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Original article

Clinical outcomes of combined necrotizing pancreatitis versus extrapancreatic necrosis alone

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ABSTRACT

Introduction: Extrapancreatic necrosis (EPN) alone, i.e., in the absence of pancreatic parenchyma necrosis has gradually come to be regarded as a separate entity of acute necrotizing pancreatitis (ANP). However, data regarding the prognostic significance of EPN are quite limited, and the outcomes of interventions for patients with EPN alone are not well elucidated. The aim of this study was to explore the differences in the outcomes of patients with EPN alone and patients with both the pancreatic parenchyma and extrapancreatic necrosis (combined necrosis).

Methods: From January 2009 to December 2013, a total of 334 patients with ANP who had received interventions in the West China Hospital in China were included. Based on the extent of necrosis as assessed with contrast-enhanced CT, the patients were divided into Group 1 ($n = 285$) in which the necrosis involved both the pancreatic parenchyma and extrapancreatic tissues (combined necrosis) and Group 2 ($n = 49$) in which the necrosis involved only the extrapancreatic tissues. Additionally, Group 3 included 443 patients with interstitial pancreatitis who were also included in the analyses. The demographic characteristics, support treatment information, organ failure information, infection necrosis, persistent systemic inflammatory response syndrome (SIRS) in the first week of onset, CT severity index, and intervention types, as well as the postoperative stay lengths, ICU utility, and complications were collected and compared.

Results: Compared with the patients in Group 1, the patients in Group 2 suffered less persistent SIRS in the first week of onset (12/24.5% vs. 145/50.9%; $P < 0.05$), less persistent organ failure (6/12.2% vs. 95/33.3%; $P < 0.05$), less persistent multiple organ failure (3/6.1% vs. 67/23.5%; $P < 0.05$), and less bacteremia (5/10.2% vs. 107/37.5%; $P < 0.001$). The intervention types were significantly different between the two groups ($P < 0.001$); initial open necrosectomy was performed in 174/61.6% and 8/16.3% of the patients in Groups 1 and 2, respectively, and initial percutaneous catheter drainage (PCD) was performed in 73/25.6% and 29/59.2% of the patients in the two respective groups. Second open necrosectomies following PCD were required in 61/83.5% and 9/31.0% of the patients in Groups 1 and 2, respectively ($P < 0.001$). A greater number of patients in Group 1 were diagnosed with infected necrosis (204/71.6% vs. 10/20.4%; $P < 0.001$) and had to be sent to the ICU for further postoperative care (221/77.5% vs. 23/46.9%; $P < 0.001$). The postoperative stay was longer for Group 1 (median: 43.0 vs. 26.5 days; $P < 0.001$). Residual necrotic tissue or abscess was the most common postoperative complication in both groups. The mortality was higher in Group 1 (52/18.2% vs. 1/2.1%; $P < 0.05$). Compared with the patients in Group 2, the patients with interstitial pancreatitis exhibited milder courses and better outcomes. Subgroup comparisons with Group 1 indicated that early multiple organ failure was significantly associated with higher mortality.

Conclusion: The patients with EPN alone exhibited significantly better prognoses than those with combined necrosis, and EPN alone should be regarded as a separate group of acute necrotizing pancreatitis. Open necrosectomy can be avoided in the majority of patients with EPN alone, who receive PCD as the initial first intervention.

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Introduction

Acute pancreatitis (AP) is a common inflammatory disorder of the pancreas with an increasing global incidence [1] and unpredictable and varied outcomes [2]. According to the widely accepted Atlanta Classification, AP can be divided into two types, i.e., interstitial odematous pancreatitis (IP) and necrotizing pancreatitis (NP). Approximately 5–10% of patients with AP will develop necrotizing pancreatitis [3]. Compared with those with IP, patients with NP often exhibit worse outcome parameters, such as longer hospital stay, greater morbidity, and greater mortality because the majority of patients with NP develop organ failure and life-threatening infections, and both of these conditions are major factors that are associated with poor prognoses [4,5].

Necrosis involving both the pancreatic parenchyma and extrapancreatic tissue (combined necrosis) is the most common manifestation of NP followed by necrosis of only the extrapancreatic tissue and the necrosis of the pancreatic parenchyma alone [3]. Howard and Wagner first recognized extrapancreatic necrosis (EPN) without pancreatic parenchyma necrosis in 1989. Since that time, EPN alone without parenchymal necrosis has gradually come to be regarded as a separate entity of NP [6]. Previous studies have suggested that patients with EPN alone exhibit more benign courses and better outcomes [7,8]. However, patients with EPN can also develop infected necrosis, and all patients with infected necrosis should undergo interventions. Open necrosectomy has long been the traditional intervention for such cases [9,10].

To our best knowledge, the published literature regarding the prognostic significance of EPN is quite limited, and the intervention outcomes of patients with EPN alone are not well elucidated. We conducted this retrospective comparative study to explore the differences in the outcomes between patients with EPN alone, patients with combined necrosis and patients with IP.

