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REVIEW ARTICLE

# Effect of indocyanine green fluorescence angiography on preventing anastomotic leakage after colorectal surgery: a meta-analysis

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## Abstract

Anastomotic leakage (AL) is a serious but not uncommon complication after colorectal surgery. We conducted this study to evaluate the effect of routine indocyanine green fluorescence angiography (ICG-FA) on reducing the AL rate after colorectal surgery. We identified all research articles about colorectal surgery using ICG-FA, published in the PubMed, EMBASE, and Cochrane Library databases from the date of database establishment to May 2020. Revman 5.3 was used for statistical analysis. We analyzed 22 controlled studies and 7 non-controlled studies on ICG-FA, including 6312 patients. The controlled studies included 2354 patients in the ICG group and 3522 patients in the non-ICG group. Meta-analysis showed that ICG-FA reduced the AL rate after colorectal surgery significantly (RR = 0.39; 95% CI 0.30–0.50; $P < 0.00001$). However, patients whose resection line was changed based on the fluorescence angiography had a higher AL rate than those whose resection line was not changed (OR = 5.37; 95% CI 2.67–10.81; $P < 0.00001$). The overall complication rate, severe complication rate, and reoperation rate in the ICG group were significantly lower than those in the non-ICG group (RR = 0.79, 95% CI 0.67–0.92, $P = 0.002$; RR = 0.67, 95% CI 0.47–0.96, $P = 0.03$; RR = 0.53, 95% CI 0.29–0.96, $P = 0.04$, respectively), whereas the postoperative ileus rate was significantly higher in the ICG group than in the non-ICG group (RR = 1.65; 95% CI 1.09–2.50; $P = 0.02$), especially in Western countries (RR = 1.6; 95% CI 1.04–2.47; $P = 0.03$).

ICG-FA may reduce the AL rate after colorectal surgery, but ICG-FA group patients with transection line change for insufficient blood perfusion to the anastomotic stoma after evaluation had a higher AL rate than those without transection line change. Therefore, ICG-FA can help to identify patients at high risk of AL and intercept its occurrence. Moreover, ICG-FA may reduce the overall complication rate, severe complication rate, and reoperation rate, but induce postoperative ileus. High-quality randomized-controlled trials with a placebo control are needed to further evaluate the effectiveness and safety of ICG-FA.

**Keywords** Anastomotic leakage · Indocyanine green · Colorectal surgery · Fluorescence angiography · Meta-analysis

**Abbreviations**

| | |
|---|---|
| ICG | Indocyanine green |
| FA | Fluorescence angiography |
| NIR | Near-infrared |
| AL | Anastomotic leakage |
| RCTs | Randomized-controlled trials |
| RCSs | Retrospective cohort studies |
| PCSs | Prospective cohort studies |

## Introduction

In the 1970s, it was discovered that protein-bound indocyanine green (ICG) could emit near-infrared (NIR) fluorescence, peaking at 840 nm under irradiation of NIR (750–810 nm) [1]. Only a small amount of the fluorescence

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signal emitted by protein-bound ICG could be absorbed by hemoglobin (Hb) or water in human tissue, allowing it to be imaged in connective tissue with a thickness of 5–10 mm. ICG was first used in the 1990s in angiography of the ocular fundus [2]. Now, ICG fluorescence imaging technology is used widely in surgery as a navigation tool. In 2006, Nagata [3] reported the application of ICG in colorectal surgery. Subsequently, fluorescence imaging technology was adopted widely in colorectal surgery to evaluate blood perfusion of the anastomotic stoma, and detect metastatic lymph nodes and liver metastasis of colorectal cancer. Anastomotic leakage (AL) is one of the most common severe complications after colorectal surgery, which not only delays postoperative radiotherapy and chemotherapy, increasing the rate of local recurrence, but also results in internal environment disorder and nutrition deficiency caused by the large volume of intestinal drainage and long-term fasting. In some serious cases, AL can lead to organ dysfunction and death. Insufficient blood flow perfusion is the major factor contributing to AL and delayed anastomotic healing [4]. Surgeons often assess anastomotic perfusion by the color of the intestinal wall, peristalsis of the intestine, pulsation of the arteries, and bleeding of the anastomosis. However, these examinations are subjective and dependent on the experience of the surgeon, which may lead to misdiagnosis. ICG fluorescence imaging is increasingly considered as a potential intraoperative tool to evaluate the blood supply of anastomotic stoma accurately and objectively, and can be used in routine practice to ensure adequate perfusion during anastomotic formation, allowing surgeons to visualize intestinal perfusion in real time in a simple operation. A recent study demonstrated the potential role of ICG fluorescence imaging in reducing AL rates by altering surgical procedures [5–7]. Many recent studies on ICG fluorescence angiography (ICG-FA) for the prevention of AL after colorectal surgery have been published [8–22]. We examined the correlation between intraoperative ICG-FA and the AL rate after colorectal surgery based on a review of all published studies.

## Materials and methods

We conducted this systematic review and meta-analysis according to the PRISMA statement [23].

### Search strategy

We searched the literature in the EMBASE, PubMed, and Cochrane Library databases to identify relevant available articles published in English from database inception to October, 2019 using the keywords: “indocyanine green”, “ICG”, “coloring agents”, “fluorescence” “fluorescein angiography”, “fluorescent dyes”, “anastomotic leak”, “anastomotic leakage”, “anastomotic perfusion”, “anastomosis, surgical”, “bowel perfusion”, “blood supply”, “perfusion assessment”, “colorectal surgery”, “colon surgery”, “rectal surgery”, “colorectal resection”, and “bowel resection”, and using the Boolean operator “OR” and “AND” for each keyword. We also reviewed the reference lists of the included studies for undetected relevant studies. We contacted the original authors to obtain extra information if necessary. Only the latest article with the largest sample size and the highest quality was selected if some studies were from the same author or research center.

### Inclusion criteria

1. Subjects: patients of any age who underwent anastomosis after colorectal or rectal resection with the effectiveness of anastomotic perfusion evaluated by ICG fluorescence imaging.
2. The original data were from published research, where there were reports about the postoperative AL rate, including randomized-controlled studies, prospective or retrospective cohort studies, and non-controlled studies.
3. Sample size: unlimited.
4. Follow-up time: Unlimited.
5. Literature language: unlimited.
6. Study type: human
7. Primary outcome: AL rate.
8. Secondary outcome: the surgical plan modification rate, overall complication rate, severe complications, wound infection, ileus, postoperative pneumonia, urinary retention, postoperative bleeding, postoperative mortality, readmission rate, and reoperation rate.

### Exclusion criteria and quality assessment

Republished studies, unpublished studies, and studies without complete information or valid data and the authors of which were unavailable were all excluded. Reviews, case reports, and animal experiments were also excluded.

