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An endoscopic or minimally invasive surgical approach for infected necrotizing pancreatitis: a systematic review and meta-analysis

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ABSTRACT

Background and aim: the incidence of acute pancreatitis is rising across the world, thus further increasing the burden on healthcare services. Approximately 10% of patients with acute pancreatitis will develop infected necrotizing pancreatitis (INP), which is the leading cause of high mortality in the late phase. There is currently no consensus with regard to the use of endoscopic or minimally invasive surgery as the first-line therapy of choice for INP. However, more clinical research with regard to the superiority of an endoscopic approach has been recently published. Therefore, we conducted a systematic review and meta-analysis to determine which of the two treatments leads to a better prognosis.

Methods: four databases (Medline, SINOMED, EMBASE and Cochrane Library) were searched for eligible studies from 1980 to 2018, comparing endoscopic and minimally invasive surgery for INP.

Results: two randomized controlled trials (RCTs) and seven clinical cohort studies were included. After the analysis of data amenable to polling, significant advantages were found in favor of the endoscopic approach in terms of pancreatic fistulas (OR = 0.10, 95% CI 0.04-

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0.30, p < 0.001) and the length of hospital stay (weighted mean difference [WMD] = -24.72, 95% CI = -33.87 to -15.57, p < 0.001). No marked differences were found in terms of mortality, multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, recurrence of pseudocysts, and length of stay (LOS) in the Intensive Care Unit (ICU), endocrine insufficiency and exocrine insufficiency.

Conclusion: compared with minimally invasive surgery, an endoscopic approach evidently improved short-term outcomes for infected necrotizing pancreatitis, including pancreatic fistula and the length of hospital stay. Furthermore, relevant multicenter RCTs are eager to validate these findings.

Key words: Endoscopic. Infected necrotizing pancreatitis. Meta-analysis. Surgery. Treatment outcome.

INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases worldwide (1) and is an inflammatory disease initiated by intra-acinar activation of proteolysis pancreatic enzymes. This disease causes a substantial service burden and hospital cost in almost all countries (2). The 2012 revised Atlanta classification divides AP into three clinical severity levels of mild, moderate and severe (3). More than half of patients with AP will develop edematous pancreatitis with a mild course, which is a self-limiting disease that resolves with conservative medical management and only requires a brief period of hospitalization (4). Moderate severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) are often accompanied by necrosis of the (peri) pancreatic tissue or (multiple) organ failure (MOF). This is still a challenge in the medical field, despite the ever-progressing level of medical treatment (5). Currently, there is no clear indicator of the development of severe pancreatitis. Gallstones and alcohol abuse are the main prevalent causes of AP. In addition, hyperlipidemia, hyperkalemia, anatomic variation and idiopathic acute pancreatitis (IAP) act as other indispensable factors for AP (6). With the development of auxiliary examinations such as endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT), most cases of IAP have a definitive etiology and could prevent the recurrence of pancreatitis (7). The implementation of cholecystectomy or

endoscopic sphincterotomy effectively prevents the incidence of recurrent biliary pancreatitis (8). The clinical course of AP can be divided into two phases. In the first phase, a systemic inflammatory response syndrome (SIRS) and MOF occur frequently and are the main cause of death. The late phase is characterized by local complications of necrosis and pancreatic fluid collections (9), which contain peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected). Approximately, 33% of cases with walled-off pancreatic necrosis (WON) and acute necrotizing pancreatitis (ANP) are often associated with infection (10) leading to bowel obstruction, bowel fistulisation, hemorrhage, prolonged hospitalization and even death (11). Early fluid resuscitation, enteral nutrition, antibiotics and intervention are of vital importance to treat infected necrotizing pancreatitis (INP) (12). Surgical resection of necrosis is an essential therapy for the INP, which should be performed at least four weeks after the onset of pancreatitis. Traditionally, these fluid collections following INP were managed surgically with open trans-peritoneal debridement (13). This approach has a mortality rate of 11.4 to 20.3% (14). Due to the high mortality rate with open surgery, the use of endoscopic and minimally invasive techniques, such as percutaneous catheter drainage (PCD), mini incision drainage (MID), video-assisted debridement (VAD), laparoscopic transgastric drainage (LTD), endoscopic ultrasound-guided transluminal drainage (ETD) and endoscopic transgastric necrosectomy (ETG), has gained increased popularity in many centers (15). Currently, endoscopic and minimally invasive surgery (MIS) have been recommended as the preferred treatment option for INP by an increasing number of guidelines. However, there is no definitive conclusion as to which treatment is more effective, thus there is a need for a meta-analysis. The aim of this systematic review and meta-analysis was to compare the two strategies for the treatment of INP.

METHODS

Ethical approval or patient consent was not required as the present study was a review of the previous published literature.

