

Percutaneous endoscopic necrosectomy (PEN) for treatment of necrotizing pancreatitis: a systematic review and meta-analysis



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ABSTRACT

Background and study aims Endoscopic necrosectomy is limited by the proximity of necrosis to the gastrointestinal tract. Percutaneous endoscopic necrosectomy (PEN) is a minimally invasive endoscopic method of percutaneous debridement. Studies regarding its efficacy and safety are lacking. The purpose of this study was to assess the efficacy and safety of PEN in necrotizing pancreatitis.

Methods Pubmed, Ovid, Cochrane, Scopus and Web of Science Database were searched from inception through February 2021. Dual extraction and quality assessment of studies using Cochrane risk of bias tool were performed independently by two authors. The primary outcome was defined as clinical success of PEN. Secondary outcomes included periprocedural morbidity, mortality, and long-term morbidity and mortality.

Results Sixteen observational studies including 282 subjects were analyzed. The average reported age of the participants was 50.3 years. Patients with reported gender included 39% females and 61% males. The success rate as defined by complete resolution of necrosis and removal of drainage catheters/stents was 82% (95% confidence interval 77–87). The mean size of pancreatic necrosis was 14.86 cm (5–54 cm). The periprocedural morbidity rate was 10%, while there was no reported periprocedural mortality. The long-term morbidity rate was reported as 23% and mortality at follow-up was 16%.

Conclusions PEN is a novel method of endoscopic management of pancreatic necrosis. Based on our meta-analysis of retrospective studies, it represents a safe treatment modality with high rates of clinical success and low rates of perioperative morbidity and mortality. This study supports the use of PEN when conventional endoscopic therapy is not feasible.

Introduction

Acute pancreatitis is the third most prominent gastrointestinal disorder requiring acute hospitalization in the United States [1]. Necrotizing pancreatitis, a complication which can occur in 20%

of patients with acute pancreatitis, remains a devastating disease with significant morbidity, mortality, and prolonged hospital stay, despite advancements in medical care, understanding of underlying etiology, and development of treatment algorithms.

Necrotizing pancreatitis mortality rate ranges from 15% in patients with sterile necrosis; with infected necrosis, the mortality rate increases up to 30% with greater association with multi-organ failure. Commonly, infected necrosis is treated with IV antibiotics; however worsening infection may call for earlier drainage and or debridement. Less invasive therapies than surgical necrosectomy, and more effective than percutaneous drainage are needed to successfully treat pancreatic necrosis as a sequela of necrotizing pancreatitis [2–5]. The current algorithm for intervention in patients with necrotizing pancreatitis and pancreatic necrosis includes a stage multidisciplinary step-up approach with endoscopic transluminal drainage (ETD) or percutaneous drainage (PCD) as an initial step [2–6]. Central collection and lesser sac collections are usually amenable to endoscopic drainage and necrosectomy, while distant flank or pelvic collections warrant percutaneous drainage [7].

ETD involves endoscopic placement of stent (plastic or metal) which connects the area of the pancreatic necrosis to the lumen of gastrointestinal tract (stomach or duodenum), thereby allowing free drainage of necrotic material and pus within the gastrointestinal tract. Placement of a metal stent can act as an entry portal to the necrosis and facilitate further endoscopic necrosectomy of the necrotic cavity.

Video-assisted retroperitoneal debridement (VARD) is a form of minimally invasive retroperitoneal necrosectomy. Commonly VARD requires a surgical incision of 5 to 10 cm for frank insertion of the laparoscope, irrigation catheter, and surgical forceps. Debridement is completed using laparoscopic forceps and large drainage catheters are placed for repeated lavage and or drainage. VARD has been studied in the TENSION trial and PANTER trial respectively demonstrating reduced rate of end point complications or death in utilizing minimally invasive step-up therapy compared to open necrosectomy in patients with necrotizing pancreatitis [8, 9].

Percutaneous drainage includes insertion of a drainage catheter evacuating liquefied necrotic fluid and purulent material under pressure. This may temporize sepsis, improve patient's clinical condition, and allow further encapsulation [10]. Despite adequate initial drainage, PCD is limited by the inability to perform necrosectomy for the solid debris where surgical necrosectomy is traditionally attempted; however, this has been associated with significant mortality [11]. Despite high mortality, surgical necrosectomy was required in up to 44% of patients undergoing PCD [12].

Dual-modality drainage is often required due to lack of symptom resolution and/or lack of adequate drainage. Solely ETD is feasible in fewer than two-thirds of patients, with the rest requiring addition of percutaneous drains or surgery [13]. Dual-modality drainage when compared to PCD alone, decreases the length of hospitalization, number of interventions (percutaneous and endoscopic), as well as the mean interval until the final drain is removed [14].

