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# Does near-infrared fluorescent cholangiography with indocyanine green reduce bile duct injuries and conversions to open surgery during laparoscopic or robotic cholecystectomy? — A meta-analysis

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ABSTRACT

*Background:* Bile duct injury and conversion-to-open–surgery rates remain unacceptably high during laparoscopic and robotic cholecystectomy. In a recently published randomized clinical trial, using near-infrared fluorescent cholangiography with indocyanine green intraoperatively markedly enhanced biliary-structure visualization. Our systematic literature review compares bile duct injury and conversion-to-open–surgery rates in patients undergoing laparoscopic or robotic cholecystectomy with versus without near-infrared fluorescent cholangiography.

*Methods:* A thorough PubMed search was conducted to identify randomized clinical trials and non-randomized clinical trials with ≥100 patients. Because all near-infrared fluorescent cholangiography studies were published since 2013, only studies without near-infrared fluorescent cholangiography published since 2013 were included for comparison. Incidence estimates, weighted and unweighted for study size, were adjusted for acute versus chronic cholecystitis, and for robotic versus laparoscopic cholecystectomy and are reported as events/10,000 patients. All studies were assessed for bias risk and high-risk studies excluded.

*Results:* In total, 4,990 abstracts were reviewed, identifying 5 near-infrared fluorescent cholangiography studies (3 laparoscopic cholecystectomy/2 robotic cholecystectomy; $n = 1{,}603$) and 11 not near-infrared fluorescent cholangiography studies (5 laparoscopic cholecystectomy/4 robotic cholecystectomy/2 both; $n = 5{,}070$) for analysis. Overall weighted rates for bile duct injury and conversion were 6 and 16/10,000 in near-infrared fluorescent cholangiography patients versus 25 and 271/10,000 in patients without near-infrared fluorescent cholangiography. Among patients undergoing laparoscopic cholecystectomy, bile duct injuries, and conversion rates among near-infrared fluorescent cholangiography versus patients without near-infrared fluorescent cholangiography were 0 and 23/10,000 versus 32 and 255/10,000, respectively. Bile duct injury rates were low with robotic cholecystectomy with and without near-infrared fluorescent cholangiography (12 and 8/10,000), but there was a marked reduction in conversions with near-infrared fluorescent cholangiography (12 vs 322/10,000).

*Conclusion:* Although large comparative trials remain necessary, preliminary analysis suggests that using near-infrared fluorescent cholangiography with indocyanine green intraoperatively sizably decreases bile duct injury and conversion-to-open–surgery rates relative to cholecystectomy under white light alone.



## Introduction

Laparoscopic cholecystectomies (LC) are among the most common surgical procedures performed worldwide, accounting for between 600,000 and 900,000 procedures annually in the United States alone.[1,2] Starting in the mid-1980s, a shift from open to laparoscopic cholecystectomies (LC) occurred, for reasons that included markedly less scarring, shortened hospital stays and recovery times, and reduced operative times and costs.[3] This

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transition has not been without problems; however, as bile duct injuries (BDI), the number one concern of surgeons performing LC,[4–6] appeared to increase in frequency with the emergence of LC, from 1 to 2 BDI per 1,000 procedures[7] to as many as 1 per 100.[8–12] This increased incidence has persisted over time,[13,14] despite the adoption of imaging techniques such as intraoperative cholangiography (IOC) and ultrasound. Such BDI may significantly prolong hospital stays, increase the need for further surgery, markedly elevate hospital costs, and result in chronic morbidity and significantly increased mortality.[15–17] Many BDI patients experience reduced quality of life for years,[18–20] and roughly 4% of BDI patients had premature mortality directly attributed to their BDI.[21,22]

Another problem that arises during LC is the need for conversion from laparoscopic to open surgery, which occurs in an estimated 6.2% of patients.[23] Such conversion also markedly increases patient morbidity and mortality, duration of hospital stay and convalescence, and healthcare costs.[24,25] In a 151-study meta-analysis published by Pucher et al in 2018,[23] which included randomized clinical trials (RCT) and prospective and retrospective non-randomized comparative and observational studies, overall encompassing over 500,000 patients, the pooled rate for BDI was 0.52%, or 52 per 10,000. In this same meta-analysis, the pooled rate for conversions from laparoscopic to open surgery was 620 per 10,000.

Studies have shown that the main cause of BDI and conversions to open surgery in patients undergoing LC is inadequate visualization of essential extra-hepatic biliary structures, such as the cystic duct.[26–28] During the past decade, new technology has emerged to facilitate the visualization of such structures, via the preoperative intravenous injection of indocyanine green (ICG), followed by the intraoperative use of near-infrared fluorescence imaging, a combined process called near-infrared fluorescent cholangiography (NIFC). In a recently published RCT that compared 321 laparoscopic cholecystectomy procedures during which NIFC was used against 318 procedures during which it was not, NIFC dramatically increased predissection visualization rates for all 7 extra-hepatic biliary structures that were assessed: cystic duct, right hepatic duct, common hepatic duct, common bile duct, cystic CBD junction, cystic gallbladder junction, and accessory ducts, with strongly statistically significant odds ratios ranging from 2.3 to 3.6.[29] Five of these 7 structures also were statistically more often visible postdissection, with odds ratios ranging from 2.4 to 3.3. To date, this just-mentioned study is the only published RCT comparing NIFC versus standard white light during LC. Although there were 2 BDI in the control group and none in the NIFC group, and 4 conversions in the control group versus 1 in the NIFC group, the study lacked the statistical power for these to be statistically significant differences ($P = .25$ and 0.17, respectively). In fact, assuming a 0.4% BDI event rate[23] and a 1:1 ratio of cases and controls, even detecting a 50% decrease between groups with 95% confidence and 80% power would require a study with almost 12,000 patients per treatment arm.[30] With an assumed 5.0% event rate for conversions to open surgery, such a study would require over 2,000 patients per group.