Randomized-controlled trials (RCTs), retrospective cohort studies (RCSs), and prospective cohort studies (PCSs) were included in this meta-analysis. Risk was assessed in RCTs according to the “risk assessment tool” recommended by the Cochrane Collaboration Network, including whether the random assignment was performed correctly, whether there was a hidden allocation scheme, whether blinding was used, whether the loss of follow-up was described, and whether an intention analysis was conducted when interviewing or withdrawing. The results were attached to the Supplement. Quality assessment of the cohort studies was based on the Newcastle–Ottawa Scale (NOS), specifically including research population selection, comparability, exposure evaluation, and outcome evaluation.

The semi-quantitative principle of the star system was used for the quality evaluation of retrospective literature, with a perfect score of nine stars. Detailed quality assessment of the included cohort studies was attached to the Supplement.

## Statistical analysis

Revman 5.3 was used for statistical analysis. The Mantel–Haenszel method was used to estimate the combined binary effective quantity (relative risk, RR/odds risk, OR). The Inverse Variance method was used to estimate the effective quantity of combined continuous data (weighted mean difference, WMD). RRs, ORs, and WMDs with a 95% CI were calculated to compare the incidence of postoperative index between the ICG group and the non-ICG group. Heterogeneity among the included studies was evaluated qualitatively using an Chi-square-based $Q$ test, and $P$ values less than 0.10 were considered significant. The level of heterogeneity among these studies was evaluated using $I^2$ statistics. $I^2 < 30\%$ indicated low heterogeneity and a fixed-effect model was applied; $30\% \le I^2 \le 50\%$ indicated moderate heterogeneity; and $I^2 > 50\%$ represented high heterogeneity. When calculating the combined effective quantity of a certain outcome index and $I^2 < 30\%$, a fixed-effect model was applied; otherwise, a random-effect model was used. Sensitivity analysis was performed by removing one study at a time to assess whether the results could be affected remarkably by a single study. The results with less heterogeneity between studies were selected if results were reversed after sensitivity analysis. Deleted literature was described in the Results section. A funnel plot was used to qualitatively evaluate publication bias. Stata software (version SE12.0) was used to calculate Begg's test and Egger's test for quantitative evaluation of publication bias of the included studies, with the significant level limited to 0.05. The details are attached in the Supplement.

## Search results and process

### Literature searching results

We studied a total of 29 articles that met the criteria for inclusion. Figure 1 shows the flowchart of literature screening. Twenty-two of the included studies were comparative studies [7 propensity score-matching (PSM) studies, 4 PCSs, 9 RCSs, and 2 RCTs] and another 7

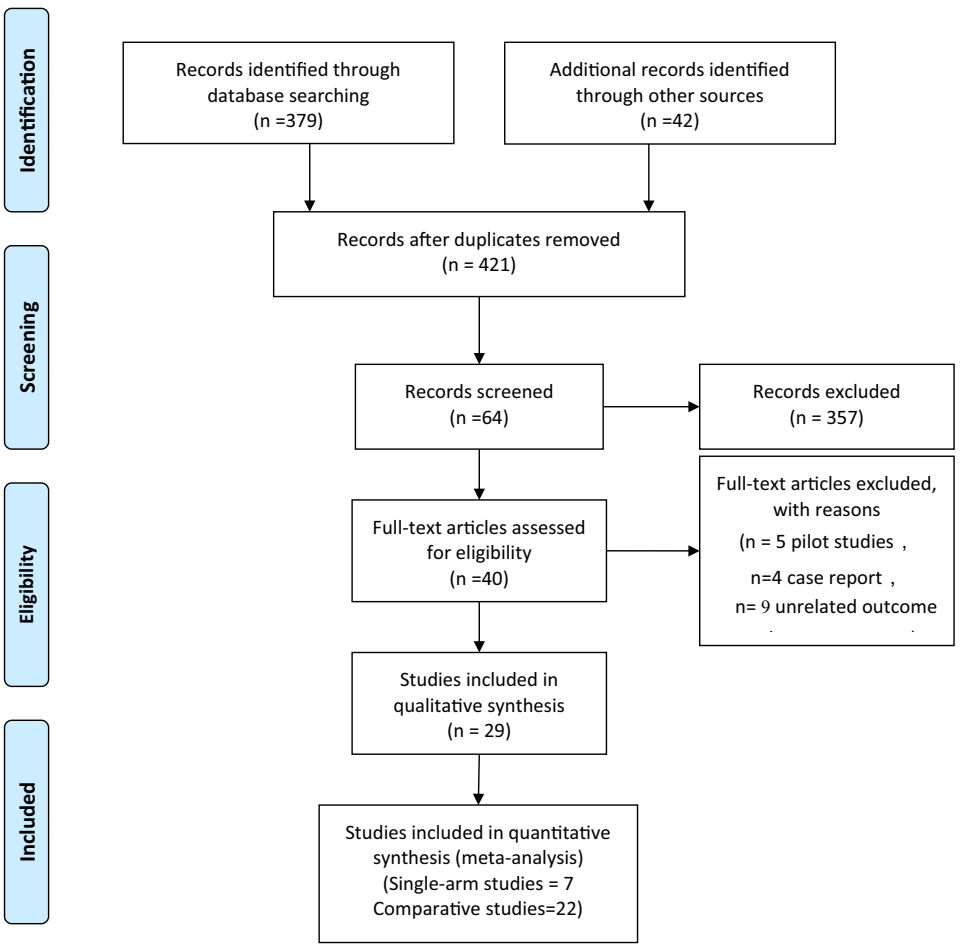


**Fig. 1** Literature searching process: PRISMA 2009 flow diagram of the literature screening

studies were non-controlled studies, including a collective total of 436 patients. These 22 studies included 5876 patients, with 2354 in the ICG group and 3522 in the non-ICG group.

### Data synthesis and analysis

We analyzed 11 postoperative outcome indexes of the ICG groups and the non-ICG groups (Table 1). Sensitivity analysis was carried out for each index. These studies were classified by countries to perform subgroup analysis (Table 2).