Methods and materials

Patients

During the study period from January 2009 to December 2013, a total of 344 consecutive patients diagnosed with acute necrotizing pancreatitis who underwent interventions at the West China Hospital following initial consultations in our emergency department were reviewed. The diagnoses of acute pancreatitis were based on the revised Atlanta Classification [3]. The necrotizing pancreatitis definition included both pancreatic parenchymal necrosis with and without peripancreatic necrosis and peripancreatic necrosis alone based on contrast-enhanced CT (CECT). Because the present study focused on the different intervention outcomes between the combined necrosis and EPN groups, the patients with NP who responded to conservative treatments, and the patients with NP who received their initial interventions in other hospitals ($n = 10$) were excluded. The patients were divided into two groups based on the extent of necrosis. Specifically, the patients with both pancreatic parenchymal necrosis and EPN were diagnosed with combined necrosis (Group 1), and the patients with EPN alone comprised Group 2. To compare the outcomes of the patients with EPN and the patients with interstitial pancreatitis, a total of 443 patients with interstitial pancreatitis who were treated in our hospital from July 2013 to December 2013 for whom complete data were available were also included (the inclusion and exclusion criteria are illustrated in Fig. 1). Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of Sichuan University.

Treatment protocol

Following admission, laboratory tests, including routine hematology and biochemical evaluations, coagulation blood tests, and arterial blood gas tests and excluding interleukin-6 (IL-6) and procalcitonin assays were performed to evaluate the severity of acute pancreatitis. All parameters of the modified Marshall scoring system and systemic inflammatory response syndrome (SIRS) were recorded daily within the first week of onset [3]. Because many patients were admitted via transfers from other hospitals in the days to weeks following the onset of acute pancreatitis, all of the parameters of the Acute Physiology and Chronic Health Examination (APACHE) II scoring system were recorded at the time of admission to our hospital. Body temperature was measured at least 3 times per day, and blood cultures were performed when these temperatures exceeded 38.0 °C.

Conservative treatments, including fluid resuscitation, the administration of analgesics, oxygen, and antiemetics, etc. were initiated for all patients following admission. Intravenous antibiotics were administered for no more than 7 days unless the patient exhibited persistent clinical manifestations of sepsis. Aggressive fluid resuscitation was initiated during the first 72 h to maintain electrolyte and acid–base homeostasis. The total rates and volumes of intravenous fluid administration were controlled to maintain hemodynamic stability. A stable hemodynamic status was defined as a central venous pressure (CVP) of 8–15 mm Hg [or a mean arterial pressure (MAP) of 65–85 mm Hg when the CVP was not available], a urine output more than 0.5 mL/kg per h, or a systolic blood pressure (SBP) greater than 90 mm Hg. Fluids for resuscitation included normal saline (NS), Ringer's lactate (RL), 6% hydroxyethyl starch (HES) 130/0.4 (Voluven, Fresenius Kabi, Germany) and plasma when necessary. Crystalloids and colloids were infused at volume ratios of 2:1 to 3:1.

Nutrition was provided following adequate fluid resuscitation (typically within 48–72 h). According to the European Society for Clinical Nutrition and Metabolism guidelines [11], parenteral nutrition (PN) was first applied for the patients who were not expected to receive normal nutrition within 3 days, when enteral nutrition (EN) was contraindicated, and when the patients could not tolerate EN. Combined (i.e., enteral and parenteral) nutrition was initiated following the recovery of gastrointestinal tract functions from paralysis. Parental nutrition was provided through a central venous catheter (CVC) or peripherally when a CVC was not available within 24–48 h of admission. This nutrition was composed of a calorie source (25–30 kcal/kg/day) consisting of 50–70% carbohydrates, 30–50% lipids [20% Lipovenoes (medium/long chain fat emulsion)], and 1.5 g/kg proteins. Enteral nutrition gradually progressed from clear water to low-fat semi-element nutrition and high predigested protein nutrition and was administered through a radiologically placed nasojejunal tube distal to the Treitz ligament. For patients with IP, oral refeeding was the first choice for nutritional support.

During the conservative treatment, CECT was performed when a patient began to exhibit persistent clinical manifestations of sepsis or 7–10 days after onset. CECT examinations were repeated when abdominal pain, severe clinical deterioration, or the clinical signs persisted or recurred. The patients who developed organ failure were sent to the ICU. Routine fine-needle aspiration was not performed on the patients with necrotizing pancreatitis unless infected necrosis could not be excluded.

CT evaluation

The CECT results were evaluated by a professional radiologist and experienced surgeons before the application of any intervention.