Search strategy and study selection criteria

A computerized search spanning from 1980 to 2018 was performed using the Medline,

SINOMED, EMBASE and Cochrane Library databases. The following search terms were used in all possible combinations: “pancreatitis”, “infected necrotizing pancreatitis”, “walled off pancreatic necrosis”, “endoscopic approach”, “endoscopic drainage”, “endoscopic necrosectomy”, “surgical step-up approach”, “minimally invasive approach”, “randomized comparative trials”, “prospective trials” and “retrospective trials”. The detailed search strategy for each database was provided (Annex 1). The search was limited to human subjects and there was no language limitation. The titles and abstracts of potentially relevant studies identified by the computerized search were reviewed. Full-text articles were obtained for detailed evaluation and eligible studies were included in the systematic review. The inclusion criteria were as follows: RCTs and observational clinical trials, the study included patients of both sexes, a clinical diagnosis of INP, both endoscopic and MIS administered as the treatment, the aim of the trial was a comparison of the endoscopic approach and MIS for the treatment of INP and the outcomes were clearly described including at least one of four major outcomes, such as the incidence of mortality, MOF, LOS and pancreatic fistula (PF).

The exclusion criteria were as follows: absence of a comparison between endoscopic and MIS approaches, the characteristics of patients and information about treatment outcome were insufficiently clear and case reports were also excluded.

Data collection and extraction

Two authors independently extracted data by reviewing all titles and abstracts of the searched articles. The following information was recorded from the trials included: first author, year of publication, number of participants. Basic data about gender, age, APACHE II score and C-reactive protein (CRP, mg/l) were extracted and analyzed. To compare the clinical outcomes of the endoscopic and surgical step-up approach groups, data on mortality and MOF, intra-abdominal bleeding, PF, new-onset diabetes or impaired glucose tolerance, exocrine insufficiency and LOS were extracted. A formula adopted by previous studies to acquire the mean and standard deviation (16) was used. According to these criteria, two independent reviewers reached a consensus in the case of discrepancies identified and selected the studies. The selection process was documented according to PRISMA criteria.

Outcome measures

The short-term outcomes were the incidence of mortality, MOF, intra-abdominal bleeding, PF, length of stay in ICU, LOS and enterocutaneous fistula. The long-term outcomes were other chronic complications, such as recurrence of pseudocysts, new-onset diabetes or impaired glucose tolerance and exocrine insufficiency.

Quality assessment and risk of bias

Two readers independently extracted and checked the data from the enrolled studies to ensure consistency. The quality of the included RCTs was determined according to the Cochrane Handbook for Systematic Reviews of Interventions, and quality assessment of the included retrospective trials was assessed by the Newcastle-Ottawa scale. The Egger test was used to assess publication bias, which was based on the odds ratio (OR) of mortality in necrotizing pancreatitis.

Statistical analyses

The number of patients for each treatment outcome was used in the analysis for alignment outcomes. ORs (ORs and variances) for the ten different complications comparing endoscopic and MIS approaches were calculated for each comparative study. The heterogeneity of all test parameters was examined with the Q-statistic test and I^2 index for sensitivity and specificity. Heterogeneity was considered to be significant if $p < 0.10$ (Q statistic) or the I^2 value was 50% or more. The associated log ORs were meta-analyzed using a restricted maximum-likelihood random effects model, after which the results were transformed back into the OR metric. The random-effects model was used regardless of whether there was a significant random-effects variation. The fixed effects model was performed as a sensitivity test. The study included both randomized clinical trials and observational studies, and subgroup analysis was performed according to the study characteristics (RCT or not) in order to analyze the sources of heterogeneity. All statistical analyses were performed using STATA 14.0. The OR and 95% CI were calculated for dichotomous outcomes in the extracted data and weighted mean difference (WMD) was used for continuous outcomes. When the interquartile range (IQR) and median were given instead of the standard deviation (SD), the data was converted using the Hozo algorithm to

estimate the SD. Sensitivity analysis was performed to assess the stability of the results and investigate the influence of each study by omitting a single study sequentially. Publication bias was shown by funnel plot.

RESULTS

Included trial characteristics and quality assessment

The initial 1,563 citations were identified based on a study of the subject and a summary of the literature; 784 articles were subsequently excluded due to duplication. After reviewing the title and abstract of the remaining 53 studies, only 14 full-text studies were evaluated for further assessment and five records were excluded due to incomplete data. Eventually, nine clinical studies were included that were consistent with the inclusion requirements (17-25). A detailed study flow-diagram is shown in figure 1.

The characteristics of the included studies are illustrated in table 1. The quality of the included RCTs, as assessed by the Cochrane Handbook for Systematic Reviews of Interventions, is shown in table 2. The quality assessment of the included retrospective trials, assessed by the Newcastle-Ottawa Scale, is summarized in table 3.

