Meta-analysis of perioperative outcomes of acute laparoscopic versus open repair of perforated gastroduodenal ulcers

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BACKGROUND: Surgery is the treatment of choice for perforated peptic ulcer disease. The aim of the present review was to compare the perioperative outcomes of acute laparoscopic versus open repair for peptic ulcer disease.

METHODS: A systematic literature search was performed for randomized controlled trials (RCTs) published in PubMed, SCOPUS, and Web of Science.

RESULTS: The search included eight RCTs: 615 patients comparing laparoscopic (307 patients) versus open peptic perforated ulcer repair (308 patients). Only few studies reported the Boey score, the Acute Physiologic Assessment and Chronic Health Evaluation score, and the Mannheim Peritonitis Index. In the RCTs, there is a significant heterogeneity about the gastric or duodenal location of peptic ulcer and perforation size. All trials were with high risk of bias. This meta-analysis reported a significant advantage of laparoscopic repair only for postoperative pain in first 24 hours (−2.08; 95% confidence interval, −2.79 to −1.37) and for postoperative wound infection (risk ratio, 0.39; 95% confidence interval, 0.23–0.66). An equivalence of the other clinical outcomes (postoperative mortality rate, overall reoperation rate, overall leaks of the suture repair, intra-abdominal abscess rate, operative time of postoperative hospital stay, nasogastric aspiration time, and time to return to oral diet) was reported.

CONCLUSION: In this meta-analysis, there were no significant differences in most of the clinical outcomes between the two groups; there was less early postoperative pain and fewer wound infections after laparoscopic repair. The reported equivalence of clinical outcomes is an important finding. These results parallel the results of several other comparisons of open versus laparoscopic general surgery operations—equally efficacious with lower rates of wound infection and improvement in some measures of enhanced speed or comfort in recovery.Notably, the trials included have been published throughout a considerable time span during which several changes have occurred in most health care systems, not least a widespread use of laparoscopy and increase in the laparoscopic skills. (*J Trauma Acute Care Surg.* 2018;85: 417–425.

LEVEL OF EVIDENCE: Systematic review and meta-analysis, level III.

KEY WORDS: Perforated peptic ulcer; gastroduodenal ulcer; laparoscopic PPU repair; open PPU repair; emergency laparoscopic surgery.

Perforated peptic ulcer (PPU) is an acute surgical emergency that demands prompt identification and management to ensure good outcomes.[1] After early and appropriate preoperative resuscitation,[2] emergency surgery to repair the visceral perforation and thoroughly clean the peritoneum is essential. In most patients, the repair may be done by a simple suture of the ulcer borders and optionally by an omental patch repair, while a gastrectomy is rarely needed.[3] For diagnostic imaging, computed tomography (CT) is most frequently used,[4] as it has superior diagnostic accuracy over erect abdominal x-ray.[5,6] However, the exact source of perforation may not always be revealed, and thus an initial laparoscopic approach for exploration is commonly performed. In most patients, the perforation is small enough to be amenable for repair by laparoscopic sutures.[7] Feasibility of this approach has been demonstrated in several retrospective series over the past few decades, with institutional preferences determining which approach has been used.[8,9] A selective approach is obvious in noncontrolled observational studies. Previous systematic reviews are largely based on retrospective case series with few randomized controlled trials (RCTs).[10] Recently, further RCTs have been published comparing laparoscopic repair versus open repair of PPU. Thus, we undertook a systematic review and meta-analysis of all available randomized trials with the aim to assess the clinical effectiveness of laparoscopic repair in PPU.

MATERIALS AND METHODS

An extensive literature search was conducted for articles published between January 1990 and August 2017 in PubMed, SCOPUS and Web of Science databases. The Preferred Reporting Items for Systematic Reviews and Meta-analyses was followed.[11]

Search and Inclusion Criteria

The search terms used were "laparoscopy/laparoscopic", "open/conventional", "peptic ulcer/duodenal ulcer/gastric ulcer", "repair/surgery/closure", and their combinations. The search was also augmented with manually screening the references of identified articles and relevant reviews. No language restrictions were applied. This review considered only RCTs in which adult patients underwent laparoscopic or open repair for PPU.

