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Early versus late endoscopic treatment of pancreatic necrotic collections: A systematic review and meta-analysis

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Key words
Endoscopic ultrasonography, Pancreas, Intervention EUS

received 28.2.2022
accepted after revision 17.5.2023
accepted manuscript online 25.5.2023

Bibliography
Endosc Int Open 2023; 11: 794–799
DOI 10.1055/a-2100-9076
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Additional material is available under https://doi.org/10.1055/a-2100-9076

ABSTRACT

Background and study aims Recently studies have compared early (<4 weeks) vs. late or standard (>4 weeks) endoscopic treatment of pancreatic necrotic collections (PNC) and have reported favorable results for early treatment. In this meta-analysis, we compared the efficacy and safety of early vs. late endoscopic treatment of PNC.

Patients and methods We reviewed several databases from inception to September 30, 2021 to identify studies that compared early with late endoscopic treatment of PNC. Our outcomes of interest were adverse events (AEs), resolution of PNC, performance of direct endoscopic necrosectomy, need for further interventions, and mean number of endoscopic necrosectomy sessions. We calculated pooled risk ratios (RRs) with 95% confidence intervals (CIs) for categorical variables and mean differences (MDs) with 95% CIs for continuous variables. Data were analyzed by random effect model. Heterogeneity was assessed by I_2 statistic.

Results We included four studies with 427 patients. We found no significant difference in rates of AEs, RR (95% CI) 1.70 (range, 0.56–5.20), resolution of necrotic or fluid collections, RR (95% CI) 0.89 (range, 0.71–1.11), need for further interventions, RR (95% CI) 1.47 (range, 0.70–3.08), direct necrosectomy, RR (95% CI) 1.39 (range, 0.22–8.80), mortality, RR (95% CI) 2.37 (range, 0.26–21.72) and mean number of endoscopic necrosectomy sessions, MD (95% CI) 1.58 (range,–0.20–3.36) between groups.

Conclusions Early endoscopic treatment of PNC can be considered for indications such as infected necrosis or sterile necrosis with symptoms or complications; however, future large multicenter studies are required to further evaluate its safety.

Introduction

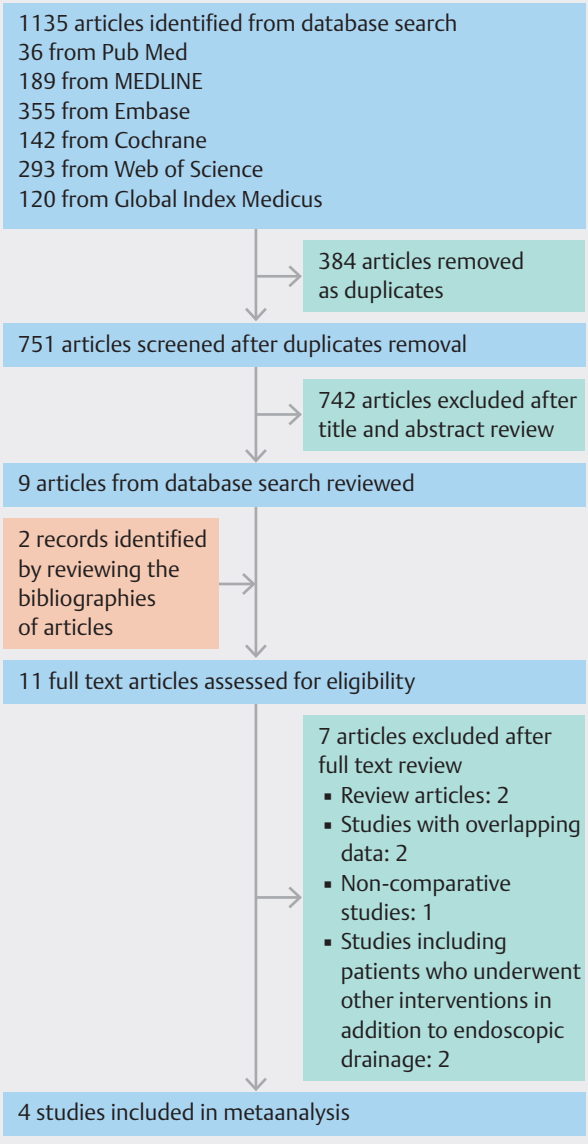
Pancreatic necrosis develops in about 20% of patients with acute pancreatitis and can be associated with substantial morbidity and mortality [1]. Drainage of pancreatic necrotic collections (PNC) is required in cases of infected necrosis or sterile necrosis with substantial symptoms or local complications [2, 3]. Drainage of PNCs has gone through a paradigm shift from open surgical necrosectomy to percutaneous and endoscopic approaches [4]. The timing of drainage of PNC is an important consideration and current guidelines suggest that drainage of PNC should be delayed until 4 weeks after the onset of acute pancreatitis to allow formation of an encapsulated collection [5]. In some cases, infected or symptomatic PNC necessitate early drainage before 4 weeks.

