Effectiveness of digestive endoscopy and surgery in the treatment of necrotizing pancreatitis: a meta-analysis and systematic review

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Background: Digestive endoscopy and surgery are the primary invasive methods for the clinical treatment of necrotizing pancreatitis. However, there are relatively few studies evaluating the effectiveness and safety of these two methods.

Methods: Randomized controlled trials (RCTs) on endoscopic and surgical treatment of necrotizing pancreatitis published from January 2000 to December 2020 were searched in the PubMed, Medline, Embase, China Biology Medicine Disc (CBM), and WanFang databases. The *Cochrane System Review Manual* was adopted to evaluate the quality of the included literature, and Review Manager 5.3 was used for data analysis.

Results: Ten articles were included in this meta-analysis, involving a total of 401 patients, including 188 in the endoscopy group and 213 in the surgery group. Meta-analysis results revealed that the clinical remission rate (CRR) [odds ratio (OR) =1.30, 95% confidence interval (CI): 0.58–2.92, P=0.52], new organ failure rate (OFR) (OR =0.53, 95% CI: 0.26–1.09, P=0.08), abdominal bleeding rate (ABR) (OR =0.62, 95% CI: 0.33–1.15, P=0.13), and intensive care unit (ICU) stay time (IST) [mean deviation (MD) =–7.33, 95% CI: –16.76 to 2.11, P=0.13] were not significantly different between the endoscopy and surgery groups. In the endoscopy group, the mortality rate (OR =0.56, 95% CI: 0.31–1.02, P=0.05), intestinal fistula rate (IFR) or gastrointestinal perforation rate (GPR) (OR =0.50, 95% CI: 0.26–0.99, P=0.05), and pancreatic fistula rate (PFR) (OR =0.09, 95% CI: 0.04–0.23, P<0.00001) were markedly lower compared to the surgery group.

Discussion: There was no obvious difference in the clinical efficacy of endoscopic and surgical treatment of necrotizing pancreatitis. However, endoscopy can greatly reduce the incidence of postoperative death and major complications in patients.

Keywords: Digestive endoscopy; surgery; necrotizing pancreatitis; incidence of postoperative complications; meta-analysis

Introduction

Acute pancreatitis is a clinically critical illness (1). According to the degree of disease, it can be divided into mild, moderate, and severe acute pancreatitis, and can be classified into interstitial edema pancreatitis and necrotizing pancreatitis according to the imaging characteristics (2). Acute necrotizing pancreatitis (ANP) accounts for approximately 20% of acute pancreatitis cases (3). In clinical practice, approximately 30% of patients with necrotizing pancreatitis develop infectious pancreatic necrosis, thus invasive intervention is required (4). Drug treatment of necrotizing pancreatitis can be divided into the following: one is to prevent shock and improve microcirculation, that is, to actively supplement fluid, electrolytes and calories to maintain the stability of circulation and balance of water and electrolyte. The second is to take the method of inhibiting pancreatic secretion, and for severe acute pancreatitis, use somatostatin or the long-acting analog octreotide. When the necrotic tissue has secondary infection, that is, infected pancreatic necrosis (IPN), it needs to use digestive endoscopy for intervention. The traditional invasive intervention treatment method is the application of open surgery to remove necrotic tissue. In recent years, minimally-invasive surgical treatment techniques, percutaneous catheter drainage (PCD), laparoscopic cystogastrostomy (LC), and video-assisted retroperitoneal debridement (VARD) have become the first choice for surgery (5-7). With the gradual development of endoscopic technology, endoscopic transgastric necrosectomy (ETN) and endoscopic transgastric drainage (ETD) technologies have also been promoted and applied clinically, realizing excellent therapeutic effects (8,9). In the past 10 years, in the invasive treatment of necrotizing pancreatitis, the traditional open debridement has been gradually replaced by minimally invasive surgery. Minimally invasive surgery can significantly reduce mortality and postoperative complications. Therefore, minimally invasive digestive endoscopic treatment is a common method for the treatment of necrotizing pancreatitis.

Surgery and digestive endoscopy treatments can both utilize the ascending steps method. Essentially, this involves further endoscopic debridement being applied when a patient's surgery proves ineffective (10). However, there are relatively few studies on the effectiveness and safety of digestive endoscopy and surgery in the treatment of necrotizing pancreatitis, with most of these being retrospective analyses. In order to provide more effective evidence-based medical evidence for the clinical treatment of necrotizing pancreatitis, clinical studies on endoscopic and surgical treatment of necrotizing pancreatitis were searched for inclusion in this meta-analysis, in order to compare the effectiveness and safety of these two methods. Recently, there are not many studies exploring the advantages and disadvantages of endoscopic treatment of necrotizing pancreatitis. Most of them are retrospective cohort studies, and there are confounding factors that lead to low reliability of the results. So far, there are 3 randomized controlled trial (RCT) endoscopic treatments for the efficacy and safety of necrotizing pancreatitis, but the number of cases in a single study is limited, the endoscopic or surgical treatment methods used in each study are not the same, and the results of the study are also different. In addition, RCT only includes IPN patients, and do not consider symptomatic aseptic necrosis, and the scope of application of the conclusion is limited. Therefore, this research combined all the published clinical research results and included a high-quality cohort study to systematically evaluate the pros and cons of endoscopic and surgical treatment of necrotizing pancreatitis, thus providing evidence for guiding the choice of invasive treatment for necrotizing pancreatitis.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/gs-21-516).