Outcomes Investigated

The primary outcomes evaluated were overall postoperative mortality rate, overall reoperations rate, overall leak rate of suture repair, postoperative intra-abdominal abscess rate, and the reoperation rate for abdominal abscesses.

The secondary outcomes evaluated were operation time, postoperative hospital stay, nasogastric aspiration time, time to return to oral diet, postoperative pneumonia, postoperative wound infection, postoperative pain in first 24 hours, postoperative pain on the third day, and postoperative analgesic requirements (Table 1).

Quality Assessment

Assessment of methodologic quality was performed by two authors who independently read studies identified according to the above criteria and assessed their methodologic quality and risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions.[12]

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TABLE 1. Data and Analyses

Outcome	Studies	Number of Participants	Statistical Method	Effect Estimate	Hetereogeneity
Primary Outcomes					
Postoperative mortality	6	481	Risk ratio (M-H, random, 95% CI)	0.45 [0.16, 1.28]	0%
Overall reoperations	4	330	Risk ratio (M-H, random, 95% CI)	1.87 [0.49, 7.11]	0%
Overall leaks of the suture repair	4	431	Risk ratio (M-H, random, 95% CI)	1.76 [0.58, 5.34]	0%
Reoperation for leaks of the suture repair	4	330	Risk ratio (M-H, random, 95% CI)	1.28 [0.28, 5.85]	0%
Intra-abdominal abscess	6	546	Risk ratio (M-H, random, 95% CI)	1.50 [0.43, 5.23]	32%
Reoperation for abdominal abscess	4	330	Risk ratio (M-H, random, 95% CI)	0.99 [0.15, 6.48]	0%
Secondary outcomes					
Postoperative pain in first 24 hours	3	211	Mean difference (IV, random, 95% CI)	−2.08 [−2.79, −1.37]	69%
Postoperative wound infection	6	546	Risk ratio (M-H, random, 95% CI)	0.39 [0.23, 0.66]	0%
Operation time	3	365	Mean difference (IV, random, 95% CI)	−5.10 [−7.38, −2.82]	0%
Postoperative hospital stay	4	326	Mean difference (IV, random, 95% CI)	−2.32 [−5.17, 0.53]	89%
Nasogastric aspiration time	3	259	Mean difference (IV, random, 95% CI)	−0.01 [−1.09, 1.07]	0%
Time to return to oral diet	2	166	Mean difference (IV, random, 95% CI)	−0.27 [−1.51, 0.97]	0%
Postoperative pneumonia	4	386	Mean difference (IV, random, 95% CI)	0.33 [0.07, 1.61]	4%
Postoperative pain in third days	2		Data were not used in the analysis		
Analgesic treatment	3		Data were not used in the analysis		
Postoperative ileus	4		Data were not used in the analysis		

The risk of bias tool addresses the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias),[13,14] incomplete outcome data (attrition bias),[15,16] and selective reporting (reporting bias).[17] Blinding and completeness of outcome data for each outcome was separately assessed and a risk of bias table was completed for each eligible study. Any disagreement was discussed among all review authors and a consensus was achieved. Funnel plots were not examined for asymmetry, as there were fewer than 10 studies in any outcome.

We assessed the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation approach.[18] This approach begins with the study design and then evaluates five reasons to possibly downgrade the quality of the body of evidence. These five domains include risk of bias, imprecision, inconsistency, indirectness, and publication bias. Where serious concerns were raised, the quality of evidence was reduced by one point, and two points were deducted for very serious concerns.[19]

For each outcome, the quality was rated as high, moderate, low, or very low. The significance of these levels is listed as follows:

- High-quality evidence: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate quality evidence: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- Low-quality evidence: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low quality: we are very uncertain about the estimate.