The primary purpose of this article is to report the results of a systematic literature review and meta-analysis conducted to compare both BDI and conversion-to-open–surgery rates in patients undergoing minimally invasive cholecystectomy with versus without NIFC. Given the recent steady rise in the percentage of cholecystectomy procedures being performed robotically (albeit still only accounting for under 10% of all cholecystectomies),[31] a decision was made to include both laparoscopic cholecystectomy (LC) and robotic cholecystectomy (RC) studies in the analysis. Secondary purposes were to compare the effects of NIFC on BDI and open conversion rates in LC and RC individually and evaluate all studies for the risk of bias.

### *Search methods*

A thorough search of the medical literature was conducted to identify all studies, published in full print or open access form, for which the incidence of BDI or open conversion was reported, assessing the effectiveness of NIFC during LC; and in which NIFC was not used during LC.

To be eligible for analysis, articles had to meet the following eligibility criteria: (1) report absolute numbers of patients who had undergone LC or RC, either with or without the use of NIFC; (2) either report on the absolute number of BDI or conversions to open surgery or provide percentages to at least 1 decimal place, so those absolute numbers could be accurately calculated; (3) be published from 2013 onward because the only NIFC studies we were able to identify were from 2013 onward; (4) have virtually all data collected from 2010 onward, to similarly reduce the use of old data published late; (5) have study cohorts consisting of at least 100 patients either receiving or not receiving NIFC, to reduce the risk of positive publication bias; (6) be available in print or full open-access form, so a full risk of bias assessment could be performed; (7) be deemed at low to, at most, moderate risk of bias, specifically related to the rate of BDI and conversions to open surgery (thereby, not concerned with the level of bias for other outcomes); and (8) not include patients with cholelithiasis, biliary atresia, or cancer as the indication for surgery. Non-English articles only were excluded if they could not be translated or otherwise interpreted by at least one of the authors.

The identification of relevant studies was conducted in 2 stages. In stage 1, a PubMed search was conducted, from April through October 2020, looking for relevant search terms, from which all abstracts were reviewed, seemingly pertinent articles read to completion, and final eligibility determined. In stage 2, all tables and bibliographies listing other pertinent studies in read articles were reviewed to identify additional articles that might be eligible for inclusion, then these articles read to determine their eligibility.

For NIFC studies, we used the following combined search terms: “fluorescence” and “cholecystectomy” ($n = 128$ abstracts); “indocyanine green” and “cholecystectomy” ($n = 114$); “robotic” and “cholecystectomy” ($n = 407$); “indocyanine green” and “bile duct injury” ($n = 30$); and “indocyanine green” and “conversion” ($n = 173$; total $n = 852$; Fig 1). For non-NIFC studies, the combined search terms used were “cholecystectomy” and “bile duct injury” ($n = 1,253$); “cholecystectomy” and “conversion” ($n = 2,478$), and “cholecystectomy” and “robotic” ($n = 407$; total $n = 4,138$). To be eligible for inclusion, studies had to also report the absolute numbers of BDI or conversions to open surgery and the number of patients treated by LC. When studies also included patients who underwent open surgery, the number of patients who had their surgery performed laparoscopically or robotically and number of BDI or conversions specifically among those patients had to be reported, accompanied by approach-specific outcomes.

Variables of interest were first author name; year of article publication; period of data collection, country where the study was conducted; surgical approach (LC versus RC); study design, objectives, and treatment arms; number of patients in each treatment arm; treatments rendered; and absolute number of BDI and conversions to open surgery.

### *Risk of bias*

Each study was assessed for bias risk using either the Cochrane Risk of Bias tool[32] for RCTs and quasi-randomized trials

