—Review Article—

EUS *versus* percutaneous management of postoperative pancreatic fluid collection: A systematic review and meta-analysis

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ABSTRACT

Postoperative pancreatic fluid collection (POPFC) is an important complication following abdominal surgery. POPFC causes significant morbidity and mortality. Management options are time-consuming and severely affect patient's quality of life. Surgical and/or percutaneous drainage (PCD) is the traditional mainstay of treatment. Studies have shown that EUS could have a role to play in the management of POPFC. Data are limited in the comparison of clinical outcomes with EUS as compared to PCD to this end. We conducted a comprehensive search of multiple electronic databases and conference proceedings including PubMed, EMBASE, Google Scholar, LILACS, and Web of Science databases (earliest inception through September 2018) to identify studies that reported on the clinical outcomes of EUS and PCD in the management of POPFC. The goals were to estimate and compare the pooled rates of technical success, clinical success, adverse events, and POPFC recurrence with EUS and PCD. A total of 13 studies were included in the analysis. Ten studies (239 patients) used EUS and 6 studies (267 patients) used PCD in the management of POPFC. The pooled rate of clinical success with EUS was 93.2% (95% confidence interval [CI] 88.2–96.2, $I^2 = 0$) and with PCD was 79.8% (95% CI 70–87, $I^2 = 74$). The difference was statistically significant, $P = 0.002$. Recurrence rate was significantly lower with EUS as compared to PCD (9.4%: 95% CI 5.2–16.5 *vs*. 25.7%: 95% CI 24.3–41.7; $P = 0.02$). Pooled rates of technical success and adverse events were similar with EUS and PCD. Our meta-analysis shows that EUS has significantly better clinical outcomes, in terms of clinical success and disease recurrence, in the management of POPFC as compared to PCD.

Key words: Abdominal surgery, EUS, percutaneous drainage, postoperative pancreatic fluid collection

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INTRODUCTION

Postoperative fluid leaks are a well-recognized adverse event-causing significant morbidity and mortality after pancreatic resection.[1] The reported incidence of pancreatic leak ranges from 5% to 20%.[2,3] The reported rates of morbidity and mortality range from 40% to 60%.[4] The leaking pancreatic fluid has potential enzymatic action and can result in various complications. It can cause bleeding from adjacent vessels, tissue necrosis, and abscess formation. Patients can present with pancreatic ascites, pancreaticopleural or pancreaticocutaneous fistulae, or just pancreatic fluid collection. Such fluid collections following pancreatic surgery are termed as postoperative pancreatic fluid collection (POPFC).

Traditionally, POPFCs have been managed by noninterventional conservative approach that includes long-term jejunal feeding, total parenteral nutrition, octreotide, and/or antibiotics. Interventional approaches such as percutaneous drainage (PCD), endoscopic retrograde cholangiography transpapillary stent placement, EUS-guided drainage, and surgical cystgastrostomy with or without debridement may be needed if the POPFC is persistent, large, or symptomatic. Treatment most often entails a time-consuming process with multiple imaging tests, multiple drainage procedures, increased intensive care unit and/or hospital length of stay, and readmission to hospital.[5,6] Surgical intervention on a POPFC increases the risk of overall morbidity and mortality.[7]

PCD has been the conventional approach to managing symptomatic POPFC. External catheters require daily care, maintenance, can cause local skin irritation, infections, fistula formation, and compromise patient's quality of life.[8] EUS-guided management of POPFC has important advantages including obviating the need for an external drain, minimizing the risk of external pancreatic fistulae, and preventing fluid and electrolyte losses. Reported literature evaluating and comparing EUS to PCD shows similar clinical outcomes.[1,8,9] The data are limited by small-sized retrospective studies, with no randomized controlled trials to this date. We therefore conducted this meta-analysis to compare EUS-guided management to percutaneous (PCD) management of POPFC.

METHODS

Search strategy

We conducted a comprehensive search of several databases and conference proceedings including PubMed, EMBASE, Google Scholar, LILACS, and Web of Science databases (earliest inception to September 2018). We followed the Preferred Reporting items for Systematic Reviews and Meta-Analyses guidelines,[10] using predefined protocol, to identify studies reporting the use of EUS and PCD in the management of POPFC. An experienced medical librarian using inputs from the study authors helped with the literature search.

Key words used in search included a combination of "postoperative," "post-surgical," "post-pancreatectomy," "pancreatic fluid collection," "abdominal fluid collection," "endoscopic management," "EUS guided drainage," and "percutaneous drainage." The search was restricted to studies in human subjects and published in English language in peer-reviewed journals. Three authors (M.B., S.M., D.S.) independently reviewed the title and abstract of studies identified in primary search and excluded studies that did not address the research question, based on prespecified exclusion and inclusion criteria. The full text of remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus and in discussion with a coauthor.

The bibliographic section of the selected articles as well as the systematic and narrative articles on the topic was manually searched for additional relevant articles.

Study selection

In this meta-analysis, we included studies that evaluated the following: (1) technical success, clinical success in EUS management of POPFC (EUS-POPFC), and (2) technical success, clinical success in PCD management of POPFC (PCD-POPFC). Studies on nonpancreatic surgery were included as long as they provided information on POPFC. Studies irrespective of the simultaneous use of transpapillary drainage, study design, inpatient/outpatient setting, geography, and abstract/manuscript status were included as long as they provided data needed for the analysis.

Following were our exclusion criteria: (1) studies with no data on pancreatic surgery, (2) studies reporting on abdominal fluid collections not classified as

pancreatic, (3) studies reporting on abdominal fluid collections without data on pancreatic collections, (4) studies on POPFC where the standard endoscope was used, (5) studies that did not report on the technical success of EUS-POPFC, (6) studies that did not report on the clinical success of EUS-POPFC, and (7) studies done in pediatric population (age <18 years).

In case of multiple publications from the same cohort, data from the most recent and/or most appropriate comprehensive report were included. In our search process, we did not encounter any such study.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least three authors (S.M., D.S., G.V.) independently, and three authors (S.M., D.A., M.B.) did the quality scoring independently.

