Endoscopic Transgastric Versus Surgical Approach for Infected Necrotizing Pancreatitis: A Systematic Review and Meta-Analysis

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Abstract: Surgical approach (SA) is the standard treatment for infected necrotizing pancreatitis (INP) and endoscopic transgastric approach (ETA) is a promising alternative treatment. This systematic review and meta-analysis aimed to compare the effectiveness and safety of ETA versus SA in INP. Several databases were systematically searched for eligible studies that compared ETA with SA for INP. Predefined criteria were used for study selection. Three reviewers independently assessed the risk of bias. Primary outcomes included clinical resolution rate, short-term mortality, major complications, and hospital stay. Study-specific effect sizes and their 95% confidence interval (CI) were combined to calculate the pooled value using fixed-effects or random-effects model. Six studies were included with 295 patients. Major complication rate [odds ratio (OR), 0.13; 95% CI, 0.06-0.29], new-onset organ failure rate (OR, 0.26; 95% CI, 0.12-0.54), postoperative pancreatic fistula rate (OR, 0.09; 95% CI, 0.03-0.28), and incisional hernia rate (OR, 0.10; 95% CI, 0.01-0.85) were lower in the ETA group. There was a shorter hospital stay (mean difference, −17.72; 95% CI, −21.30 to −14.13) in the ETA group. No differences were found in clinical resolution, short-term mortality, postoperative bleeding, perforation of visceral organ, and endocrine or exocrine insufficiency. Compared with SA, ETA showed comparable effectiveness and safety for the treatment of INP based on current evidence.

Key Words: necrotizing pancreatitis, endoscopy, endoscopic transgastric, surgical approach, meta-analysis

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Acute pancreatitis is a common and potentially lethal disease with increasing incidence.[1] However, ~20% of patients develop necrotizing pancreatitis, which is associated with a mortality rate of 15%.[1–2] About 30% of patients with necrotizing pancreatitis develop infected necrosis and generally need an intervention during the disease course.[3–4] The traditional treatment of necrotizing pancreatitis with secondary infection of necrotic tissue was open necrosectomy to completely remove the infected necrotic tissue.[5–6] In the past decade, several minimally invasive surgical approaches (SAs) have emerged, which included percutaneous catheter drainage, laparoscopic necrosectomy, video-assisted retroperitoneal debridement, etc. However, all SAs were still associated with high rates of complications (15% to 95%) and death (11% to 39%).[7–13]

Recently, as a less invasive technique, the endoscopic transgastric approach (ETA) has been evolving, which involves drainage and direct retroperitoneal endoscopic necrosectomy through the gastric wall using endoscopic ultrasound guidance.[14] ETA is normally performed under conscious sedation without the need for general anesthesia and potentially reduces the inflammatory response and the risk of procedure-related complications such as multiple organ failure in already ill patients.[15] ETA can be performed in a step-up manner, starting with endoscopic transgastric drainage, only to be followed by endoscopic necrosectomy if drainage does not result in clinical improvement. A recent randomized trial[16] demonstrated that the endoscopic step-up approach was superior to the surgical step-up approach in reducing the incidence of pancreatic fistula and shortening the length of hospital stay. Meanwhile, 3 single-arm meta-analyses[17–19] analyzed the results of endoscopic necrosectomy in the management of pancreatic necrosis, which indicated that the pooled proportion of successful resolution of pancreatic necrosis was about 82% and the incidence of complications ranged from 21% to 36%. Until recently, there are no meta-analyses comparing the effectiveness and safety between ETA and SA as treatment for infected necrotizing pancreatitis (INP). Therefore, the aim of the present meta-analysis was to systematically review the published literature and evaluate the effectiveness and safety between ETA and SA in treating INP. Our results could serve as a reference for clinical practice.

MATERIALS AND METHODS

This meta-analysis has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement and Assessing the Methodological Quality of Systematic Reviews Guidelines.

Literature Search

Three authors (D.L., X.L., and J.D.) independently performed a literature search of the PubMed, Embase, Cochrane Library, and Web of Science for eligible studies that compared ETA with SA for INP. The search terms included the following: acute necrotizing pancreatitis, necrotizing pancreatitis, infected necrosis, walled-off necrosis, walled-off pancreatic necrosis, pancreatic necrosis, endoscopic, endoscopy, surgical, surgical necrosectomy, open necrosectomy, debridement, drainage, and step-up approach. To obtain additional studies on this topic, the reference lists of the included articles were also reviewed. The search was limited to papers published in English from January 1, 2000, to July 4, 2018.