Percutaneous endoscopic necrosectomy (PEN) was described as an adjunct to the aforementioned methods, in which a flexible endoscope is percutaneously inserted and used for debridement of solid necrosis, leading to resolution of sepsis and achieving adequate necrosectomy [15]. The versatility of a

flexible endoscope allows for better access into the retroperitoneum.

Since its initial description over 20 years ago, its use is still limited and it is not exclusively incorporated into strategies for necrotizing pancreatitis management [16]. This in part is due to the lack of larger prospective studies studying its benefits and adverse events (AEs). To date, no meta-analysis has addressed PEN therapy clinical success, AEs, and mortality. For these reasons, we conducted a systematic review with meta-analysis of all eligible studies to determine the clinical success achieved with PEN, perioperative morbidity, mortality, as well as long-term mortality.

Description of percutaneous endoscopic necrosectomy technique

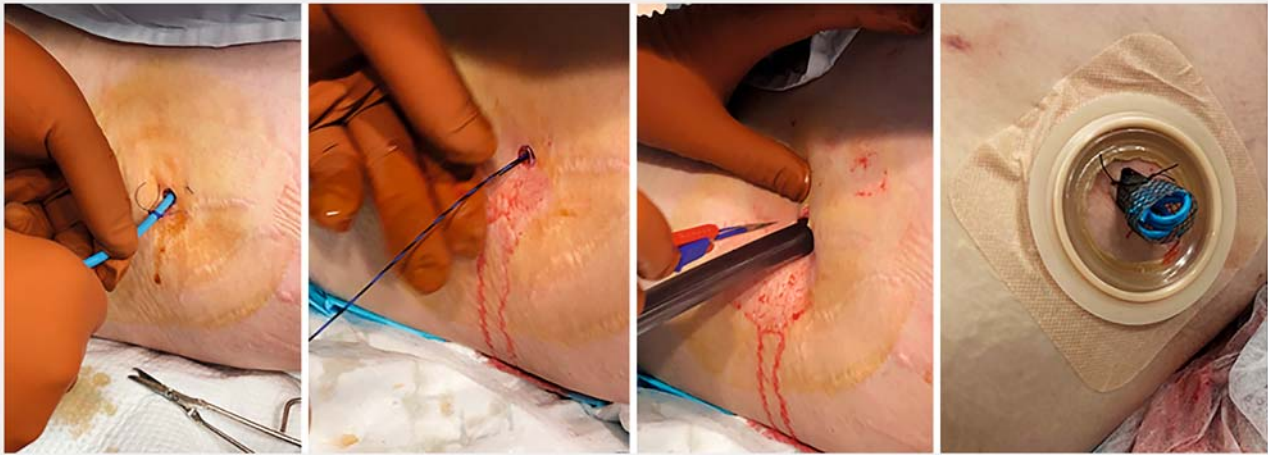
Studies described below used an overall similar technique, with a few differences that are individualized and summarized in the Supplementary Table 1.

After a lack of improvement and lack of adequate drainage of distal necrotic collection not amenable to endoscopic drainage, multidisciplinary assessment of percutaneous drainage is assessed. In a few cases where transillumination is achieved by endoscope present within the necrotic cavity, direct percutaneous access with a needle can be performed, using the endoscope transillumination light as a guide, similar in fashion to percutaneous gastrostomy tube placement. After initial access, a percutaneous catheter is placed, and can be incrementally upsized over time. Then a wire is used to guide transcatheter balloon, or bougie dilation of the tract, with latter placement of covered esophageal stent. In some patients, the wire method with balloon dilation can be used immediately after needle access is achieved. The percutaneous drain will remain for interim drainage between necrosectomy sessions, or a wire-guided esophageal covered stent is placed. The stent ending is sutured to the skin and the stent is left for access of recurrent PEN. In between necrosectomy sessions, spontaneous drainage is achieved through the percutaneous drain or the covered stent, which is covered by the ostomy pouch. Stents that have previously been studied include double pigtail plastic stent (7–10F), fully covered self-expanding metal stent (FCSEMS) (6–10 mm), and LAMS (8–20 mm). After resolution of necrotic cavity, the drain/stent is removed and the tract spontaneously closed, in similar fashion to the removal of a PEG tube (► Fig. 1).

