

# Timing of Intervention in Necrotizing Pancreatitis

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## Abstract

**Background** The best available evidence suggests that surgical intervention should be delayed where possible until four weeks after the onset of pancreatitis. Subgroups that may benefit from early or delayed intervention have not been identified.

**Methods** This study reviewed a prospective database with 223 patients of necrotizing pancreatitis who received intervention. A subgroup analysis was performed to compare the results of different surgical timing.

**Results** The median timing of intervention was 32 days. The mortality rates in the early ( $\leq 30$  days) intervention and delayed intervention ( $>30$  days) groups were 21 % (28/136) and 10 % (9/87), respectively ( $P=0.04$ ). In patients with persistent early organ failure, mortality and re-intervention rates were higher in the early group compared with the delayed group (23/61 vs. 3/21,  $P=0.04$ ; 17/61 vs. 2/21,  $P=0.01$ ). In patients without persistent early organ failure who underwent treatment, mortality rates, and re-intervention rates were similar between the early group and delayed group (5/75 vs. 6/66,  $P=0.59$ ; 7/75 vs. 3/66,  $P=0.27$ ). In patients with infected necrosis, mortality rate was similar with the early group and delayed group (17/77 vs. 7/57,  $P=0.14$ ).

**Conclusion** Early intervention in patients without persistent organ failure showed similar outcomes with patients who received delayed intervention.

**Keywords** Acute pancreatitis · Surgery · Clinical trial

The timing of intervention in necrotizing pancreatitis has changed considerably over the years, from early necrosectomy to delayed intervention. A consensus was reached that intervention should be postponed until approximately 1 month after disease onset, whenever possible.<sup>1</sup> Previous trials have indicated that postponed intervention is associated with decreased mortality and reoperation rate.<sup>2–5</sup> Nevertheless, as a complex disease, recommended timing of intervention in necrotizing pancreatitis still seems vague and confusing. Should all the patients receiving intervention 1 month after onset or just for some of the patients? For which

patients do we need prompt intervention? In addition, the aforementioned trials indicated that patients in the early intervention group had higher preoperative Acute Physiology, Age, and Chronic Health Evaluation (APACHE)-II scores and higher rate of organ failure.<sup>4,5</sup> Thus, better understanding of the characteristics of necrotizing pancreatitis makes it necessary to determine the appropriate timing of intervention based on different disease subgroups.

In this study, patients with necrotizing pancreatitis were divided into subgroups, and outcomes of different surgical timing were investigated. The main aim of this study was to evaluate whether different disease subgroups of necrotizing pancreatitis might benefit from earlier or delayed intervention.

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## Methods

### Patients and Treatment Protocol

Patients diagnosed with acute pancreatitis with pancreatic necrosis or peripancreatic necrosis confirmed by contrast-enhanced computed tomography (CECT) were included in a

prospective cohort study from January 2009 to June 2012 in West China Hospital.<sup>6</sup> Treatment protocol details and data collection of this cohort have been described previously.<sup>6</sup> Interventional treatment were performed on patients with suspected or confirmed infected necrosis. Infected necrosis was defined as a positive culture of pancreatic necrosis or peripancreatic necrosis obtained through fine-needle aspiration or from the first operation or the presence of gas in the peripancreatic collection on CECT. Suspected infected necrosis was defined as persistent clinical manifestations of sepsis without the presence of gas in the peripancreatic collection on CECT. In this study, intervention was postponed until approximately 4 weeks after the onset of disease, whenever possible. However, when severe clinical deterioration persisted, a prompt intervention was performed. Open pancreatic necrosectomy, retroperitoneal pancreatic necrosectomy,<sup>7</sup> or primary percutaneous catheter drainage with pigtail plastic stents were the possible types of intervention. Indication of each interventional procedure has been described previously.<sup>6</sup> Cultures were taken during all primary procedures to confirm the diagnosis of infected necrosis. The study was conducted in accordance with the principles in the Declaration of Helsinki. All patients or their legal representatives provided written informed consent. The ethics review board of West China Hospital approved the study.

