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ORIGINAL

Early versus delayed catheter drainage for patients with necrotizing pancreatitis and early persistent organ failure (TIMING): a multicenter randomized controlled trial

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Abstract

Purpose: Acute necrotic collection (ANC) is an early, local complication of necrotizing pancreatitis, and guidelines recommend a deliberate delay in treating ANC. In patients with early persistent organ failure, such delay may be harmful. This study aimed to assess whether early intervention for ANC confers clinical benefits in this patient population.

Methods: This is a multicenter, open-label, randomized controlled trial. At 7 days after disease onset, patients with ANC and persistent organ failure were screened for: (1) organ failure lasting longer than 7 days; (2) organ failure worsening in severity; or (3) new-onset organ failure. If one or more criteria were met, they were randomized to receive either early percutaneous catheter drainage or standard care. The primary outcome was a composite of major complications and/or death during the index admission.

Results: Overall, 120 patients were randomized to early intervention ($N=63$) or standard care ($N=57$). There was no difference in the primary composite outcome (33.3% [21/63] versus 36.8% [21/57]; risk difference [RD] − 3.5%; 95% CI, − 20.6 to 13.6%) or the individual components, including mortality. The study groups did not differ in terms of organ failure free days to 21 days after randomization (4 days [interquartile range 0–14] versus 1 day [interquartile range 0–15]). The requirement for minimally invasive debridement and open surgery was comparable between groups.

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Conclusion: Early catheter drainage for ANCs in patients with necrotizing pancreatitis and early persistent organ failure, compared with standard delayed care, did not improve clinical outcomes. Future larger trials are needed to confirm our findings.

Keywords: Necrotizing pancreatitis, Acute necrotic collection, Organ failure, Early intervention

Introduction

Acute pancreatitis is a common gastrointestinal disease with a variable clinical course [1, 2]. While death arising from mild pancreatitis is very rare, the onset of severe acute pancreatitis is associated with a significant risk of mortality, ranging from 7.9 to 43.8% in different geographical areas [3]. Severe acute pancreatitis is defined by the presence of persistent organ failure lasting longer than 48 h [4]. Typically, organ failure develops in the first few days after disease onset [5] due to acute pancreatitis per se (sterile systemic inflammation) [6].

Many patients with severe acute pancreatitis develop acute necrotic collections (ANC), which is an early, local complication of necrotizing pancreatitis [3, 7]. Because it is accepted that most ANCs remain sterile and spontaneously resolve over time [8], early interventions have been contraindicated due to concerns about introducing infection [9]. The recommendation is for delayed intervention triggered by the onset of suspected or confirmed infection in clinically stable patients [9–11]. In patients with ANC and early organ failure, the symptoms of sterile inflammation and infection often overlap during the second and third weeks of the disease [12]. The observational data suggested that early intervention might confer multiple clinical benefits in this context [13]. This is physiologically plausible because: (1) infection of pancreatic necrosis can occur early [14]; (2) ANCs contain inflammatory mediators and activated pancreatic enzymes (including lipase-induced lipotoxicity) that help drive the systemic inflammatory response and multiple organ dysfunction [15]; (3) the presence of ANC contributes to intra-abdominal hypertension [16], which is associated with worse outcomes in acute pancreatitis [17]. However, there is a lack of objective evidence comparing the relative patient benefits from earlier versus delayed interventions in this population.

We conducted a small pilot trial [18] that demonstrated early percutaneous drainage, triggered by the development of organ failure rather than infected pancreatic necrosis, was safe, did not increase the risk of infection, and may improve clinical outcomes in patients with ANC and early persistent organ failure developed during the first week of the disease. Based on this preliminary data, we designed and conducted a multicenter, randomized, controlled trial to assess whether early intervention for ANC could improve clinical outcomes in patients with necrotizing pancreatitis complicated by early persistent organ failure. The clinical outcomes were assessed using a validated composite measure of major complications and survival [19, 20]. The main results of this trial were presented at the *European Pancreatic Club* (EPC) 2024 and published as an abstract [21].

Take-home message

Compared with standard care, early percutaneous drainage did not result in improved clinical outcomes in patients with necrotizing pancreatitis and early persistent organ failure. Current guideline recommendations for delayed intervention should be followed in this population to avoid harm.

Methods

Study design

The present trial was an investigator-initiated, open-label, parallel-group, randomized, controlled trial that was designed and conducted by the trial management committee. The members of the trial management committee are listed in the appendix (pp 3–5). The trial was endorsed by the Chinese Acute Pancreatitis Clinical Trials Group (capctg.medbit.cn).

