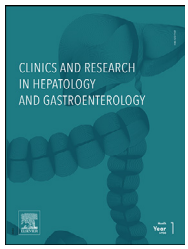
Clinics and Research in Hepatology and Gastroenterology 47 (2023) 102105

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com



ORIGINAL ARTICLE

Timing of minimally invasive step-up intervention for symptomatic pancreatic necrotic fluid collections: A systematic review and meta-analysis

ZheYu Liu[a], Pi Liu[b,*], Xuan Xu[a], Qian Yao[a], YuWen Xiong[a]

[a] *Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China*
[b] *Department of Gastroenterology, Affiliated Longhua People's Hospital, Southern Medical University, 518109, Shenzhen, China*

Available online 28 February 2023

KEYWORDS
Pancreatic necrotic fluid collections;
Minimally invasive intervention;
Step-up approach;
Early intervention;
postponed intervention

Abstract
Background and AIMS: Minimally invasive step-up interventions are now the standard treatment recommended by current guidelines for symptomatic pancreatic necrotic fluid collections (PNFC); however, it is controversial whether delayed treatment after four weeks should always be used in patients who have failed conservative treatment and whose condition has not improved or worsened. The aim of this meta-analysis was to evaluate the impacts of the different timing of interventions on the clinical outcomes and prognosis of patients with symptomatic PNEC requiring intervention.
Methods: We searched Embase, Cochrane Library, PubMed and Web of Science databases to identify comparative studies assessing the safety and efficacy of early and postponed interventions in treating symptomatic PNFC. Primary outcome: Mortality. Secondary outcomes included some major complications, need for further minimally invasive necrosectomy and length of hospital stay.
Results: This meta-analysis included ten studies (2 RCTs and 8 observational studies) with a total of 1178 symptomatic PNFC patients who required intervention. Pooled results showed that there was no significant difference between early minimally invasive intervention and postponed intervention in mortality(OR 1.41, 95%CI 0.93—2.12;$p = 0.10$) and the incidence of early and late complications, but the early intervention group had a significantly increased need for further minimally invasive necrosectomy compared with postponed intervention (OR 2.04,95%CI 1.04—4.03; $p = 0.04$). There was no increase in length of stay for patients who received early intervention compared to postponed drainage (MD 3.53, 95% CI -4.20, 11.27; $p = 0.37$).

Abbreviations: PNFC, pancreatic necrotic fluid collections; ANP, acute necrotizing pancreatitis; ANCs, acute necrotic collections; WON, wall-off necrosis; VARD, video-assisted retroperitoneal debridement.

* Corresponding author at: Department of Gastroenterology, Affiliated Longhua People's Hospital, Southern Medical University, 518109, Shenzhen, China.
E-mail address: liupi126@sina.com (P. Liu).

https://doi.org/10.1016/j.clinre.2023.102105

Conclusion: Intervention before four weeks should be considered for patients with PNFC complicated by persistent organ failure or infections, who have been treated conservatively to the maximum extent possible.

Introduction

Acute pancreatitis is a serious health and safety concern and is the leading gastrointestinal diagnosis leading to hospitalization [1]. While most patients progress to mild pancreatitis, acute necrotizing pancreatitis occurs in 20% of patients, resulting in parenchymal necrosis, peripancreatic tissue necrosis, or a mixture of both, requiring advanced medical and interventional treatment [2]. Most patients with acute necrotizing pancreatitis (ANP) will develop pancreatic necrotic fluid collections, which are an important local complication of pancreatitis [3]. Depending on the duration and degree of encapsulation of the collections, within 4 weeks the necrotic collections of pancreas or peri-pancreas are known as acute necrotic collections (ANCs) and beyond 4 weeks some of the necrotic collections develop into wall-off necrosis (WON) which includes necrotic fluid and solid tissue fragments [4].

Treatment for asymptomatic pancreatic necrosis is typically conservative [5]. Common indications in the invasive treatment of pancreatic necrosis are confirmed or suspected infection, persistent organ failure and clinical signs due to compression of adjacent vital structures [6]. The current standard of treatment for symptomatic necrotic collections of the pancreas is minimally invasive step-up treatment [6]. This step-up treatment involves an initial step of percutaneous catheter or endoscopic drainage, and if clinical symptoms do not resolve after catheter drainage, minimally invasive necrosectomy is performed. Depending on the initial drainage route a video-assisted retroperitoneal debridement (VARD) or an endoscopic transluminal necrosectomy is used [6,7]. International guidelines recommend that invasive treatment of pancreatic necrosis is usually delayed until four weeks after the onset of the disease, in order to form adequate encapsulation of the pancreatic and/or peripancreatic necrosis [4,8]. Delaying invasive intervention can make drainage and necrosectomy easier and reduce the risk of complications or death. However, recommendations to delay intervention are based primarily on studies involving open surgical intervention [9—11]. For minimally invasive treatment, the answer to the question of whether treatment is delayed still needs to be clarified.

An updated clinical guideline from the American Gastroenterological Association suggests that patients with symptomatic pancreatic necrotic fluid collections (PNFC) in the early stages of the disease should consider catheter drainage [12]. In addition, some experts suggest that patients with pancreatic necrosis in early persistent organ failure have a higher mortality rate and that delaying intervention for up to 4 weeks may affect mortality risk [13]. Therefore, postponed invasive intervention is controversial in patients with symptomatic PNFC that have failed with conservative treatment.

To investigate the appropriate timing of intervention for patients with symptomatic PNFC, this study used a meta-analysis to evaluate the impacts of different timing of interventions on the clinical outcomes and prognosis of patients with symptomatic PNFC.

Method

Search strategy

Two researchers (ZYL and YWX) performed a comprehensive search, following established guidelines for reporting systematic evaluations and meta-analyses (PRISMA) [14]. A literature search of Embase, Cochrane Library, PubMed and Web of Science (earliest inception to 1 October 2022) was conducted to identify suitable studies. Use the following keywords: (“Pancreatic necrotic collections” OR “Acute pancreatic necrosis” OR “Acute necrotic collections” OR “Necrotizing Pancreatitis”) AND (“Early intervention” OR “Early drainage” OR “Postponed intervention” OR “Delayed drainage’’) were searched in the literature. There were no limitations on year of publication or language, and the reference lists of eligible articles were searched manually for more relevant articles.

Selection criteria

Inclusion criteria

Population [1]: Patients suffering from acute necrotizing pancreatitis with pancreatic and/or peripancreatic necrotic collections proven on imaging (enhanced CT, MRI, etc.) [2], Patients with symptomatic PNFC who have undergone optimal conservative treatment but whose condition has not improved or deteriorated requiring invasive intervention.

Interventions [1]: all patients were treated using a “step-up” intervention strategy [2], Early minimally invasive interventions include an initial percutaneous catheter or endoscopic transluminal drainage, and if necessary, subsequent minimally invasive necrosectomy in the form of a video-scopic-assisted retroperitoneal debridement or endoscopic transluminal necrosectomy.

Comparison: postponed minimally invasive intervention (the initial drainage and the necessary minimally invasive necrosectomy).

Exclusion criteria

The study included [1]: Patients not suffering from pancreas necrosis and/or peri-pancreas necrosis [2], patients who did not use the "step-up" intervention strategy [3], clinical trials with patients with chronic pancreatitis were excluded.

Data extraction

Independently, two authors (ZYL and YWX) assessed potential studies based on eligibility. References for inclusion in the article were also screened to identify studies that were not identified in the initial search. Disagreements were

handled through conversations with senior third-party adjudicators (PL) in order to obtain a consensus. The following features extracted from the eligible studies were: name of the first author, year of article publication, country from which this study was conducted, type of study, patient demographics, definition of timing of early intervention, initial route of intervention, type of subsequent minimally invasive necrosectomy, extent of encapsulation of necrotizing collections and primary clinical outcomes.

Outcomes

Primary outcome: Mortality. Secondary outcomes included some major complications: bleeding resulting in intervention, gastrointestinal perforation or fistula, pancreatic fistula, wound infection and endocrine pancreatic insufficiency, need for further minimally invasive necrosectomy and length of hospital stay.