#### Data Collection and Definitions

The medical records of all patients included in this study were recorded and entered into a database for analysis. In this study, a post hoc analysis of the database was conducted, focusing on patients who received intervention. All patients who received intervention were divided into the early group ( $\leq 30$  days) and delayed group ( $> 30$  days) based on surgical timing. The baseline characteristics and outcomes were compared between the two groups. Baseline characteristics included age, gender, body mass index (BMI), etiology, American Society of Anesthesiologists (ASA) classification on admission, APACHE-II score on admission, organ failure, CECT findings, nutritional support at any time before surgery, and development of sterile or infected necrosis.

Organ failure and infection are two major complications of necrotizing pancreatitis. Several studies have proven that patients in the early intervention group had higher preoperative APACHE-II scores and higher rate of organ failure before intervention. In this study, patients who received intervention were divided into the organ failure (patients with persistent early organ failure) and no organ failure (patients without persistent early organ failure) groups. These two groups were then subdivided into early or delayed intervention groups. The effect of organ failure was determined by comparing the outcomes between these two groups. We tried to determine whether a difference in the outcomes exists between the early

and delayed intervention subgroups in the organ failure and no organ failure groups. At the same time, patients were subdivided into sterile and infected groups based on the development of sterile or infected necrosis. Outcomes were evaluated to determine whether a difference exists between the early and delayed intervention subgroups of the two groups. The primary outcome parameter was mortality, whereas the secondary parameters were major complications, including intra-abdominal bleeding, enterocutaneous fistula, new-onset organ failure, and re-intervention. The definitions of organ failure and outcomes are listed in Table 1.

#### Statistical Analysis

Continuous data are presented as median with interquartile range. Differences were tested by using the Mann–Whitney test. Proportions were compared by using the chi-square test, Fisher's exact test, or linear-by-linear association test. Two-sided  $P < 0.05$  was considered statistically significant.

**Table 1** Definitions

Organ failure
Pulmonary failure
$\text{PaO}_2 < 60$ mm Hg, despite $\text{FiO}_2$ of 0.30, or a need for mechanical ventilation.
Circulatory failure
Circulatory systolic blood pressure $< 90$ mm Hg, despite adequate fluid resuscitation, or a need for inotropic catecholamine support.
Renal failure
Creatinine level $> 177$ $\mu\text{mol/L}$ after rehydration or a new need for hemofiltration or hemodialysis.
Multiple organ failure
Failure of at least two organ systems on the same day.
Persistent organ failure
Presence of organ failure lasting for more than 48 h.
Outcomes
Intra-abdominal bleeding
Bleeding requiring surgical, radiological, or endoscopic intervention.
Enterocutaneous fistula
Secretion of fecal material from a percutaneous drain or drainage canal after the removal of drains or from a surgical wound; secretion comes from either the small or large bowel and is confirmed with imaging or during surgery and requires intervention.
New-onset organ failure
Organ failure that had not been present before intervention.
Re-intervention
Clinical signs of sepsis, either persistent or recurrent, as well as the presence of pancreatic or peripancreatic fluid collection confirmed by an additional CECT, requiring further intervention.