The trial protocol was approved by the ethics committees of all the participating sites and was published previously [22]. The full protocols and the statistical analysis plan are available in the Supplemental files. The trial was registered with the Chinese Clinical Trials Registry before the commencement of patient enrollment (ChiCTR1800014963). All the patients or their next of kin provided written informed consent. An independent data safety and monitoring board was formed and reviewed the safety data every six months, given the study population was considered to be at high risk of death.

Participants

Patients between 18 and 70 years of age who were admitted to one of the five participating sites (all tertiary teaching hospitals with sufficient expertise) were assessed for eligibility. The patients who were diagnosed with acute pancreatitis [4] within 7 days of the onset of abdominal pain and had computed tomography (CT) confirmed ANCs, which could be accessed percutaneously, and who had persistent (at least 48 h) and unresolved organ failure

(respiratory, renal, or cardiovascular as per the Revised Atlanta Classification [4]) on day 7 after the onset of abdominal pain, were identified for additional screening. Organ failure in this study was defined by the modified Marshall score (respiratory and renal) or sequential organ failure assessment (SOFA) score ≥ 2 (cardiovascular) for the individual organ system.

The patients who were found to be pregnant, and had chronic pancreatitis or tumor-related pancreatitis, received intervention before admission to the study sites, and patients who had a history of cardiopulmonary resuscitation or severe comorbidities were excluded.

During the second and third week from the onset of the disease, the patients were enrolled and randomized after obtaining informed consent if at least one of the following three criteria were met: (1) the original organ failure worsened in severity; (2) the development of new-onset organ failure; (3) the original organ failure had now persisted for more than 7 days. The study patients were consecutively enrolled during the trial, except for the period between January and August 2020, when the trial recruitment was suspended due to the COVID-19 pandemic.

Randomization and masking

Permuted block randomization (variable block sizes of 4 and 6), stratified by the participating site, was used according to a computer-generated randomization sequence. The randomization assignments were put in sequentially numbered, sealed, opaque envelopes, which were opened after consent was obtained at the time of randomization. Envelope numbers and patient group assignments were audited at trial close-out [23].

The trial was open-label, given the nature of the study interventions. However, outcome assessors were blinded to patient allocation and the trial statistician was blinded at the time of analysis.

Procedures

In patients allocated to the early intervention group, image-guided (either CT or ultrasound) percutaneous catheter drainage was performed within 24 h of randomization. At least one drainage catheter with a size from 12 to 16F was placed to drain the ANC. Multiple drains were permitted if considered necessary. The percutaneous drain was audited on a daily basis and removed when the volume of drainage was no more than 50 mL for three consecutive days, while no infection of pancreatic necrosis was suspected or confirmed. Endoscopic drainage was not allowed as the initial intervention since it precludes volume audit.

In patients allocated to the standard care group, interventions, including catheter drainage and necrosectomy, were delayed until the patient developed suspected or confirmed infected pancreatic necrosis, preferably at least 4 weeks from the onset of the disease, when the necrosis was encapsulated [10]. Either percutaneous or endoscopic transluminal drainage was used as the initial intervention in standard care patients, depending on the site's preference.

In both groups, confirmed infected pancreatitis required a positive culture from a fine-needle aspiration or from the index percutaneous drain or the presence of gas configurations within pancreatic/peripancreatic necrosis on CT before intervention. Infected necrosis can be considered after the first two weeks of onset when there is persistence of inflammatory markers (body temperature > 38.5 °C or elevated C-reactive protein/procalcitonin levels) for at least three consecutive days [24].

Apart from the trial intervention, all study participants' treatment was consistent with international guidelines, including organ support treatments, nutrition therapy, and antibiotics [10]. Prophylactic antibiotics for infected pancreatic necrosis were not allowed, and antibiotics were given when infection was suspected or confirmed. The step-up approach was used to guide the treatment of infected pancreatic necrosis by either surgical or endoscopic debridement [20]. The decision to perform debridement of the infected necrosis, by either means, was made by the local treating physicians, and the need for open surgery was also determined by the local team.

Data were collected using a web-based electronic data capturing system (Unimed Scientific Inc., Wuxi, China). Before the commencement of patient recruitment, an educational start-up meeting was held at each participating site. The trial coordinating center was responsible for routine management to ensure compliance with the trial protocol and monitoring to ensure timely and accurate data collection.

Outcomes

The primary outcome was a composite outcome comprised of major complications and/or death occurring during the index admission. The major complications included new-onset organ failure (cardiovascular, renal, and respiratory), bleeding requiring intervention, and gastrointestinal perforation or fistula requiring intervention [20].

The secondary outcomes included: all individual components of the composite primary outcome; organ failure free days to 21 days after randomization; intra-abdominal pressure to 21 days after randomization; the incidence of infected pancreatic necrosis; onset of sepsis; symptomatic splanchnic vein thrombosis occurrence; pancreatic fistula occurrence, and procedure-related measures during the index admission. Based on the follow-up conducted 90 days after randomization, intensive care unit

(ICU) and hospital free days and 90-day landmark mortality were also reported. Detailed definitions of all study outcomes can be found in the published protocol [22] and the Supplementary files.

