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Early versus late drainage of pancreatic necrotic fluid collections: a systematic review and meta-analysis

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Abstract

Background Necrotizing pancreatitis can be complicated by necrotic fluid collections (NFCs). International guidelines recommend waiting 4 weeks for the collection to mature before interventional management. With the advances in endoscopic drainage, the need to delay drainage by 4 weeks is unclear. We aimed to compare early drainage (ED: <4 weeks) vs. late drainage (LD: ≥4 weeks) of NFCs.

Methods Literature searches through multiple databases were performed to identify studies that investigated outcomes of ED vs. LD of NFCs. Our primary outcome was the complication rate among these groups. The secondary outcomes included the number of patients requiring subsequent necrosectomies, and mortality.

Results We identified 9 studies with 855 patients (320 ED and 535 LD). The complication rates (rate ratio 1.060, 95% confidence interval [CI] 0.79-1.42; P=0.69; I^2=51.61) and the number of patients requiring subsequent necrosectomies (odds ratio [OR] 2.15, 95% CI 0.86-5.35; P=0.099; I^2=79.81) were similar in both groups. Mortality was slightly higher in the ED group (OR 1.94, 95%CI 1.05-3.59; P=0.033; I^2=0).

Conclusions Our study suggests that ED can be performed if needed in carefully selected patients without an increase in complications or subsequent necrosectomies. However, mortality was slightly higher compared to LD. A multidisciplinary team approach is necessary for considering ED.

Keywords Necrotizing pancreatitis, necrotic fluid collections, acute necrotic collections, walled-off necrosis, early drainage

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Introduction

Acute pancreatitis represents one of the most common gastrointestinal diseases and reasons for hospitalization worldwide, with an annual incidence and mortality of 2,814,972 and 115,053, respectively [1,2]. In the United States, healthcare costs associated with acute pancreatitis hospitalizations exceed $2.5 billion dollars, with over 270,000 admissions per year [2]. While the majority of cases are mild and self-limited, there is a subset of patients, roughly 15-20%, who develop severe pancreatitis associated with organ failure and/or death [3-6]. Necrotizing pancreatitis is a worrisome complication that can prolong hospitalization and lead to a multitude of complications, including necrotic fluid collections (NFCs). NFCs, when infected, can significantly increase the mortality by up to 20-30% [6,7]. NFCs are categorized by their duration and their contents. Encapsulation and maturation of NFCs usually takes at least 4 weeks. Therefore, international guidelines have typically advised postponement of interventional management (drainage and/or debridement)

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Conflict of Interest: None

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of NFCs in order for the acute necrotic collection to develop into a well-defined, walled-off necrosis [3,8,9].

However, there are clinical scenarios in which patients develop symptomatic fluid collections from necrotizing pancreatitis, which warrant earlier intervention within the first 4 weeks of onset. Historically, patients underwent an open surgical necrosectomy, but the use of that procedure is now limited, because of its high morbidity and the emergence of minimally invasive, endoscopic and percutaneous modalities [10]. An endoscopic step-up approach is recommended as the first-line therapy for symptomatic and infected NFCs, whereas percutaneous intervention can be considered when endoscopic drainage is not technically feasible or unsuccessful [6]. The advent of endoscopic ultrasound (EUS)-guided intervention has challenged the idea that waiting 4 weeks before intervention is required, especially since earlier studies focused primarily on surgical approaches [11]. Clinically this is important, as patients who decompensate despite goal-directed medical therapy may indeed benefit from early intervention, especially in cases of infection, obstruction, nutritional failure or pain [6]. We conducted a systematic review and meta-analysis of studies comparing early drainage (ED) (<4 weeks) vs. late drainage (LD) (≥4 weeks) of NFCs using minimally invasive therapies.

Materials and methods

We performed this systematic review in accordance with the Cochrane handbook of systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12,13] (Supplementary Table 1).

A comprehensive search of several databases was conducted, from each database's inception to January 21, 2022, for papers in the English language. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator.

Controlled vocabulary supplemented with key words were used to search early vs. late drainage of pancreatic NFCs. The actual strategy listing all the search terms and how they were combined is given in Appendix 1.

The key words used in the search included a combination of "pancreatic necrotic fluid collections," "walled-off pancreatic necrosis (WON)," "drainage/intervention," and "early vs delayed." Two authors (SB, AKM) independently reviewed the titles and abstracts from the search results to identify the studies that were relevant to this systematic review and meta-analysis, based on predefined inclusion and exclusion criteria. The remaining full-text articles were then reviewed to include all the studies that met the inclusion criteria with all relevant information. Any discrepancies in study selection were resolved by consensus and in discussion with the senior author (RK). The bibliography sections of the selected studies and related review articles were searched for additional relevant studies.

Studies that met the following inclusion criteria were included in this meta-analysis: 1) studies consisting of mainly endoscopic drainage or an endoscopic "step-up" drainage approach to pancreatic NFC and WON; 2) studies that compared outcomes related to early (<4 weeks) vs. delayed intervention; 3) studies that reported adverse events, mortality, need for reinterventions with subsequent necrosectomies and/or surgery, and length of hospital stay (LOS); and 4) studies with a sample size of more than 10 patients. Studies were excluded if they 1) did not directly compare outcomes between early vs. delayed drainage of NFC/WON; 2) performed only surgical or percutaneous drainage without endoscopic drainage; 3) were not in the English language; 4) were animal studies; 5) were studies on pediatric populations; or 6) were letters to the editor, case reports, editorials or review articles. If multiple publications from the same cohort or a duplication of cohorts was identified, the most recent and the most comprehensive report analyzing the outcomes of interest was included.

After the relevant studies with pertinent outcomes of interest had been identified, 2 authors independently abstracted the data on study characteristics and the outcomes of interest on a standardized form. The abstracted outcomes that were reported as medians, ranges and confidence intervals, were converted into means and standard deviations, as per previously reported methods [14,15]. The risk of bias and quality assessment of the included studies were independently performed by 2 authors using the modified Newcastle-Ottawa scale (NOS) for retrospective studies and the Cochrane risk-of-bias for randomized trials (RoB2) tool [16,17]. Based on the modified NOS scale, the studies were assigned scores under 3 broad perspectives: 1) selection (4 questions with 1 point each); 2) comparability of study groups (2 points maximum); and (3) ascertainment of the outcome of interest (3 questions with 1 point each). An extra point was awarded for studies published as full manuscripts, while no points were awarded to studies published as abstracts. Studies with a total score of ≥9, 6-8 and ≤5 points were considered high, medium and low-quality studies, respectively. Discrepancies in data extraction, quality assessment and assessment of bias were resolved by the combined assessment of 2 authors.

The primary outcome of the current meta-analysis was the complication rates during the study period in the ED vs. LD groups. Secondary outcomes were the number of subsequent endoscopic or minimally invasive necrosectomies, mortality, number of endoscopic sessions needed, and the number of patients requiring salvage surgical intervention during treatment of WON and LOS.