Methods

Inclusion and exclusion criteria

The inclusion criteria were defined as follows: (I) studies whose subjects were diagnosed with necrotizing pancreatitis; (II) articles involving intervention treatment measures for patients, including digestive endoscopy and surgery treatment groups [digestive endoscopy can be divided into: ETD and ETN, and surgical treatment can be divided into PCD, LC, VARD, and open necrosectomy (ON)]; (III) studies involving ≥3 patients; (IV) no limitation on the research type; and (V) no limitation on the language.

The exclusion criteria were defined as follows: (I) repeatedly published articles; (II) studies with unclear patient diagnosis criteria; (III) articles without clear research analysis methods; (IV) articles without clear main outcome variables; (V) studies whose original research data could not be obtained; and (VI) studies involving patients who had previously received other invasive surgery.

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Retrieval of related articles

Articles published between January 2000 and December 2020 in the PubMed, Medline, Embase, China Biology Medicine Disc (CBM), and WanFang databases were retrieved. The retrieval strategy and principles were as follows: (I) the subject terms and free words included "necrotizing pancreatitis", "endoscopy", and "surgery"; (II) the above phrases were optimally combined and searched, so as to obtain the most relevant documents; (III) the search term could be found in the title, keywords, or abstract; and (IV) part of the references of the articles could be traced back, so that the full text could be manually searched and included.

Article screening and data extraction

Two experts were invited to read the titles and abstracts of the articles to screen and extract the required data. Any disagreements between the experts were resolved through discussion, and arbitration by a third expert (if needed).

The extracted data included the following: first author, publication year, research method, sample size, surgical treatment method, complication rate, mortality rate, clinical sustained-release rate, hospital stay, and number of operations. The researcher was required to verify the data for subsequent systematic analysis.

Risk of bias and quality assessment of articles

The Cochrane randomized trial risk assessment tool was applied to evaluate the quality of the included articles. The evaluation included the following six items: (I) the random sequence generation method; (II) whether there was bias in the allocation process; (III) whether the blind research was adopted; (IV) whether the results data was complete; (V) whether there was selective reporting of the research results; and (VI) other deviations.

Sensitivity analysis

Sensitivity analysis was used to evaluate whether the results of meta-analysis were stable and reliable. Some controversial and low-quality literatures were excluded. Different statistical methods/effect models were undertaken to analyze the same set of data, and observe the changes in the results of meta-analysis. If the sensitivity analysis did not substantially change the results, it indicated that the results were reliable; on the contrary, it indicated that

research should be very cautious in interpreting the results and drawing conclusions.

Statistical analysis

Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was adopted for statistical analysis. Binary variables included the odds ratio (OR) or relative risk (RR), and the 95% confidence interval (CI) was used for each effect size. $P<0.05$ was considered to indicate a statistically significant difference. The I^2 statistic was utilized to quantitatively evaluate the heterogeneity of the articles. If $I^2<50\%$, there was no obvious heterogeneity, and the fixed effects model (FEM) could be used for analysis. However, if $I^2>50\%$, the articles showed obvious heterogeneity, and the random effects model (REM) was adopted for analysis. A funnel chart was drawn to analyze the publication bias of the included articles. In addition, the symmetry of the funnel chart and the concentration of the sample towards the midline were evaluated.

Results

Article retrieval and characteristics analysis

Based on the Cochrane system search strategy, a total of 1,618 articles were retrieved. After the titles, abstracts, and full texts were read carefully, repeatedly published articles and those failing to meet the inclusion criteria were excluded. Finally, 10 articles, involving a total of 401 patients, were included in this study (11-20), including 188 patients in the endoscopy group and 213 patients in the surgery group. The article retrieval process is shown in *Figure 1*, and the basic information of the included research articles is shown in *Table 1*. For the included studies, the treatment effects of the two methods were compared according to the main methods used, and the methodological quality of each research in the intervention results was medium or above, at the same level of literature quality, and there was no methodological heterogeneity. Therefore, this systematic review did not conduct sensitivity analysis.