Statistical analysis

Using the data from our pilot trial, it was estimated that 50% of the trial participants undergoing standard care would experience a composite primary outcome event, and the treatment effect size was estimated at 25% absolute risk reduction (ARR) (50% relative risk reduction) [18]. Using the standard formula, it was estimated that a trial with 120 participants would provide 80% power to detect a 25% ARR at a standard two-sided *P* value level of 0.05 (PASS V.11, NCSS software, Kaysville, USA).

The primary analyses were based on the intention-to-treat (ITT) population. The sensitivity analyses were conducted on the per-protocol population (PP). Continuous data are reported as mean and standard deviation or as median and interquartile range (IQR), as appropriate. Normality was assessed by the Shapiro–Wilk test. Categorical data are expressed as numbers and percentages. The generalized linear model was employed to compare group differences and calculate the risk difference and relative risk for the primary outcome, together with its 95% confidence interval (CI). The primary analysis was additionally adjusted for a priori identified potential confounders, including age, sex, body mass index (BMI), SOFA, and CT severity score at randomization. In addition, we performed a post-hoc analysis to address potential baseline unbalances. Comparisons of baseline characteristics were performed using Fisher's exact test, Student's *t*-test, or Mann–Whitney's test as appropriate. Parameters with *P* values < 0.2 between groups were included for adjustment. The generalized linear model was also employed to analyze secondary outcomes. Kaplan–Meier curves were calculated to compare the cumulative incidence of mortality 90 days after randomization and assessed using the nonparametric log-rank test. The analyses were conducted using SAS (version 9.4). Statistical tests were two-sided, with a *P*-value of less than 0.05 deemed statistically significant.

Five subgroup analyses were stipulated a priori; these were in relation to (1) age (≥ 50 and < 50 years old); (2) sex; (3) hypertriglyceridemic vs. non-hypertriglyceridemic; (4) extent of pancreatic necrosis (> 50% and ≤ 50%) and (5) CT severity score (≥ 8 and < 8).

Results

Enrollment, randomization, and treatment

During the study period, a total of 531 patients with necrotizing pancreatitis were screened for eligibility, and 120 patients were enrolled and randomized. Sixty-three patients were allocated to the study intervention and 57 were allocated to receive standard care. The first patient was randomized on March 13, 2019 and the last patient was enrolled on April 20, 2022, with follow-up completed on July 10, 2022. All the patients were successfully followed up until the index hospital discharge or death. The numbers of cases from each site are shown in the supplementary appendix (p 12, Table S1).

The baseline characteristics of the study patients are reported in Table 1. The median age of the study patients was 42 (IQR 34–50) years old, and 76.7% (92/120) were male. Fifty-four percent of patients (65/120) presented with hypertriglyceridemia as the cause of acute pancreatitis and the most common type of organ failure was respiratory failure (96.7%, 116/120).

Two patients in the early intervention group did not receive the study intervention: one patient's family withdrew consent to the study intervention but explicitly provided consent to follow-up, and the second patient resolved spontaneously overnight and was transferred to the ward. Surgical intervention was considered unnecessary in this patient. One patient in the standard care group had an intervention 4 days after randomization without indication for either emergency intervention or suspicion of infection. Follow-up was completed in all the three patients and they were included in the ITT analysis (Fig. 1). The imaging characteristics of ANCs at randomization for both groups are shown in Table S2. After the trial intervention, the median maximum diameters of the ANCs in the long axis were reduced from a median of 9 (IQR 7–10) cm to 7 (IQR 5–8) cm, and in the short axis was reduced from a median of 5 (IQR 4–6) cm to 4 (IQR 3–4) cm. The post intervention CT was obtained at a median of 8 (IQR 7–10) days after the trial intervention. The daily drainage volume from ANCs gradually decreased from a median of 300 (IQR 100–500) mL on Day 1 to 220 (IQR 100–437.5) mL on Day 7 (supplementary appendix p14, Table S3).

Primary and secondary outcomes

During the index admission, the primary composite outcome occurred in 33.3% (21/63) of patients in the early intervention group and 36.8% (21/57) of patients in the standard care group (risk difference [RD], −3.5%; 95% CI, −20.6% to 13.6%; *P* = 0.69; Table 2). Adjustment for prespecified potential confounders and potential baseline unbalances did not change these results (Table 2).