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Inclusion and Exclusion Criteria

The following criteria should be met for a study to be included. (1) Patients: the individuals were diagnosed with INP and had an indication for invasive intervention. (2) Intervention and comparison: ETA consisted of endoscopic transgastric ultrasound-guided drainage, endoscopic necrosectomy, and endoscopic step-up approach that consisted of endoscopic drainage followed by endoscopic necrosectomy if required. On the contrary, SA consisted of percutaneous catheter drainage, minimally invasive retroperitoneal necrosectomy, open necrosectomy, and a surgical step-up approach that consisted of percutaneous drainage followed by video-assisted retroperitoneal necrosectomy if required. (3) Outcomes: the primary outcomes consisted of clinical resolution rate, short-term mortality (in-hospital mortality or mortality within 6 months), major postoperative complications (new-onset organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention except for the intentionally made perforation during endoscopic treatment and pancreatic fistula), fluid collection recurrence after successful drainage, and hospital stay. The secondary outcomes included new-onset organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention, pancreatic fistula, and endocrine or exocrine insufficiency. (4) Study design: randomized controlled trial (RCTs) and cohort studies were preferred. A study that meets the following condition should be excluded: studies that included patients who received previous invasive interventions for necrotizing pancreatitis. When a study was published with duplicated experimental data, the most recent publication was selected and previous articles were used to supplement necessary information in the new study.

Study Selection and Data Extraction

Three reviewers (D.L., X.L., and J.D.) independently read the full texts. The following data were extracted: first author, publication year, country, study design, interventions, sample size, clinical traits of patients, and outcomes. The authors were contacted via e-mail to obtain any missing information. For quantitative data without mean and standard deviation (SD), if we were unable to obtain the missing information from the authors, a method[20–21] of estimating the mean and SD based on the median, range, and sample size was used.

Methodological Quality Assessment

The methodological quality for the included studies was assessed independently by 3 researchers (D.L., X.L., and J.D.). The methodological quality of the RCTs was evaluated using the Cochrane collaboration tool[22] on the basis of 7 different aspects. The included trials were graded as low quality, high quality, or moderate quality based on the following criteria: (1) trials were considered low quality if either randomization or allocation concealment was assessed as a high risk of bias, regardless of the risk of other items. (2) Trials were considered high quality when both randomization and allocation concealment were assessed as a low risk of bias and all other items were assessed as low or unclear risk of bias in a trial. (3) Trials were considered moderate quality if they did not meet the criteria for high or low risk. The methodological quality of the included cohort studies was assessed using the Newcastle-Ottawa Scale (NOS).[23] This scale rated the quality of the included studies on 3 topics: selection of study population, comparability of the groups under study, and outcome assessment. The maximum score of this scale was 9, and we assigned a high methodological quality to a study if a score >5 was given. We resolved disagreements by consensus.

Statistical Analysis

The study-specific odds ratio (OR) for categorical variables, mean difference for continuous variation, and their 95% confidence interval (CI) were combined to calculate the pooled value of each study using the Cochrane Review Manager software (RevMan; version 5.3.5). Heterogeneity was investigated using the χ^2 text and I^2 statistics. For I^2 of between 0% and 30%, heterogeneity was considered probably unimportant, between 30% and 60% moderate, between 50% and 90% (or if the P-value of I^2 was <0.10) substantial, and between 75% and 100% considerable.[22] If heterogeneity existed ($>30\%$), we analyzed data using a random-effects model. If heterogeneity was not important, a fixed-effects model was used. Sensitivity analysis was performed by removing one study at a time and repeating the meta-analysis to assess whether any one study significantly affected the pooled estimates. If the number of included studies exceeded 10, the potential publication bias would be assessed by visual inspection of the funnel plots based on the primary outcomes. The conclusion indicating "no publication bias" was usually made if the figure was presented with good symmetry.

RESULTS

Search Results, Characteristics, and Quality of Included Studies

Literature selection was conducted using the designed strategy, and 1587 relevant citations were identified after removing the duplicates. A total of 1564 citations were excluded after reviewing the titles and abstracts. The remaining 23 citations were assessed for eligibility by reviewing the full text. Among these citations, 17 were excluded. Finally, 2 RCTs[15,16] and 4 retrospective cohort studies[24–27] were recruited into this meta-analysis. Details of the literature selection process are presented in Figure 1. A total of 295 patients with INP and an indication for invasive intervention were enrolled. The characteristics of each included study are displayed in Table 1. Generally, the included studies showed moderate to high methodological quality. One RCT[16] was graded as high quality and the other[15] as moderate quality. The risk of bias in each domain and each study is summarized in Figure 2. For these retrospective cohort studies, NOS scores ranged from 7 to 9, indicating high-quality studies (Table 2). Therefore, the methodological quality of the included studies was moderate to high.

Meta-Analysis of the Rate of Clinical Resolution

Three studies[24,25,27] explored the clinical resolution rate. There was no significant difference in the proportion of conversion between ETA group and SA group (OR, 1.54; 95% CI, 0.65-3.65). No significant heterogeneity was found ($P=0.75$; $I^2=0\%$) (Fig. 3). The robustness of the result was confirmed by the sensitivity analysis.

