STRATEGIES FOR IMPROVED BILIARY INTERVENTIONS

Ph.D. thesis

Norbert Kovács M.D.

Supervisor:

Szabolcs Ábrahám M.D., Ph.D.

University of Szeged, Albert Szent-Györgyi Medical School

Doctoral School of Clinical Medicine

Head of the Doctoral School: Lajos Kemény M.D., Ph.D., D.Sc.

Translational Medicine Program

Program Director: Péter Hegyi, M.D., Ph.D., D.Sc.

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. *et al*. 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., *et al*. 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)

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. INTRODUCTION

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Laparoscopic cholecystectomy (LC) has emerged as the "gold standard" for treating cholecystolithiasis. Despite the benefits of LC, it carries inherent risks, among which bile duct injury (BDI) is a major concern. Consequences of BDI are severe, contributing to increased postoperative mortality, morbidity, and reduced quality of life. Therefore, numerous guidelines

and meta-analyses have attempted to offer recommendations for preventing BDI. Among the interventions studied intraoperative cholangiography (IOC) has garnered significant attention.

The purpose of IOC is to help surgeons identify BDI, any abnormalities or obstructions in the bile ducts. There is no firm evidence to which extent IOC should be used. Some recommend performing it routinely at every cholecystectomy. Others recommend omitting it altogether or performing it selectively, only in certain clinical scenarios, like unclear biliary anatomy or suspicion of BDI or CBD stone.

Proponents of IOC argue that using it routinely mitigates the risk of BDI by clarifying ambiguous or aberrant biliary anatomy, and it aids the intraoperative detection and treatment of BDI, thus reducing postoperative complications. Another argument for the routine approach is that previously asymptomatic CBD stones can be detected. Opponents contend that BDI is relatively rare (0.3% to 0.5%), and routine IOC increases the intraoperative identification of previously asymptomatic bile duct stones, leading to unnecessary interventions. They favor the "wait-and-see strategy" over endoscopic treatment of asymptomatic stones. Complications occur in 4% to 15.9% of cases when bile duct stones are removed via endoscopic retrograde cholangiopancreatography (ERCP). These include post-ERCP pancreatitis (PEP), cholangitis, bleeding, and perforation, with PEP being the most prevalent. A third party argues that IOC may not be necessary as a routine practice, except in cases where CBD stones are suspected or in patients deemed at high risk of BDI.

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 the prevention of CBD stone-related complications.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Endoscopic biliary stent placement represents a minimally invasive intervention utilized in patients with benign biliary strictures and as a palliative therapy for malignancies causing biliary obstruction, aiming to alleviate symptoms and enhance quality of life. The main concerns in the endoscopic management of biliary obstruction are stent occlusion and duration of stent patency. Since its development, no stent with permanent patency has been identified. Several variables, like stent diameter, composition of the stent material, presence of side holes on the stent, bacterial adherence to the stent surface, and accumulation of dietary fibers within the stent lumen are thought to influence stent obstruction. Earlier publications investigated different aspects of endobiliary stents and were eager to find measures to extend their functional

lifespan. After an experiment done on dog models the authors suggested that stent position might influence stent patency.

The conventional technique for biliary stent insertion involves transpapillary stent (TPS) position. In this approach, the stent traverses the papilla and the sphincter of Oddi (SO), with the distal end extending into the duodenum. Another less common method, termed suprapapillary stent (SPS) position, involves placing the biliary stents with the distal end above the SO within the CBD, keeping the major papilla intact. The main arguments against SPS are that they are more prone to stent migration or dislocation, and their position may make them harder to remove.

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 procedure-related complications associated with SPS and TPS placements.

II. 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.

Search Strategy and Eligibility Criteria

We carried out a 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.

We employed the PICO framework to establish eligibility criteria. Articles were included if the population (P) comprised laparoscopic cholecystectomy or a mixed population of open and LCs. 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 IOC and 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 randomized control trials (RCT) and observational studies were deemed eligible.

Outcomes

The assessment of the groups was based on primary outcomes, including the rate of perioperative BDI and retained stone rate, as well as secondary outcomes such as readmission rate, the conversion rate from laparoscopic 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.