Assessment of methodological quality

The quality of the methods was independently assessed depending on the type of study using proper tools by two authors. The risk of bias in the RCTs was evaluated using the Cochrane Collaboration Tool [15], and in observational research, the Newcastle-Ottawa Scale was used [16]. The third author will debate any disagreements to obtain a consensus.

Statistical analysis

Meta-analysis illustrated with forest diagrams. Dichotomous variables were summarized by estimating odds ratios (ORs) and 95% confidence intervals (CIs), whereas continuous variables were summarized using mean differences and 95% CIs. If the study's continuous variables included only the median, range, or interquartile range, we transformed them to mean and standard deviation (SD) using the formula [17]. The I^2 statistic was used in each meta-analysis to assess statistical heterogeneity between studies. I^2 values above 50% showed moderate heterogeneity, and I^2 values above 75% indicated significant heterogeneity. If no heterogeneity is found ($I^2<50\%$), the analysis of the results applies a fixed effects model; conversely, a random effects model is applied. For continuous outcomes, the inverse variance approach was chosen, whereas the Mantel-Haenszel (MH) model was used for dichotomous outcomes. Results $P<0.05$ represented a statistically significant difference. Subgroup analyses were performed on mortality, bleeding resulting in intervention, need for further minimally invasive necrosectomy and length of hospital stay according to the type of study design. Visual assessment of the funnel plot verified potential publication bias when the number of included studies was at least 10. Statistical analysis was performed using Stata17 (StataCorp, College Station, TX) software.

Results

Study selection

1006 studies were identified through the initial database search, and 830 were screened after removing duplicates (Fig. 1). The eligibility of the remaining 53 studies was evaluated. Of these, studies that did not include patients with

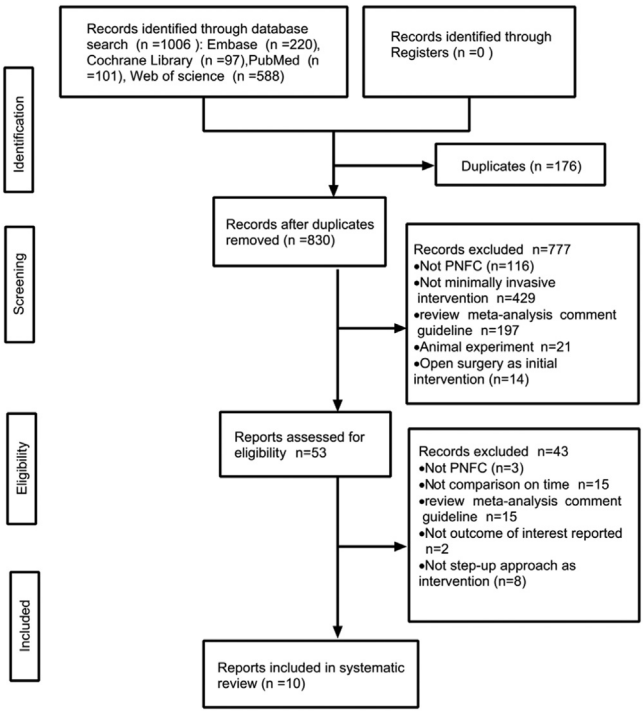


Fig. 1 Flow diagram that summarizes the results of the literature search.

pancreatic necrosis collections (n = 3), studies that did not compare based on the timing of the intervention (n = 15), or Studies that lacked clinical outcomes of interest (n = 2), or studies that did not use a step-up approach as an intervention strategy (n = 8), 18 reviews, meta-analyses, comments and guidelines were excluded. Ten studies considered eligible were included in the meta-analysis [18—27].

Study characteristics

A total of 1178 symptomatic PNFC patients requiring intervention were included in the ten clinical studies (471 patients receiving early intervention, 707 patients postponing intervention). Details of the studies included are provided in Table 1. The studies by Boxhoorn et al. and Ke et al. were RCTs, two studies by Dost et al. and Jagielski et al. were cohort studies, and the other six studies were case-control studies. Regarding the type of intervention for each study (based on the initial drainage pathway), four trials included only patients whose initial intervention was percutaneous drainage in their treatment strategy [18,20,25,27]. Four trials included only patients whose initial intervention was endoscopic transluminal drainage in the treatment strategy [21—24]. The study by Boxhoorn et al. used a minimally invasive surgical or endoscopic-centered treatment strategy, which depended on the initial drainage pathway [26]. The study by Bomman et al. used a dual drainage pattern (a combination of percutaneous and endoscopic drainage) as an initial intervention in a step-up strategy [19].

Patient characteristics

Four of the ten clinical studies accounted for the time to encapsulation of necrotic collections in ANP patients

Table 1 Characteristics of clinical studies included in the meta-analysis.

Study	Country	Study type	No. of patients (early/ Postponed)	The interval from the onset of symptoms to the intervention		Type of intervention		Encapsulation of necrosis at the time of receiving the intervention—no. (%)
				Early intervention	postponed intervention	initial intervention	Subsequent intervention	
Lu et al.	China	Case control study	43/55	Mean 15.26 days	Mean 50.86 days	Percutaneous catheter drainage	Surgically centered step-up interventions	unclear
Bomman et al.	USA	Case control study	39/173	Median 22 days	Median 52 days	Percutaneous and endoscopic transluminal catheter drainage	Mainly endoscopically centered step-up interventions	unclear
Dost et al.	PAK	Prospective cohort study	65/65	Unclear	Unclear	Percutaneous catheter drainage	Unclear	unclear
Trikudanathan et al.	USA	Case control study	76/117	Median 20 days	Median 78 days	Endoscopic transluminal drainage	Mainly endoscopically centered step-up interventions	Early:32/76(42.1), postponed:88/117(75.2)
Jagielski et al.	Poland	Prospective cohort study	25/46	Median 16.4 days	Median 74.5 days	Endoscopic transluminal drainage	Endoscopically centered step-up interventions	unclear
Oblizajek et al.	USA	Case control study	19/19	Median 23 days	Median 64 days	Endoscopic transluminal drainage	Endoscopically centered step-up interventions	Early:8/19(42.1) post-poned:17/19(89.5)
Rana et al.	India	Case control study	34/136	Mean 24 days	Mean 75 days	Endoscopic transluminal drainage	Endoscopically centered step-up interventions	early:26/34(74.2), postponed:136/136(100)
Zhang et al.	China	Case control study	100/31	Median 19 days	Median 33 days	Percutaneous catheter drainage	Surgically centered step-up interventions	unclear
Boxhoorn et al.	The Netherlands	Randomized controlled trial	55/49	Median 24 days	Median 34 days	Percutaneous or endo-scopic transluminal catheter drainage	Endoscopically and surgically cen-tered step-up interventions were both adopted	early:33/55(60), postponed:22/49(44.9)
Ke et al.	China	Randomized controlled trial	15/15	Median 15.5 days	Median 22 days	Percutaneous catheter drainage	Surgically centered step-up interventions	unclear

Table 2 Definitions of intervention timing.

Study	Early intervention	postponed intervention
Lu et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Bomman et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Dost et al.	Immediate drainage within 24 h after infected necrosis was diagnosed	>4 weeks
Trikudanathan et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Jagielski et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Oblizajek et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Rana et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Zhang et al.	<4 weeks after onset of symptoms of ANP	>4 weeks
Boxhoorn et al.	Immediate drainage within 24 h after infected necrosis was diagnosed	intervention until necrotic collections were largely or fully encapsulated
Ke et al.	<3 weeks after onset of symptoms of ANP	>4 weeks

[21,23,24,26]. The four studies included 184 patients who received early intervention and 321 patients who received postponed intervention. 99 patients (53.8%) in the early group whose pancreatic and peripancreatic necrosis was largely or completely encapsulated at the time of receiving the intervention and 263 patients (81.9%) in the late group whose necrosis was encapsulated at the time of receiving the intervention (Table 1).