In the situation of randomized trials, and case–control studies, the data collection was done as number of reported events (*n*) out of total number of patients (*N*) from each study. The collected data were treated akin to cohort studies, and therefore, we used the Newcastle–Ottawa scale for cohort studies to assess the quality of studies.[11] This quality score consisted of 7 questions: representative of the average adult in the community (1 point for population-based studies, 0.5 point for multicenter studies, 0 point for a single-center hospital-based study); cohort size (1 point for >40 patients, 0.5 point for 39–20, and 0 point for <20 patients); information on technical and clinical success (1 point if reported, 0.5 point if not reported and had to be derived from percentage value, 0 point if not reported); outcome not present at start of study (1 point if not present, 0 point if present); factors comparable with PCD group (1 point if yes, 0 point if no); adequate clinical assessment (1 point if yes, and 0 point if no), long enough follow-up time for outcomes to occur (1 point if yes, 0 point if not mentioned); adequate follow-up time for outcome to occur (1 point if yes, 0 point if no); and adequacy of follow-up (1 point if all patients were accounted for, 0.5 point if <50% patients lost to follow-up, 0 point if >50% patients lost to follow-up). A score of >6, 4–6, and ≤3 were considered suggestive of high-quality, medium-quality, and low-quality study, respectively.

Outcomes assessed

1. Pooled rates of technical success and clinical success in the management of POPFC: EUS-POPFC *versus* PCD-POPFC
2. Pooled rates of adverse events and rates of recurrence in POPFC.

Assessment methodology and definitions

The collected data were matched between the EUS and PCD management groups. The baseline patient characteristics, symptomatology, indication for surgery, time to drain placement, and the number of drains used were comparable between the groups. Although this model of comparison is indirect and should be considered weak when compared to a randomized controlled trial, the approach is comparable to a retrospective case–control study with matched groups.[12]

In the included studies, technical success with EUS and PCD management was defined as follows:

1. Successful deployment of at least one endoscopically placed stent into the fluid collection, and/or
2. The ability to access and drain a collection by placement of one or more transmural drains
3. The ability to access and drain a collection by placement of one or more percutaneous catheters under computed tomography (CT) or ultrasound guidance.

Clinical success was evaluated at the end of follow-up period and was defined as follows:

1. Stable, ambulatory patient with no external drainage, with resolution of sepsis, no antibiotics treatment, and on normal oral food intake, and/or
2. Resolution of the fluid collection on follow-up CT scan, and/or
3. Resolution of symptoms present before the procedure(s), and/or
4. Resolution of symptoms at 6–8 weeks of follow-up, and/or.

Procedure-related complications or adverse events were defined as follows:

1. Any newly developed complications after procedure, such as bleeding, peritonitis, or symptomatic pneumoperitoneum
2. Sepsis or infection was considered if it occurred after the initial endoscopy or IR procedure and caused by contamination of the POPFC and proven by new-onset fever, positive blood cultures, or by positive fluid cultures obtained at re-endoscopy

3. Stent migration within and/or outside the collection was considered as a complication only if a repeat endoscopy was needed to retrieve the stent and/or to drain the collection
4. Bleeding was included as an adverse event if the patient required endoscopic therapy, transfusion of packed red blood cells, or inpatient observation
5. Perforation was included when pneumoperitoneum was evident on imaging with peritoneal signs; and
6. Recurrence was defined by the occurrence of the collection after removal of the stents or drains after initial resolution.

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random effects model and our application can be seen to fit within their general approach (where effect is measured by probability of risk).[13] When the incidence of an outcome was zero in a study, a correction of 0.5 was added to the number of incident cases before statistical analysis.[14] We assessed heterogeneity between study-specific estimates using Cochran Q statistical test for heterogeneity, 95% prediction interval (PI), which deals with the dispersion of the effects,[15,16] and the I^2 statistics.[17,18] In this, values of <30%, 30%–60%, 61%–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[19] Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test.[20] When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's 'Trim and Fill' test was used to ascertain the impact of the bias.[21] Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there were no bias. The impact was reported as minimal if both versions were estimated to be the same, modest if effect size changed substantially but the final finding would still remain the same, and severe if basic final conclusion of the analysis is threatened by the bias.[22]

All analyses were performed using Comprehensive Meta-Analysis software, version 3 (BioStat, Englewood, NJ, USA).

RESULTS

Search results and population characteristics

From an initial total of 4084 studies, 128 records were screened and 39 full-length articles were assessed. Thirteen studies were included in the final analysis.[1,7-9,23-31] Out of the 13 studies, 10 studies provided data on the use of EUS in POPFC management (EUS-POPFC)[1,8,9,24-30] and 6 provided data on the use of PCD in POPFC (PCD-POPFC).[7-9,23,27,31]

The schematic diagram of study selection is illustrated in Figure 1.

Baseline population characteristics were comparable in EUS and PCD groups. The mean and/or median age was from 53 to 67 years, with predominantly male population (range 40%–80%). Commonly reported symptoms were abdomen pain, nausea and/or vomiting, fever and/or leukocytosis with or without signs of sepsis. The most common surgical procedure was distal pancreatectomy (57%) and the most frequently encountered pathologic indications were pancreatic adenocarcinoma, neuroendocrine tumor of the pancreas, intraductal papillary mucinous neoplasms (IPMNs), and mucinous cyst neoplasms. The maximum fluid dimension ranged from 7 to 10 cm. Time to drain placement after index surgery ranged from 2 to 547 days. Transgastric was the most commonly used route (86%). Median number of stents placed was

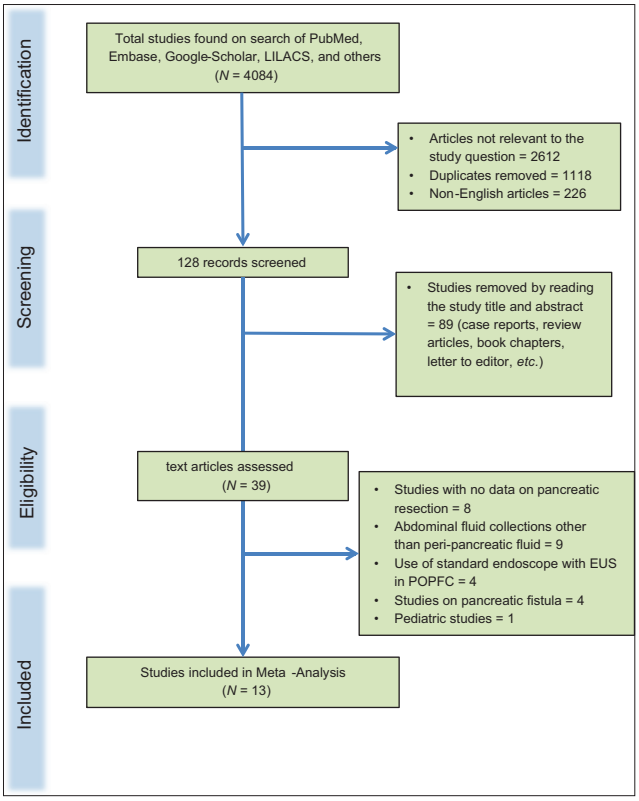

Figure 1. Preferred Reporting items for Systematic Reviews and Meta-Analyses study flow selection. POPFC: postoperative pancreatic fluid collection