Methods

Study selection

The search strategy, inclusion and exclusion criteria were defined before the search with the consensus of three authors. Our study has been performed in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses statement (PRISMA statement) [17, 18]. A search strategy using combination of text words and subject heading was constructed to identify studies reporting use of PEN. Five databases were included: PubMed, Medline Ovid, Cochrane Central, Scopus and Web of Science. Published studies, articles in press, and abstracts were included for further analysis. Specific Medi-



► **Fig. 1** Percutaneous access for future endoscopic necrosectomy as performed in our institution.

cal Subject Headings (MeSH) terms included “percutaneous,” “endoscopic,” “necrosectomy,” “sinus tract,” “endoscopy”. The specific inclusion criteria for the systematic review and meta-analysis were: all randomized control trials or prospective studies or retrospective studies in patients more than 18 years of age undergoing PEN where there is description of endoscopic technique, follow-up of patients and evaluation of success, AEs and mortality. Only full-text articles available in English language were included. Case reports were excluded.

Study design and intervention

Observational prospective, retrospective studies, and case series were included for full review if the outcomes from the ongoing intervention were reported. The study intervention was defined as flexible PEN utilized as a therapy for complications of necrotizing pancreatitis.

Study characteristics and quality assessment

Non-randomized studies were evaluated using the preferred ROBINS-I tool (Newcastle- Ottawa scale). For each study, we assessed the methodology and ascertained the risk of bias due to confounding, classification of interventions, selection of participants, measurement of outcomes and reported results. Quality assessments were also conducted independently, and discrepancies were resolved by consensus. The terms used were “low risk” and “high risk” of bias at the study level for scoring system.

Outcome measures

Primary outcomes

The primary outcome was the clinical success rate for PEN, defined as clinical resolution of an underlying peripancreatic collection with subsequent removal of percutaneous drains. This was expressed as a pooled event rate and 95% confidence interval (95% CI). Subgroup analysis was performed based on the diameter of endoscope used for necrosectomy: small diameter

endoscope (4.2–5.5 mm) versus large diameter endoscope (8.8–12.9 mm). In addition, subgroup analysis was performed based on the type of drainage catheter used as a bridging catheter between PEN sessions: covered self-expandable metal stent (FCSEMS) versus percutaneous drain (PCD).

Secondary outcomes

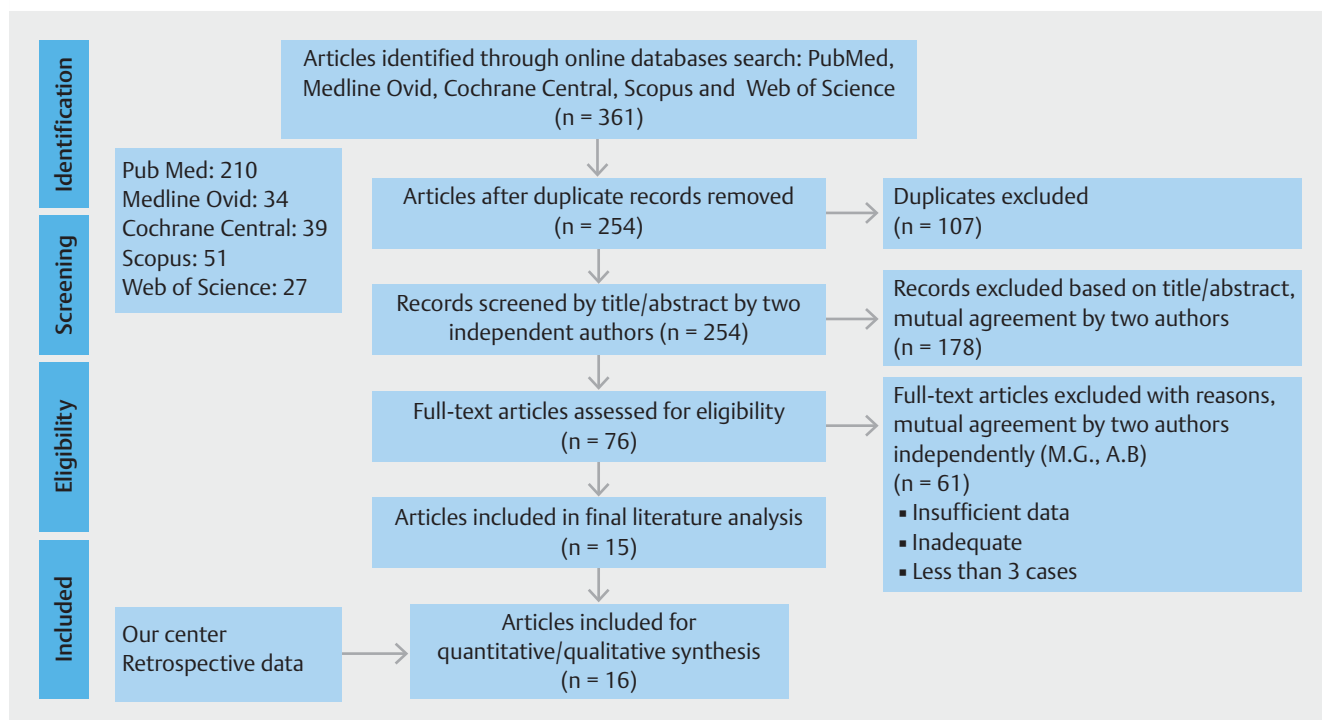
Predefined secondary outcomes included perioperative morbidity and mortality as well as long-term morbidity and mortality. Perioperative morbidity and mortality were defined as events occurring during or immediately after the performance of PEN, being a direct consequence of the PEN. Long-term mortality and morbidity were defined as events occurring at the time of follow-up, being correlated to the prior PEN. Subgroup analysis was also performed with the same criteria as above.