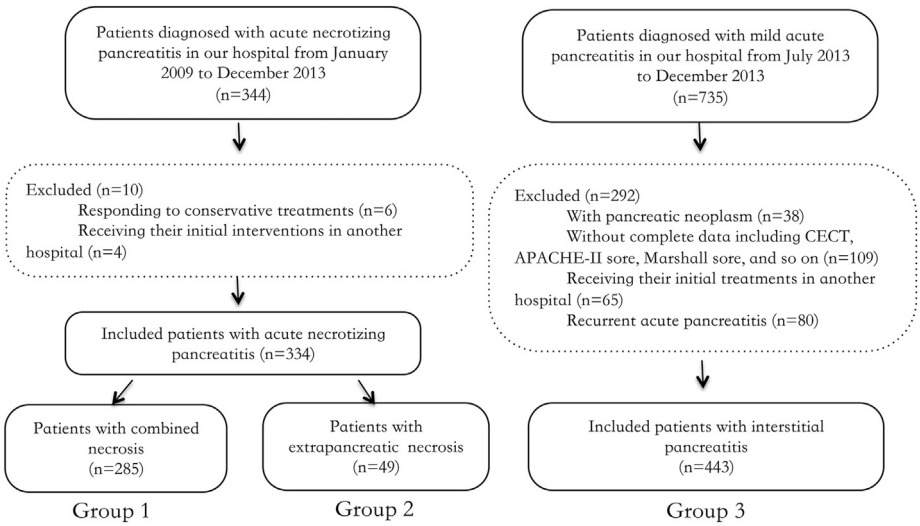

Fig. 1. Inclusion and exclusion criteria.

Pancreatic necrosis was defined as focal or diffuse non-enhancement in the pancreas. EPN alone without pancreatic parenchymal necrosis was defined by extrapancreatic changes exceeding fat stranding with complete enhancement of the pancreatic parenchyma (Fig. 2). The patients with both pancreatic parenchymal necrosis and EPN were diagnosed with combined necrosis (Fig. 3). Infected necrosis was presumed if the presence of extraluminal gas in the pancreatic and/or peripancreatic tissues was observed.

Indications for the interventions

Confirmed infection and suspected infection were the indications for the interventions. Prior to any intervention, experienced surgeons discussed the potential interventions with the radiologist in terms of the intervention type (i.e., open pancreatic necrosectomy (OPN), retroperitoneal pancreatic necrosectomy (RPN), or primary percutaneous catheter drainage (PCD) with pigtail plastic stents) and timing. The timing of the intervention was postponed until approximately 4 weeks after the onset of AP whenever possible. Abdominal compartment syndrome (ACS) in the early course of the disease was not considered an indication for emergency laparotomy except in cases of perforation or bleeding of a visceral organ.

Data collection

Detailed data, including age, gender, etiology, the preoperative details [i.e., body mass index (BMI), American Society of Anesthesiology (ASA) score, APACHE-II score, the incidence of persistent SIRS, organ failure information, laboratory blood tests, the number of CECT examinations performed prior to any intervention, the time from onset to the first intervention, the CT severity index, the nutritional support types at all times before any intervention, the total volume of fluid administered during the first 72 h following admission, and the intervention types] and postoperative information (i.e., the need for transport to the ICU, postoperative stay, microbiological data and complications) were recorded and entered into a database for analysis. For the patients who were transferred to our hospital, the related data were obtained by contacting the transferring hospitals. Some important definitions are listed in Table 1.

Statistical analysis

For the quantitative data, the results are expressed as the means ± the standard deviations or the medians and the

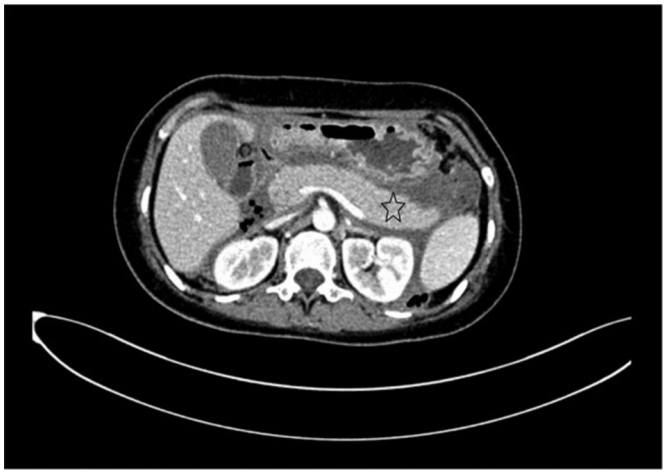

Fig. 2. Extrapancreatic necrosis alone; the star indicated complete enhancement of the pancreatic parenchyma.

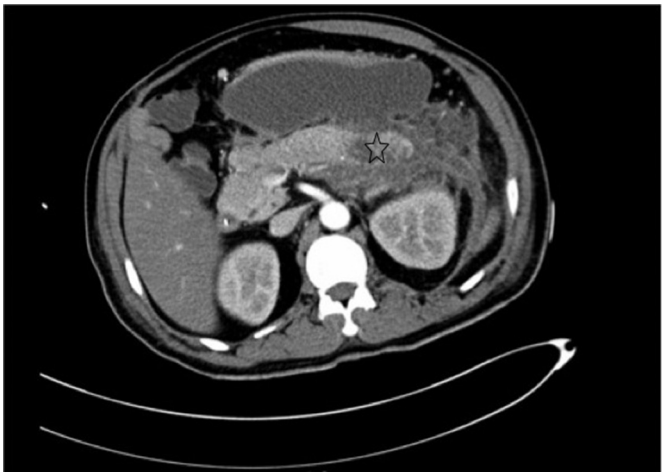

Fig. 3. Combined necrosis; the star indicated necrosis involving both the pancreas and peripancreatic tissues.

