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REVIEW

The clinical outcome from early versus delayed minimally invasive intervention for infected pancreatic necrosis: a systematic review and meta-analysis

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Abstract
Background While the management of infected pancreatic necrosis (IPN) has evolved in the last two decades with the adoption of minimally invasive interventions (drainage ± debridement), it is unknown whether the principle of delaying intervention inherited from the open surgery era still applies. The aim of the current study was to investigate the impact of the timing of minimally invasive intervention on the outcomes of patients with IPN requiring intervention.
Methods PubMed, Embase, MEDLINE and Web of Science databases were searched for appropriate studies. The primary outcome of interest was hospital mortality, the secondary outcomes were the incidence of complications during the hospitalization, including new-onset organ failure, gastrointestinal fistula or perforation, bleeding and length of hospital or intensive care unit (ICU) stay.
Results Seven clinical studies were included with a total of 742 patients with IPN requiring intervention, of whom 321 received early intervention and 421 delayed intervention. Results from the meta-analysis showed that early minimally invasive intervention did not increase hospital mortality (odds ratio 1.65, 95% confidence interval 0.97–2.81; $p = 0.06$) but was associated with a remarkably prolonged hospital stay and an increased incidence of gastrointestinal fistula or perforation when compared with delayed intervention.
Conclusions Although no firm conclusion can be drawn because of the quality of available studies, it does appear that timing of intervention is a risk factor for adverse outcomes and ought to be investigated more rigorously in prospective studies.

Keywords Infected pancreatic necrosis · Minimally invasive intervention · Early intervention · Delayed intervention · Clinical outcomes

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Introduction

Pancreatic or peri-pancreatic necrosis complicates about 20% of all acute pancreatitis (AP) episodes [1]. While a majority of necrosis remains sterile, in approximately 30–40% of these patients, infection of (peri) pancreatic necrosis occurs, which is usually considered an indication for invasive intervention [2, 3]. Some evidence-based guidelines recommend that infected pancreatic necrosis (IPN) should be managed with a step-up approach, starting with either percutaneous or endoscopic catheter drainage, followed by, if necessary, a videoscopic-assisted retroperitoneal debridement or endoscopic transluminal necrosectomy (depending on the route of initial drainage) [4–6]. There has been widespread agreement that delaying intervention until the IPN has become encapsulated, which usually requires 3–4 weeks [7]. It has been argued that this

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delay ensures more efficient and effective intervention, reducing the risk of complications and mortality [8, 9].

The principle of delayed intervention has been inherited from the open surgery era, and it is unknown whether this is applicable in the minimally invasive era [10, 11]. The arbitrary cutoff of 4 weeks [12] has been questioned because up to 30% of patients have evidence of infection before then [13, 14]. It has been suggested that earlier intervention could be considered even in the absence of encapsulation if there is clinical deterioration despite maximal medical support in patients with IPN [3, 15].

The optimal timing of intervention for IPN is still contentious, especially in relation to infected acute necrotic collections (ANC) [12] and with the advent of minimally invasive interventions [3, 8, 15–17]. The aim of this study was to systematically review and meta-analyse data to investigate the impact of the timing of minimally invasive intervention on the outcomes of patients with IPN requiring intervention.

Materials and methods

This systematic review was prepared using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for literature review, extraction of data and reporting of results [18].

Search strategy

The following keywords or MeSH headings were used: ("necrotizing pancreatitis" OR "pancreatic necrosis") AND ("early drainage" OR "delayed drainage") for the literature search. Two investigators (LG and HZ) independently searched PubMed, Embase, MEDLINE and Web of Science from their inception to March 15, 2022 for appropriate articles. The reference lists of the included studies were checked for additional relevant studies. No restriction on the year or language of publication was imposed.

Selection criteria

Inclusion criteria

1) Population: adult patients with suspected/confirmed infected pancreatic necrosis requiring intervention;
2) Intervention: early minimally invasive interventions (including percutaneous catheter drainage or endoscopic transluminal drainage functioned as the first step, minimally invasive necrosectomy—videoscopic-assisted retroperitoneal debridement or endoscopic transluminal necrosectomy) with the timing of intervention ('early') defined in the included studies (Table 1);
3) Comparison: delayed minimally invasive interventions;
4) Outcomes: hospital mortality, complications and length of hospital/intensive care unit (ICU) stays;

Exclusion criteria

Studies were excluded if they did not include a comparison or control arm, involved open surgery as the initial intervention, in which clinical outcomes of interest were not reported or conducted in patients with chronic pancreatitis.