Risk of Bias Assessment and Certainty of Evidence

The assessment of the risk of bias was done using the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool for non-randomized studies and the RoB 2 tool for RCTs. The evaluation of the certainty of evidence followed the guidelines of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) workgroup recommendations. We created several GRADE evidence profile tables, separately for each comparison group (routine *vs.* selective IOC and IOC *vs.* no IOC).

Statistical Analysis

All statistical analyses were conducted using StataIC (version 16). 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). A p-value less than 0.05 denoted a statistically significant difference. Heterogeneity was assessed by Cochran's Q test and Higgins' I^2 indicator. A p-value less than 0.10 indicated significant heterogeneity.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Our systematic review and meta-analysis was conducted following the guidelines outlined in the PRISMA Statement.

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).

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 our PICO criteria were considered eligible.

Risk of Bias Assessment and Certainty of Evidence

The ROBINS-I tool was utilized for assessing risk of bias in the case of non-randomized studies, while RCTs were assessed using RoB2. To evaluate the certainty of evidence the GRADE workgroup recommendations were followed. GRADE evidence profile tables were constructed for each investigated outcome.

Statistical Analysis

All statistical analyses were conducted within the R environment. For dichotomous outcomes, odds ratios (OR) were computed, and for continuous variables, WMDs were calculated, with 95% CIs. A p-value less than 0.05 denoted a statistically significant difference. Meta-analysis results are visually presented in forest plots. Heterogeneity was assessed using I^2 statistics, following the Cochrane Handbook guidelines. Heterogeneity with a p-value < 0.1 was considered significant.

III. RESULTS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Systematic Search and Selection

A systematic exploration of the literature revealed a total of 19,863 articles. At the end of the selection process we found 38 eligible articles for qualitative and 32 for quantitative synthesis.

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. Our analysis indicated that neither group exhibited a protective effect against BDI (RR = 0.91, 95% CI 0.66; 1.24, $I^2 = 0.0\%$, p = 0.805). 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; $I^2 = 0.0\%$, p = 0.420). Within the same comparison, we conducted additional subgroup analyses to investigate MBDI. When exploring both open and laparoscopic cholecystectomy 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). Similarly, no discernible difference was observed when considering only laparoscopic cholecystectomy cases (RR = 0.39, 95% CI 0.05; 3.28; $I^2 = 7.9\%$, p = 0.297).

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; $I^2 = 96.5\%$, p = 0.000). A subgroup analysis of ten studies focusing solely on laparoscopic cholecystectomy found no significant difference between the two strategies, including a total of 706,336 patients (RR = 1.19, 95% CI 0.79; 1.79, $I^2 = 82.4\%$, p = 0.000). 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), another with studies reporting on MBDI (RR = 1.01, 95% CI 0.70; 1.45; $I^2 = 96.7\%$, p = 0.000), and the third involving studies with MBDI in laparoscopic cholecystectomy only (RR = 1.09, 95% CI 0.35; 3.34; $I^2 = 74.8\%$, p = 0.003). 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, $I^2 = 13.7\%$, p = 0.327) within a one-year follow-up period.

Secondary Outcomes

1. Routine *vs.* Selective IOC

Examining the success rate of IOC during laparoscopic cholecystectomy 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).

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.

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, $I^2 = 0.4\%$, p = 0.336), favoring IOC with a lower risk of conversion to open surgery compared to the no IOC group. 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). 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). 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). 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).

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. Every analyzed outcome was appraised as having a very low level of evidence. The study designs included, the presence of uncontrolled confounding factors, and substantial heterogeneity significantly impacted the quality of evidence.

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 13 articles while quantitative synthesis incorporated 12.

1. Stent Patency

The analysis of stent patency time involved 11 studies encompassing 875 patients. 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). 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). We conducted separate analyses for stent patency times in SPS and TPS positions, considering metal and plastic stents. Five studies involving 597 patients utilized self-expanding metal stents (SEMS). 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). 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). In the plastic stent subgroup, six publications with a total of 278 patients were included. 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).

2. Stent Migration

Analyzing seven articles encompassing 376 patients, 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). Only one publication indicated a significant increase in stent migration with SPS placement compared to TPS, while all other studies demonstrated no significant differences in this aspect. The subgroup analysis focusing on plastic stent placement, involving

four publications and 163 patients, 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).