Statistics

Meta-analysis was conducted using the Review Manager Version 5.3 computer program.[20] Quantitative data analysis for dichotomous data was performed using the Mantel-Haenszel method; in the summary statistics, the risk ratio (RR) is preferred over odds ratio. For continuous data, the weighted mean difference was used. Ninety-five percent confidence intervals were also produced for both quantitative and continuous data.

Where the mean and standard deviation for continuous data were not reported, these were calculated using the methods described by Hozo et al.[21] available online.[22,23] Because substantial heterogeneity between trials was usually reported, we performed the analysis using the random-effects model. Clinical heterogeneity was tested by means of the I^2 value, where a value exceeding 50% was indicative of heterogeneity.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for the systematic review is presented in Supplemental Digital Content 1 (http://links.lww.com/TA/B140). The initial search yielded 1,191 potentially relevant articles. After removal of duplicates, screening titles/abstracts for relevance and assessment for eligibility, 609 full-text articles were evaluated. Of these articles, 566 were excluded, resulting in 43 studies. After full-text analysis, 35 were determined to be nonrandomized trial designs and were excluded (Supplemental Digital Content 2, http://links.lww.com/TA/B141).[24–58]

Eight RCTs were eventually included in this systematic review and meta-analysis (Supplemental Digital Content 3, http://links.lww.com/TA/B142).[59–66] Altogether, these trials included 615 patients and compared 307 patients underwent laparoscopic repair against 308 open repair for perforated PPU.

Characteristics of the Studies

Overall, 615 patients across the eight RCTs were randomized. Only five of the eight trials reported the number of patients that were assessed and suspected to have a PPU.[59,61–63,66] Within these five studies, 596 were suspected of PPU and 529 (88.76%) were included for randomization. The data presented in the eight

trials collectively span 16 years, from August 1992[59] to June 2014.[64] Four single-center trials were conducted in China[59–62] along with one single-center study each in Italy,[63] Egypt,[64] and India,[65] respectively. Only one multicenter trial was included, and this was performed in the Netherlands.[66] Ge et al.[62] was the only trial that was listed on an official registry, the Chinese Clinical Trial Registry; however, they also disclosed an academic grant. Other disclosures included Bertleff et al.[66] who declared that they received an industry sponsorship (Supplemental Digital Content 3, http://links.lww.com/TA/B142).

Diagnosis of Perforation and Inclusion of Patients in RCTs

In all trials, the enrolment criteria were the clinical diagnosis and/or suspicion of PPU. Two studies had an additional radiological diagnostic criteria,[63,64] but all trials' inclusion criteria included a PPU confirmed by exploration. The exclusion criteria varied considerably among the trials. The most frequent criteria were poor general condition, gastric outlet obstruction, bleeding ulcer, and previous upper abdominal surgery (Supplemental Digital Content 4, http://links.lww.com/TA/B143).

Patients' sex, age, shock, duration of symptoms, American Society of Anaesthesiologists III and IV, and gastric or duodenal location of peptic ulcer and perforation were not significantly of different size between the laparoscopic repair and open repair groups in all trials (Supplemental Digital Content 5, http://links.lww.com/TA/B144). However, there was significant heterogeneity perforation size of the gastric or duodenal location of peptic ulcer between each trial (Supplemental Digital Content 6, http://links.lww.com/TA/B145). Only a few studies reported the scoring systems used to grade the severity of PPUs: Boey score,[61,62,64] Acute Physiologic Assessment and Chronic Health Evaluation score,[59,63] and Mannheim Peritonitis Index[63,66] (Supplemental Digital Content 7, http://links.lww.com/TA/B146).