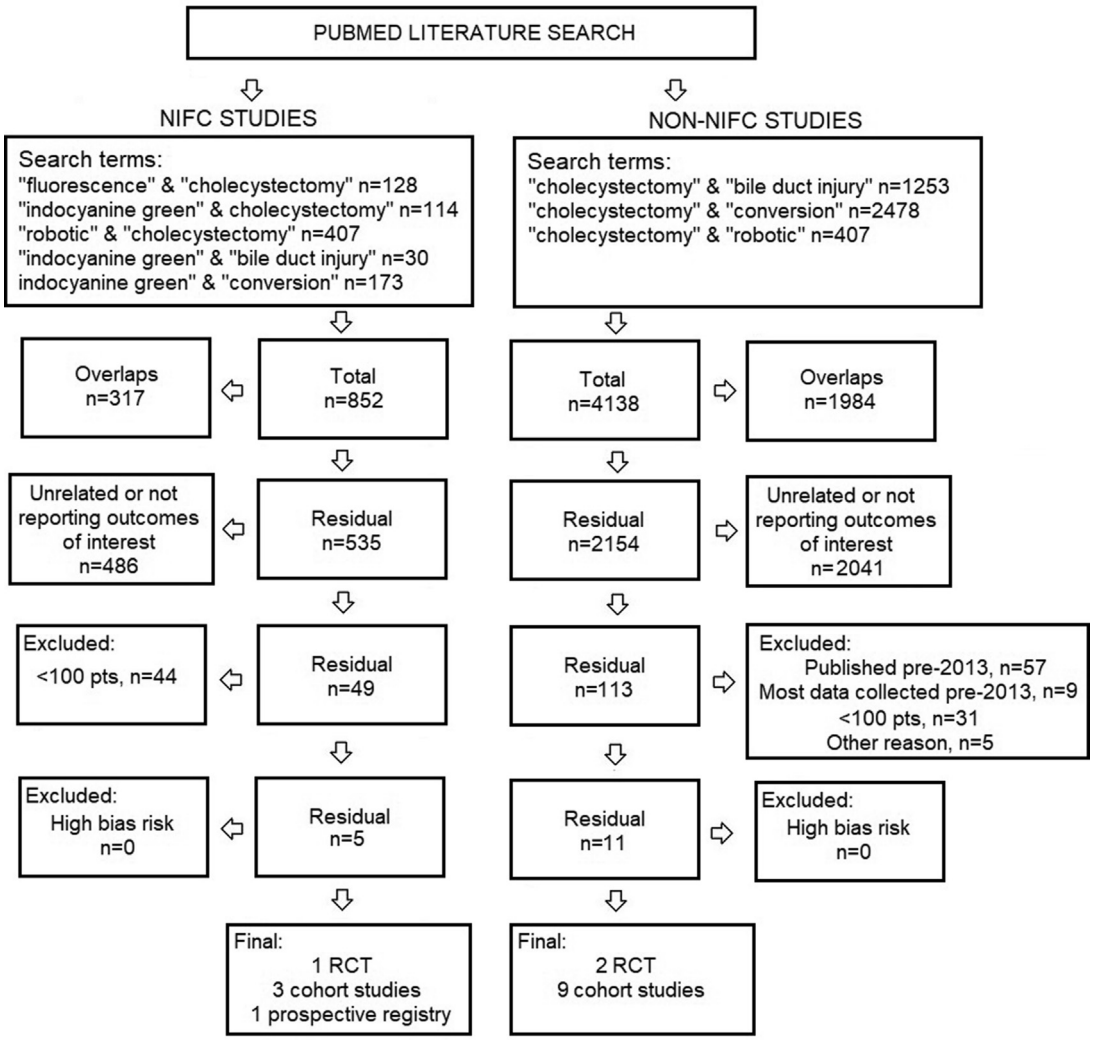


**Fig 1.** PRISMA flow chart demonstrating study selection process. *NIFC*, near-infrared fluorescent cholangiography; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; *RTC*, randomized clinical trial.

or the Cochrane ROBINS I tool[33] for non-RCTs. Using the Cochrane Risk of Bias tool,[32] each RCT was evaluated for the 6 of 8 potential sources of bias deemed relevant (excluding mortality and long-term outcomes): random sequence generation and allocation concealment (both for selection bias), blinding of patients and personnel (performance bias), blinding of outcome assessments (detection bias), completeness of short-term data (attrition bias), and selective reporting (selection bias). Using the Cochrane ROBINS I tool,[33] studies were assessed for potential confounding, subject selection, intervention classification, unintended differences and contamination between treatment arms, missing data, measurement bias, and selective reporting. The risk of bias for each study was rated as very low, low, moderate, or high, specifically pertaining to the determination of BDI and conversion-to-open–surgery rates, as follows: very low, if the study was judged at low risk across all domains; low, if no more than one domain was judged at moderate risk, and no domain at high risk; moderate, if judged to be at moderate risk in more than one domain, but at high risk in none; high, if any domain was considered at high risk. Domains for which data were not clearly reported were automatically deemed a source of moderate risk. Studies considered at high risk were excluded from additional analysis.

*Statistical analysis*

The 2 primary outcomes of interest were the incidence of BDI and incidence of conversions to open surgery, each expressed as the number of events per 10,000 patients, weighted for the number of subjects per study. Unweighted rates also were calculated, by averaging incidence rates over all studies, to adjust for large variations in study size. To account for acute cholecystitis, the number of patients who underwent LC or RC for acute cholecystitis was extracted from each study to allow for calculation of the overall percentage of acute cholecystitis patients in each of the 2 patient cohorts (NIFC versus non-NIFC), after which BDI and open-conversion rate estimates were multiplied by a product of this percentage difference and the estimated difference in BDI or conversion rate from other studies (outside the current analysis) restricted to acute cholecystitis patients. To account for potential differences between LC and RC, rates for BDI and open conversions were estimated combining LC and RC patients, and with LC and RC patients analyzed separately, after which weighted estimates were generated using the same method described above for acute cholecystitis.