Quality assessment of included articles

The bias risk assessment tool recommended by the *Cochrane System Review Manual* was applied to evaluate the quality of the 10 articles included in this study, and
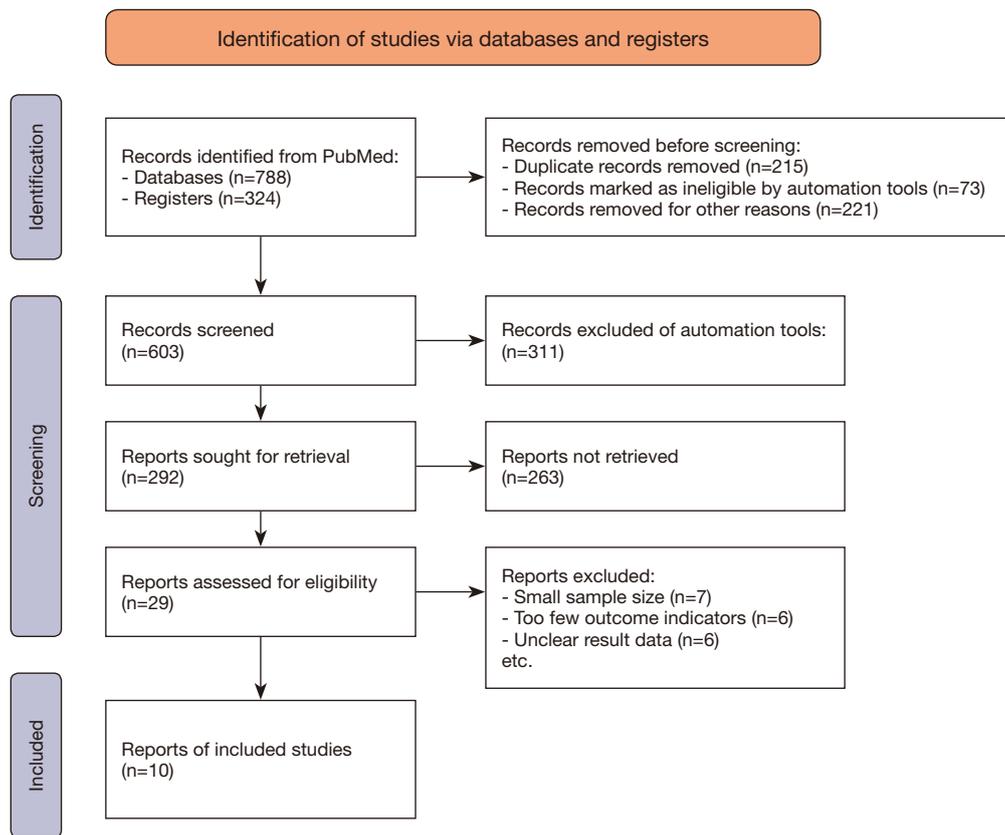
Figure 1 Article retrieval process.

Table 1 The basic characteristics of the included articles

First author	Publication year	Number of cases (E/S)	Endoscopy group	Surgery group
Bakker	2012	10/10	ETN	ON + VARD
Bang	2019	34/32	ETD + ETN	LC + VARD
Bausch	2012	18/44	ETN	ON + VARD
He	2017	11/13	ETD + ETN	PCD + ON
Khreiss	2015	20/20	ETD + ETN	LC
Kumar	2014	12/12	ETN	LC + ON
Mui	2005	9/4	ETD + ETN	ON
Tan	2014	11/21	ETD + ETN	ON
van Brunschot	2018	51/47	ETN	PCD + VARD
Woo	2017	12/10	ETD + ETN	PCD + ON

E/S, endoscopy group/surgery group; ETN, endoscopic transgastric necrosectomy; ETD, endoscopic transgastric drainage; ON, open necrosectomy; VARD, video-assisted retroperitoneal debridement; LC, laparoscopic cystogastrostomy; PCD, percutaneous catheter drainage.
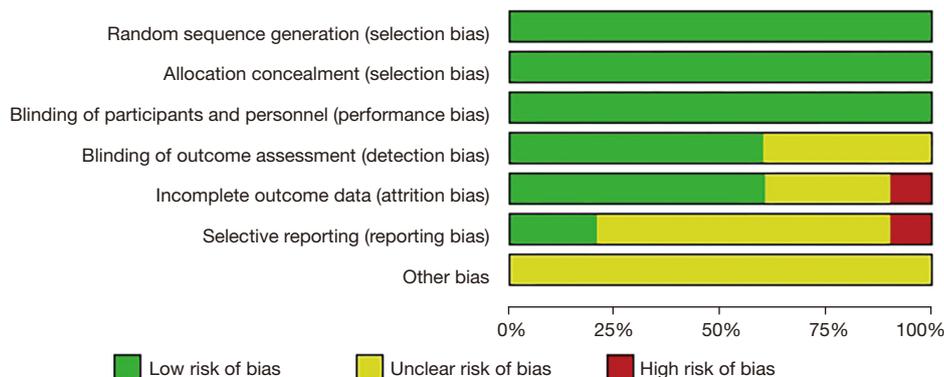
Figure 2 Risk of bias assessment of the included articles.
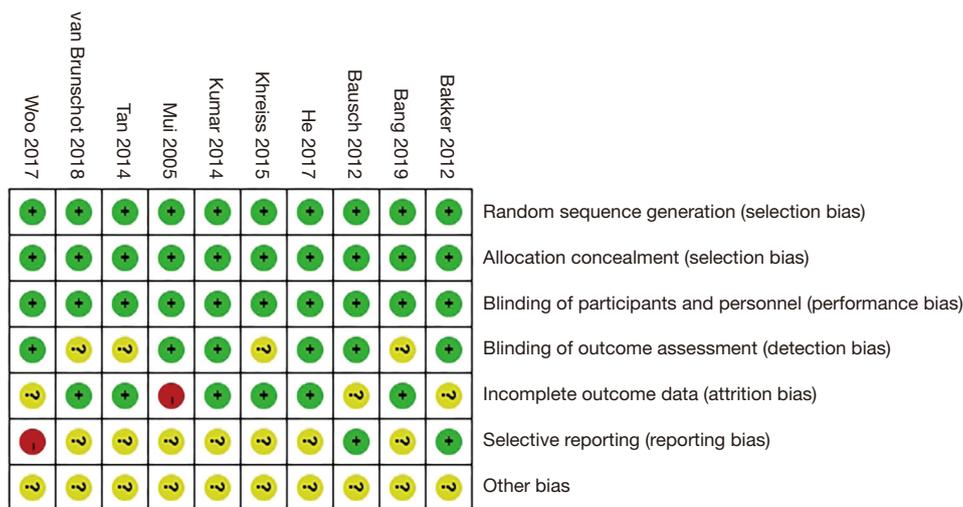
Figure 3 Risk bias evaluation results of included articles.

