Article published online: 2022-04-14

Endoscopic or surgical treatment for necrotizing pancreatitis: Comprehensive systematic review and meta-analysis

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submitted 9.7.2021
accepted after revision 10.11.2021

Bibliography
Endosc Int Open 2022; 10: E420–E428
DOI 10.1055/a-1783-9229
ISSN 2364-3722

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Supplementary material is available under https://doi.org/10.1055/a-1783-9229

ABSTRACT

Background and study aims Treatment of necrotizing pancreatitis is changed over the past two decades with the availability of endoscopic, and minimally invasive surgical approaches. The aim of this systematic review was to assess outcomes of endoscopic drainage, and different types of surgical drainage approaches in necrotizing pancreatitis.

Methods Medline, Embase, Scopus, and Web of Science were searched from 1998 to 2020 to assess outcomes in endoscopic drainage and various surgical drainage procedures. The assessed variables consisted of mortality, development of pancreatic or enteric fistula, new onset diabetes mellitus, and exocrine pancreatic insufficiency.

Results One hundred seventy studies comprising 11,807 patients were included in the final analysis. The pooled mortality rate was 22% (95% confidence interval [CI]: 19%–26%) in the open surgery (OS), 8% (95%CI:5%–11%) in minimally invasive surgery (MIS), 13% (95%CI: 9%–18%) in step-up approach, and 3% (95%CI:2%–4%) in the endoscopic drainage (ED). The pooled rate of fistula formation was 35% (95%CI:28%–41%) in the OS, 17% (95%CI: 12%–23%) in MIS, 17% (95%CI: 9%–27%) in step-up approach, and 2% (95%CI: 0%–4%) in ED. There were 17 comparative studies comparing various surgical drainage methods with ED. The mortality rate was significantly lower in ED compared to OS (risk ratio [RR]: 30; 95%CI: 0.20–0.45), and compared to MIS (RR: 0.40; 95%CI: 0.26–0.6). Also, the rate of fistula formation was lower in ED compared to all other surgical drainage approaches.

Conclusions This systematic review demonstrated lower rate of fistula formation with ED compared to various surgical drainage methods. A lower rate of mortality with ED was also observed in observational studies. PROSPERO Identifier: CRD42020139354

Introduction

Acute pancreatitis is one of the most common diagnoses made in gastroenterology wards worldwide which causes a great deal of pain and expense along with fatal complications [1].

While most patients present with mild and interstitial form of pancreatitis, 10 % to 20 % of patients progress to necrotizing pancreatitis that result in significant morbidity and mortality [2].

Initial conservative management may be feasible in necrotizing pancreatitis [3]. However, 30 % to 70 % of the patients with necrotizing pancreatitis develop infected necrosis [4, 5], and eventually, more than 70 % of patients with necrotizing pancreatitis will require a drainage procedure for infected necrosis or persistent symptoms [5].

Drainage procedures for necrotizing pancreatitis include open surgery, minimally invasive surgery, percutaneous drainage, and endoscopic drainage (ED). Percutaneous drainage (PCD) alone is effective in about half of patients with necrotizing pancreatitis requiring a drainage procedure, and the rest of the patients require surgical drainage [6]. Therefore, PCD is often used as part of surgical step-up approach [7].

A randomized controlled trial (RCT) reported a lower rate of composite outcome of major complications or death with a minimally invasive surgical step-up approach compared to open surgical necrosectomy. However, the mortality rate did not differ between the two groups [7]. Another RCT compared ED with a surgical step-up approach in patients with infected necrotizing pancreatitis [8]. In this trial, there was no statistically significant difference between the two groups in term of composite outcome of major complications or death. In a subsequent RCT comparing ED with minimally invasive surgery, the rate of composite outcome of major complications or death was lower in the ED group; however, there was no significant difference in mortality [9]. Therefore, it is important to compare mortality and each of major complications with various drainage procedures in a systematic review. Most of the recently published systematic reviews combined different surgical drainage procedures as a single treatment procedure, which resulted in heterogeneity of the results [10], or did not compare outcomes in detail with various drainage procedures [6, 11–13].

The aim of this comprehensive systematic review was to compare mortality and major complications in various drainage procedures, including open surgery, minimally invasive surgery, a surgical step-up approach, and ED.

