

A Comparison of the Postoperative Outcomes Between Intraoperative Leak Testing and Non-Intraoperative Leak Testing for Gastric Cancer Surgery: A Systematic Review and Meta-analysis

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Abstract

Purpose

Postoperative anastomotic leakage (PAL) is a serious complication of gastric cancer surgery. Although perioperative management has made significant progress, anastomotic leakage (AL) cannot always be prevented. Intraoperative leak testing (IOLT) may reduce the incidence of PAL and other postoperative complications. The aim of this study is to assess the relationship between IOLT and postoperative surgical complications in gastric cancer surgery.

Materials and methods

In this meta-analysis, we searched the PubMed, Embase, and Cochrane Library databases for clinical trials to assess the application of IOLT in gastric cancer surgery. Studies comparing the postoperative outcomes of IOLT and non-intraoperative leak testing (NIOLT) were included. Quality assessment, heterogeneity, risk of bias, and the level-of-evidence of the inclusions were evaluated. PAL, anastomosis-related complications, 30-day mortality, and reoperation rates were compared between the IOLT and NIOLT group.

Results

Our literature search returned 975 results, from which 3 trials (929 total patients) were included in our meta-analysis. Statistical heterogeneity was low. The primary outcome was PAL. IOLT statistically reduced the risk of PAL [3.08% vs9.54%; risk ratios (RR) 0.336, 95% CI, 0.189–0.600, P = 0.000]. It was also found that IOLT can lower the incidence of other postoperative outcomes. Anastomosis-related complication rates [3.94% vs13.14%; risk ratios (RR) 0.323, 95% CI, 0.182–0.572, P = 0.000] were significantly higher in the NIOLT group than the IOLT group. Moreover, IOLT was associated with lower reoperation rates [2.36% vs9.14%; risk ratios (RR) 0.301, 95% CI, 0.145–0.621, P = 0.001].

Conclusion

Due to the lower incidence of PAL, anastomosis-related complications, and reoperation rates, IOLT is recommended in gastric cancer surgery.

Introduction

Gastric cancer is the fifth most commonly diagnosed cancer with over one million patients worldwide diagnosed annually (1, 2). Approximately one out of every twelve oncological deaths can be attributed to gastric cancer(3). Surgery is often the only curative treatment option for gastric cancer(4). Although progress has been made in perioperative management, postoperative complication rates remain high following gastric cancer surgery, especially in low-volume centers(5).

There are various prevention strategies for PAL. IOLT may be one of the most important preventive measures that can be performed during gastric cancer surgery. If the intraoperative test is positive, the leak can be fixed during the operation to minimize the possibility of PAL.

Review articles and multicenter studies that used IOLT to prevent anastomotic leakage in colorectal surgery and bariatric surgery were reviewed (6–8). A meta-analysis, which explored the role of IOLT in the prevention of PAL in colorectal surgery, suggested that IOLT did not significantly reduce the rates of PAL. However, IOLT was still necessary in patients with a higher risk for anastomotic leakage(6). Also, another multicenter analysis did not recognize the benefit of IOLT in sleeve gastrectomy (7). Studies with small sample sizes and single center studies also focused on IOLT in gastric surgery (9–12)

The application and effectiveness of IOLT in gastric surgery need to be studied further. In this meta-analysis, we undertook the first-ever meta-analysis of observational studies comparing the postoperative outcomes with or without IOLT in gastrectomy.

Methods

Literature search strategy

We conducted and reported this systematic review and meta-analysis following the PRISMA statement. We performed a literature search for clinical studies using the PubMed, Embase, and Cochrane Library databases. Our search is focused on human studies. The following search strategy was used in PubMed and modified in other databases accordingly: ((stomach neoplasms) and(endoscopy)and (intraoperative) and (anastomotic Leak)) or ((stomach neoplasms) and stomach tube and (intraoperative) and (anastomotic Leak)) or ((stomach neoplasms) and endoscopy and (intraoperative leak testing)) or ((stomach neoplasms) and stomach tube and (intraoperative leak testing)) or ((Gastrectomy) and stomach tube and (intraoperative leak testing)) or ((Gastrectomy) and endoscopy and (intraoperative) and (anastomotic Leak)) or ((Gastrectomy) and stomach

tube and (intraoperative) and (anastomotic Leak)) or ((Gastrectomy) and stomach tube and (intraoperative) and (anastomotic Leak)) or ((endoscopy and (intraoperative) and (anastomotic Leak)) or ((stomach tube and (intraoperative) and (anastomotic Leak)) or ((endoscopy and (intraoperative leak testing)) or ((stomach tube and (intraoperative leak testing))). Studies using both an IOLT group and NIOLT group were included. Clinical studies published before September 2021 were also included. Moreover, we attempted to find all relevant literature by looking through the references of clinical articles. In addition, we searched grey and unpublished literature through the PubMed, Embase, and Cochrane Library databases and the references attached to the relevant literature. We then analyzed the full text to find eligible studies. Ultimately, a total of three studies were accepted in the meta-analysis.