Data extraction and quality assessment

Data were extracted by two authors (M.G and A.B.) independently and then compared. Titles and or abstracts considered potentially relevant by either reviewer were retrieved for review. The lists of full manuscripts meeting inclusion criteria from the two reviewers were compared, and any disagreements were resolved by discussion and consensus. Third (senior) author (M.K) served as the final arbitrator if consensus was not achieved.

Data synthesis and analysis

All statistical analyses were conducted using the Comprehensive Meta-Analysis software package (Biostat, Englewood, New Jersey, United States). The final pooled risk estimates were obtained using random effects models. Mean values for the primary and secondary outcomes were pooled using weighted means. The Cochrane Q and the I² statistics were calculated to assess heterogeneity between studies. $P < 0.05$ was considered statistically significant. The I statistic was used to estimate heterogeneity across studies, where values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high de-



► **Fig. 2** Flowchart of paper selection for the systematic review and meta-analysis following eligibility criteria in "Methods."

degrees of heterogeneity. Probability of publication bias was assessed using funnel plots and with Egger's test. To explore differences between studies that might be expected to influence the effect size, we performed random effects (maximum likelihood method) multivariate meta-regression analyses. Studies that did not report standard deviations, or if standard deviations could not be calculated, then the reported mean of the study was used as an estimate of its standard deviation to be able to include them in the meta-analysis.

Results

We identified 361 citations that matched our initial search criteria from our databases. After initial review and removal of duplicate studies, 254 studies remained for subsequent analysis. On further review, 35 studies were subsequently analyzed, and a total of 15 studies were included in the analysis with a total of 275 subjects (► **Fig. 2**). Of these studies, 12 were retrospective case series studies, two were prospective observational studies, and two were observational cross-sectional studies. Gray literature was not found at this juncture during our literature search [19]. The summary of studies included is presented in ► **Table 1** [15, 20–33]. Each study's detailed approach for performing necrosectomy and treating patients is shown in ► **Table 2**.

A total of 282 patients were included in our analysis. The average reported age of the participants was 50.3 years. Patients with reported gender included 39% females and 61% males (► **Table 3**). Reported etiology of pancreatitis included: gallstone pancreatitis (50%), alcohol induced pancreatitis

(39%), post-endoscopic retrograde cholangiopancreatography pancreatitis (4%), hypertriglyceridemia (8%) and other (20%).

In regard to PEN, the mean size of pancreatic necrosis prior to PEN was 15 cm (5–54 cm). Large diameter endoscope (8.8–12.9 mm) was used in 13 studies, while small diameter (4.2–5.5 mm) in 3 studies. Percutaneous drain was used for percutaneous drainage between sessions in 11 studies while covered metal stent (fully or partially covered) was used in five studies. Mean number of necrosectomy sessions was 3.5 (1–18 sessions), median number of sessions 3.7. Some studies reported multiple percutaneous drains in the same patient (up to 5), but the majority of patients had one percutaneous drain. Duration from symptoms to percutaneous drain, conversion to stent and interventions are presented in Supplementary Table 1.

Average length of hospital stay was 67.5 days (7–220 days) (► **Table 3**). There was no reported periprocedural mortality, while the periprocedural morbidity rate was 6.5% (16 of 244 patients that were evaluated for periprocedural morbidity) (► **Table 4**). Of 244 patients with individual report on morbidity, six were reported to have intraprocedural bleeding, two peritonitis, two pneumoperitoneum, two aspiration pneumonia, one paralytic ileus, one subcutaneous emphysema, one colon perforation, and one drain dislodgement. The average long-term follow-up was 22 months. During this follow-up, the mortality rate irrespective of underlying cause was reported to be 12% (33 of 282 patients).

► **Table 1** Baseline demographics and outcomes summary for included studies.