Data extraction

Data from included studies were extracted by two independent authors (LG and HZ) and discrepancies were resolved through discussion with a senior third-person adjudicate (LK) until consensus was reached. The data extracted from the included studies was: the first author's name, year of publication, the country where the study was from, study type (retrospective or prospective), number of patients, study population, the definitions of early versus delayed interventions, the type of intervention (endoscopically or surgically centered step-up interventions) and main clinical outcomes.

Outcomes

The primary outcome of interest in the current study was hospital mortality, the secondary outcomes included the incidence of complications during the hospitalization and length of hospital/ICU stay. With regard to the severe complications that occurred after invasive intervention for IPN, new-onset organ failure, including pulmonary, circulatory, and renal failure, gastrointestinal fistula or perforation and bleeding, which would need blood transfusion or subsequent intervention for hemostasis, were the mainly concerned ones. Combined severe complications, which combined all the abovementioned three adverse events, were included. It is worth noting that the adverse events were mathematically combined in this study in view of the fact that the percentage of patients which had two or more severe complications in each study could not be precisely extracted.

Assessment of risk of bias

For randomized controlled trials (RCTs), Cochrane Collaboration tool was used to assess the risk of bias [19]. Quality items assessed consisted of random sequence

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

Study	Country	Study type	No. of patients	Early intervention	Delayed intervention	Interval from onset of symptoms to intervention	Type of intervention
Jagielski et al. [22]	Poland	Prospective cohort study	25/46 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: median 16 days delayed intervention: median 56.5 days	Endoscopically centered step-up interventions; initial intervention: endoscopic transluminal catheter drainage
Boxhoorn et al. [15]	The Netherlands	Randomized controlled trial	55/49 (early/delayed)	Immediate drainage within 24 h after randomization once infected necrosis was diagnosed	Postponed drainage until the stage of walled-off necrosis was reached	Immediate drainage: mean 24 days postponed drainage: mean 34 days	Endoscopically and surgically centered step-up interventions were both adopted; initial intervention: percutaneous or endoscopic transluminal catheter drainage
Rana et al. [13]	India	Retrospective cohort study	34/136 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: mean 24 days delayed intervention: mean 75 days	Endoscopically centered step-up interventions; initial intervention: endoscopic transluminal catheter drainage
Zhang et al. [23]	China	Retrospective cohort study	100/31 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: median 19 days delayed intervention: median 33 days	Surgically centered step-up interventions; initial intervention: percutaneous catheter drainage
Oblizajek et al. [17]	The USA	Retrospective cohort study	19/19 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: median 23 days delayed intervention: median 64 days	Endoscopically centered step-up interventions; initial intervention: endoscopic transluminal drainage
Trikudanathan et al. [3]	The USA	Retrospective cohort study	76/117 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: median 20 days delayed intervention: median 78 days	Mainly endoscopically centered step-up interventions; initial intervention: endoscopic transluminal drainage or percutaneous drainage
Chantarojanasiri et al. [21]	Japan	Retrospective cohort study	12/23 (early/delayed)	Early intervention was carried out within 4 weeks after AP onset	Delayed intervention was carried out after 4 weeks	Early intervention: median 23 days delayed intervention: median 85 days	Endoscopically centered step-up interventions; initial intervention: endoscopic ultrasound guided drainage

AP acute pancreatitis

generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each item was assigned a low, unclear or high risk of bias. For observational cohort studies, Newcastle–Ottawa quality assessment scale was adopted. This scale is based on three dimensions, including selection, comparability, and outcomes. Studies would be considered at low risk of bias when they scored nine or eight stars, studies that scored seven or six stars were regarded as medium risk, and studies that scored below six were considered to have high risk of bias [20].