Methods

This systematic review was performed in accordance with the PRISMA-P guidelines [14]. To identify relevant articles on treatment of necrotizing pancreatitis, a systematic search was performed on the most comprehensive international databases including Medline/Pubmed, Embase, Scopus, and Web of Science from January 1998 through May 2020. Also, reference lists of retrieved articles and reviews were hand-searched to find additional eligible studies. The search terms were developed based on the topics of research question and restricted to human subjects. The search terms included ["Pancreatitis, Acute Necrotizing" OR "Necrotizing pancreatitis" OR "infected necrotizing pancreatitis" OR "walled-off pancreatic necrosis") AND ("ED" OR "Surgical drainage" OR "endoscopic approach" OR "endoscopic necrosectomy" OR "minimally invasive approach" OR "surgical step-up approach"].

The start date of the search was 1998 to coincide with the publication date of the first article on minimally invasive surgical drainage of necrotizing pancreatitis [15]. Literature on other types of drainage (e. g. open surgical, endoscopic, and percutaneous) had already been published that year.

Studies published in full articles were considered eligible for the systematic review. Studies were restricted to English language. When repetitive data were published from the same authors or institution, only one article with the most complete description of data was included. The corresponding authors were contacted through email to obtain missing information. The study was registered in PROSPERO (registration number: CRD42020139354).

Inclusion criteria

RCTs or observational studies were included if they reported surgical or ED in patients with necrotizing pancreatitis in which one of the following variables were clearly described: mortality, enteric or pancreatic fistula, exogenous pancreatic insufficiency, new onset diabetes mellitus (DM). The studies included patients of both sexes with no restriction for age.

Exclusion criteria

Based on defined eligibility criteria, the exclusion criteria were as follows: studies on non-human-subjects, duplicate citations, studies with sample size of less than 10, studies reporting ED of necrotizing pancreatitis through trans-papillary route, studies with publication date before 1998, studies with drainage procedures on pancreatic pseudocyst, and studies published as congress abstract. Some studies reported drainage procedures in pancreatic fluid collection in general and did not provide specific outcomes for pancreatic pseudocyst and walled-off pancreatic necrosis. Such studies were also excluded from the analysis.

Selection of studies

After conducting literature searches, the retrieved articles were imported into an Endnote library. The titles and abstracts of the identified studies were reviewed by two reviewers. Then, the full text of the potentially relevant studies was reviewed in-depth by two reviewers to identify relevant articles.

Quality assessment

Quality assessment of the relevant articles was conducted independently by two expert reviewers. The quality of study design, sampling strategy, and measurement quality were assessed based on Consort 2010 check list [16], and STROBE quality assessment tools for observational (e. g. cohort, case-control, and cross-sectional) studies [17].

The kappa statistic for agreement on quality assessment was 0.92. The discrepancies were resolved by the third expert reviewer.

Data extraction

The following data were extracted from the relevant studies: first author, year of publication, journal name, total number of patients with necrotizing pancreatitis, type of drainage procedure, number of patients in each drainage procedure, and outcomes for each drainage procedure. Also, detailed information about the type of endoscopic procedure, and performance of endoscopic necrosectomy were recorded. The data were extracted by two authors. The differences were resolved by agreement.

Definition of procedures

Open surgery was defined as open surgical drainage of pancreatic necrosis. In the included studies, open surgery varied from laparotomy with necrosectomy through retrogastric or transgastric approaches. Minimally invasive surgery included pancreatic debridement through video-assisted retroperitoneal debridement (VARD) and laparoscopic necrosectomy through retrogastric or transgastric approaches. A step-up approach consisted of percutaneous drainage of pancreatic necrosis with the intention of avoiding surgery, and proceeding to open or minimally invasive surgery in case of failure of percutaneous drainage. ED included transmural drainage of pancreatic necrosis with stent placement, nasocystic drainage, or endoscopic necrosectomy. Sinus tract endoscopy (defined as dilation of percutaneous drainage tract followed by advancement of flexible endoscope through the tract and necrosectomy) was also considered as an ED method.

Statistical analysis

The primary aims of the meta-analysis were the pooled rate of mortality, fistula formation, new onset DM, and exocrine pancreatic insufficiency. The secondary aims were the risk ratio (RR) of ED to other drainage methods.