Meta-Analysis of the Short-term Mortality

Five studies[15,16,24–26] investigated the short-term mortality. There was no significant difference observed between groups (OR, 0.30; 95% CI, 0.07-1.33). A moderate heterogeneity was found ($P=0.06$; $I^2=56\%$) (Fig. 4A). A more homogenous result ($P=0.80$; $I^2=0\%$) was obtained, and pooled estimate changed (OR, 0.12; 95% CI, 0.03-0.42) in sensitivity analysis when one trial[16] was excluded (Fig. 4B).

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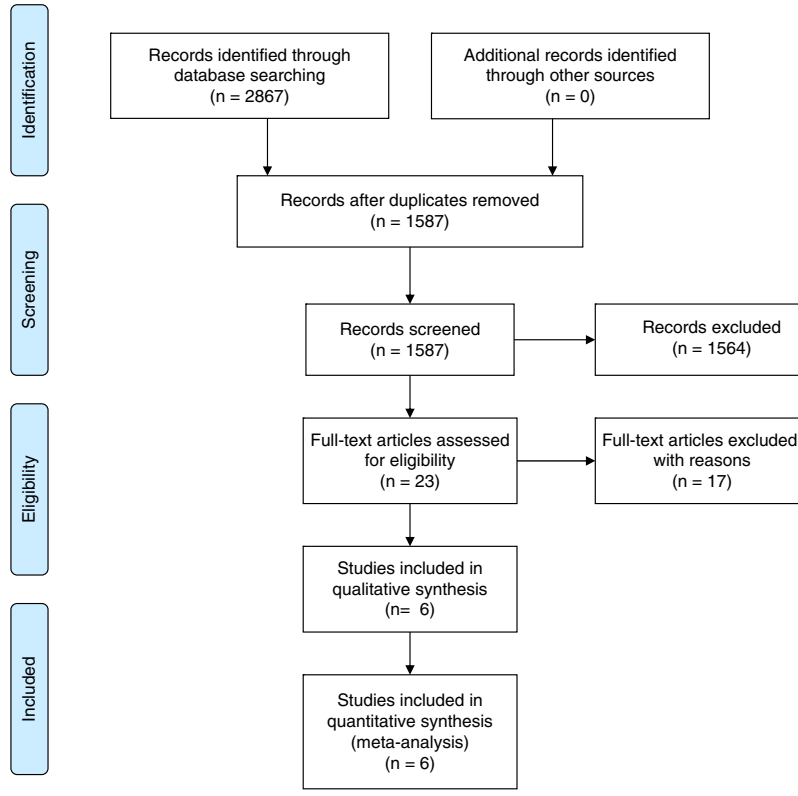

FIGURE 1. Flow diagram of literature selection. PubMed, Embase, Cochrane Library, and Web of Science were searched for the eligible studies with designed searching terms. After screening titles, abstracts and then the full text for relevance step by step, 6 studies were considered suitable to conduct such a meta-analysis in the end.

Meta-Analysis of the Rate of Major Complications

The rate of major complications was reported in 5 studies.[15,16,24–26] The rate of major complications was significantly lower in the ETA group (OR, 0.18; 95% CI, 0.06-0.55). There was a substantial heterogeneity among the trial results ($P = 0.03$; $I^2 = 62\%$) (Fig. 5A). A more homogenous result ($P = 0.41$; $I^2 = 0\%$) was obtained in sensitivity analysis when one trial[16] was excluded, but the result did not change (OR, 0.13; 95% CI, 0.06-0.29) (Fig. 5B).

Meta-Analysis of the Rate of New-onset Organ Failure

Four studies[15,16,25,26] evaluated the outcome. A lower rate of new-onset organ failure was found in the ETA group (OR, 0.26; 95% CI, 0.12-0.54). No significant heterogeneity was found ($P = 0.32$; $I^2 = 15\%$) (Fig. 6). The sensitivity analysis showed consistent result.

Meta-Analysis of the Rate of Postoperative Pancreatic Fistula

The rate of postoperative pancreatic fistula was reported in 4 studies.[15,16,24,26] There was a lower pancreatic fistula rate in the ETA group (OR, 0.09; 95% CI, 0.03-0.28). No significant heterogeneity was found ($P = 0.94$; $I^2 = 0\%$) (Fig. 7). The robustness of the result was confirmed by sensitivity analysis.

Meta-Analysis of the Rate Incisional Hernia

Two studies[16,26] explored the rate of incisional hernia. There was a lower incisional hernia rate in the ETA group (OR, 0.10; 95% CI, 0.01-0.85). No significant heterogeneity was found ($P = 0.45$; $I^2 = 0\%$) (Fig. 8).