## Results

### Patient Characteristics

A total of 223 patients with pancreatic necrosis or peripancreatic necrosis who received intervention were included. Among the 223 patients, 134 had infected necrosis, confirmed by positive culture. The overall mortality rate was 17 % (37/223). Median timing of intervention was 32 days (7 to 95 days). Sixteen patients (7 %) were operated on within 14 days, 120 patients (54 %) within 15 to 30 days, and 87 patients (39 %) after 30 days, and the mortality rate was 50 % (8/16), 17 % (20/120), and 10 % (9/87), respectively. Patient characteristics and outcomes of both early and delayed groups are shown in Table 2. Patients in the early intervention group had higher preoperative APACHE-II scores and higher rate of organ failure before intervention ( $P<0.05$ ) than patients in the delayed intervention group. The mortality rate in the early group was 21 % (28/136), whereas the delayed group had a mortality rate of 10 % (9/87) ( $P=0.04$ ). The incidences of intra-abdominal bleeding, enterocutaneous fistula, new-onset organ failure, and re-intervention were 16 % (35/223), 11 % (24/223), 12 % (27/223), and 13 % (29/223), respectively. The intra-abdominal bleeding rates in the early and delayed groups were 20 % (27/136) and 9 % (8/87), respectively ( $P=0.03$ ). The re-intervention rates in the early and delayed groups were 18 % (24/136) and 6 % (5/87), respectively ( $P=0.01$ ).

### Disease Subgroups

#### Organ Failure

Persistent organ failure started in the first week of onset occurred in 82 out of 223 patients, among whom 59 % had persistent MOF (48/82). The mortality rate of these patients was 32 % (26/82). During the study period, the mortality rate of patients with persistent organ failure started in the first week of onset who received conservative treatment was 72 % (18/25), which is significantly higher than that of patients who received interventional treatment ( $P<0.001$ ). The median time between presentation and death in these patients was 26 days (range 8 to 68 days). The mortality rate was 32 % (26/82) in the organ failure group and 8 % (11/141) in the no organ failure group ( $P<0.001$ ). The intra-abdominal bleeding, re-intervention, and new-onset organ failure rates were higher in the organ failure group than in the no organ failure group (27/82 vs. 8/141,  $P<0.001$ ; 24/82 vs. 5/141,  $P<0.001$ ; 20/82 vs. 7/141,  $P<0.001$ , respectively). The enterocutaneous fistula rate was similar between the organ failure and no organ failure groups (9/82 vs. 15/141,  $P=0.93$ ). As shown in Table 3, for patients with persistent early organ failure, mortality and re-intervention rates were higher in the early group than in the delayed group (23/61 vs. 3/21,  $P=0.04$ ; 17/61 vs.

2/21,  $P=0.01$ , respectively). In patients without persistent early organ failure, mortality rates, and re-intervention rates were similar between the early and delayed groups (5/75 vs. 6/66,  $P=0.59$ ; 7/75 vs. 3/66,  $P=0.27$ , respectively). In patients with persistent early organ failure, 46 of 82 patients had organ failure persisting until intervention, and most of them were in the early intervention group (40/46). Among the 82 patients, 36 had organ failure recovered before intervention. The median time from onset of disease to recovery of organ failure was 14 days (3 to 32 days), and most of the patients recovered within 14 days (28/36).

#### Infected Necrosis

The mortality rate was 15 % (24/134) in the sterile necrosis group and 18 % (13/89) in the infected necrosis group ( $P=0.52$ ). The re-intervention, intra-abdominal bleeding, enterocutaneous fistula, and new-onset organ failure rates were similar between the sterile necrosis and infected necrosis groups (Table 4). In the patients with sterile necrosis, re-intervention rates were higher in the early group than in the delayed group (14/59 vs. 2/30,  $P=0.04$ ), and mortality rate was not significantly higher in the early group than in the delayed group (11/59 vs. 2/30,  $P=0.13$ ). In patients with infected necrosis, mortality and re-intervention rates were not significantly higher in the early group than in the delayed group (17/77 vs. 7/57,  $P=0.14$ ; 10/77 vs. 3/57,  $P=0.13$ ).

## Discussion

Our study evaluated the characteristics and clinical outcomes of a prospective cohort of patients with necrotizing pancreatitis based on different surgical timings. We investigated the outcome of different subgroups based on varying interventional timing to determine the best timing for different cases. Results show that patients without persistent organ failure had the same prognosis regardless of the timing of intervention. To our knowledge, this study is the first to report on the appropriate interventional timing for different subdivided groups of necrotizing pancreatitis patients.