Previously studies have shown that percutaneous drainage can be safely performed before 4 weeks [6, 7]. There was a lack of data about the feasibility and safety of early endoscopic drainage of PNCs until recently when some studies showed it can be safely performed before 4 weeks [8, 9]. Chantarojanasiri et al [8] found that early (<4 weeks) endoscopic treatment of PNC was feasible for encapsulated collections adherent to the structures in the upper gastrointestinal tract. Additional studies have compared early vs late endoscopic treatment of PNC and have reported favorable results [9, 10, 11]. In this systematic review and meta-analysis we compared the efficacy and safety of early versus late or standard endoscopic treatment of PNC.

Patients and methods

Data sources and search strategy

We followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). A comprehensive search strategy to identify studies on the timing (before or after 4 weeks) of drainage of all types of pancreatic fluid collections was constructed using truncated keywords and phrases and was developed in Embase (Embase.com, Elsevier) by an experienced health sciences librarian [WL-S]. This strategy was translated to MEDLINE (OVID platform, NCBI), Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley), the Web of Science Core Collection, and Global Index Medicus with all searches performed on September 30, 2021. We have provided full search strategies from all databases in **Supplementary Table 1**. There was no restriction of publication language in conducting the search. Two authors (F.K. and S.S.) independently reviewed the titles and abstracts of the retrieved articles and excluded those that did not provide data on our outcomes of interest. Full texts of remaining articles were reviewed. We also reviewed the bibliographies of these articles to identify any additional relevant studies. The screening results are illustrated in the form of a PRISMA flowchart in ▶ **Fig. 1** [12].



▶ **Fig. 1** PRISMA Flowchart. From: *Page MJ, McKenzie JE, Bossuyt PM* et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71 For more information, visit: http://www.prisma-statement.org/

Inclusion and exclusion criteria

Two authors (F.K. and M.A.K.) independently searched for original studies based on predefined inclusion criteria, which are detailed below. We included only the studies that compared early (<4 weeks) with late or standard (>4 weeks) endoscopic treatment of pancreatic fluid collections or pancreatic necrosis. We excluded the studies in which modalities other than endoscopic treatments such as percutaneous drainage and surgical treatment were employed for early or late treatment. We also excluded review articles. All citations were downloaded into Endnote X9 (Clarivate, Philadelphia, Pennsylvania, United States), a bibliographic database manager. Duplicate citations were re-

moved by successive field matching algorithms with manual inspection.

Data extraction and quality assessment

Two authors (F.K. and M.A.K.) independently assessed the eligibility of included studies and collected data using data extraction forms designed for this study. Any disagreement between individual authors was resolved by a repeat review of data and discussion with a third reviewer (T.H.B.). Extracted data included year of publication, types of stents used, time of treatment after onset of acute pancreatitis, length of stay, inclusion criteria, exclusion criteria, and for each group, technical success, complications, resolution of necrotic collection, need for further interventions, performance of direct necrosectomy, mortality, and mean number of endoscopic necrosectomy sessions. We used Methodological Index for Nonrandomized Studies (MINORS) criteria for assessment of quality of observational studies [13]. Two authors (U.F. and Z.E.) independently performed the quality assessment and any disagreement was discussed with a third reviewer (F.K.). The quality assessment of studies is summarized in **Supplementary Table 2**.