Surgeons' Skill and Learning Curve

The skill level of surgeons enrolled in the trial was reported only from Lau[59] as "previous experience in this operation, laparoscopic cholecystectomy, and laparoscopic appendicectomy, and …training course including surgery in animals and simulators. Surgeons with limited experience of the operation were assisted by a more experienced colleague" (Supplemental Digital Content 8, http://links.lww.com/TA/B147).

Type of Treatment

Limited data were available describing the type of toilet and lavage. The laparoscopic repair of PPU was also performed with different techniques (Supplemental Digital Content 8, http://links.lww.com/TA/B147).

Bias Assessment in Studies

All trials were with a high risk of bias. For details on the risk of bias of each trial, see Characteristics of Included Studies (Supplemental Digital Content 3, http://links.lww.com/TA/B142). For an overview of the review authors' judgments about each risk of bias item for individual studies and across all studies, see Supplemental Digital Contents 9 and 10 (http://links.lww.com/TA/B148 and http://links.lww.com/TA/B149).

Primary Outcomes

Only overall postoperative mortality was marginally improved in laparoscopic group (rate of postoperative mortality: 1.6% in laparoscopic repair vs 4.2% open repair) (Fig. 1). Open repair seemed to have better clinical outcomes compared to laparoscopic repair; however, these differences did not reach statistical significance between the two groups—overall reoperations rate, 1.83% in open repair vs 4.21% laparoscopic repair; rate of overall leaks of the suture repair, 1.7% in open repair versus 3.7% in laparoscopic repair; intra-abdominal abscess, 3.3% in open repair versus 4.4% in laparoscopic repair; reoperation for abdominal abscess, 1.2% in open repair versus 1.2% in laparoscopic repair (Table 2; Figs. 2–4).

Secondary Outcomes

No significant differences were reported in most of the secondary clinical outcomes between the two groups; however, there was less postoperative pain in the first 24 hours (−2.08; 95% confidence interval, −2.79 to −1.37; I^2 = 69%) (Supplemental Digital Content 11, http://links.lww.com/TA/B150) and fewer wound infections after laparoscopic repair (5.34% in laparoscopic repair versus 15.55% in open repair RR 0.39, 95% confidence interval, 0.23–0.66; I^2 = 0%) (Supplemental Digital Content 12, http://links.lww.com/TA/B151). The other outcomes that marginally improved in the laparoscopic group were operation time, postoperative hospital stay, nasogastric aspiration time, time to return to oral diet, and rate of postoperative pneumonia. All studies reported the operation time; however, the definition used varied (Supplemental Digital Content 13, http://links.lww.com/TA/B152). The studies reported different evaluation on postoperative pain at different time-point; for this reason, it was not possible to perform the analysis for this outcome (Supplemental Digital Content 14, http://links.lww.com/TA/B153). The analgesia treatment protocol varied considerably, and only three trials[62,64,66] used the same protocol, therefore preventing meaningful analysis of this outcome (Supplemental Digital Content 15,

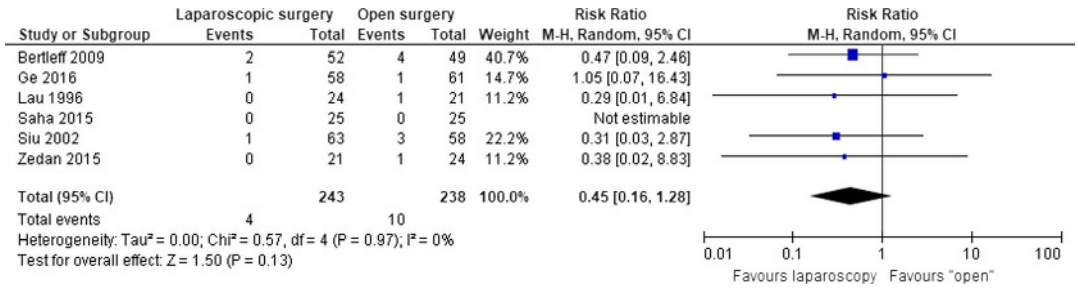

Figure 1. Overall postoperative mortality rate.