Author	Publication year	Type of study	No of patients	Mean age	Female (%)	Mean size of necrosis (cm)	Average hospital stay (days)	Periprocedural morbidity ¹	Periprocedural mortality ²	Long-term morbidity ³	Mortality during follow-up period
Trikudathan [20]	2020	Retrospective	4	47	25%	10	NR	1/4 (25%);	0%	NR	1/4 (25%)
Moyer [21]	2019	Retrospective	23	51	52%	14	NR	NR	0%	3/23 (13%): fistula (3)	2/23 (8%)
Jain [22]	2019	Prospective	53	39	35%	NR	59	7/53	NR	15/53 (28%)	11/53 (20%)
Ke [23]	2019	Retrospective	23	44	26%	NR	34	1/23 (4%)	0%	11/23 (48%)	7/23 (30%)
Thorsen [24]	2018	Retrospective	5	44	80%	33	NR	0/5 (0%)	0%	2/5 (40%)	1/5 (20%)
Tringali [25]	2018	Retrospective	3	49	0%	15	NR	0/3 (0%)	0%	0%	0%
Goenka [26]	2018	Observational, cross-sectional study	10	44	30%	7	25	2/10 (20%)	0%	0%	0%
Liu [27]	2017	Retrospective	15	53	33%	NR	51	NR	NR	8/15 (53%)	0%
Saumoy [28]	2018	Prospective	9	62	22%	10	NR	0/9 (0%)	0%	0%	1/9 (11%)
Jürgensen [29]	2017	Retrospective	14	56	50%	NR	NR	1/14 (7%)	0%	3/14 (21%)	2/14 (14%)
Dhingra [30]	2015	Observational, cross-sectional study	15	35	33%	NR	54	1/15 (6%)	0%	3/15 (20%)	1/15 (6%)
Castellanos [31]	2012	Prospective	32	55	50%	NR	79	0/32 (0%)	0%	3/32 (9%)	5/32 (15%)
Tang [32]	2010	Retrospective	42	NR	40%	NR	45	0/42 (0%)	0%	4/42 (10%)	0%
Mui [33]	2005	Retrospective	13	53	38%	NR	96	2/13 (15%)	0%	1/13 (8%), colonic fistula	1/13 (8%)
Carter [15]	2000	Retrospective	14	49	50%	NR	60	1/14 (7%)	0%	1/14 (7%)	2/14 (14%)

N/A, not applicable; NR, not reported; WON, walled off necrosis.

¹ Abdominal pain is excluded.

² Pancreatic duct leak was not considered as morbidity unless it was specifically stated that it was caused by the necrosectomy.

³ Persistent fluid collection or recurrence was considered as failure of success rather than adverse event; de-novo development was considered as adverse event.

Primary outcomes

Resolution rate

The success rate, as defined by complete resolution of necrosis and removal of drainage catheters/stents, was 82% (95% CI 77–87) based on all included studies (► **Fig. 3**). Study analysis did not reveal significant heterogeneity ($I^2=0$). Subgroup analysis was performed to evaluate these results based on the caliber

of endoscope and type of bridging catheter used. A small-diameter endoscope yielded a pooled resolution rate of 86% (95% CI 74–93), and a large-diameter endoscope resulted in a pooled resolution rate of 81% (95% CI 75–86) (► **Fig. 3** and Supplementary Fig. 1). In terms of type of catheter used for bridging, studies that were using covered stent yielded a pooled resolu-

► **Table 2** Summary of necrosectomy procedures per study and respective percutaneous drains, conversion to stent and interventions.

Author	Tract bridged between procedures with (sizes)	Diameter of flexible endoscope used ¹	Accessories for necrosectomy:	Mean procedure time (minutes)	Mean number of PEN sessions	Number of percutaneous drains (range)	Concurrent transluminal endoscopic drainage	Concurrent ERCP
Trikudanthan [20]	PCD (24F, 24F, 20F, 24F)	Small	snare, roth net, extraction balloon	115	4.7	1–3	yes	NR
Moyer [21]	PCD (28F)	Large	snare	NR	2.1	1–3	no	NR
Jain [22]	PCD (28–30F)	Small	snare, roth net	NR	6.2	NR	no	NR
Ke [23]	FCSEMS (18 mm)	Large	snare, forceps	NR	2.5	NR	yes, 12/23	NR
Thorsen [24]	FCSEMS (20 mm)	Large	snare, basket, tripod	NR	5	1–5	yes, 2/5	NR
Tringali [25]	PCSEMS (18, 20, 20 mm)	Large	basket	NR	3	1	no	NR
Goenka [26]	PCD (32F)	Large	snare, basket, forceps, roth net	45	2.3	NR	yes, 2/10	NR
Liu [27]	PCD double catheter device (size not reported)	Large	forceps	NR	NR	NR	no	NR
Saumoy [28]	FCSEMS (18 mm)	Large	snare, basket	68	3.1	NR	yes, 6/9	YES
Jürgensen [29]	PCD (16–18F)	Large	snare, forceps, roth net	NR	1.7	NR	yes, 6/14	YES
Dhingra [30]	PCD (28F)	Large	snare, basket, roth net	NR	4.9	1–3	no	NO
Castellanos [31]	PCD (32F drainage tube, 18F lavage tube)	Large	forceps	NR	4.4	2	no	NR
Tang [32]	PCD (22F)	Small	forceps	NR	8.5	1–5	NR	NR
Mui [33]	PCD (18–30F)	Small	basket, forceps	NR	5	NR	no	YES
Carter [15]	PCD (28F)	Large	snare, forceps	NR	2	NR	NR	YES

PCD, percutaneous drain; FCSEMS, fully covered self-expandable metallic stent; PCSEMS, partially covered self-expandable metallic stent.