2 and median number of procedure session was 1. Median follow-up time ranged from 15 to 44 months.

The details are given in Table 1, and the outcome data are summarized in Table 2.

Characteristics and quality of included studies

All 13 studies were of retrospective nature.[1,7-9,23-31] Out of the included 13 studies, none were population based. Two studies[27,28] were from multicenter data and rest were from single center. Four studies had more than 40 patients,[7,24,27,31] seven studies had 20–39 patients,[23,25-30] and the rest had <20 patients in their study group. All studies reported adequately on the technical success and clinical success outcomes. All baseline patient characteristics between the studies were comparable, except for the interventions. Seven studies had no mention on the duration of follow-up.[1,7,9,23,28,31] Overall, five studies[24-27,29] were considered of high quality and rest were considered medium quality. There were no low-quality studies. The detailed assessment of study quality is given in Supplementary Table 1.

Procedure description

EUS

Procedures were done under general anesthesia or sedation. The therapeutic linear echoendoscope was used for the initial puncture in all studies. The puncture site was selected based on minimal distance between the EUS transducer and the collection without interposed vessels on Doppler assessment. After puncturing the gastric or duodenal wall to gain access to the collection, the fluid was aspirated. With the help of a guide wire inserted into the cavity, the tract was dilated and double pigtail stents were placed. In cases where a lumen-apposing metal stent (LAMS) was used, the LAMS delivery system was advanced and the flanges were deployed, distal followed by proximal, under EUS guidance.

Percutaneous drainage

Majority of studies reported the use of CT guidance, with few using ultrasound guidance, to select a safe drainage route. After procedural sedation and local anesthesia to the skin, a 21-gauge needle was inserted into the fluid collection. Fluid aspiration was done to characterize the fluid and send it for laboratory tests. Using the Seldinger or the trocar method, a 7–14 Fr self-retaining pigtail drainage catheters were placed into the fluid collection.

Postoperative pancreatic fluid collection

Ten studies (239 patients) reported the outcomes of EUS in POPFC management (EUS-POPFC)[1,8,9,24-30] and 6 studies (267 patients) reported the outcomes of PCD in POPFC management (PCD-POPFC).[7-9,23,27,31]

Technical success

The pooled rate of technical success in EUS-POPFC was 97.3% (95% confidence interval [CI] 94.0–98.8) (95% PI 93.2–99.0, I^2 = 0) and in PCD-POPFC was 97.2% (95% CI 93.9–98.7) (95% PI 92.0–99.1, I^2 = 0). There was no statistical significance to the difference, P = 0.93 [Figure 2].

Clinical success

The pooled rate of clinical success in EUS-POPFC was 93.2% (95% CI 88.2–96.2) (95% PI 86.9–96.6, I^2 = 0) and in PCD-POPFC was 79.8% (95% CI 70.0–87.0) (95% PI 32.9–97.0, I^2 = 74). The difference was statistically significant, P = 0.002 [Figure 3].

Adverse events and recurrence

Nine studies (200 patients) reported an overall of 18 adverse events and 14 recurrences in

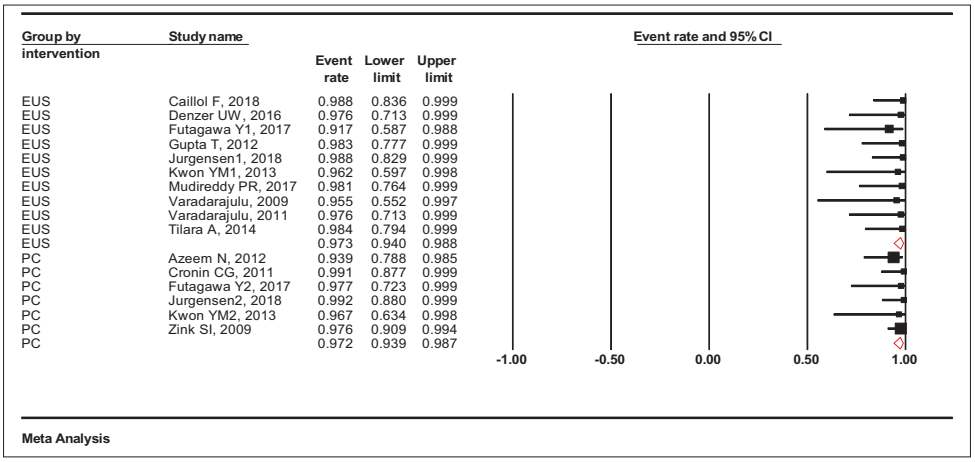

Figure 2. Forest plot. Technical success in postoperative pancreatic fluid collection: EUS *versus* percutaneous drainage

