Early on-demand drainage or standard management for acute pancreatitis patients with acute necrotic collections and persistent organ failure: a pilot randomized controlled trial

(**Short title：** Early drainage in acute pancreatitis)

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ABSTRACT

Background/Purpose: The current standard care for acute pancreatitis with acute necrotic collections (ANC) is to postpone invasive intervention for four weeks when indicated. However, in patients with persistent organ failure (POF), this delayed approach may prolong organ failure. In this study, we aimed to assess the feasibility and safety of earlier drainage for acute pancreatitis patients with ANC and POF.

Methods: A single-center, randomized controlled trial was conducted. Eligible patients were randomly assigned to either the early on-demand (EOD) group or the standard management(SM) group. Within 21 days of randomization, early drainage was triggered by unremitted or worsening organ failure in the EOD group. The primary endpoint was a composite of major complications/death during 90-days follow-up.

Results: 30 patients were randomized. Within 21 days of randomization, 8/15 patients (53%) in the EOD group underwent percutaneous drainage, while 4/15 patients (27%) in the SM group did so (P=0.26). The primary outcome occurred in 3/15 (20%) patients in the EOD group and 7/15(46.7%) in the controls (p=0.25, relative risk 0.43, 95%CI 0.14 to1.35).

Conclusions: Although the EOD approach did not result in significant differences between groups, the primary outcome assessed in this trial demonstrated the potential for clinical benefits favoring early drainage.

Keywords: acute pancreatitis, acute necrotic collections, persistent organ failure, percutaneous drainage

The trial was registered on ISRCTN (ISRCTN16728921).

Introduction

A majority of patients with acute necrotizing pancreatitis (ANP) will develop acute necrotic collection (ANC)[1], with about one-third of these patients also developing infection of pancreatic necrosis, which is associated with significantly increased morbidity and mortality[2, 3].

Authoritative clinical practice guidelines recommend a "delayed" approach to the treatment of infected pancreatic/peripancreatic necrosis because it is believed that delaying any invasive intervention for an arbitrary four weeks after onset of disease allows time for an acute necrotic collection (ANC) to become encapsulated as walled off necrosis[4-6]. However, the guidelines also state that intervention should be considered when organ failure persists for weeks, but they do not define how many weeks[4, 6].

A recent 639 patient observational study conducted by Van Grinsven et al. showed that almost half of patients with ANP were encapsulated by three weeks from disease onset[7]. Thus, some experts have suggested that to defer intervention for four weeks might result in a missed opportunity to treat early infected ANC and therefore prolong organ failure, impacting the risk of mortality[8]. Moreover, even when sterile, ANCs may contain inflammatory mediators and pancreatic enzymes, which contribute to systemic inflammation and prolonged organ failure[9]. Thus, both infected and sterile ANC patients may benefit from earlier intervention than currently recommended by major guidelines[10].

The primary aim of this pilot randomized controlled trial was to assess the feasibility and safety of an approach providing earlier percutaneous drainage (PCD) for patients

with ANC and early persistent organ failure (POF), initiated based on the presence of unremitted or worsening organ failure. This earlier approach was compared to standard management. A secondary aim was to provide data for the design and power of a large-scale, multicenter, randomized controlled trial.

Material Methods

Design and study oversight

This study is a pilot, single-center, single-blinded, parallel, randomized controlled trial conducted in the Center for Severe Acute Pancreatitis, Jinling Hospital, from July 2, 2018 (the first enrollment) to August 12, 2019 (the last enrollment). Jingling Hospital is a 2,000-bed tertiary care referral hospital that admits and treats approximately 800 acute pancreatitis patients per year.

Written informed consent was obtained from all patients or their next of kin. The study protocol was approved by the institutional ethics committee of Jinling Hospital (2018NZKY-009-01) and registered on ISRCTN (ISRCTN16728921). The study was funded by the Key Research and Development Program Foundation of Jiangsu Province of China (No. BE 2016749). The funders had no role in the design of the study, data collection and analysis, and preparation of the manuscript. The coordinating center of the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG) is responsible for data quality and privacy. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

All patients with symptoms and signs consistent with acute pancreatitis(AP) admitted to the hospital during the study period were screened for eligibility. The day of onset of abdominal pain was defined as the onset of AP (Day0). Patients aged between 18 to 70 years who developed ANC confirmed by CT with available routes for percutaneous drainage and who had POF unresolved seven days after onset of AP were considered eligible. Organ failure was defined using the Modified Marshall Score, with a grade of two or higher for either the respiratory, renal, or cardiovascular scales used to define failure[11].