Timing of intervention

Table 2 provides definitions of the timing of interventions across studies. The studies by Dost et al. and Boxhoorn et al. defined "early" intervention as a diagnosis of infected necrosis as soon as it was diagnosed and drainage within 24 h of randomization, while "postponed" intervention was defined as the pancreatic and peripancreatic necrotic collections being largely or completely encapsulated. In the other eight studies, the timing of early and postponed interventions was separated by a 4-week cut-off.

Assessment of methodological quality

Table 3 provides a risk assessment of bias among the included articles. The studies by Boxhoorn et al. and Ke et al. were RCTs. Using Cochrane risk of bias estimates, the two studies used randomized samples and explained the particular method of concealing allocation. It is not possible to be completely blind as a result of the characteristics of the intervention. 2 studies were also blinded in their outcome assessments. Newcastle-Ottawa scale was used to assess non-randomized controlled trials; for the cohort studies, two studies were rated as moderate-quality [20,22]. For case-control studies, five studies were rated as high-quality [18,21,23-25], and 1 study was rated as moderate-quality [19].

Primary outcome

Mortality

All studies reported mortality [18—27]. Pooled analysis demonstrated that early intervention had a slightly higher impact on mortality than postponed intervention; however, no differences that were statistically significant were identified (OR 1.41, 95% CI 0.93, 2.12; p = 0.10; Fig. 2). These studies had a low degree of heterogeneity (I^2=12.05%, p.0.33). Meta-analysis of subgroups in two randomised controlled trials showed no significant difference in mortality between the early and postponed intervention groups (OR 0.82, 95% CI 0.32, 2.12; Fig. 2). The subgroup heterogeneity was low (I^2=28.60%).

Secondary outcomes

Bleeding. The occurrence of bleeding was reported in all ten trials [18—27]. Pooled analysis showed that the incidence of bleeding was not affected by the timing of the intervention (OR 0.99, 95% CI 0.69, 1.42; p = 0.96; Fig. 3). These studies had a low degree of heterogeneity (I^2=39.24%, p.0.10). Meta-analysis of subgroups in two randomised controlled trials showed no significant difference in the occurrence of bleeding in the early and postponed groups (OR 0.72, 95% CI 0.29, 1.80; Fig. 3). No heterogeneity in subgroup (I^2=0%).

Gastrointestinal fistula or perforation. Data on the occurrence of gastrointestinal fistula or perforation were available for eight included studies [18—22]' [25—27]. Pooled analysis demonstrated that the early intervention strategy slightly increased the occurrence of gastrointestinal fistula or perforation but was not statistically significant when compared with postponed intervention (OR 1.32, 95% CI 0.86—2.03; p = 0.20; Fig. 4). No heterogeneity (I^2=0%, p.0.80).

Pancreatic fistula. Five studies reported on the rate of pancreatic fistula [19,20,25-27]. Meta-analysis showed that early intervention had a tendency to increase the rate of pancreatic fistula compared to postponed intervention; however, no statistical differences were identified (OR 1.38, 95% CI 0.70, 2.71; p = 0.35; Fig. 5). No heterogeneity (I^2=0%, p.0.89).

Wound infection. Data on wound infection resulting in intervention were available for three of the included trials [19,20,26]. Pooled results showed that early intervention strategy was related to decrease in the occurrence of wound infection but not statistically significant when compared with postponed intervention (OR 0.56, 95%CI 0.23, 1.36; p = 0.20; Fig. 6). No heterogeneity (I^2=0%, p.0.85).

Endocrine pancreatic insufficiency. Data on endocrine pancreatic insufficiency came from five of the included studies

Table 3 Risk of bias assessment of included studies.

Risk of bias assessment of the randomized controlled trial								
study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Reporting bias	Other bias	
Boxhoorn et al.	Low	Low	High	High	Low	Low	Low	
Ke et al.	Low	Low	High	Low	Low	Low	Low	
Newcastle—Ottawa quality assessment scale for cohort studies								
study	Selection Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability Comparability of cohorts on the basis of the design or analysis	Outcome Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Dost et al.	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	independent blind assessment	No	No statement
Jagielski et al.	Truly representative	Same hospital	Secure record	Yes	Gender matched	independent blind assessment	Yes	Complete follow-up
Newcastle—Ottawa quality assessment scale for case control studies								
study	Selection Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability Comparability of cases and controls on the basis of the design or analysis	Expose Ascertainment of exposure	The same method of ascertainment for cases and controls	Non-Response rate
Lu et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	Same rate
Bomman et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	no description
Trikudanathan et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	Same rate
Oblizajek et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	Same rate
Rana et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	Same rate
Zhang et al.	Yes	Consecutive or obviously representativeness	Same hospital	No history of the disease	Age and gender matched	Secure record	Same method	Same rate

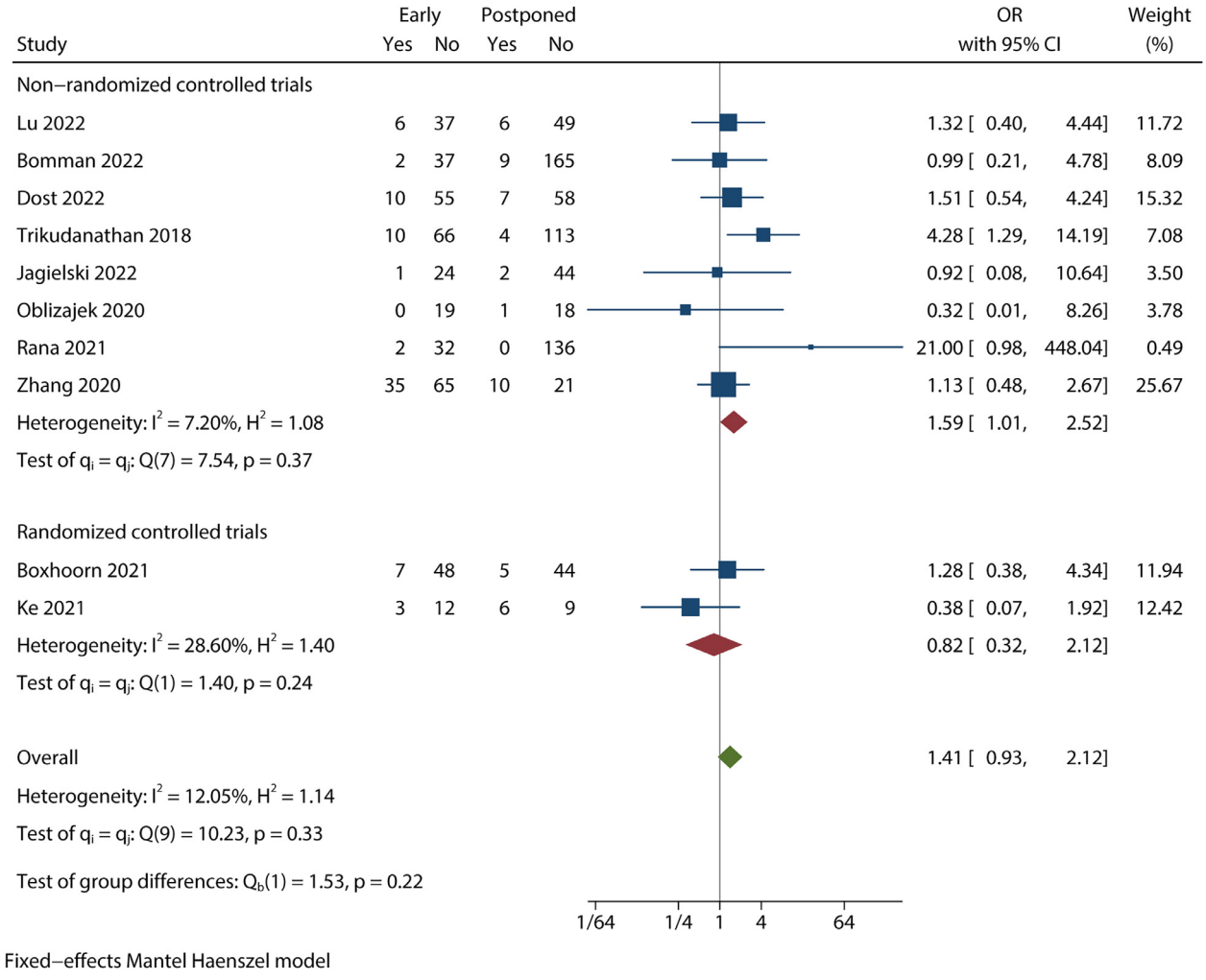


Fig. 2 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on mortality compared with postponed intervention stratified by the type of study design.