**Table 1** Meta-analysis of the measured outcomes of all available studies

| Measured outcomes | Subgroup | No. studies | No. patients | Heterogeneity test | | Model | RR/OR | 95% CI | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $I^2$ (%) | *P* | | | | |
| Anastomotic leakage | Total | 22 | 2354 vs. 3522 | 0 | 0.6 | Fixed | 0.39 | 0.30–0.50 | **< 0.00001** |
| | PSM | 7 | 735 vs. 873 | 0 | 0.79 | Fixed | 0.34 | 0.23–0.49 | **< 0.00001** |
| | RCT | 2 | 305 vs. 312 | 0 | 0.98 | Fixed | 0.56 | 035–0.90 | **0.02** |
| Overall complication | Total | 9 | 1062 vs. 1298 | 0 | 0.5 | Fixed | 0.77 | 0.67–0.90 | **0.0006** |
| Severe complication | Total | 6 | 625 vs. 770 | 0 | 0.61 | Fixed | 0.67 | 0.47–0.96 | **0.03** |
| | PSM | 4 | 312 vs. 312 | 0 | 0.44 | Fixed | 0.52 | 0.32–0.85 | **0.009** |
| Wound infection | Total | 12 | 1159 vs. 1529 | 0 | 0.89 | Fixed | 0.99 | 0.60–1.62 | 0.96 |
| | PSM | 3 | 272 vs. 272 | 0 | 0.75 | Fixed | 1 | 0.34–2.93 | 1 |
| Ileus | Total | 7 | 676 vs. 847 | 0 | 0.78 | Fixed | 1.65 | 1.09–2.50 | **0.02** |
| Pneumonia | Total | 4 | 411 vs. 502 | 0 | 0.59 | Fixed | 1.13 | 0.60–2.11 | 0.71 |
| Urinary retention | Total | 4 | 339 vs.462 | 0 | 0.43 | Fixed | 0.55 | 0.20–1.48 | 0.24 |
| Bleeding | Total | 7 | 714 vs. 856 | 0 | 0.95 | Fixed | 1.33 | 0.65–2.74 | 0.43 |
| Mortality | Total | 6 | 613 vs. 695 | 0 | 0.61 | Fixed | 0.86 | 0.19–3.84 | 0.84 |
| Readmission | Total | 3 | 228 vs. 352 | 0 | 0.63 | Fixed | 0.92 | 0.50–1.71 | 0.8 |
| Reoperation rate | Total | 6 | 462 vs.593 | 0 | 0.58 | Fixed | 0.53 | 0.29–0.96 | **0.04** |
| AL rates of the anastomotic line-changed ICG group vs. the anastomotic line-unchanged ICG group | | | | | | | OR | | |
| | Total | 13 | 149 vs. 700 | 0 | 0.5 | Fixed | 5.17 | 2.74–9.73 | **< 0.00001** |

*AL* anastomosis leakage, *PSM* propensity score matching, *RCT* randomized-controlled trial, *No.* number of, *RR* relative risk, *OR* odds risk, *CI* confidence interval

Statistical significance is shown in bold

**Table 2** Meta-analysis of the measured outcomes of the subgroup studies

| Measured outcomes | Subgroup | No. studies | No. patients | Heterogeneity test | | Model | RR/OR | 95% CI | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $I^2$ (%) | *P* | | | | |
| Anastomotic leakage | Western | 15 | 1331 vs. 1800 | 0 | 0.94 | Fixed | 0.42 | 0.31–0.57 | **< 0.00001** |
| | East Asia | 7 | 1023 vs. 1722 | 49 | 0.07 | Random | 0.38 | 0.20–0.73 | **0.004** |
| Overall complication | Western | 6 | 493 vs. 639 | 0 | 1 | Fixed | 0.88 | 0.74–1.06 | 0.19 |
| | East Asia | 3 | 569 vs. 659 | 17 | 0.3 | Fixed | 0.64 | 0.49–0.82 | **0.0004** |
| Wound infection | Western | 7 | 527 vs. 612 | 0 | 0.57 | Fixed | 0.93 | 0.44–1.95 | 0.84 |
| | East Asia | 5 | 632 vs. 917 | 0 | 0.92 | Fixed | 1.04 | 0.54–2.00 | 0.91 |
| Ileus | Western | 7 | 527 vs. 612 | 8 | 0.37 | Fixed | 1.6 | 1.04–2.47 | **0.03** |
| | East Asia | 3 | 581 vs. 713 | 25 | 0.26 | Fixed | 0.53 | 0.29–0.96 | **0.04** |
| Bleeding | Western | 5 | 455 vs. 544 | 0 | 0.99 | Fixed | 1.04 | 0.46–2.37 | 0.92 |
| | East Asia | 2 | 259 vs. 312 | 0 | 0.72 | Fixed | 3.26 | 0.59–17.96 | 0.18 |
| Reoperation rate | Western | 4 | 188 vs. 314 | 0 | 0.66 | Fixed | 0.68 | 0.33–1.42 | 0.31 |
| | East Asia | 2 | 275 vs. 279 | 16 | 0.27 | Fixed | 0.32 | 0.11–0.95 | 0.04 |

*No.* number of, *RR* relative risk, *OR* odds risk, *CI* confidence interval

Statistical significance is shown in bold

## Results

### Anastomotic leakage

Twenty-two studies reported AL rates [8–22, 24–31], with low heterogeneity observed among them ($I^2 = 0\%$, $P = 0.6$). A fixed model was applied, and the combined effect was RR = 0.39, 95% CI (0.30–0.50), $P < 0.00001$ Table 3. The AL rate was significantly lower in the ICG group than in the non-ICG group. The combined effect of PSM studies and RCTs were RR = 0.34, 95% CI (0.23–0.49), $P < 0.00001$; RR = 0.56, 95% CI (0.35–0.90), $P = 0.02$, respectively (Fig. 2). Subgroup analysis showed that in Western and East Asia, the AL rate was significantly lower in the ICG group than in the non-ICG group [RR = 0.42, 95% CI (0.31–0.57), $P < 0.00001$; RR = 0.38, 95% CI (0.20–0.73), $P = 0.004$, respectively]. No reversal of the meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 2).

### Overall complications

Ten studies reported overall complications [8, 13, 17–20, 22, 27, 29, 30]. The study by Shaper et al. [18] was excluded from our statistics as there was a significant bias in overall complications, resulting in high heterogeneity ($I^2 = 50\%$, $P = 0.03$). Low heterogeneity was observed in the other studies ($I^2 = 0\%$, $P = 0.5$). A fixed model was applied and the combined effect was RR = 0.77, 95% CI (0.67–0.90), $P < 0.00006$. The overall complication rate was significantly lower in the ICG group than in the non-ICG group. No reversal of meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 3a). Subgroup analysis indicated that there was no significant difference between the ICG group and the non-ICG group [RR = 0.88, 95% CI (0.74–1.06), $P = 0.19$] in Western, but the overall complication rate was significantly lower in the ICG group than in the non-ICG group in East Asia [RR = 0.64, 95% CI (0.49–0.82), $P = 0.0004$].

### Severe complications

Six studies reported severe complications [8, 17, 19, 20, 22, 30]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.61$). A fixed model was applied, and the combined effect was RR = 0.67, 95% CI (0.47 ~ 0.96), $P < 0.03$. The rate of severe complications was significantly lower in the ICG group than in the non-ICG group. Low heterogeneity was observed among the PSM studies ($I^2 = 0\%$, $P = 0.44$), with the combined effect of RR = 0.52, 95% CI (0.32–0.85), $P = 0.003$. No reversal of meta-analysis result was observed after sensitivity analysis (Fig. 3b).

### Wound infection

Twelve studies reported the wound infection rate [8, 13–18, 24, 25, 27, 29, 30]. Low heterogeneity was observed these among studies ($I^2 = 0\%$, $P = 0.86$). A fixed model was applied, and the combined effect quantity was RR = 0.99, 95% CI (0.60–1.62), $P = 0.96$. No significant difference in the wound infection rate was observed between the ICG group and the non-ICG group. Low heterogeneity was observed among the PSM studies ($I^2 = 0\%$, $P = 0.44$), with the combined effect of $RR = 1.00$, $95\%CI$ (0.34–2.93), $P = 1.00$. No significant difference in wound infection rates was observed between the ICG group and the non-ICG group in the PSM studies (Fig. 4a). No reversal of the meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis. Subgroup analysis revealed no significant difference in wound infection rates between the ICG group and the non-ICG group in Western and East Asia [RR = 0.93, 95% CI (0.44–1.95), $P = 0.84$; RR = 1.04, 95% CI (0.54 ~ 2.00), $P = 0.91$, respectively].