Table 1. Study and patient characteristics

Study name	Intervention	Study design	Age	Sex male (%)	Fluid size (max dimension in cm)	Drainage route	Surgery	Pathology (top 5)	Follow-up time (months)	Drain duration	Stent: Number, type	Number of sessions	Time to drain placement (median)
Caillol F, 2018	EUS	Retrospective, single center, December 2008-April 2016	Mean 61 (SD 12.8)	47	7.6	39 TG, 2 TD	7 whipple, 2 median pancreatectomy, 26 left pancreatectomy, 6 enucleation	12 pancreatic adenocarcinoma, 9 endocrine tumors, 8 IPMN without carcinoma, 3 liposarcoma, 3 mucinous cysts	Median 44.75 (29.24-65.74)	NR	76% 2 stents, 95% plastic stents	NR	NR
Denzer UW, 2016	EUS	Retrospective, single center, September 2009-November 2014	Median 61.5	40	Median 7.25	All TG	14 distal pancreatectomy, 3 Whipple's, 3 others	15 pancreatic tumors, 3 pancreatitis -associated lesions, 2 duodenal adenomas	Median 21	89 days	Mean 2.1; all plastic pigtail stents	Mean 1	2 days
Futagawa Y, 2017	EUS	Retrospective, single center, May 2012-January 2016	63 (39-75)	42	8.0×5.0×5.7	All TG	11 distal pancreatectomy, 1 pancreaticoduodenectomy	5 pancreatic cancer, 2 IPMN, 1 Neuroendocrine tumor, 2 mucinous cystic neoplasm	NR	NR	ENAD in first session, pigtail in second session	Median 2	11.5 days
	PCD		65 (43-83)	81	8.5×4.6×9.0	PCD	7 distal pancreatectomy, 12 pancreaticoduodenectomy, 1 central pancreatectomy	8 bile duct cancer, 4 IPMN, 3 pancreatic cancer, 2 serous cystadenoma, 1 neuroendocrine tumor	NR	NR	8 or 10 Fr pigtail catheter	NR	14 days
Gupta T, 2012	EUS	Retrospective, single center, January 2002-July 2011	53 (15-82)	50	9.6	42 TG, 3 TD, 3 TJ, 1 TE	28 pancreatic surgery, 7 bariatric surgery, 6 splenectomy, 2 liver resection, 2 renal surgery, other 4	NR	15 months	NR	7F or 8.5F plastic pigtail stents, median 1	Median 1	4 days
Kwon YM, 2013	EUS	Retrospective, single center, January 2008-December 2010	62	50	8.9	All TG	7 distal pancreatectomy, 2 enucleation	3 adenocarcinoma, 5 neuroendocrine tumor, 2 mucinous cystic neoplasm, 1 other	NR	57 (32-217)	1-3 pigtail catheters	Median 2	NR
	PCD		56	50	10	PCD	7 distal pancreatectomy	3 adenocarcinoma, 2 neuroendocrine tumor, 1 mucinous cystic neoplasm, 1 IPMN, 1 other	NR	44.5 (2-87)	8.5 or 10.2 Fr drainage catheters	Median 2	NR
Mudireddy PR, 2017	EUS	Retrospective, multicenter, January 2012-August 2016	54	56	7.9	34 TG, 5 TD, others 8	23 pancreatic tail resections, 3 pancreatic head resections, 21 others	NR	NR	36	All LAMS	Median 1	4-180 days

Contd...

Table 1. Contd...

Study name	Intervention	Study design	Age	Sex male (%)	Fluid size (max dimension in cm)	Drainage] route	Surgery	Pathology (top 5)	Follow-up time (months)	Drain duration	Stent: Number, type	Number of sessions	Time to drain placement (median)
Varadarajulu, 2009	EUS	Retrospective, single center, January 2006-June 2008	56.8	60	9.14	9 TG, 1 TE	All distal pancreatectomy	5 neuroendocrine tumor, 2 focal chronic pancreatitis, 1 mucinous cyst neoplasm, 1 adenocarcinoma, 1 trauma	30	96-280 days	Two 7 Fr or one 10 Fr double-pigtail catheters	Median 1	NR
Varadarajulu, 2011	EUS	Retrospective, single center, July 2008-January 2010	54.5 (23-75)	30	7.85	17 TG, 3 TE	All distal pancreatectomy	7-Mucinous cyst neoplasm, 5-neuroendocrine tumor, 5-pancreatic adenocarcinoma, 2-trauma, 1-focal chronic pancreatitis	24	8 weeks	7F pigtail stents, two stents: 17; one stent: 3	Median 1	10-118 days
Tilara A, 2014	EUS	Retrospective, single center, March 2008-March 2013	Median age 61 (20-83)	42	8.5×6 (15×13-4.7×3)	30 TG, 1 TD	15-distal pancreatectomy, 7-central, 9-pancreaticoduodenectomy	12 adenocarcinoma, 5 neuroendocrine tumor, 4-serous cystadenoma, 2-solid pseudopapillary tumor, 3-desmoid tumor, accessory spleen, fibromatosis	NR	Median 64 (26-219) days	7 F or 10 F pigtail stents, median 2 stents	Median 1	5-547 days
Azeem N, 2012	PCD	Retrospective, single center, December 1998-April 2011	53 (21-82)	43	Median 6.4 (2.8-16)	PCD	4 distal pancreatectomy, 19 distal pancreatectomy with splenectomy, 10 distal pancreatectomy with multiorgan resection	Adenocarcinoma, Islet cell tumor, Cystadenoma, Pseudocyst, IPMN	Median 14	29	8-10 Fr locking loop catheter	Median 1	3-151 days
Cronin CG, 2011	PCD	Retrospective, single center, January 2001-February 2009	53.4	50	7.3	PCD	All distal pancreatectomy	12 neuroendocrine tumor, 6 IPMN, 6 mucinous cystadenoma, 5 adenocarcinoma, 4 serous cystadenoma	NR	39.7	8Fr-14Fr self-retaining locking pigtail catheters	NR	2-120 days
Zink SI, 2009	PCD	Retrospective, single center, February 1995-March 2007	NR	NR	7.4	PCD	All pancreaticoduodenectomy	NR	NR	28	10-14 Fr catheters	Average 3.4	1-71 days
Jurgensen, 2018	EUS	Retrospective, multicenter, 2011-2017	60 (55-69)	55	4 (2.5-6)	NR	Pylorus preserving pancreaticoduodenectomy, Whipple procedure, distal pancreatic resection, pancreatectomy	NR	NR	NR	Double -pigtail or self-expanding metal stents	Median 1	5-144 days
	PCD		66 (59-74)	49	7 (5-9)	PCD		NR	NR	NR	NR	Median 1	3-43 days

ENAD: Endoscopic nasoabscess drain, TG: Transgastric, TD: Transduodenal, TE: Transesophageal, TJ: Transjejunal, PCD: Percutaneous drainage, NR: Not reported, IPMN: Intraductal papillary mucinous neoplasms, LAMS: Lumen-apposing metal stent