TABLE 2. 'Summary of Findings' Tables (SOFT)

Certainty Assessment							No. of Patients		Effect		
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Laparoscopic Intervention**	**Open Repair**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**
Postoperative mortality											
6	Randomized trials	Not serious*	Not serious	Not serious	Very serious**	None	4/243 (1.6%)	10/238 (4.2%)	RR 0.45 (0.16 to 1.28)	23 fewer per 1.000 (from 12 more to 35 fewer)	⊕⊕○○ Low
Overall reoperations											
4	Randomized trials	Not serious†	Not serious	Not serious	Very serious**	None	7/166 (4.2%)	3/164 (1.8%)	RR, 1.87 (0.49–7.11)	16 more per 1.000 (from 9 fewer to 112 more)	⊕⊕○○ Low
Overall leaks of suture repair											
6	Randomized trials	Serious‡	Not serious	Not serious	Very serious**	None	9/243 (3.7%)	4/238 (1.6%)	RR, 1.76 (0.58–5.34)	14 more per 1.000 (from 8 fewer to 82 more)	⊕○○○ Very low
Reoperation for leak											
4	Randomized trials	Not serious†	Not serious	Not serious	Very serious**	None	3/166 (1.8%)	2/164 (1.2%)	RR 1.28 (0.28 to 5.85)	**3 more per 1.000** (from 9 fewer to 59 more)	⊕⊕○○ LOW
Intra abdominal abscess											
6	Randomized trials	Serious§	Not serious	Not serious	Very serious**	None	12/275 (4.4%)	9/271 (3.3%)	RR 1.50 (0.43 to 5.23)	**17 more per 1.000** (from 19 fewer to 140 more)	⊕○○○ VERY LOW
Reoperation for abdominal abscess											
4	Randomized trials	Not serious†	Not serious	Not serious	Very serious**	None	2/166 (1.2%)	2/164 (1.2%)	RR 0.99 (0.15 to 6.48)	**0 fewer per 1.000** (from 10 fewer to 67 more)	⊕⊕○○ LOW

*We did not downgrade for risk of bias because only two of five had unclear allocation concealment; and despite that all the trials might be exposed to detection bias, we considered the outcome objective.
**We downgraded by two levels because of very serious concern of imprecision: too few outcomes and large confidence intervals.
†We did not downgrade for risk of bias because only one of four had unclear allocation concealment; and despite that all the trials might be exposed to detection bias, we considered the outcome objective.
‡The outcome of interest was considered objective. Hence, we downgraded the risk of bias by one level because of detection bias across all the trials. No concern was detected with regard to selection bias.
§We downgraded by one level because of serious concern of risk of bias (three of six reported unclear allocation concealment; all the trials exposed to detection bias).
CI, confidence interval; RR, risk ratio.

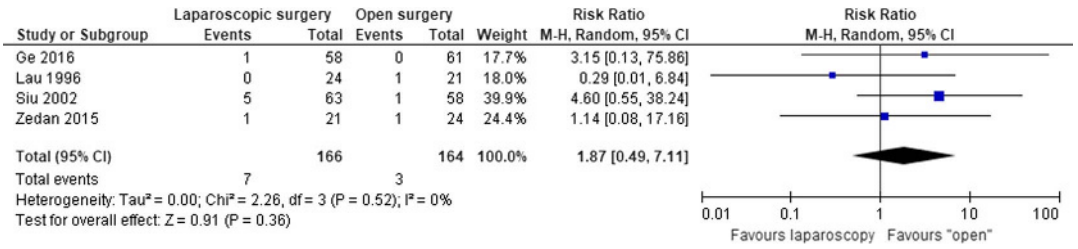

Figure 2. Overall reoperations rate.

http://links.lww.com/TA/B154). Four studies reported data about prolonged postoperative ileus.[59,61,62,66] However, only Lau described the definition of prolonged postoperative ileus used; therefore, it was not possible to perform a pooled analysis for this outcome.