### Ileus

Ten studies reported the rate of ileus [8, 13, 14, 16–18, 24, 25, 27, 29]. The study by Kim et al. [27] was excluded from the analysis as there was a significant bias in ileus, resulting in high heterogeneity ($I^2 = 45\%$, $P = 0.06$). Low heterogeneity was observed in the remaining studies ($I^2 = 11\%$, $P = 0.34$). Studies by Shapera [18] and Wada [29] were also excluded from the analysis as the meta-analysis result showed a reversal change and the heterogeneity significantly reduced after these two studies were gradually eliminated from the sensitivity analysis. A fixed model was applied to the remaining seven studies [8, 13, 14, 16, 17, 24, 25] and the combined effect was RR = 1.65, 95% CI (1.09–2.50), $P < 0.02$. The ileus rate was significantly higher in the ICG group than in the non-ICG group (Fig. 4b). Subgroup analysis showed that the ileus rate was significantly higher in the ICG group than in the non-ICG group [RR = 1.6, 95%CI (1.04–2.47), $P = 0.03$] in seven studies from Western countries [8, 13, 16–18, 24, 25], whereas it was significantly lower in the ICG group than in the non-ICG group [RR = 0.53, 95% CI (0.29–0.96), $P = 0.04$] in three studies from East Asia [14, 27, 29].

### Postoperative pneumonia

Five studies reported postoperative pneumonia [13, 14, 18, 24, 29]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.59$). A fixed model was applied and

**Table 3** Basic characteristics and quality assessment of enrolled documents

| Study | Country | Type of study | Case | | Approach | Location | Perfusion | Perfusion dosage | Surgery change | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ICG | Non-ICG | | | Observing time | | Rate (%) | (NOS) |
| Alekseev 2020 [8] | Russia | RCT | 187 | 190 | O/L | Colorectal | 2–3 min | 0.2 mg/kg | 19.3 | – |
| Bonadi 2020 [9] | Italy | RCS | 33 | 33 | L | Rectal | 90 s | 0.2 mg/kg | 18.2 | 7 |
| Boni 2017 [24] | Italy | RCS | 42 | 38 | L | Colorectal | 30~45 s | 0.2 mg/kg | 4.8 | 7 |
| Dinallo 2019 [11] | UK | RCS | 234 | 320 | O/L/R | Colorectal | 60 | 2 ml | 5.6 | 7 |
| Hasegawa 2020 [12] | Japan | PSM | 141 | 703 | L | Rectal | 14–107 s | 5 mg | 17 | 8 |
| Impellizzeri2020 [13] | Italy | RCS | 98 | 98 | O/L | Colorectal | 33–37 s | 12.5 mg | 8.2 | 8 |
| Ishii 2019 [14] | Japan | PSM | 223 | 265 | L | Colorectal | 60 s | 5 mg | 3.1 | 8 |
| Jafari 2012 [25] | USA | RCS | 16 | 22 | L/R | Colorectal | NA | 6–8 mg | 18.8 | 6 |
| Kim 2017 [26] | Korea | RCS | 310 | 347 | L | Rectal | 60 s | 10 mg | NA | 7 |
| Kojima 2019 [15] | Japan | PSM | 27 | 27 | L | Colorectal | 20 s | NA | NA | 8 |
| Mizrahi 2018 [16] | USA | RCS | 30 | 30 | L | Low rectal | NA | 0.1–0.3 mg/kg | 13.1 | 7 |
| Nardi 2020 [10] | Italy | RCT | 118 | 122 | L | Colorectal | 60 s | 0.3 mg/kg, two times | 11 | – |
| Otero-Piñeiro2020 [17] | Spain | PCS | 80 | 204 | T | Rectal | NA | 2.5 mg/ml | 28.7 | 7 |
| Ris 2018 [30] | Switzerland | PCS | 90 | 365 | L | Colorectal | 29 s | 7·5 mg | 5.8 | 7 |
| Shapera 2019 [18] | USA | RCS | 74 | 30 | R | Colorectal | Within 60 s | 25 mg | 5.4 | 6 |
| Skrovina 2020 [19] | Czech | RCS | 50 | 50 | L/R | Low rectal | NA | 0.2 mg/kg | 12 | 7 |
| Spinelli 2019 [20] | Switzerland | PSM | 32 | 32 | L/O | Whole colorectal | 30 s | 25 mg | 3.1 | 8 |
| Tsang 2020 [21] | China | PCS | 63 | 68 | O/L/R | Colorectal | NA | 10 mg | 1.6 | 7 |
| Wada 2019 [28] | Japan | PSM | 48 | 101 | L | Rectal | NA | 5 mg (before) | 27.1 | 8 |
| Watanabe 2019 [29] | Japan | PSM | 211 | 211 | L | Rectal | 60 s | 0.25 mg/kg (before) | 7.6 | 8 |
| Wojcik 2020 [22] | France | PCS | 46 | 65 | L | Colorectal | NA | 0.1 mg/kg | 10.9 | 7 |
| Kudszus 2010 [27] | Germany | PSM | 201 | 201 | O/L | Colorectal | NA | 0.2–0.5 mg/kg | 13.9 | 7 |

*ICG* indocyanine green, *RCT* randomized-controlled trial, *PCS* prospective cohort study, *RCS* retrospective cohort study, *PSM* propensity score matching, *L* laparoscopic, *R* robotic, *O* open, *T* transanal, *NOS* Newcastle–Ottawa Scale, *NA* not available, not applicable