The complications associated with ED and LD were defined and classified based on the American Society for Gastrointestinal Endoscopy lexicon or the Clavien-Dindo classification [18,19]. The need for subsequent necrosectomies was defined as endoscopic and minimally invasive necrosectomies, such as video-assisted retroperitoneal debridement. Patients requiring salvage surgical interventions were those who needed open surgical intervention for the treatment of NFC, or management of complications related to NFC drainage. In addition, the mortality reported during the study period was compared between the ED and LD groups.

Statistical analysis

In this meta-analysis, we calculated the pooled rates of outcomes using the random-effects model described by DerSimonian and Laird [20]. The pooled outcomes compared the 2 groups with 95% confidence intervals (CI). Heterogeneity was calculated using Cochran's Q statistical test and the I^2 statistic [21,22]. The Q-statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). When the expected value of Q exceeds the degrees of freedom, the null hypothesis is rejected, and variations across the studies and heterogeneity are accepted to exist. The I^2 statistic estimates the proportion of total variation across studies that is related to heterogeneity rather than by chance. Values of <30%, 30-60%, 61-75% and >75% were considered suggestive of low, moderate, substantial and considerable heterogeneity, respectively [21]. A P-value of <0.05 was considered to be statistically significant. Even though there were <10 studies included in the meta-analysis, we assessed for publication bias qualitatively, by visual inspection of a funnel plot, and quantitatively, by the Egger test. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

Results

A total of 1039 studies were identified based on our search criteria. Eliminating the duplicates resulted in 978 studies that were screened based on their titles and abstracts. There were 753 irrelevant studies and 165 studies pertaining to editorials, review articles, pediatric studies, case reports and case series with less than 10 patients that were excluded. Forty-nine studies were thoroughly reviewed after the exclusion. Twenty-six studies were excluded as they involved cases with surgical or percutaneous drainage only. Fourteen studies were removed as there was no comparison between the timelines of drainage, and the data were incomplete. We identified 9 studies, with a total of 855 patients (320 ED vs. 35 LD), that met the inclusion criteria and were included in this meta-analysis (Fig. 1).

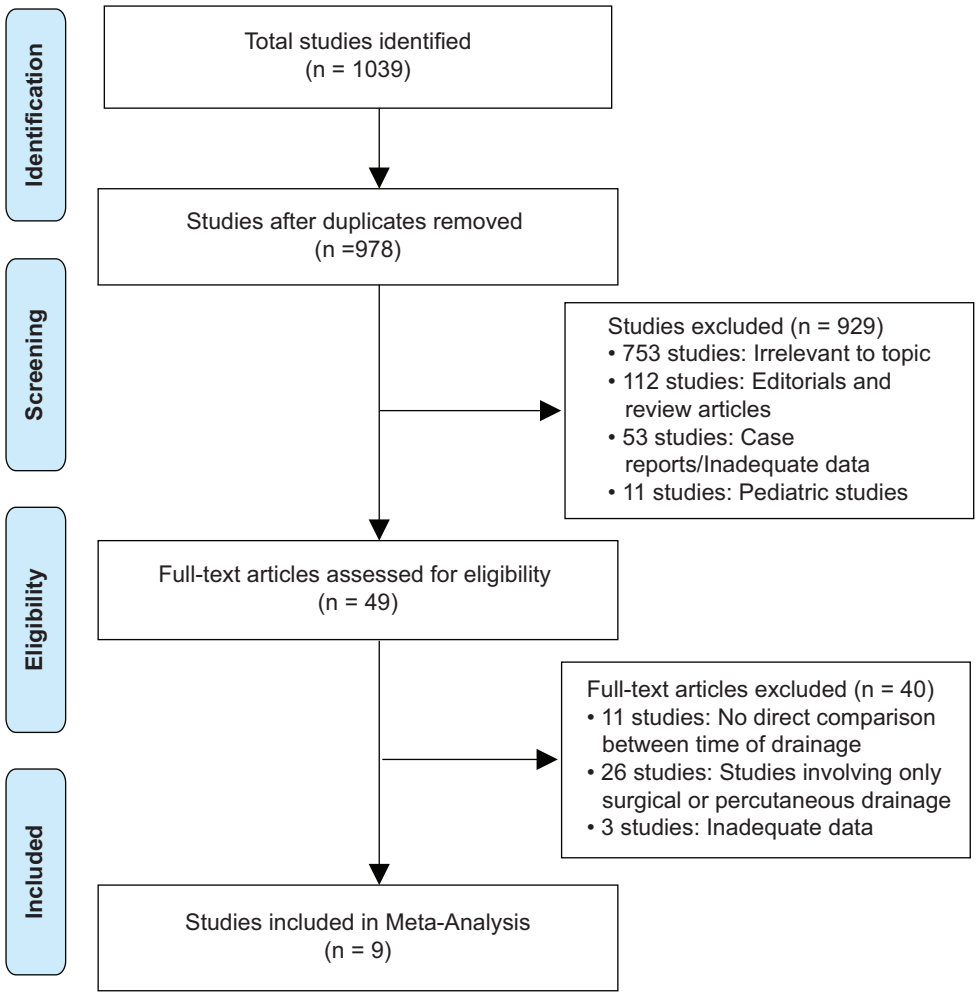


Figure 1 Flowchart summarizing study selection process

One study was a multicenter randomized controlled trial (RCT) [23] and 1 study was a single-center prospective study [24]. The remaining 7 studies were single-center, retrospective studies [11,25-30]. Four studies were based in the United States [11,26,28,29]. One study was from Japan [25], 1 study was from India [27], 2 studies were from Europe [23,24] and 1 study was from Australia [30]. While all the studies compared the outcomes of early vs. late drainage of NFCs using predominantly endoscopic drainage, 2 studies utilized an endoscopically centered "step-up" approach [11,23]. Six studies compared the outcomes of early vs. delayed endoscopic drainage only [24-27,29,30], and 1 study utilized dual modality drainage, which involves simultaneous endoscopic and percutaneous drainage of NFCs [28] (Table 1).

The overall complication rates of ED vs. LD during the study periods were similar, with a rate ratio of 1.060 (95% CI 0.79-1.42; P=0.69; Q=14.46, I^2=51.61). Heterogeneity was moderate, with the Q value above the degrees of freedom and an I^2 of 51.61 (Fig. 2).

The mortality rate was mildly higher in the ED compared to the LD group (odds ratio [OR] 1.94, 95%CI 1.05-3.59; P=0.033; Q=5.71, I^2=0). Heterogeneity was minimal (Fig. 3). The number of patients requiring subsequent necrosectomies for the treatment of NFC was similar in both groups (OR 2.15, 95%CI 0.86-5.35; P=0.099; Q=29.72, I^2=79.81) (Fig. 4). Similarly, the number of endoscopic sessions needed for the treatment of NFC was similar among the ED and LD groups (OR 3.39, 95%CI 0.78-14.68; P=0.10; Q=128.97, I^2=95.34 (Fig. 5).