Forest plots of the weighted data were generated for BDI and conversions for each of 3 comparisons: (1) all patients, LC and RC,

**Table I**
Documented BDI in patients undergoing laparoscopic cholecystectomy with ICG

| Author | Year | Country | Study design | Procedure | Indication | Subjects | Bdi | Incidence | Conversions | Incidence |
|---|---|---|---|---|---|---|---|---|---|---|
| Bleszynski et al[36] | 2020 | Canada | PCoS | LC | Elective LC | 108 | 0 | 0.000% | 0 | 0.00% |
| Agnus el al[35] | 2020 | Europe | Registry | LC | AC, CC | 314 | 0 | 0.000% | *n*/a | *n*/a |
| Dip et al[29] | 2019 | Intercontinental | RCT | LC | AC, CC | 321 | 0 | 0.000% | 1 | 0.31% |
| Gangemi et al[34] | 2017 | USA | RCoS | RC | AC, CC | 676 | 1 | 0.148% | 1 | 0.15% |
| Daskalaki et al[37] | 2014 | USA | RCoS | RC | AC, CC | 184 | 0 | 0.000% | 0 | 0.00% |
| Weight, % | | | | | | 1,603 | 1 | 0.062% | 2 | 0.155% |
| Unweighted, % | | | | | | | | 0.030% | | 0.115% |

*AC*, acute cholecystitis; *CC*, chronic cholecystitis; *ICG*, indocyanine green; *LC*, laparoscopic cholecystectomy; *PCoS*, prospective cohort study; *RCoS*, retrospective cohort study; *RC*, robotic cholecystectomy; *RCT*, randomized clinical trial.

who underwent LC with NIFC versus no NIFC; (2) NIFC versus non-NIFC just among LC patients; and (3) NIFC versus non-NIFC just among RC patients.

## Results

### *Study selection and bias risk assessment*

#### *NIFC studies (N = 5)*

Among the 852 abstracts reviewed specifically searching for studies on the use of NIFC during LC or RC, there was considerable overlap ($n = 317$; Fig 1). Ultimately, 46 articles deemed relevant, on the basis of having patients who underwent LC or RC for whom BDI or open conversion data were available, were identified, with 3 additional articles located via a reference list, ultimately yielding 49 articles for additional review. Of these, 44 failed to meet the criterion of at least 100 subjects and were excluded from additional analysis. The remaining 5 studies[29,34–37] encompassed 1,603 patients and ranged in size from 108 to 676 (median = 321, mean = 321.6). These studies included 1 RCT, 3 non-RCT, and 1 international (European) registry of prospectively collected data specifically designed and developed to gather data on NIFC use during LC (Table I). All 5 articles reported data on BDI, while 4 ($n = 1,289$ patients, 80.4% of the sample) provided data on conversion to open surgery. Data were available on clinical indication for surgery for 1,289 of the patients, among whom acute cholecystitis was the indication for 203 (15.7%). Robotic surgery was used in 2 studies,[34,37] totaling 860 patients (53.6% of the sample). No study was excluded on the basis of its risk of bias assessment, with 3 of 5 deemed of low risk, and 2 of moderate risk (Table II). The 1 non-randomized study deemed of moderate risk lacked adequate information regarding potential confounders and subject selection. The only NIFC RCT was considered of moderate risk because it was (obviously) impossible to blind surgeons as to whether or not NIFC was used.

#### *Non-NIFC studies (N = 11)*

Among the 4,138 abstracts reviewed specifically searching for studies on LC or RC in which NIFC was not used, there again was considerable overlap ($n = 1,984$; Fig 1). Ultimately, 109 relevant articles were identified, with 4 additional articles located via reference lists, ultimately yielding 113 articles for additional review. Of these, 57 were published before 2013, 9 were large studies for which at least a sizeable proportion of data had been collected before 2010, 31 had fewer than 100 subjects, and 5 were excluded for other reasons like treatment contamination (eg, multiple procedures), or ineligible surgical indication (eg, gallstones; gallbladder cancer). The remaining 11 studies[34,38–47] encompassed 5,070 patients and ranged in size from 108 to 2,020 (median = 237, mean = 460.9) subjects. These studies included 2 RCTs and 9 retrospective cohort studies (Table III). Nine of the 11 articles reported data on BDI ($n = 4,739$ patients, 93.5% of the sample), while 10 ($n = 2,990$, 59.0%) provided data on conversion to open surgery. Data were available on clinical indication for surgery for all 5,070 non-NIFC patients, among whom acute cholecystitis was the indication for 1,042 (20.6%). Five of the studies were on LC alone, 4 on RC alone, and 2 included both procedures, with per-procedure event rates available for analysis. As for the 5 NIFC studies, no study that reached this stage of eligibility was excluded on the basis of its risk of bias assessment, with 10 considered of moderate and 1 of low risk (Table III). The most common source of bias among nonrandomized trials was inadequate information on potential confounders, such as surgeon experience, time to surgery, and patient obesity. The 2 RCTs both were deemed of moderate risk because surgeons could obviously not be blinded to treatment arm.

### *Bile duct injuries*

Among the 1,603 patients who underwent LC or RC under fluorescence guidance, there was but one “minor” BDI, yielding a BDI rate, weighted by the number of subjects in each study, of 6.2 per 10,000 patients (95% confidence interval: 0, 18), and a non-weighted BDI rate of 3.0 per 10,000. This one BDI occurred among the 860 RC patients, for an event rate among patients undergoing RC with NIFC of 11.6 per 10,000 versus zero in LC-NIFC patients. In the study in which this 1 BDI occurred among 676 RC procedures, 4 BDI occurred among 289 patients in the other treatment arm who underwent LC without NIFC.[34]

Among the 5,070 patients encapsulated by the 11 non-NIFC studies, there were 4,739 patients in whom data on BDI were available, among whom there were 12 BDI: 11 among 3,497 LC patients (BDI rate = 31.5/10,000) and 1 among 1,242 RC patients (8.1/10,000), for an overall weighted BDI rate of 25.3 per 10,000 (unweighted 23.3/10,000; 95% confidence interval [CI], 11%–40%). Please see Fig 2 for Fox plots.