Study selection

Studies were included in the meta-analysis if they met these criteria: 1) They are clinical trials comparing the postoperative outcomes of IOLT and NIOLT. 2) PAL is a study outcome and the study also reported at least one of the following clinical outcomes: 30-Day mortality rates, reoperation rates, or anastomosis-related complications. 3) The study was published as a full text in the English language. 4) Valid data and a full text of the study could be obtained successfully. In this paper, we define overall complications for greater than Grade II or more severe complications according to Clavien-Dindo classification (13). Anastomosis-related complications was defined as one of the following complication: postoperative anastomotic leakage, postoperative anastomotic bleeding, postoperative anastomotic stenosis, anastomotic ischemia, and anastomotic ulcer.

Patients in the studies must meet the main diagnostic criteria for gastric cancer and have undergone a curative-intent gastric cancer surgery. Patients were excluded if they had previously received neoadjuvant chemotherapy, radiotherapy, or had other primary malignancies, recurrent cancer, or gastric remnant carcinomas.

Data Extraction

Articles were screened independently by two reviewers according to title and abstract. Disputes were resolved by a third reviewer. This process was then repeated with a full-text review for data extraction of the publication year, the type of study, the study period, the number of patients, the age of patients, the sex of patients, and all the measured outcomes.

Quality Assessment

Quality assessment of the acceptable studies was completed with the Newcastle-Ottawa Scale (NOS) (14). Using this scale, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and whether IOLT was performed. Stars are awarded for each quality item and the highest quality studies are awarded up to nine stars. A study is considered of good quality if there are 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Statistical Analysis

For non-low-probability events, relative risks (RR) were calculated. The Mantel-Haenszel method was used for dichotomous data, and the RR with 95% CIs was presented. To assess the significance in study heterogeneity, the Cochran's P statistic and I² were reported. We used either a fixed-effect model with no heterogeneity or a random-effects model. Postoperative surgical outcomes such as PAL, anastomosis-related complications, overall complication, 30-Day mortality rates, and reoperation rates were compared between the IOLT and NIOLT groups. Statistical analysis was performed with the Stata 15.0 software. Sensitivity analysis was also used to evaluate the robustness of the results. For all tests, a P-value < 0.05 was considered statistically significant. Institutional Review Board approval and written consent were not needed in this paper.

Results

Literature search results

The systematic search revealed a total of 975 publications for possible inclusion. Based on title and abstract review, irrelevant publications, duplicate publications or those not fitting our inclusion criteria were excluded. 35 publications were excluded based on the full text, leaving 3 studies to be included in the final analysis (Fig. 1). This included 1 prospective cohort study and 2 retrospective cohort studies (10–12).

Study Characteristics

The study included 929 patients with 489 in the IOLT group and 440 in the NIOLT group. Two published studies (10, 15) implemented intraoperative endoscopy while another study used intraoperative stomach tube for leak testing (11). Table 1 shows features of the included studies. Table 2 presents the quality of the overall body of evidence supporting each outcome, and the combined postoperative results.

Table 1
The features of included studies

First author, year	Type of study	Study period	Indication for surgery	Intervention	Group	Number	Age	Sex (male/female)	Outcomes reported
Eva lie, 2010(10)	Prospective study	2005–2006	Gastric cancer	Endoscopy, Air testing	IOLT	62	57.0	73/45	*,†,§,
					NIOLT	80	54.0	92/56	
Celik, 2016(11)	Retrospective study	2007–2014	Gastric or junctional cancer	Tube, Methylene blue testing	IOLT	108	55.1	49/59	*,§
					NIOLT	90	56.9	51/39	
Ji-Ho Park, 2019(12)	Retrospective study	2013–2016	Gastric cancer	Endoscopy, air testing	IOLT	319	61.7	124/195	*, †, ‡, §,
					NIOLT	270	62.4	196/74	
					NIOLT	107	65.5	86/21	

IOLT = Intraoperative leak testing was performed during gastric cancer surgery. NIOLT = Nointraoperative leak testing was performed during gastric cancer surgery.

Outcomes reported: *postoperative anastomotic leakage; †post-operative anastomosis-related complications; ‡Overall complication; §30-Day mortality; ||reoperation

Table 2
Quality assessment of included studies.