Sequencing of meta-analyses was done for each primary and secondary aims, presented as rates or RRs. The combined effect sizes (rate or risk ratio) were weighted by the inverse of their variance, offering more weight to studies with higher sample sizes, and therefore more precision around the estimates. The combined rates or RR and their 95 % confidence intervals (CIs) were calculated using DerSimonian-Laird random effects models or generic inverse variance approach fixed effects models [18]. Forest plots were drawn showing the variation in prevalence among all studies together with the pooled measure [19]. The Q test and I2 statistics were calculated to evaluate for statistical heterogeneity of effect sizes [20]. A significant Q test recommends that study variability in effect size estimates is bigger than the sampling error. The I^2 statistic (changing from 0 %–100 %) measured the percentage of total variation across the studies provoked from clinical or methodological heterogeneity rather than by chance. An $^{I}2$ value < 50 % showed low heterogeneity; 50 % to 75 %, moderate; and more than 75 %, high [21]. Selection of the model (random or fixed) was determined based on Q statistics. When Q statistics (P < 0.10) pointed to heterogeneity, the random effects model was employed for meta-analysis. When Q statistics (P > 0.10) indicated the absence of evidence for heterogeneity, then a fixed effect model was applied for meta-analysis. Then, a series of sensitivity analyses by leave-one-out method were performed to examine robustness of the observed prevalence and association. The sensitivity analysis provided a minimum and a maximum value of the combined effect sizes for each meta-analysis. An Egger regression test was carried out to afford a quantitative value for further assessment of publication bias (or small-study effects) and P < 0.1 was considered as the presence of publication bias [21, 22]. Except for the I^2 statistic and Egger test, a two-sided P < .05 was considered statistically significant. A software program (STATA, version 16; StataCorp LP) was used for the meta-analyses. The metaprop, metan, meta bias, and metaninf commands of STATA were used as appropriate.

Results

Eligible studies and quality assessment

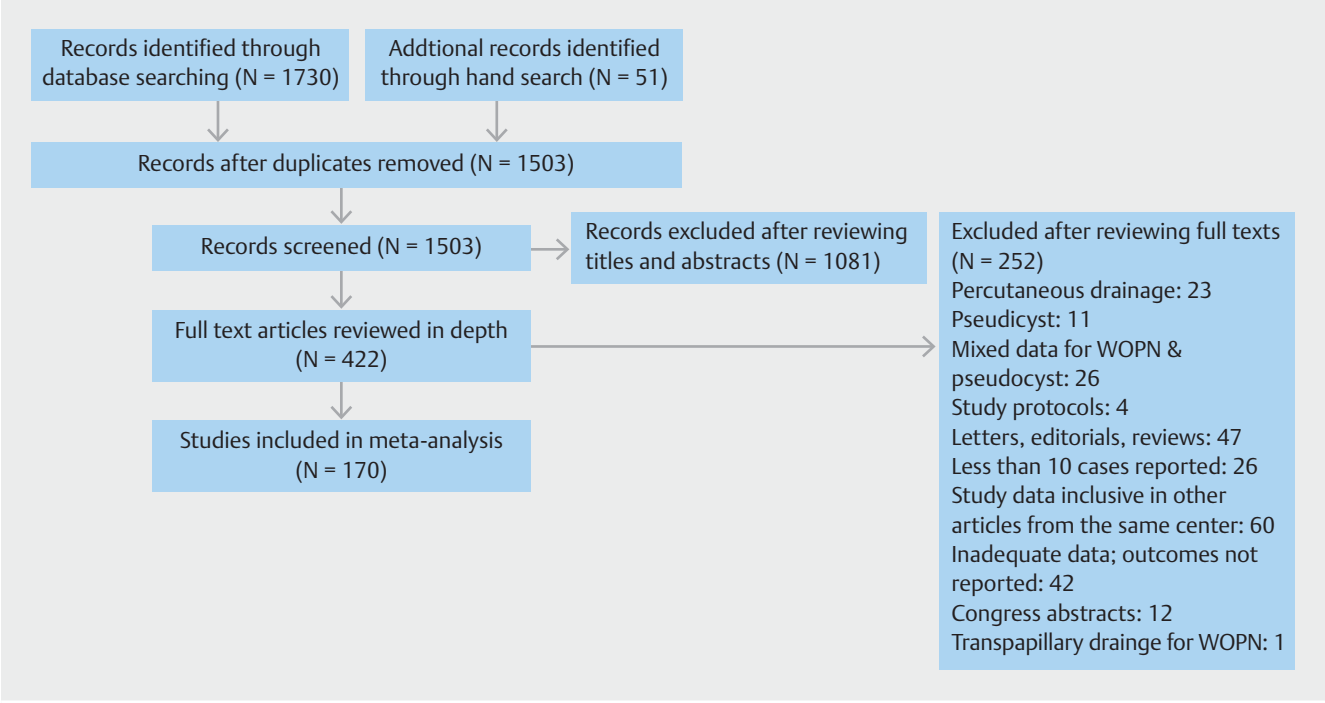
The original search generated 1730 studies. Another 51 studies were identified through hand searching. After removing duplicates, and studying titles and abstracts of the studies, 1081 studies were excluded and 422 articles were reviewed in-depth. Among these, 170 studies consisting of 11,807 patients were included in the final analysis. ▶ **Fig. 1** shows the flow diagram of the search results.