[21-23,26,27]. Pooled odds ratios showed that the occurrence of endocrine pancreatic insufficiency was comparable in the early and postponed groups (OR 1.13, 95% CI 0.72, 1.76; *p* = 0.59; Fig. 7). No heterogeneity (I^2=0%, p.0.59).

Minimally invasive necrosectomy. Data on the need for further minimally invasive necrosectomy were available for eight included studies [18,19,21,23-27]. Pooled odds ratios showed that compared to the postponed intervention, the early intervention group had a significantly increased need for further minimally invasive necrosectomy (OR 2.04, 95% CI 1.04−4.03; *p* = 0.04; Fig. 8). Significant heterogeneity was observed across the included studies (I^2 = 69.08%, *p* = 0.00).

Meta-analysis of subgroups in two randomised controlled trials showed the early intervention strategy significantly increased need for further minimally invasive necrosectomy, compared to delayed intervention (OR 2.99, 95% CI 1.39−6.42; Fig. 8). No heterogeneity in subgroup (I^2=0%).

Length of hospital stay. Seven trials in the meta-analysis reported on hospital length of stay [18,20,21,23,25-27]. The pooled results showed that the timing of the intervention had no effect on the length of hospital stay (MD 3.53, 95% CI −4.20, 11.27; *p* = 0.37; Fig. 9).These studies had a significant degree of heterogeneity (I^2=81.98%, *p* = 0.00). Meta-analysis of subgroups in two randomised controlled trials showed no significant difference in length of hospital stay between the early and postponed groups (MD 5.92, 95% CI −4.03, 15.87; Fig. 9). No heterogeneity in subgroup (I^2=0%).

Publication bias. A visual examination of funnel plots revealed no asymmetry in the distribution of studies. We found no indication of considerable publication bias in our meta-analysis (Fig. 10, 11).

Discussion

It is currently controversial when to perform a minimally invasive procedure for PNFC that needs treatment. Some pancreatic experts support conservative treatment until a necrotic encapsulation has formed and then treated with puncture drainage. These experts argue that [1]: in the initial stages of the disease, the extent of pancreatic necrosis is blurred from normal tissue. Early intervention is more traumatic for the patient, increasing the risk of

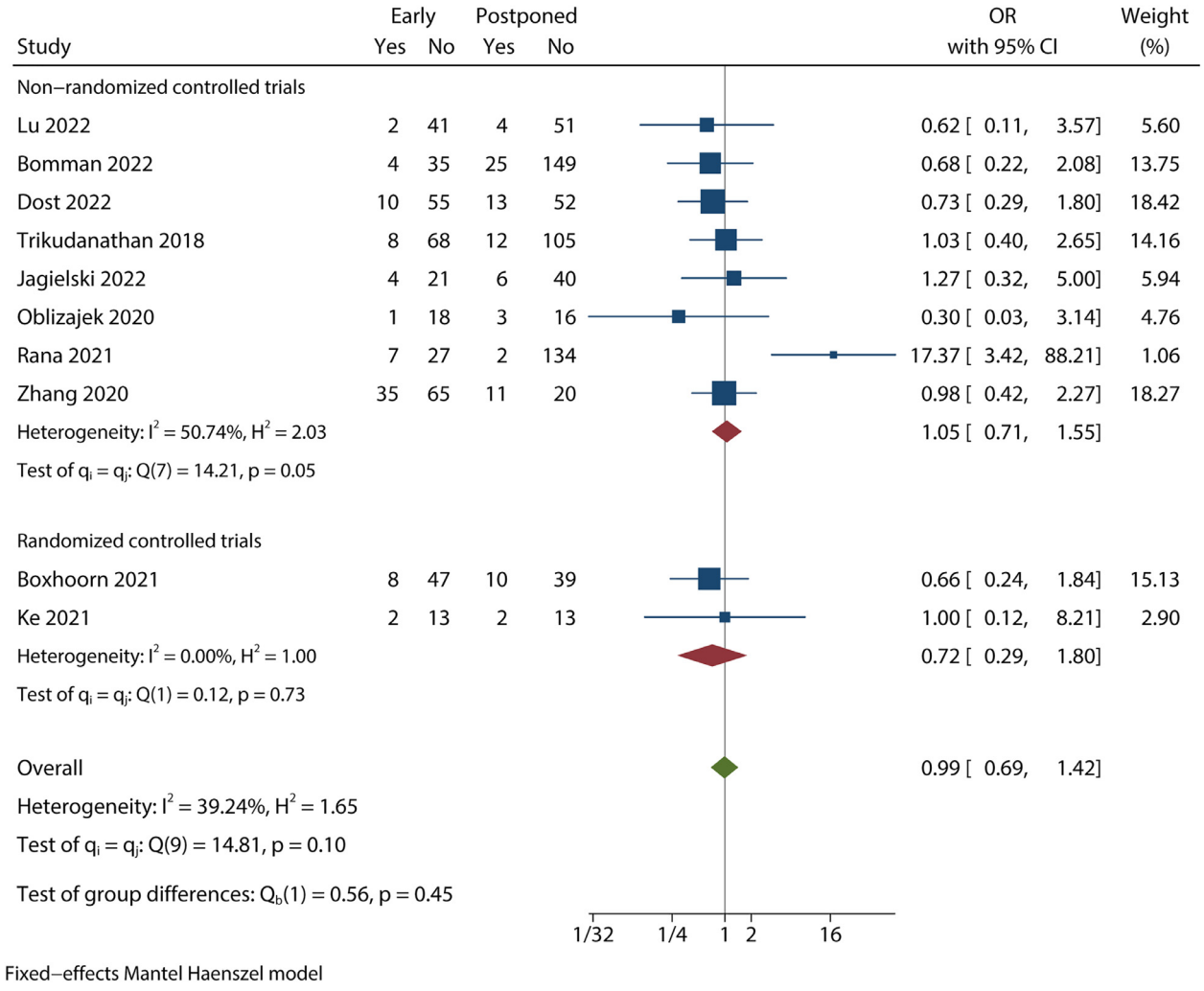


Fig. 3 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the incidence of bleeding, which would need a blood transfusion or subsequent intervention for hemostasis compared with postponed intervention stratified by the type of study design.

complications and adverse outcomes [28],[2]. Some ANP patients may develop improvement simply by conservative care without invasive intervention [26]. Other pancreatic experts think that after symptomatic PNFC patients have failed conservative treatment, early minimally invasive intervention should be carried out [1]. These experts believe that the concept of postponed intervention originated in the period when open surgery was performed, and it is debatable whether this concept is followed in the period of minimally invasive surgery [29],[2]. Catheter drainage can control the infection source and promote necrotic tissue encapsulation [30]. Theoretically, pancreatic necrotic tissue contains inflammatory agents and pancreatic enzymes, and timely drainage can reduce systemic inflammatory response syndrome (SIRS) and prevent the development of systemic organ dysfunction and further clinical deterioration [27].

The Revised Atlanta Classification states that it usually takes four weeks for the pancreatic and peripancreatic necrotic collections to be encapsulated [4]. However, there is currently a dearth of accurate data to prove this statement. The study by Van Grinsven et al. reported that walled-off necrosis was observed at all stages of the disease in patients with necrotizing pancreatitis. Despite the fact that walled-off necrosis became more common as time passes, nearly half of patients developed a “largely” or “complete” wall within the first three weeks of disease onset [31]. The study by S R Choudhury et al. also reported that more than one-third of the necrotic collections in the current CT-based analysis had complete walls by the third week and more than 50% of the collections had complete walls in the fourth week [32]. Four of the articles in our included studies counted necrotic tissue forming “largely” or “complete” walls by four weeks [21,23,24,26]. The formation of “largely” or “complete” walls by four weeks accounted for approximately 42.1%−74.2% of patients with early intervention (Table 1). These results suggest that arbitrary definitions of the four-week threshold for walled-off necrosis may be inaccurate and that arbitrary delays may be pointless.