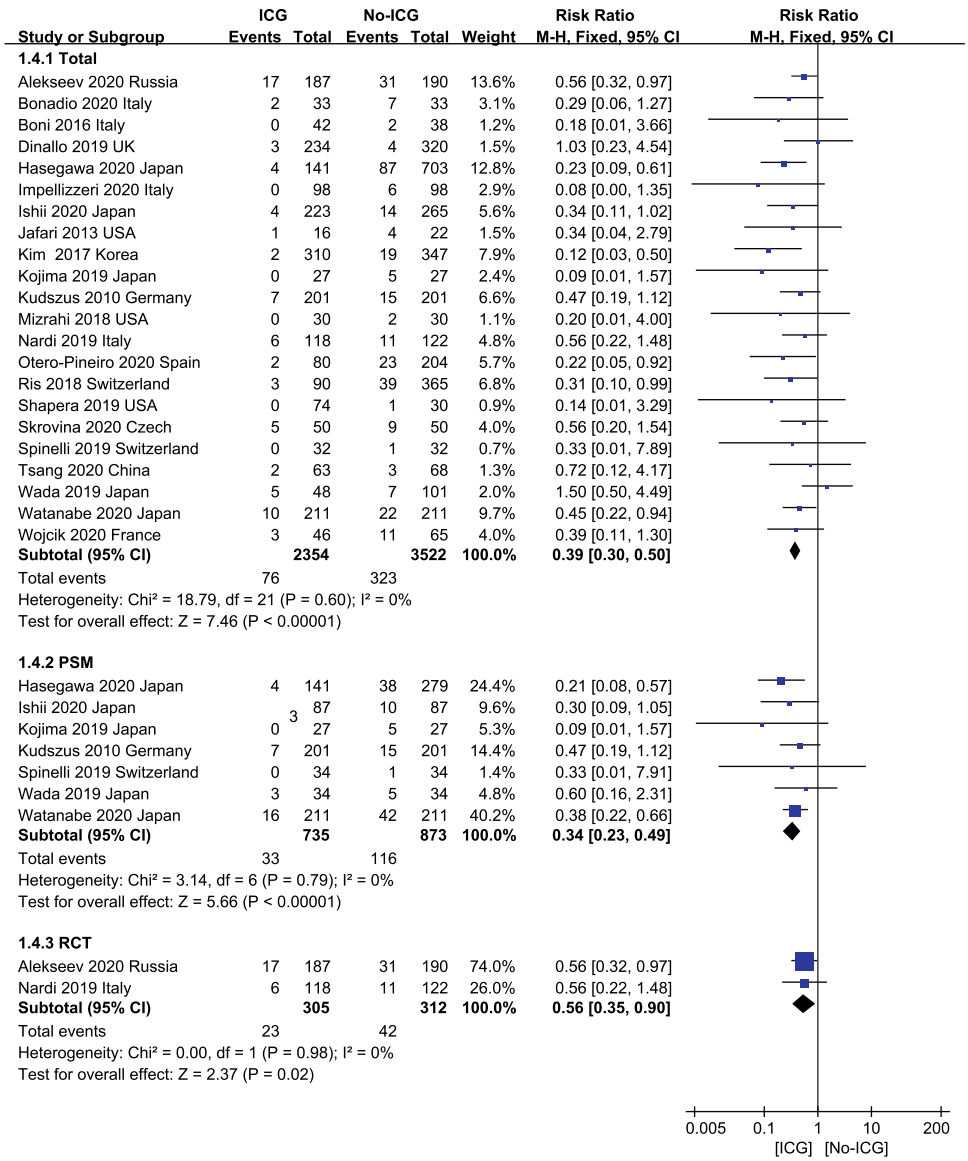


**Fig. 2** Forest plot of anastomotic leakage

the combined effect was RR = 1.13, 95% CI (0.60–2.11), $P = 0.71$. There was no significant difference in postoperative pneumonia rate between the ICG group and the non-ICG group. No reversal of meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 5a).

## Urinary retention

Four studies reported urinary retention [8, 16, 17, 24]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.43$). A fixed model was applied and the combined effect was RR = 0.55, 95% CI (0.20–1.48), $P = 0.24$. There was no significant difference in the urinary retention rate between the ICG group and the non-ICG group. No reversal of the meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 5b).

## Postoperative bleeding

Seven studies reported postoperative bleeding [8, 13, 17, 18, 25, 29, 30]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.95$). A fixed model was applied, and the combined effect was RR = 1.33, 95% CI (0.65–2.74), $P = 0.43$. There was no significant difference in the postoperative bleeding rate between the ICG group and the non-ICG group. No reversal of the meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 5c). Subgroup analysis showed no significant difference in the postoperative bleeding rate between the ICG group and the non-ICG group in Western and East Asia

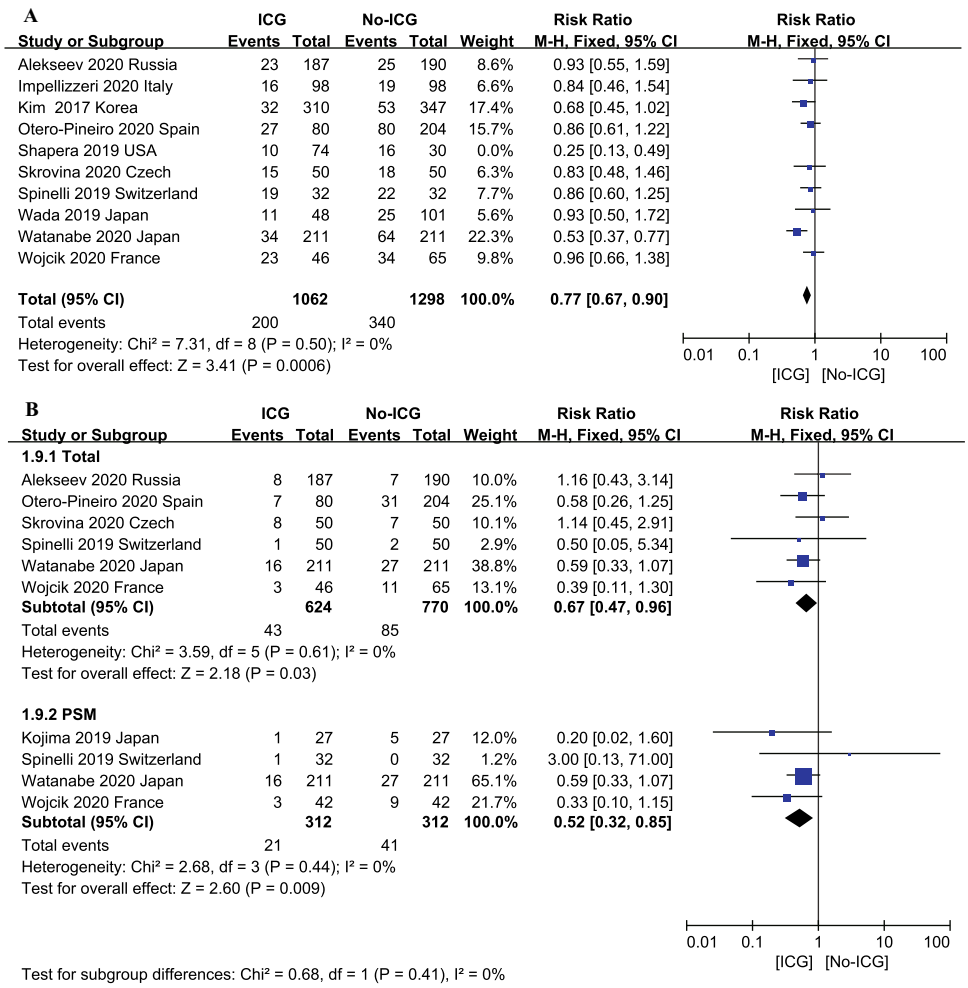


**Fig. 3** **a** Forest plot of overall complications. **b** Forest plot of serious complications

[RR = 1.04, 95% CI (0.46–2.37), $P = 0.92$; RR = 3.26, 95% CI (0.59–17.96), $P = 0.18$, respectively].

## Postoperative mortality

Six studies reported on postoperative mortality [11, 16, 19, 22, 24, 30]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.61$). A fixed model was applied, and the combined effect was RR = 0.86, 95% CI (0.19–3.84), $P = 0.84$. There was no significant difference in postoperative mortality between the ICG group and the non-ICG group. No reversal of meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 5d).

