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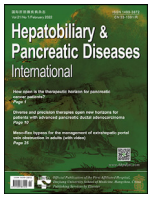

Original Article/Pancreas

Early versus delayed intervention in necrotizing acute pancreatitis complicated by persistent organ failure

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ABSTRACT

Background: Current guidelines for the treatment of patients with necrotizing acute pancreatitis (NAP) recommend that invasive intervention for pancreatic necrosis should be deferred to 4 or more weeks from disease onset to allow necrotic collections becoming "walled-off". However, for patients showing signs of clinical deterioration, especially those with persistent organ failure (POF), it is controversial whether this delayed approach should always be adopted. In this study, we aimed to assess the impact of differently timed intervention on clinical outcomes in a group of NAP patients complicated by POF.

Methods: All NAP patients admitted to our hospital from January 2013 to December 2017 were screened for potential inclusion. They were divided into two groups based on the timing of initial intervention (within 4 weeks and beyond 4 weeks). All the data were extracted from a prospectively collected database.

Results: Overall, 131 patients were included for analysis. Among them, 100 (76.3%) patients were intervened within 4 weeks and 31 (23.7%) underwent delayed interventions. As for organ failure prior to intervention, the incidences of respiratory failure, renal failure and cardiovascular failure were not significantly different between the two groups ($P > 0.05$). The mortality was not significantly different between the two groups (35.0% vs. 32.3%, $P = 0.83$). The incidences of new-onset multiple organ failure (8.0% vs. 6.5%, $P = 1.00$), gastrointestinal fistula (29.0% vs. 12.9%, $P = 0.10$) and bleeding (35.0% vs. 35.5%, $P = 1.00$), and length of ICU (30.0 vs. 22.0 days, $P = 0.61$) and hospital stay (42.5 vs. 40.0 days, $P = 0.96$) were comparable between the two groups.

Conclusion: Intervention within 4 weeks did not worsen the clinical outcomes in NAP patients complicated by POF.

Introduction

Pancreatic necrosis is an uncommon but devastating local complication of acute pancreatitis (AP), which frequently requires invasive intervention when it gets infected or causes obstructive symptoms [1–3]. Current guidelines recommend that invasive intervention should be delayed until 4 or more weeks after AP onset for collections becoming "walled-off" [4–6] and the development of a fibrous wall around the initially solid or semisolid pancreatic necrosis takes approximately 3–4 weeks [4,7]. However, for patients with clinical deterioration, especially those with persistent organ failure (POF), it is controversial that if delayed intervention should always be adopted [8].

Organ failure is one of the most important complications of AP and is deemed as the key determinant of outcomes in AP patients, and POF is proven to be strongly associated with substantial morbidity and mortality [9–11]. A previous study showed that the duration of organ failure was significantly related to mortality, implicating that shortening the duration of organ failure in the early stage may exert survival benefits on this subgroup of AP patients [10]. Furthermore, a previous study [12] demonstrated

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that timely interventions should be indicated when organ failure cannot be alleviated with conservative measures. Although early intervention has underlying risks, for instance, the introduction of infection to the sterile collections, dogmatic postponement of intervention may cause organ failure deterioration and even worsen clinical outcomes [13–15].

In a recent study conducted by Trikudanathan et al. comparing early intervention ($<$ 4 weeks) with delayed intervention ($\geq$ 4 weeks) in patients with necrotizing acute pancreatitis (NAP), the results showed that the most common indication for early intervention was infection (90.8%), and the patients in the early intervention group had similar complication rates, similar improvement in organ failure, slightly increased need for surgery, and relatively low mortality, indicating that early intervention should serve as an option for some "high-risk" patients like those with suspected early infection [16]. However, we observed that most patients in this study were managed with an endoscopically centered step-up strategy. Therefore, the generalizability of the results was in doubt for patients managed with surgical approaches [17].

In the present cohort study, we aimed to evaluate the effects of differently timed initial interventions (early versus delayed) in NAP patients complicated by POF treated majorly with a surgical step-up approach.

Methods

Patients

A consecutive series of NAP patients requiring interventions from January 2013 to December 2017 admitted to the Center of Severe Acute Pancreatitis (CSAP), Jinling Hospital were screened for potential inclusion. Patients who were older than 75 years or younger than 18 years, admitted more than 28 days from disease onset, suspected of chronic pancreatitis, had no POF before intervention, or intervened before admission were excluded. All the data were extracted from a prospectively collected database with the approval of the institutional review board (2018 JLAPDMC-008). Routine written informed consent was obtained for data collection, storage, and academic use of data from all patients or next of kin at admission. Additional informed consent from individuals was waived due to the retrospective and anonymous nature of this study.