In-hospital mortality was 22.2% (14/63) in the early intervention group and 19.3% (11/57) in the standard care group (RD 2.9%; 95% CI, −11.6% to 17.4%; *P* = 0.69; Table 2). Mortality also did not differ on study Day 90 (14/63 vs. 12/57, *P* = 0.88; supplementary appendix p 9, Fig. S1). None of the individual components of

Table 1 Baseline characteristics of the intention-to-treat population

Characteristics	Early intervention (*N* = 63)	Standard Care (N = 57)
Age (years)	43 (35–49)	41 (32–49)
Sex		
Female	16 (25%)	12 (21%)
Male	47 (75%)	45 (79%)
BMI (kg/m^2)	27.8 (24.2–29.6)	26.6 (24.2–29.4)
Aetiology		
Alcoholic	2 (3%)	3 (5%)
Biliary	24 (38.1%)	20 (35.1%)
Idiopathic	3 (4.8%)	3 (5.3%)
Hypertriglyceridemia	34 (54.0%)	31 (54.4%)
The interval between AP onset and hospital admission (days)	3 (2–5)	4 (2–5)
The interval between AP onset and randomization (days)	9 (8–10)	9 (8–10)
APACHE II score	15 (10–18)	16 (10–19)
Modified SOFA* score	4 (3–7)	5 (3–7)
Abdominal pressure (mmHg)	15.0 (12.0–18.0)	15.0 (11.5–18.0)
CTSI score	8 (6–8)	8 (6–8)
Bacteremia	4 (6.3%)	5 (8.8%)
Presence of organ failure		
Respiratory	52 (82.5%)	51 (89.5%)
Renal	31 (49.2%)	31 (54.4%)
Cardiovascular	12 (19.0%)	16 (28.1%)
Receipt of organ support		
Mechanical ventilation	44 (69.8%)	31 (54.4%)
Renal replacement therapy	22 (34.9%)	17 (29.8%)
Vasopressors	12 (19.0%)	16 (28.1%)

Data are *n* (%) or median (IQR)

IQR Interquartile Range, *BMI* Body Mass Index, *AP* Acute Pancreatitis, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *CTSI* Computed Tomography Severity Index

* Only respiratory, renal and cardiovascular systems were involved

the primary outcome differed between groups (Table 2). The results from the PP population did not differ from the ITT population (supplementary appendix pp 15–17, Table S4).

The study groups did not differ in terms of organ failure free days to 21 days after randomization (4 [IQR 0–14] days versus 1 [IQR 0–15] days; $P = 0.98$; Fig. 2) or the development of intra-abdominal pressure after the study intervention (supplementary appendix p 10, Fig. S2). The study groups did not differ in terms of ICU- and hospital-free days, occurrence of infected pancreatic necrosis, or the other secondary outcomes, including sepsis, pancreatic fistula, and symptomatic splanchnic vein thrombosis (see Table 2 for complete details).

In the standard care group, 56.1% (32/57) of patients were treated conservatively without any invasive intervention, whereas 96.8% (61/63) of the patients allocated to an early intervention actually received an invasive intervention. The study groups did not differ with regard to the requirement of minimally invasive debridement or open/laparoscopic surgery, the number of drainage or debridement procedures, or costs (see Table 2 for complete details).

Adverse events and serious adverse events

The early intervention group had a significantly higher incidence of overall adverse events (25.4% [16/63] versus 12.3% [7/57]; $P = 0.007$; supplementary appendix pp18–19, Table S5). Serious adverse events were not different between the groups (4.8% [3/63] in the early intervention group versus 1.8% [1/57] in the standard care group, $P = 0.621$; Table S5).

Subgroup analyses

The five prespecified subgroup analyses did not demonstrate any significant treatment effect (supplementary appendix p 11, Fig. S3).