The number of patients requiring open surgical intervention were similar in both groups (risk difference [RD] 0.023, 95%CI -0.009-0.05; P=0.15; Q=3.64, I^2=0) (Fig. 6). The LOS was similar among the ED and LD groups (OR 1.01, 95%CI 0.40-2.54; P=0.97; Q=23.6, I^2=83.05) (Fig. 7).

The risk of bias and quality assessment of the studies were performed using the RoB2 tool or the NOS for RCTs and the remaining studies, respectively. The only RCT involved in the analysis was deemed to be at low risk for bias (Supplementary Fig. 1). According to the NOS assessment of the remaining 8 studies, 5 studies were deemed to be high quality, while 3 were deemed to be medium quality (Supplementary Table 2). Despite the lower number of studies, the assessment of publication bias based on visualization of the funnel plot, imputation adjustments based on Duval and Tweedie's trim and fill technique, and Egger's regression test were performed for the complication rate and the mortality. The analyses using these techniques did not show any significant publication bias (Supplementary Fig. 2,3).

Subgroup analyses were performed to analyze the difference between specific adverse events, such as bleeding and perforation, when they were reported in the study. There was no difference between the ED vs. the LD group in bleeding complications (RD 0.015, 95%CI -0.03-0.06; P=0.587). Similarly, there was no difference in perforation complications (RD -0.02, 95%CI -0.05-0.008; P=0.147) (Supplementary Fig. 4).

Subgroup analysis of only the high-quality studies did not reveal any differences between the ED vs. the LD group in terms of complication rate or mortality (Supplementary Fig. 5,6).

A sensitivity analysis was performed by removing 1 study at a time to evaluate if any single study had a major impact on an outcome. No single study had a significant impact on the complication rate (Supplementary Fig. 7). However, when the

Table 1 Study characteristics

Study/Year/Region [ref.]	Study type	Total N (ED vs. LD)	Drainage type	Stent Type
Trikudanathan *et al* 2018; USA [11]	Single-center Retrospective	193 (76 vs. 117)	Endoscopically centered step-up approach	Plastic, LAMS, other metal
Chantarojanasiri *et al* 2018; Japan [25]	Single-center Retrospective	35 (12 vs. 23)	Endoscopic drainage	Plastic, other metal
Oblizajek *et al* 2020; USA [26]	Single-center Retrospective	38 (19 vs. 19)	Endoscopic drainage only	Plastic, LAMS, other metal
Bomman *et al* 2021; USA [28]	Single-center Retrospective (Abstract only)	74 (37 vs. 37)	Dual modality drainage*	Plastic, LAMS
Cuvillier *et al* 2020; USA [29]	Single-center Retrospective (Abstract only)	112 (42 vs. 70)	Endoscopic drainage	LAMS
Rana *et al* 2021; India [27]	Single-center Retrospective	170 (34 vs. 136)	Endoscopic drainage	Plastic, LAMS
Boxhoorn *et al* 2021; The Netherlands [23]	Randomized Controlled Trial	104 (55 vs. 49)	Endoscopically centered step-up approach	Plastic
Mckay *et al* 2021; Australia [30]	Single-center Retrospective (Abstract only)	58 (20 vs. 38)	Endoscopic drainage	Plastic, LAMS
Jagielski *et al* 2022; Poland [24]	Single-center Prospective	71 (25 vs. 46)	Endoscopic drainage	Plastic, LAMS

*Combined simultaneous endoscopic and percutaneous drainage

ED, early drainage; LD, late drainage; LAMS, lumen-apposing metal stent

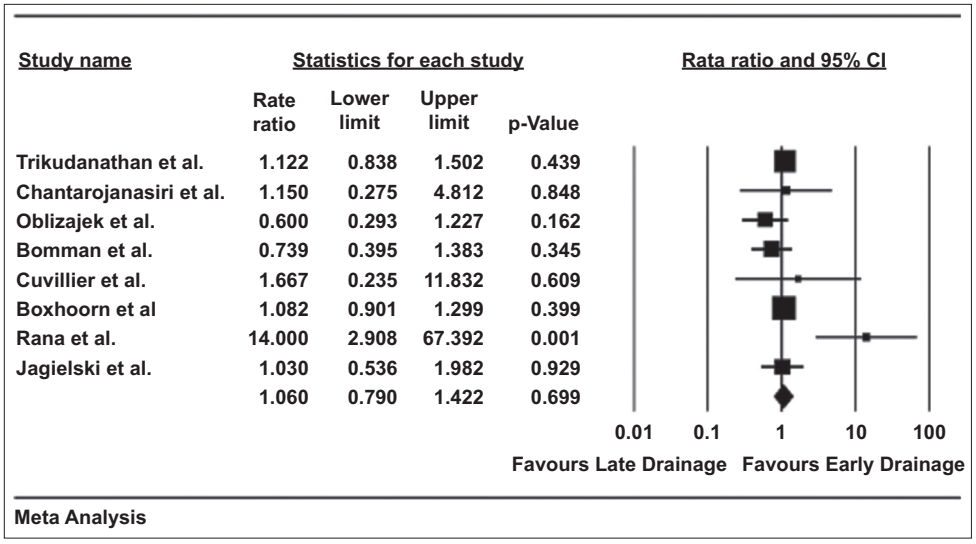


Figure 2 Forest plot for complication rate in early vs. late drainage
CI, confidence interval

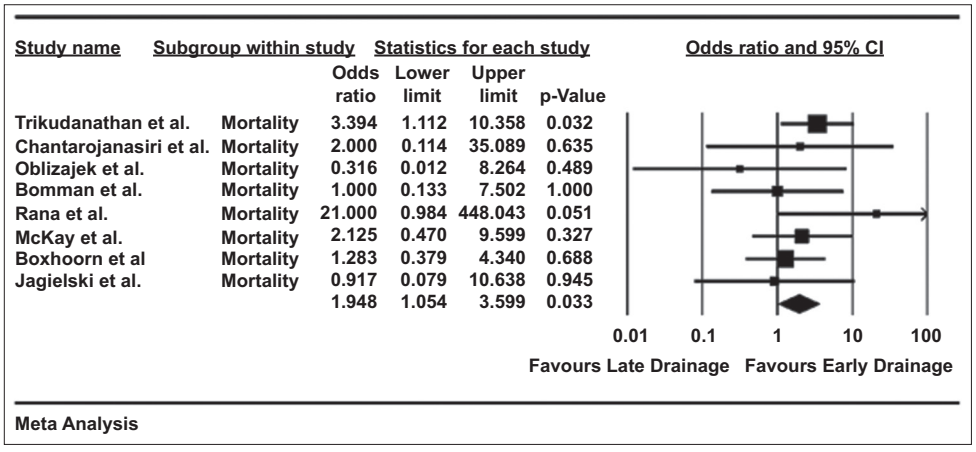


Figure 3 Forest plot for mortality in early vs. late drainage
CI, confidence interval