## Readmission rate

Three studies reported the readmission rate [13, 17, 20]. Low heterogeneity was observed among these studies ($I^2 = 0\%$, $P = 0.63$). A fixed model was applied and the combined effect was RR = 0.92, 95% CI (0.50–1.71), $P = 0.8$. There was no significant difference in the rate of readmission between the ICG group and the non-ICG group. No reversal of meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 6a).

## Reoperation rate

Seven studies reported the reoperation rate [8, 17, 20, 21, 24, 25, 30]. Low heterogeneity was observed among these studies ($I^2 = 9\%$, $P = 0.36$). A fixed model was applied, and the combined effect was RR = 0.67, 95% CI (0.40–1.14), $P = 0.14$. There was no significant difference in the reoperation rate between the ICG group and the non-ICG group. The meta-analysis result was reversed, and the heterogeneity was reduced ($I^2 = 0\%$, $P = 0.58$) after eliminating the study by Alekseev [8], with the combined effect of RR = 0.53, 95% CI (0.29–0.96), $P = 0.04$. The reoperation rate was significantly lower in the ICG group than in the non-ICG group after eliminating the above study (Fig. 6b). No significant difference in the reoperation rate was observed between the ICG group and the non-ICG group in five studies from Western countries [8, 17, 20, 24, 25], but in two studies from East Asia [21, 30], the reoperation rate was significantly lower in

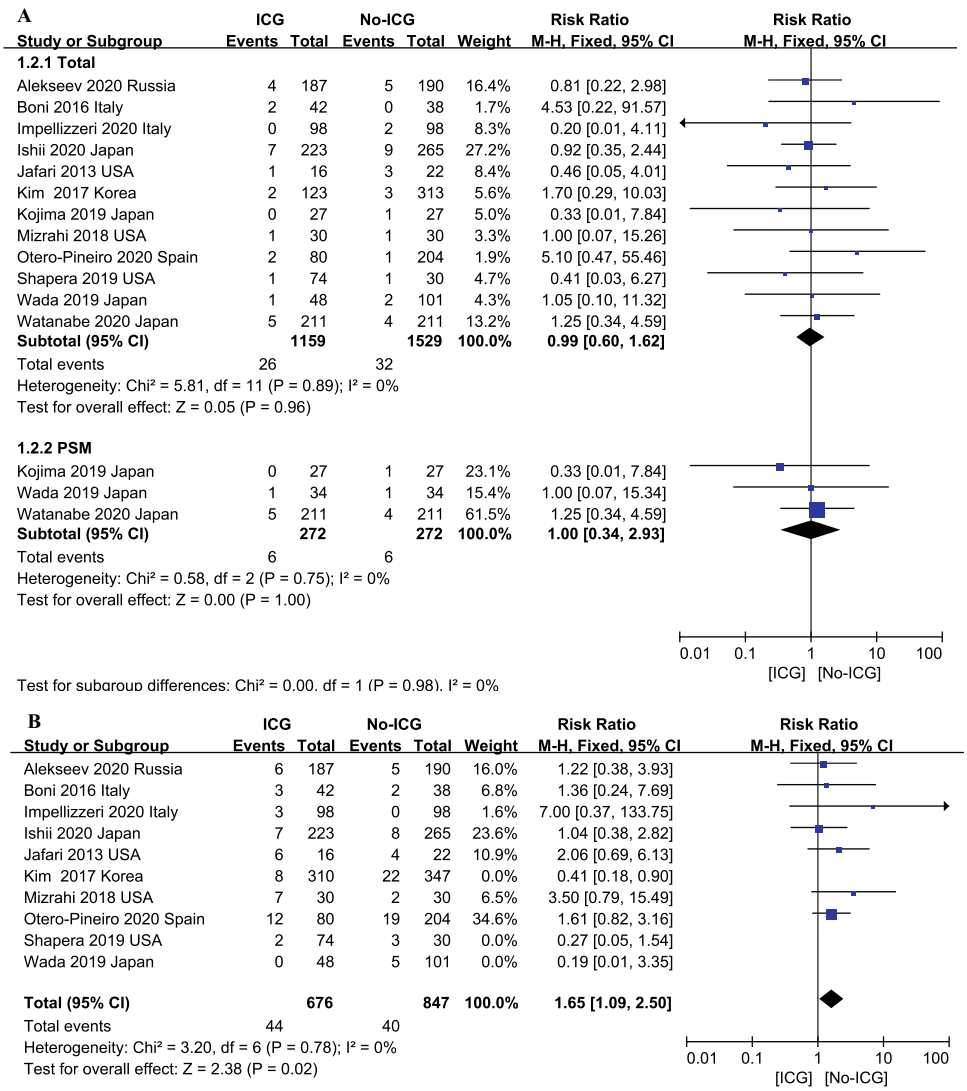


**Fig. 4** **a** Forest plot of wound infection. **b** Forest plot of ileus

the ICG group than in the non-ICG group [RR = 0.32, 95% CI (0.11–0.95), $P = 0.04$].

## AL rates in the anastomotic line-changed group vs. the anastomotic line-unchanged group after ICG evaluation

Five controlled studies and seven non-controlled studies reported the AL rates in an anastomotic line-changed ICG group vs. an anastomotic line-unchanged ICG group [24, 25, 29–38]. Low heterogeneity was observed ($I^2 = 0\%$, $P = 0.50$). A fixed model was applied and the combined effect was OR = 5.17, 95% CI (2.74 ~ 9.73), $P < 0.00001$. The AL rate was significantly higher in the anastomotic line-changed ICG groups than in the anastomotic line-unchanged ICG groups. No reversal of the meta-analysis result or significant change in heterogeneity was observed after sensitivity analysis (Fig. 6c).

## Sensitivity analysis, subgroup analysis, and publication bias

Sensitivity analysis was conducted by gradually excluding each study from each set analysis. No reversal of the accumulative analysis result was observed in almost all of the outcome indexes after sensitivity analysis, except for the ileus rate and the reoperation rate. Subgroup analysis based on the factors that might affect the result is described in each outcome index section. A funnel plot was used to evaluate publication bias and showed symmetrical distribution without obvious extreme distribution (Fig. 7). No publication bias was detected by Begg's test and Egger's test. The results of Begg's test and Egger's test for each outcome index are attached to the Supplement. Table 3 summarizes the basic characteristics and quality evaluation scores of the included literature.