Our analysis showed a slight increase in mortality with the early intervention compared to postponed intervention, but no statistical difference. Infected pancreatic necrosis

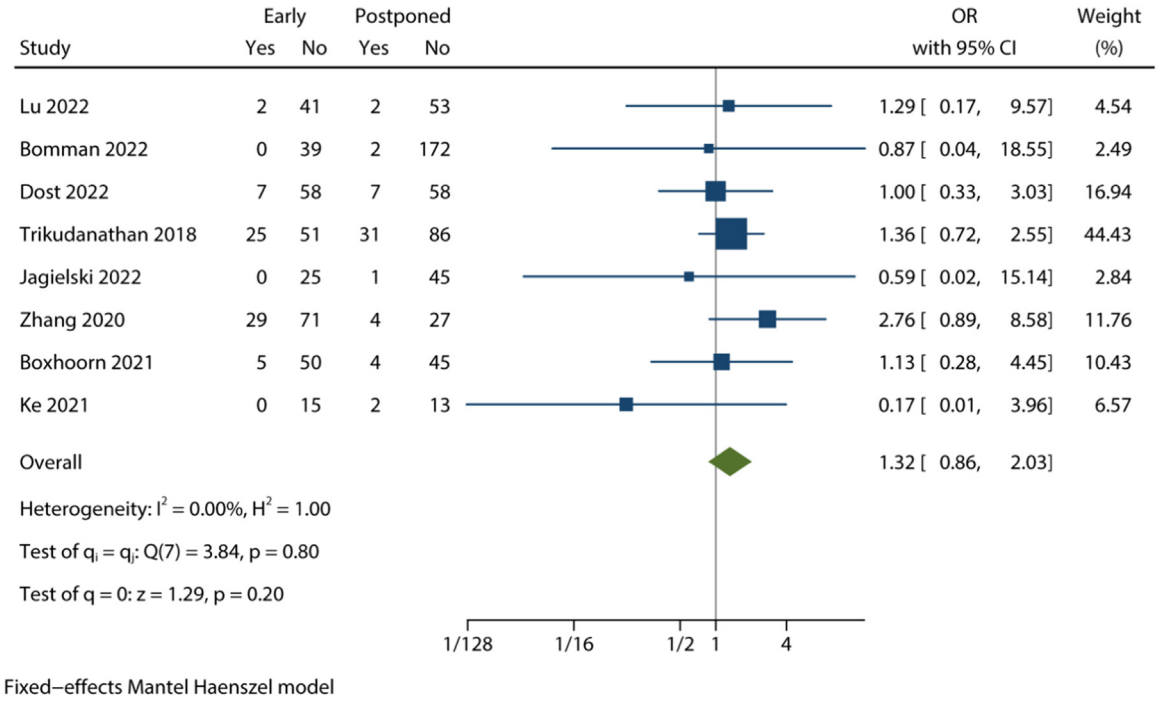


Fig. 4 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the incidence of gastrointestinal perforation or fistula compared with postponed intervention.

and organ failure are the most important factors determining the prognosis of patients with acute necrotizing pancreatitis [33]. In a recent research involving 805 patients with AP, it was shown that early sterile organ failure due to pancreatitis had a higher mortality rate relative to late organ failure due to infected pancreatic necrosis and that drainage of necrotic collections or infected fluid provided an opportunity to delay sepsis and secondary organ failure [34]. Moreover, patients with persistent organ failure are inclined to produce infected necrosis, which is a cause of late mortality. In a retrospective study, IPN occurred in 40 of 53 patients (75%) with AP in persistent organ failure [35]. Early organ failure is related to a significant mortality risk, with late development of infectious necrosis exacerbating the initial injury and worsening the outcome [36]. In the study by Trikudanathan et al., an endoscopic-centered intervention

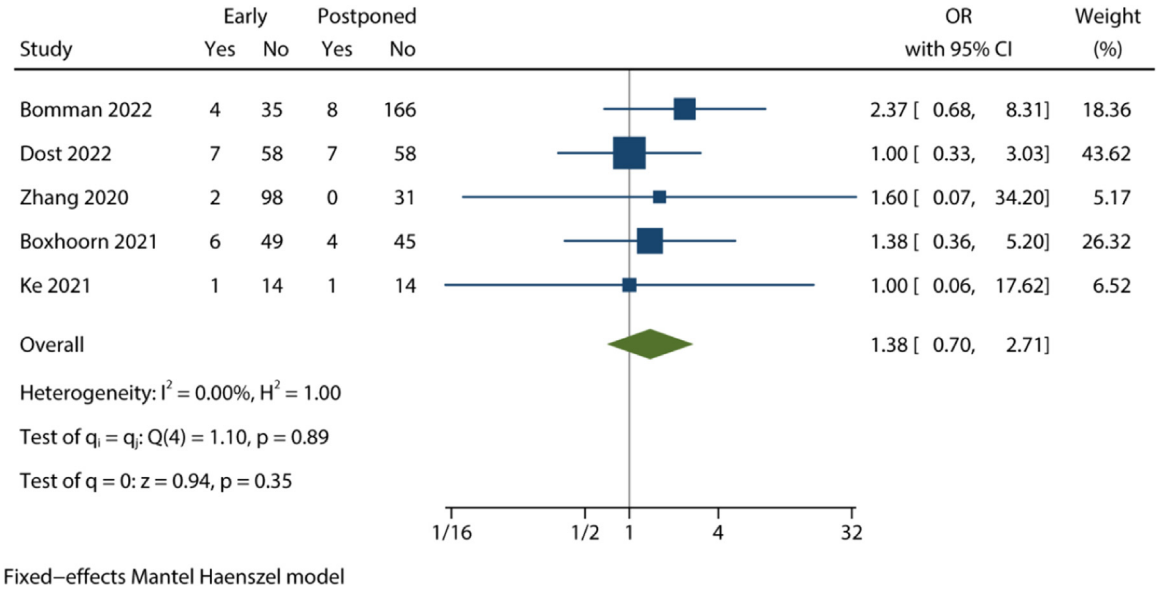


Fig. 5 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the incidence of pancreatic fistula compared with postponed intervention.

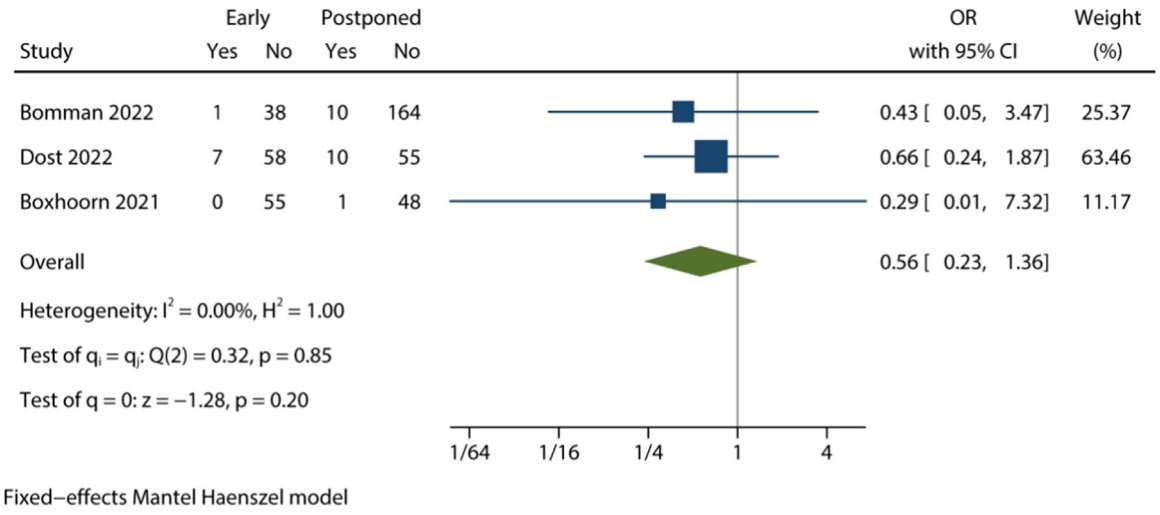


Fig. 6 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the incidence of wound infection compared with postponed intervention.

strategy for patients with collections of pancreatic necrosis resulted in significant improvements in organ failure after both early and postponed intervention. Most patients were successfully discharged from relevant organ support therapy [21]. Patients suffering from acute pancreatitis accompanied by organ failure or pancreatic/peripancreatic tissue necrosis, or both, have been found to have a mortality rate of 20−40% [1]. In our study, the mortality rate for patients receiving early intervention was 16%. In PNFC, where optimal conservative treatment has failed, earlier intervention to improve organ failure and control the source of infection is sometimes required to stabilize the clinical state.