Statistical analysis

The results were presented as forest plots through the odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data and mean difference (MD) with 95% CI for continuous data. The I^2 statistic was used to assess statistical heterogeneity among the studies in each meta-analysis. Values of I^2 greater than 50% indicated moderate heterogeneity, and over 75% indicated a high level of heterogeneity. An inverse variance method was used for continuous outcomes and a Mantel–Haenszel (MH) method for dichotomous outcomes. If heterogeneity was observed ($I^2 \geq 50\%$), the random effects model was applied; otherwise, a fixed effects model was used. Tests for publications, such as the funnel plot was not carried out in this study in view of the low number of included studies (less than ten). Data were analyzed by Review Manager 5.3 software (The Nordic Cochrane Center, Copenhagen, Denmark). A two-sided p value < 0.05 was considered statistically significant.

Results

Study selection

Initial database search identified 1530 studies. After excluding duplicates, 973 studies were screened by title and abstract, of which 850 studies were excluded. The remaining 123 studies were assessed for eligibility. Notable exclusions included studies that involved open surgery (mainly necrosectomy) as initial intervention (n = 27), or in which no comparisons were made based on intervention timing (n = 59), or no outcome of interest was reported (n = 7). Eighteen review/commentary articles and five case reports were excluded. In the end, there were seven studies included in this systematic review and meta-analysis (Fig. 1) [3, 15–17, 21–23].

Study characteristics

The seven clinical studies included a total of 742 patients with IPN requiring intervention, of whom 321 received early intervention and 421 delayed intervention. Table 1 provides the details of the included studies. The study by

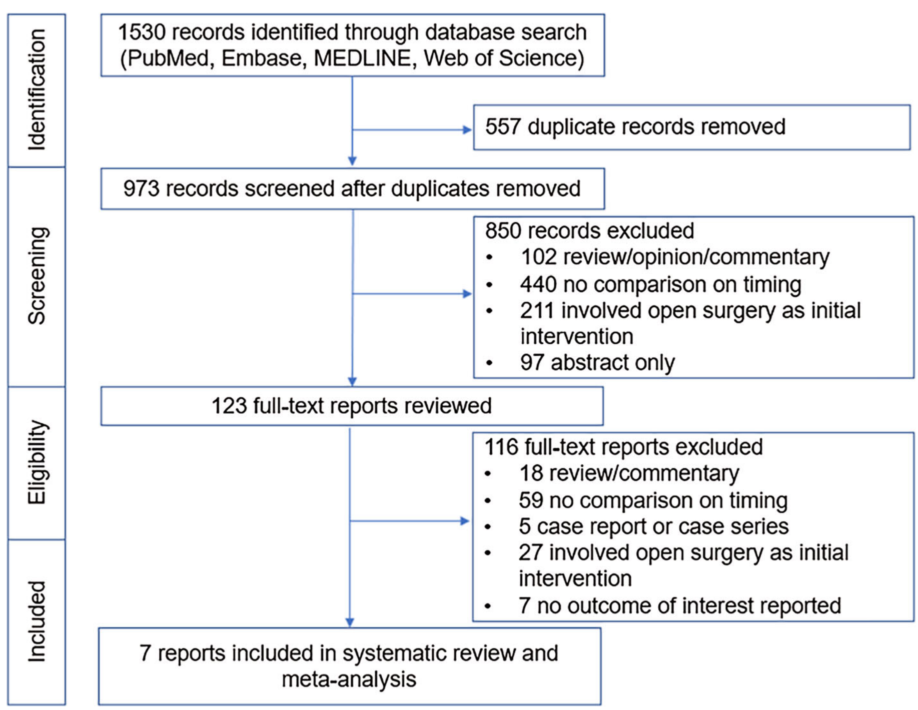


Fig. 1 Flow diagram that summarizes the results of the literature search

Table 2 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	Selective reporting	Other bias
Boxhoorn et al. [15]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias

Newcastle–Ottawa quality assessment scale for cohort studies

Item	Selection				Comparability	Outcome		
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Jagielski et al. [22]	Truly representative	Same hospital	Secure record	Yes	Gender matched	Independent blind assessment	Yes	Complete follow-up
Rana et al. [13]	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	Independent blind assessment	Yes	Complete follow-up
Zhang et al. [23]	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	Independent blind assessment	No, in-hospital	Complete follow-up
Oblizajek et al. [17]	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	Independent blind assessment	Yes	Subjects lost to follow-up unlikely to introduce bias
Trikudanathan et al. [3]	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	Independent blind assessment	Yes	Complete follow-up
Chantarojanasiri et al. [21]	Truly representative	Same hospital	Secure record	Yes	Age and gender matched	Independent blind assessment	Yes	Complete follow-up