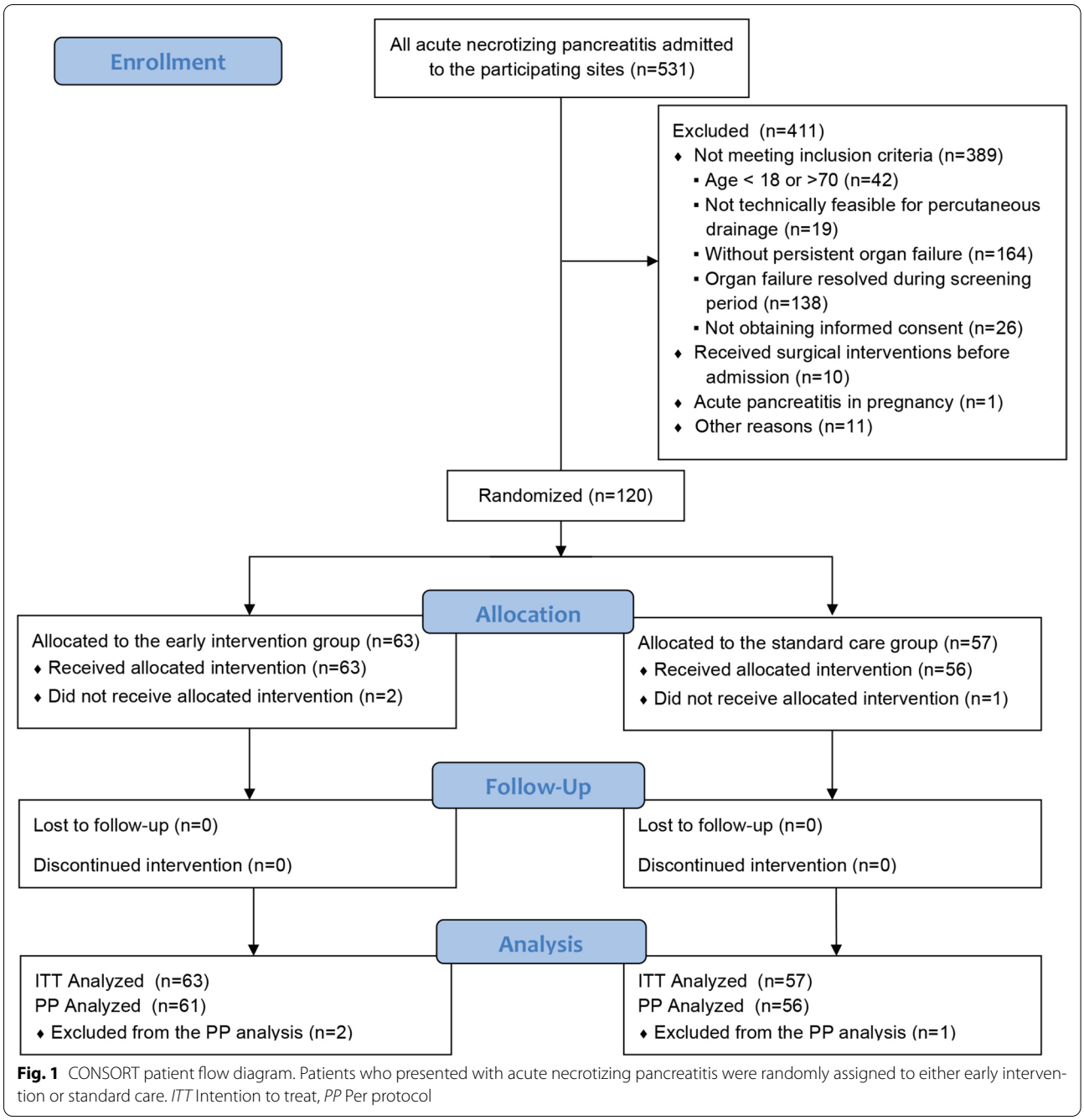

Fig. 1 CONSORT patient flow diagram. Patients who presented with acute necrotizing pancreatitis were randomly assigned to either early intervention or standard care. *ITT* Intention to treat, *PP* Per protocol

Discussion

This multicenter, randomized trial compared early intervention for ANC in patients with necrotizing pancreatitis complicated by early persistent organ failure to standard delayed care. Early image-guided percutaneous catheter drainage did not decrease the incidence of the composite primary outcome (major complications and/or death). In the standard care group, almost half of the patients resolved without intervention. The results of the current trial do not provide any evidence to support the original hypothesis that early intervention may improve clinical outcomes in this specific subgroup of patients who have a high risk of death and complications [25, 26].

Delayed intervention indicated for suspected or confirmed infected pancreatic necrosis is the current guideline-recommended standard of care for patients with necrotizing pancreatitis. However, this approach can face significant challenges in patients with persistent organ

Table 2 Primary and secondary outcomes according to the intention-to-treat analysis