Patients were not eligible for enrollment if they: were pregnant; had chronic pancreatitis; had pancreatic tumor-related pancreatitis; underwent drainage or surgery before admission; had a history of cardio-pulmonary resuscitation during the present hospital admission; were expected to die within 48 hours; required emergency surgery due to active bleeding, bowel ischemia or necrosis, etc.; or had a known history of severe co-morbidities defined as (1) greater than New York Heart Association class II heart failure; (2) active myocardial ischemia; (3) history of cirrhosis; (4) chronic kidney disease with creatinine clearance< 40 mL/min; or (5) chronic obstructive pulmonary disease requiring home oxygen.

Allocation concealment and blinding

All study subjects were randomized to either the early PCD group or the standard management group on Day7 after the onset of AP. The randomization sequence was generated by computer and was blocked in groups of six. The randomization assignments were placed in sequentially numbered, opaque envelopes and were sealed

by a research coordinator. Envelopes were opened sequentially by the same research coordinator when a study participant was consented and enrolled. Independent outcome assessors were blinded to the treatment group.

Study treatments

Early on-demand (EOD) PCD

Patients who were randomized to the EOD group could receive PCD within 21 days of randomization (the intervention window) when one of the following criteria was met:

1) Persistent single or multiple organ systems failure (respiratory, renal, and/or cardiovascular) unresolved for seven days after randomization or;
2) New-onset organ failure arising after Day 7.
3) Any worsening of any individual organ failure documented to be present on Day7.

After the PCD procedure, the drains placed were audited by the investigators on a daily basis and were removed when the daily drainage volume was less than 50ml for three consecutive days, and infection was not suspected or confirmed.

Standard management

For the standard management (SM) group, PCD was postponed until four weeks after onset of abdominal pain whenever possible when infection was suspected or confirmed in line with current guidelines.

For both treatment groups, all PCD procedures were performed by the same experienced team using 12F, 14F, or 16F pig-tail catheters (UreSil, IL, US). Contents

drained from the site were cultured to determine whether it was sterile or infected. The size and number of drains placed were decided by the treating physicians.

Management of Acute Pancreatitis

Apart from the study intervention, all patients received standardized treatment according to international guidelines[4], including appropriate fluid resuscitation, early enteral nutrition, and routine medical treatment such as analgesics, proton-pump inhibitors, or organ system support (e.g., mechanical ventilation, renal replacement therapy, and vasoactive agent) as required.

For infected pancreatic necrosis, once the diagnosis was made, all patients were managed with a step-up approach, as described in detail previously[12]. Fine needle aspiration was not applied in this study, and prophylactic antibiotics were avoided as well. Emergency surgery was indicated if active bleeding occurred and could not be controlled with arterial embolization or upon suspicion of bowel necrosis and gastrointestinal perforation leading to peritonitis.

Study outcome measures

The primary composite endpoint of this study was death and/or major complications within 90 days of randomization. Major complications were defined as new-onset organ failure not present at the time of randomization, bleeding requiring intervention and gastrointestinal perforation, or fistulas requiring intervention. If multiple events occurred within the same patient, only the more serious event was counted. We updated

the primary outcome to improve the comparability between this study and previous major studies[13, 14] before initiation of patients recruitment as reported on the ISRCTN registry(https://www.isrctn.com/)[15].

Secondary outcomes (within 90 days of randomization) included all the individual components of the primary outcome plus infected pancreatic necrosis, sepsis according to the SEPSIS 3.0[16] definition, external pancreatic fistula, length of ICU and hospital stay (days), the requirement for PCD, minimally invasive necrosectomy (percutaneous endoscopic necrosectomy) as we described before[17]), the requirement for open surgery, total number of PCD procedures, requirement for re-operation and total expense. The duration of organ failure and organ support were compared within 21 days of randomization. We used "free days"(e.g., ventilator-free days and organ failure-free days) rather than "length of" (e.g., length of mechanical ventilation and length of organ failure) to avoid misleading impressions caused by increased mortality, and as recommended by previous studies in critically ill patients[18]. An additional follow-up was arranged 180 days after randomization if discharged before, and death by 180 days after randomization served as a secondary outcome as well. As a process measure, PCD placement rates were compared between treatment groups over the first 21 days after randomization.