Table 2. Study data

Study name	Intervention	Total (*n*)	Technical success	Clinical success	AE	Early	Delayed	Bleeding	Stent migration	Perforation	Infection	Others	Death	Recurrence
EUS														
Caillol F, 2018	EUS	41	41	38	9	4	4	3	2		5		0	0
Denzer UW, 2016	EUS	20	20	18	0	0	0						0	1
Futagawa Y, 2017	EUS	12	11	11	0	0	0							4
Gupta T, 2012	EUS	28	28	25	6	4	2	2	2					3
Jurgensen, 2018	EUS	39	39	38	NR	NR	NR						0	6
Kwon YM, 2013	EUS	12	12	11/11	0	0	0	0						0
Mudireddy PR, 2017	EUS	26	26	25	0	0	0							0
Varadarajulu, 2009	EUS	10	10	9	1	1	NR	0	1					0
Varadarajulu, 2011	EUS	20	20	20	0	0	0							0
Tilara A, 2014	EUS	31	31	29	2	1	NR	1						0
PCD														
Azeem N, 2012	PCD	33	31	26/32	3					0	0	1 acute pancreatitis		6
Cronin CG, 2011	PCD	57	57	34	1					1		1 pneumothorax		17
Futagawa Y, 2017	PCD	21	21	21	0									NR
Jurgensen, 2018	PCD	59	59	54	4								4	NR
Kwon YM, 2013	PCD	14	14	11	5					1		1 fistula, 1 pain		3
Zink SI, 2009	PCD	83	81	66	4					3	1			NR

AE: Adverse events

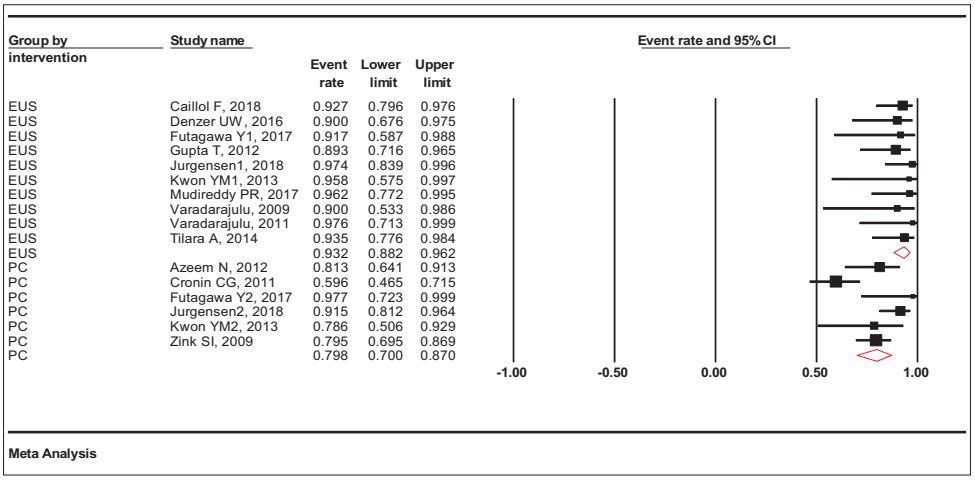

Figure 3. Forest plot. Clinical success in postoperative pancreatic fluid collection: EUS *versus* percutaneous drainage

EUS-POPFC.[1,8,9,24-26,28-30] Six studies (267 patients) reported an overall of 17 adverse events and 26 recurrences in PCD-POPFC.[7-9,23,27,31]

The pooled rate of all adverse events in EUS-POPFC was 9.3% (95% CI 4.4–18.6) (95% PI 1.9–34.8, I^2 = 33.0%) and in PCD-POPFC was 7.9% (95% CI 3.6–16.6) (95% PI 0.5–60.4, I^2 = 67.7%). The difference was not statistically significant, P = 0.77.

The pooled rate of early adverse events in EUS-POPFC was 7.9% (95% CI 4.5–13.2) (95% PI 4.1–14.6, I^2 = 0%) and the pooled rate of delayed adverse events in EUS-POPFC was 6.3% (95% CI 3.3–12.0) (95% PI 2.6–14.5, I^2 = 0%).

The pooled rate of POPFC recurrence after EUS was 9.4% (95% CI 5.2–16.5) (95% PI 1.6–39.4, I^2 = 39.7%) and after PCD was 25.7% (95% CI 24.3–41.7) (95% PI 0.3–97.5, I^2 = 0%). The difference was statistically significant, P = 0.02.

All the results along with the calculated pooled rates for bleeding, perforation, and stent-migration are summarized in Table 3 [Supplementary Figures 1-4].

Table 3. Results

	POPFC (95% CI, I^2)		
	EUS	PCD	*P*
Technical success	97.3 (94.0-98.8, 0)	97.2 (93.9-98.7, 0)	0.93
Clinical success	93.2 (88.2-96.2, 0)	79.8 (70.0-87.0, 74)	0.002
Recurrence	9.4 (5.2-16.5, 39.7)	25.7 (14.3-41.7, 0)	0.02
Adverse events	9.3 (4.4-18.6, 33)	7.9 (3.6-16.6, 67.7)	0.77
Early adverse events	7.9 (4.5-13.2, 0)	NA	-
Delayed adverse events	6.3 (3.3-12.0, 0)	NA	-
Bleeding	6.1 (2.9-12.2, 0)	NA	-
Stent migration	6.5 (2.7-14.8, 0)	NA	-
Perforation	NA	3.3 (1.4-7.4, 0)	-

POPFC: Postoperative pancreatic fluid collection, PCD: Percutaneous drainage, NA: Not applicable (due to limited study and/or data), CI: Confidence interval

VALIDATION OF META-ANALYSIS RESULTS

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed dispersion of the calculated rates using the PI and I^2 percentage values, which are mentioned above with each resulted outcome. The PI gives an idea of the range of the dispersion and I^2 tells us what proportion of the dispersion is true *versus* chance. Our significant finding was a narrow PI with no heterogeneity in the rates of technical success and clinical success with EUS-POPFC. Clinical success with PCD-POPFC and the rates of all adverse events had a wide dispersion with substantial heterogeneity.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias. Further statistics using the fail-safe N test and Duval and Tweedie's "Trim and Fill" test revealed

that the impact of the possible publication bias appeared to be minimal and would not change the calculated estimate or the conclusion of this meta-analysis [Supplementary Figure 5].