The 170 included studies consisted of seven RCTs and 163 observational and descriptive studies published between 1998 and 2020 that originated from 30 countries on five continents (supplementary references 1 through 170 in supplementary materials). Details of the included studies are described in **Supplementary Table S1** and **Supplementary Table S2**. The qualities of the relevant studies are shown in **Supplementary Table S3** and **Supplementary Table S4**.

Sixty-two studies consisting of 3752 patients reported open surgical drainage for necrotizing pancreatitis. Also, 34 studies reported minimally invasive surgical drainage in 1563 patients. A step-up approach was reported in 1194 patients from 23 studies; ED was reported in 90 studies with 5298 patients. There were 36 studies comparing various types of drainage procedures. Five of the comparative studies were RCTs and 31 were retrospective cohorts. The details of comparative studies are summarized in **Supplementary Table S2**. There were also two RCTs among the ED studies comparing oblique-viewing with forward-viewing echoendoscopes [23], and lumen apposing metallic stents with plastic stents [24].

Mortality rate

The pooled mortality rate for open surgery was 22 % (95 %CI: 19%–26 %). It was 8 % (95 %CI:5 %–11 %) in minimally invasive surgery, and 13 % (95 %CI: 9 %–18 %) for the step-up approach. The mortality rate was 3 % (95 %CI: 2 %–4 %) in the ED studies (▶ **Table 1**, **Supplementary Fig. S1a**, **Supplementary Fig. S1b**, **Supplementary Fig. S1c**, **Supplementary Fig. S1d**).



▶ **Fig. 1** Flow diagram of eligible studies.

Fistula formation

The pooled rate of fistula formation was 35 % (95 %CI: 28 %–41%) for open surgery, 17 % (95 %CI: 12–23 %) for minimally invasive surgery, 17 % (95 %CI: 9 %–27 %) for the step-up approach, and 2 % (95 %CI: 0–4 %) for ED (▶ **Table 1**, **Supplementary Fig. S2a**, **Supplementary Fig. S2b**, **Supplementary Fig. S2c**, **Supplementary Fig. S2 d**).

New onset diabetes mellitus

The pooled rate of new onset DM was 33 % (95 %CI:24 %–42 %) in the open surgery group. It was 13 % (95 %CI:6 %–21 %) in the minimally invasive surgery group, 24 % (95 %CI:13 %–35 %) in the step-up approach group, and 15 % (95 %CI:9 %–22 %) in the ED group (▶ **Table 1**, **Supplementary Fig. S3a**, **Supplementary Fig. S3b**, **Supplementary Fig. S3c**, **Supplementary Fig. S3d**).

Exocrine pancreatic insufficiency

The pooled rate of pancreatic insufficiency was 33 % (95 %CI: 2%–45 %) in the open surgery studies, 15 % (95 %CI: 3 %–30 %) in the minimally invasive surgery, 20 % (95 %CI: 5 %–42 %) in the step-up approach studies, and 22 % (95 %CI: 15 %–30 %) in the ED studies (▶ **Table 1, Supplementary Fig. S4a**, **Supplementary Fig. S4b**, **Supplementary Fig. S4c**, **Supplementary Fig. S4d**).

Comparative studies

The pooled mortality rate was assessed in comparative studies comparing ED to other drainage methods.

There were 17 comparative studies comparing various surgical drainage methods with ED. One of the articles was pooled analysis of individual data from 13 previously published studies and unpublished cohorts [25].

The mortality rate was significantly lower for ED compared to open surgical drainage (RR: 30; 95 %CI: 0.20 %–0.45) (▶ **Fig. 2a**, ▶ **Table 2**). The mortality rate was also significantly lower for ED compared to minimally invasive surgery (RR: 0.40; 95 % CI: 0.26–0.6) (▶ **Fig. 2b**, ▶ **Table 2**). However, there was no significant differences in mortality between ED and the step-up approach (RR: 0.63; 95 %CI: 0.37–1.07) (▶ **Fig. 2c**, ▶ **Table 2**).