the results are shown in *Figures 2,3*. The figures revealed that there was no random sequence generation (selection bias), allocation concealment (selection bias), and blinding of outcome assessment (detection bias) in six articles. Mui *et al.* (17) exhibited a high risk due to incomplete outcome data (attrition bias), while Woo *et al.* (20) showed a high risk due to selective reporting (reporting bias). The other studies were either low risk or unknown risk.

Meta-analysis results

Clinical remission rate (CRR)

Differences in the CRR of patients in the endoscopy and surgery groups were compared and analyzed, (as shown in *Figure 4*). Based on the I^2 statistic, it was observed that there

was no obvious heterogeneity in the CRR of patients in the endoscopy and surgery groups ($I^2=0\%$, P=0.99), so the FEM was used for statistical analysis thereafter. The results demonstrated that the meta-analysis effect value of the CRR after treatment in the endoscopy and surgery groups patients was OR (95% CI): 1.30 (0.58–2.92), and the statistical test structure was Z=0.65 (P=0.52). In summary, the difference in CRR between endoscopy and surgery group patients after treatment was not statistically significant (P>0.05).

Mortality rate

Differences in the mortality rate of patients in the endoscopy and surgery groups after treatment was analyzed and compared (as shown in *Figure 5*). Based on the I^2 statistic, it was observed that there was no obvious
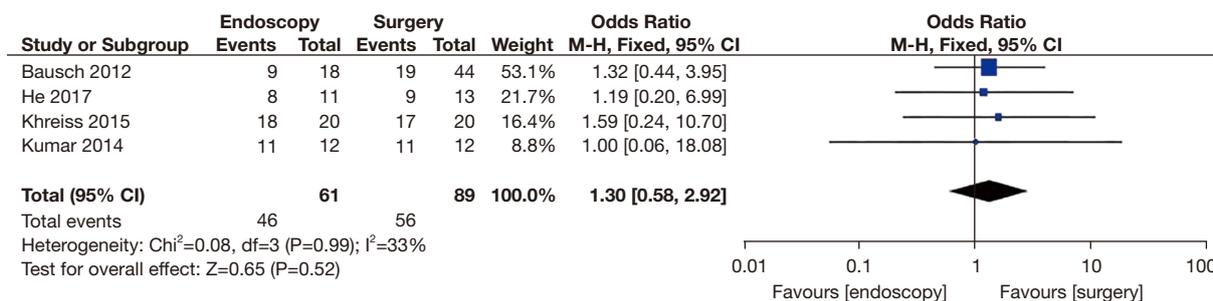
Figure 4 Forest map for CRR comparison of patients after treatment. CRR, clinical remission rate; CI, confidence interval.
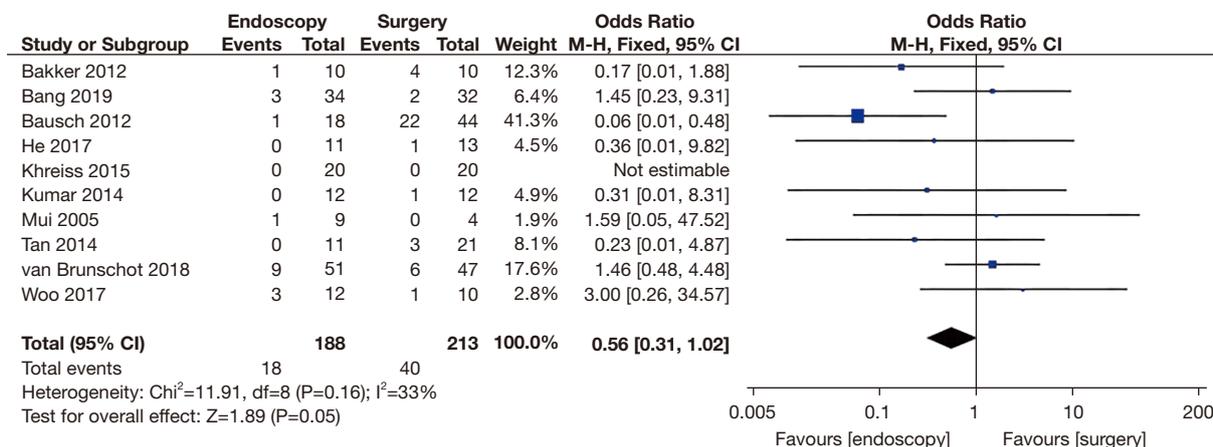
Figure 5 Forest map for mortality rate comparison of patients after treatment. CI, confidence interval.