DISCUSSION

POPFCs are established adverse events after pancreatic resection and can occur despite efforts to prevent it. Surgery and/or PCD has been the traditional mainstay of treatment. These approaches are associated with reduced quality of life, risk of infection, and nonhealing fistula with fluid and electrolyte losses.[1,8,23,30] Retrospective studies have reported that EUS-guided drainage may provide long-lasting results with minimal complications in the treatment of abdominal fluid collections.[23,26,30,32] The fluid collection can be potentially drained internally resulting in less chances of infection, avoiding fluid and/or electrolyte loss, and additional treatment modalities such as necrosectomy and debridement can be performed.[8]

Based on our analysis, EUS had better clinical outcomes in the management of POPFC when compared to PCD. We report a statistically significant clinical success rate in EUS-POPFC (93.2% *vs.* 79.8%, $P = 0.002$) and significantly lower rates of POPFC recurrence with EUS when compared to PCD (9.4% *vs.* 25.7%, $P = 0.02$). Our calculated rates of technical success were similar in EUS and PCD groups (97.3% *vs.* 97.2). In prior studies that evaluated the role of EUS in the management of POPFC, the technical success ranged from 96% to 100%, clinical success from 80% to 100%, but the outcomes were similar when compared to PCD.[8,23,33] Our calculated rates fall within the range reported in literature; however, using meta-analysis, we demonstrate a statistical significance to the calculated rates of clinical success and rates of POPFC recurrence with EUS as compared to PCD.

Appropriate patient selection and technique is important for a successful outcome. Expertise and access to resources determine the choice of treatment. After the index surgery, the time to place a drain depends on clinical indication and patient symptoms. Drains were placed as soon as 5 days in studies by Tilara *et al.*[1] and Jürgensen *et al.*[27] In EUS-POPFC, the transgastric route was used in 86% of the patients. Therefore, appropriate imaging modalities are important to ascertain ease of access from the gastric cavity. In majority of patients, adequate drainage was achieved with a median of one procedure session and using a median of two plastic stents. The endoscopist has to take into consideration the fluidity of the aspirate and the amount of necrotic debris to help decide the appropriate number of stents needed. Owing to their larger diameter, LAMS may have an advantage over plastic stents in this regard. Repeat procedures and catheter exchanges may be needed based on clinical course. Serial measurement of amylase in the draining fluid is an important parameter in PCD to ascertain cessation of pancreatic leak. This does not apply to EUS-POPFC, as the fluid is internally drained. The adequate follow time is unknown and ranged from 15 to 44 months in the studies included in our analysis.

In our analysis of the adverse events, similar rates were noted for early and delayed adverse events after EUS-POPFC. Nine studies reported 10 early adverse events with a calculated pooled rate of 7.9% and 7 studies reported 6 delayed adverse events with a calculated pooled rate of 6.3%. The most commonly reported adverse events with EUS-POPFC were bleeding (5 events reported from 5 studies) and stent migration (5 events reported from 3 studies). The most common reported adverse event in PCD-POPFC group was perforation (5 events reported from 4 studies). Infection was another important adverse event. 5 events were reported in EUS-POPFC group and 1 event was reported in PCD-POPFC group. Risk of infection due to enteric contamination is a theoretical possibility that should not be overlooked with EUS. In the PCD-POPFC group, there were 1 reported event each of acute pancreatitis, pneumothorax, and intractable pain. The data were limited to calculate the pooled rates. There was no death reported in EUS-POPFC group. Four deaths were reported in the PCD group and they were not procedure related. Overall, the pooled rates for all adverse events were similar in EUS-POPFC and PCD-POPFC groups (9.3% *vs.* 7.9%, $P = 0.77$).

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good-quality studies with detailed extraction of data, rigorous evaluation of study quality, matching basic patient and study characteristics between the study groups, and statistics to establish and/or refute the validity of the results of our meta-analysis. To the best of our knowledge, our study is the first meta-analysis to evaluate the role of EUS in the management of POPFC and compare it to PCD. The statistically significant clinical success rate and recurrence rate

are the key findings of our study. A randomized trial between EUS and PCD in POPFC is unlikely to be performed due to the complexity of the condition and the treatment process.

There were limitations to this study, most of which are inherent to any meta-analysis. The included studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. All studies included in the analysis were of retrospective nature, thereby contributing to selection bias. Heterogeneity with wide prediction intervals was noted in the analysis of clinical success and recurrence in PCD-POPFC. The stent type, size, repeat procedures, exchanges, and the need for pancreatic duct stenting varied within and across studies. Since we had only one study that exclusively evaluated LAMS,[28] we were not able to assess the outcomes comparing plastic stents to LAMS. Although we were able to adjust for most of these parameters between the EUS and PCD groups, variability within the group still existed and our analysis has the element of indirect comparison. Nevertheless, in the real world, POPFCs constitute a very small population, and our study is still the best evidence available to counsel patients. Novel lumen-apposing, fully covered, and self-expanding metal stents have gathered lot of interest in the drainage of pancreatic fluid collections, and studies are needed to evaluate their role in the treatment of EUS-POPFC.

CONCLUSION

Our meta-analysis demonstrates significantly better clinical success with EUS in the management of POPFC with significantly less chances of recurrence, when compared to the percutaneous route of management. Bleeding and stent migration were the main adverse events reported with EUS, whereas perforation was the most common with PCD.