The rate of fistula formation was significantly lower in ED studies compared to all other drainage methods (▶ **Table 2**, **Supplementary Fig. S5a**, **Supplementary Fig. S5b**, **Supplementary Fig. S5c**).

However, the rate of new onset DM, or exocrine pancreatic insufficiency was not different in ED compared to all other drainage methods (▶ **Table 2**).

There were three RCTs comparing ED with minimally invasive surgery [9, 26, 27]. The pooled rate of fistula formation was significantly lower in the ED (RR: 0.08; 95 %CI: 0.02–0.38); however, the mortality rate did not differ between the two groups (RR: 0.64; 95 %CI: 0.19–2.13) (**Supplementary Fig. S6a**, **Supplementary Fig. S6b**, **Supplementary materials**). There was single RCT comparing ED with step-up approach [8]. The rate of fistula was significantly lower in the ED (OR: 0.15; 95 %CI: 0.04–0.62), but mortality rate was similar in both groups (OR: 1.38; 95 %CI: 0.53–3.59).

Subgroup analyses

To exclude the effect of early intervention on mortality, analysis was repeated on studies with the median time from pancreatitis onset to surgery of 4 weeks or more. In this subgroup analysis,

▶ **Table 1** Pooled prevalence of outcomes with various drainage procedures.

Meta-analysis	No. studies	Total sample size	Pooled rate % (95 % CI%)	I^2 statistic %	Q Cochran *P* value	Sensitivity analysis		Egger's *P* value
						Minimum estimate% (95 % CI%)	Maximum estimate% (95 % CI%)	
Open surgery: mortality	59	3662	22 (19–26)	85.05	<0.0001	23 (19–26)	25 (22–29)	0.899
Mis: mortality	34	1563	8 (5–11)	61.84	<0.0001	10 (4–16)	13 (8–18)	0.244
Step-up mortality	23	1194	13 (9–18)	72.03	<0.0001	13 (8–19)	16 (9–23)	0.459
Endoscopy: mortality	89	5272	3 (2–4)	73.44	<0.0001	4 (1–7)	5 (2–7)	0.597
Open surgery: Enteric or pancreatic fistula	45	3097	35 (28–41)	92.44	<0.0001	35 (29–41)	37 (30–43)	0.940
MIS: Enteric or pancreatic fistula	26	1318	17 (12–23)	78.63	<0.0001	18 (12–23)	20 (13–26)	0.528
Step-up enteric or pancreatic fistula	16	873	17 (9–27)	89.62	<0.0001	20 (11–29)	22 (14–31)	0.371
Endoscopy: Enteric or pancreatic fistula	42	2422	2 (0–4)	83.47	<0.0001	3 (0–8)	6 (2–10)	0.276
Open surgery: New onset DM	11	331	33 (24–42)	60.40	<0.0001	30 (19–41)	35 (23–47)	0.504
MIS: New onset DM	11	374	13 (6–21)	68.85	<0.0001	11 (0–21)	14 (0–27)	0.222
Step-up: New onset DM	8	212	24 (13–35)	66.12	<0.0001	20 (6–33)	26 (11–42)	0.199
Endoscopy: New onset DM	13	707	15 (9–22)	76.17	<0.0001	16 (8–25)	21 (13–29)	0.525
Open surgery: exocrine pancreatic insufficiency	9	312	33 (22–45)	76.55	<0.0001	29 (17–40)	37 (24–49)	0.126
MIS: Exocrine pancreatic insufficiency	8	173	15 (3–30)	79.92	<0.0001	11 (0–26)	18 (1–35)	0.179
Step-up: Exocrine pancreatic insufficiency	5	136	20 (5–42)	82.76	<0.0001	15 (0–35)	30 (9–51)	0.514
Endoscopy: Exocrine pancreatic insufficiency	8	371	22 (15–30)	58.92	0.02	21 (10–33)	27 (14–39)	0.864

MIS, minimally invasive surgery; DM, diabetes mellitus; CI, confidence interval.

the pooled rate of mortality was 16 % (95 %CI: 10 %–22 %) in the open surgery, 7 % (95 %CI: 4 %–11 %) in the minimally invasive surgery. It was 10 % (95 %CI: 6 %–13 %) in the step-up approach, and 4 % (95 %CI: 3 %–6 %) in the ED studies (**Supplementary Fig. S7a**, **Supplementary Fig. S7b**, **Supplementary Fig. S7c**, **Supplementary Fig. S7d**).