Table 1
Definitions.

Confirmed infected necrosis A positive culture from the fine-needle aspiration, the first drainage procedure or operation, or the presence of extraluminal gas based on CECT.
Suspected infected necrosis Progressive clinical deterioration and persistent sepsis despite optimal conservative treatments, without any evidence of confirmed infected necrosis.
Organ failure Pulmonary failure: PaO_2 < 60 mm Hg, despite 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 μmol/L after rehydration or a new need for hemofiltration or hemodialysis. Multiple organ failure (MOF): Failure of at least 2 organ systems on the same day. Persistent organ failure: The evidence of organ failure in the same organ system for 48 h or more.
Persistent systemic inflammatory response syndrome The presence of two or more criteria for 48 h or more: Heart rate > 90 beats/min; Core temperature <36 °C or >38 °C; White blood count < 4×10^9/L or >12×10^9/L; Respirations > 20/min or P_{CO_2} < 32 mm Hg
Extrapancreatic infectious complications Bacteremia: Positive blood culture. Pneumonia: Coughing, dyspnea, and chest film indicating infiltrative abnormalities or a positive sputum culture.
Postoperative complications Postoperative complications (Grades I-V) were defined according to the Clavien–Dindo Classification of Surgical Complications.

interquartile ranges (IQRs). For the categorical data, the results are expressed as the numbers and percentages of cases. All statistical analyses, including *T*, Mann–Whitney *U*, χ^2, and Fisher's exact tests, were performed using the SPSS statistical software package (version 19.0, SPSS Inc., Chicago, IL, USA). The level for rejection of the null hypothesis was set at a *P* value of <0.05.

Results

Basic information of the included patients (Table 2)

Only three of the 334 patients (0.9%) had pancreatic parenchyma necrosis alone, the limited number of these 3 cases prevented statistical comparisons with the other groups, and necrosis unanimously involved pancreatic parenchyma in these 3 isolated pancreatic necrosis cases and the 282 combined necrosis cases. These 3 patients were thus included in Group 1 for further analyses. No significant differences in age, gender, etiology, or BMI were observed in the comparisons of Group 2 with Groups 1 and 3. Compared with the patients in Group 2, greater proportions of the patients in Group 1 suffered from mild (ASA II) and severe (ASA III) systemic diseases (148/51.9% vs. 20/40.8% and 70/24.6% vs. 8/16.3%, respectively; $P < 0.05$). The median APACHE-II scores on admission for both groups were 8.0. Persistent SIRS within the first week of onset was detected in twice as many patients in Group 1 compared with Group 2 (145/50.9% vs. 12/24.5%; $P < 0.05$). Similar outcomes were observed in the comparisons of Group 2 and Group 3 with the exception that the patients in Group 3 exhibited a lower median of APACHE-II score on admission (7.0 vs. 8.0, $P < 0.05$).

Laboratory and clinical data (Table 3)

There were no significant differences between Groups 1 and 2 in terms of white blood cell counts or C-reactive protein levels within 72 h of onset, the time from onset to the first intervention, the nutritional support type, the total volume of administered fluid during the first 72 h after admission or the occurrence of pneumonia. The patients in Group 1 were scanned more frequently than those in Group 2 (3 vs. 2; $P < 0.05$) prior to any intervention. The CT severity index of Group 1 was significantly greater than that in Group 2 (7 vs. 4; $P < 0.001$). Bacteremia was more frequent in Group 1 than Group 2 (107/37.5% vs. 5/10.2%; $P < 0.001$). In detail, there were 28 patients (42.4%) and one patient (12.5%) receiving parenteral nutrition alone developed bacteremia in Groups 1 and 2 respectively. With the exception of the white blood cell count, the other parameters displayed in Table 3 were significantly different between Groups 2 and 3. Because interventions, PN, and combined nutritional support were not required for the patients in Group 3, comparisons of these parameters were not performed.

Organ failure data (Table 4)

Organ failure was one of the main indexes used to evaluate the prognosis of acute necrotizing pancreatitis. The median of the highest modified Marshall score within the first week of onset in Group 2 was lower than that in Group 1 and higher than that in Group 3 (2 vs. 8, and 2 vs. 0, respectively; $P < 0.001$ for both). Compared with the patients in Group 2, greater proportions of patients in Group 1 exhibited single organ failure in the first week, suffered MOF at any time before surgery, and exhibited MOF within the first week, whereas smaller proportions of patients in Group 3 exhibited single organ failure (at any time before surgery or within the first week) and suffered MOF at any time before surgery. The differences in organ failure (i.e., different organ failure types and transient/persistent failures) between the three groups are detailed in Table 4.