	Early intervention (*N* = 63)	Standard care (*N* = 57)	Treatment effect* (95% CI)	*P* value
Primary composite outcome				
Death and/or major complications (during the index admission) – no. (%)				
Unadjusted	21 (33.3%)	21 (36.8%)	− 3.5 (− 20.6 to 13.6)	0.69
Adjusted model 1[a]			0.91 (0.49 to 1.70)[b]	0.76
Adjusted model 2[c]			− 7.5 (− 24.0 to 9.0)	0.37
Individual components of the primary outcome				
Death (in hospital)	14 (22.2%)	11 (19.3%)	2.9 (− 11.6 to 17.4)	0.69
Major complications	15 (23.8%)	18 (31.6%)	− 7.8 (− 23.8 to 8.2)	0.16
New-onset organ failure	6 (9.5%)	8 (14.0%)	− 4.5 (− 16.1 to 7.1)	0.45
Respiratory	0	0	. .	. .
Renal	0	2 (3.5%)	. .	. .
Cardiovascular	6 (9.5%)	7 (12.3%)	− 2.8 (− 13.9 to 8.4)	0.42
Bleeding requiring intervention	11 (17.5%)	9 (15.8%)	1.7 (− 11.7 to 15.0)	0.91
Gastrointestinal perforation or fistula requiring intervention	6 (9.5%)	7 (12.2%)	− 2.8 (− 13.9 to 8.4)	0.79
Secondary outcomes				
Clinical outcomes				
Death (90 days)	14 (22.2%)	12 (21.0%)	1.2 (− 13.6 to 15.9)	0.88
Death or presence of organ failure on Day 14 after randomization	39 (61.9%)	29 (50.9%)	11.0 (− 6.6 to 28.7)	0.22
Death or presence of organ failure on Day 21 after randomization	27 (42.9%)	27 (47.4%)	− 4.5 (− 22.3 to 13.3)	0.62
Infected pancreatic necrosis	32 (50.8%)	24 (42.1%)	8.7 (− 9.1 to 26.5)	0.34
Sepsis	16 (25.0%)	11 (19.3%)	6.1 (− 8.8 to 20.9)	0.42
Pancreatic fistula	14 (22.2%)	8 (14.0%)	8.2 (− 5.5 to 21.9)	0.24
Splanchnic vein thrombosis (symptomatic)	2 (3.2%)	3 (5.3%)	− 2.1 (− 9.3 to 5.1)	0.57
ICU-free days to Day 90, days	67 (36–76)	65 (12–75)	MD: 0 (− 4 to 7)	0.60
Hospital-free days to Day 90, days	39 (0–67)	45 (0–67)	MD: 0 (− 10 to 6)	0.75
Outcomes related to interventions and resource utilization				
The interval between disease onset and initial intervention, days[d]	9 (8–10)	17 (12–23)	MD: − 8 (− 10 to − 6)	< 0.001
Receipt of PCD	61 (96.8%)	25 (43.9%)	53.0 (39.4 to 66.6)	< 0.001
Receipt of Endoscopic drainage	2 (3.2%)	1 (1.8%)	1.4 (− 4.1 to 6.9)	0.61
Receipt of MI debridement	18 (28.6%)	12 (21.1%)	7.5 (− 7.8 to 22.9)	0.34
Receipt of open surgery	6 (9.5%)	4 (7.0%)	2.5 (− 7.3 to 12.3)	0.62
Receipt of reoperation	2 (3.2%)	1 (1.8%)	1.4 (− 4.1 to 6.9)	0.61
Total number of drainage procedures[d]	3 (2–6)	4 (2–6)	MD: 0 (− 1 to 1)	0.39
Total number of MI debridement procedures[d]	2 (2–3)	2 (1–4)	MD: 0 (− 1 to 1)	0.63
Total cost, 1000$	34.4 (19.4–61.1)	29.9 (15.1–62.5)	MD: 3.1 (− 6.6 to 13.5)	0.93

Data are *n* (%) or median (IQR)

IQR Interquartile Range, *ICU* Intensive Care Unit, *CI* Confidence Interval, *MD* Median Difference, *BMI* Body Mass Index, *SOFA* Sequential Organ Failure Assessment, *CT* Computed Tomography, *PCD* Percutaneous Catheter Drainage, *MI* Minimally Invasive

* Reported as risk difference unless otherwise specified

[a] Adjusted model 1 was adjusted for age, sex, BMI, SOFA, and CT severity score at randomization

[b] Reported as relative risk since risk difference was not available in the adjusted Generalized Linear Model due to not converging

[c] Adjusted model 2 was adjusted for receipt of mechanical ventilation at enrollment