DISCUSSION

This meta-analysis of eight RCTs comparing laparoscopic to open surgery for patients with PPU reports less early postoperative pain and fewer wound infections in favor of laparoscopy. Overall postoperative mortality rates were 4.2% in open repair versus 1.6% in laparoscopic repair; reoperations rates were 1.83% in open repair versus 4.21% laparoscopic repair; rates of overall leaks of the suture repair were 1.7% in open repair versus 3.7% in laparoscopic repair; intra-abdominal abscess rates were 3.3% in open repair versus 4.4% in laparoscopic repair; and reoperation rates for abdominal abscess were 1.2% in open repair versus 1.2% in laparoscopic repair.

In the other primary and secondary outcomes investigated, there was no significant difference between laparoscopic and open access. This equivalence of clinical outcomes is an important finding and parallels the results of previous comparisons of open versus laparoscopic repairs, which found that they are equally efficacious. Notably, the trials included have been reported over a considerable time span during which several changes have occurred in most health care systems, not at least a more widespread use of laparoscopy among most general surgeons.

Further six systematic reviews and meta-analysis have been reported previously on this topic; the quantity and type of studies included in these six reviews are extremely heterogeneous, ranging from 3 to 29 observational studies and from two to six RCTs[67–72] (Supplemental Digital Content 16a-c, http://links.lww.com/TA/B155). The patient populations in these six reviews ranged from 289[71] to 5,268.[68] In contrast, our systematic review and meta-analysis included only RCTs, with the highest number to date (eight RCTs and 615 participants), thus providing more updated and robust data. The "risk of bias" analysis shows reliable results, except for the blinding assessment, which is a known technical difficulty inherent to surgical studies and particularly emergency general surgery.[73,74] In contrast to the current meta-analysis, some of the previous systematic reviews reported significant advantages for laparoscopic repair in postoperative mortality,[68,71] overall postoperative complications,[68] operative time,[68] nasogastric tube duration,[67] and time to resume diet.[68] This may be due to inclusion of different subsets of studies, including observational and retrospective designs, which may introduce a bias in selection of patients. By including only RCTs in the current meta-analysis, we believe that the risk of bias is reduced, compared to previous studies.

Laparoscopic PPU repair also has an economic advantage by reducing postoperative hospital stay; however, this is difficult to evaluate in a meta-analysis due to variations in each country's health systems.[24]

The main cause for reoperation following surgical repair is suture-site leak.[64,74] One explanation proposed has been the difficulty in laparoscopic knot tying; however, it has been shown that improvements in surgical skill can improve this outcome.[68,75]

Arguably, there seems to be equipoise between the two approaches, as neither clear benefit nor clear harm could be derived from either procedure. Previous reviews have remarked on the paucity in clinical trials for laparoscopic repair in PPU, which prevent a definite conclusion on its role. Along with this, the suspected increase in leaks and reoperations has resulted in the downgrading/absence of the recommendation for laparoscopic approach in PPU treatment guidelines. Considering the results of this review, these reservations seem no longer relevant. The lack of significance on major outcomes in this review of eight RCTs suggests that a laparoscopic approach is equivalent to open repair. Given the equivalence in primary outcomes and the advantages for laparoscopy in postoperative pain and wound

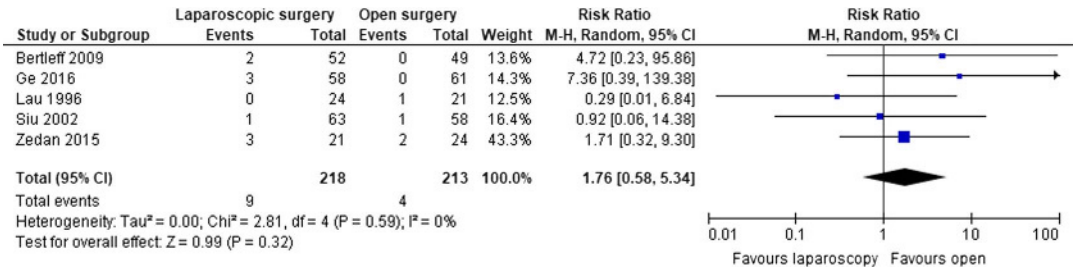

Figure 3. Overall leaks of the suture repair.