Perioperative data (Tables 5 and 6)

Because none of the included patients with interstitial pancreatitis required interventions, comparisons were only performed between Groups 1 and 2 in the subsequent sections. The distributions of intervention types significantly differed between the two groups ($P < 0.001$). More of the patients in Group 1 underwent OPN compared with the patients in Group 2 (174/61.1% vs. 8/16.3%), and fewer patients in Group 1 received PCD compared with the patients in Group 2 (73/25.6% vs. 29/59.2%). RPNs were performed in 38/13.3% and 12/24.5% of the patients in Groups 1 and 2, respectively. Second open necrosectomies following PCDs were required in 61/83.5% and 9/31.0% of the patients in Groups 1 and 2, respectively ($P < 0.001$). Compared with the patients in Group 2, the postoperative stay times were longer in Group 1 (43.0 days vs. 26.5 days; $P < 0.001$), and more patients in Group 1 required ICU admission for further care (221/77.5% vs. 23/46.9%; $P < 0.001$). Infected pancreatic necrosis was more frequent among the patients with combined necrosis (204/71.6% vs. 10/20.4%; $P < 0.001$), and the bacterial species in each group are detailed in Table 6.

Table 2
Basic information of the included patients.

Parameters	Group 1 ($n = 285$)	Group 2 ($n = 49$)	Group 3 ($n = 443$)	$P1$	$P2$
Age (years)	45.8 ± 12.6[a]	42.3 ± 10.7[a]	44.9 ± 10.7[a]	0.075	0.117
Gender (male/female)	191/94	29/20	255/188	0.285	0.827
Etiology, *n* (%)				0.302	0.080
Gallstones	146 (51.2%)	21 (42.9%)	201 (45.4%)	/	/
Alcohol abuse	38 (13.3%)	5 (10.2%)	85 (21.2%)	/	/
Others	101 (35.5%)	23 (46.9%)	91 (33.4%)	/	/
BMI* on admission (kg/m^2)	28.2 ± 3.4[a]	28.2 ± 3.0[a]	27.9 ± 3.3[a]	0.916	0.837
ASA* class on admission, *n* (%)				<0.05	<0.001
I – healthy status	67 (23.5%)	21 (42.9%)	368 (83.1%)	/	/
II – mid systemic disease	148 (51.9%)	20 (40.8%)	75 (16.9%)	/	/
III – severe systemic disease	70 (24.6%)	8 (16.3%)	0 (0%)	/	/
APACHE-II* score on admission	8.0 (5.0–10.5)[b]	8.0 (4.0–8.5)[b]	7.0 (4.0–8.0)[b]	0.307	<0.05
Persistent SIRS* in the first week of onset, *n* (%)	145 (50.9%)	12 (24.5%)	51 (11.5%)	<0.05	<0.05

BMI*: Body mass index calculated as the weight in kilograms divided by height in meters squared.
ASA*: American Society of Anesthesiologists.
APACHE-II*: Acute Physiology and Chronic Health Examination-II.
SIRS*: Systemic inflammatory response syndrome.
*P*1: Comparisons between Groups 1 and 2.
*P*2: Comparisons between Groups 2 and 3.
[a] The data are expressed as the means ± the standard deviations.
[b] The data are expressed as the medians and the interquartile ranges (IQRs).

Table 3
Laboratory and clinical data.

Parameters	Group 1 ($n = 285$)	Group 2 ($n = 49$)	Group 3 ($n = 443$)	$P1$	$P2$
Laboratory test within 72 h of onset					
White blood cell ($\times 10^9$/L)	15.5 ± 9.2[a]	13.6 ± 5.4[a]	15.4 ± 6.2[a]	0.163	0.076
C-reactive protein (mg/L)	208.2 ± 100.4[a]	180 ± 72.8[a]	140.7 ± 101.5[a]	0.066	<0.05
Number of CECTs* performed per patients before any intervention	3 (2–4)[b]	2 (1–3)[b]	0 (0–1)[b]	<0.05	<0.001
Time from onset to the first intervention (days)	25.0 (18.5–33.0)[b]	27.0 (18.0–32.0)[b]	/	0.712	/
Initial PCD* (days)	21.0 (16.0–27.5)[b]	21.0 (17.0–29.0)[b]	/	0.979	/
RPN* (days)	23.5 (19.0–33.0)[b]	29.0 (20.0–34.0)[b]	/	0.562	/
OPN* (days)	25.0 (20.0–33.0)[b]	24.5 (18.0–39.0)[b]	/	0.962	/
CT severity index	7 (6–8)[b]	4 (3–4)[b]	0 (0–1)[b]	<0.001	<0.001
Nutritional support at any time before surgery (PN* alone vs. combined nutrition*)	66/219	8/41	Oral refeeding[c]	0.287	/
Total volume of fluid administered during the first 72 h after admission (mL)	11,200 (8600–15,500)[b]	10,700 (9500–14,200)[b]	9100 (8600–12,800)[b]	0.940	<0.05
Extrapancreatic infectious complications, *n* (%)					
Pneumonia	69 (24.2%)	6 (12.2%)	6 (1.4%)	0.064	<0.001
Bacteremia	107 (37.5%)	5 (10.2%)	0 (0%)	<0.001	<0.001

