, guiding me towards success.

A special thanks goes to Péter Hegyi’s and Bálint Erőss’s expertise, visionary way of thinking, and encouragement have also been pivotal in my path and helped me navigate challenges along the way.

I would like to express my deepest gratitude to my family, friends, and colleagues for their unwavering support, encouragement, and understanding throughout this journey. Your belief in me and your continuous support have been instrumental in reaching this milestone.

Also, Eszter Uhrin has been a beacon of inspiration, helping me face challenges, discover my strengths, and grow both personally and professionally. Your presence in my life has been a source of strength, comfort, and inspiration, propelling me forward during both the highs and lows. Your belief in me, even when I doubted myself, has constantly reminded me of my capabilities and potential.

Thank you all for being a part of this incredible journey. Your contributions have not only enriched my experience but have also made this achievement possible.

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