Details of the trial process

Nine studies were selected with a total of 358 patients; 170 patients underwent the endoscopic approach and 188 patients underwent MIS. The two RCTs were a multi-center, randomized, superiority trial that recruited adult cases (≥ 18 years of age) from several university medical centers and teaching hospitals of the Dutch Pancreatitis Study Group. The two prospective cohort studies compared initial endoscopic transluminal drainage and direct endoscopic necrosectomy with the MIS method for the treatment of INP. These studies recorded the mortality, MOF and other complications. The other five retrospective studies reported on the different outcomes of endoscopic, minimally invasive surgery and open necrosectomy for the treatment of INP. These studies all have a more than three-months of follow-up, recording both the short-term outcomes (mortality, MOF, PF and intra-abdominal bleeding) and long-term conditions of prognosis (new-onset diabetes or impaired glucose tolerance).

Meta-analysis results

Short-term outcomes: mortality, MOF

All nine studies (17-25) presented data on the incidence of mortality related to endoscopic and MIS approaches. None of the patients died in the study by Mohmmad et al. A random effect model was applied, even if there was no heterogeneity among them (I^2 = 0.0%, p = 0.650). The results of the subgroup analysis from the RCT and retrospective studies were as follows. There was no significant reduction in mortality for the RCT studies (OR = 0.65, 95% CI 0.08-5.14, p = 0.683), retrospective studies (OR = 0.43, 95% CI 0.14-1.30, p = 0.133) and whole studies (OR = 0.68, 95% CI 0.32-1.44, p = 0.310) (Fig. 2A). Six studies (17-20, 23, 24) reported the incidence of MOF. Five of 108 (4.63%) patients in the endoscopic group and 19 of 98 (19.39%) patients in the MIS group had a MOF during the treatment period. The random effect model was applied and there was no heterogeneity among them (I^2 = 22.5%, p = 0.265). There were significant differences between the two groups with regard to MOF of the RCT studies (OR = 0.19, 95% CI 0.04-0.81, p = 0.024), but there were no differences in the retrospective studies (OR = 0.60, 95% CI 0.12-2.93, p = 0.529) and whole studies (OR = 0.36, 95% CI 0.11-1.14, p = 0.082) (Fig. 2B).

Short-term outcomes: PF, intra-abdominal bleeding, enterocutaneous fistula

Six studies (17-19,21,23,24) recorded that pancreatic fistulas were external (i.e., pancreaticocutaneous fistulas) and there was no heterogeneity (I^2 = 0.0%, p = 0.904) among them. After aggregation of the data, the endoscopic approach was found to be associated with a significant reduction in the rate of PF of the RCT studies (OR = 0.09, 95% CI 0.02-0.32, p < 0.001), retrospective studies (OR = 0.14, 95% CI 0.02-0.85, p = 0.033) and whole studies (OR = 0.10, 95% CI 0.04-0.30, p < 0.001) (Fig. 2C). Eight studies reported intra-abdominal bleeding (17-24) and there was no heterogeneity (I^2 = 0.0%, p = 0.489) among them. There was no significant reduction in the RCT studies (OR = 1.02, 95% CI 0.39-2.67, p = 0.972), retrospective studies (OR = 0.40, 95% CI 0.14-1.17, p = 0.094) and whole studies (OR = 0.67, 95% CI 0.33-1.37, p = 0.271) (Fig. 2D). There was no heterogeneity among the eight studies of enterocutaneous fistula (I^2 = 18.5%, p = 0.288) (17-25). The differences between the RCT studies (OR = 0.36, 95% CI 0.11-1.19, p = 0.094), retrospective studies (OR = 0.84, 95% CI 0.16-4.41, p = 0.832) and whole studies (OR = 0.54, 95% CI 0.19-1.54, p = 0.248) (Fig. 2E)

with regard to the endoscopic approach were not significant.

Medical resources: length of stay in hospital, days in intensive care

All the studies compared the endoscopic procedure (n = 170) with the MIS procedure (n = 188) with the median or mean hospital stay and days in intensive care. However, some studies provided the median and IQR that made the analysis impossible. Six studies (17,19-20,23,25) had a significant heterogeneity among them (I^2 = 54.9%, p = 0.064). There were obvious differences between the two groups in terms of LOS for the retrospective studies (WMD = -27.26, 95% CI = -38.91 to -15.60, p < 0.001) and whole studies (WMD = -24.72, 95% CI = -33.87 to -15.57, p < 0.001) (Fig. 2F). The endoscopic approach group had a shorter length of hospital stay compared with the MIS group, although the days in intensive care did not show a significant advantage. Four studies (17,19,20,23) record this data and there was a significant heterogeneity among them (I^2 = 63.9%, p = 0.063); these were whole studies (WMD = -8.56, 95% CI = -19.12 to -2.00, p = 0.112) (Fig. 2G).