Data collection

Data were collected using a standardized case report form. All CT scan results were reviewed by at least two experienced radiologists. Modified Marshall Score was

assessed for each participant for 21 consecutive days (the intervention period) after randomization. Outcome measures were evaluated by two independent investigators who were unaware of the study allocation. If disagreement occurred between two investigators with regards to any study outcome assessed, a third investigator was consulted and majority decisions prevailed.

Statistical analysis

Since this was a pilot study, a formal sample size calculation was not performed. A pragmatic sample size of 30 participants was chosen because it was accepted to provide meaningful safety information and would also minimize potential exposure to harms. All analyses were conducted based on the intention-to-treat principle. We present continuous data as median (interquartile range) in this study unless explicitly reported otherwise. Comparisons of continuous data were conducted using the Mann-Whitney U test or Student's t-test as appropriate. Categorical data were assessed with Fisher's exact test or chi-square test, as indicated. Risk ratios with 95% confidence intervals (CIs) were calculated for categorical variables. We considered a two-sided p-value of less than 0.05 to be statistically significant.

Results

Study population

During the study period, 157 patients were screened for eligibility, and a total of 30 patients were consented and randomized (Figure 1). All included patients were followed

up for 180 days after randomization. One patient in the SM group declined ongoing active treatment and was discharged 23 days after hospital admission to palliative care at home. She was confirmed deceased during follow-up at 26 days after hospital discharge. This patient did not withdraw consent for participation or follow-up, so she is included in all analyses. Baseline characteristics were equally distributed between groups. See Table 1.

Process measures

Within 21 days after randomization (the intervention window), 8/15 patients in the EOD group underwent PCD (six due to organ failure persisting for seven days and two for worsening organ failure), while only 4/15 patients in the SM group were intervened during the same period because of suspected infection and poor response to conservative treatment alone (p=0.26). All patients in the EOD group were successfully intervened when meeting the predefined indication. The median interval from onset of symptoms to the intervention was 15.5 days (n=8) in the EOD group and 22 days (n=4) in the SM group (p=0.01). Only one of the eight patients in the EOD group had positive culture obtained from the first drain, while three of four had a positive culture in the SM group. Four out of the eight patients undergoing early intervention in the EOD group had their drains removed 4, 4, 5, 3 days after placement, respectively, based on the predefined criteria for catheter removal. Moreover, two patients in the EOD group received PCD on 43 days and 54 days after randomization for infected walled-off necrosis, and two in the controls did so on 22 days after randomization for the same

cause. The rest of the study patients (5/15 in the EOD group and 8/15 in the SM group) did not receive invasive intervention throughout the study period.

There were no serious adverse events reported during study participation.

Primary outcome

As shown in Table 2, the primary endpoint occurred in 3/15 (20%) patients in the EOD group and 7/15 (46.7%) in the SM group (p=0.25, relative risk 0.43, 95 CI 0.14-1.35) by 90 days after randomization. We observed no significant difference for all the individual components of the primary composite endpoint either, including mortality, new-onset organ failure, bleeding, and gastrointestinal perforation or fistula. The causes of death did not differ between the two groups, with most patients dying on account of sepsis-related organ failure (2 of 3 in the EOD and 5 of 6 in the SM). One patient in the EOD group died of persistent cardiovascular failure without evidence of infection, while one patient in the SM group declined further active treatment and was discharged to palliative care at home.

Secondary outcomes

No difference was observed regarding the length of ICU (median 29 vs. 24 days, p=0.71) or hospital stay (median 35 vs. 32 days, p=0.54) between the two groups (Table 2). The incidence of infected pancreatic necrosis did not differ between the two groups (40% vs. 46.7%, p=1.0, Table 2). Moreover, for infected pancreatic necrosis related treatment, 4/15 patients in the EOD group, and 3/15 in the SM group underwent

minimally invasive necrosectomy (p=1.0). Open surgery was required for 1/15 patients in the EOD group and 5/15 patients in the SM group (p=0.17; Table 3).