Selection					Comparability of cases and Controls on Basis of Design of Analysis	Outcome			Score
Author, Year	Adequate Case Definition	Representative of Cases	Selection of Controls	Definition of Controls		Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate	
Eva lie, 2010	☐	☐	☐	☐	☐☐	☐	☐		8
Celik, 2016	☐	☐	☐	☐	☐	☐	☐		7
Ji-Ho Park, 2019	☐	☐	☐	☐	☐☐	☐	☐		8

Study quality

When using the NOS for case-control studies, the quality assessment of the included studies ranged from 7 to 8. Table 2 shows the NOS quality scores of the included studies.

Postoperative anastomotic leakage

The PAL rates were 3.08% (15/489) in the IOLT group, and 9.54% (42/440) in the NIOLT group. There was no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.667$) when a fixed-effect model was used. PAL was significantly lower in the IOLT group than that in the NIOLT group (RR = 0.336, 95%CI 0.189–0.600, $P = 0.000$) (Fig. 2).

Postoperative anastomosis-related complications

Two studies involving 731 patients evaluated the incidence of postoperative anastomosis-related complication rates. Rates in the IOLT group were 3.94% (15/381), and 13.14% (46/350) in the NIOLT group. A fixed-effect model was used with no heterogeneity ($I^2 = 0.0\%$, $p = 0.420$). There was a statistically significant decrease in postoperative anastomosis-related complication rates in the IOLT group, which was not seen in the NIOLT group (RR = 0.323, 95% CI 0.182–0.572, $P = 0.000$) (Fig. 3).

30-Day mortality rates

All three studies included 30-Day mortality rates. The 30-day mortality rates were 0.20% (1/489) in the IOLT group, and 1.6% (5/440) in the NIOLT group. Due to the lack of inter-study heterogeneity ($I^2 = 0.0\%$, $P = 0.744$), a fixed-effect model was used. The meta-analysis showed no significant

difference in 30-day mortality rates between the two groups (RR = 0.334, 95%CI 0.065–1.727, P = 0.191) (Fig. 4).

Reoperation rates

Two studies involving 731 patients compared the incidence of reoperation rates. No heterogeneity was detected ($I^2 = 0.0\%$, $P = 0.548$). We found that IOLT was associated with a lower risk of reoperation rates (2.36% vs 9.14%; RR = 0.301, 95% CI 0.145–0.621, $P = 0.001$) (Fig. 5).

Discussion

Postoperative anastomotic leakage (PAL) is the most common complication of gastric cancer surgery, affecting 2.1–14.6% of all patients (16–19). PAL is regarded as one of the most serious complications and is consistently associated with high postoperative mortality rates, reaching as high as 60% in some studies (20, 21). PAL can be regarded as one of the key indicators of surgical quality, since it is related to the level of expertise of the surgeon(22). PAL has also had a significant impact on several other postoperative outcomes (23).

Whether the use of IOLT in gastrectomy can significantly reduce PAL rate is yet to be decided. IOLT involves injecting air and methylene blue into the anastomosis, which can help observe the integrity of the anastomosis directly. Any defects in the anastomosis can be repaired during surgery. Katsunori Nishikawa was the first to test the efficacy of IOLT in gastric cancer surgery. Previous single center, small sample studies demonstrated that IOLT can detect anastomotic leakage and allow for the repair of the defects and thus a reduction in PAL rates (24). However, some researchers insist that IOLT has no place in bariatric surgery since they found that IOLT does not reduce postoperative complications (25, 26). Some other disadvantages are IOLT prolonged operation time and increased resource utilization. Some researchers found that IOLT cannot prevent all anastomotic leakage, such as late leakage and leakage caused by other factors, such as poor surgical technique or the age of the patient(10, 15). Therefore, the preventive effect of IOLT on postoperative complications remainsto be further studied.

PAL may lead to serious complications, including hemodynamic instability, sepsis, multi-organ failure, and even death(27). This study comprehensively evaluated the efficacy of IOLT as measured by PAL and other postoperative complications. Through retrospective analysis and meta-analysis of relevant articles, our research found that IOLT can reduce the incidence of PAL (moderate quality evidence), anastomotic-related complications (moderate quality evidence), and reoperation rates (moderate quality evidence) for gastric cancer surgery. According to the Cochrane manual, publication bias testing is required for more than 10 articles included in a meta-analysis. As such, bias testing was not performed in this study. When determining the overall quality of evidence, we assumed that there was no publication bias between overall evidences on the basis of the risk of bias in a single study and the degree to that each study contributed to the estimated effect (28).