### *Conversion to open surgery*

Among the 1,289 patients who underwent either LC ($n = 429$) or RC ($n = 860$) with NIFC, 2 patients (one each undergoing LC and RC) required conversion to open surgery, for an overall weighted conversion rate of 15.5 per 10,000 (95% CI, 0%–37%; unweighted 11.5/10,000), with LC and RC rates of 23.3 and 11.6/10,000, respectively. Among the 2,820 patients who underwent LC ($n = 1,608$) or RC ($n = 1,242$) without NIFC, corresponding weighted open conversion rates were 271 (95% CI, 213%–329%; unweighted = 311), 255, and 322 per 10,000. Please see Fig 3 for Fox plots.

### *Adjusted estimates for BDI and open conversion*

Adjusting for acute cholecystitis was infeasible with the data extracted from the 16 studies analyzed here because no NIFC study was restricted to acute cholecystitis patients and only a single non-NIFC study, with only 120 patients, was thus restricted.[44] None of

**Table II**
Risk of bias assessment

| Nonrandomized clinical trials | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Author (year published, study location) | Confounders | Subject selection | Classification of interventions | Deviations in interventions | Missing data | Biased measurements | Biased reporting | Overall bias rating |
| NIFC studies | | | | | | | | |
| Bleszynski et al[36] (2020, Canada) | Low | Low | Low | Low | Low | Low | Low | Low |
| Agnus et al[35] (2020, Europe) | Low | Low | Low | Low | Low | Low | Low | Low |
| Gangemi et al[34] (2017, USA) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Daskalaki et al[37] (2014, USA) | Low | Low | Low | Low | Low | Low | Low | Low |
| Non-NIFC studies | | | | | | | | |
| Sharma et al[47] (2018, USA) | Moderate | Low | Moderate | Low | Low | Low | Low | Moderate |
| Jeong et al[41] (2018, S. Korea) | Moderate | Low | Low | Low | Low | Low | Low | Moderate |
| Lee (2018, S. Korea)[43] | Low | Low | Low | Low | Low | Low | Low | Low |
| Balachandran et al[46] (2017, USA) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Gangemi et al[34] (2017, USA) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Strosberg et al[45] (2017, USA) | Moderate | Low | Moderate | Moderate | Moderate | Low | Low | Moderate |
| Kubat et al[42] (2016, USA) | Moderate | Low | Low | Low | Low | Low | Low | Moderate |
| Chung et al[39] (2015, USA) | Moderate | Moderate | Moderate | Moderate | Moderate | Low | Low | Moderate |
| Gonzalez et al[40] (2013, USA) | Low | Low | Moderate | Moderate | Moderate | Low | Low | Moderate |
| Randomized clinical trials | | | | | | | | |
| Author (year published, study location) | Use of NIFC yes/no | Randomization | Allocation concealment | Blinding of pts/personnel | Blinding of assessments | Missing data | Selective reporting | Overall bias rating |
| Dip et al[29] (2019, intercontinental) | Yes | Low | Moderate | Moderate | Moderate | Low | Low | Moderate |
| Saber et al[44] (2014, Egypt) | No | Low | Moderate | Moderate | Moderate | Low | Low | Moderate |
| Agarwal et al[38] (2014, India) | No | Low | Moderate | Moderate | Moderate | Low | Low | Moderate |

*NIFC*, near-infrared fluorescent cholangiography; *pts*, patients.

**Table III**
Incidence of bile duct injury during endoscopic cholecystectomies without ICG

| Author | Year | Country | Study Design | Indication | Procedure | Subjects | Bdi | Incidence | Conversions | Incidence |
|---|---|---|---|---|---|---|---|---|---|---|
| Sharma et al[47] | 2018 | USA | RCoS | AC, CC, other | LC | 191 | n/a | n/a | 17 | 8.90% |
| Jeong et al[41] | 2018 | South Korea | RCoS | AC, CC, other | RC | 108 | 0 | 0.000% | 0 | 0.00% |
| Lee | 2018 | South Korea | RCoS | AC, CC, other | LC | 2080 | 5 | 0.240% | *n*/a | *n*/a |
| Balachandran et al[46] | 2017 | USA | RCoS | AC, CC, other | RC | 678 | 0 | 0.000% | 26 | 3.83% |
| Gangemi et al[34] | 2017 | USA | RCoS | AC, CC, other | LC | 289 | 4 | 1.384% | 11 | 3.81% |
| Strosberg et al[45] | 2017 | USA | RCoS | AC, CC, other | RC | 140 | 0 | 0.000% | 1 | 0.71% |
| Strosberg et al[45] | | USA | RCoS | AC, CC, other | LC | 97 | 0 | 0.000% | 7 | 7.22% |
| Kubat et al[42] | 2016 | USA | RCoS | AC, CC, other | RC | 150 | 1 | 0.667% | 1 | 0.67% |
| Chung et al[39] | 2015 | USA | RCoS | AC, CC, other | RC | 140 | n/a | n/a | 12 | 8.57% |
| Saber et al[44] | 2014 | Egypt | RCT | AC | LC | 120 | 0 | 0.000% | 4 | 3.33% |
| Agarwal et al[38] | 2014 | India | RCT | AC, CC, other | LC | 745 | 2 | 0.268% | 2 | 0.268% |
| Gonzalez et al[40] | 2013 | USA | RCoS | AC, CC, other | RC | 166 | 0 | 0.000% | 0 | 0.00% |
| Gonzalez et al[40] | 2013 | USA | RCoS | AC, CC, other | LC | 166 | 0 | 0.000% | 0 | 0.00% |
| Weighted, % | | | | | | 5,070 | 12 | 0.253% | 81 | 2.709% |
| Unweighted, % | | | | | | | | 0.233% | | 3.11% |