heterogeneity in the mortality rate of patients in the two groups after treatment (I^2=33%, P=0.16), so the FEM was used for statistical analysis thereafter. The results revealed that the meta-analysis effect value of the mortality rate of patients in both groups after treatment was OR (95% CI): 0.56 (0.31–1.02), and the statistical test structure was Z=1.89 (P=0.05). In summary, the mortality rate of patients in the endoscopy group after treatment was clearly lower than that in the surgery group, and the difference was statistically significant (P<0.05).

Postoperative organ failure rate (OFR)

Differences in the postoperative OFR between patients in the endoscopy and surgery groups were compared and analyzed (as shown in *Figure 6*). Based on the I^2 statistic, it was observed that there was no significant heterogeneity (I^2=0%, P=0.53) in the postoperative OFR for patients in the endoscopy and surgery groups, so the FEM was used for statistical analysis thereafter. The results suggested that

the meta-analysis effect value of postoperative OFR was OR (95% CI): 0.53 (0.26–1.09), and the statistical test structure was Z=1.74 (P=0.08). In summary, the difference in postoperative OFR of patients in the endoscopy and surgery groups was not statistically significant (P>0.05).

Postoperative abdominal bleeding rate (ABR)

Differences in the postoperative ABR between patients in the endoscopy and surgery groups were compared and analyzed (as shown in *Figure 7*). Based on the I^2 statistic, it was observed that there was no significant heterogeneity (I^2=0%, P=0.90) in the postoperative ABR of patients in the endoscopy and surgery groups, so the FEM was used for statistical analysis thereafter. The results suggested that the meta-analysis effect value of postoperative ABR was OR (95% CI): 0.62 (0.33–1.15), and the statistical test structure was Z=1.51 (P=0.13). In summary, the difference in postoperative ABR of patients in the endoscopy and surgery groups was not statistically significant (P>0.05).
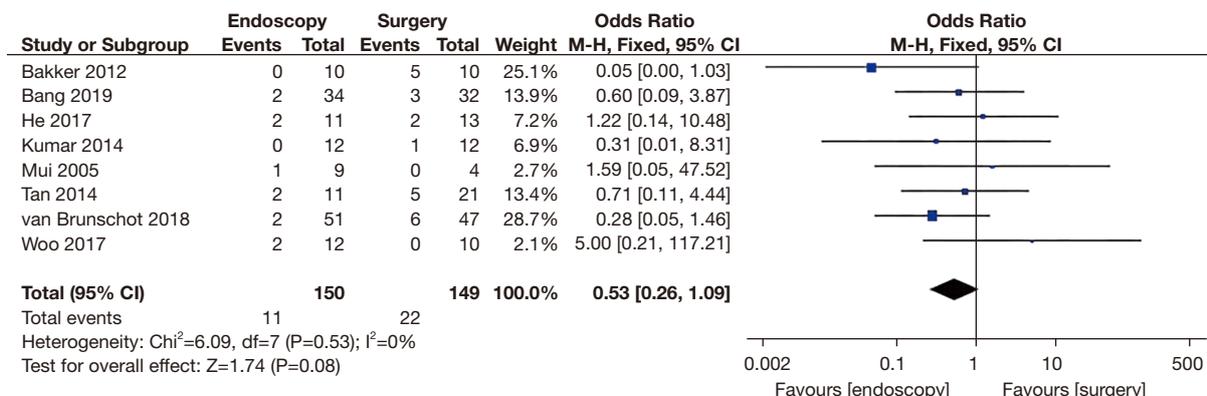
Figure 6 Forest map for postoperative OFR comparison of patients after treatment. OFR, organ failure rate; CI, confidence interval.
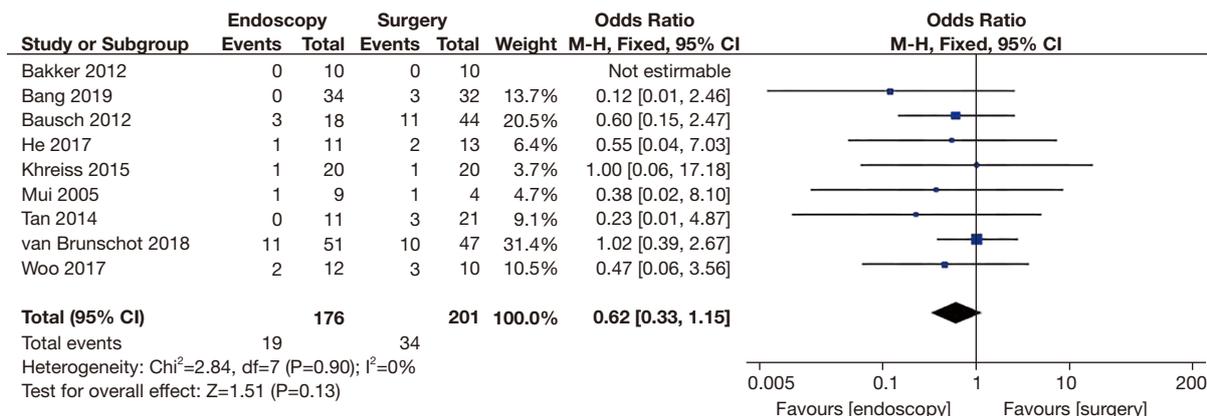
Figure 7 Forest map for postoperative ABR comparison of patients after treatment. ABR, abdominal bleeding rate; CI, confidence interval.