3. Cholangitis

Data on cholangitis rates from six studies involving a total of 598 patients were included in our analysis. Among these, only one publication indicated that SPS placement led to significantly lower cholangitis rates than the transpapillary method. 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). 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). 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). 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).

4. Pancreatitis

Data on the rate of pancreatitis were available from five articles, encompassing a total of 426 patients. 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). Following a sensitivity analysis that excluded the study reported solely as an abstract, the same result persisted (OR: 0.38, 95% CI: 0.08, 1.66; p = 0.197; I^2 = 22%, p = 0.277). 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).

5. Cholecystitis

Three articles, with a combined total of 230 patients explored the occurrence of cholecystitis in the context of metal stents. 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).

Risk of Bias Assessment and Certainty of Evidence

In the eligible non-randomized publications, the risk of bias in the domains of "bias due to confounding" and "bias in the selection of reported results" were judged as serious and moderate risks in most studies, respectively. The overall risk of bias was mainly assessed as serious. In the case of the two eligible RCTs, we identified "some concerns" in the "randomization process" domain in one study, and we identified some concerns in the "selection of the reported result" domain in both publications. The overall risk of bias was deemed at "some concerns". The investigated endpoints were 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.

IV. 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

Most of the experts agree that IOC is important in detecting CBD stones and preventing BDIs. However, there are differing recommendations on how often it should be used in everyday practice. Our findings do not endorse the protective effect of routine IOC compared to selective IOC in the prevention of BDI. Additionally, IOC does not offer a clear advantage over the omission of IOC; hence, a selective approach may be more judicious than entirely omitting it. We believe the pivotal question revolves around the timing of IOC: whether it should be performed routinely or selectively based on clinical indications.

The many different conclusions and opinions regarding this question might be the result of the study design researchers used, the method of how patients were enrolled, the potential presence of biases and confounding factors, also the statistical methodology applied. Studies using large databases relied on indirect definitions of BDI due to the lack of exact definitions, which also affected the results.

Retained Biliary Stones after Cholecystectomy

Our findings indicate that routine IOC does not substantially decrease the number of residual CBD stones diagnosed after surgery. Proponents of IOC argue that it can detect previously asymptomatic CBD stones and prevent complications by treating them. Opponents contend that this can lead to unnecessary interventions. Current guidelines suggest using ERCP for the management of asymptomatic CBD stones, however, some believe it should not be done for every asymptomatic stone because ERCP itself carries high risks.

Secondary Outcomes

We found no significant differences between routine and selective IOC regarding the success rate of IOC and operation time. 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. 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. Some state that increased operative time can be mitigated as routine IOC makes staff more efficient. 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

It has been suggested that SPS position might increases the stent patency time by keeping the sphincter of Oddi intact, preventing duodenobiliary reflux, and reducing sludge and biofilm formation. Our analysis revealed significantly prolonged stent patency times in the SPS group. Most of the investigated studies favored SPS, only one study reported longer patency with TPS placement. This phenomenon can be explained by the higher rate of stent migration observed in the SPS group. In the subgroup analysis involving metal stents only, no significant difference was observed between the two stenting methods. This finding aligns with a previous assumption that the advantages of SPS may be neutralized by the material properties of metal stents, because it might hinder the deposition of debris.

Stent Migration

One of the earliest studies suggested that stent migration occurs more frequently with SPS and recommended TPS instead. This might explain why SPS is often thought to be more likely to dislocate. In this study, the distal flaps of the stents were removed in half of the patients, and most had pancreatic cancer which is associated with significant axis deviation contributing to stent migration. Surprisingly, most of the investigated studies indicated a lower incidence of SPS migration, although the results were not statistically significant.

Cholangitis

Prior research suggests TPS placement may predispose individuals to reflux cholangitis. SPS position might reduce complication rates by preserving the integrity of the SO as a physiological barrier against bacterial and debris reflux into the common bile duct. Based on our results, there is no significant difference between the two investigated groups regarding the rate of cholangitis. When investigating exclusively full-text articles focusing on malignant indications, we identified a significantly reduced rate of cholangitis in SPS position. No significant difference was found within the subgroup analysis limited to metal stents.