Boxhoorn et al. was the only randomized controlled trial, the study by Jagielski et al. was a prospective cohort study, and all the remaining five studies were retrospective cohort studies. Concerning the type of intervention in each study, endoscopically centered step-up interventions were adopted in five studies [3, 16, 17, 21, 22]. In contrast, surgically centered step-up interventions were only used in one study [23], and the study by Boxhoorn et al. followed endoscopically or surgically centered step-up strategies depending on the route of initial drainage [15].

Timing of intervention

Regarding the definitions of intervention timing (Table 1), the study by Boxhoorn et al. defined 'early' intervention as immediate drainage within 24 h after randomization once infected necrosis was diagnosed compared to 'postponed' drainage after walled-off necrosis (WON) had developed. In the other six studies, early and delayed intervention was defined by the cutoff of 4 weeks. [3, 16, 17, 21–23].

Risk of bias assessment

The risk of bias assessment for the included studies is shown in Table 2. The study conducted by Boxhoorn et al. was a randomized controlled trial, and it was considered to be of low risk across all domains according to the Cochrane Collaboration tool. For the cohort studies, three studies [3, 16, 21] were considered low risk (eight stars) and the other three studies [17, 22, 23] were considered medium risk (seven stars) according to the Newcastle–Ottawa quality assessment scale.

Meta-analysis

Hospital mortality

All the seven studies were included in the meta-analysis for hospital mortality. The results showed that compared with delayed intervention, a trend toward increased hospital mortality was shown in the early intervention group but not statistically significant (OR 1.65, 95% CI 0.97–2.81; $p = 0.06$) (Fig. 2). The study heterogeneity was found to be low ($I^2 = 6\%$).

Incidence of complications

New onset organ failure Two studies [15, 23] involving a total of 235 patients were included in the meta-analysis of new-onset organ failure. The incidence of new-onset organ failure was comparable between the two intervention groups (OR 1.36, 95% CI 0.74–2.49; $p = 0.33$) (Fig. 3a). The data among these studies were found to have low heterogeneity ($I^2 = 0\%$).

Gastrointestinal fistula or perforation Five studies [3, 15, 21–23] involving a total of 534 patients reported the rate of gastrointestinal fistula or perforation. The result from the meta-analysis showed that compared with delayed intervention, early intervention was associated with an increased incidence of gastrointestinal fistula or perforation (OR 1.65, 95% CI 1.03–2.62; $p = 0.04$) (Fig. 3b).

Bleeding The meta-analysis of six studies [3, 15, 16, 21–23] involving a total of 704 patients showed that there was no significant difference in the incidence of bleeding between the early and delayed intervention (OR 1.73, 95% CI 0.71–4.19; $p = 0.22$) (Fig. 3c). The study heterogeneity was found to be medium ($I^2 = 67\%$), so a random model was adopted.