Postoperative intestinal fistula rate (IFR) or gastrointestinal perforation rate (GPR)

Differences in the postoperative IFR or GPR between patients in the endoscopy and surgery groups were compared and analyzed (as shown in *Figure 8*). Based on the I^2 statistic, it was observed that there was no significant heterogeneity (I^2=0%, P=0.43) in the postoperative IFR or GPR of patients in the endoscopy and surgery groups, so the FEM was used for statistical analysis thereafter. The results suggested that the meta-analysis effect value of postoperative IFR or GPR was OR (95% CI): 0.50 (0.26–0.99), and the statistical test structure was Z=1.99 (P=0.05). In summary, the differences in the postoperative IFR or GPR of patients in the endoscopy and surgery groups were not statistically significant (P>0.05).

Postoperative pancreatic fistula rate (PFR)

Differences in the postoperative PFR between patients

in the endoscopy and surgery groups were compared and analyzed (as shown in *Figure 9*). Based on the I^2 statistic, it was observed that there was no significant heterogeneity (I^2=0%, P=0.99) in the postoperative PFR of patients in the endoscopy and surgery groups, so the FEM was used for statistical analysis thereafter. The results suggested that the meta-analysis effect value of postoperative PFR was OR (95% CI): 0.09 (0.04–0.23), and the statistical test structure was Z=5.16 (P<0.00001). In summary, the difference in postoperative PFR of patients in the endoscopy and surgery groups was statistically significant (P<0.05).

Postoperative intensive care unit (ICU) stay time (IST)