Long-term outcomes: recurrence of pseudocyst

A long-term prognosis is also a crucial criterion for determining the quality of treatment methods. A small number of patients relapsed with pancreatic cysts in all studies over a follow-up period of six months. With regard to five studies (18,19,21,23,24) with no heterogeneity (I^2 = 46.7%, p = 0.111), there was no significant difference between the two treatment methods for the retrospective studies (OR = 1.12, 95% CI 0.18-7.07, p = 0.906) and whole studies (OR = 0.82, 95% CI 0.19-3.64, p = 0.797) (Fig. 2H).

Long-term outcomes: new-onset diabetes, exocrine insufficiency

Five studies (17-20,24) provided data on endocrine insufficiency, which included 82 cases in the endoscopic approach group and 87 cases in the MIS group. Twelve of 82 (15.85%) patients who underwent the endoscopic procedure were diagnosed with new-onset diabetes, compared to 27 of 87 (31.03%) patients who underwent the MIS procedure. There was a significant heterogeneity among them (I^2 = 48.7%, p = 0.099). A pooled analysis with follow-up durations of > 3 months showed that there were no significant differences between the two groups with regard to the induction of endocrine insufficiency. This

included RCT studies (OR = 0.83, 95% CI 0.27-2.48, p = 0.732), retrospective studies (OR = 0.12, 95% CI 0.02-0.59, p = 0.009) and whole studies (OR = 0.30, 95% CI 0.08-1.14, p = 0.077) (Fig. 2I). Data with regard to exocrine insufficiency were available in four trials (17,18,20,24) and there was no heterogeneity among them (I^2 = 36.9%, p = 0.191). There were no significant differences with regard to the induction of exocrine insufficiency between the endoscopic and MIS groups in the RCT studies (OR = 0.38, 95% CI 0.02-8.64, p = 0.546), retrospective studies (OR = 0.73, 95% CI 0.21-2.52, p = 0.622) and whole studies (OR = 0.75, 95% CI 0.27-2.12, p = 0.588) (Fig. 2J).

Subgroup and sensitivity analyses

Subgroup analyses were performed to evaluate whether the ORs of outcome measures were different among the study characteristics. There were significant differences in MOF in the RCT studies but not for the retrospective studies. Based on a stratified analysis of the results of the RCT and retrospective studies, there was no difference between endoscopic and MIS. Sensitivity analysis was performed to assess the stability of pooled results. Among the nine studies, the significant results were not altered after sequentially omitting each study. In the pooled results that compared the incidence of mortality, after excluding the Sandra van Brunschot (17), he heterogeneity decreased significantly (OR = 0.719, 95% CI = 0.277-1.865, p = 0.497, I^2 = 28%). Furthermore, there was no significant difference in preventing the incidence of mortality between the two groups and it was therefore regarded as a result of heterogeneity. Likewise, the other studies were considered as the source of heterogeneity as the heterogeneity significantly changed and there was no significant difference in the prevention of mortality incidence between the two groups when excluding each of these studies in the pooled results. A sensitivity analysis was performed to determine whether the exclusion of this study would alter the result, which did not substantially influence the results when eliminated from the meta-analysis.

Two RCTs and seven retrospective trials were included in this part of the study. The funnel plots of the ORs for mortality and necrotizing pancreatitis were used to assess publication bias. The Egger's test results showed a Pr > jzj = 1.00 (Fig. 3), therefore we believe that the risk of publication bias is low in this meta-analysis.

DISCUSSION

Summary of the main results

With the rising incidence of INP, a feasible and effective management is greatly needed (26). At present, endoscopic and MIS procedures play an important role in the treatment of INP (27) and it is hard to say which one is more effective. However, there have been many recent studies of the preponderance of endoscopic procedures (28-30), including the direct single use of endoscopic and combined endoscopic and percutaneous approach. However, these studies have their many shortcomings, such as the small number of research subjects and a lack of a multi-center study. Therefore, the focus of this analysis was to evaluate the efficacy of two different approaches for the treatment of INP. This meta-analysis also identified seven published studies that assessed the outcomes of patients with INP who underwent an endoscopic or MIS approach. There are few published RCTs due to the lack of patients, necessary equipment and technical experts, in addition to the presence of an uncontrollable risk during treatment. Most of the evidence of the effects cannot be adequately studied in randomized trials, such as long-term and rare outcomes. Therefore, all cohort studies were analyzed in this study. In general, there was no notable difference in mortality and MOF between the two methods for patients with infected necrosis. Improved short-term outcomes, including a reduced incidence of PF and decreased LOS, were found in patients who underwent an endoscopic approach. With regard to the outcome of new-onset diabetes and exocrine insufficiency, the endoscopic procedure of exocrine insufficiency (follow-up time > 2 months) was not better compared to patients who underwent a MIS procedure. There has been a great controversy between pancreatitis and diabetes. The Malka study in 2000 suggested that the long-term development of pancreatic insufficiency was not reliant on the type of surgical procedure but may be related to the features of chronic pancreatitis (31). The study by Shen of matched controls concluded that the risk of diabetes increased by twofold after INP (32).