In a randomized controlled trial, results showed that open necrosectomy is associated with poorer outcomes when performed within 72 h compared with delaying intervention in patients with necrotizing pancreatitis beyond the first 12 days.<sup>2</sup> A previous study on timing of intervention in necrotizing pancreatitis suggests having a longer interval between admission and intervention to reduce the risk of mortality.<sup>3</sup> Another retrospective study also indicated that patients in the early intervention group had significantly higher mortality than those in the delayed intervention group.<sup>4</sup> The 2012 IAP/APA guidelines based on these currently available evidence

**Table 2** Characteristics of patients with necrotizing pancreatitis

Characteristic	All patients (N=223)	Time from onset to intervention		P value
		≤30 days (N=136)	>30 days (N=87)	
Age (years), median (range)	47 (22–74)	44 (22–74)	48(26–72)	0.08
Male, no. (%)	136 (61)	80 (59)	56 (64)	0.41
Etiology, no. (%)				
Biliary	108 (48)	67 (49)	41 (47)	0.76
Alcohol abuse	24 (11)	13 (10)	11 (13)	0.47
Others	91 (41)	56 (41)	35 (40)	0.89
BMI on admission, median (range)	29 (20–34)	27 (20–33)	31 (22–34)	0.23
ASA class on admission, no. (%)				0.18
I—healthy status	77 (35)	49 (36)	28 (32)	
II—mild systemic disease	112 (50)	65 (48)	47 (54)	
III—severe systemic disease	34 (15)	22 (16)	12 (14)	
APACHE II score on admission, median (range) <sup>a</sup>	8 (2–32)	10 (2–32)	6 (2–30)	0.02
Organ failure				
Persistent organ failure started in the first week of onset, no. (%)	82 (37)	61 (45)	21 (24)	0.002
Persistent MOF started in the first week of onset, no. (%)	48 (22)	36 (26)	12 (14)	0.03
Highest modified Marshall score in the first week of onset, median (range)	3 (0–10)	3 (0–10)	2 (0–10)	0.003
Computed tomography				
Pancreatic necrosis, no. (%)	156 (70)	90 (66)	66 (76)	0.12
Peripancreatic necrosis alone, no. (%)	67 (30)	46 (34)	21 (24)	0.12
Extent of pancreatic necrosis, no. (%)				0.14
<30	89 (40)	52 (38)	37 (42)	
30–50	58 (26)	37 (27)	22 (25)	
>50	76 (34)	47 (35)	29 (33)	
Nutritional support at any time before surgery				
Parenteral nutrition only, no. (%)	53 (24)	27 (20)	25 (29)	0.13
Enteral and parenteral nutrition, no. (%)	170 (76)	109 (80)	62 (71)	0.13
Time (days) from onset to intervention, median (range)	32 (7–95)	20 (7–30)	49 (31–95)	<0.001
Surgical type				
Open pancreatic necrosectomy	141 (63)	90 (66)	51 (59)	0.26
Retroperitoneal pancreatic necrosectomy	45 (20)	24 (18)	21 (24)	0.30
Primary percutaneous catheter drainage	37 (17)	22 (16)	15 (17)	0.85
Infected necrosis	134 (60)	77 (57)	57(66)	0.19
Intra-abdominal bleeding, no. (%)	35 (16)	27 (20)	8 (9)	0.03
Enterocutaneous fistula, no. (%)	24 (11)	12 (9)	12 (14)	0.24
New-onset organ failure, no. (%)	27 (12)	20 (15)	7 (8)	0.14
Re-intervention, no. (%)	29 (13)	24 (18)	5 (6)	0.01
Mortality, no. (%)	37 (17)	28 (21)	9 (10)	0.04

<sup>a</sup> Data for 51 patients are unavailable because these patients were transferred from other hospitals

MOF multiple organ failure

state that for patients with proven or suspected infected necrotizing pancreatitis, invasive intervention should be delayed if possible, until at least 4 weeks after initial presentation to enable the collection to become “walled-off.”<sup>1</sup> However, in the retrospective study, the early intervention group had higher preoperative organ failure rate and higher preoperative APACHE-II scores than the delayed intervention group.<sup>4</sup> The

results were similar to those of a prospective study.<sup>5</sup> The presence of organ failure before intervention, particularly persistent organ failure, is significantly associated with mortality. This study thus aimed to provide a new perspective on timing of intervention in necrotizing pancreatitis.