For organ failure and requirement of organ support, patients in the EOD group showed numerically longer median days alive and free of respiratory (7 vs. 0 median days, p=0.49) and renal failure (14 vs. 0 median days, p=0.35) by 21 days of randomization with corresponding longer median days alive and free of mechanical ventilation (12 vs. 10 median days, p=0.62) and renal replacement therapy (10 vs. 5 days, p=0.84, Table 4), although not reaching statistical significance.

Discussion

In this pilot single-center, single-blinded, randomized, controlled trial, we assessed the safety and feasibility of an early PCD approach compared to the standard management in patients with acute pancreatitis complicated by ANC and early POF. The EOD approach was successfully implemented, leading to more and earlier drainage for ANC. Still, it failed to demonstrate statistically significant improvements in key clinical outcomes, including mortality, the incidence of major complications, and length of hospital stay. However, our results also did not demonstrate any evidence that earlier PCD increases infectious complications, which is a major concern hindering early drainage of ANC[19].

As a pilot RCT, an important objective of this study was to offer direction for the design of subsequent large trials. Although no statistical difference was detected for all the endpoints measured, we found a numerical tendency towards improvements across

multiple important outcomes: reduced mortality/major complications, shorter duration of organ failure, etc. Apart from the limited sample size, the lack of statistical significance may also be attributed to an important fact that a substantial proportion of the study subjects (5 in the study group and 8 in the controls) never received PCD. Taken together, although we did not find statistical differences, the numerical superiority of this novel EOD drainage approach suggests a more extensive study is needed. Furthermore, we believe we are able to use baseline characteristics to identify a cohort of ANP patients who will require PCD and, thus, whose outcome may be improved by an earlier approach. Accordingly, we have conducted a larger, adequately powered, multicenter trial, and the protocol had been published recently[20].

There is no consensus regarding the optimal timing for invasive intervention in ANP patients complicated by POF, especially during the first two to three weeks of disease onset[10]. Therefore we set up an "intervention window" covering a time frame from the 2nd to the 4th week after onset of AP to determine if the earlier approach could help optimize clinical decisions and improve patient outcomes during this highly controversial period. The current "delayed" approach descends from previous studies on the timing of open necrosectomy[21], but the management of infected pancreatic necrosis has shifted from open surgery to minimally invasive interventions, and the effect of postponing any invasive intervention for four weeks has not been proven by any randomized controlled trial in the background of newer techniques.

Moreover, infection is the primary indication for intervention in the current guidelines[4], and there is also no consensus on whether intervention should proceed

311 when infection is only suspected or wait until it is confirmed[10]. Mortele et al.
312 demonstrated that the presence of multiple organ failure rather than infection was a
313 more important indicator of outcome and that intervention during sterile necrosis did
314 not affect the effectiveness of PCD[22]. Therefore we proposed an organ failure based
315 earlier approach instead of the traditional infection-centered delayed approach for the
316 management of ANP patients complicated by early POF.

317 Our small underpowered pilot study demonstrated a numerical decrease in organ
318 failure duration in the EOD group. However, we do acknowledge this was not
319 statistically significant. The primary hypothesis underlying the potential benefits of our
320 novel EOD approach is that timely intervention triggered by unremitted or worsening
321 organ failure could reduce the duration and severity of organ failure and therefore
322 improve outcomes. Schepers et al. showed that organ failure mostly developed during
323 the first week in ANP patients, and early POF is believed to be the most important
324 precursor to mortality[23]. Our findings are numerically consistent with our original
325 hypothesis and warrant a large trial to further clarify this critical finding.

326 Clinical concerns regarding the use of earlier PCD drainage mostly center about
327 inducing nosocomial infection. However, our results failed to show any increase in the
328 incidence of infected pancreatic necrosis, or any other infections, even though more
329 patients in the EOD group received PCD and PCD was begun much sooner. Moreover,
330 only one patient in the EOD group required open surgery, while five in the SM group
331 underwent operation, suggesting that more timely intervention may even obviate the
332 requirement for open surgery. Possible explanation may be that early intervention could

help control early infection, and therefore facilitate capsulation and following necrosectomy if needed. Moreover, early drainage of enzyme-riched fluid in the ANCs may alleviate erosion of vascular, thereby preventing abdominal bleeding, which may lead to emergency surgery[24].