Based on the timing of initial intervention, all the study subjects were divided into two groups: early intervention group included patients receiving invasive interventions for pancreatic necrosis within four weeks after AP onset, while patients who were intervened after four weeks were assigned to the delayed intervention group.

Definitions

The diagnosis and severity classification of AP were defined according to the Revised Atlanta Classification (RAC) [18]. SAP was defined when single or multiple POF (e.g., pulmonary, renal, cardiovascular) occurred. The criteria for organ failure were based on the modified Marshall score system, as suggested by the RAC [18]. modified Marshall score $\geq$ 2 for each single organ system was considered as the presence of organ failure, and POF was defined as organ failure lasting for 48 h or more. Suspicion of infection was based on clinical signs like persistent fever and increased inflammatory markers. Infection of pancreatic necrosis was confirmed when there was extraluminal gas in the pancreatic and/or peripancreatic collections on CT, or the results of percutaneous drains culture showed positive [18].

Drainage strategy

Briefly, when invasive interventions were indicated, image-guided percutaneous catheter drainage (PCD) was considered as the primary choice in the study cohort. In patients who responded poorly to catheter drainage and intermittent irrigation, additional "double catheterization cannula" would be applied for continuous negative pressure irrigation followed by percutaneous endoscopic necrosectomy (PEN) through the sinus tract established by the cannula at the treating physician's discretion. If patients showed no clinical improvement after repeated endoscopic procedures, open necrosectomy would be arranged to facilitate debridement [19,20].

The primary indications for intervention included: confirmed or suspected infection, gastric outlet obstruction, bleeding, disconnected pancreatic duct, etc.

Outcome measures

The primary outcome measure for the present study was mortality during the index admission. The secondary outcomes including new-onset organ failure were defined as organ failure occurring after the initial intervention and not present before the initial intervention, abdominal bleeding, gastrointestinal fistula, symptomatic vein thrombosis (SVT), length of ICU and hospital stay, and intervention related measures like the requirement of minimally invasive debridement, the requirement of surgery, etc.

Data collection

Demographic data, including age, sex, and etiologies, were collected. The modified Marshall score was assessed at admission and collected every day thereafter during hospitalization. Intervals between symptom onset and hospital admission, as well as between the first PCD procedure and admission, were calculated. Besides, the invasive intervention associated measures, such as the number of interventional procedures and requirement of surgery, etc., and clinical outcomes including mortality, the duration and type of organ failure, the incidence of gastrointestinal fistula and bleeding events, length of hospital stay and length of ICU stay were also recorded. The class of antibiotics used and the culture results of the drains obtained during the initial intervention were also collected for the study subjects.

Statistical analysis

SPSS 22.0 statistical software package (IBM Analytics, Armonk, NY, USA) was adopted for the statistical analyses in this study. Continuous variables were expressed as means $\pm$ standard deviations (SD) or medians (interquartile ranges, IQR) as appropriate, and categorical variables were described in absolute numbers and percentages (%). For between-group comparisons, χ^2 test or Fisher's exact test was used for analyzing categorical variables and Student's *t*-test or Mann-Whitney test for continuous variables depending on the distribution of the data. A $P < 0.05$ (2-tailed) was deemed statistically significant.

Results

Baseline characteristics

A total of 589 NAP patients admitted to our center were screened. As shown in Fig. 1, 131 patients were included for final analysis and divided into two groups based on the timing of intervention: 100 (76.3%) in the early intervention group and 31 (23.7%) in the delayed intervention group. The demographic and baseline clinical characteristics of the patients are shown in Table 1. Almost