Data synthesis and statistical analysis

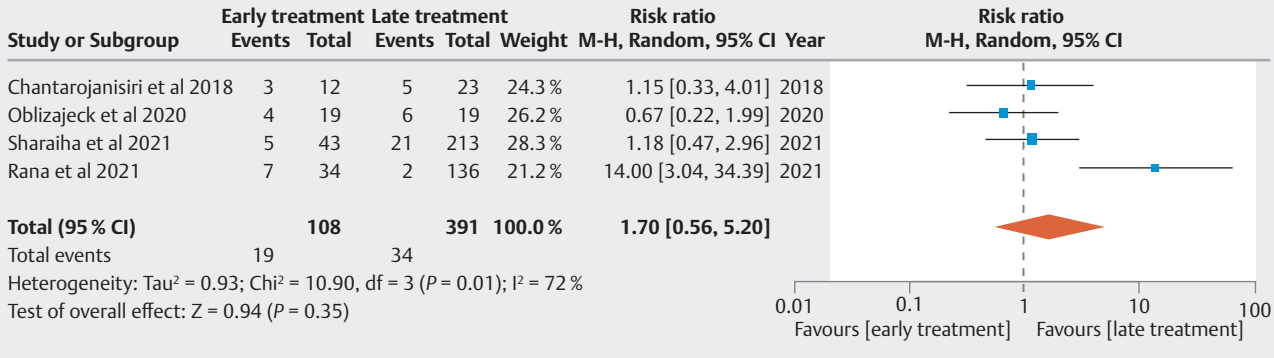
Our primary outcome of interest was comparison of adverse events (AEs) between early vs late treatment groups. Secondary outcomes of interest were resolution of PNC, performance of direct endoscopic necrosectomy (at time of initial stent placement), need for further interventions such as endoscopic or surgical necrosectomy or percutaneous drainage, and comparison of mean number of endoscopic necrosectomy sessions between groups. We calculated pooled risk ratios (RRs) with 95% confidence intervals (CIs) for analysis of categorical variables. We calculated mean differences (MDs) with 95%s CI for analysis of continuous variables. Sensitivity analyses were performed by excluding the study by Rana et al [11] because this study had substantial differences compared to other studies included in the analysis, so it was considered to be an outlier. In the study by Rana et al, a significantly higher proportion of patients in early treatment group had infected necrosis compared to the late treatment group (79.4% vs. 32.9%). Also in this study, the mean size of walled off necrosis was significantly greater in the early treatment compared to the late treatment group (12.3 vs. 10.5). We used Review Manager (RevMan, version 5.4 for Windows; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014) and comprehensive meta-analysis software for statistical analyses. We used a random effects model to analyze the data. We assessed heterogeneity using the I^2 statistic. $P < 0.1$ for Cochrane Q test or $I^2 > 50\%$ indicated significant heterogeneity. We did not assess for publication bias as the total number of studies that we included was less than 10.