Differences in the postoperative IST between patients in the endoscopy and surgery groups were compared and analyzed (as shown in *Figure 10*). Based on the I^2 statistic, it was observed that there was significant heterogeneity (I^2=78%, P=0.010) in the postoperative IST of patients in
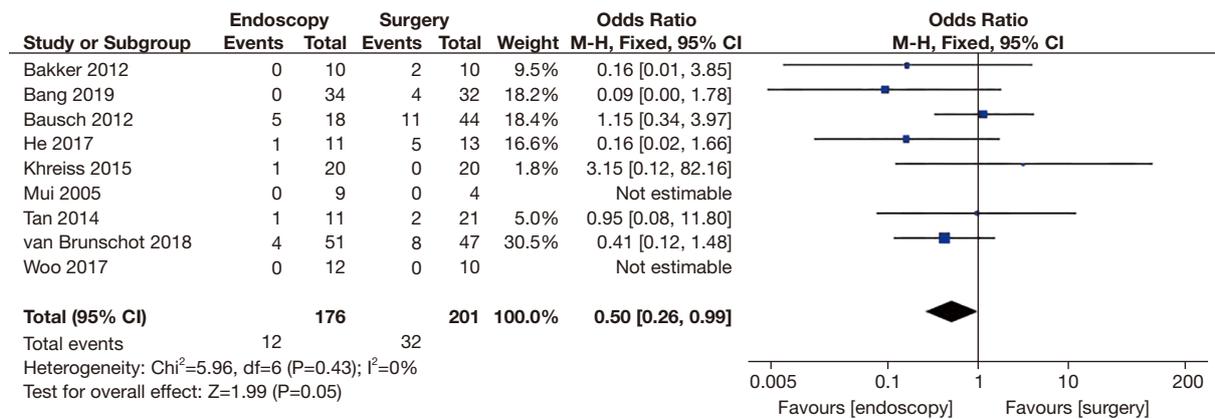
Figure 8 Forest map for postoperative IFR or GPR comparison of patients after treatment. IFR, intestinal fistula rate; GPR, gastrointestinal perforation rate; CI, confidence interval.
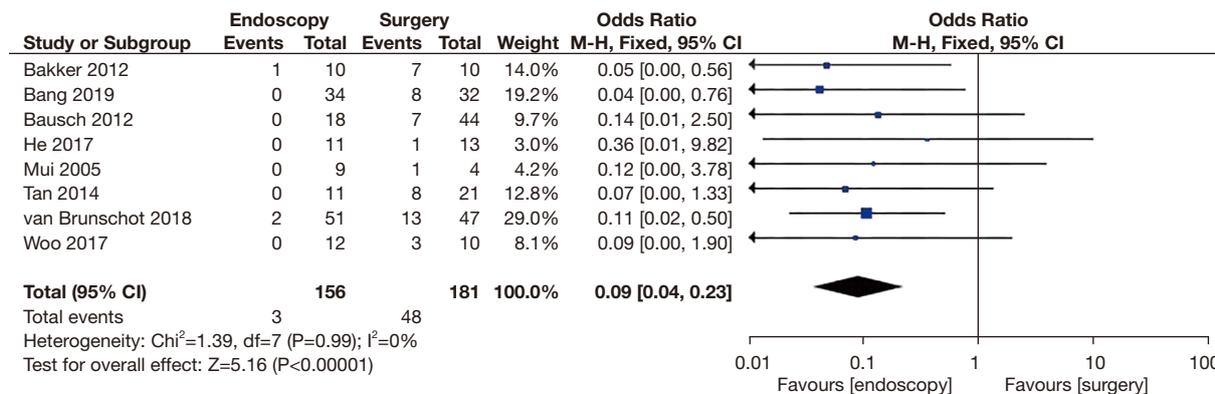
Figure 9 Forest map for postoperative PFR comparison of patients after treatment. PFR, pancreatic fistula rate; CI, confidence interval.
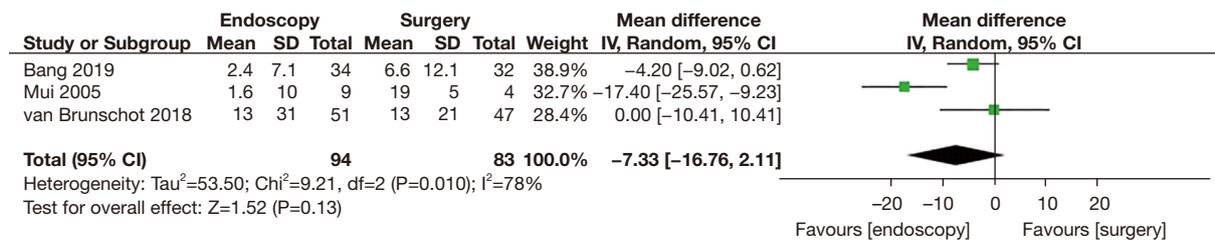
Figure 10 Forest map for postoperative IST comparison of patients after treatment. IST, ICU stay time; ICU, intensive care unit; CI, confidence interval.

the endoscopy group and surgery group, so the REM was used for statistical analysis thereafter. The results suggested that the meta-analysis effect value of postoperative IST was OR (95% CI): –7.33 (–16.76 to 2.11), and the statistical test structure was Z=1.52 (P=0.13). In summary, the difference

in postoperative IST of patients in the endoscopy and surgery groups was not statistically significant (P>0.05).

Publication bias analysis

Figures 11-13 illustrate the publication bias of indicators

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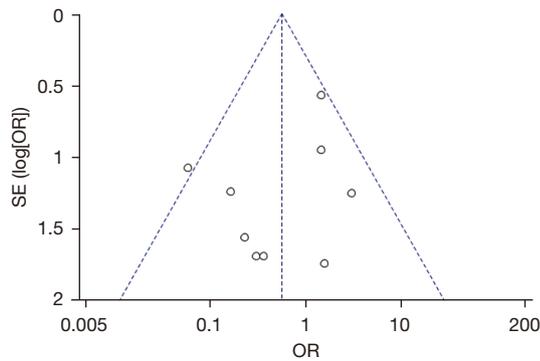
Figure 11 Funnel chart for the postoperative mortality rate of patients. SE, standard error; OR, odds ratio.
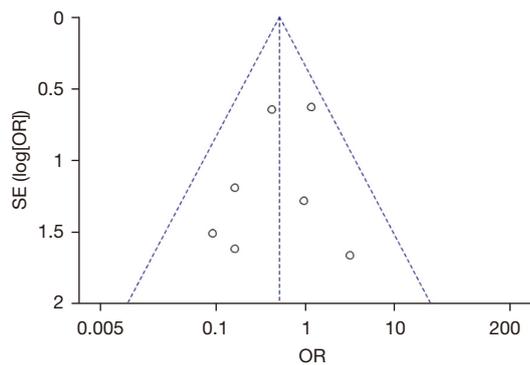
Figure 12 Funnel chart for the postoperative IFR or GPR of patients. IFR, intestinal fistula rate; GPR, gastrointestinal perforation rate; SE, standard error; OR, odds ratio.
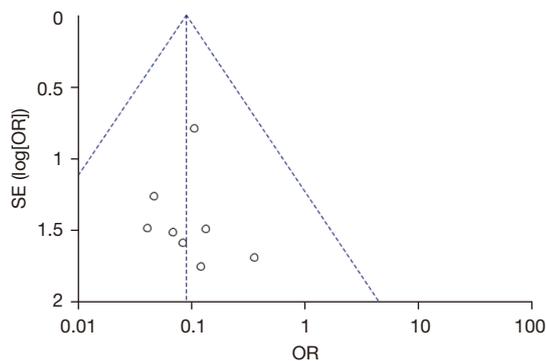
Figure 13 Funnel chart for the postoperative PFR of patients. PFR, pancreatic fistula rate; SE, standard error; OR, odds ratio.