Meta-Analysis of the Rate of Postoperative Bleeding

Three studies[16,24,26] explored the rate of postoperative bleeding. There was no significant difference between groups (OR, 0.76; 95% CI, 0.36-1.61). No significant heterogeneity was found ($P = 0.59$; $I^2 = 0\%$) (Fig. 9). The robustness of the result was confirmed by sensitivity analysis.

Meta-Analysis of the Rate of Perforation of a Visceral Organ

Four studies[15,16,24,26] investigated the outcome. There was no significant difference between groups (OR, 0.56; 95% CI, 0.25-1.23). No significant heterogeneity was found ($P = 0.71$; $I^2 = 0\%$) (Fig. 10). The robustness of the result was confirmed by sensitivity analysis.

Meta-Analysis of the Rate of Endocrine Insufficiency

Four studies[15,16,25,26] explored the rate of endocrine insufficiency. There was no significant difference between groups (OR, 0.47; 95% CI, 0.13-1.75). There was a substantial heterogeneity among the trial results ($P = 0.14$; $I^2 = 45\%$) (Fig. 11). The robustness of the result was confirmed by sensitivity analysis.

TABLE 1. Characteristics of Included Studies

References	Country	Study Design	Intervention	Sample Size			Clinical Traits of Patients	Disease Severity (APACHE II)		Outcomes
				Total	Endoscopic	Surgical		Endoscopic	Surgical	
Bausch et al[24]	Germany	Retrospective cohort	ETD+ETN vs. MIRN +ON	62	18	44	Suspected infected necrotizing pancreatitis	NR	NR	Clinical resolution rate, short-term mortality, bleeding, perforation, pancreatic fistula
Bakkeret al[15]	Netherlands	RCT	ETN vs. MIRN +ON	20	10	10	Suspected or established infected necrotizing pancreatitis	10 (6-14)	11 (7-14)	New-onset organ failure, short-term mortality, bleeding, enterocutaneous fistula, pancreatic fistula, endocrine or exocrine insufficiency
Kumar et al[25]	American	Retrospective cohort	ETN vs. surgical step-up approach	24	12	12	Suspected or established infected WOPN	10.1 ± 1.1	9.4 ± 1.2	Clinical resolution rate, new-onset organ failure, short-term mortality, endocrine or exocrine insufficiency, hospital stay
Tan et al[26]	France	Retrospective cohort	ETN vs. ON	32	11	21	Infected necrotizing pancreatitis	9 (5-11)	12 (10-16)	Short-term mortality, new-onset organ failure, bleeding, enterocutaneous fistula, pancreatic fistula, incisional hernia, hospital stay
Nemoto et al[27]	American	Retrospective cohort	ETD+ETN vs. PCD	59	49	10	Symptomatic or infected WOPN	4.3 (0-14)	8.2 (0-17)	Clinical resolution rate, hospital stay
Van Brunschot et al[16]	Netherlands	RCT	Endoscopic step-up approach vs. surgical step-up approach	98	51	47	Established infected necrotizing pancreatitis	9 (5-13)	10 (6-13)	Short-term mortality, new-onset organ failure, bleeding, perforation, pancreatic fistula, endocrine or exocrine insufficiency, incisional hernia, hospital stay

ETD indicates endoscopic transgastric drainage; ETN, endoscopic transgastric necrosectomy; MIRN, minimally invasive retroperitoneal necrosectomy; NR, not reported; ON, open necrosectomy; PCD, percutaneous catheter drainage; RCT, randomized controlled trial; WOPN, walled-off pancreatic necrosis.

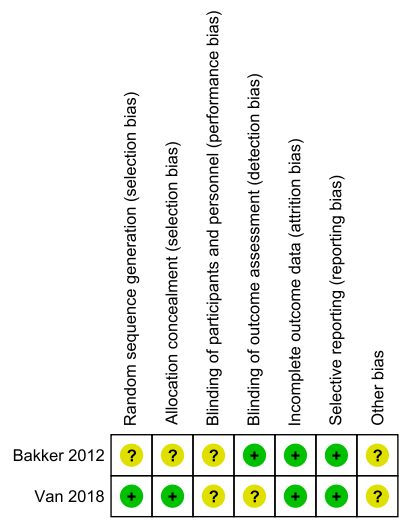

FIGURE 2. Risk of bias summary of included randomized controlled trials.

Meta-Analysis of the Rate of Exocrine Insufficiency

Four studies[15,16,25,26] investigated the rate of exocrine insufficiency. There was no significant difference between groups (OR, 0.93; 95% CI, 0.47-1.84). No significant heterogeneity was found ($P = 0.32$; $I^2 = 15\%$) (Fig. 12). The robustness of the result was confirmed by sensitivity analysis.

Meta-Analysis of Fluid Collection Recurrence After Successful Drainage

None of the studies reported the fluid collection recurrence after successful drainage.