Also, mortality rate was assessed in studies only including patients with suspected or confirmed infected walled-off pancreatic necrosis (WOPN). The pooled mortality rate was 24 % (95 %CI: 16 %–33 %) in open surgical drainage, 10 % (95 %CI: 4 %–16 %) in minimally invasive surgery, 11 % (95 %CI: 7 %–16 %) in step-up approach, and 8 % (95 %CI: 5 %–12 %) in ED (**Supplementary Fig. S8a**, **Supplementary Fig. S8b**, **Supplementary Fig. S8c**, **Supplementary Fig. S8d**).

To assess the most contemporary data, studies conducted after 2010 (e. g. after publication of the landmark RCT to compare open necrosectomy with step-up approach [7]) were analyzed. The pooled mortality was 15 % (95 %CI: 0 %–48 %) in open surgery, 4 % (95 %CI: 1–10 %) in minimally invasive surgery, 14 % (95 %CI: 9 %–21 %) in step-up approach, and 3 % (95 %CI: 1 %–5 %) in ED (**Supplementary Fig. S9a**, **Supplementary Fig. S9b**, **Supplementary Fig. S9c**, **Supplementary Fig. S9d**).

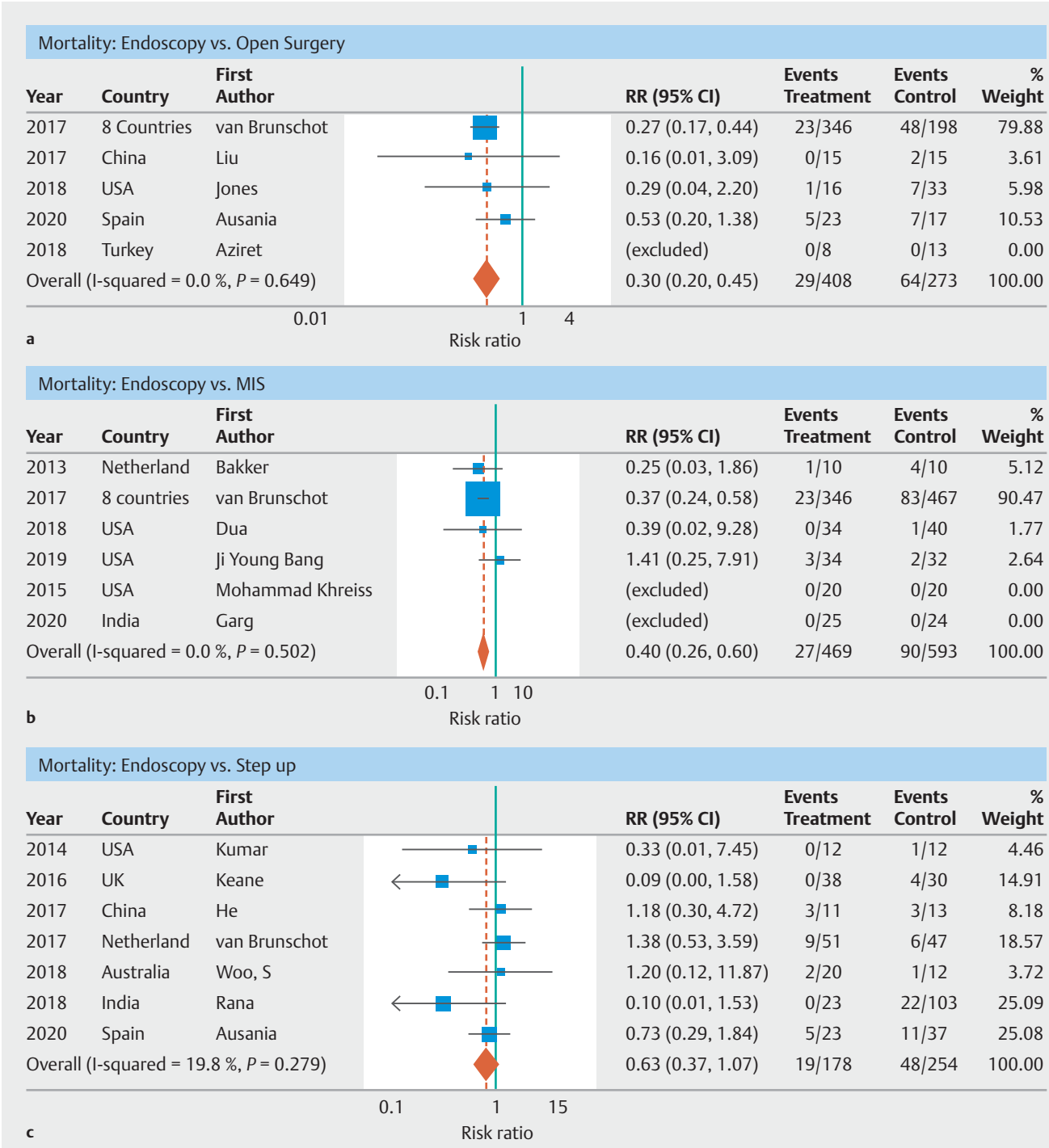
Discussion

The incidence of acute pancreatitis is trending upward in the United States with $2.6 billion annual health care costs [28]. Necrotizing pancreatitis is a serious form of acute pancreatitis with significant morbidity and mortality [29].

Open surgery has been traditional treatment modality in necrotizing pancreatitis, but newer minimally invasive drainage procedures are being increasingly used in the recent years.

This is the largest and most comprehensive systematic review in this topic including over 11,000 patients with necrotizing pancreatitis to assess the rate of mortality and major complications with ED, and various surgical drainage procedures. The start year for the search was 1998, which was when literature about all types of drainage including percutaneous drainage, ED, minimally invasive, or open surgery had already been published. Therefore, the outcomes of various drainage procedures were compared in the era of modern patient care.

The pooled rate of mortality was observed to be 3 % with ED, 8 % with minimally invasive surgery, 13 % with step-up approach, and 22 % with open necrosectomy. The findings were further confirmed on evaluation of comparative studies show-



▶ **Fig. 2** Forest plot comparing mortality rate between endoscopic drainage (ED) and other types of drainage procedures in comparative studies. **a** ED vs. open surgery. **b** ED vs. minimally invasive surgery. **c** ED vs. step-up approach.

ing significantly lower rate of mortality with ED compared to open, or minimally invasive surgery.