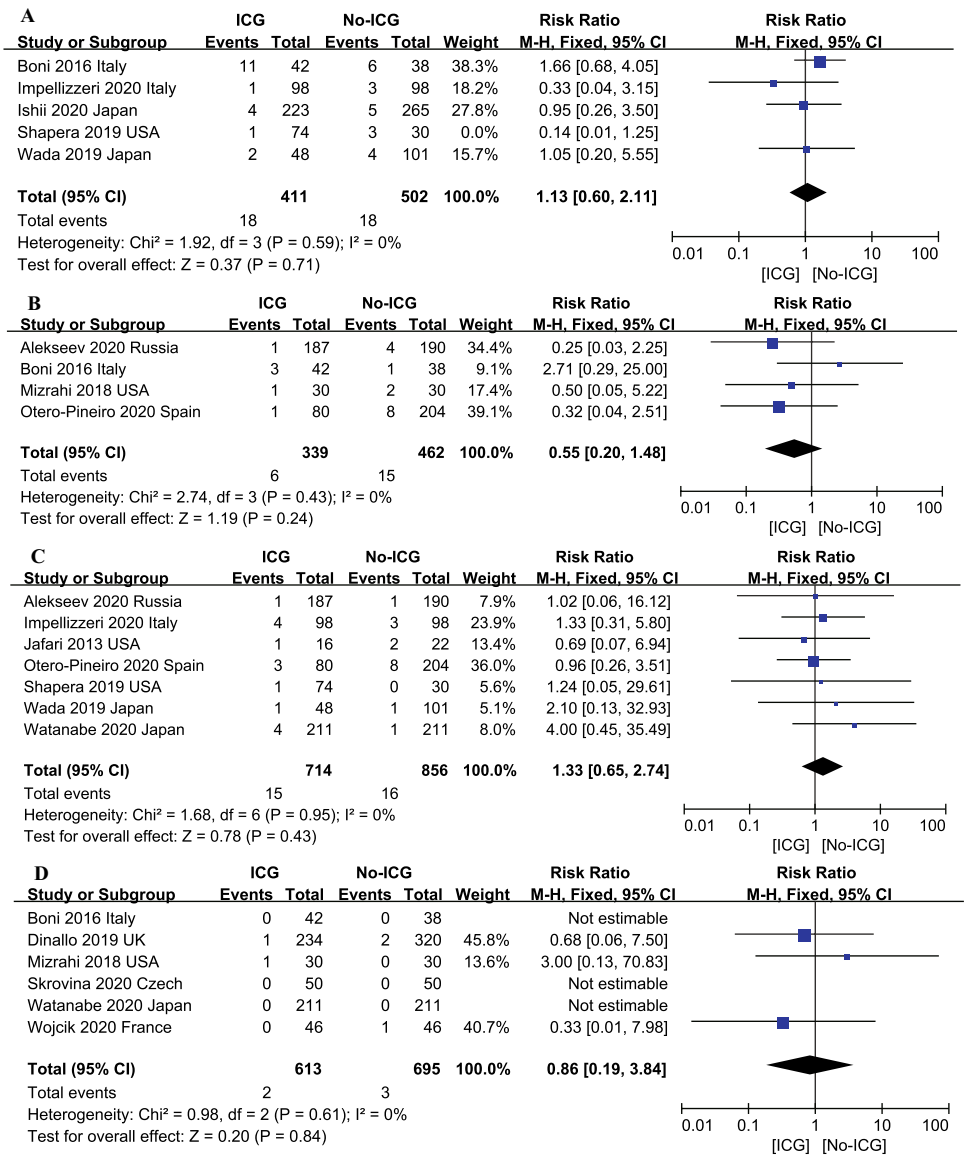


**Fig. 5** **a** Forest plot of postoperative pneumonia. **b** Forest plot of urinary retention. **c** Forest plot of postoperative bleeding. **d** Forest plot of postoperative mortality

## Discussion

Anastomotic leakage (AL) is one of the most serious postoperative complications of colorectal surgery, prolonging hospitalization and increasing costs, local recurrence, and mortality. Currently, the overall AL rate after colorectal surgery ranges from 1 to 19%, being 1–8% for the ileocolon, 2–3% for the colon, 3–7% for the ileorectum, and 5–19% for the colorectum or coloanus. [39]. Decreased blood perfusion is the most likely cause of AL, but near-infrared laparoscopy combined with indocyanine green (ICG) can be used to observe microcirculation before the anastomosis, allowing surgeons to select the best transverse site in the perfusion area. ICG can be used as an objective tool for surgeons to examine the blood supply of the anastomotic stump and select an ideal anastomotic site with good perfusion effect. ICG is usually injected intravenously after severing the distal intestine tract and separating the proximal mesentery from the precut line to observe the blood supply and decide whether to change the precut line. Kudszus [28] was the first to report that ICG-FA resulted in 13.9% of proximal resection line changes, with the AL rate decreasing by 4%. Jafari [25] described the application of ICG-FA in Da Vinci robot-assisted LAR. Using ICG allowed 19% of the proximal resection lines to be changed, whereby the AL rate decreased to 6%. Our meta-analysis identified that the AL rate was lower in the ICG group than in the control group (3.23% vs. 9.17%), which is consistent with previous meta-analyses [5–7].

Although ICG-FA can build better perfusion anastomoses, the AL rate in patients whose precut line was changed was relatively high. According to the included study, the

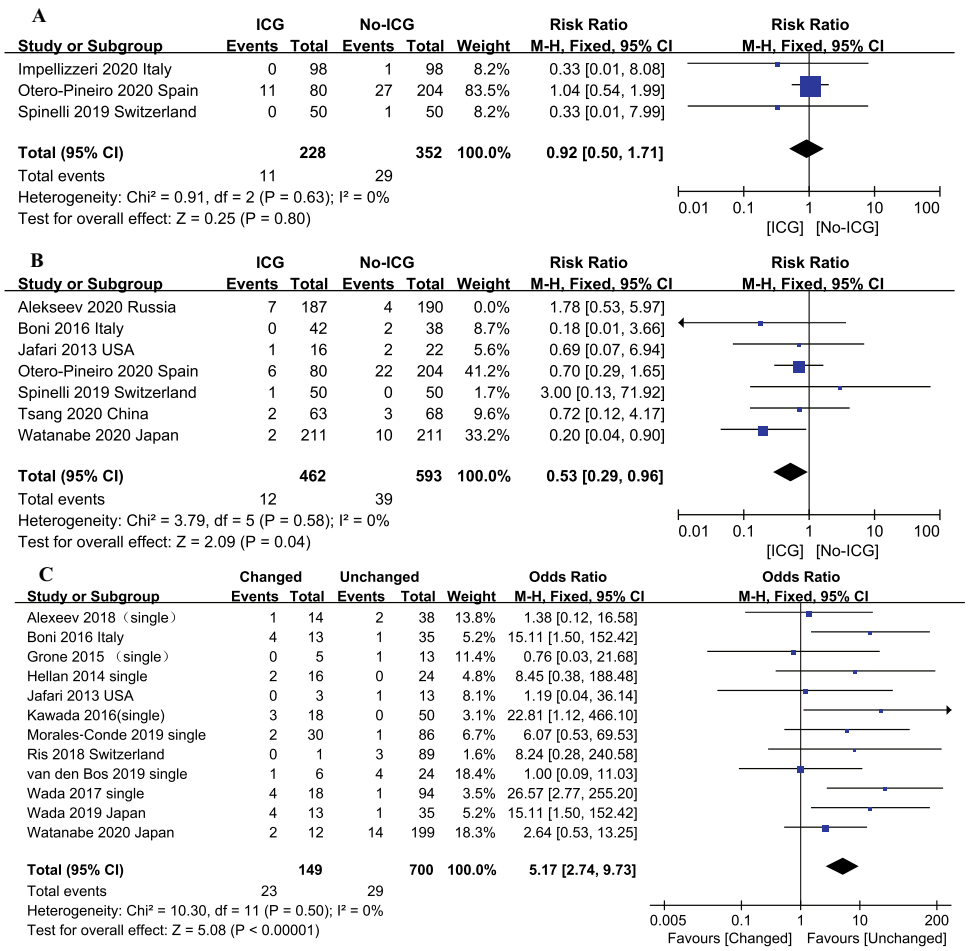


**Fig. 6** **a** Forest plot of the readmission rate. **b** Forest plot of the reoperation rate. **c** Forest plot of the anastomotic leakage rates of the ICG group with anastomotic line change vs. the ICG group without anastomotic line change