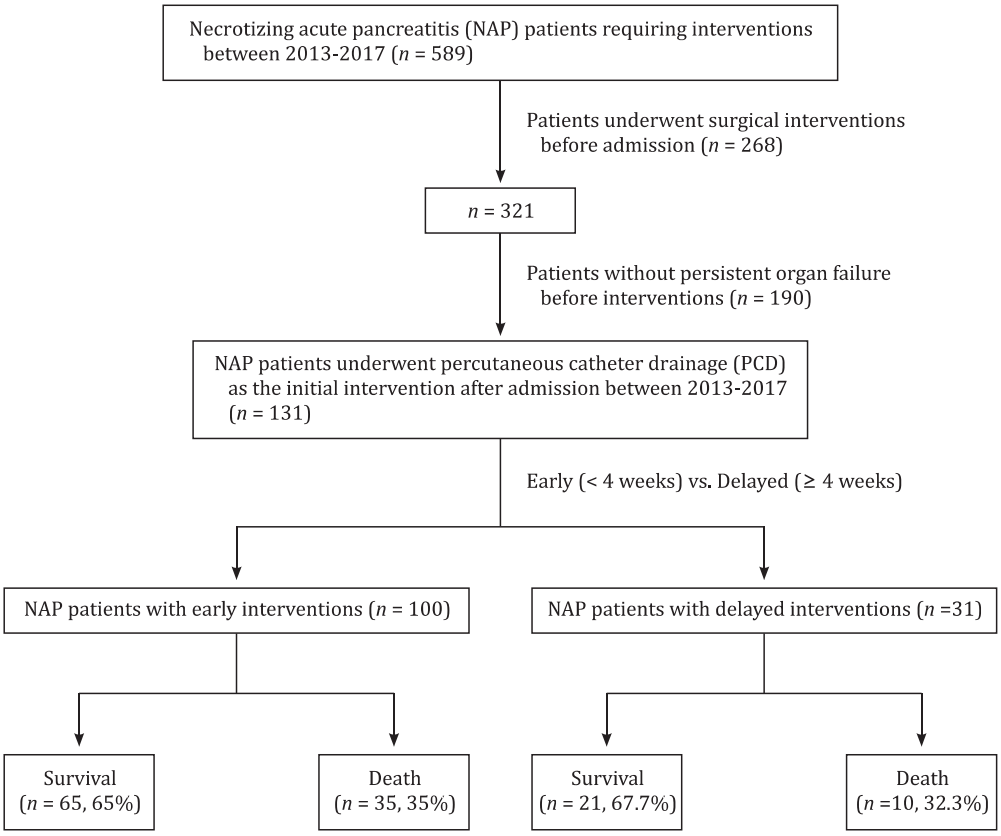

Fig. 1. The flow chart of the current study.

all patients included in this study were referrals, and the median time from symptom onset to admission was 10.0 ± 7.1 days in the early intervention group versus 12.1 ± 7.9 days in the delayed intervention group ($P = 0.17$). Suspected infection was the most common indication for intervention in all study subjects, and more patients in the early intervention group were intervened for this indication (90.0% vs. 67.7%, $P = 0.01$).

As shown in Table 1, the highest values of the modified Marshall score for each individual organ system (pulmonary, renal, and cardiovascular) prior to intervention were compared between the two groups. The incidences of respiratory failure (86.0% vs. 87.1%, $P = 1.00$), renal failure (87.0% vs. 71.0%, $P = 0.05$) and cardiovascular failure (63.0% vs. 45.2%, $P = 0.10$) were not significantly different between the two groups.

Clinical outcomes

As shown in Table 2, there was no significant difference between the two groups in terms of mortality during the index admission (35.0% vs. 32.3%, $P = 0.83$). As for the secondary outcomes, the incidences of new-onset organ failure (8.0% vs. 6.5%, $P = 1.00$), bleeding (35.0% vs. 35.5%, $P = 1.00$), gastrointestinal fistula (29.0% vs. 12.9%, $P = 0.10$) as well as SVT (6.0% vs. 6.5%, $P = 1.00$) in the two groups were also comparable. So were the lengths of hospital (42.5 vs. 40.0 days, $P = 0.96$) and ICU stay (30.0 vs. 22.0 days, $P = 0.61$).

Intervention procedures associated measures

The number of PCD procedures required in the early intervention group was equivalent to that in the delayed intervention group. After the initial PCD intervention, 39 (39.0%) patients in the early intervention group versus 8 (25.8%) patients in the delayed intervention group required endoscopic debridement, and almost half of these patients (48.9%) received repeated procedures. The proportion of patients undergoing open surgery were comparable in the two groups (29.0% vs. 22.6%, $P = 0.65$) (Table 3).

Microbiological results and antibiotics

As shown in Table 4, patients in the early intervention group had significantly more positive culture results from initial drains (79.0% vs. 58.1%, $P = 0.03$), and *Klebsiella pneumoniae* was the leading bacteria in both groups. For the use of antibiotics, significantly more patients in the early intervention group required carbapenems (85.0% vs. 61.3%, $P = 0.01$) and tigecycline (47.0% vs. 22.6%, $P = 0.02$), suggesting more severe infection in the early intervention group.

Discussion

In this study, we assessed the impact of different timing (early versus delayed) of intervention on clinical outcomes in NAP patients complicated by POF. Suspected infection was the most common indication for intervention, and patients in the two groups showed similar clinical outcomes, including mortality, new-onset organ failure, severe complications as well as hospital/ICU stays. Although there was no statistical difference between the two groups in terms of organ failure prior to intervention, patients in the early intervention group had numerically more renal, cardiovascular failures than that in the delayed intervention group.