TABLE 2. The Quality of Retrospective Cohort Studies With Newcastle-Ottawa Scale Scores

Studies	Selection	Comparability	Exposure	Scores
Bausch et al[24]	★★★★	—	★★★	7
Kumar et al[25]	★★★★	★★	★★★	9
Tan et al[26]	★★★★	★★	★★★	9
Nemoto et al[27]	★★★★	★★	★★★	9

★ indicates one point.

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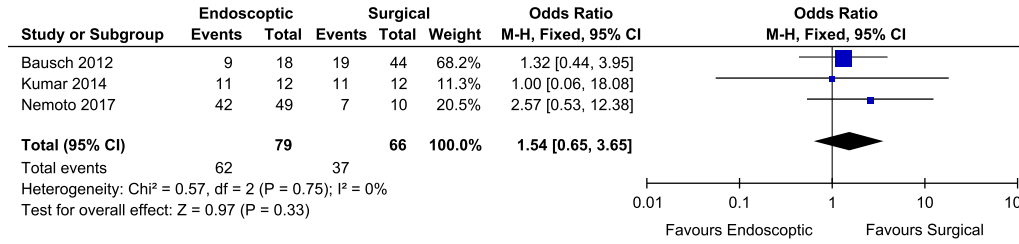

FIGURE 3. Forrest plot of the clinical resolution for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

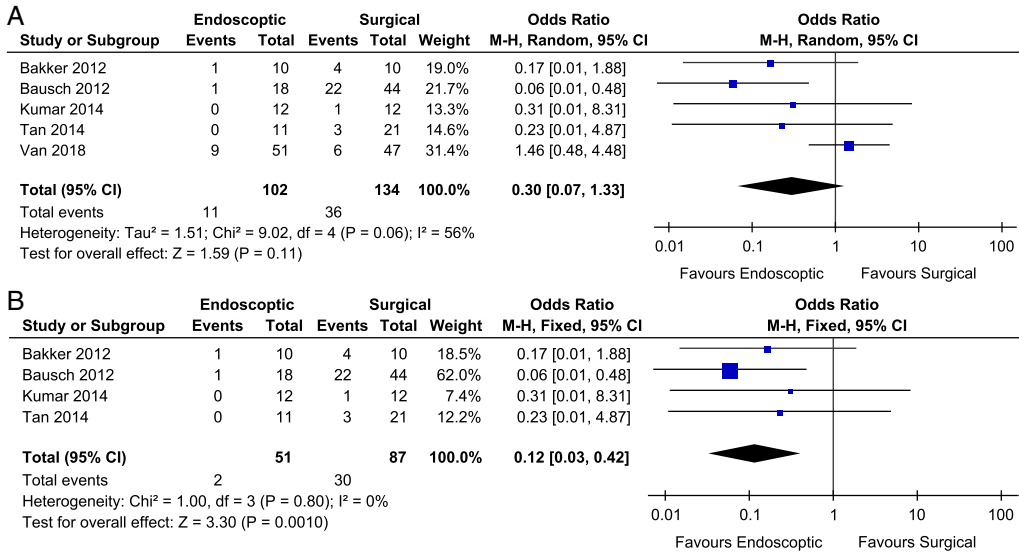

FIGURE 4. A, Forrest plot of the short-term mortality for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. B, Forrest plot of the short-term mortality for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis after removing Van's study. CI indicates confidence interval; *df*, degree of freedom.

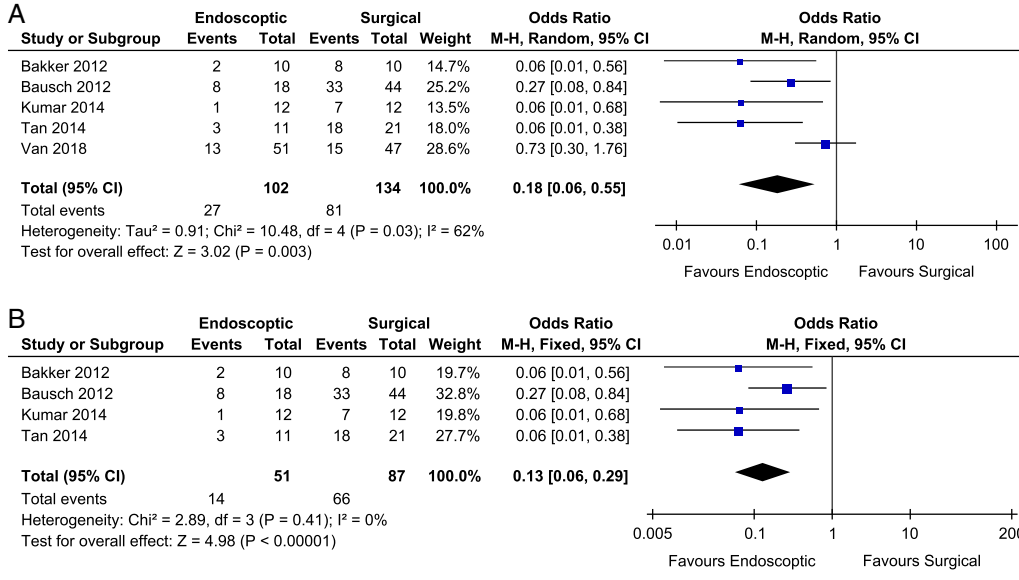

FIGURE 5. A, Forrest plot of the major complications for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. B, Forrest plot of the major complications for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis after removing Van's study. CI indicates confidence interval; *df*, degree of freedom.