CECT*: Contrast-enhanced CT.
PCD*: Percutaneous catheter drainage.
RPN*: Retroperitoneal pancreatic necrosectomy.
OPN*: Open pancreatic necrosectomy.
PN*: Parenteral nutrition.
Combined nutrition*: Parenteral plus enteral nutrition.
*P*1: Comparisons between Groups 1 and 2.
*P*2: Comparisons between Groups 2 and 3.
[a] The data are expressed as the means ± the standard deviations.
[b] The data are expressed as the medians and the interquartile ranges (IQRs).
[c] One patient developed persistent organ failure within the first week of onset and received parenteral nutrition, and the others received oral refeeding.

Postoperative complications (Table 7)

Because each patient may have suffered from more than one complication, we have listed the numbers of Grades I–IV postoperative complications rather than calculating the occurrences in each group. Specifically, the mortality was higher in Group 1 than in Group 2 (52/18.2 vs. 1/2.1%; $P < 0.05$). There were no deaths in Group 3 (data not shown). The managements of the postoperative complications are detailed in the Discussion section.

Early vs. late MOF (Table 8)

Early organ failure (within the first week of onset) has been reported to be associated with poor outcomes in patients with acute pancreatitis [12–14]. In Group 1, there were 44 and 37 patients with early and late MOF, respectively. Compared with the patients with late MOF in Group 1, more patients with early MOF exhibited persistent SIRS in the first week (77.3% vs. 56.8%; $P < 0.05$), and these patients had higher APACHE-II scores on admission (8.0 vs. 7.0; $P < 0.05$) and exhibited higher mortality

Table 4
Organ failure data.

Parameters	Group 1 ($n = 285$)	Group 2 ($n = 49$)	Group 3 ($n = 443$)	*P*1	*P*2
Highest modified Marshall score in the first week of onset	8 (6–12)[a]	2 (1–3)[a]	0 (0–1)[a]	<0.001	<0.001
Single organ failure at any time before surgery, *n* (%)	105 (36.8%)	12 (24.5%)	5 (1.1%)	0.094	<0.001
Single organ failure beginning in the first week, *n* (%)	67 (23.5%)	4 (8.2%)	3 (0.7%)	<0.001	<0.05
Transient organ failure (pulmonary/renal/circulatory)	4/3/3	4/2/0	2/2/0	/	/
Persistent organ failure (pulmonary/renal/circulatory)	55/29/11	4/1/1	1/0/0	/	/
MOF* at any time before surgery, *n* (%)	81 (28.4%)	3 (6.1%)	0 (0%)	<0.05	<0.05
MOF beginning in the first week, *n* (%)	44 (15.5%)	2 (4.1%)	0 (0%)	<0.05	0.495
Transient MOF (P + C/P + R/C + R/P + C + R)*	7/4/4/0	0/0/0/0	0/0/0/0	/	/
Persistent MOF (P + C/P + R/C + R/P + C + R)*	41/9/6/11	3/0/0/0	0/0//0/0	/	/

MOF*: Multiple organ failure.
(P + C/P + R/C + R/P + C + R)*: P, pulmonary; C, circulatory; R, renal.
*P*1: Comparisons between Groups 1 and 2.
*P*2: Comparisons between Groups 2 and 3.
[a] The data are expressed as the medians and interquartile ranges (IQRs).

Table 5
Perioperative data.

Variables	Group 1 ($n = 285$)	Group 2 ($n = 49$)	*P*
Initial intervention type, *n* (%)			<0.001
PCD*	73 (25.6%)	29 (59.2%)	/
RPN*	38 (13.3%)	12 (24.5%)	/
OPN*	174 (61.1%)	8 (16.3%)	/
PCDs per patient			0.385
Single PCD (=1)	38 (52.1%)	19 (65.5%)	/
Double PCDs (=2)	28 (38.4%)	7 (24.1%)	/
Multiple PCDs (>2)	7 (9.6%)	3 (10.3%)	/
Second open necrosectomy after PCD, *n* (%)	61 (83.5%)	9 (31.0%)	<0.001
Postoperative stay (days)*	43.0 (26.5–63.0)[a]	26.5 (21.5–38.0)[a]	<0.001
Postoperative ICU* utility, *n* (%)	221 (77.5%)	23 (46.9%)	<0.001

PCD*: Percutaneous catheter drainage.
RPN*: Retroperitoneal pancreatic necrosectomy.
OPN*: Open pancreatic necrosectomy.
Postoperative stay (days)*: Patients who died were not included in the calculation of this parameter ($n = 53$).
ICU*: Intensive care unit.
[a] The data are expressed as the medians and the interquartile ranges (IQRs).

(40.9% vs. 18.9%; $P < 0.05$). Due to the limited number of cases with MOF in Group 2, we have only listed the detailed information of the two patients with early MOF (Cases 1 and 2) and the single patient with late MOF (Case 3). None of the patients in Group 3 developed MOF (Table 4).