In this study, we found that PAL rates were lower in the IOLT group than the NIOLT group. Z Wu, et al found that the PAL rate was 4.8% in the IOLT group compared to 6.1% in the NIOLT group. This result suggests that IOLT did not significantly reduce PAL rates after colorectal surgery in this meta-analysis. The lack of statistically significant difference may be due to the fact that one study is substantially influencing the sensitivity analysis of the meta-analysis (6). A randomized controlled trial with small sample size found that intraoperative endoscopy could prevent technical defect-related leaks in laparoscopic Roux-en-Y gastric bypass bariatric surgery(29). The significance of our study is that IOLT not only has a preventive effect on PAL, but can also significantly reduce other postoperative complications, such as postoperative anastomotic-related complications and reoperation rates in gastric surgery.

The technique of IOLT has been applied in various ways in clinical practice, although there is no consensus on the standardization of IOLT. According to published articles on IOLT for gastric cancer surgery, bariatric surgery, colorectal surgery and our own experience, we found that IOLT can be performed by gastroscopy or gastric tubes. Interestingly, researchers found that IOLT performed with gastroscopy had statistically significant lower PAL rates than IOLT performed with gastric tubes had (30, 31). When compared with IOLT using gastric tubes, intraoperative gastroscopy had the advantage of detecting and preventing severe complications such as esophageal perforation. However, a gastric tube maybe a viable option for IOLT when there is no gastroscopy device or professional endoscopists available. The method of intraoperative leakage test has not been unified. Some scholars use the air testing(32) while another scholars use the methylene blue testing(11). Which method is better is currently the controversial point. We recommend the combination of air testing and methylene blue testing(31).

Intraoperative air pressure plays a crucial role in the process of IOLT. Biomechanically, standardizing the volume of injected liquid or air can be difficult due to the complexity of the human anatomy. It is important to keep the anastomotic pressure within a safe range to avoid excessive perfusion pressure or anastomotic bursting pressure. Excessive perfusion pressure can lead to insufficient blood perfusion, inadequate oxygen supply, and an increased risk of postoperative obstruction, dyspnea, and anastomotic rupture(23). The anastomotic blasting pressure wascarried out in animals and in vitro experiments (33–35). One experimental study showed that the colorectal anastomosis can be ruptured at 70–184 mmHg pressure, which demonstrates that there was a risk of rupture when 400ml liquid was injected (35). Anastomotic pressure monitoring is thus recommended for IOLT. Further studies are needed for finding safe pressures in IOLT.

There are three limitations of our study. The first limitation is that only 3 observational studies were included in this meta-analysis since IOLT is not widely used in gastric cancer. Second, the quality of overall evidences was not high. Lastly, the ways of IOLT were not uniform. This may be a confounding factor.

Conclusions

Due to the lower incidence of PAL, anastomosis-related complications, and reoperation rates, IOLT is strongly recommended in gastric cancer surgery. Moreover, a standardized IOLT procedure should be further investigated in future high-quality clinical research studies. Moreover, IOLT has extensive implications for gastric surgery. Including IOLT in the next set of clinical guidelines for future gastric cancer surgery is imperative.

Declarations

Availability of data and materials

The datasets of the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate – This is a meta analysis on anonymised data so ethical approval is considered unnecessary.

Consent for publication – No individual person's data is included in this study.

Availability of data and materials – The dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests – The authors declare that they have no competing interests.

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Author's contributions – All authors contributed to the study design as well as the collection and analysis of the data. Yunhong Tian and Shunying Liu contributed equally to this work. Yunhong Tian, Shunying Liu, and Jiani Hu designed the research. Dan Bai, Shouliang Qi, and Xiangzhi Qin performed the clinical research. Shunying Liu, Wentao Huang wrote the paper. Yong Peng, Mingyang Ren, and Yunhong Tian performed the statistical analysis. All authors approved the final version of the manuscript.