¹ Small diameter is 4.2–5.5 mm; large diameter is 8.8–12.9 mm.

tion rate of 72% (95% CI 57–83) while studies with PCD had resolution rate of 85% (85% CI 79–89) (Supplementary Fig. 1).

Secondary outcomes

Morbidity

Periprocedure-related morbidity was defined as morbidity occurring during the procedure or during the immediate recovery period. It was pooled as 10% (95% CI 5%–17%) (► Fig. 4).

Similarly, subgroup analysis was performed for the secondary endpoints. Based on the endoscope diameter, there was periprocedural morbidity of 10% for small sized and 9.8% for large sized endoscope. Regarding the bridging catheter used, there was periprocedural morbidity of 15% for covered stents and 10% for PCD catheters (Supplementary Fig. 2).

Long-term morbidity was reported up to the end of study patient follow-up. Overall, pooled long-term morbidity was 23% (95% CI 16–31) (► Fig. 5). Long-term morbidity was 9.2% for small and 27% for large endoscopes. In regard to the bridging catheter used, there was periprocedural morbidity of 30% for covered stents and 21% for PCD catheters (Supplementary Fig. 3).

Most common periprocedural complication was bleeding, which occurred during the initial and subsequent necrosectomies. Other causes of periprocedural morbidity were reported as aspiration pneumonia, pneumoperitoneum, peritonitis, paralytic ileus, subcutaneous emphysema, colon perforation, and drain dislodgement (► Table 4).

► Table 3 Descriptive summary of patients, etiology, necrosis, and intervention based on available individual patient data.

	Mean value or percentage	Number of patients with individually reported value (n)
Age (years)	50.3 (18–85)	149
Gender		
Female	39%	111/282
Male	61%	171/282
Pancreatitis etiology		
Gallstones	50%	115/230
Alcohol	19%	43/230
Post-ERCP	4%	9/230
Hyperlipidemia	8%	18/230
Other	20%	45/230
Size of necrosis (cm)	14.8 (5–54)	50
Number of endoscopic sessions	3.5 (1–18)	149
Time from initial PEN to removal of drains (days)	61 (6–214)	46
Length of hospital stay (days)	67.5 (7–220)	91
Length of follow-up (months)	22 (1–144)	121

ERCP, endoscopic retrograde cholangiopancreatography; PEN, pancreatic endoscopic necrosectomy.

Mortality

There was no periprocedural mortality reported in any of the studies included. Periprocedural mortality was defined as AEs leading to death during the performance of PEN.

Long-term mortality was reported up to the end of study patient follow-up. Overall, pooled long-term mortality was 16% (95% CI 11%–21%) (► Fig. 6). The long-term mortality rate was 7.4% for small and 17% for large endoscopes (Supplementary Fig. 4). In regard to the bridging catheter used, there was a long-term mortality rate of 23% for covered stents and 14% for PCD catheters (Supplementary Fig. 4).

Discussion

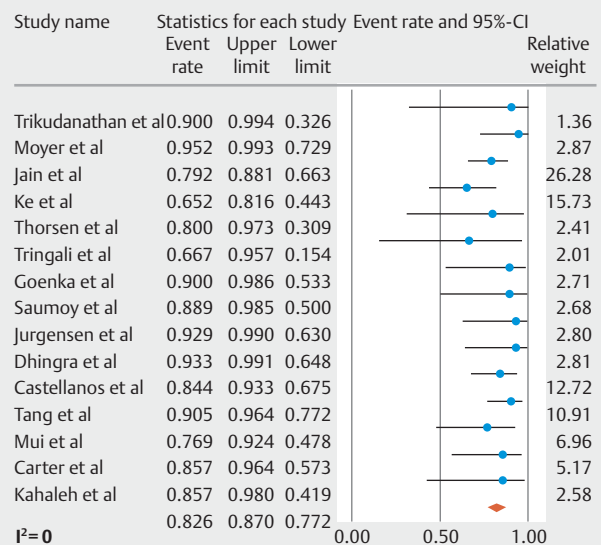
Necrotizing pancreatitis accounts for 5% to 10% of patients with pancreatitis and most commonly presents as necrosis of both pancreatic and peripancreatic fat tissues [29, 34]. Most common etiologies of necrotizing pancreatitis are gallstones and alcohol consumption [8, 35].