Pancreatitis

Hypothetically, the SPS position might mitigate the incidence of PEP by potentially alleviating stress on the major duodenal papilla, thereby preventing obstruction of pancreatic juice secretion into the duodenum. While we observed no significant disparity between TPS and SPS placements, a trend towards a lower PEP rate in the SPS cohort was evident. Notably, a significantly reduced rate of pancreatitis was apparent in the subgroup analysis focusing on SEMS.

STRENGTH AND LIMITATIONS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

Our research is distinguished by its comprehensiveness and the inclusion of a large number of patients. We placed emphasis on investigating the routine IOC *vs.* selective IOC approaches. Furthermore, we conducted several subgroup analyses (including exclusively LC cases, MBDI, and prospective studies) to enhance the quality of evidence and ensure a more exhaustive review.

Most included articles were retrospective cohort studies, which draw data from large-scale databases with potential sources of bias and lack of control or partial adjustment for confounding variables. Additionally, our findings are somewhat weakened by the presence of statistical heterogeneity for certain endpoints. Moreover, IOC is a diagnostic tool for detecting BDI in some cases, which could introduce a potential distortion effect.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Our research represents the most exhaustive synthesis, consolidating available data and thoughts on SPS and TPS placement via ERCP. Also, we conducted several subgroup analyses to provide a more thorough review and increase practicality. The methodology is transparent and reproducible, adhering to rigorous standards throughout the research process.

Most included studies were non-randomized and non-prospective, thus yielding data and evidence of low quality. Additionally, studies published solely as abstracts were included. Confounding factors are likely present in the included studies, many of which were deemed to carry a serious risk of bias. The populations across the included studies exhibit heterogeneous etiology of biliary obstruction. Variations in endoscopic sphincterotomy, may have affected the natural protective effect of the SO on duodenobiliary reflux. Heterogeneity was substantial in pooled publications regarding stent patency time and migration.

V. CONCLUSION

A. INTRAOPERATIVE CHOLANGIOGRAPHY

The necessity of IOC in every case is not definitive, and its selective implementation could serve as an alternative to a standardized policy. Employing selective IOC in conjunction 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, alongside procedures for detecting CBD stones perioperatively, such as abdominal ultrasound, endoscopic ultrasound, and magnetic resonance cholangiopancreatography, should be taken into consideration.

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). Future research endeavors should establish a universally accepted indication system, guiding surgeons in determining when to perform IOC. There is a pressing need for high-quality prospective studies that meticulously address potential biases and confounding factors.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

Our findings suggest that the SPS could serve in some cases as a viable alternative to the more commonly employed TPS. SPS demonstrates associations with prolonged stent patency and reduced complications in certain scenarios, albeit with a comparable migration rate. These advantages could potentially lead to fewer supplementary interventions, thereby enhancing patient quality of life and reducing healthcare costs. Regarding stent revision, the incorporation of threads at the distal ends of both plastic and covered metal stents might facilitate their removal, offering a promising approach in this regard.

Further high quality RCTs are demanded to establish the certain advantageous effects of SPS positioning over TPS. 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 could investigate various aspects e.g., insertion success rates, endoscopic revision success rates, stent removability, stent patency times, and post-procedural complication rates associated with both stent positions, the necessity and effect of EST, and the effect of prophylactic pancreas stent. Cost-effectiveness analyses would provide valuable insights for future clinical guidelines.

VI. SUMMARY OF NEW FINDINGS

A. INTRAOPERATIVE CHOLANGIOGRAPHY

1. The necessity of IOC in every case is not conclusive.
2. Selective IOC may be as good as routine IOC in preventing BDI, selective IOC could serve as an alternative to a routine practice.
3. The rate of BDI was comparable between IOC and no IOC groups.
4. The rate of residual CBD stone 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 imperative to establish precise selection criteria for IOC, also to improve the quality of evidence.

B. SUPRAPAPILLARY AND TRANSPAPILLARY STENT

1. SPS potentially leads to prolonged 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. Placing metal SPS might result in a lower rate of pancreatitis compared to metal TPS in cases of malignant biliary obstruction.
5. Further RCTs are needed to improve the quality of evidence.