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Figures

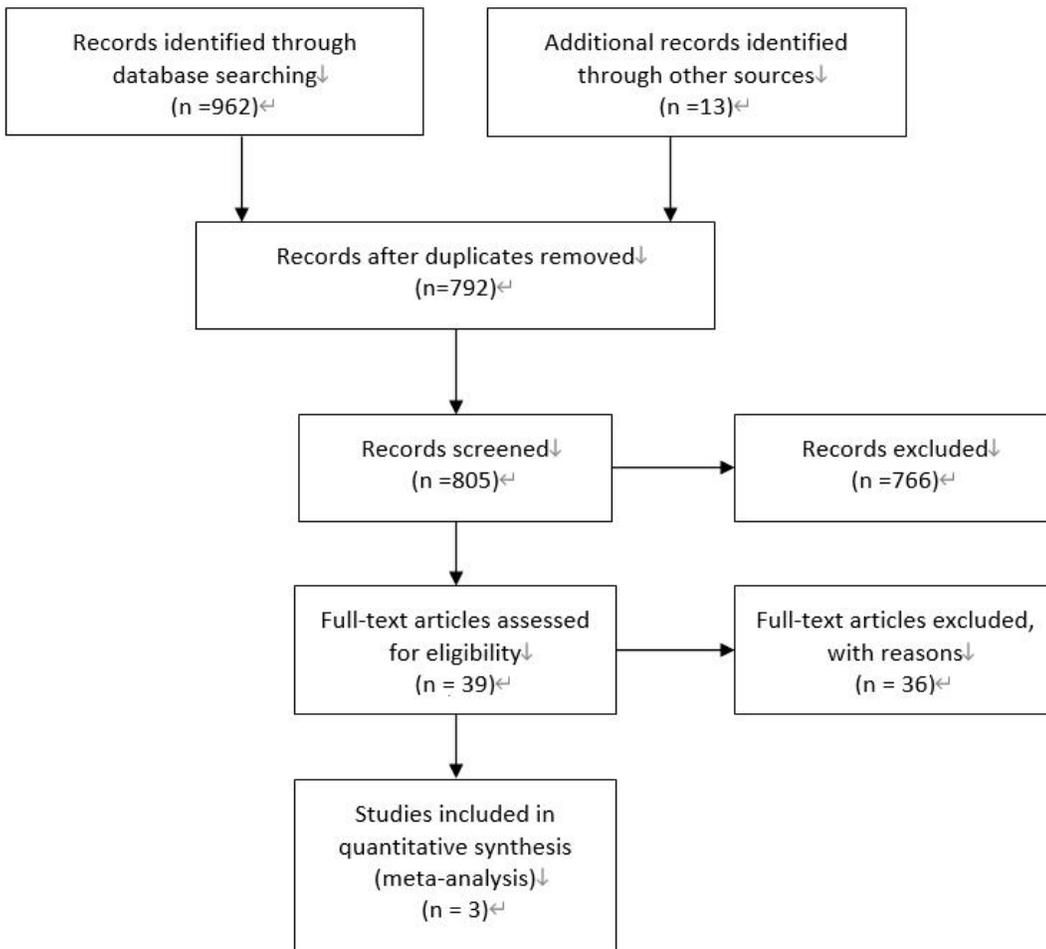


Figure 1

PRISMA flow diagram