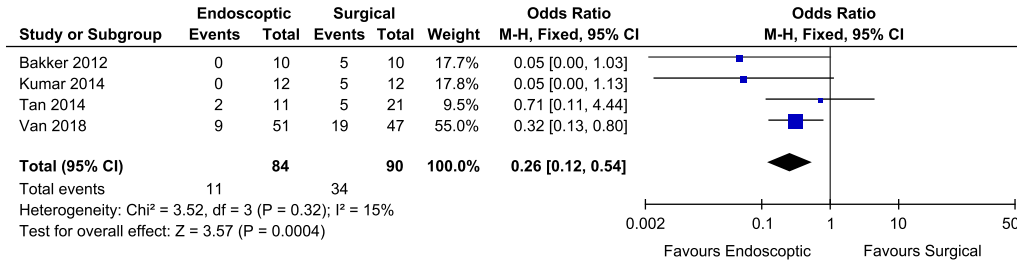

FIGURE 6. Forrest plot of the new-onset organ failure for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

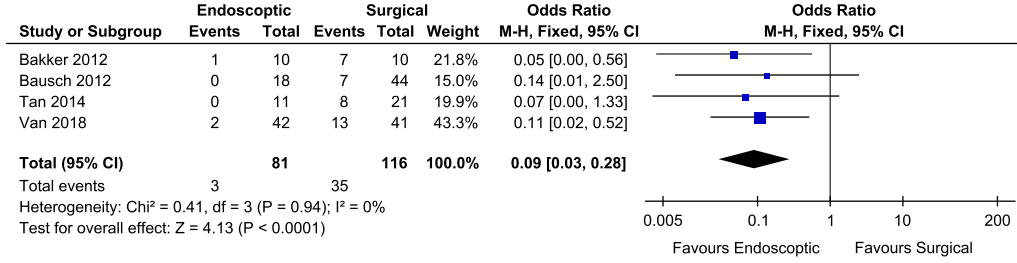

FIGURE 7. Forrest plot of the pancreatic fistula for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

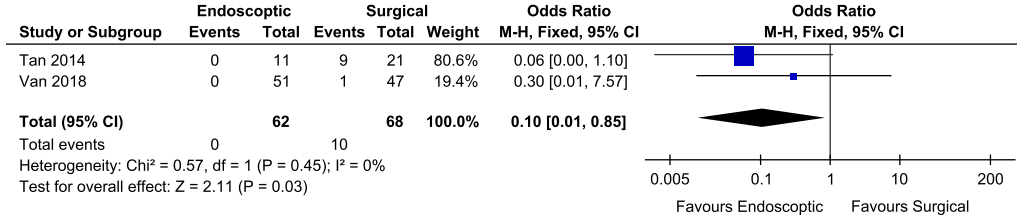

FIGURE 8. Forrest plot of the incisional hernia for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

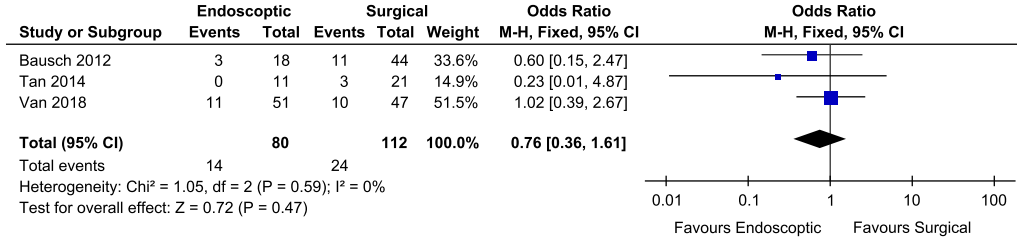

FIGURE 9. Forrest plot of the postoperative bleeding requiring intervention for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