ED of pancreatic necrosis has evolved from transmural stent placement to endoscopic necrosectomy over the past decade or so. Endoscopic necrosectomy involves debridement of pancreatic necrosis through a minimal access route thereby avoiding further surgical insults in already severely unwell patients and reducing potential morbidities of more extensive operations [30]. The reduced mortality and morbidity with ED may be explained in part by the lower rate of systemic inflammatory response syndrome imposed by ED as compared to surgical procedures [9].

In this study, subgroup analysis showed that in those with infected WOPN who are the most severely ill group of patients,

▶ **Table 2** Outcomes in studies comparing endoscopic vs. surgical drainage methods.

	Mortality		Fistula formation		New onset DM		Exogenous pancreatic insufficiency	
	No. participants (no. studies)	RR (95 % CI)	No. participants (no. studies)	RR (95 % CI)	No. participants (no. studies)	RR (95 % CI)	No. participants (no. studies)	RR (95 % CI)
Endoscopy vs. open surgery	681 (5)	0.30 (0.20 – 0.45)[1]	480 (4)	0.29 (0.09 – 0.99)[1]	51 (1)	0.44 (0.18 – 1.08)	33 (1)	0.69 (0.19 – 2.57)
Endoscopy vs. MIS	1062 (6)	0.40 (0.26 – 0.60)[1]	709 (4)	0.22 (0.12 – 0.41)[1]	89 (2)	0.81 (0.31 – 2.12)	90 (2)	0.54 (0.22 – 1.35)
Endoscopy vs. step-up	432 (7)	0.63 (0.37 – 1.07)	116 (2)	0.24 (0.11 – 0.52)[1]	131 (3)	0.32 (0.04 – 2.49)	107 (2)	1.0 (0.61 – 1.75)

MIS, minimally invasive surgery; DM, diabetes mellitus; RR, risk ratio; CI, confidence interval.
[1] Statistically significant difference.

the mortality rate with ED was 8 %, which is acceptable as compared with 10 % rate of mortality with minimally invasive surgery and 24 % with open surgery.

In this meta-analysis, the pooled rate of fistula formation was 35 % for open surgery, 17 % for minimally invasive surgery and the step-up approach, and only 2 % for ED. Rates of fistula formation were also significantly lower with ED compared to all other drainage procedures in comparative studies. Some drainage procedures including percutaneous drainage or VARD create at least a temporary externally drained pancreatic fistula in all patients, which may become more persistent in some cases [31]. Also, patients with other types of external drainage, including laparoscopic or open surgery, are at high risk of developing pancreatic or enteric fistulas. Fistula may result in significant morbidity and often requires prolonged hospitalization [31]. Therefore, the lower rate of fistula formation with ED is considered an important advantage for this procedure.