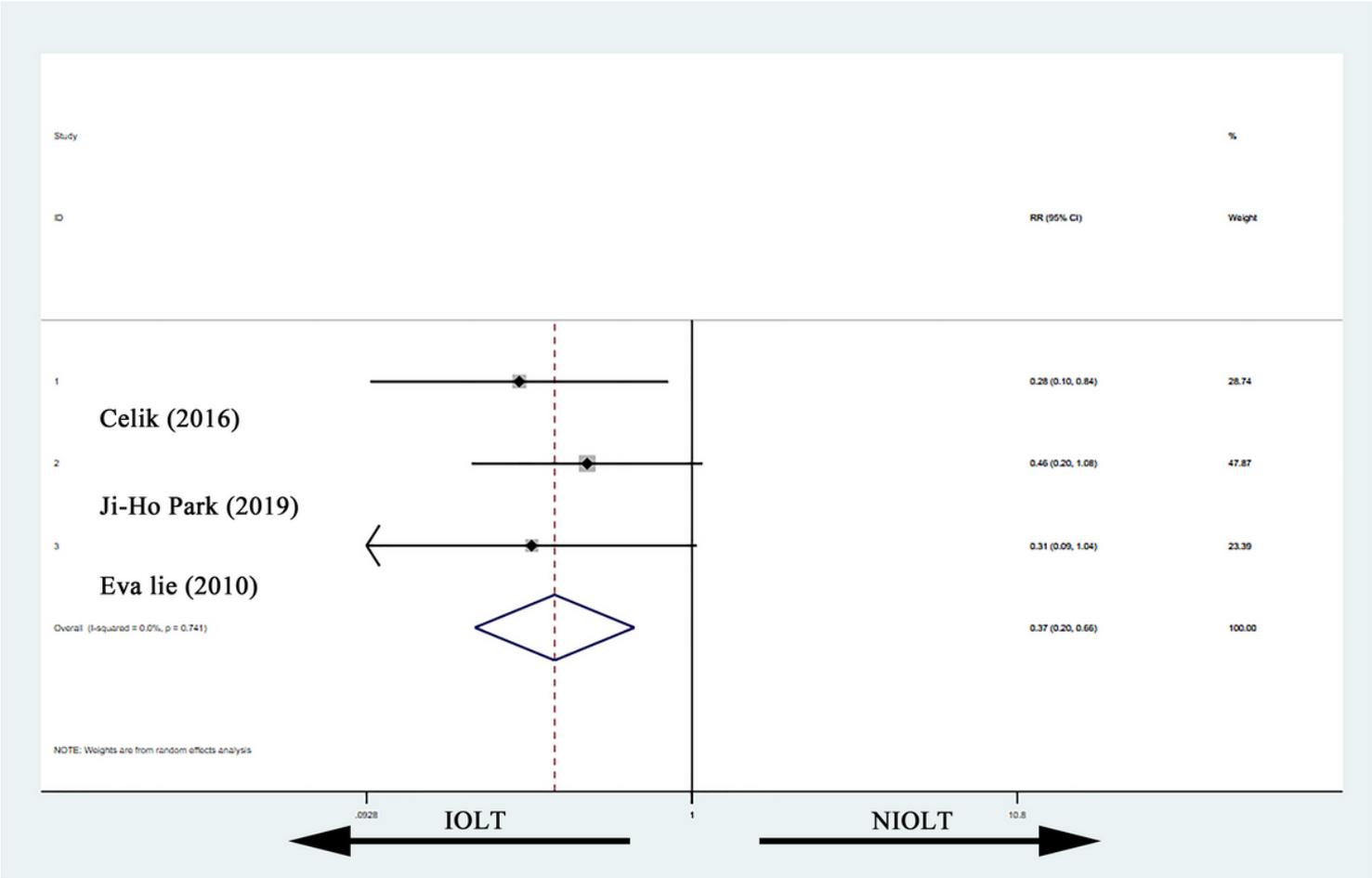


Figure 2

postoperative anastomotic leakage

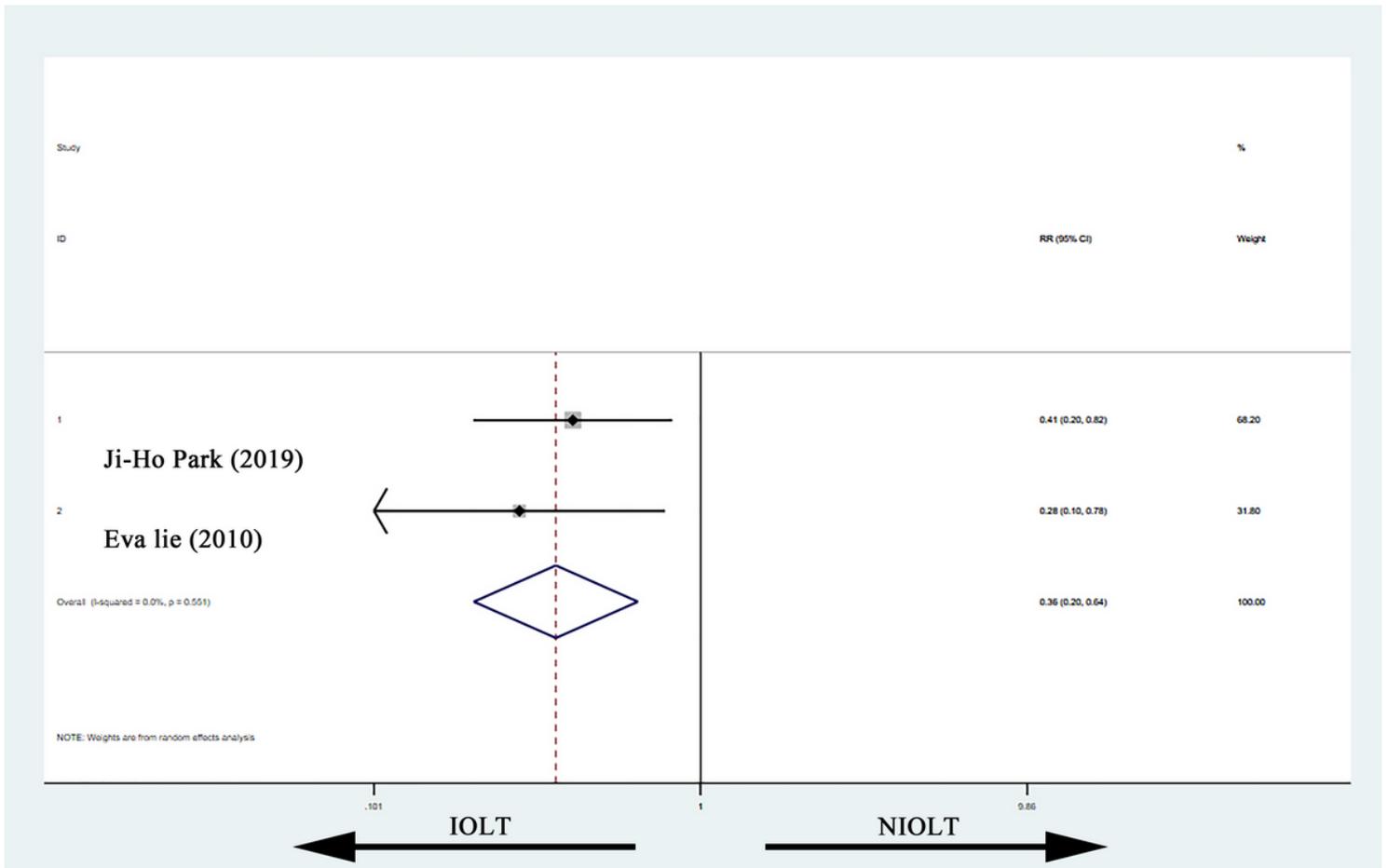


Figure 3