Results of the analysis revealed no significant differences in the early and late complications among the different timing intervention groups. In a previous meta-study by Gao et al. on the timing of intervention in infected necrotizing pancreatitis, the incidence of bleeding and gastrointestinal perforation or fistula due to intervention was analyzed, and this study revealed that early intervention was not associated with a significant increase in the rate of bleeding compared to postponed intervention, while the incidence of gastrointestinal perforation or fistula was significantly increased [37]. However, this study did not analyze pancreatic fistula, wound infection and endocrine pancreatic insufficiency. When analyzing the length of stay in the hospital for early and postponed interventions, we found that the timing of the intervention had no effect on the length of hospital stay. In a recent research meta-study by Ramai et al. on the endoscopic drainage of pancreatic walled-off fluid

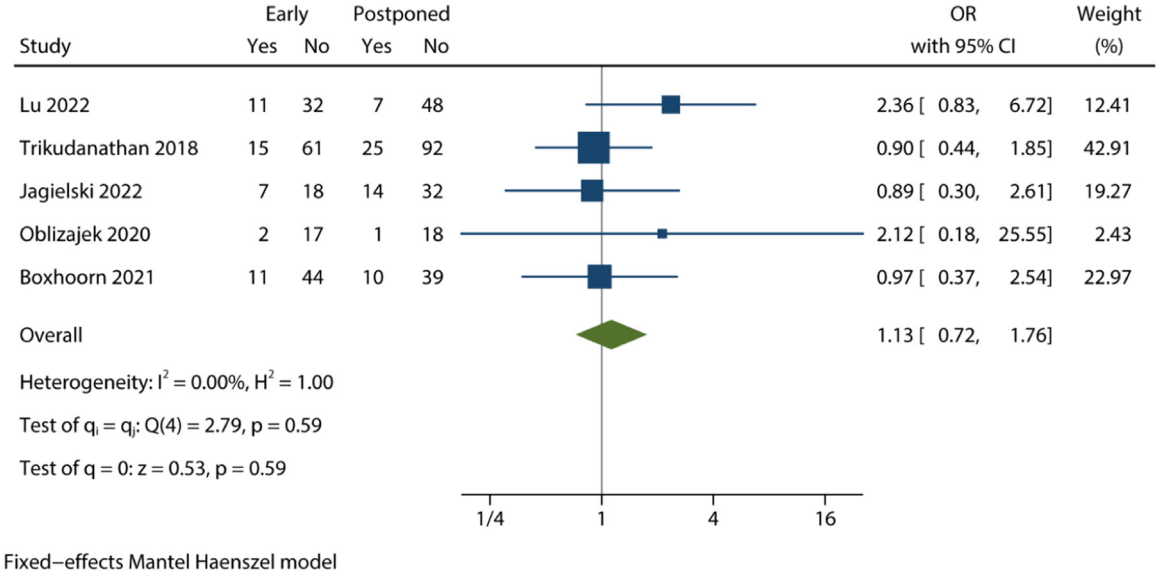


Fig. 7 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the incidence of endocrine pancreatic insufficiency compared with postponed intervention.

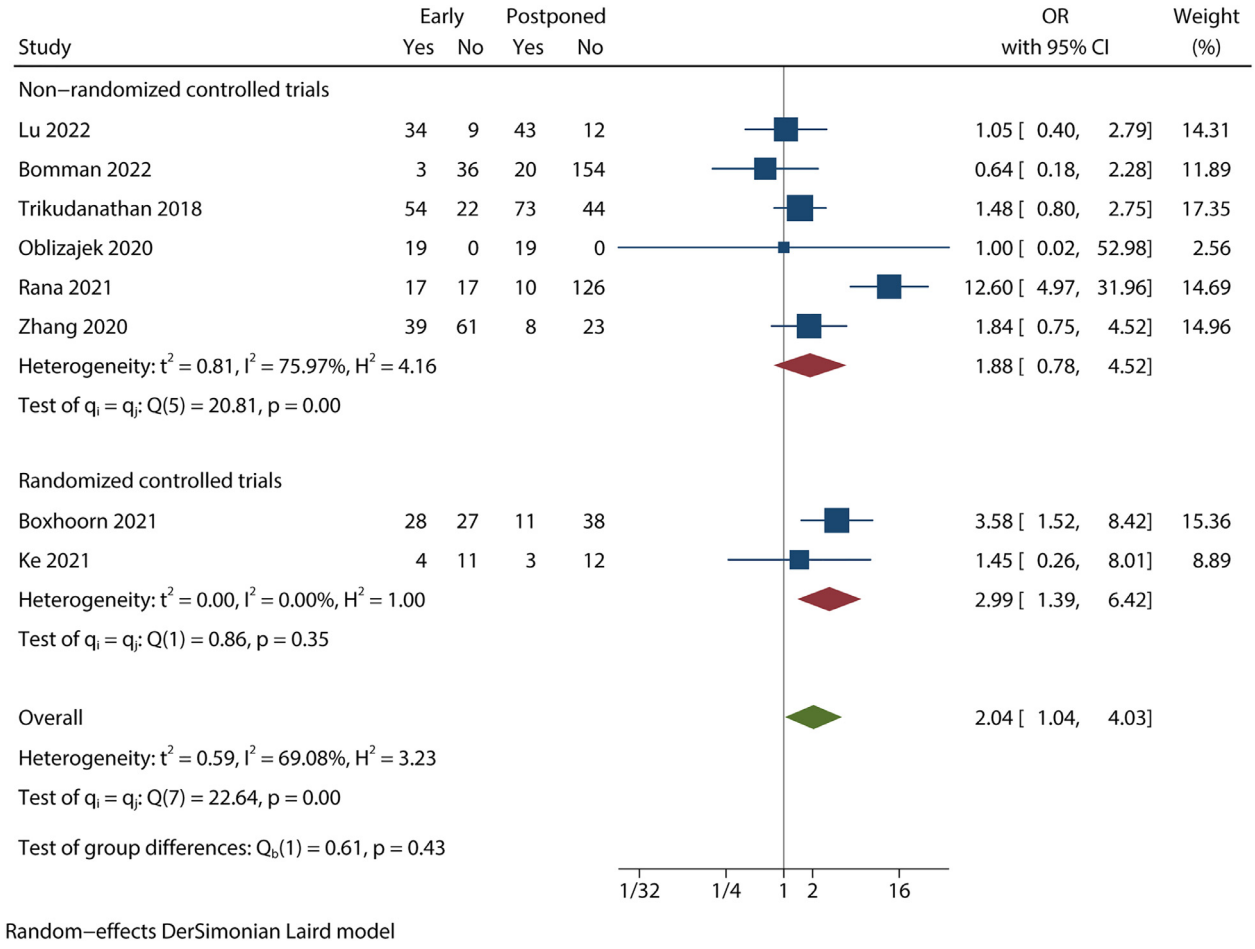


Fig. 8 Forest plot of the effect of early intervention for symptomatic pancreatic necrotic fluid collections on the further minimally invasive necrosectomy compared with postponed intervention stratified by the type of study design.

collections, patients undergoing early intervention had an increased length of hospital stay compared to postponed drainage [38]. The possible reason for the different results is that our study included patients whose initial route was percutaneous drainage. Early intervention increased the need for further minimally invasive necrosectomy compared to postponed intervention. As the necrotic collections are encapsulated, the necrotic tissue liquefies over time, and the boundary between necrotic and viable tissue becomes more clearly defined [39]. This reduced the need for further necrosectomy in the postponed intervention group. Although early intervention increases the need for necrosectomy, it may be reasonable to intervene before four weeks in patients who present with persistent organ failure or infection and whose condition has not significantly improved or deteriorated in spite of maximized conservative treatment.