Observational studies confirm the potential for benefits arising from earlier PCD. In a matched case-control study conducted by Oblizajek et al., the resolution of the collection was achieved in all patients undergoing early intervention, although they did not report the status of organ failure in their population[25]. In our study, more patients in the EOD group underwent early intervention (<4 weeks), mostly during their early third week from disease onset, which was within our expectation. The potential benefits early intervention could offer include: 1) relieving necrosis related systemic complications, which are at least partly caused by pro-inflammatory cytokines, chemokines, free radicals, etc. released by local necrotic collection[9, 26]; 2) resolution of pressure symptoms like severe intra-abdominal hypertension, which is an important predictor for unfavorable outcomes[27, 28] and; 3) timely drainage of early pancreatic infection, which was reported to be more common in patients with early POF[29, 30], that is, our study population.

This small pilot study has several limitations. First of all, the study was not powered enough to detect a difference in death/major complications. However, although small, this study does provide important safety information. In addition, as almost half of the patients in the EOD group did not receive PCD within 21 days of randomization, more focused selection criteria should be developed for future trials.

In conclusion, the substitution of the standard delayed approach with an EOD percutaneous drainage approach did not harm the study patients and may reduce major morbidity and mortality. These potential benefits warrant investigation in a subsequent trial adequately powered to find these potentially important treatment effects.

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Disclosure statement

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Figure legends：

Figure 1：Flow of enrollment, randomization, and follow-up of the study participants. ANC denotes acute necrotic collection, and WON denotes walled-off necrosis.

Figure 2: CT images of typical accessing routes for percutaneous catheter drainage of acute necrotic collections. A, A 14-Frech pig-tail catheter was placed in the right paracolic necrotic cavity; B. A 14-Frech pig-tail catheter was placed in the posterior gastric necrotic cavity; C. A 16-Frech pig-tail catheter was placed in the left anterior pararenal necrotic cavity. CT denotes computerized tomography

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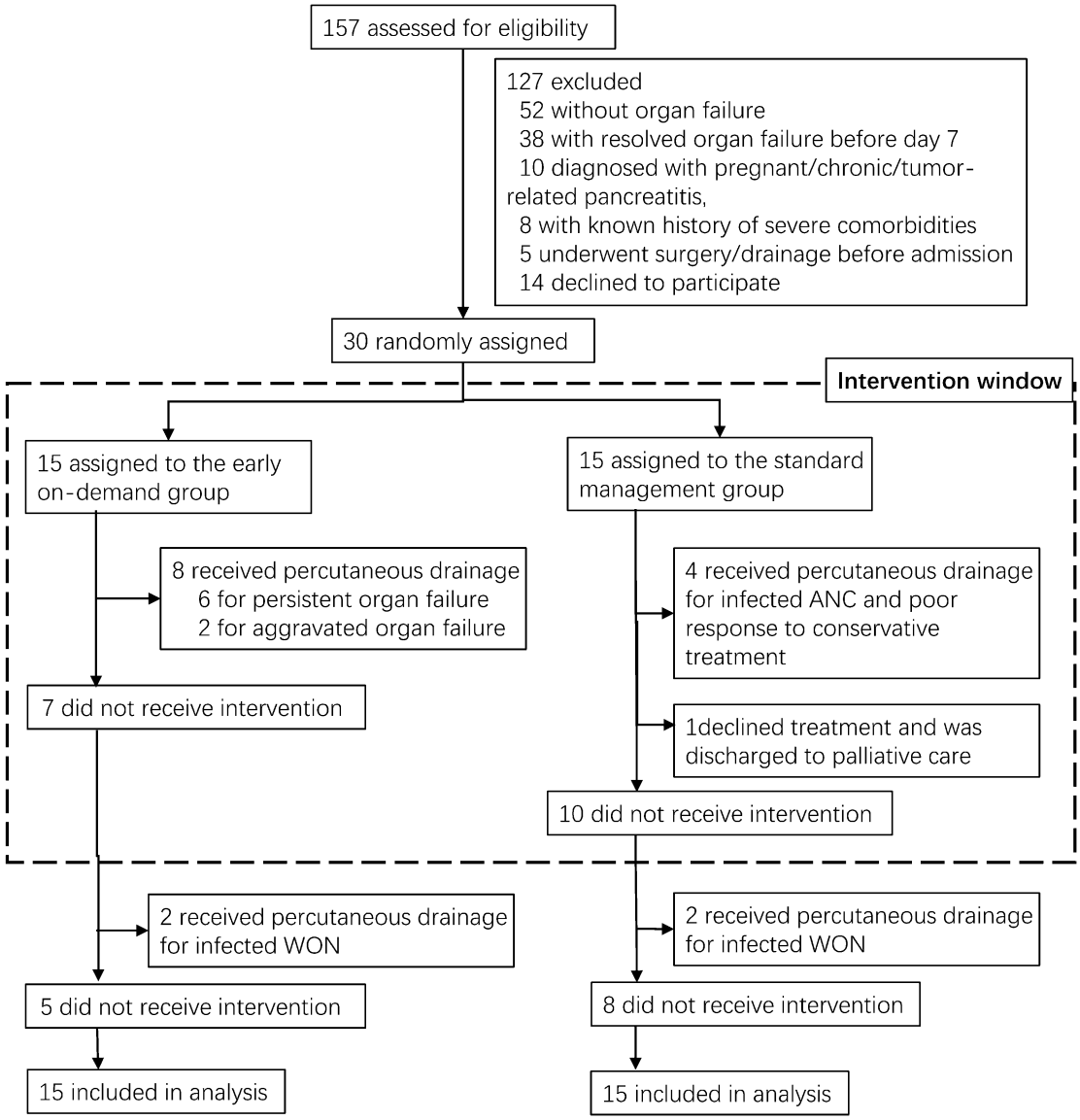