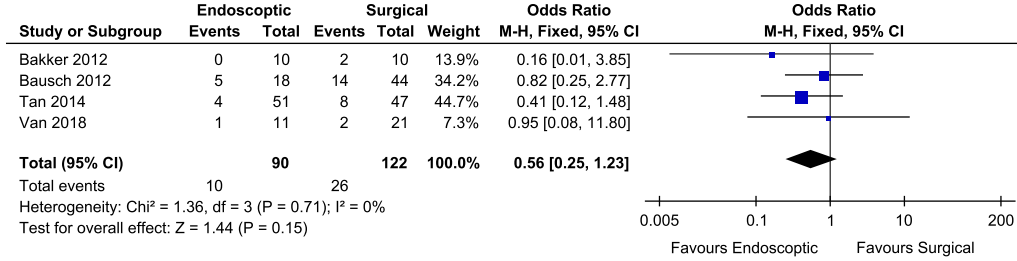

FIGURE 10. Forrest plot of the perforation of a visceral organ for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

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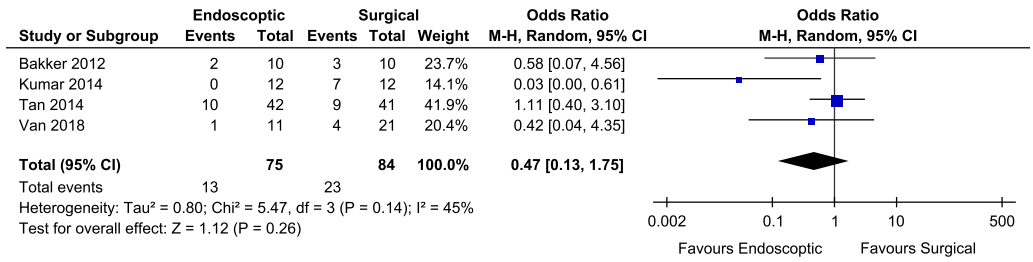

FIGURE 11. Forrest plot of the endocrine insufficiency for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

Meta-Analysis of Hospital Stay

Four studies[15,16,25,27] investigated the length of hospital stay. There was a shorter hospital stay in the ETA group (mean difference, −17.72; 95% CI, −21.30 to −14.13). No significant heterogeneity was found ($P = 0.40$; $I^2 = 0\%$) (Fig. 13). The robustness of the result was confirmed by the sensitivity analysis.

Publication Bias

The number of the included studies with each outcome was <10; thus, the funnel plot was not used to evaluate the publication bias.

DISCUSSION

This meta-analysis showed that ETA was superior to SA in reducing major complications, new-onset organ failure, postoperative pancreatic fistula, and incisional hernia in patients with infected necrosis. Furthermore, a shorter hospital stay in the ETA group was also observed in this meta-analysis.

During the last decade, minimally invasive interventions have essentially replaced traditional open necrosectomy in an attempt to reduce morbidity and mortality associated with open necrosectomy. Besides percutaneous drainage and minimally invasive surgery, endoscopic transgastric drainage and necrosectomy have been described in multiple studies as an alternative for open surgery.[15,16,28–31] Although endoscopic intervention for pancreatic necrosis is increasingly performed, enough evidence for superiority of ETA over SA is still lacking. Only several observational studies[24,26] and small RCT[15] indicated clinical superiority of endoscopy. Furthermore, 3 single-arm systematic reviews[17–19] showed that endoscopic transgastric necrosectomy was a safe and effective minimally invasive treatment in necrotizing pancreatitis. However, an article[16] from 2018 reported an RCT that evaluated the effectiveness of endoscopic step-up approach versus surgical step-up approach. This article did not show the superiority of the endoscopic step-up approach in reducing major complications or death in patients with INP, but suggested that additional investigations are still needed to confirm the current studies. To show the superiority of endoscopy, we designed the first meta-analysis to compare the effectiveness and safety between the 2 approaches.

In previous single-arm systematic reviews,[17–19] the pooled proportion of successful resolution of pancreatic necrosis using endoscopic transgastric necrosectomy was ~80%. In line with these systematic reviews, a high clinical resolution rate (average, 78%; range, 50% to 91%) was found in the ETA group in this systematic review. Meanwhile, the SA showed a similar clinical resolution rate. In addition, according to this systematic review, the lower rate of major complications after ETA relative to SA was consistent with previous studies.[24–26] Theoretically, by avoiding a laparotomy and general anesthesia, endoscopic transgastric techniques provoke less surgical trauma and can reduce the number of complications such as new-onset organ failure, pancreatic fistula, and incisional hernia.[16] Furthermore, general anesthesia is known to induce or prolong systemic inflammation in critically ill patients.