There are several limitations to this systematic review and meta-analysis. First, although the Cochrane collaborative tool and the Newcastle-Ottawa scale were used to evaluate the quality of all articles, with the exception of two randomized controlled studies, all included articles were observational studies. So we were unable to exclude heterogeneity due to the type of article study. Moreover, although strict inclusion and exclusion criteria were defined to reduce the sources of heterogeneity to a minimum, heterogeneity in our study was inevitable because of other confounding factors, including differences in initial drainage routes, definitions of intervention timing and the origin of cases from different countries. Finally, some studies had relatively small sample sizes, which may also have affected the accuracy of the results.

Conclusion

In symptomatic PNFC patients, early intervention did not increase the incidence of mortality or complications; however, the need for further minimally invasive necrosectomy was increased compared with postponed intervention. The timing of the intervention had no effect on the length of hospital stay. For patients with pancreatic necrotizing fluid collections complicated by persistent organ failure or infection, if conservative treatment has been performed to the maximum extent possible, intervention should be considered before four weeks. To identify the appropriate time to intervene in symptomatic PNFC, future valuable prospective randomized controlled trials are essential to assess the clinical outcomes, adverse events and potential costs of early intervention in these challenging patients.

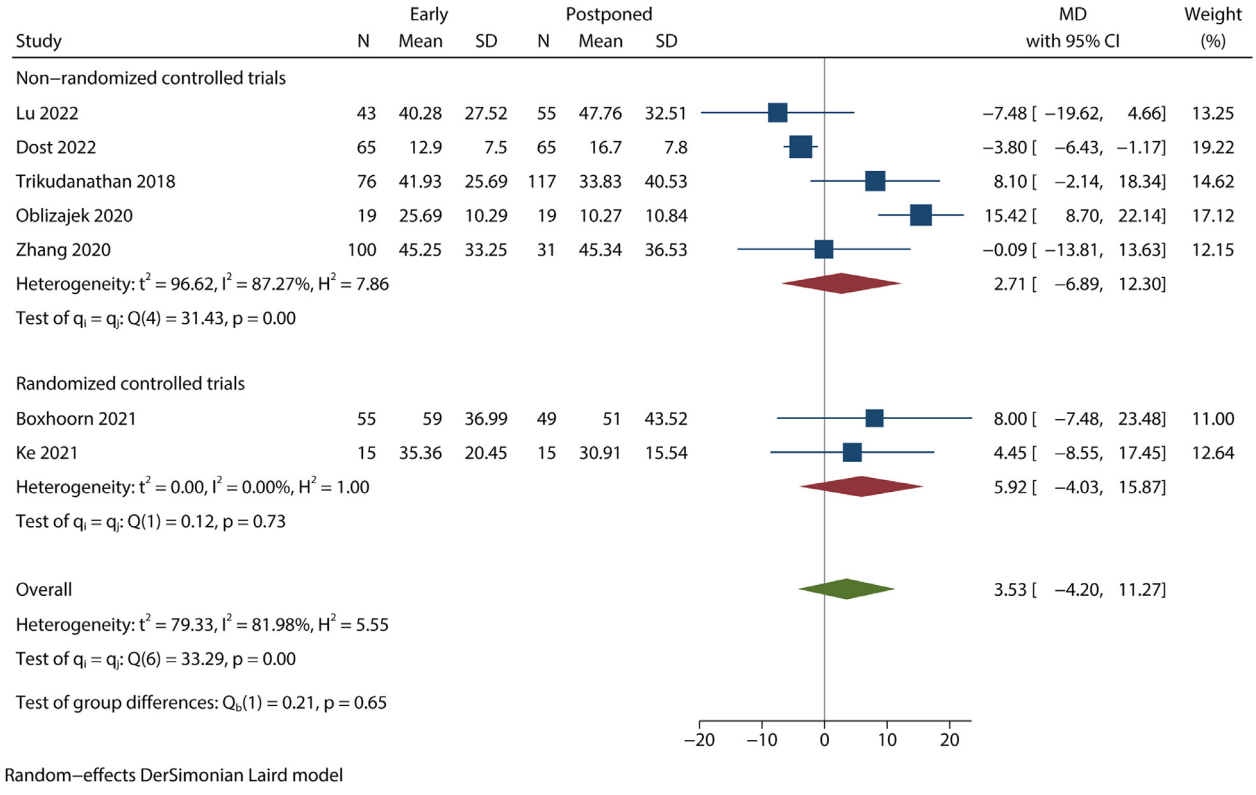


Fig. 9 Forest plot of the effect of the early and postponed intervention for symptomatic pancreatic necrotic fluid collections on the length of hospital stay stratified by the type of study design.

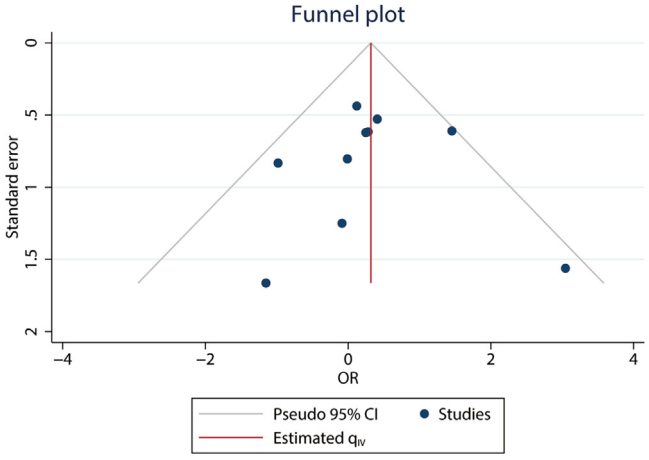


Fig. 10 Funnel plot of publication bias for mortality.

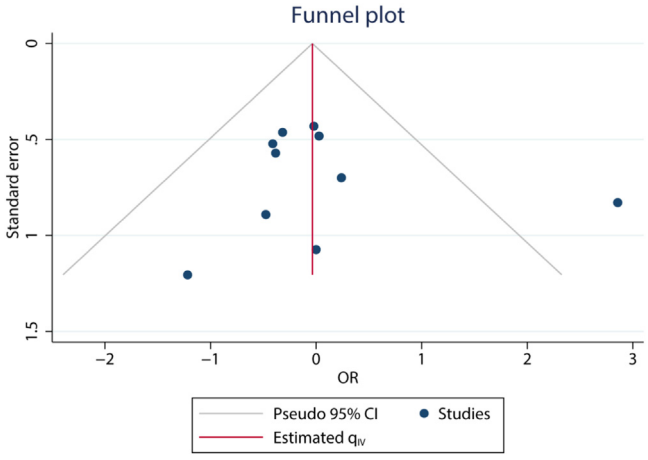


Fig. 11 Funnel plot of publication bias for the incidence of bleeding.

Author contributions

ZheYu Liu acquisition of data, analysis and interpretation of data, drafting the article, final approval

Xuan Xu interpretation of data, revising the article, final approval

Qian Yao interpretation of data, revising the article, final approval

YuWen Xiong acquisition of data, final approval

Pi Liu conception and design of the study, critical revision, final approval

Funding

Supported by the National Natural Science Foundation of China (81860123).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Reference

[1] Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: a review. JAMA 2021;325(4):382–90. doi: 10.1001/jama.2020.20317.

[2] 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(7):1994–2007 e3. doi: 10.1053/j.gastro.2019.01.269.