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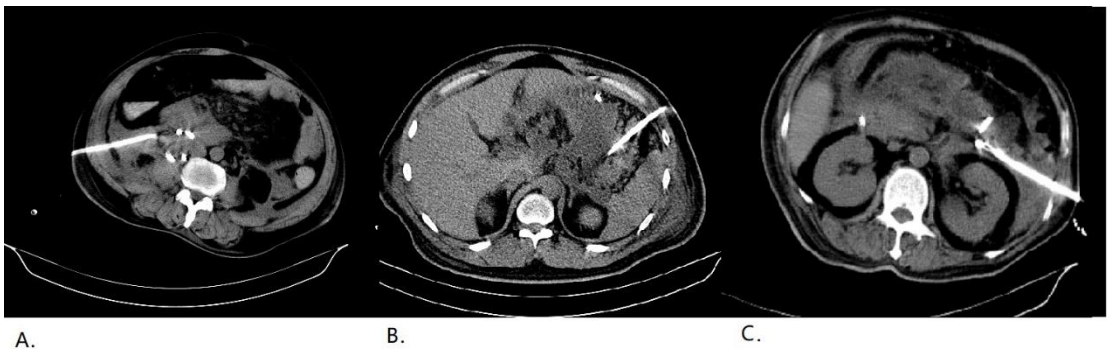

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Table 1：Baseline and demographic characteristics

	EOD group（N=15）	SM group（N=15）	*P* value
Age (years)	36 (28 to 50)	39 (31 to 51)	0.68
BMI (kg/m^2)	29.7 (26.5 to 30.9)	26.4 (23.7 to 30.1)	0.09
Gender			0.44
Male	11(73.3%)	9 (60%)	
Female	4 (26.7%)	6 (40%)	
Etiology			0.46
Biliary	7 (46.7%)	5 (33.3%)	
Hypertriglyceridemia	8 (53.3%)	10 (66.7%)	
APACH II at randomization	16 (7 to 18)	13 (10 to 20)	0.62
Charlson Score	1 (0 to 1)	1 (0 to 1)	0.65
Persistent organ failure at randomization			
Respiratory	15 (100%)	13 (93.1%)	0.48
Renal	10 (66,7%)	11 (73.3%)	1.00
Cardiovascular	5 (33.3%)	5 (33.3%)	1.00
Organ support at randomization			
Mechanical ventilation	12 (80.0%)	13 (86.7%)	1.00
RRT	11 (73.3%)	11 (73.3%)	1.00
Vasopressors	5 (33.3%)	5 (33.3%)	1.00
Size of ANC			
AP axis(cm)	5.78 (5.11 to 7.88)	6.11 (4.24 to 9.44)	0.486
Transverse axis(cm)	8.22 (6.41 to 15.82)	11.47 (6.69 to 14.23)	0.648
Extent of ANC			0.33
<30%	3 (20%)	2 (13.3%)	
30-50%	6 (40.0%)	3 (20%)	
>50%	6 (40.0%)	10 (66.7%)	
ANC extending to lower abdomen/pelvis	12 (80%)	13 (86.7%)	1.00