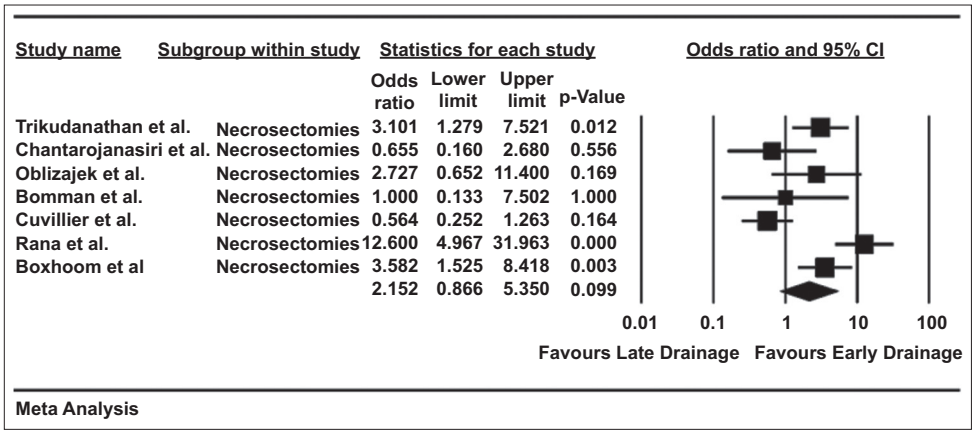


Figure 4 Forest plot for number of patients requiring subsequent necrosectomies
CI, confidence interval

studies by Trikudanathan *et al*, Rana *et al* and McKay *et al* were individually removed from the analysis, the difference in mortality between ED vs. LD group was obliterated (Supplementary Fig. 8).

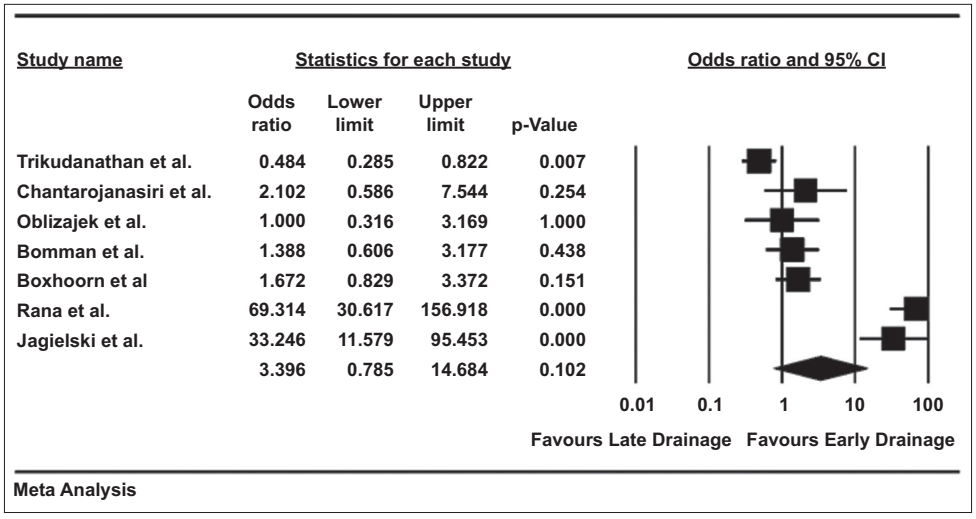


Figure 5 Forest plot for the total number of endoscopic sessions in early vs. late drainage
CI, confidence interval

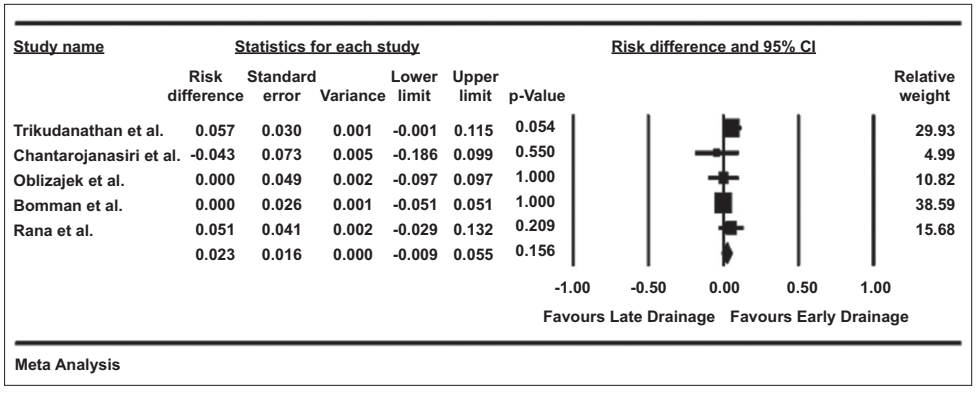


Figure 6 Forest plot for salvage surgery requirement in early vs. late drainage
CI, confidence interval

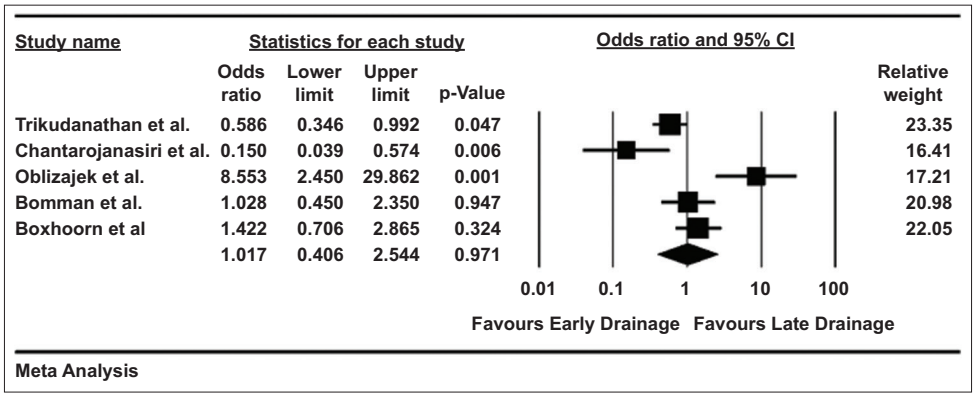


Figure 7 Forest plot for mean length of stay in early vs. late drainage
CI, confidence interval

Discussion

The present study shows that ED was not associated with a higher incidence of complications or a greater need for subsequent endoscopic or surgical procedures. However, ED was associated with higher mortality compared to LD, probably because these patients were critically ill with symptomatic fluid collections. Although

conservative management is the initial treatment of choice for NFCs, clinical deterioration can occur regardless of optimal medical therapy. Infected pancreatic necrosis has a 30% associated mortality rate and approximately half of these infections typically occur within the first week of admission [4]. The traditional approach to delay management in order for the fluid collection to mature was thought to decrease the risk of complications; however, the introduction of minimally invasive therapies has shifted this paradigm. Three recent multicenter randomized trials comparing endoscopic to surgical necrosectomy found that an endoscopic transluminal approach was associated with lower rates of multiorgan failure, proinflammatory responses, pancreatic fistulas and LOS [31-33]. These studies have shifted the doctrine by providing increasing evidence that an endoscopic step-up approach can reduce complications with no change in mortality.