Discussion

Since it was first reported by Howard and Wagner in 1989 [6], extrapancreatic necrosis in the absence of pancreatic parenchymal necrosis has gradually come to be regarded as a separate entity of acute necrotizing pancreatitis because it can display a different course than combined pancreatic necrosis [7,8,15]. The preoperative diagnosis of EPN is primarily based on the CECT. If the last CECT prior to any intervention exhibits extrapancreatic morphological changes that are more extensive than fat stranding with complete enhancement of the pancreatic parenchyma and without any sign of pancreatic parenchyma necrosis, the diagnosis of EPN is established. However, given that extrapancreatic morphological changes can indicate fluid collection only rather than fat necrosis, the accuracy of CECT in the diagnosis of EPN can be questioned. In the present study, we observed several factors that suggested that EPN was accurately evaluated using CECT. First, previous studies have concluded that CECT exhibits a good accuracy in the diagnosis of EPN based on observations of fat necrosis during operations and autopsies [16,17]. Second, in the current study, the extrapancreatic effusions all exceeded 5 cm in diameter and were less easily absorbed in the early course of the disease, which resulted in some degree of extrapancreatic tissue necrosis [18], and CECT can easily detect the change from effusion to necrosis. Third, the APACHE-II scores on admission and the C-reactive protein levels within 72 h were comparable between Groups 1 and 2, which suggests that the patients with only small extrapancreatic effusions or interstitial pancreatitis did not have EPN.

Previously, Sakorafas and colleagues reported that 12/19.0% patients in a cohort of 62 patients had EPN alone, which indicated that the patients with EPN benefited more from surgical debridement in terms of reductions in mortality, the incidence of postoperative pancreatic fistulas and postoperative bleeding [7]. Singh and colleagues compared the outcomes of 149 patients with interstitial pancreatitis and those of 8 patients with EPN and concluded that the patients with EPN had more severe diseases because the incidences of persistent SIRS and organ failure were higher and the hospital stay was longer among these patients [19]. More recently, a multicentre study comprising 315/49.0% patients with EPN and 324/51.0% patients with combined necrosis indicated that EPN alone caused fewer complications, including organ failure, MOF, sterile/infected necrosis, and mortality [8]. In the present study, we did not compare the outcomes of the patients with interstitial pancreatitis and those with combined necrosis because the clinical symptoms of interstitial pancreatitis often resolved within the first week [19]. In accordance with the results of previous studies, persistent SIRS, infected necrosis and persistent (multiple) organ failure occurred frequently in the patients with combined necrosis. However, the findings regarding the occurrence of persistent (multiple) organ failure in the present study contrast with those of the study by Rana et al. [15]. The latter study reported similar frequencies of persistent organ failure in patients with

Table 6
Microbiological data.

Variables	Group 1 ($n = 285$)	Group 2 ($n = 49$)	*P*
Infected pancreatic necrosis, *n* (%)	204 (71.6%)	10 (20.4%)	<0.001
Escherichia coli	73	4	/
Enterococcus	62	2	/
Klebsiella	13	0	/
Baumanii	18	1	/
Other bacillus	14	1	/
Fungal infection	14	1	/
Staphylococcus	9	0	/
Pseudomonas aeruginosa	1	1	/

combined necrosis and patients with EPN. The discrepancy might have resulted from differences in patient selection, CECT assessments of EPN, and study design. Organ failure in acute necrotizing pancreatitis is multifactorial, although previous studies have reported that pancreatic necrosis is associated with an increase in the frequency of organ failure due to the production and release of cytokines and the activation of pro-inflammatory pathways [20–22], and other studies have reported contrasting results [23,24]. Therefore, the causes of organ failure in acute pancreatitis and the reasons for the differences in the occurrence of organ failure in patients with combined necrosis and patients with EPN alone require further exploration.

Early organ failure should be distinguished from late organ failure because the courses of these conditions are different. Systemic inflammation drives early organ failure, while infection drives late failure. In the past few years, many studies have focused on the role of MOF in the prognosis of severe acute pancreatitis and indicated that early MOF (within one week of the onset of illness) was a powerful marker of poor outcomes in these severe diseases and was associated with a mortality rate of 20.0–78.0% [12–14,25,26]. Johnson and Abu-Hilal included 290 patients with predicted severe acute pancreatitis and explored the relationship between persistent organ failure during the first week following onset and mortality and concluded that persistent organ failure during with the first week of onset was significantly associated with the risk of death (35.0% mortality) [14]. In another study that included 64 patients with predicted severe acute pancreatitis, persistent early organ failure (either matter single or multiple) in the course of the disease was found to be a major determinant of poor outcomes; the mortality of these patients was 66.7% [12]. In the present study, in Group 1, the occurrence of persistent SIRS within the first week, the APACHE-II scores on admission, and the mortality were significantly higher in the patients with early MOF than in the patients with late MOF. These findings are consistent with those of the previous studies mentioned above. However, due to the limited number of patients with MOF in Group 2, the association of early MOF with the risk of death in the patients with extrapancreatic necrosis alone could not be definitively confirmed. A trial with a larger sample size is required to reach a clear conclusion.