Supplementary Materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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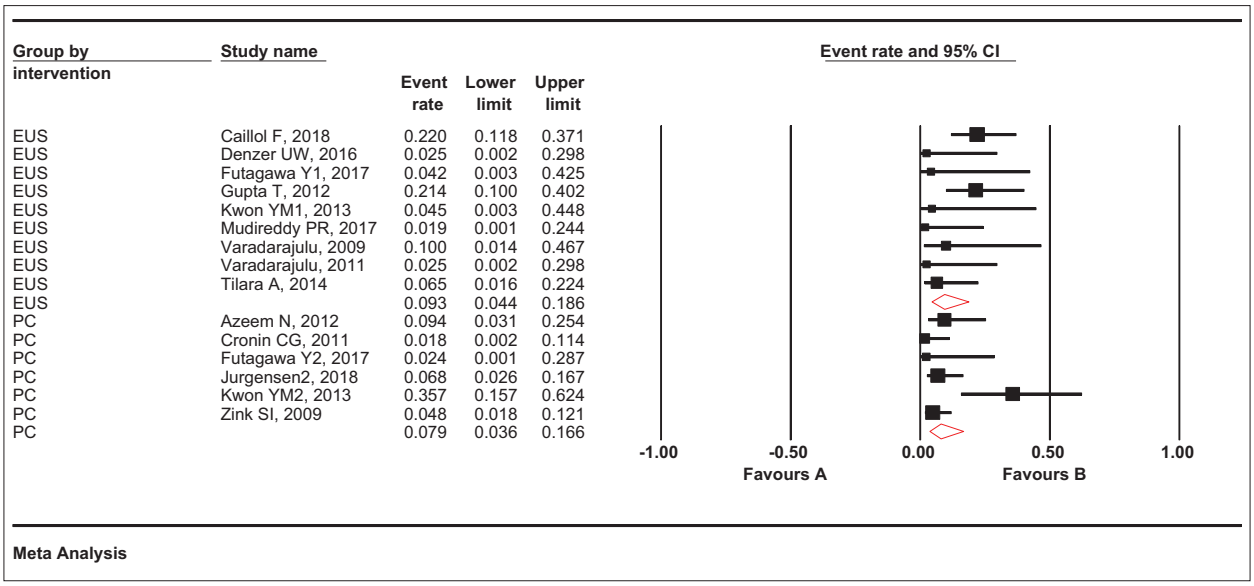
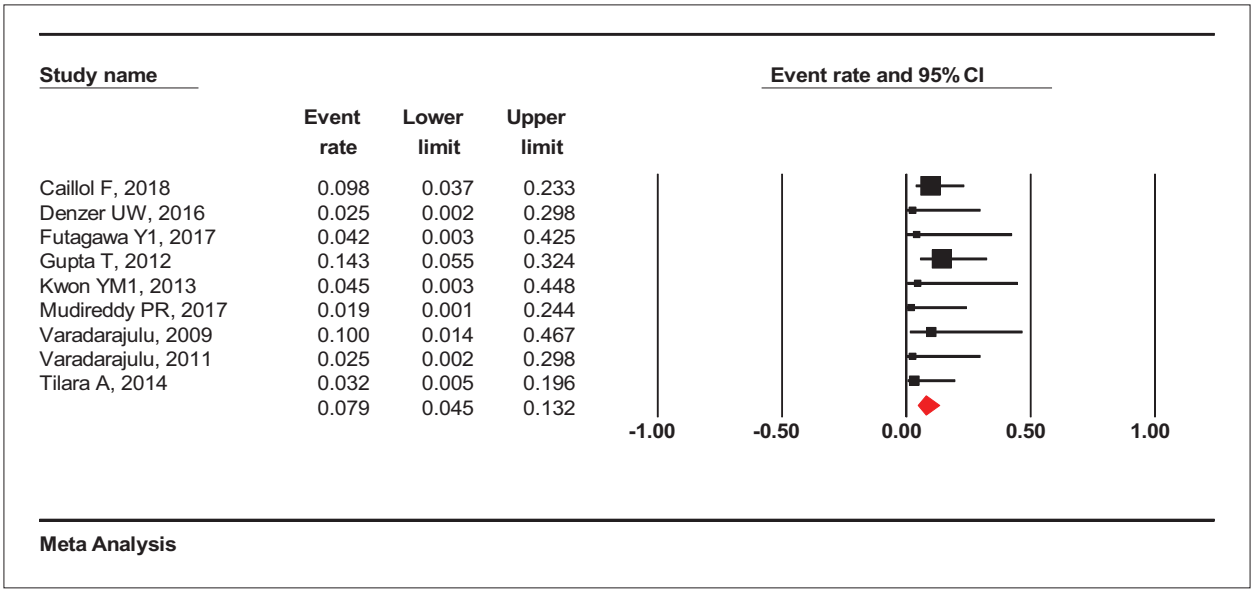
Supplementary Table 1. Study quality assessment

	Selection			Comparability		Outcome			Score	Quality
Newcastle-Ottawa scale	Representativeness of the average adult in community	Cohort size	Information on technical and clinical success	Outcome not present at start	Factors comparable between EUS and PCD group	Adequate clinical assessment	Long enough follow-up time for outcome to occur	Adequacy of follow-up	Maximum=8, high>6, medium 4-6, low≤3	
Study	Population based: 1; multicenter: 0.5; single center: 0	>40 patients: 1; 39 -20: 0.5; <20: 0	Information with clarity: 1; information derived from percentage value: 0.5; unclear: 0	Not present: 1; present: 0	Yes: 1; no: 0	Yes: 1; no: 0	Yes: 1; not mentioned: 0	All patients followed up: 1; >50% followed up: 0.5; <50% followed up: 0		
Caillol F, 2018	0	1	1	1	1	1	1	1	7	High
Denzer UW, 2016	0	0.5	1	1	1	1	1	1	6.5	High
Futagawa Y, 2017	0	0	1	1	1	1	0	1	5	Medium
Gupta T, 2012	0	0.5	1	1	1	1	1	1	6.5	High
Jurgensen, 2018	0.5	1	1	1	1	1	1	1	7.5	High
Kwon YM, 2013	0	0.5	1	1	1	1	0	1	5.5	Medium
Mudireddy PR, 2017	0.5	0.5	1	1	1	1	0	1	6	Medium
Varadarajulu, 2009	0	0	1	1	1	1	1	1	6	Medium
Varadarajulu, 2011	0	0.5	1	1	1	1	1	1	6.5	High
Tilara A, 2014	0	0.5	1	1	1	1	0	1	5.5	Medium
Azeem N, 2012	0	0.5	1	1	1	1	0	1	5.5	Medium
Cronin CG, 2011	0	1	1	1	1	1	0	1	6	Medium
Zink SI, 2009	0	1	1	1	1	1	0	1	6	Medium