Given these developments, the studies included in this meta-analysis aimed to determine if the timing of drainage could alter clinical outcomes. In our study, there was slightly greater pooled mortality in the ED group (OR 1.94, 95%CI 1.05-3.59; P=0.033). However, only an association, and not causality due to the ED procedure, can be established from this analysis. There have been no clear subgroups which have been identified to benefit from ED, and it has been reported that delaying intervention by 30 days may actually improve mortality [5]. As a result, it is safe to assume that, in the included retrospective studies, ED was performed as an inevitable option in critically ill patients who had failed conservative management, which may have introduced some bias. Moreover, it is important to take into consideration that these mortality rates are notably lower compared to a 2010 meta-analysis of 14 studies (n=1478 patients) that showed that infected pancreatic necrosis was associated with a 32% mortality [34]. Regardless of ED vs. LD, the endoscopic techniques currently available are superior. Our findings support LD as a potentially preferable approach if clinical deterioration is not present.

In terms of adverse events (AE), no difference was seen between ED and LD. While only 1 of the included studies reported a statistically significantly greater incidence of AE in the ED group, the study only reported bleeding complications [27]. Our subgroup analysis of pooled rates of bleeding complications did not show a difference between the ED and the LD group.

While perforation is a theoretical concern in ED, there were no significant differences observed. These findings may be due to improved EUS-guided drainage techniques and equipment in recent years. Furthermore, the advent of lumen-apposing metal stents (LAMS) has greatly improved this procedure, especially since minimally invasive endoscopic necrosectomies can be performed through the LAMS when indicated. In our meta-analysis, most studies, with the exception of 2, utilized LAMS. Six studies also utilized plastic and other metal stents for NFC drainage. It is possible that adverse events could be further reduced with widespread use of LAMS in future studies [35].

Pancreatic NFCs evolve over time, as the solid necrotic content becomes liquefied and encapsulation occurs. Theoretically, procedures done before encapsulation should require a greater number of necrosectomies or reinterventions, since the necrotic contents are not liquefied. However, our study did not show a greater number of subsequent necrosectomies, endoscopic reinterventions or salvage surgeries when comparing ED to LD. The timeline of 4 weeks to allow the optimal morphological changes to occur before drainage of NFCs is arbitrary, and there are instances when encapsulation can occur before 4 weeks. The use of high-resolution imaging studies, such as contrast-enhanced computed tomography and EUS, can help assess and guide an appropriate NFC drainage timeline. Some studies have noted encapsulation in 40% of the patients even before 4 weeks [11,26]. Moreover, it has also been postulated that encapsulation may not be relevant in the era of minimally invasive techniques [7,36]. In the meta-analysis by Bomman *et al*, the earliest intervention occurred at 10 days following the onset of pancreatitis, although the majority of the included studies performed intervention at 3 weeks [28]. In light of these findings, a multidisciplinary approach is paramount when determining an appropriate treatment course, and it is likely that the contents of the fluid collection are equally as important as the timing.

There are a few limitations to highlight. Firstly, most of the included studies were retrospective, with an inherent risk of bias. In addition, a few studies were reported as abstracts only. Secondly, all studies were conducted at high-volume tertiary care centers with experienced endoscopists. Therefore, the widespread applicability of these techniques may be limited—especially in resource-limited settings. Lastly, the heterogeneity was moderate to high in many of the assessed outcomes. Different modalities were used in the drainage of NFCs. Furthermore, various types of stents such as plastic, LAMS and other metal stents were used in different studies, which could have led to variability in drainage outcomes. It is possible that the increased use of LAMS may impact treatment outcomes in the future. The strengths of our study include the use of a comprehensive literature search of multiple databases, with careful data extraction and elimination of redundant studies.

In conclusion, this is the first meta-analysis to compare the outcomes of early vs. late endoscopic drainage of NFCs. Our findings show that, when clinically indicated, earlier drainage can be performed in carefully selected patients. A multidisciplinary team approach involving expert therapeutic endoscopists, interventional radiologists and hepatopancreaticobiliary surgeons is necessary for considering ED.

Summary Box

What is already known:

- Necrotizing pancreatitis can be complicated by necrotic fluid collections
- International guidelines recommend waiting 4 weeks for the collection to mature before interventional management
- With advances in endoscopic drainage, the necessity to delay drainage by 4 weeks is unclear

What the new findings are:

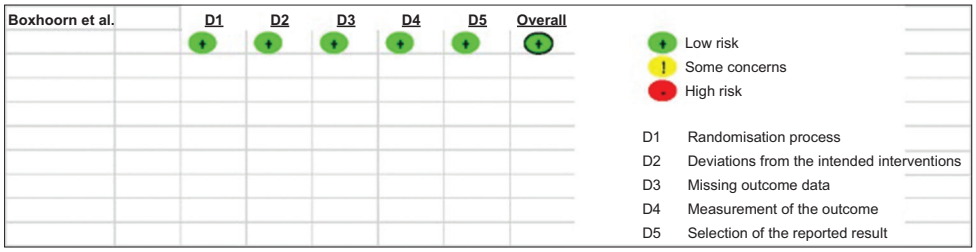
- Early drainage (<4 weeks) can be performed if needed in carefully selected patients, without an increase in complications or subsequent necrosectomies
- However, mortality was slightly higher with early drainage compared to late drainage (>4 weeks)
- A multidisciplinary team approach is necessary for considering early drainage