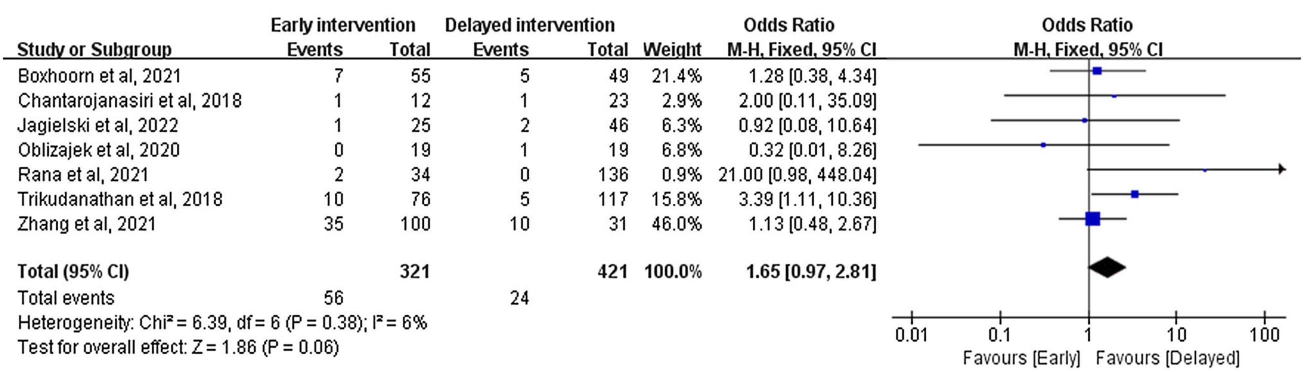
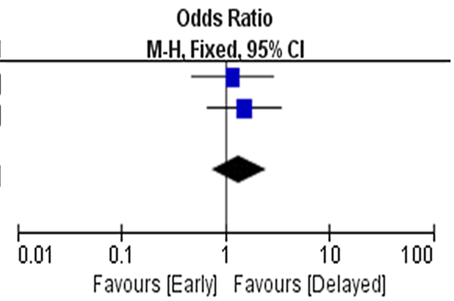


Fig. 2 Forest plot of the effect of early intervention for infected pancreatic necrosis on hospital mortality compared with delayed intervention. *M-H* Mantel–Haenszel, *CI* confidence interval, *Chi*^{2} chi-square statistic, *df* degrees of freedom, I^2 I-square heterogeneity statistic, *Z* Z statistic

a Incidence of new-onset organ failure

Study or Subgroup	Early intervention Events	Early intervention Total	Delayed intervention Events	Delayed intervention Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Boxhoorn et al, 2021	14	55	11	49	48.1%	1.18 [0.48, 2.91]
Zhang et al, 2021	49	100	12	31	51.9%	1.52 [0.67, 3.46]
Total (95% CI)		**155**		**80**	**100.0%**	**1.36 [0.74, 2.49]**
Total events	63		23			

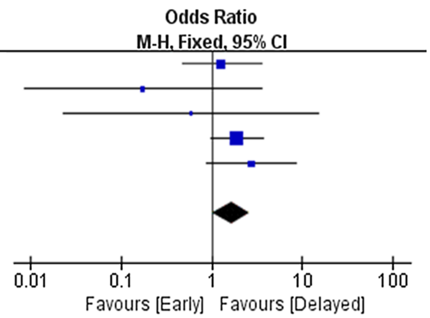
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)



b Incidence of gastrointestinal fistula or perforation

Study or Subgroup	Early intervention Events	Early intervention Total	Delayed intervention Events	Delayed intervention Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Boxhoorn et al, 2021	11	55	8	49	24.3%	1.28 [0.47, 3.50]
Chantarojanasiri et al, 2018	0	12	4	23	10.9%	0.17 [0.01, 3.51]
Jagielski et al, 2022	0	25	1	46	3.8%	0.59 [0.02, 15.14]
Trikudanathan et al, 2018	25	76	24	117	45.5%	1.90 [0.99, 3.66]
Zhang et al, 2021	29	100	4	31	15.6%	2.76 [0.89, 8.58]
Total (95% CI)		**268**		**266**	**100.0%**	**1.65 [1.03, 2.62]**
Total events	65		41			

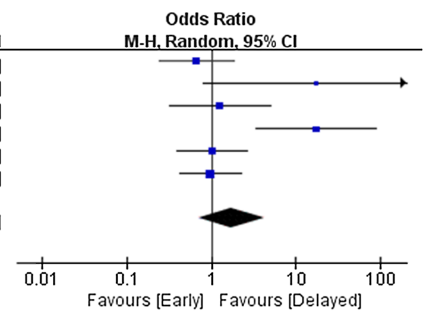
Heterogeneity: Chi² = 3.75, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)



c Incidence of bleeding

Study or Subgroup	Early intervention Events	Early intervention Total	Delayed intervention Events	Delayed intervention Total	Weight	Odds Ratio M-H, Random, 95% CI
Boxhoorn et al, 2021	8	55	10	49	20.1%	0.66 [0.24, 1.84]
Chantarojanasiri et al, 2018	3	12	0	23	6.4%	17.32 [0.81, 368.38]
Jagielski et al, 2022	4	25	6	46	16.5%	1.27 [0.32, 5.00]
Rana et al, 2021	7	34	2	136	14.2%	17.37 [3.42, 88.21]
Trikudanathan et al, 2018	8	76	12	117	20.9%	1.03 [0.40, 2.65]
Zhang et al, 2021	35	100	11	31	21.9%	0.98 [0.42, 2.27]
Total (95% CI)		**302**		**402**	**100.0%**	**1.73 [0.71, 4.19]**
Total events	65		41			