Postoperative anastomosis-related complications

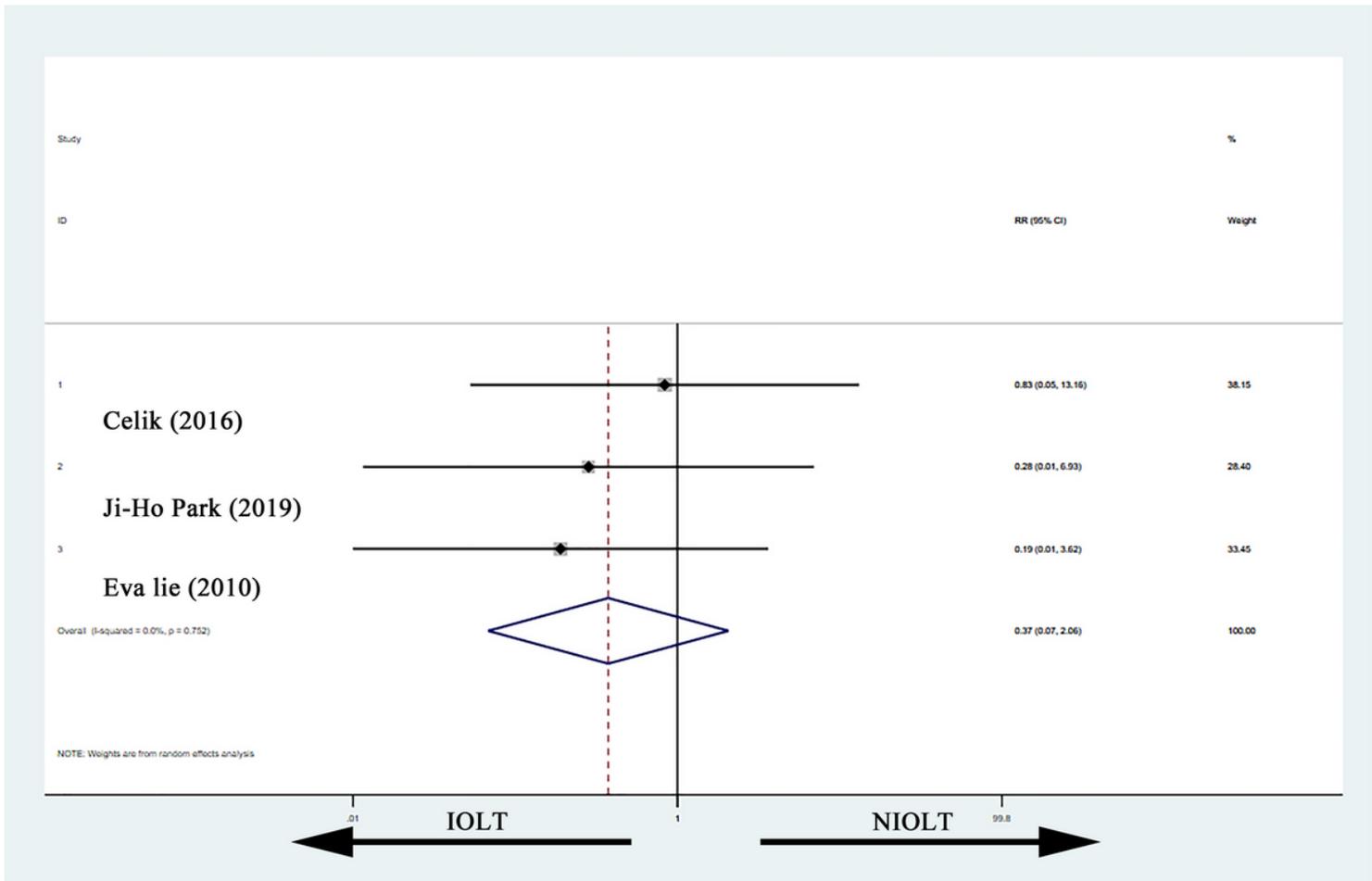


Figure 4

30-Day mortality rates