While necrotizing pancreatitis has greater morbidity and mortality than acute pancreatitis, infected necrosis increases mortality rate up to 30%; hence early identification and initiation of therapy is necessary [36]. Infected and/or symptomatic

► Table 4 Summary of periprocedural and long-term morbidity based on individually reported cases.

Periprocedural morbidity	6.5% (16/244)
Periprocedural bleeding	2% (6)
Pneumoperitoneum	1% (2)
Peritonitis	1% (2)
Aspiration pneumonia	1% (2)
Paralytic ileus	<1% (1)
Subcutaneous emphysema	<1% (1)
Colon perforation	<1% (1)
Drain dislodgement	<1% (1)
Long-term morbidity	19% (55/278)
Fistula	9% (27)
Bleeding	7% (20)
Splanchnic vein thrombosis	1% (5)
Pseudocyst (new)	1% (5)
Recurrence	<1% (2)
Organ Failure	<1% (2)
Ileus	<1% (2)
Arrhythmia	<1% (1)

Pooled collection resolution rate

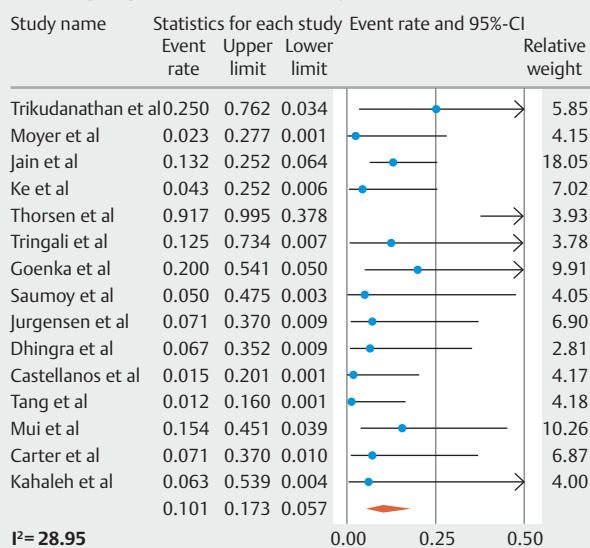


► Fig. 3 Pooled resolution rate defined by complete resolution of necrosis and removal of drainage catheters/stents.

pancreatic necrotic collections require further management by drainage, which can be endoscopic, percutaneous or surgical.

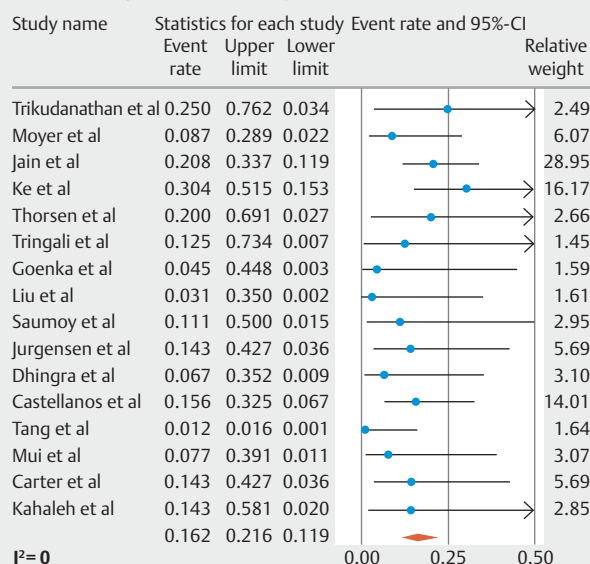
The staged multidisciplinary approach to management of necrotizing pancreatitis is the standard to which patients with

Pooled periprocedural morbidity rate



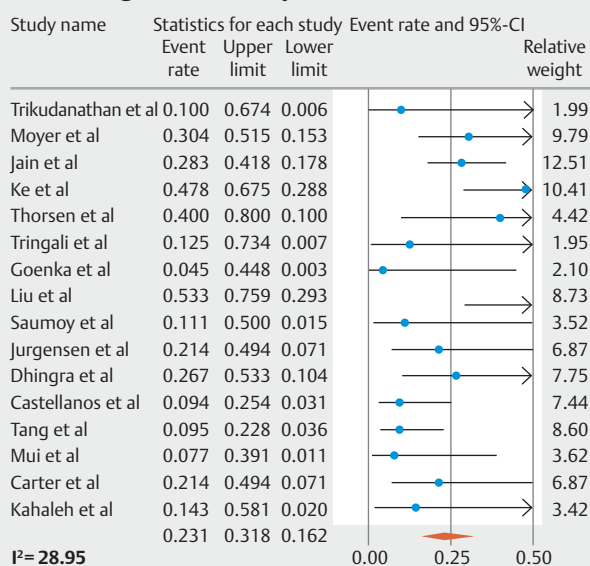
► **Fig. 4** Pooled periprocedural morbidity defined as morbidity occurring during the procedure or within the immediate recovery period.