Results

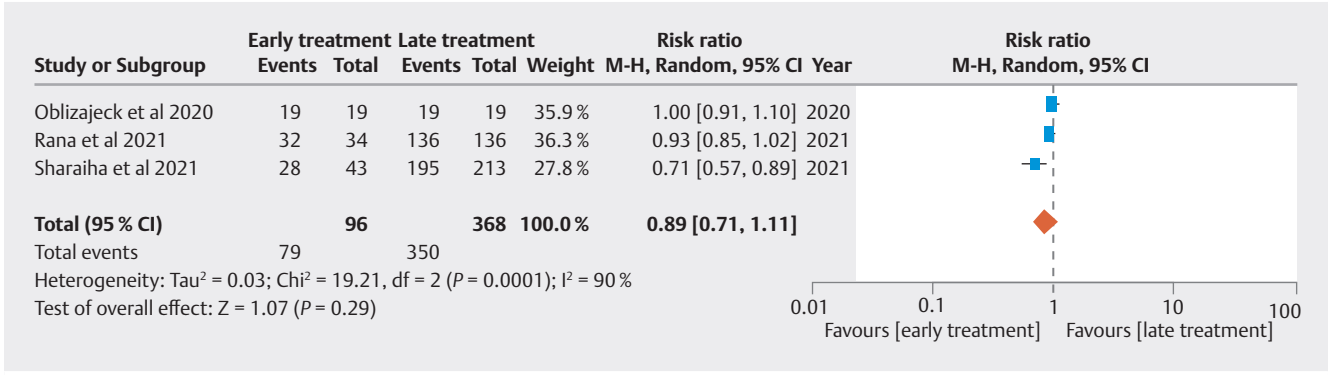
The search strategy produced 1137 articles, 384 of which were removed as duplicates (▶ **Fig. 1**). From the remaining 751 articles, 742 were removed after title and abstract review. Two additional relevant articles were identified from review of bibliographies [11, 14]. Full texts of 11 articles were reviewed. One non-comparative study, two studies with overlapping data, and two review articles were excluded. Two studies [14, 15] were excluded because they included patients who underwent percutaneous or surgical drainage as well in addition to those that underwent endoscopic drainage. Finally, four studies with 427 patients were included [8, 9, 10, 11]. Three studies with 171 patients were full publications and one study with 256 patients was available in abstract form. A total of 108 patients underwent early intervention (<4 weeks) and 319 patients underwent late or standard (>4 weeks) endoscopic interventions. Three studies [9, 10, 11] only included patients with necrotic collections. In one study [8], 80% of the included patients had necrotic collections and 20% patients had peri-pancreatic fluid collections (acute peri-pancreatic fluid collection or pseudocysts).

Adverse events

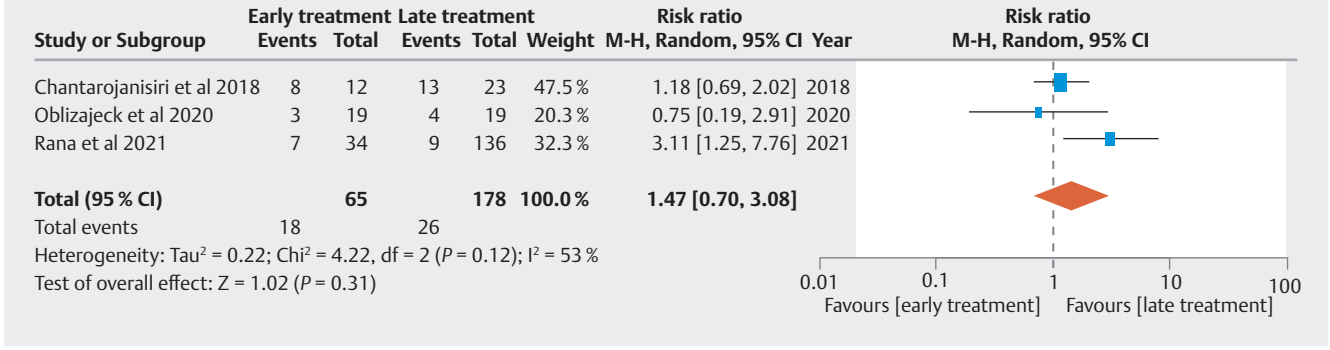
Pooled rates of AEs in early and late treatment groups were 17% and 9%, respectively. There was no significant difference in rate of AE between groups, RR (95% CI) 1.70 (range, 0.56–5.20), I^2 = 72% (▶ **Fig. 2**). Sensitivity analysis excluding the study by Rana et al showed similar results, RR (95% CI) 0.98 (range, 0.53–1.81) with substantial decrease in heterogeneity (I^2 = 0%).