In AP patients, the presence of infected pancreatic necrosis may cause substantial morbidity, which is strongly associated with

Table 1
The baseline and demographic data of NAP patients in the two groups.

Variables	Early intervention group (< 4 weeks) (n = 100)	Delayed intervention group (≥ 4 weeks) (n = 31)	P value
Age (yr)	46.4 ± 14.4	50.0 ± 15.7	0.24
Sex			0.56
Male	59 (59.0%)	19 (61.3%)	
Female	41 (41.0%)	12 (38.7%)	
Etiology			
Biliary	51 (51.0%)	15 (48.4%)	0.84
Hyperlipidemia	42 (42.0%)	13 (41.9%)	0.58
Others	7 (7.0%)	3 (9.7%)	0.70
Interval from AP onset to admission (d)	10.0 ± 7.1	12.1 ± 7.9	0.17
Interval from AP onset to first procedure (d)	19.0 (13.3–23.8)	33.0 (29.0–47.0)	**0.01**
Marshall score before intervention			
Pulmonary			0.36
0-1	14 (14.0%)	4 (12.9%)	1.00
2	8 (8.0%)	6 (19.4%)	0.10
3	45 (45.0%)	12 (38.7%)	0.68
4	33 (33.0%)	9 (29.0%)	0.83
Renal			0.15
0-1	13 (13.0%)	9 (29.0%)	0.53
2	7 (7.0%)	2 (6.5%)	1.00
3	46 (46.0%)	9 (29.0%)	0.10
4	34 (34.0%)	11 (35.5%)	1.00
Cardiovascular			0.25
0-1	37 (37.0%)	17 (54.8%)	0.10
2	38 (38.0%)	8 (25.8%)	0.28
3	21 (21.0%)	6 (19.4%)	1.00
4	4 (4.0%)	0	0.57
Organ failure before intervention			
Pulmonary	86 (86.0%)	27 (87.1%)	1.00
Renal	87 (87.0%)	22 (71.0%)	0.05
Cardiovascular	63 (63.0%)	14 (45.2%)	0.10
MOF	83 (83.0%)	21 (67.7%)	0.08
Primary indications for intervention			
Infection	90 (90.0%)	21 (67.7%)	**0.01**
Gastric outlet obstruction	2 (2.0%)	6 (19.4%)	**<0.01**
Other indications[a]	8 (8.0%)	4 (12.9%)	0.48

Other indications[a] —— bleeding, or disconnected pancreas duct; AP: acute pancreatitis; MOF: multiple organ failure.

Table 2
Clinical outcomes in the two groups.

Outcomes	Early intervention group (< 4 weeks) (n = 100)	Delayed intervention group (≥ 4 weeks) (n = 31)	P value
Primary outcome			
Mortality	35 (35.0%)	10 (32.3%)	0.83
Secondary outcomes			
Complications			
Bleeding	35 (35.0%)	11 (35.5%)	1.00
Gastrointestinal fistula	29 (29.0%)	4 (12.9%)	0.10
Pancreatic fistula	2 (2.0%)	0	1.00
SVT	6 (6.0%)	2 (6.5%)	1.00
New-onset organ failure			
Renal	10 (10.0%)	1 (3.2%)	0.46
Pulmonary	12 (12.0%)	5 (16.1%)	0.55
Cardiovascular	35 (35.0%)	8 (25.8%)	0.39
New-onset MOF	8 (8.0%)	2 (6.5%)	1.00
Length of hospital stay (d)	42.5 (24.3–68.5)	40.0 (24.0–71.0)	0.96
Length of ICU stay (d)	30.0 (17.0–48.0)	22.0 (9.0–55.0)	0.61

SVT: symptomatic vein thrombosis. MOF: multiple organ failure; ICU: intensive care unit.