Comparison with previous studies

The best treatment has obviously improved when considering the long history of medical development and the widespread application of AP. A conservative treatment of INP was the major choice rather than surgery before the 20th century (33). As the understanding of

the disease deepened, surgical treatment (open necrosectomy) of severe pancreatitis gradually reached a consensus ten years ago. In fact, multiple multicenter RCT and meta-analyses support this view (34,35). In the 21st century, increasing evidence has proven that minimally invasive treatment is superior to open surgery (36-40). There are many diverse minimally invasive treatments to cure INP used in most hospitals. Over the past few years, many studies have reported the advantage of endoscopic procedures (41,42). However, RCTs are still scarce. Gurusamy et al. addressed the advantage of different interventions for necrotizing pancreatitis with very low quality evidence in 2016. However, the review mainly evaluated the open necrosectomy and minimally invasive step-up approach for the treatment of necrotizing pancreatitis. Luigiano et al. published a review of the comparison of endoscopic *versus* non-endoscopic techniques. The key focus of this study was endoscopic necrosectomy rather than a comparison between endoscopic and MIS. Overall, this is a novel systematic review and meta-analysis to compare endoscopic and MIS procedures for the treatment of INP. Due to the insufficient evidence, this meta-analysis is presented by consolidating multiple studies to enable an enhanced clinical decision making in the future.

Limitations of the study

Despite a comprehensive analysis, there are also many limitations that should be taken into consideration in this meta-analysis. First, the studies included in the meta-analysis were not all RCTS. Second, all the included studies of the endoscopic approach were not completely similar and whether the location of WON adjacent to the gastrointestinal (GI) lumen affects the final curative effect is still unknown. Third, it was difficult to avoid these slight differences due to the different intervention timings. Fourth, partially missing information in a few articles may lead to biased results. We have attempted to contact researchers or study sponsors to verify key study characteristics and obtain missing numerical outcome data. The Hozo algorithm was used to estimate means and standard deviations for those studies that did not include these data, which may have introduced bias. Moreover, clinical and methodological heterogeneities were observed in several parameters due to the variation in surgical techniques, patient composition and preferences among different centers. Finally, the assessment indices of the postoperative clinical complications were not

unified. Furthermore, there were differences within each operative technique, such as surgical skills, incision length and surgery time, which may also affect the results. True heterogeneity and poor methodological quality could also lead to an asymmetric plot (43,44). In the future, larger, higher quality clinical trials that compare the two approaches are expected. In fact, we will perform a more detailed subgroup analysis to explore the sources of heterogeneity to obtain a more reliable conclusion.

CONCLUSION

In summary, there was no difference in the therapeutic effect between the two methods in terms of long-term effects. However, improved short-term outcomes, including PF and LOS, were shown in patients who underwent an endoscopic approach. There is a huge need for more RCTs to confirm these advantages. In addition, future studies will be required to further define the optimal time and technique for the endoscopic procedure.

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Table 1. Main characteristics of the included studies

Author year	*Study period*	*Country*	*Study design*	*Center*	*Group (E/S)*	*Age (y)* (E/S)*	*Male (%) (E/S)*	*Pathology (%) (E/S)*	*Intervention*	*APACHEI score**	*CRP (mg/)**
Van Brunschot et al., 2017	Sep 20th 2011-Jan 29th 2015	Netherlands	RCT	Multicenter	51/47	63 (14)/60 (11)	34 (67)/29 (62)	Biliary 26 (51)/30 (64) Alcohol 7 (14)/7 (15) Other† 18 (35)/10 (21)	Endoscopic/surgical step-up	9 (5-13)/10 (6-13)	168 (105-258)/189 (136-301)
Bakker OJ et al., 2012	Aug 20th 2008-March 3rd 2010	Netherlands	RCT	Multicenter	10/10	62 (58-70)/64 (46-72)	6 (60)/8 (80)	Biliary 6 (60)/7 (70) Alcohol 2 (20)/2 (20) Other† 2 (20)/1 (10)	Endoscopic/surgical necrosectomy	10 (614)/11 (7-14)	141 (11-196)/232 (140-275)
Woo S et al., 2018	Jan 1st 2011-Dec 31st 2016	Australian	Retrospective	Single center	12/8	69 (31-81)/60 (32-72)	8 (67)/6 (75)	Biliary 8 (67)/2 (25) Alcohol 0 (0)/1 (12.5) Post-ERCP 1(8)/1 (12.5) Other† 3 (25)/4 (50)	Endoscopic drainage/PCD	Not reported	320 (212-525)/222 (46-469)
He W et al., 2016	May 17th 2013-Dec 6th 2014	China	Prospective	Single center	13/13	48 (27-55)/48 (43-59)	5 (45.5)/7 (53.8)	Biliary 5 (45.5)/7 (53.8) Alcohol 4 (36.4)/2 (15.4) Hypertriglyceridemia 1 (9.1)/4 (30.8) Hypercalcei1(9.1)/ 0 (0)	Endoscopic/surgical step-up	7 (6-10)/10 (8-14)	179 (118-258)/172 (106-351)
Khreiss M et al., 2015	2008-2013	USA	Retrospective	Single center	20/20	55 (42.566)/ 55.37-60.5	9 (45)/16 (80)	Biliary 9 (45)/13 (65) Alcohol 3 (15)/3 (12) Idiopathic 2 (10)/3 (15)	Endoscopic/surgical step-up	Not reported	Not reported
Kumar N et al., 2014	Jan 2009-	USA	Prospective	Single	12/12	58.9 (3.9)/53.	8 (66.7)/9	Alcohol 3 (25)/3 (25) Biliary 7 (58.3)/5 (41.6)	Endoscopic/surgical step-up	10.1 (1.1)/9.4 (1.2)	Not reported