Without operation, the mortality of the patients with multiple organ dysfunction secondary to sepsis from infected

**Table 3** Outcome of patients who received interventional treatment with or without persistent organ failure started in the first week after onset

Outcome	Organ failure (N=82)		P value	No organ failure (N=141)		P value
	≤30 days (N=61)	>30 days (N=21)		≤30 days (N=75)	>30 days (N=66)	
Intra-abdominal bleeding, no. (%)	24 (39)	5 (24)	0.20	3 (4)	3 (5)	0.87
Enterocutaneous fistula, no. (%)	6 (10)	3 (14)	0.57	6 (8)	9 (14)	0.28
New-onset organ failure, no. (%)	16 (26)	6 (29)	0.42	4 (5)	1 (2)	0.24
Re-intervention, no. (%)	17 (28)	2 (10)	0.01	7 (9)	3 (5)	0.27
Mortality, no. (%)	23 (38)	3 (14)	0.04	5 (7)	6 (9)	0.59

pancreatic necrosis approaches 100 %, but with operation, this rate can be reduced to 24 to 39 %.<sup>5,8,9</sup> Proven infected necrosis, as well as septic complications resulting from pancreatic infection, are accepted to be indications for surgical intervention.<sup>1,10</sup> However, when sterile necrosis is associated with organ failure, the function of surgery remains controversial.<sup>11</sup> During the study period, the mortality rate of patients with persistent organ failure starting during the first week of onset who received conservative treatment was 72 % (18/25), which was significantly higher than that of patients who received interventional treatment at 32 % (26/82) ( $P<0.001$ ). Notably, all patients with documented infected necrosis received interventional treatment in this study, which indicates that most patients with sterile necrosis and organ failure died without intervention. Based on these results, we recommend that persistent organ failure, regardless of the kind of necrosis present, should be considered an indication for necrotizing pancreatitis. In the literature, several studies discussed the function of conservative management in infected pancreatic necrosis.<sup>12–14</sup> These studies indicated that a small proportion of patients with documented infected necrosis who remain clinically stable can be treated conservatively with favorable outcomes. This finding provides another alternative for patients who are in extraordinarily good clinical condition. However, this strategy should be managed under close monitoring because a part of these patients need additional interventional management.<sup>13,14</sup>

In this study, we confirmed that the mortality rate was higher in the early group (21 %) than in the delayed group

(10 %) ( $P=0.04$ ), and intervention within 2 weeks was associated with significantly higher mortality than after 2 weeks. These results were comparable with those of other studies.<sup>3,5,15</sup> From the pathophysiological aspect, in the early phase of the natural course of acute pancreatitis, the systemic inflammatory response caused by activated cytokine cascades develop and can progress to multiple organ dysfunction, usually lasting for 1 to 2 weeks.<sup>16–18</sup> At this time, tissue injury caused by surgical trauma can aggravate the inflammatory response, which results in an increased incidence of organ failure.<sup>19–21</sup> Thus, intervention should be delayed whenever possible until at least 2 weeks after onset.

When we analyzed subgroups of these patients, results showed that mortality rate in patients with persistent organ failure started in the first week after onset and was higher in the early group than in the delayed group (23/61 vs. 3/21,  $P=0.04$ ). By contrast, in patients without organ failure, mortality rate was similar between the early and delayed groups (5/75 vs. 6/66,  $P=0.59$ ). The possible explanation for the similar outcomes in patients without organ failure is that these patients always exhibit good clinical condition, and invasive intervention can be delayed to enable the collection to become walled-off. Thus, we suggest the timing of intervention for the patients without persistent early organ failure can be delayed to at least 4 weeks after initial presentation.