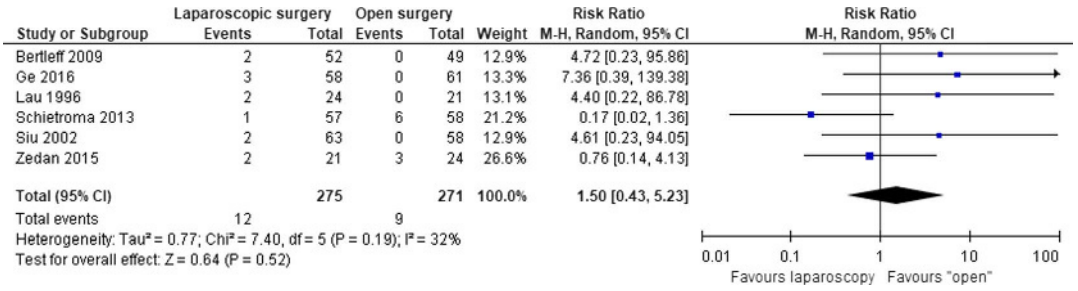

Figure 4. Intra-abdominal abscess rate.

infection, a minimally invasive approach, where logistically and situationally appropriate, is justified.

The limited number of clinical trials prevents a definitive conclusion. Previously published recommendations for a laparoscopic approach in gastroduodenal perforation, has been downgraded by recent guidelines, based on the suspected increase in leaks and reoperations for laparoscopy. These suspicions, however, have been unsubstantiated by our data. In fact, the lack of significance on these outcomes in published RCTs suggests that a laparoscopic approach is comparable to open repair with regard to major morbidity and safety issues. However, these outcomes were neither the primary outcomes in the studies, nor were their definitions standardized, and consequently reporting may have been different between studies. However, we believe the results to be fairly robust and consistent based on the rates reported in the studies. The advantages with regard to postoperative pain and wound infection justify then a minimally invasive approach as the treatment of choice.

Further research should include both registry-based data, longitudinal observations, but also RCTs with updated methodology and appropriately powered study sizes. Additionally, the skills of the surgeons operating laparoscopically should also be assessed, along with data for cost and resource use.

CONCLUSIONS

Current best evidence suggests there is no difference in postoperative mortality between laparoscopic and open repair of PPU. Modest benefits of a faster recovery and shorter stay may suggest laparoscopy should be entertained when available as a treatment choice for surgeon and patient. Outcomes in subpopulations such as the elderly or in patients with severely compromised vital functions or in septic shock needs further investigation. Future research in patients with PPU should include patient-reported outcome assessments to better understand patients' perspectives, as well as evaluation of the cost-effectiveness of the two modalities. Long-term outcomes beyond one year and standardized outcome measures for 30- or 90-day mortality should be used for better comparison between studies and centres.

AUTHORSHIP

RC and SDS conceptualized and designed the study.
RC, KS, and SDS acquired the data.
RC, KS, IA, and SDS analyzed and interpreted the data.
RC, KS, and SDS drafted the manuscript.
RC, KS, SDS, ER, AA, MZ, IA, NV, and MC critically revised the manuscript.
RC, KS, SDS, ER, AA, MZ, IA, NV, and MC gave final approval of the manuscript.

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DISCLOSURE

The authors declare no conflicts of interest.

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