	Dec 2010			center		3 (3.0)	(75)	Hypertriglyceridemia 0 (0)/1 (8.3) Post-ERCP 0 (0)/1 (8.3) Unknown 2 (16.7)/2 (16.7)			
Tan V et al., 2014	May 20th-Sep 5th 2011	France	Retrospective	Multicenter	11/21	51 (42-57)/52 (47-60)	9 (82)/14 (67)	Biliary 5 (45)/6 (29) Alcohol 4 (36)/3 (21.4) Other† 2 (18)/9 (43)	Endoscopic/surgical step-up	9 (5-11)/12 (10-16)	Not reported
Bausch D et al., 2012	2002-2010	Germany	Retrospective	Single center	18/14	58 (15-84)/61 (20-75)	10 (55.6)/11 (78.5)	Alcohol 4 (22.2)/3 (21.4) Biliary 5 (27.8)/4 (28.6) Unknown 7 (38.9)/2 (14.3) Post-ERCP 1 (5.5)/2 (14.3)	Endoscopic/MIS/ONE	Not reported	163 (3-276)/248 (4-396)
Gluck M et al., 2010	Jan 2006-Aug 2009	USA	Retrospective	Single center	23/43	59 (14)/54 (17)	18 (78)/25 (58)	Alcohol 4 (17)/6 (14) Biliary 13 (56)/24 (56) Idiopathic 4 (17)/3 (7) Post-ERCP 0 (0)/1 (2)	Endoscopic + PCD/PCD	Not reported	Not reported

*Mean (SD) or median (IQR). †It includes medication, anatomic abnormalities and unknown etiology, among others. RCT: randomized controlled trials; E/S: endoscopic/minimally invasive surgical approach; ERCP: endoscopic retrograde cholangiopancreatography; APACHE: Acute Physiology and Chronic Health Evaluation; CRP: C-reactive protein; PCD: percutaneous catheter drainage; MIS: minimally invasive surgery; ONE: open necrosectomy.

Table 2. Quality assessment of included studies: quality of the included RCTs

Study	*Adequate sequence generation*	*Adequate allocation concealment*	*Blinding*	*Incomplete outcome data adequately addressed*	*Free of selective reporting*	*Free of other bias*
Sandra van Bruschot	Yes	Yes	No	Yes	Yes	No
Olaf J. Bakker	Yes	Yes	No	Yes	Yes	No

Table 3. Quality assessment of included studies: quality of the included prospective studies

Ref.	*Representativeness of treated arm*	*Selection of the comparative treatment arm(s)*	*Ascertainment of the treatment regimen*	*Demonstration that outcome of interest was not present at star of study*	*Comparability between patients in different treatment arms: main factor*	*Comparability between patients in different treatment arms: secondary factor*	*Assessment of outcome with independency*	*Adequacy of follow-up length (to assess outcome)*	*Lost to follow-up acceptable (less than 10% and reported)*
Woo Shanan	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Wen HuaHe	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Mohammad Khreiss	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Nitin Kumar	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Virianne Tan	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Dirk Bausch	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Micheal Gluck	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes

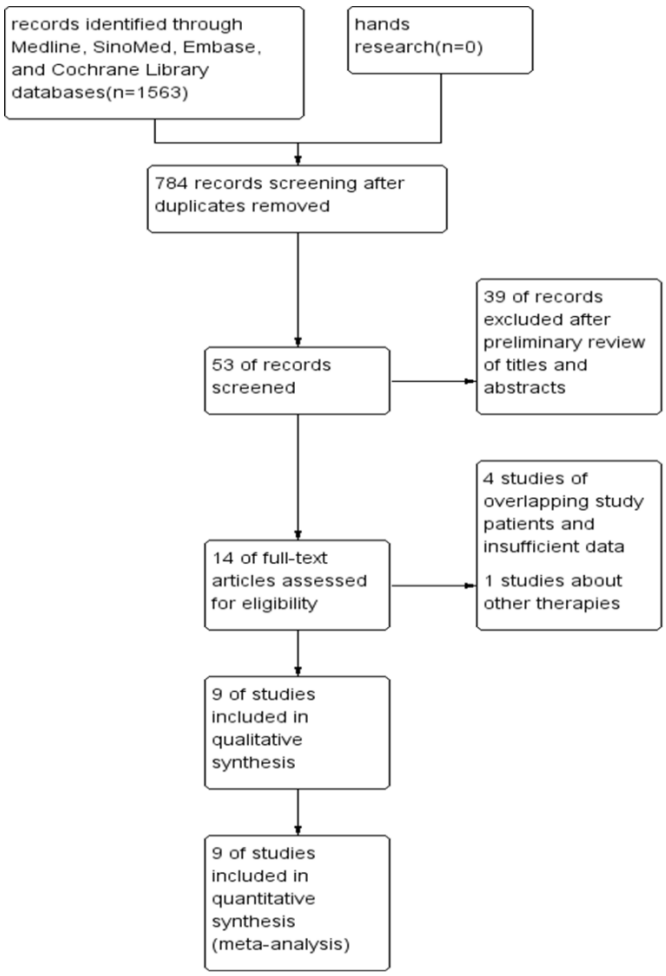

Fig. 1. Flow diagram for selection of studies included in the meta-analysis.

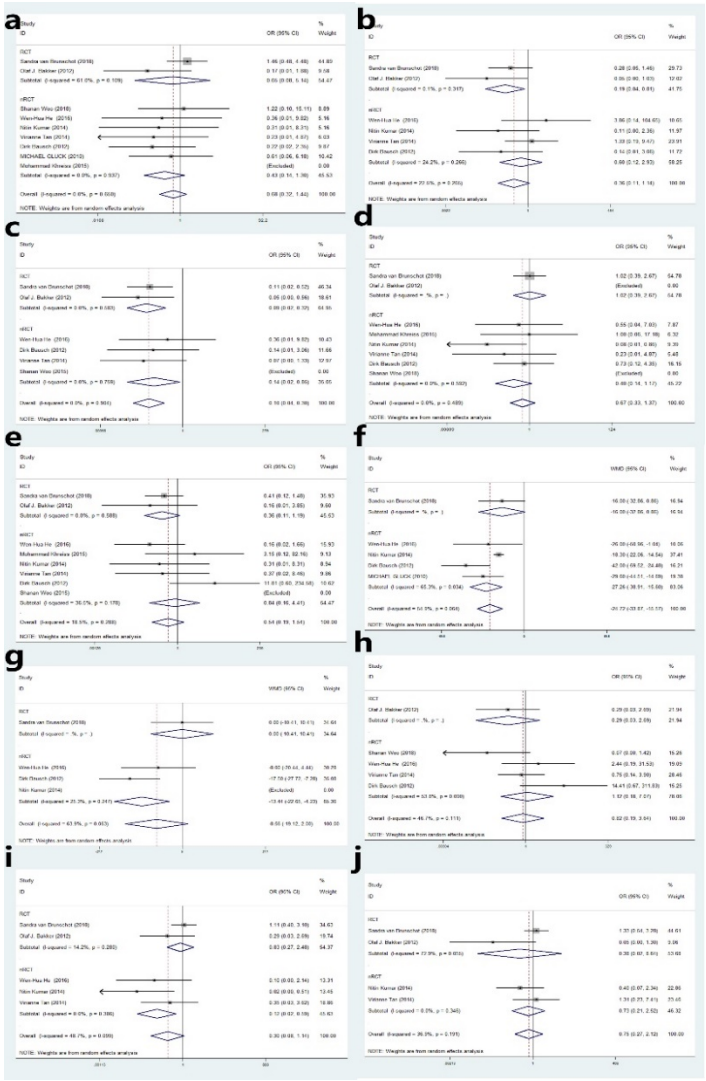

Fig. 2. Forest plot of the merits between endoscopic and a minimally invasive surgical approach in light of short-term outcomes and long-term outcomes. A. Mortality. B. Multiple organ failure. C. Pancreatic fistula. D. Intra-abdominal bleeding. E. Enterocutaneous fistula. F. Length of stay in hospital. G. Length of stay in ICU. H. Recurrence of pseudocysts. I. New-onset diabetes. J. Exocrine insufficiency. CI: confidence interval; OR: odds risk; WMD: weighted mean difference.