▶ **Fig. 2** Forest plot to compare adverse events between groups.



▶ **Fig. 3** Forest plot to compare rate of resolution of necrotic collection between groups.



▶ **Fig. 4** Forest plot to compare rate of further interventions between groups.

Resolution of necrotic collection

Pooled rates of resolution of necrotic or fluid collection in the early and late treatment groups were 82% and 95%, respectively. There was no significant difference in rate of resolution of necrotic or fluid collections between groups, RR (95% CI) 0.89 (range, 0.71–1.11), I^2 =90% (▶ **Fig. 3**). Sensitivity analysis excluding the study by Rana et al showed similar results, RR (95% CI) 0.85 (range, 0.46–1.56), I^2=96%.

Further interventions

Pooled rates of further interventions in the early and late treatment groups were 28% and 15%, respectively. There was no significant difference in need for further interventions between groups, RR (95% CI) 1.47 (range, 0.70–3.08), I^2=53% (▶ **Fig. 4**). Sensitivity analysis excluding the study by Rana et al showed similar results, RR (95% CI) 1.11 (0.67, 1.83), I^2=0%.

Direct necrosectomy

Pooled rates of direct necrosectomy in the early and late treatment groups were 28% and 15%, respectively. There was no significant difference in rate of direct necrosectomy between groups, RR (95% CI) 1.39 (range, 0.22–8.80), I^2=94% (▶ **Fig. 5**). Sensitivity analysis excluding the study by Rana et al did not change the results (RR [95% CI] 0.71 (range, 0.46–1.10) but there was a substantial decrease in heterogeneity (I^2=0%)

Mortality

Pooled rates of mortality in the early and late treatment groups were 4% and 1%, respectively. There was no significant difference in mortality between groups, RR (95% CI) 2.37 (range, 0.26–21.72), I^2=41% (**Supplementary Fig. 1**). Sensitivity analysis excluding the study by Rana et al showed similar results, RR (95% CI) 0.92 (range, 0.12–7.04), I^2=0%.

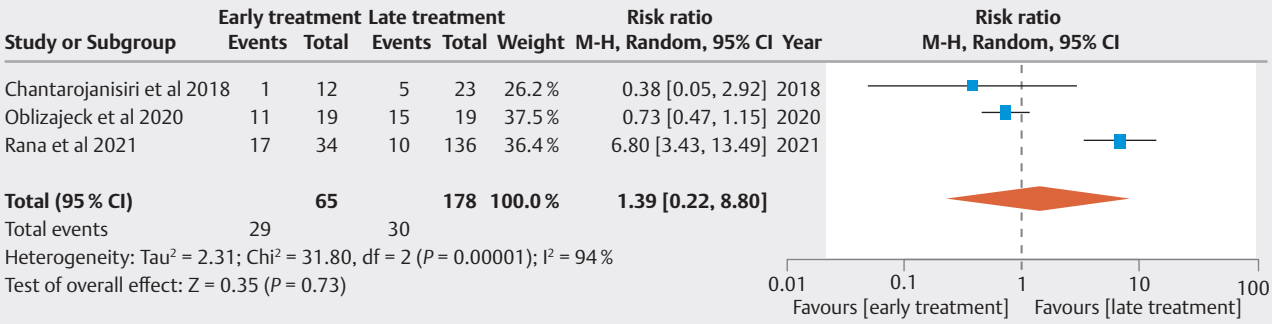
Mean number of endoscopic necrosectomy sessions

We found no significant difference in the mean number of endoscopic necrosectomy sessions between groups, MD (95% CI) 1.58 (range, –0.20–3.36), I^2=80% (**Supplementary Fig. 2**).

Discussion

Endoscopic drainage is a well-established treatment for PNC and studies have shown better outcomes with endoscopic treatment compared to surgical necrosectomy [16, 17]. Although it is recommended that treatment of PNC be delayed until 4 weeks after onset of acute pancreatitis, in some cases, early treatment is necessary for symptomatic or infected collections. Our meta-analysis showed that endoscopic drainage can be safely performed before 4 weeks with outcomes comparable to delayed drainage.