with statistically obvious differences for patients in the endoscopy and surgery groups. The funnel charts of mortality rate and IFR or GPR were more symmetrical, and the data was also more concentrated. The funnel chart for PFR was relatively offset and not symmetrical enough; however, all of the included articles fell into the chart and were close to the midline. This suggested that the publication bias of the included articles was low and met the requirements.

Discussion

Infectious necrosis and symptomatic aseptic necrosis in acute pancreatitis are the main complications after invasive treatment (21). Necrotizing pancreatitis accounts for approximately 20% of acute pancreatitis cases, some of which are moderate acute pancreatitis or accompanied by transient organ failure, and the mortality rate is less than 5%. The remaining cases are accompanied by persistent organ failure, which can develop into severe acute pancreatitis, exhibiting accumulation of acute necrotic substances in the early stage, and the mortality rate can reach 10% (22). In recent years, a large number of studies have demonstrated that in the invasive treatment of necrotizing pancreatitis, minimally invasive surgery has gradually replaced traditional open debridement and shown lower postoperative complications and mortality (23,24). With the rapid development of endoscopic technology, endoscopic drainage, and debridement treatment have also been widely used in clinical practice, achieving excellent therapeutic effects (25). Compared with surgery, endoscopic treatment can significantly reduce the incidence of three complications in the composite outcome variable, including new organ failure, intestinal cutaneous fistula or perforation of the digestive tract, and pancreatic fistula. It shows that the safety of endoscopic treatment is higher than that of surgical treatment.

However, there are relatively few studies on the effectiveness and safety of endoscopic and surgery debridement in the treatment of necrotizing pancreatitis. This may be due to the relatively small clinical proportion of necrotizing acute pancreatitis (only approximately 20%), so the number of cases requiring debridement treatment is relatively small (approximately 4%) (26). In

addition, the risk of open surgery is high, so there are few clinical studies on the use of surgical open surgery alone (27). Endoscopic treatment is a newly-developed method, and the organizations that can utilize this technology for treatment are currently very limited, thus the clinical application data for this technology are still in the emerging stage (28).

Most of the current studies on the endoscopic and surgical treatment of necrotizing pancreatitis are retrospective analyses. Therefore, recent clinical studies on endoscopic and surgical treatment of necrotizing pancreatitis were retrieved in this study for meta-analysis and systematic review. The results showed that the postoperative mortality, intestinal cutaneous fistula, gastrointestinal perforation, and pancreatic fistula were significantly lower in patients who underwent endoscopic debridement treatment. Also, there was no significant difference in the CRR of patients after endoscopic or surgical treatment. These results suggested that endoscopic debridement can greatly reduce the incidence of postoperative complications in patients with necrotizing pancreatitis while ensuring adequate therapeutic effect.

Conclusions

In this study, a total of 10 related articles were included for meta-analysis of the effects of endoscopic and surgical debridement of necrotizing pancreatitis, in order to systematically evaluate the clinical effectiveness and safety of these treatments. The results revealed that endoscopic treatment can effectively reduce the mortality rate of postoperative patients, and can also reduce the probability of intestinal cutaneous fistula or gastrointestinal perforation and pancreatic fistula after surgery. At present, the application of endoscopic surgery has been relatively mature. During the operation, the endoscope can be used to locate the necrotic site, which can significantly improve the treatment efficiency and safety.

However, there were some limitations in this study that should be noted. Firstly, only existing articles were included in the systematic evaluation. The patients included in the articles did not receive one treatment method only. Therefore, a single rate analysis of the effect of endoscopic and surgical treatment of necrotizing pancreatitis is required in future research. Yet, the results of this study can provide a reference for the clinical application of endoscopic treatment of necrotizing pancreatitis.

Footnote

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(English Language Editor: A. Kassem)