*AC*, acute cholecystitis; *CC*, chronic cholecystitis; *ICG*, indocyanine green; *LC*, laparoscopic cholecystectomy; *PCoS*, prospective cohort study; *RCoS*, retrospective cohort study; *RC*, robotic cholecystectomy; *RCT*, randomized clinical trial.

the other 15 studies had BDI or conversion data specifically isolated to acute cholecystitis patients. To get around this, we performed another, side meta-analysis, of 24 randomized clinical trials published from 2000 onward on laparoscopic cholecystectomies performed without NIFC,[3,38,44,48–70] among which 8 were restricted to acute cholecystitis patients, while the remaining 16 studies had both acute and chronic cholecystitis patients, as well as patients with other nonmalignant biliary disorders. Across the 24 studies, event rates for BDI and open conversion were 47 and 799 per 10,000. When the 8 studies restricted to acute cholecystitis patients were excluded from analysis, the rate of BDI increased by 15% to 54/10,000, while the rate of conversions declined, by 33%, to 535/10,000, meaning that the rates of BDI and conversions were 15% lower and 33% higher overall, respectively, in studies restricted to acute cholecystitis patients. Using these percentages, combined with the 4.9% greater percentage of acute cholecystitis patients in the 11 non-NIFC versus 5 NIFC studies in the present analysis, the mean BDI rate across the former 11 non-NIFC studies was adjusted by ((1−[0.049 x 0.15]) x 25.3), to decline from 25.3 to 25.1 per 10,000, versus 6.2 per 10,000 in the 5 NIFC studies. Meanwhile, the mean open conversion rate was adjusted by ((1 + [0.049 × 0.33] × 270.9), to increase from 270.9 to 271.6 per 10,000, versus 15.5 per 10,000 in the NIFC studies.

Weighting for the percentage of RC versus LC patients in each comparison group yielded weighted BDI and conversion rates for NIFC versus non-NIFC of 7.1 versus 21.8 per 10,000, and of 19.1 versus 240 per 10,000, respectively.

## Discussion

Near-infrared fluorescent cholangiography is increasingly emerging as an intraoperative imaging modality to enhance outcomes and reduce complications across a wide range of surgical specialties, with a rapidly expanding body of evidence, including numerous recently published meta-analyses and systematic reviews, documenting its effectiveness facilitating the evaluation of tissue perfusion[71–75]; detection and prediction of anastomotic leaks[72,76–79]; localization and resection of tumors[80–86]; isolation of sentinel lymph nodes for malignancies such as breast,[87–91] gynecological,[92–96] and gastric

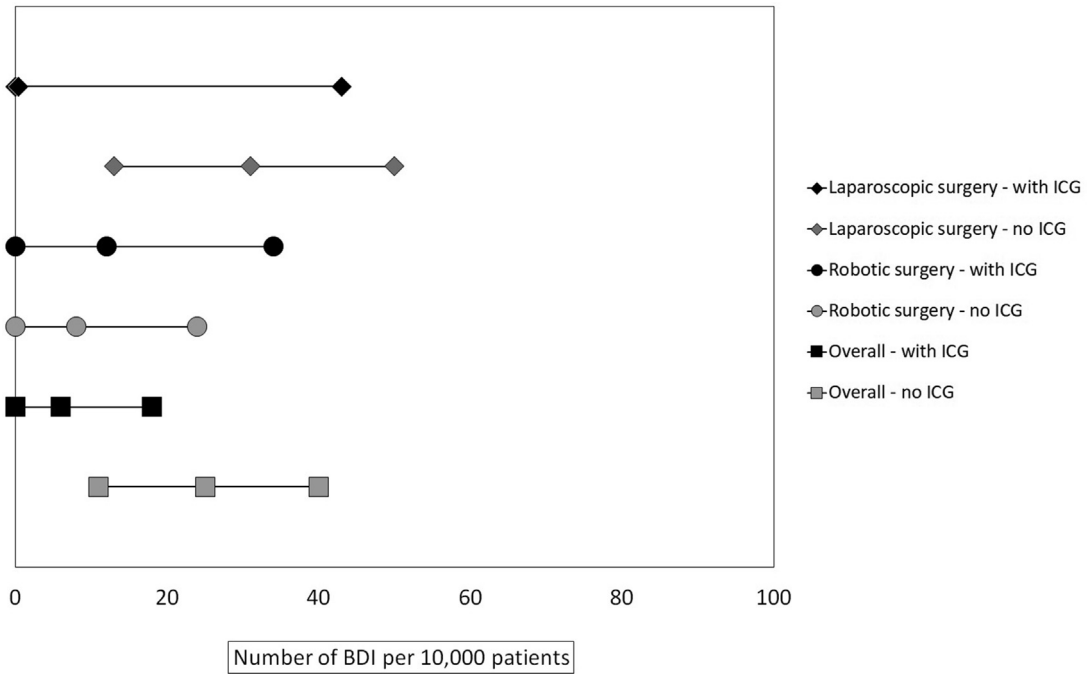


**Fig 2.** Estimates of bile duct injury incidence per 10,000 patients. *BDI*, bile duct injury; *ICG*, indocyanine green.