BMI: body mass index, EOD: early on-demand, SM: standard management, RRT: renal replacement therapy;

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Table 2： Primary and secondary endpoints

	EOD group（N=15）	SM group（N=15）	*P* value	Relative risk (95%CI)
Primary endpoint*				
Death and/or major complications	3(20%)	7 (46.7%)	0.25	0.43 (0.14-1.35)
Secondary endpoints				
Death	3 (20.0%)	6 (40.0%)	0.43	0.50 (0.15-1.64)
Death by Day180 after randomization	3 (20.0%)	6 (40.0%)	0.43	0.50 (0.15-1.64)
New-onset organ failure				
Respiration	0	2(13.3%)	0.48	
Renal	0	0		
Cardiovascular	1(6.7%)	3(20%)	0.60	0.33 (0.04-2.85)
Bleeding requiring intervention	2(13.3%)	2(13.3%)	1.00	1.00 (0.16-6.20)
Gastrointestinal perforation or fistulas requiring intervention	0	2(13.3%)	0.48	
Infected pancreatic necrosis	6 (40.0%)	7 (46.7%)	1.00	0.86 (0.38-1.95)
Sepsis	4 (26.7%)	7 (46.7%)	0.45	0.57 (0.21-1.55)
Pancreatic fistula	1 (6.7%)	1 (6.7%)	1.00	1.00 (0.07-14.55)
Length of ICU stay (day)	29 (19 to 42)	24 (16 to 40)	0.71	
Length of hospital stay(day)	35 (23 to 48)	32 (21 to 40)	0.54	

*All endpoints are reported within 90 days after randomization unless mentioned otherwise. EOD: early on-demand, SM: standard management

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Table 3： Interventions and medical resources utilization

	EOD group（N=15）	**SM group（N=15）**	***P* value**	**Relative risk (95%CI)**
New receipt of organ support*				
Respiration	0(0.0%)	2(13.3%)	0.48	
Renal	0(0.0%)	0(0.0%)	1.00	
Cardiovascular	1(6.7%)	3(20.0%)	0.60	0.33 (0.04-2.85)
Requirement for PCD	10(66.7%)	6(40.0%)	0.07	1.83 (0.92-3.66)
Requirement for MI necrosectomy	4(26.7%)	3(20.0%)	1.00	1.33 (0.36-4.97）
Requirement for open surgery	1(6.7%)	5(33.3%)	0.17	0.20 (0.03-1.51)
Requirement for reoperation	0 (0.0%)	2(13.3%)	0.48	
Emergency surgery	1(6.7%)	3(20.0%)	0.60	0.33 (0.04-2.85)
Total number of PCD procedures	1 (0 to 3)	0 (0 to 1)	0.16	
Total number of MI necrosectomy procedures	0 (0 to 1)	0 (0 to 1)	0.81	
Expense (thousand yuan)	336 (137 to 640)	316 (194 to 525)	0.74	

* All endpoints are reported within 90 days after randomization unless stated otherwise, EOD: early on-demand, SM: standard management, PCD: percutaneous catheter drainage; MI: minimally-invasive

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Table 4：Duration of organ failure and supportive measures between randomization and Day28(21 days)

	EOD group（N=15）	SM group（N=15）	*p* value
Median days alive and free of any OF	0 (0 to 11)	0(0 to 6)	0.46
Duration of organ failure			
Days alive and free of respiratory failure	7 (0 to 13)	0 (0 to 10)	0.49
Days alive and free of renal failure days	14 (0 to 21)	0 (0 to 21)	0.35
Days alive and free of cardiovascular failure	21 (19 to 21)	21 (18 to 21)	0.84
Duration of organ support			
Days alive and free of mechanical ventilation	12 (0 to 21)	10 (0 to 16)	0.62
Days alive and free of RRT	10 (0 to 21)	5 (0 to 21)	0.84
Days alive and free of Vasopressors	21 (19 to 21)	21 (18 to 21)	0.84

EOD: early on-demand, SM: standard management, OF: organ failure