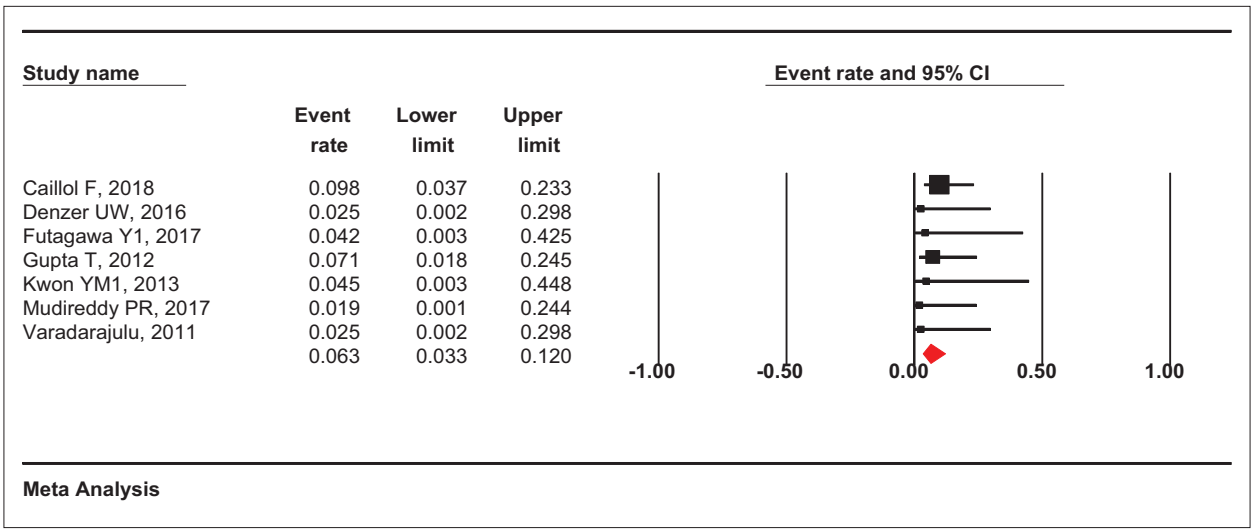
PCD: Percutaneous drainage



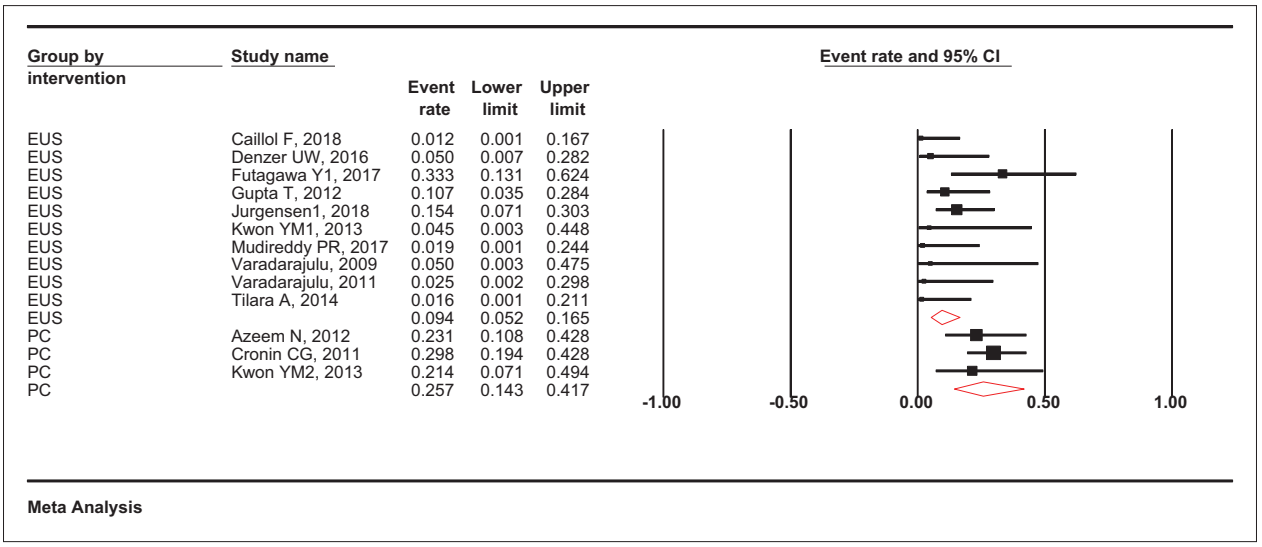
Supplementary Figure 1. Forest plot. Adverse events in postoperative pancreatic fluid collection: EUS *versus* percutaneous drainage



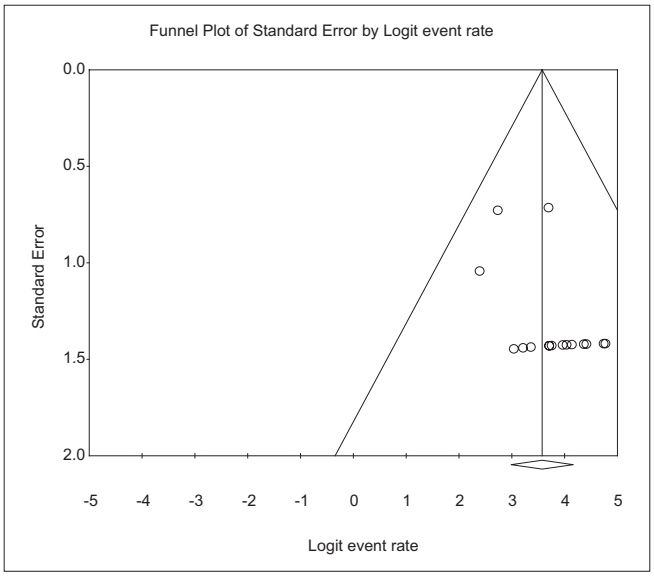
Supplementary Figure 2. Forest plot. Early adverse events. EUS-postoperative pancreatic fluid collection



Supplementary Figure 3. Forest plot. Delayed adverse events. EUS-postoperative pancreatic fluid collection



Supplementary Figure 4. Forest plot. Recurrence in postoperative pancreatic fluid collection: EUS *versus* percutaneous drainage



Supplementary Figure 5. Funnel plot for all studies