[3] Manrai M, Kochhar R, Gupta V, Yadav TD, Dhaka N, Kalra N, et al. Outcome of acute pancreatic and peripancreatic collections occurring in patients with acute pancreatitis. Ann Surg 2018;267(2):357–63. doi: 10.1097/sla.0000000000002065.

[4] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–11. doi: 10.1136/gutjnl-2012-302779.

[5] Tenner S, Baillie J, DeWitt J, Vege SS. American college of gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108(9):1400–15 16. doi: 10.1038/ajg.2013.218.

[6] IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4):e1–15 [et al.] Suppl 2. doi: 10.1016/j.pan.2013.07.063.

[7] van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362(16):1491–502. doi: 10.1056/NEJMoa0908821.

[8] Freeman ML, Werner J, van Santvoort HC, Baron TH, Besselink MG, Windsor JA, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas 2012;41(8):1176–94. doi: 10.1097/MPA.0b013e318269c660.

[9] da Costa DW, Boerma D, van Santvoort HC, Horvath KD, Werner J, Carter CR, et al. Staged multidisciplinary step-up management for necrotizing pancreatitis. Br J Surg 2014;101(1):e65–79. doi: 10.1002/bjs.9346.

[10] Mier J, León EL, Castillo A, Robledo F, Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg 1997;173(2):71–5. doi: 10.1016/s0002-9610(96)00425-4.

[11] van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141(4):1254–63. doi: 10.1053/j.gastro.2011.06.073.

[12] Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: management of Pancreatic Necrosis. Gastroenterology 2020;158(1):67–75 e1. doi: 10.1053/j.gastro.2019.07.064.

[13] Shi N, Liu T, de la Iglesia-Garcia D, Deng L, Jin T, Lan L, et al. Duration of organ failure impacts mortality in acute pancreatitis. Gut 2020;69(3):604–5. doi: 10.1136/gutjnl-2019-318241.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed) 2009;339:b2535. doi: 10.1136/bmj.b2535.

[15] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD , et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2011;343:d5928. doi: 10.1136/bmj.d5928.

[16] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5. doi: 10.1007/s10654-010-9491-z.

[17] Cai S, Zhou J, Pan J. Estimating the sample mean and standard deviation from order statistics and sample size in meta-analysis. Stat Methods Med Res 2021;30(12):2701–19. doi: 10.1177/09622802211047348.

[18] Lu J, Cao F, Zheng Z, Ding Y, Qu Y, Mei W, et al. How to identify the indications for early intervention. in acute necrotizing pancreatitis patients: a long-term follow-up study 2022;9. doi: 10.3389/fsurg.2022.842016.

[19] Bomman S, Sanders D, Coy D, La Selva D, Pham Q, Zehr T, et al. Safety and clinical outcomes of early dual modality drainage (< 28 days) compared to later drainage of pancreatic necrotic fluid collections: a propensity score-matched study. Surg Endosc 2022. doi: 10.1007/s00464-022-09561-8.

[20] Dost W, Qasemi F, Ali W, Aini T, Rasully MQ, Niazi J, et al. Immediate catheter drainage versus delayed drainage in the management of infected necrotizing pancreatitis. Cureus 2022;14(7):e26485. doi: 10.7759/cureus.26485.

[21] Trikudanathan G, Tawfik P, Amateau SK, Munigala S, Arain M, Attam R, et al. Early (<4 Weeks) Versus Standard (≥ 4 Weeks) endoscopically centered step-up interventions for necrotizing pancreatitis. Am J Gastroenterol 2018;113(10):1550–8. doi: 10.1038/s41395-018-0232-3.

[22] Jagielski M, Piątkowski J, Jackowski M. Early endoscopic treatment of symptomatic pancreatic necrotic collections. Sci Rep 2022;12(1):308. doi: 10.1038/s41598-021-03924-2.

[23] Oblizajek N, Takahashi N, Agayeva S, Bazerbachi F, Chandrasekhara V, Levy M, et al. Outcomes of early endoscopic intervention for pancreatic necrotic collections: a matched case-control study. Gastrointest Endosc 2020;91(6):1303–9. doi: 10.1016/j.gie.2020.01.017.

[24] 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 Gastrointestinal Surg 2021;25(9):2328–35. doi: 10.1007/s11605-021-04945-y.

[25] Zhang H, Gao L, Mao WJ, Yang J, Zhou J, Tong ZH, et al. Early versus delayed intervention in necrotizing acute pancreatitis complicated by persistent organ failure. Hepatobiliary Pancreatic Dis Int: HBPD INT 2022;21(1):63–8. doi: 10.1016/j.hbpd.2020.12.019.

[26] Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, et al. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med 2021;385(15):1372–81. doi: 10.1056/NEJMoa2100826.

[27] Ke L, Dong X, Chen T, Doig GS, Li G, Ye B, et al. Early on-demand drainage or standard management for acute pancreatitis patients with acute necrotic collections and persistent organ failure: a pilot randomized controlled trial. J Hepatobiliary Pancreat Sci 2021;28(4):387–96. doi: 10.1002/jhbp.915.

[28] van Grinsven J, van Brunschot S, Bakker OJ, Bollen TL, Boermeester MA, Bruno MJ, et al. Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study. HPB: Off. J. Int. Hepato Pancreato Biliary Assoc. 2016;18(1):49–56. doi: 10.1016/j.hpb.2015.07.003.

[29] Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg 2007;142(12):1194–201 (Chicago, Ill: 1960). doi: 10.1001/archsurg.142.12.1194.

[30] van Grinsven J, van Santvoort HC, Boermeester MA, Dejong CH, van Eijck CH, Fockens P, et al. Timing of catheter drainage in infected necrotizing pancreatitis. Nat Rev Gastroenterol Hepatol 2016;13(5):306–12. doi: 10.1038/nrgastro.2016.23.

[31] van Grinsven J, van Brunschot S, van Baal MC, Besselink MG, Fockens P, van Goor H, et al. Natural history of gas configurations and encapsulation in necrotic collections during necrotizing pancreatitis. J Gastrointestinal Surg 2018;22(9):1557–64. doi: 10.1007/s11605-018-3792-z.

[32] Choudhury SR, Manoj M, Gupta P, Samanta J, Mandavdhare H, Kochhar R. Wall maturation in necrotic collections in acute pancreatitis: a computed tomography based evaluation. Acta Gastroenterol Belg 2022;85(3):463–7. doi: 10.51821/85.3.9701.

[33] 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(3):813–20. doi: 10.1053/j.gastro.2010.06.010.

[34] Padhan RK, Jain S, Agarwal S, Harikrishnan S, Vadiraja P, Behera S, et al. Primary and secondary organ failures cause mortality differentially in acute pancreatitis and should be distinguished. Pancreas 2018;47(3):302–7. doi: 10.1097/mpa.0000000000000998.

[35] Garret C, Péron M, Reignier J, Le Thuaut A, Lascarrou JB, Douane F, et al. Risk factors and outcomes of infected pancreatic necrosis: retrospective cohort of 148 patients admitted to the ICU for acute pancreatitis. United European Gastroenterol J 2018;6(6):910–8. doi: 10.1177/2050640618764049.

[36] Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. Gastroenterology 2019;156(7):2008–23. doi: 10.1053/j.gastro.2018.12.041.

[37] Gao L, Zhang H, Li G, Ye B, Zhou J, Tong Z, et al. The clinical outcome from early versus delayed minimally invasive intervention for infected pancreatic necrosis: a systematic review and meta-analysis. J Gastroenterol 2022;57(6):397–406. doi: 10.1007/s00535-022-01876-6.

[38] Ramai D, Enofe I, Deliwala SS, Mozell D, Facciorusso A, Gkolfakis P, et al. Early (<4 weeks) versus standard (≥4 weeks) endoscopic drainage of pancreatic walled-off fluid collections: a systematic review and meta-analysis. Gastrointest Endosc 2022. doi: 10.1016/j.gie.2022.11.003.

[39] Rana SS, Bhasin DK, Reddy YR, Sharma V, Rao C, Sharma RK, et al. Morphological features of fluid collections on endoscopic ultrasound in acute necrotizing pancreatitis: do they change over time? Ann Gastroenterol 2014;27(3):258–61.