Heterogeneity: Tau² = 0.74; Chi² = 14.95, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 1.21 (P = 0.22)



d Combined severe complications

Study or Subgroup	Early intervention Events	Early intervention Total	Delayed intervention Events	Delayed intervention Total	Weight	Odds Ratio M-H, Random, 95% CI
Boxhoorn et al, 2021	33	55	29	49	23.7%	1.03 [0.47, 2.27]
Chantarojanasiri et al, 2018	3	12	4	23	13.3%	1.58 [0.29, 8.62]
Jagielski et al, 2022	4	25	7	46	16.8%	1.06 [0.28, 4.05]
Rana et al, 2021	7	34	2	136	13.9%	17.37 [3.42, 88.21]
Trikudanathan et al, 2018	33	76	36	117	26.0%	1.73 [0.95, 3.15]
Zhang et al, 2021	100	100	27	31	6.2%	32.89 [1.72, 629.69]
Total (95% CI)		**302**		**402**	**100.0%**	**2.31 [1.01, 5.26]**
Total events	180		105			

Heterogeneity: Tau² = 0.59; Chi² = 13.82, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 1.98 (P = 0.05)

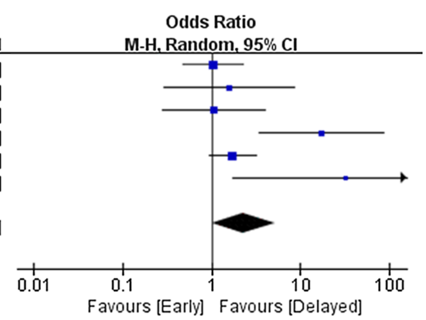


Fig. 3 Forest plot of the effects of early intervention for infected pancreatic necrosis on incidence of severe complications during the hospitalization compared with delayed intervention. **a** the incidence of new-onset organ failure, including pulmonary, circulatory, and renal failure; **b** the incidence of gastrointestinal fistula or perforation; **c** the incidence of bleeding which would need blood transfusion or subsequent intervention for hemostasis; **d** the incidence of combined severe complications, which means the mathematical combination of the abovementioned three severe complications. *M-H* Mantel–Haenszel, *CI* confidence interval, *Tau*^{2} tau-square statistic, *Chi*^{2} chi-square statistic, *df* degrees of freedom, *I*^{2} I-square heterogeneity statistic, *Z* Z statistic