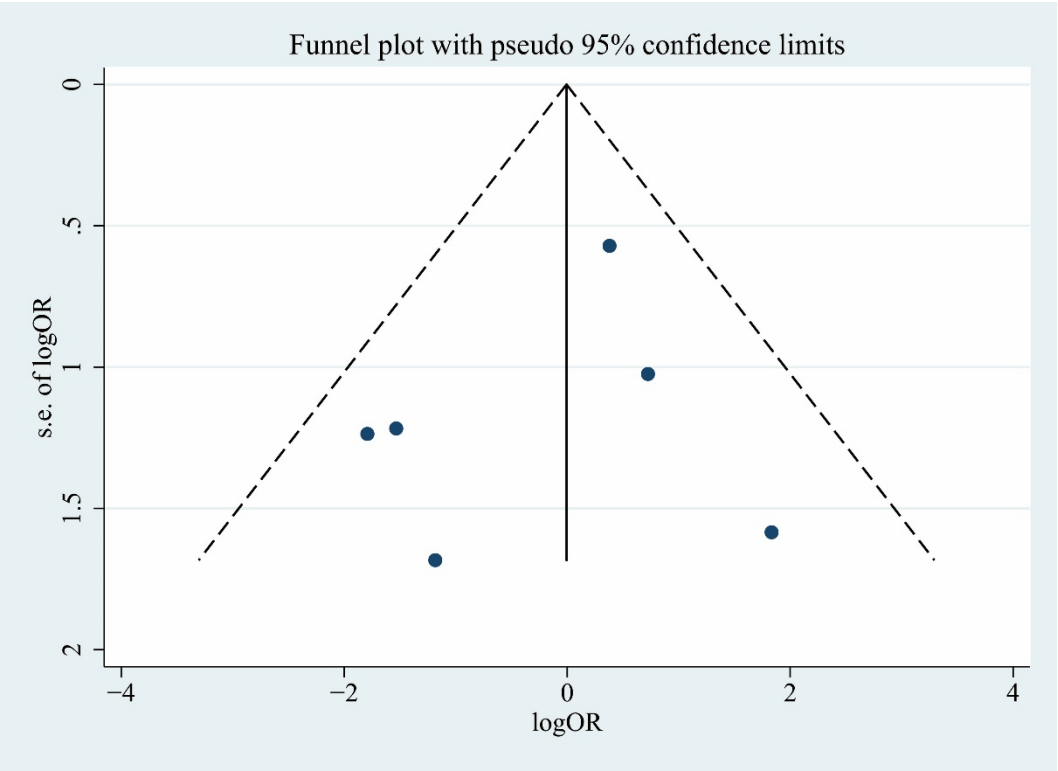

Fig. 3. Funnel plot of two interventions for outcome of mortality. OR: odds risk; SE: standard error.

Annex 1

MEDLINE search from 1980 to November 2016 under the search words: (((endoscopic * OR endoscopic transluminal drainage * OR endoscopic transgastric necrosectomy * OR endoscopic step-up approach *) AND (surgical approach *)) OR minimally invasive surgical) AND ("acute pancreatitis" OR "walled-off pancreatic necrosis" OR "acute necrotizing pancreatitis" OR "infected pancreatic necrosis" OR infected necrotizing pancreatitis) AND (randomized controlled trial [pt] OR clinical trial [pt])

EMBASE search from 1980 to October 2018:

1 (endoscopic * OR endoscopic transluminal drainage * OR endoscopic transgastric necrosectomy * OR endoscopic step-up approach *).af.

2 exp surgical approach/

3 1 or 2

4 (minimally invasive surgical * or minimally invasive necrosectomy *).af.

5 exp minimally invasive surgical/

6 4 or 5

7 3 and 6

8 (acute pancreatitis OR walled-off pancreatic necrosis OR acute necrotizing pancreatitis OR infected pancreatic necrosis OR infected necrotizing pancreatitis).af.

9 exp acute pancreatitis/

10 8 or 9

11 (randomized controlled trial * OR clinical trial *).af.

12 exp clinical trial /

13 11 or 12

14 7 and 8 and 13

SINOMED is a China biomedical literature service system, thus the search strategy is in Chinese: "急性胰腺炎"[全字段] OR "坏死感染性胰腺炎"[全字段] OR "包裹性坏死"[全字段]) AND "内镜手术"[全字段] AND "微创化手术"[全字段] AND "临床研究"[全字段]

Cochrane Library databases search from 1980 to October 2018:

1 MeSH description of surgical approach explode all trees

2 (endoscopic * OR endoscopic transluminal drainage * OR endoscopic transgastric necrosectomy * OR endoscopic step-up approach *) AND minimally invasive surgical *

3 1 or 2

4 MeSH description of acute pancreatitis explode all trees

5 (walled-off pancreatic necrosis) OR (acute necrotizing pancreatitis) OR (infected pancreatic necrosis) OR infected necrotizing pancreatitis

6 4 or 5

7 3 AND 6