We found no significant difference in the rate of AEs between groups, RR (95% CI) 1.70 (range, 0.56–5.20). However,



▶ **Fig. 5** Forest plot to compare rate of direct necrosectomy between groups.

pooled rates of AEs were higher in the early treatment group (17%), compared to the late treatment group (9%). Also, the CI was broad (range, 0.56–5.20), raising the possibility of type II error due to small sample size. Hence our findings regarding risk of AEs based on this analysis are inconclusive and more studies with larger sample sizes are required to further evaluate this issue. Perforation of the necrotic cavity is a concern when performed early for PNC due to the potentially less robust wall. Only one study included in our meta-analysis specifically reported data on perforation and no case of perforation in the early treatment group was seen compared to four cases in the late treatment group. Patients should be carefully selected for early treatment and a careful assessment of wall formation should be performed with pre-procedure imaging because the collections with partially formed walls can perforate during the procedure. Among all studies included in our meta-analysis, only Rana et al [11] showed a higher risk of AEs in the early treatment group. In this study, a significantly higher proportion of patients in the early treatment group had infected necrosis compared to the late treatment group. Also, the mean size of walled off necrosis was significantly greater in the early treatment compared to the late treatment group. Both of these factors can possibly cause a higher risk of AEs in the early treatment group.

EUS-guided drainage before 4 weeks can be challenging because of predominantly solid content of the necrotic collection. In contrast, mature collections after 4 weeks often have more of a liquid component, making drainage technically easier. In theory, early treatment should require direct necrosectomy more often and may also require a greater number of subsequent endoscopic necrosectomy sessions. However, we found no significant difference in the rates of direct necrosectomy between groups; RR (95% CI) 1.39 (range, 0.22–8.80) and the mean number of endoscopic necrosectomy sessions between groups, MD (95% CI) 1.39 (range, 0.22–8.80).

This is the first systematic review and meta-analysis to compare early and delayed EUS-guided treatment of PNC. We only included studies in which all patients underwent endoscopic treatment and consequently only excluded two studies in which some patients underwent percutaneous drainage or surgical necrosectomy [14, 15]. This meta-analysis has several limitations. All of the included studies were observational. Observational studies have risks of measured and unmeasured confounding. To date, no randomized controlled trials have compared the two modalities. Most of the analyses were limited by substantial to considerable heterogeneity. We were able to explain the heterogeneity in most of the analyses by performing sensitivity analysis excluding the study by Rana et al. Only four studies met our inclusion criteria and could be included in this meta-analysis. Therefore, the overall sample size is too small to make firm conclusions. We also found evidence of clinical heterogeneity across studies. The types of stents used varied across studies and also during follow-up. Lately lumen-apposing metal stents (LAMS) have become the predominant stents used for endoscopic drainage. In one of the included studies [8], LAMS were not available at their institution during the study period and plastic stents or fully-covered self-expanding metal stents were used. In the study by Oblizajek et al [9], only plastic stents were used in 50% of the patients and the metal stents that were used evolved over the course of the study. In the study by Rana et al [11], either plastic stents or LAMS were used as per endoscopist discretion, percentage of solid necrotic debris, and patient preference depending upon affordability due to economic considerations and availability of health insurance.

Conclusions

In conclusion, the safety of early EUS-guided treatment of PNC should be further evaluated in future large multicenter studies. The results of our meta-analysis are limited by small sample size and high levels heterogeneity and definite conclusions cannot be made regarding the safety of early EUS-guided treatment of PNC. Comparative studies using LAMS in larger numbers of patients are needed to make firm conclusions.

Conflict of Interest

Dr. Todd Baron is a speaker and consultant for Boston Scientific, Cook Endoscopy, W.L. Gore and CONMED. Other authors have no relevant conflicts of interest.

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