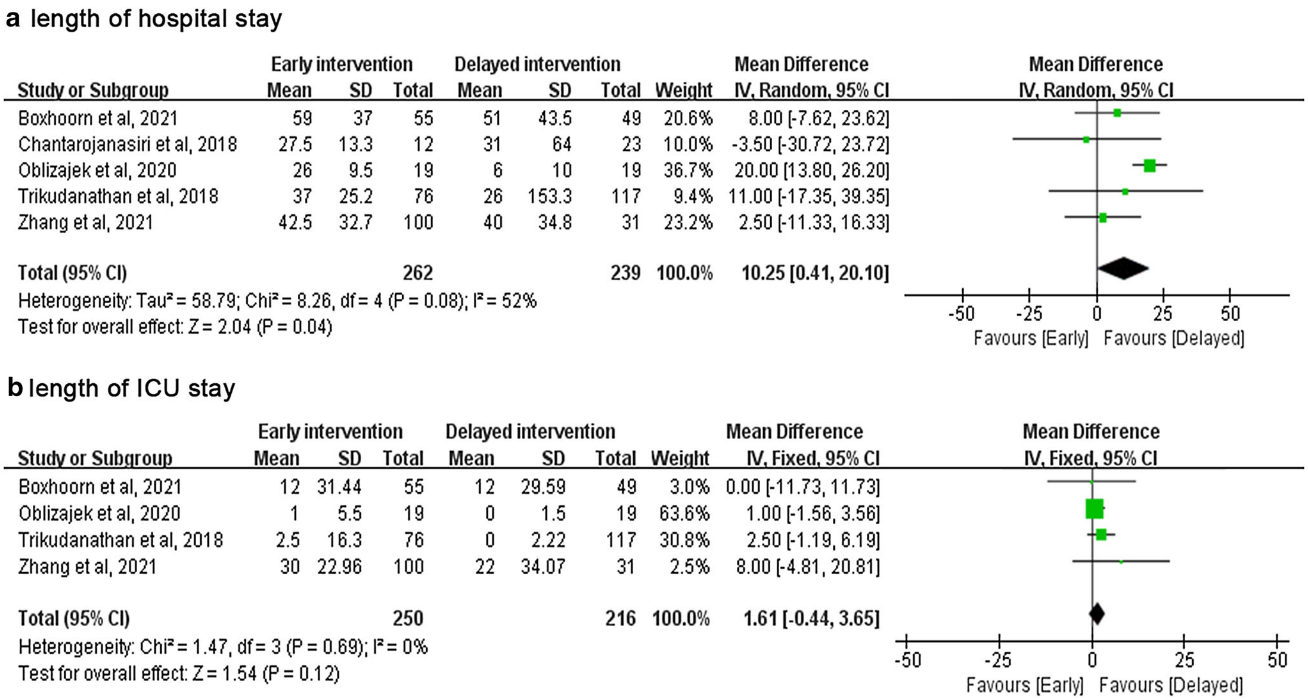


Fig. 4 Forest plot of the effects of early intervention for infected pancreatic necrosis on **a** length of hospital stay and **b** length of intensive care unit (ICU) stay compared with delayed intervention. *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *Tau*^{2} tau-square statistic, *Chi*^{2} chi-square statistic, *df* degrees of freedom, I^2 I-square heterogeneity statistic, *Z* Z statistic

Combined severe complications The meta-analysis of six studies [3, 15, 16, 21–23] involving a total of 704 patients showed a trend toward increased incidence of severe complications associated with early intervention group but no statistical significance was shown (OR 2.31, 95% CI 1.01–5.26; $p = 0.05$) (Fig. 3d) when compared to the delayed group.

Length of hospital stay and ICU stay

Five studies [3, 15, 17, 21, 23] involving a total of 501 patients were included in the meta-analysis of length of hospital stay. Results from this analysis showed that the length of hospital stay was significantly longer in patients undergoing early interventions (MD 10.25, 95% CI 0.41–20.10; $p = 0.04$) (Fig. 4a). The study heterogeneity was found to be medium ($I^2 = 52\%$). As for the length of ICU stay, the meta-analysis of four studies [3, 15, 17, 23] failed to demonstrate a significant difference between the two groups (MD 1.61, 95% CI − 0.44–3.65; $p = 0.12$) (Fig. 4b).

Discussion

This study investigates the impact of the timing of minimally invasive intervention on the clinical outcomes of patients with IPN requiring intervention. This meta-analysis has shown that early intervention is associated with potentially higher hospital mortality and a longer length of hospital stay. As most of the included studies are observational and the number of included patients is limited, the findings are susceptible to selection bias, meaning that these findings warrant confirmation.

The main complications, including new-onset organ failure, gastrointestinal fistula or perforation and bleeding were analyzed separately and combinedly. In view of the limited sample size in each meta-analysis and the rarity of the adverse events, a pooled incidence of combined severe complications was calculated in this study. The higher incidence of severe complications, for instance, gastrointestinal fistula or perforation, is likely to be the basis of the potentially higher mortality in patients undergoing the early intervention. Organ failure is the most important determinant of mortality, and a previous research showed that organ failure was associated with mortality in 30% of patients with infected necrosis [24]. It is worth noting that early intervention was not associated with an increased incidence of new-onset organ failure ($p = 0.33$), which implies that persistent or worsening organ failure might also be a contributor to increased mortality, although not directly assessed. As reported in a previous study [15], patients receiving early intervention underwent more procedures for IPN, whereas the postponement strategy averted the need for intervention in a notable proportion (nearly

40%) of patients assigned to the delayed group. These more frequent early interventions would in turn increase the risk of complications, which may prolong the hospital stay and potentially cause more deaths.