References

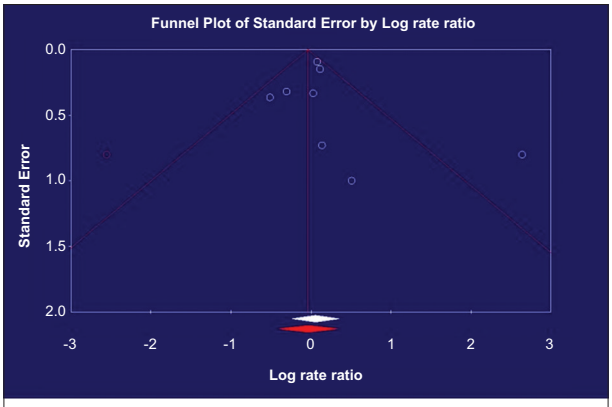
1. Li CL, Jiang M, Pan CQ, Li J, Xu LG. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990-2019. *BMC Gastroenterol* 2021;**21**:332.
2. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology* 2015;**149**:1731-1741.
3. Banks PA, Bollen TL, Dervenis C, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;**62**:102-111.
4. Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013;**108**:1400-1415; 1416.
5. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;**13**:e1-e15.
6. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association clinical practice update: management of pancreatic necrosis. *Gastroenterology* 2020;**158**:67-75.
7. Trikudanathan G, Wolbrink DRJ, van Santvoort HC, Mallery S, Freeman M, Besselink MG. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. *Gastroenterology* 2019;**156**:1994-2007.
8. Arvanitakis M, Dumonceau JM, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy* 2018;**50**:524-546.
9. Isayama H, Nakai Y, Rerknimitr R, et al. Asian consensus statements on endoscopic management of walled-off necrosis Part 1: Epidemiology, diagnosis, and treatment. *J Gastroenterol Hepatol* 2016;**31**:1546-1554.
10. van Santvoort HC, Besselink MG, Bakker OJ, et al; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010;**362**:1491-1502.
11. Trikudanathan G, Tawfik P, Amateau SK, et al. Early (<4 weeks) versus standard (≥4 weeks) endoscopically centered step-up interventions for necrotizing pancreatitis. *Am J Gastroenterol* 2018;**113**:1550-1558.
12. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5 (Updated August 2024). Cochrane, 2024. Available from: https://training.cochrane.org/handbook [Accessed 16 January 2025].
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.
14. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;**14**:135.
15. Julian PT Higgins TL. Chapter 6: Choosing effect measures and computing estimates of effect | Cochrane Training. In: Cochrane; 2022. Available from: https://training.cochrane.org/handbook/current/chapter-06#section-6-5-2 [Accessed 16 January 2025].
16. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 16 January 2025].
17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205-213.
19. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;**71**:446-454.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
21. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* 2011;**64**:1294-1302.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-560.
23. Boxhoorn L, van Dijk SM, van Grinsven J, et al; Dutch Pancreatitis Study Group. Immediate versus postponed intervention for infected necrotizing pancreatitis. *N Engl J Med* 2021;**385**:1372-1381.
24. Jagielski M, Piątkowski J, Jackowski M. Early endoscopic treatment of symptomatic pancreatic necrotic collections. *Sci Rep* 2022;**12**:308.
25. Chantarojanasiri T, Yamamoto N, Nakai Y, et al. Comparison of early and delayed EUS-guided drainage of pancreatic fluid collection. *Endosc Int Open* 2018;**6**:E1398-E1405.
26. Oblizajek N, Takahashi N, Agayeva S, et al. Outcomes of early endoscopic intervention for pancreatic necrotic collections: a matched case-control study. *Gastrointest Endosc* 2020;**91**:1303-1309.
27. Rana SS, Sharma R, Kishore K, Dhalaria L, Gupta R. Safety and efficacy of early (<4 weeks of illness) endoscopic transmural drainage of post-acute pancreatic necrosis predominantly located in the body of the pancreas. *J Gastrointest Surg* 2021;**25**:2328-2335.
28. Bomman S, La Selva D, Larsen M, et al. Safety and outcomes of performing early dual modality drainage (<28 days) of pancreatic necrotic collections—a matched case control study. *Gastrointest Endosc* 2021;**93**:AB240.
29. Cuvillier C, Sims A, Chittajallu V, et al. Su1472 Safety and success of early (<4 weeks) endoscopic intervention in symptomatic pancreatic necrosis. *Gastroenterology* 2020;**158** Suppl 1:S-593-S-594.
30. McKay O, Roberts A, Ma Y, et al. Tick tock, tick tock: Early versus

late endoscopic drainage of pancreatic necrotic collections. Does timing really matter? *J Gastroenterol Hepatol* 2021;**36**(Suppl 3): 7.
31. Bakker OJ, van Santvoort HC, van Brunschot S, et al; Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012;**307**:1053-1061.
32. Bang JY, Arnoletti JP, Holt BA, et al. An endoscopic transluminal approach, compared with minimally invasive surgery, reduces complications and costs for patients with necrotizing pancreatitis. *Gastroenterology* 2019;**156**:1027-1040.
33. van Brunschot S, van Grinsven J, van Santvoort HC, et al; Dutch Pancreatitis Study Group. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *Lancet* 2018;**391**:51-58.
34. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010;**139**:813-820.
35. Guzmán-Calderón E, Chacaltana A, Díaz R, Li B, Martinez-Moreno B, Aparicio JR. Head-to-head comparison between endoscopic ultrasound guided lumen apposing metal stent and plastic stents for the treatment of pancreatic fluid collections: A systematic review and meta-analysis. *J Hepatobiliary Pancreat Sci* 2022;**29**:198-211.
36. van Baal MC, van Santvoort HC, Bollen TL, Bakker OJ, Besselink MG, Gooszen HG; Dutch Pancreatitis Study Group. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br J Surg* 2011;**98**:18-27.

Supplementary material



Supplementary Figure 1 Risk of bias assessment of randomized controlled trial using RoB2 tool



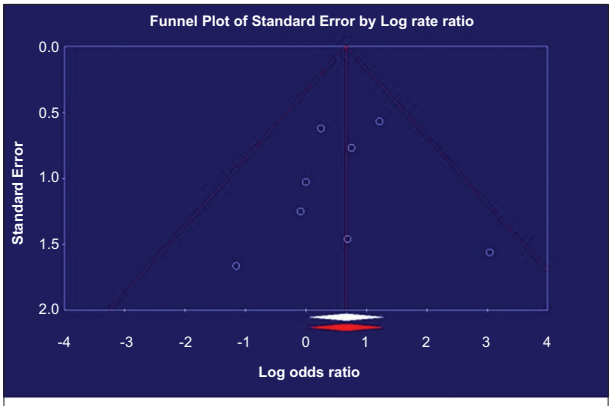
Duval and Tweedie's trim and fill

	Studies Trimmed	Fixed Effects Point Estimate	Fixed Effects Lower Limit	Fixed Effects Upper Limit	Random Effects Point Estimate	Random Effects Lower Limit	Random Effects Upper Limit	Q Value
Observed values		1.06832	0.92705	1.23112	1.05972	0.78991	1.43168	14.46788
Adjusted values	1	1.04598	0.90819	1.20469	0.96657	0.66742	1.39980	25.02104

Egger's regression intercept

Intercept	0.41893
Standard error	0.83634
95% lower limit (2-tailed)	-1.62952
95% upper limit (2-tailed)	2.46337
t-value	0.49851
df	6.00000
P-value (1 tailed)	0.31793
P-value (2-tailed)	0.63587