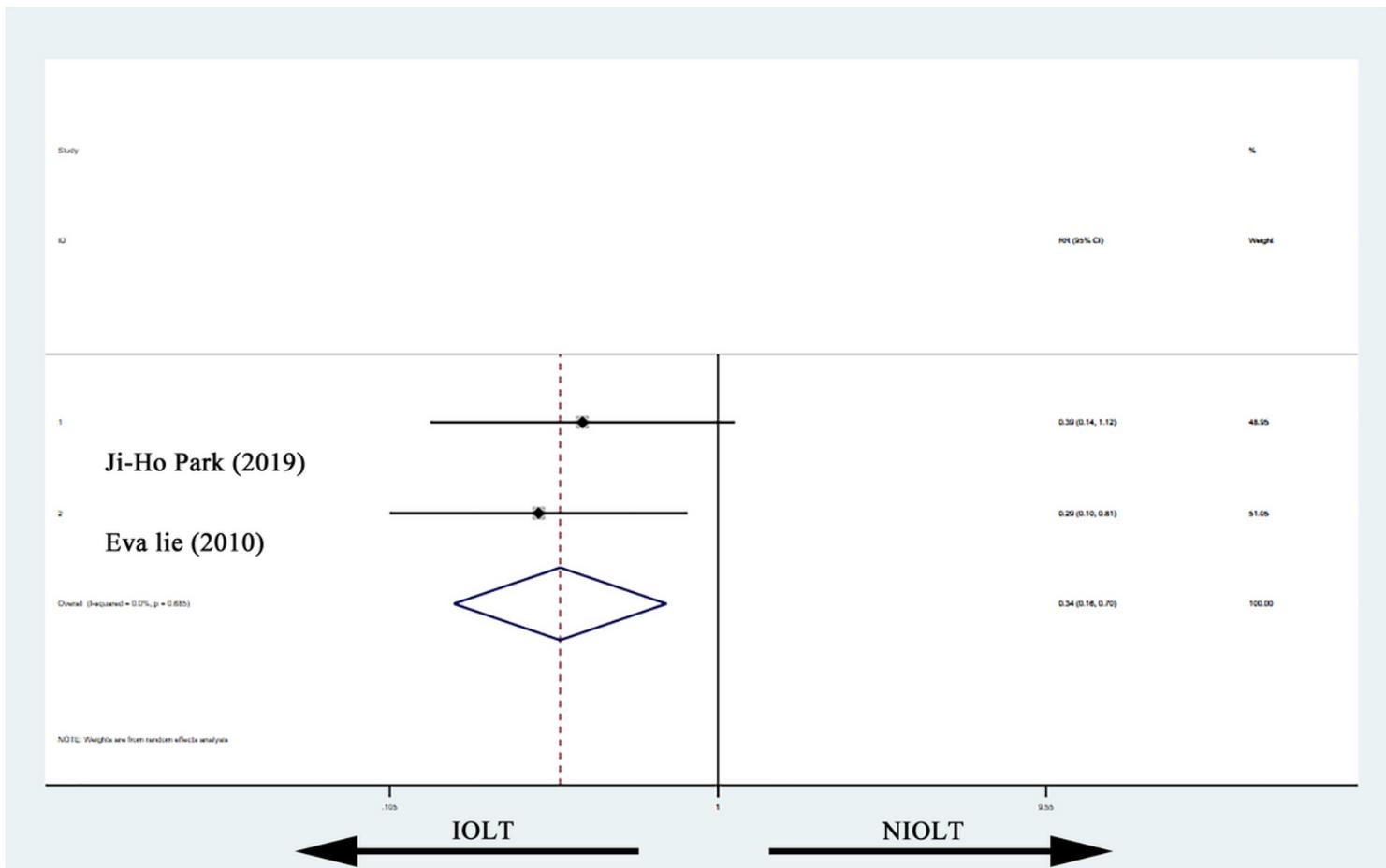


Figure 5

Reoperation rates

Supplementary Files

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