The rate of new onset DM or exocrine pancreatic insufficiency was not different in endoscopic or surgical procedures. Such long-term functional abnormalities may be in part related to the loss of viable pancreatic tissue in necrotizing pancreatitis especially in those with extensive necrosis. Performing debridement through either endoscopic or surgical necrosectomy further aggravates tissue loss and may lead to new onset DM or exocrine pancreatic insufficiency [32].

Endorotor is an automated device for endoscopic necrosectomy which is recently authorized for marketing by FDA [33, 34]. Further controlled studies should be conducted to assess the effect of such dedicated devices on reducing the number of procedures or duration of hospital stay.

This study has some limitations. First, considering the large number of included studies (e. g. 170 articles), it was not feasible to obtain raw data from the authors of the studies. This point is important to control the possibility of reusing patients in several articles from the same authors. To decrease the chance of this issue, we looked at the study periods and participating institutions and excluded studies with suspected reused data from the same institutions. In this systematic review, 60 articles with suspected reused patient data were excluded from the analysis (▶ **Fig. 1**). Second, there are several factors that may affect risk of death in necrotizing pancreatitis, including presence of infected necrosis, the amount of solid necrotic materials inside the collection, timing of intervention, and presence of organ failure [29]. All of these factors could not be taken into account in this large-scale meta-analysis. To consider the effect of confounding variables on mortality, subgroup analysis was performed on studies with the median time from pancreatitis onset to surgery of ≥ 4 weeks. Also, the mortality rate was assessed only in studies that included patients with suspected or confirmed infected WOPN. Third, there were heterogeneities in the included studies in terms of types of drainage procedures, timing of intervention, and severity of the illness. We attempted to control heterogeneities by dividing surgical procedures into three different groups of minimally invasive, step-up, and open surgery. We also performed various subgroup analyses to assess the variables in more homogeneous groups of patients. It may be argued that more severely ill patients with more solid components were more likely to be referred for open surgical necrosectomy. This may be a confounding variable that could explain, in part, a higher rate of mortality in open surgery observed in this study. To address this concern, we assessed mortality rates in studies conducted after 2010 when the landmark and practice changing article published and demonstrated inferiority of open surgery to minimally invasive approaches in necrotizing pancreatitis [7]. It was expected that after this date, open surgery was not reserved for severely ill patients. In this analysis, the pooled mortality remained high at 15 % for open surgery, and it was 4 % for minimally invasive surgery, 14 % for a step-up approach, and 3 % for ED. This finding further corroborates the validity of the low mortality rate observed with the ED approach. Fourth, more papers about open surgery were published in early 2000, and the papers about ED were published more recently. This could be responsible, in part, for better outcomes with ED. The subgroup analysis of studies conducted after 2010 addressed this

concern and demonstrated a mortality rate of 15 % for open surgery, and 3 % for ED.

Fifth, there were only seven RCTs of 170 included studies in the systematic review. This potentially weakens the conclusion from the analysis. We performed a separate analysis of RCTs comparing endoscopic and surgical drainages. A pooled analysis of RCTs showed a lower rate of fistula formation with ED compared to minimally invasive surgery, although the pooled rate of mortality did not differ between the two groups.

Conclusions

In conclusion, this comprehensive systematic review showed that ED has a lower rate of fistula formation and of mortality compared to various surgical drainage approaches for necrotizing pancreatitis. It should be noted that necrotizing pancreatitis is a heterogeneous disease and "one size" treatment does not fit all [31], and the management of such patients should be discussed in multidisciplinary meetings. WOPN patients with extension of necrosis into the paracolic gutters or pelvis may require percutaneous drainage as an adjunct to an endoscopic procedure [2]. Also, patients with residual necrosis burden after endoscopic necrosectomy may need to undergo additional percutaneous or surgical drainage [2].

Competing interests

Dr. Kahaleh has received grant support from Boston Scientific, Fujinon, Xlumena Inc., W.L. Gore, MaunaKea, Apollo Endosurgery, Cook Endoscopy, ASPIRE Bariatrics, GI Dynamics, Nine Point Medical, Merit Medical, Olympus, ERBE, and MI Tech. He is a consultant for Boston Scientific, Concordia Laboratories, Inc., ABBvie, and MaunaKea Tech. None of this funding was related to this paper.

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