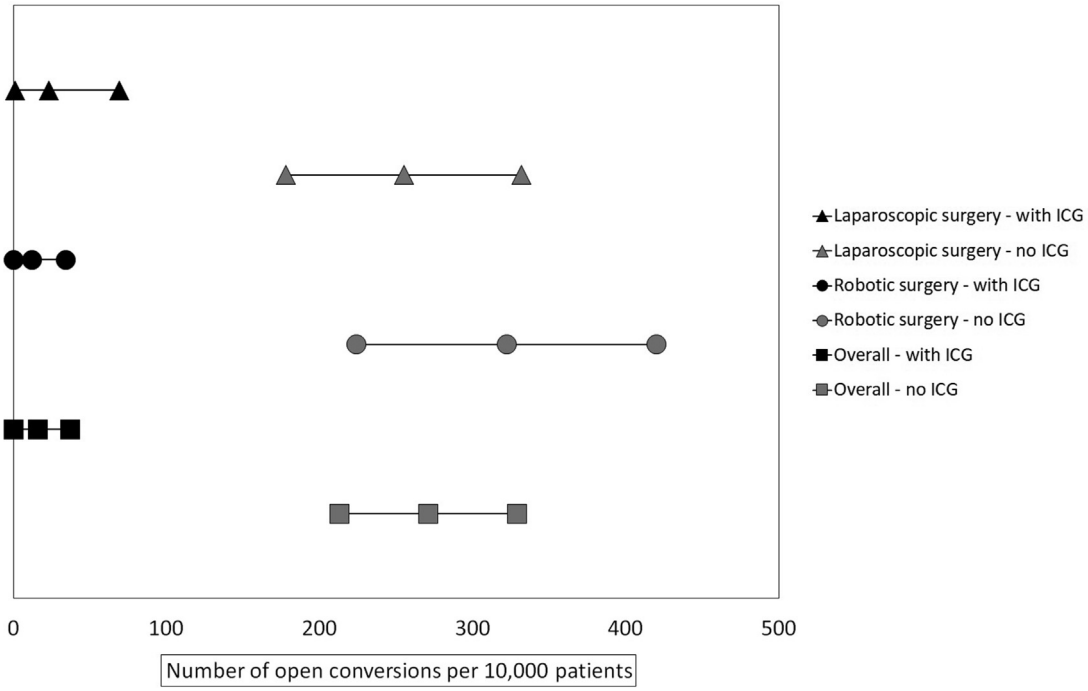


**Fig 3.** Estimates of conversion-to-open-surgery incidence per 10,000 patients. *ICG*, indocyanine green

cancer[97–101]; resection of endocrine glands[102–104]; and prevention and treatment of lymphedema,[105] among numerous other purposes.

Also, throughout the past decade, NIFC has emerged as a potentially safer, more effective, and less-costly alternative to conventional nonfluorescent intraoperative cholangiography (IOC) as a means to augment the visualization of extra-hepatic biliary structures during LC.[7,29,106–109] This said, it must be emphasized that direct comparisons between NIFC and IOC are lacking. NIFC also must not be mistaken as a replacement, but rather as a complement to IOC, both of which are currently only performed in only a small minority of patients.[110] One advantage of performing NIFC routinely is the ability to recognize the CBD before dissection and identify the cystic duct before an incision is made to perform an IOC, thereby preventing Strasberg type 1 injuries. Other advantages of NIFC over IOC are that, whereas the image obtained with IOC does not correlate directly with the surgical field, cannot be repeated endlessly, and requires the surgeon's interpretation of the image obtained on the radiology versus surgical monitor,

the image with NIFC is on the same monitor and surgical field, can be repeated as needed, and does not require interpretation.

Fluorescent imaging also does not replace all the other basic tenets of safe conduct that are essential to performing minimally invasive surgery, such as establishing a critical view of safety.[26,28] Its use is not suggested for the detection of gallstones, which can obstruct the flow of ICG. And it relies on the availability of expensive cameras that are not currently available at some hospitals, especially for emergency and urgent procedures. This issue of relative unavailability will, hopefully, decrease over time, if evidence continues to accumulate documenting the effectiveness of this technique.