Table 3
Intervention procedures associated indicators

Indicators	Early intervention group (< 4 weeks) (n = 100)	Delayed intervention group (≥ 4 weeks) (n = 31)	P value
PCD times			
1	49 (49.0%)	10 (32.3%)	0.15
2	16 (16.0%)	10 (32.3%)	0.07
≥ 3	35 (35.0%)	11 (35.5%)	1.00
PEN	39 (39.0%)	8 (25.8%)	0.21
Secondary PEN	18 (18.0%)	5 (16.1%)	1.00
ON	29 (29.0%)	7 (22.6%)	0.65
Secondary ON	10 (10.0%)	1 (3.2%)	0.46

PCD: percutaneous catheter drainage; PEN: percutaneous endoscopic necrosectomy; ON: open necrosectomy.

poorer outcomes [21]. For early acute necrotic collection (ANC), despite the sterile nature, ANC often contains numerous enzymes or inflammatory cytokine, which was reported to play important roles in the development of systemic inflammation and following organ failures [22]. Although current guidelines all recommend infection as the primary indication for intervention [4–6], given the difficulties in early diagnoses of infection, earlier intervention should still be considered in patients showing clinical decompensation like new-onset organ failure or aggravation of pre-existing organ failure. Furthermore, POF may serve as a good indication for timely intervention, as organ failure, different from early infection, could be easily detected and quantified [10].

Almost all the present guidelines suggest delayed intervention in patients with pancreatic necrosis or secondary infection in order to make collections become “walled-off” [4–6] and to allow liquefaction of the necrosis [23]. It has been suggested that the capsulation enables easier drainage and debridement and mitigates the risk of complications or even death. However, in some patients, despite adequate medical treatment, serious complications or adverse clinical events can occur within four weeks due to the systematic inflammation caused by pancreatic necrotic tissues [24], and early intervention may help. In addition, van Grinsven et al. reported that clinically relevant walled-off necrosis frequently occurs

Table 4
Results of cultures of drains obtained during the initial intervention.

Bacteriology variables	Early intervention group (n = 100)	Delayed intervention group (n = 31)	P value
Positive	79 (79.0%)	18 (58.1%)	**0.03**
Klebsiella pneumoniae	34 (34.0%)	6 (19.4%)	0.18
Escherichia coli	13 (13.0%)	5 (16.1%)	0.77
Pseudomonas aeruginosa	13 (13.0%)	3 (9.7%)	0.76
Baumanii	9 (9.0%)	1 (3.2%)	0.45
Enterococcus faecium	5 (5.0%)	5 (16.1%)	0.06
Morganella Fulton	4 (4.0%)	2 (6.5%)	0.63
Others	25 (25.0%)	4 (12.9%)	0.22

within the first three weeks, which is opposed to the four-week cliché, suggesting that arbitrary delaying could be pointless or even deleterious [7]. Hence, in NAP patients complicated by POF, who are at risk of substantial morbidity and mortality, the optimal timing for intervention should be cautiously considered, and the pros and cons of different intervention timing were not scrupulously studied yet [25].

The research from Trikudanathan et al. reported that an earlier than four weeks endoscopically centered step-up approach may be utilized in the management of NAP [16]. The research from Chandigarh, India, also indicated that PCD should be selected for the specific need or indication irrespective of the duration of disease [26], and the outcomes of early intervention appeared to be similar to the typically recommended four-week delayed intervention. However, these studies included a group of moderate-severe patients, who were deemed as low-risk for both morbidity and mortality, making the results less generalizable in high-risk patients, namely, SAP [16,26]. Our results indicated that early intervention in NAP patients complicated by POF did not worsen the clinical outcomes. Hence, in line with the abovementioned studies, timely intervention for pancreatic necrosis should be contemplated when there is a strong indication like infection, especially in patients with persistently unremitted organ failure.

The present study has some limitations that need to be addressed. First of all, the retrospective nature of our study, the relatively arbitrary grouping criteria we adopted, and the highly unbalanced sample size and some important baseline characteristics like indication for intervention between the two groups may bring bias into the interpretation of our results. Moreover, with patients admitted to our center at varying time points from a few days to 2-3 weeks after onset of the disease, the impact of before-admission treatment could not be accurately assessed.

In conclusion, our study demonstrated that early intervention of pancreatic necrosis did not worsen the clinical outcomes in NAP patients complicated by POF. A prospective multicenter randomized study controlling the potential cofounders is required to validate the conclusions.

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CRediT authorship contribution statement

He Zhang: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Lin Gao**: Methodology, Writing - original draft, Writing - review & editing. **Wen-Jian Mao**: Formal analysis, Investigation, Methodology, Software, Writing - review & editing. **Jie Yang**: Methodology, Software. **Jing Zhou**: Investigation. **Zhi-Hui Tong**: Conceptualization, Funding acquisition, Project administration, Resources, Supervision. **Lu Ke**: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Wei-Qin Li**: Project administration.

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Ethical approval

All the data were retrospectively extracted from a prospectively collected database with the approval of institutional review board (2018 JLAPDMC-008). Informed consent from individuals was waived due to the retrospective, observational and anonymous nature of the current study.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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