Pooled longterm morbidity rate



► **Fig. 6** Pooled long-term mortality defined as adverse events leading to death as a direct or indirect cause of the necrotizing pancreatitis.

Pooled longterm morbidity rate



► **Fig. 5** Pooled long-term morbidity defined as morbidity occurring during follow up, directly or indirectly caused as a result of the necrotizing pancreatitis and percutaneous endoscopic necrosectomy.

scopic drainage requires additional percutaneous access and drainage [36, 37]. Percutaneous drainage is dependent on the size of percutaneous drains with the lack of necrosectomy capabilities and/or rigidity of surgical instruments [20, 29]. In these cases, use of flexible endoscope with working channel allows for more significant necrosectomy using several types of debridement tools while reaching pockets that a rigid instrument cannot reach. This technique may be used singularly or adjacent to transluminal endoscopic drainage [23, 29, 38].

The effectiveness of safety of this technique is limited to case reports and case series only; therefore, most of the results are only descriptive. To our knowledge, this is the first meta-analysis evaluating the effectiveness and safety of PEN. Based on our results, PEN represents a safe approach of treating pancreatic necrosis with difficult to reach transluminal endoscopic drainage and necrosectomy. The pooled success rate of PEN is 82%, with a good overall safety profile and low morbidity and mortality rates. The most common periprocedural morbidity event was bleeding that resolved spontaneously in most reported cases. There was no reported periprocedural mortality and pooled long-term mortality was 16%, which is lower than the prior reported mortality of surgically managed necrotizing pancreatitis with morbidity of (34%–95%) and mortality (11%–39%) rates [39].

There are several limitations to our study which need to be taken into consideration when interpreting the results. First, the lack of sufficient number of randomized controlled trials which make our meta-analysis comprised mostly of retrospective observational studies and case series. Therefore, the quality of our meta-analysis is limited to the quality of individual studies. Second, the moderate heterogeneity in certain out-

necrotizing pancreatitis are currently treated. Endoscopic approach is favored over open necrosectomy because of the lower rate of pancreatic fistulas and length of hospital stay when compared to surgical approach [34]. The presence of more distant pancreatic necrosis not reachable with transluminal endo-

comes may not adequately reflect clinical outcomes and could over or under report its efficacy and AEs [19]. Also, certain studies used concomitant transluminal endoscopic necrosectomy, while others were performed prior to the era of transluminal necrosectomy. Some studies reported multiple percutaneous drains in same patients, however the majority of patients had one percutaneous drain. Many studies did not report on the use of concomitant ERCP and prevention of pancreatic ductal leak, which similarly may alter the primary outcome of our meta-analysis. Unfortunately, in review, factors indicating time of intervention during patient's clinical course including onset of pancreatic necrosis and percent necrosis were not uniformly discussed across previously published literature. As aforementioned, commonly FCSEMS, LAMS, and plastic stents have commonly been utilized, but studies have been limited comparing clinical efficacy, safety, leading to inconsistent results [40]. Minimally invasive drainage via step-up approach, VARD and PEN, has shown superior drainage, debridement in comparison to frank surgical approach with regard to complications and long-term morbidity with no paper reporting direct comparison. Lastly, the length of follow-up varied among studies.

Conclusions

In conclusion, PEN is a minimally invasive endoscopic therapy for necrotizing pancreatitis with walled off pancreatic necrosis which may be a safe modality in treating necrosis not easily accessible by transluminal approach. This is a technique that could be utilized as an adjunct to the transluminal necrosis to achieve adequate necrosectomy and debridement. Given our findings, future prospective data with recorded timing of onset of pancreatitis, percent necrosis, uniform technique selection, as well as comparison directly with VARD, may further elucidate technical and clinical success of PEN as a guideline therapeutic modality in treating pancreatic necrosis.

Competing interests

Dr. Sarkar has done consulting work for US Endoscopy and Obalon Therapeutics. Dr. Shahid has done consulting work for US Endoscopy. Dr. Tyberg has done consulting work for EndoGastric Solutions, and Obalon Therapeutics. Dr. Kahaleh has done consulting work for Boston Scientific, Interscope Med, and Abbvie and has received research grants from Boston Scientific, Emcision, Conmed, Pinnacle, Cook, Gore, Merit, and Olympus. Dr. Gaidhane has done consulting work for 3D Matrix.

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