Supplementary Figure 2 Funnel plot for complication outcomes



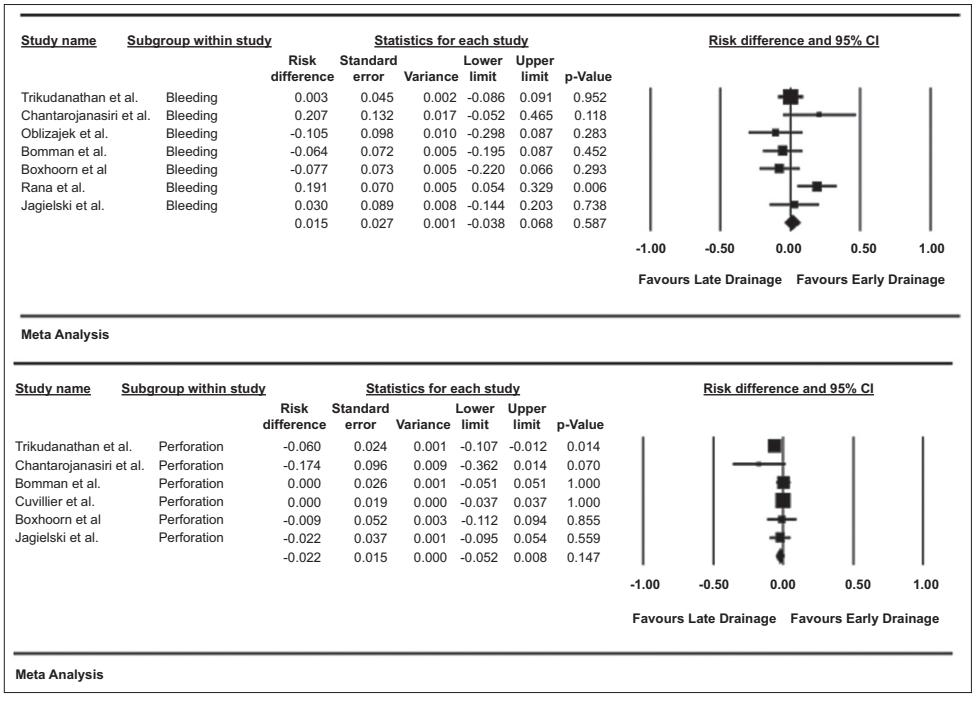
Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.94783	1.05404	3.59953	1.94783	1.05404	3.59953	5.71001
Adjusted values	0	1.94783	1.05404	3.59953	1.94783	1.05404	3.59953	5.71001

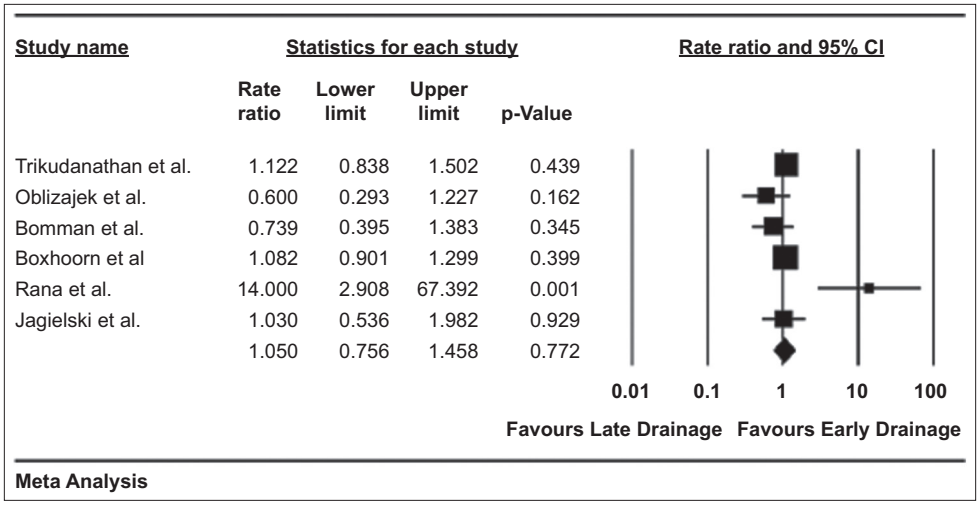
Egger's regression intercept

Intercept	-0.33884
Standard error	0.90499
95% lower limit (2-tailed)	-2.55326
95% upper limit (2-tailed)	1.87558
t-value	0.37442
df	6.00000
P-value (1 tailed)	0.36048
P-value (2-tailed)	0.72097

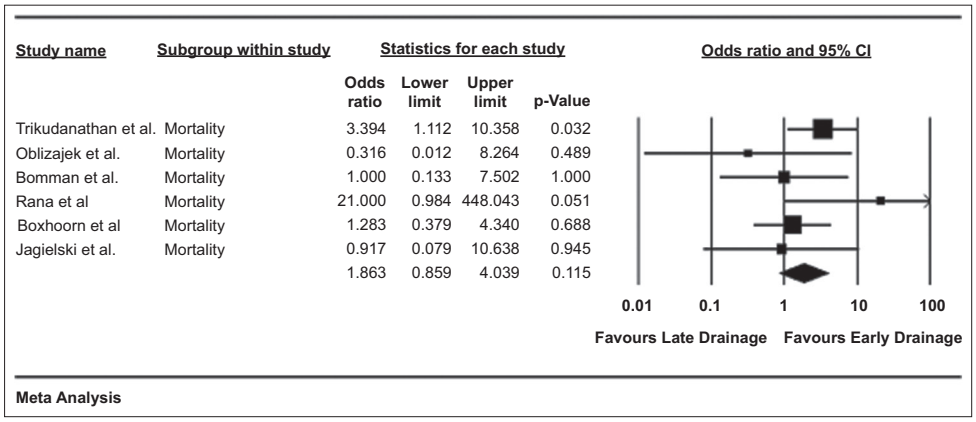
Supplementary Figure 3 Funnel plot for mortality outcome