In patients with persistent organ failure started in the first week of onset, 54 of 82 patients had organ failure persisting until intervention, and most were in the early intervention group (50/54). Conceivably, patients in the early group were

**Table 4** Outcome in subgroups with infected necrosis or sterile necrosis who received interventional treatment

Outcome	Infected necrosis (N=134)		P value	Sterile necrosis (N=89)		P value
	≤30 days (N=77)	>30 days (N=57)		≤30 days (N=59)	>30 days (N=30)	
Intra-abdominal bleeding, no. (%)	15 (19)	5 (9)	0.09	12 (20)	3 (10)	0.22
Enterocutaneous fistula, no. (%)	7 (9)	8 (14)	0.37	5 (8)	4 (13)	0.47
New-onset organ failure, No. (%)	11 (14)	4 (7)	0.19	9 (15)	3 (10)	0.49
Re-intervention, no. (%)	10 (13)	3 (5)	0.13	14 (24)	2 (7)	0.04
Mortality, no. (%)	17 (22)	7 (12)	0.14	11 (19)	2 (7)	0.13

in a more severe condition than those in the delayed group before intervention because most patients in the delayed group recovered from organ failure. Thus, the persistent presence of organ failure before intervention is the critical reason why the mortality rate is higher in the early group than in the delayed group.<sup>22–25</sup> However, we cannot conclude that intervention for all the patients should be delayed after 1 month. As shown by the results, the median time between presentation and death in patients with persistent organ failure who received conservative treatment was 26 d (range 8 to 68 days), which indicates that some patients with persistent organ failure cannot wait 1 month for the intervention. Besides, among the patients with persistent early organ failure, 46 had organ failure that persisted until the first intervention and 36 had organ failure recovered before intervention. The median time from onset of disease to recovery of organ failure was 14 days (3 to 32 days), and most of the patients recovered within 14 days (28/36). Thus, we recommend that patients with persistent organ failure, with or without signs of sepsis, should be closely monitored for at least 14 days, and prompt intervention has to be performed before 3–4 weeks of onset unless signs of recovery from organ failure are observed. Future prospective studies should focus on the necessity and optimal timing of intervention for the patients with persistent organ failure.

The major early complications after intervention were intra-abdominal bleeding, new-onset organ failure, enterocutaneous fistula, and re-intervention.<sup>26–28</sup> The major late complications include pancreatic fistula, delayed collections, exocrine insufficiency, and endocrine insufficiency.<sup>26–28</sup> However, early complications were commonly analyzed in previous studies. Furthermore, new-onset multiple organ failure and postoperative hemorrhage were identified to be independent predictors of mortality in a retrospective review.<sup>26</sup> In this study, intra-abdominal bleeding and re-intervention rates were higher in the early group than in the delayed group. Walled-off necrosis is generally believed to occur 4 weeks after the onset of necrotizing pancreatitis with a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. The possible explanation for the higher intra-abdominal bleeding and the re-intervention rates in the early group than in the delayed group is that some necroses in the early group were immature, and the necrosis tissue might progress even after an initial intervention. When we analyzed the outcomes between the subdivided sterile and infected groups, results showed that all the outcomes were similar between the sterile necrosis and infected necrosis groups. In the patients with sterile necrosis, although without significant difference, re-intervention and mortality rates were higher in the early group than in the delayed group. These results were similar in with those in patients with infected necrosis.

In summary, this study showed that intervention in the patients with necrotizing pancreatitis within 2 weeks was

associated with significantly higher mortality compared with intervention performed after 2 weeks. Early intervention in patients without persistent organ failure shows a similar outcome when compared with those who received delayed intervention. Patients with persistent organ failure should be closely monitored. Intervention in patients showing recovery from organ failure can be delayed until collections have become walled-off.

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