The reduction of organ failure with endoscopy is clinically relevant because organ failure is one of the major causes of long-term morbidity and death following acute pancreatitis, which especially coincided with infected necrosis.[32] The reduction of new-onset multiple organ failure using endoscopic approach compared with SA might be explained by 2 factors. First, with the use of a natural orifice as access route to the retroperitoneal cavity, surgical dissection to reach the omental sac or retroperitoneum is no longer needed. Second, endoscopic necrosectomy is performed under conscious sedation and does not require general anesthesia, which might attenuate the systemic inflammation in critically ill patients.[33] Pancreatic fistula is one of the main causes of other complications and death.[34] All pancreatic fistulas in the included studies were external, which could led to a series of

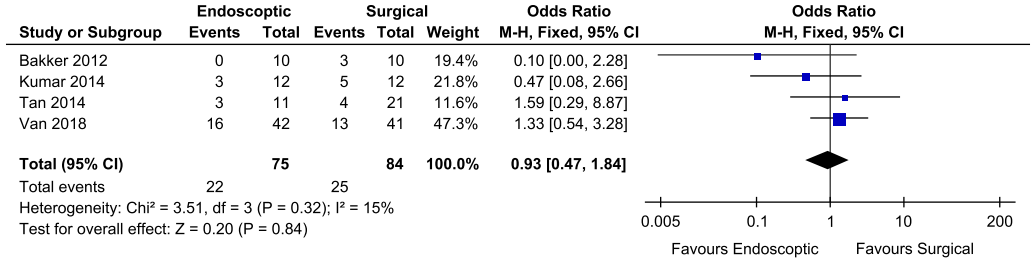

FIGURE 12. Forrest plot of the exocrine insufficiency for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

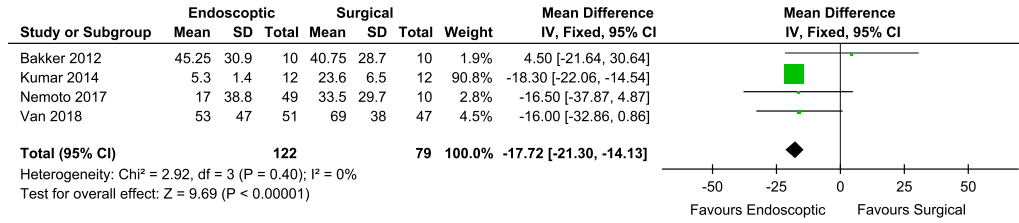

FIGURE 13. Forrest plot of hospital stay for endoscopic transgastric versus surgical approach for infected necrotizing pancreatitis. CI indicates confidence interval; *df*, degree of freedom.

complications (ie, infection, hemorrhage, consistent pain, pancreatic juices), additional interventions, and prolonged hospital stay. Therefore, the lower rate of pancreatic fistula in the ETA group is meaningful in clinical work. In addition, this systematic review also indicated that ETA lowered the risk of incisional hernia. Incisional hernias often cause disabling discomfort and pain, carry a risk of small-bowel strangulation, and frequently require surgical intervention.[35] ETA is operated through a natural channel with no incision in the abdominal wall so that the incidence of postoperative incisional hernia can be reduced.

Because heterogeneity was found among the studies in terms of 2 outcomes (short-term mortality and major complications rate), the random-effects model was used in our analysis. Then, sensitivity analysis was performed by removing one study for each time and repeating the meta-analysis to assess whether any one study significantly affected the pooled estimates. As the outcome of major complications rate, the estimates changed slightly after the sensitivity analysis, strengthening the results from this meta-analysis. However, as the outcome of short-term mortality, the estimates completely changed. Heterogeneity, however, disappeared when Van et al's study[16] was excluded, which indicated this study might be the source of heterogeneity. Van's results were not in line with a small RCT by Bakker et al[15] and observational studies.[24–26] Further, Van's study did not show the superiority of the endoscopic approach to the SA in reducing death or major complications. A few possible explanations contributed to the different outcomes. First, compared with previous studies, in Van's RCT, the inclusion criteria were strict and were confirmed by an expert panel. Second, the designs were partly different. Van's study compared step-up approaches between the endoscopic and surgical groups, whereas Bakker's RCT compared the results between endoscopic transgastric necrosectomy and surgical necrosectomy and Kumar's study compared direct endoscopic necrosectomy with step-up approach, etc. Furthermore, the patients in Van's trial were more severely ill than those included in the other 5 studies in terms of intensive care unit stay, presence of systemic inflammatory response syndrome, single or multiple organ failure at randomization, and high percentage of patients with confirmed infected necrosis compared with the patients included in previous observational studies.

This systematic review has some limitations. First, we only included articles written in English, so we might have missed some relevant studies published in other language. Second, the overall sample size was still relatively small. Only 2 RCTs and 4 retrospective studies with a total of 295 patients were included in our study. Third, as mentioned above, most included studies were retrospective analyses. Because of the selection bias, the ETA group might have a lower APACHE II score before interventions. Furthermore, the standard of infected necrosis was not strictly defined in some studies; thus, patients with suspected infected and even sterile necrosis might also be included in some included studies. It could lead to comparisons between less severe cases and patients with infected necrosis. These limitations indicate that the conclusions of our study may only be used for clinical reference.

In conclusion, this systematic review showed partly the superiority of ETA over SA in terms of the effectiveness and safety in patients with infected necrosis. To verify the reliability and validity of our conclusion, more high-quality RCTs are still required.

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