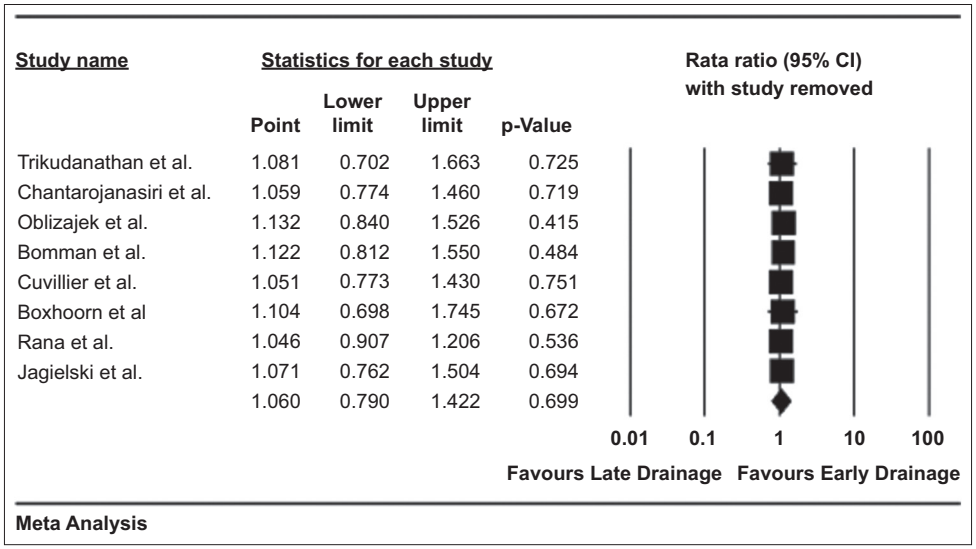
Supplementary Figure 4 Subgroup analysis comparing bleeding and perforation complications among the early and late drainage groups
CI, confidence interval



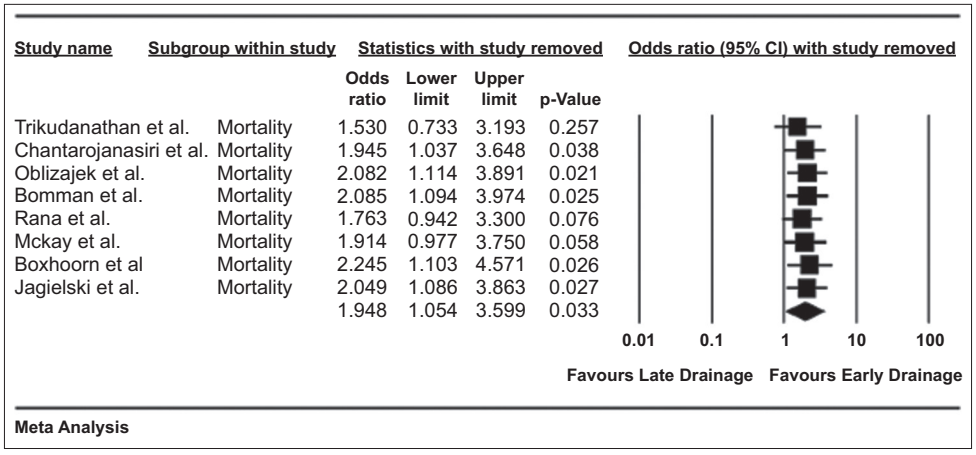
Supplementary Figure 5 Subgroup analysis comparing the complication rate only among high quality studies in early vs. late drainage
CI, confidence interval



Supplementary Figure 6 Subgroup analysis comparing the mortality only among high quality studies in early vs. late drainage
CI, confidence interval



Supplementary Figure 7 "Leave 1 study out analysis" for complication rates in early vs. late drainage.
CI, confidence interval



Supplementary Figure 8 "Leave 1 study out analysis" for mortality in early vs. late drainage
CI, confidence interval

Appendix 1 Search strategies

Searches run on January 21, 2022

OVID

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** December 2021**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to January 20, 2022, **Ovid MEDLINE(R) ALL** 1946 to January 20, 2022**, Embase** 1974 to 2022 January 20

#	Searches	Results
1	pancreas/ or exp pancreas disease/ or acute hemorrhagic pancreatitis/ or exp pancreatic diseases/ or pancreatitis, acute necrotizing/ or pancreas.mp. or pancreatic.mp.	975354
2	necrosis/ or necrosis.mp. or necrotic.mp.	1230357
3	drainage/ or drain.mp. or drainage.mp. or fluid collection.mp.	360416
4	time factor/ or time factors/ or early.mp. or late. mp. or delayed.mp.	6646850
5	1 and 2 and 3 and 4	1336
6	limit 5 to English language [Limit not valid in CDSR; records were retained]	1091
7	remove duplicates from 6 EBM Reviews - Cochrane Central Register of Controlled Trials <December 2021 >6 Embase <1974 to 2022 January 20 >703 Ovid MEDLINE(R) ALL <1946 to January 20, 2022 >96	805

PubMed (MEDLINE), 355 results (English only)

("Pancreas"[Mesh] OR "Pancreatic Diseases"[Mesh] OR "Pancreatitis, Acute Necrotizing"[Mesh] OR pancreas [tiab] OR pancreatic [tiab])

AND ("Necrosis"[Mesh] OR necrosis [tiab] OR necrotic [tiab])

AND ("Drainage"[Mesh] OR drain [tiab] OR drainage [tiab] OR fluid collection [tiab])

AND ("Time Factors"[Mesh] OR early [tiab] OR late [tiab] OR delayed [tiab])

Scopus (Elsevier)

1	TITLE-ABS-KEY ([pancreas OR "pancreatic disease" OR "acute necrotizing pancreatitis" OR pancreatic] AND [necrosis OR necrotic] AND [drain OR drainage OR "fluid collection"] AND [early OR late OR delayed])	638
2	(LIMIT-TO [LANGUAGE, "English"])	483

Web of Science, 378 results (English only)

(pancreas OR "pancreatic disease" OR "acute necrotizing pancreatitis" OR pancreatic) AND (necrosis OR necrotic) AND (drain OR drainage OR "fluid collection") AND (early OR late OR delayed)

2021. total article references

982. duplicates found in EndNote

1039. total references in EndNote

Supplementary Table 1 PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page- 1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Section/topic	#	Checklist item	Reported on page #
		RESULTS	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8,9
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10, Figs
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10, Figs
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11,12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13,14
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 2 The detailed assessment process of cohort studies included in the present meta-analyses

Studies [ref.]	Selection 1)	Selection 2)	Selection 3)	Selection 4)	Comparability 1)	Exposure 1)	Exposure 2)	Exposure 3)	Score*
Trikudanathan [11]	a)	a)	a)	a)	a)	a)	a)	a)	8+1=9
Oblizajek [26]	a)	a)	a)	a)	a) b)	a)	a)	b)	9+1=10
Chantarojanasiri [25]	a)	a)	a)	a)	a)	a)	a)	d)	7+1=8
Bomman [28]	a)	a)	a)	a)	a) b)	a)	a)	a)	9+0=9
Rana [27]	a)	a)	a)	a)	a)	a)	a)	a)	8+1=9
Cuvillier [29]	a)	a)	a)	a)	a)	a)		d)	6+0=6
Jagielski [24]	a)	a)	a)	a)	a)	a)	a)	b)	8+1=9
Mckay [30]	a)	a)	a)	a)	a)	a)		b)	7+0=7

*1 extra point was awarded to manuscripts published as full articles, and no points were awarded to those published as abstracts only