The revised Atlanta classification has defined the morphological characteristics of local complications and used the time elapsed after onset of illness (± 4 weeks), the contents of the cavities (solid or liquid), and encapsulation of the wall (present or not) [12, 25]. According to the criteria, ANCs occur within the first 4 weeks while WON after 4 weeks. Thus, the difference between early and delayed intervention in the current study can be seen the same as interventions for ANC and WON. IPN is traditionally regarded as a late event in the disease course of pancreatitis, while it may emerge early within the first 4 weeks in up to one third of patients [10, 26]. Most guidelines for managing AP [4, 5, 7, 27, 28] and expert opinion/consensus recommend delaying invasive interventions until the formation of WON. During the encapsulation process, it is expected that conservative management (including antibiotics) will be required to bridge the period between infection of necrosis and the formation of WON [29, 30]. However, clinical deterioration can occur before capsulation and sometimes mandate earlier intervention to control the source of infection, thereby improving organ function and stabilizing clinical status.

Given that some patients appear to justify early intervention (with evidence of infection and clinical deterioration despite maximal intensive care treatment), whether a more individualized approach is warranted is not confirmed yet. The difficulty mainly rests on how these patients can be accurately identified to avoid either overtreatment or undertreatment. In our previous randomized controlled trial [31], an early on-demand strategy was tested, where early drainage was triggered by unremitted or worsening organ failure, in patients with necrotizing pancreatitis combined with persistent organ failure. The results showed that major complication/death occurred in 3/15 (20%) patients in the early on-demand group and 7/15 (46.7%) in patients receiving usual care ($p = 0.25$, relative risk 0.43, 95% CI 0.14–1.35), implying the potential for clinical benefits favoring the novel strategy. Since the primary indication for invasive intervention in this study was persistent organ failure but not infection, this pilot study was not included in the current meta-analysis. In another study [3], all patients undergoing an endoscopically centered step-up approach were categorized as early or standard based on the timing of intervention (< 4 weeks or ≥ 4 weeks from AP onset). The results demonstrated that early (< 4 weeks) interventions triggered by infection or decompensated organ failure did not result in an increase in complications.

Although not directly supported by the findings of this first meta-analysis, it is still possible that a subset of patients who fail to show clinical improvement within the 4-week period might benefit from early intervention. Identifying this subset presents a challenge. The diagnosis of infection is not sufficient because not all documented infection requires intervention [32]. Organ failure is an alternative since it is readily detected and quantified [12], is the most important determinant of mortality [24], and its persistence or escalation reflects deterioration. The issue is that organ failure can occur before the development of IPN and can occur in the absence of a drainable collection. Intervention still requires a drainable target, but if present in a patient with persistent organ failure (despite maximal intensive care treatment), it is possible that intervention before 4 weeks might be justified. This abovementioned early on-demand approach had been shown to be safe and potentially beneficial in our pilot study [31]. A multicenter trial based on the pilot trial is now ongoing, and the results may provide solid evidence on this topic [33]. The POINTER trial [15] has also highlighted the issue of timing for intervention with IPN and more research is required.

This meta-analysis is limited by there being only one randomized controlled trial, and the small number of patients included, given the infrequency of the outcomes of interest. In addition, Data were not available on the long-term outcomes (endocrine and exocrine function, quality of life, etc.) of early and delayed intervention, which would be helpful in determining the optimal timing of intervention.

Conclusion

In patients with IPN requiring intervention, early minimally invasive intervention does not increase hospital mortality but is associated with a remarkably prolonged hospital stay and an increased incidence of gastrointestinal fistula or perforation when compared with delayed intervention. Although no firm conclusion can be drawn because of the quality of available studies, it does appear that timing is a risk factor for adverse outcomes and ought to be investigated more rigorously in order to determine the optimal timing of intervention and how best to determine it in the individual patient.

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Declarations

Confict of interest The authors declare that there is no conflict of interest regarding the research, authorship, and/or publication of this paper.

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