Among the hastily enlarging number of studies supporting the use of NIFC are 2 RCTs, the most recently published a noninferiority study that compared NIFC and IOC, and detected no difference in the rates of visualization (82% and 85%, respectively) of the critical junction between the cystic, common hepatic, and common bile ducts,[111] despite NIFC requiring less than half the time to complete.[108,111] In the same study, among the 60 patients assigned to the NIFC arm, NIFC was performed successfully in all 60; conversely, IOC only was feasible in 51 of 60 patients in the IOC arm.[111] In a larger, 8-center, inter-continental RCT, which included 321 patients undergoing LC with NIFC and 318 controls whose LC was performed under white light alone, NIFC increased the visualization rate for all essential extra-hepatic biliary structures by up to 260% and was favored over white light by over 80% of the 37 participating surgeons.[29]

By far the greatest concern that surgeons performing minimally invasive cholecystectomy have is bile duct injury (BDI), despite the complication's relative rarity. This is because patients who sustain a BDI may have significantly reduced quality of life, across several life domains, for years afterwards.[18–20] Serious long-term complications of BDI include biliary strictures, hepatic atrophy, cholangitis and intrahepatic lithiasis; and, later, fibrosis or even secondary biliary cirrhosis and portal hypertension, which can be exacerbated by prolonged biliary obstruction associated with recurrent cholangitis.[112] Secondary biliary cirrhosis can ultimately cause hepatic failure and/or digestive tract hemorrhage due to portal hypertension, both of which are substantial risk factors for morbidity and death, even after bile duct repair.[112] A percentage of BDI patients even ultimately require liver transplantation, which itself is associated with a postoperative mortality rate of 30% or greater.[113–115] In a study of Swedish registry data encompassing 51,040 open and laparoscopic cholecystectomy procedures performed from 2005 to 2010, the 1-year mortality rate among the 747 patients who sustained a BDI was almost 4-fold that observed among those who did not (3.9% vs 1.1%).[22] Similarly, among 800 BDI patients referred for treatment of their BDI in The Netherlands, the mortality rate directly ascribed to BDI was 4.2%.[116] A similarly high mortality rate, of 5.0%, has also been identified in patients with acute cholecystitis who require conversion from laparoscopic to open surgery.[24]

The primary objective of enhancing the visualization of biliary structures with tools such as IOC, intraoperative ultrasound, and NIFC has always been to reduce the rate of complications, particularly BDI. To date, however, no study has even come close in size to the 24,000 or so patients likely required to detect a statistically significant reduced rate of BDI; nor is one ever likely to. It was for this reason that we elected to generate rate estimates for BDI and conversion to open surgery using data extracted from already-published studies and compare these rates against rates in the literature for LC and RC performed under white light. To reduce the risk of bias caused by comparing procedures that are different beyond the use of NIFC, we excluded all patients who did not undergo conventional LC or RC. Although our results must be considered preliminary and inferential analysis cannot be reasonably justified, given that the rates for LC with and without NIFC were estimated using entirely distinct datasets, they nonetheless reveal roughly a 4-fold lower rate of BDI and more than a 17-fold lower rate of conversions when NIFC is used during LC or RC. These large differences persist after adjusting for different distributions of acute versus chronic cholecystitis and for laparoscopic versus robotic surgery. The rate for BDI among NIFC patients was less than half that of even the most optimistic registry, published in 2018[117] (estimated BDI rate = 14 per 10,000), consistent with the reduced BDI rate in the LC studies published over time identified by Pucher et al: from 69 to 22 per 10,000 between 1994 to 1999 and 2010 to 2015 ($P = .011$), respectively.[23] Together, what all this means is that, no matter how we adjust for our data to reduce various sources of bias, sizeable, clinically significant reductions in both BDI and conversion-to-open–surgery rate remain evident in NIFC patients versus all other datasets.

The present study has both strengths and limitations. Among its strengths is that data for both populations were collected over roughly the same timeframe, with all the articles published from 2013 onward and the vast majority of data collected from 2010 onward. Not only does this account for the decreasing rate of complications during minimally invasive cholecystectomy procedures identified in the meta-analysis by Pucher et al,[23] it also is almost 2 decades since use of a critical view of safety was initially described,[26,28] meaning that this procedure was long-established and variations in its use should not have impacted our results. Second, laparoscopic and robotic cholecystectomy patients were well represented in both databases, increasing the generalizability of our results. Third, we attempted to adjust for cohort differences by statistically adjusting for differences in the distribution of acute versus nonacute biliary disease patients and the 2 different approaches to surgery (LC, RC).

The foremost study limitation is the numerous potential sources of bias that might have existed in our 2 study cohorts that we could not adjust for, such as patient obesity, degree of inflammation, time from presentation to surgery, and surgeon experience, because data on these variables were not adequately available to allow for their inclusion. Another concern is that all but 4 of the 16 studies were considered of moderate risk of bias. That being said, both BDI and conversion-to-open-surgery are discreet events that commonly were the primary outcomes of analysis. As such, if any data in such studies can be trusted, it should be these. Another potential source of bias or error relates to the exclusion versus inclusion of some studies over others (for example, only including studies with >100 patients either undergoing or not undergoing NIFC); to compensate for this, we applied the criteria uniformly and without exception, even rejecting from analysis 1 study with 96 patients undergoing RC with NIFC. Finally, given the extremely variable nature of data collection, we felt that any statistical analysis other than estimating event rates with confidence intervals was unjustified. On the other hand, BDI and conversion rates among NIFC patients were profoundly decreased relative to those whose surgery lacked NIFC, no matter what adjustments were made, suggesting that these differences may be real.

Certainly, the present results should spur additional study into the effectiveness of NIFC to reduce complication rates in patients undergoing minimally invasive surgery. They also might justify sizing studies to detect more than the 30% difference between treatment arms typically used for such trials, which in itself could markedly reduce the size of study needed.

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