[d] Calculated in patients receiving the corresponding procedures

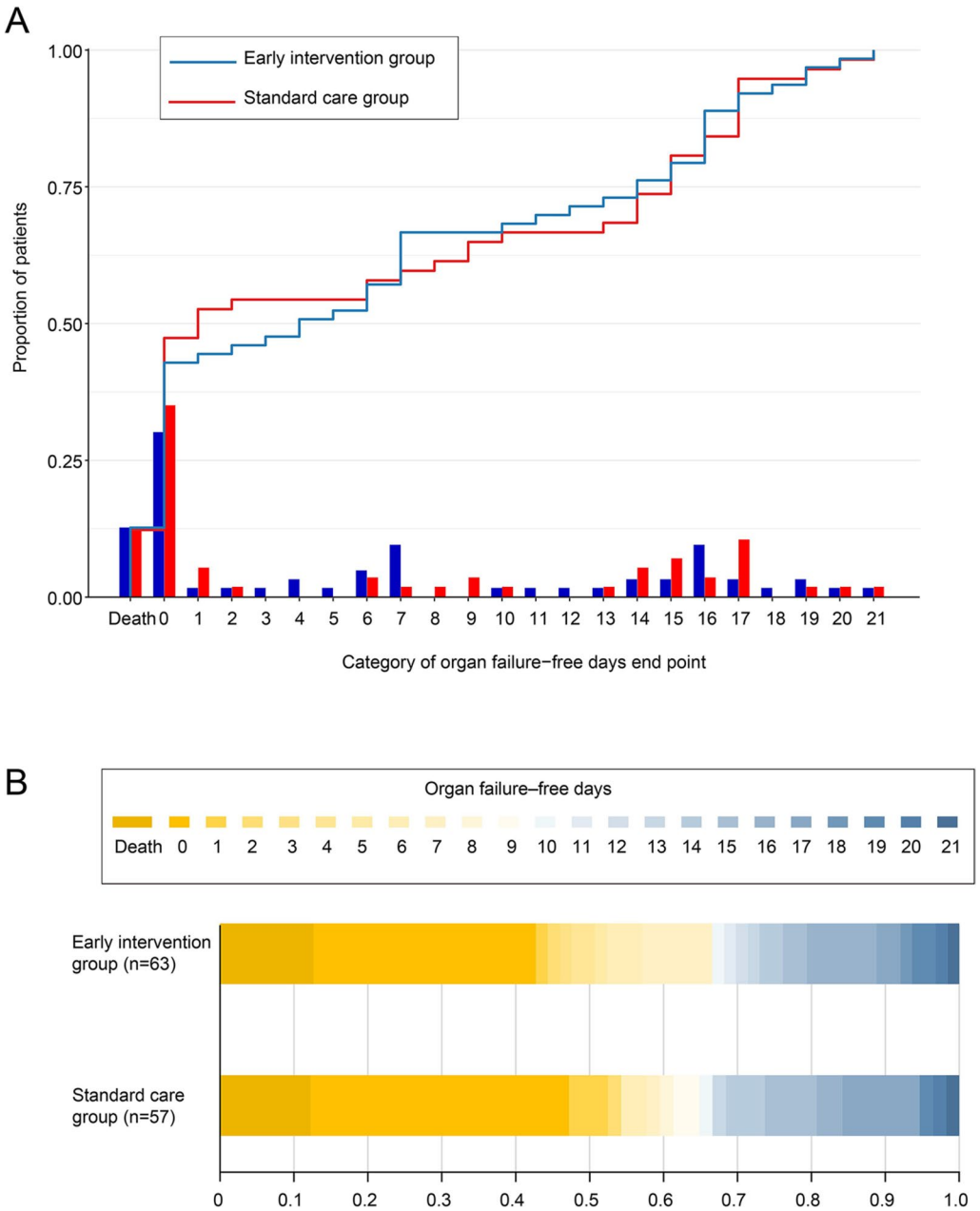

Fig. 2 The organ failure free days (alive and without organ failure) to trial Day 21 after randomization. **Panel A** the ordinal scale includes death (the worst outcome) and a score of 0 to 21 (the number of days alive and without organ failure) as the cumulative proportion (y-axis) for each group by day (x-axis). The height of each curve at the "Death" point reflects the mortality during the first 21 days after randomization for that group. On any given day, the height of the curve represents the proportion of patients who experienced that number or fewer organ failure free days (e.g., at Day 7, the height indicates the proportion of patients with ≤ 7 organ failure free days). The distance between curves illustrates differences in outcomes across groups. **Panel B** provides a visual comparison of outcomes using color-coded bars: blue shades indicate more organ failure free days (better outcomes), and yellow shades indicate fewer days (worse outcomes). The darkest blue corresponds to 21 full days without organ failure, while the darkest yellow indicates zero days

failure extending to the second week of the disease since systemic inflammation-related organ failure can hardly be distinguished from infection-related organ failure in this stage [9, 10]. Previous studies [13, 27] and our pilot trial [18] suggested that early intervention might confer clinical benefits in patients with ANC and organ failure. The feasibility and justification for such a trial have also been promoted by the development of minimally

invasive (surgical and endoscopic) drainage and debridement techniques [28], which are less likely to incite new-onset organ failure as occurred with open surgery [20]. To ensure safety, we did not mandate a specific technical approach (surgical or endoscopic) for drainage and debridement of infected pancreatic necrosis except for the trial intervention. Though this design may bring in some bias, the landmark TENSION trial showed that the choice of technical approach did not affect the primary outcome of this trial [19]. Until now, there have been no large-scale RCTs published investigating whether there is any benefit with early intervention in patients with necrotizing pancreatitis and early persistent organ failure, noting that the target lesion has not yet encapsulated and infection may not have occurred. The present trial was designed to address this gap.

The Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis (POINTER) trial compared immediate drainage within 24 h once infected necrosis was diagnosed, with drainage that was postponed until the stage of 'walled off' or encapsulated [29]. Results from this milestone trial failed to show any benefit from immediate drainage over postponed drainage, while it did report that 35% of patients with infected pancreatic necrosis could be successfully treated with antibiotics only [29]. The negative results of the POINTER trial are consistent with the results of the current trial, but the research question and the trial setup differ significantly in several key aspects: (1) In the POINTER trial, study patients had less severe acute pancreatitis, with only 20% (21 of 103) patients having organ failure at baseline, whereas all participants in the current trial had organ failure; (2) The intervention in the POINTER trial was indicated for infected peripancreatic or pancreatic necrosis, while in the current trial, early drainage was triggered by the development of organ failure; (3) The median intervention timing in the "immediate" group was beyond the third week in the POINTER trial (24 days) but early drainage occurred within the second week in the current trial (9 days). Taken together, both trials do not provide evidence that current guideline recommendations for delayed intervention should be altered [9].

The trial has several strengths and limitations: first, although this patient population is relatively rare and the trial was suspended during the COVID-19 pandemic, which may lead to selection bias, recruitment across five high-volume sites allowed us to achieve the target sample size. However, the relatively small sample size ($N=120$) and the number of participating sites ($N=5$) means that the mortality may not be representative or generalizable. Also, the sample size calculation was based on a small pilot trial of 30 patients and may have been overly optimistic given the degree of imprecision arising from the small pilot trial. Therefore, larger randomized trials are needed to confirm our findings in the future. Second, the predominant etiology of pancreatitis in almost half of the study patients was hypertriglyceridemia. Although this distribution may be different from the global distribution, which may impact the generalizability of the results from the current trial, our a priori planned subgroup analysis based on etiology (Fig. S3) did not show a strong signal of a differential treatment effect. Third, standard care concerning the intervention for ANC at our study sites was relatively uniform as treating clinicians were comfortable withholding interventions until the onset of apparent signs of infection in standard care patients based on international guidelines and consensus [9, 10]. However, the median timing of intervention in the control group (calculated in 25/57 patients who had intervention) was only 8 days later than the trial intervention, which may have influenced the results.

Given the known high risk of mortality due to persistent organ failure in the study population [3, 5], the most important research priority is early intervention or treatment to decrease the incidence and duration of organ failure. The question posed in this trial was whether earlier intervention for ANC (may or may not infected) in patients with persistent organ failure would improve clinical outcomes. Given the findings of this trial and the POINTER trial, this seems improbable.

Conclusion

In conclusion, early catheter drainage for acute necrotic collections in patients with necrotizing pancreatitis and early persistent organ failure, compared with standard delayed care, did not improve clinical outcomes. Given that the current trial is likely underpowered, future larger trials are needed to confirm our findings and provide definite evidence.

Supplementary Information

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Author contributions
The TIMING trial was designed by WL, JW, ZT and LK. WL, ZT, LK, GL, CQ,WM, WH, LX, FG, YL, QF, ZL, BL and YZ collected the data. ZT obtained the funding. LK and GL provided the technical support. WM, CL, TC and GD provided methodology support. WL, ZT and LK supervised this trial. TC and CL supervised the statistical analysis. TC, CL, LK, GL, WM, LW and LG accessed and verified all data analysis and produced the manuscript figures and tables. LK and the writing committee wrote the manuscript. GD, SJ, GP, YL and JW reviewed and edited the drafts of the paper. WL and ZT are joint corresponding authors and the guarantors. All authors had final responsibility for the decision to submit for publication. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials
Deidentified individual participant data are available indefinitely in the electronic database. Data can be accessed through capctg.medbit.cn with the approval of the authors. The study Protocol and Statistical Analysis Plan are included as supplement files and are available in the online version of this article.

Declarations

Conflicts of interest
Dr. Weiqin Li reports consultancy fees from Nutricia. Dr. Lu Ke reports speaker fees from Nhwa Pharmaceuticals. Dr. Jaber is the Editor in Chief of Intensive Care Medicine. He has not taken part in the review or selection process of this article. Dr. Jaber also reports receiving consulting fees from Drager, Medtronic, Mindray, Fresenius, Baxter, and Fisher & Paykel. Dr. Windsor reports consulting fees and grants from Fisher and Paykel Healthcare and Viatris Ltd. The other authors have no relevant conflict of interest to declare.

Ethical approval
This study was approved by the ethics committee of the Jinling Hospital (2018NZKY-009-04). The study protocol received approval from the ethics committees of all participating centers, adhering to local laws and the Declaration of Helsinki.

Consent to participate
Consent to participate was provided prospectively from all participants or their next of kin. The signed consent forms for all participants included consent to publication of aggregate data. The authors all consent to publication of the manuscript.

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