AL rate in patients whose precut line was changed after being evaluated by ICG-FA as having insufficient perfusion (23/149, 15.44%) was higher than that of patients whose precut line was not changed after being evaluated by ICG-FA as having adequate perfusion (29/700, 4.14%) and also of patients who did not undergo ICG-FA evaluation (323/3522, 9.17%). This meta-analysis showed that the AL rate was significantly higher in ICG group patients with precut line change than in those without a need for precut line change (OR = 5.17, 95% CI (2.74–9.73), $P < 0.00001$). This might be due to the fact that patients in whom poor perfusion was initially identified might have other risk factors for AL that could affect systemic tissue perfusion, such as coronary heart disease, hypertension, or diabetes. This mechanism needs further investigation. Based on this result, temporary fistulas should be considered in patients with transverse section change. Moreover, patients in the ICG group without transverse line change had a lower AL rate (4.14% vs. 9.17%) than the control group, which might be because those patients identified by ICG-FA had good perfusion with less possibility of anastomotic ischemia. Thus, we speculated that ICG-FA can identify high-risk factors of AL during surgery and change the anastomosis line to improve perfusion, but it cannot reduce the systemic high-risk factors of AL. Ris [31] also indicated that the AL rate would be close to the historical level if AL occurs in all patients with colorectal anastomotic line change after NIR-ICG evaluation.

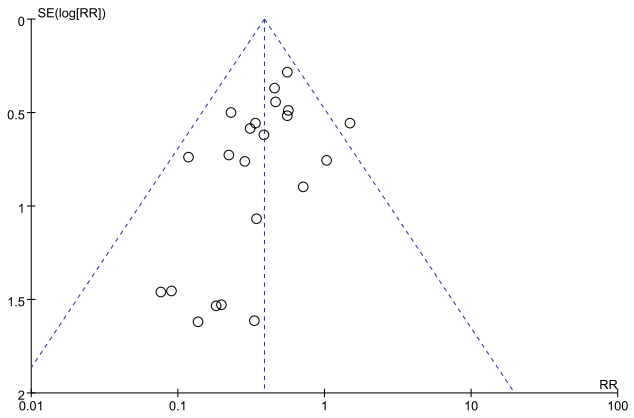


**Fig. 7** Funnel plot of the anastomotic leakage rate

Our meta-analysis found that the overall complication, severe complication, and reoperation rates were lower in the ICG group than in the non-ICG group, whereas the ileus rate was higher in the ICG group than in the non-ICG group. Furthermore, subgroup analysis showed that the ileus rate was significantly lower in the ICG group than in the non-ICG group in East Asia, but it was reversed in Western countries. Interestingly, a significant difference in overall complication and reoperation rates between the ICG group and the non-ICG group was found only in East Asia. The safety of ICG injection needs further verification by prospective placebo-controlled trials.

An important limitation in the assessment of anastomotic perfusion by ICG-FA is that the imaging quality requires subjective evaluation by surgeons, which may be affected by many factors, such as the dosage and time of ICG administration, the distance between the endoscopic tip and the intestinal tract, NIR intensity, surrounding lighting, and the heterogeneity among patients, including blood pressure, liver function, and BMI [40]. Whether ICG-FA can predict postoperative anastomotic leakage by quantitative analysis of anastomotic perfusion is still under investigation. Matsui [41] and Diana [42] confirmed the feasibility of ICG-FA in a quantitative analysis of anastomotic perfusion and prediction of intestinal ischemia in animal experiments in 2011 and 2014, respectively. In 2017, Wada [38] analyzed, retrospectively, a video of 112 ICG-FA guided laparoscopic left hemicolectomies or proctectomies with spectral analysis software and found that an $F_{max}$ (fluorescence intensity, *F*) value less than 52.0 was related to AL, with a sensitivity of 100% and a specificity of 92.5%. Wada also found that the time of postoperative defecation was related to the $T_{max}$ (time, *T*) value. In 2019, Son [43] found that $T_{1/2max}$ and TR ($T_{1/2max}/T_{max}$) were related to AL after quantitatively analyzing 86 CRC patients who underwent ICG-FA during surgery between 2015 and 2017, with sensitivity of 100% and 83.3%, and specificity of 83.7% and 96.3%, respectively. Currently, the existing laparoscopic ICG-FA system is unable to collect the fluorescence signal quantitatively. An automatic analysis software program is needed to establish accurate and objective unified standards for the evaluation of ICG perfusion.

## Conclusion

ICG fluorescence imaging seems to reduce the postoperative AL rate after colorectal cancer surgery. However, the postoperative AL rate was higher in patients with anastomotic line change after ICG-FA evaluation showed insufficient perfusion than in patients without anastomotic line change. Based on these findings, ICG-FA can identify patients at high risk of AL and facilitate preventative strategies. Moreover, ICG-FA may reduce the overall complication rate, severe complication rate, and reoperation rate, but cause some potential adverse events. Thus, the effectiveness and safety of ICG-FA needs further verification by high-quality randomized-controlled trials with a placebo.

## Limitation

This review had several limitations. First, most of the included studies were retrospective, resulting in selection bias. Second, the included studies contained different approaches; namely, the laparoscopic approach and the robot-assisted laparoscopic approach, which limited the applicability of this meta conclusion. Third, the number of ICG cases included was small. Many studies were still in the learning-curve stage and needed an operator to evaluate anastomotic perfusion and decide whether to change the resection line, which required experience and consistent learning. Fourth, the ICG-FA procedure included in each study was not standardized. There was no standard for blood perfusion evaluation, the time that ICG fluorescence was visible, or the dosage of ICG used during surgery. Moreover, the definition of adequate or inadequate preoperative perfusion was not clear, because most of the imaging systems lacked the ability for quantitative tissue perfusion, leading to higher heterogeneity and weakening the interpretation of the merged results.

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## Compliance with ethical standards

**Conflict of interest** Drs. Zhang Wei and Che Xu have no conflicts of interest or financial ties to disclose.

**Ethical approval** Ethical approval was not necessary, as this study was a "Systematic Review and Meta-analysis." There are no individual person's data or details of case reports disclosed in this article.

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