Nutritional support is important in severe acute pancreatitis, and several studies and meta-analyses have concluded that parenteral nutrition is detrimental to patients with acute pancreatitis due to the failure of the intestinal barrier [27,28]. Therefore, in our clinical work, parenteral nutrition was avoided when possible. However, in the current study, the use of PN alone or combined nutrition primarily depended on the disease itself; thus, it is possible that parenteral nutrition elicited some adverse effects in the patients with combined necrosis or EPN alone that might have resulted in some biases. Therefore, we did not analyze the whether PN was a risk factor for poor outcome, and this issue represents a limitation of this study.

Acute necrotizing pancreatitis is a challenging disease that commonly requires surgical treatment. The step-up approach from minimally invasive drainage to open necrosectomy has become an important and well-accepted treatment for acute necrotizing pancreatitis in the recent years [29–31]. However, randomized trials documenting the superiority of either minimally invasive or open necrosectomy are currently sparse [32]. In the current study, the initial intervention type applied to each patient was carefully discussed by experienced surgeons and an experienced radiologist following the review of the most recent CECT. Open necrosectomy was still the dominant intervention in Group 1 (174/61.1%). PCD was initially performed in 73/25.6% of the patients in Group 1 for several reasons. First, successful PCD was difficult when the fluid collection or the necrotic tissue was not close to the abdominal wall, and in such cases, PCD might lead to gastrointestinal perforation. Second, some patients required second open necrosectomies following repeated PCDs. In Group 2, PCD was initially performed in more than half of the patients (29/59.2%) because the extrapancreatic necrosis and fluid collection were closer to the abdominal wall, and fewer of these patients developed persistent SIRS and organ failure, which suggested that open necrosectomy could be avoid. However, 9/31.0% of the patients in Group 2 who were treated with initial PCD required open necrosectomy due to the lack of clinical improvement within 72 h of the additional PCD.

In addition to surgical interventions, the management of postoperative complications is also important for patients with acute necrotizing pancreatitis because the surgical approach is associated with high rates of complications (up to 90.0%) in this severe disease, and some of these complications are life threatening [33,34]. A previous well-conducted multicentre study compared the step-up approach to open necrosectomy for acute necrotizing pancreatitis and indicated that the occurrence of postoperative complications was lower in the step-up group, but the mortalities of the groups were similar [29]. In the present study, we did not compare the occurrence of postoperative complications (Grades I–IV) between the two groups because the disease itself rather than the intervention type may be associated with the complications, the intervention types were heterogeneous between the two groups, and a single patient may suffer from more than one complication. Here, we focused only Grades III–IV complications that required surgical, endoscopic, or radiological intervention or ICU management. As listed in Table 7, residual necrotic tissue or abscess was the most common complication (80 cases in Group 1 and 5 cases in Group 2), and repeated necrosectomies under general anesthesia or repeated peritoneal lavage under intravenous anesthesia were performed in these cases. Exploratory laparotomy or hemostasis via compression through the incision on the loin with a gauze bandage was performed when intraabdominal bleeding (>500 mL of blood/24 h) was detected based on examinations of the drainage tubes, and endoscopic intervention was the first choice for alimentary tract bleeding. Patients with sepsis should stay in the ICU for further supportive therapy. The effective management of a pancreatic fistula in the early postoperative period prior to the establishment of a fistulous tract is associated with reduced incidences of recurrent intraabdominal sepsis and organ failure in the late postoperative period. Grade C pancreatic fistulas occurred in 11 cases in the present study. In addition to enhanced nutritional support, antibiotics, and somatostatin, CT-guided percutaneous drainage was initially performed in these cases, and reoperations and surgical drainage were required when percutaneous drainage failed. The two patients with postoperative complete ileus underwent enterolysis, and the 67 patients with postoperative colonic fistulas underwent ileostomy.

The mortality (Grade V complication) of patients with combined necrosis has been reported to be approximately 20.0%, and the mortality of patients with EPN alone has been reported to be approximately 8.0% in previous comparative studies [7,8,15]. The 18.2% mortality of the patients with combined necrosis observed in the present study is comparable to the results of previous reports. However, the mortality of 2.1% among the patients with EPN alone was lower than the previously reported 8.0%, and this difference was potentially due to differences in patient characteristics, sample sizes, and perioperative supportive therapies. Nevertheless, a similar pattern of significantly higher mortality among patients with combined necrosis compared with patients with EPN alone was also detected in this study.

From the pathophysiological perspective, the better clinical outcomes of the patients with EPN relative to those of the patients with combined necrosis are attributable to several factors.

Table 7
Postoperative complications.

Variables	Group 1 ($n = 285$)	Group 2 ($n = 49$)	P
Grades I–II	Wound infection (29) Incomplete Ileus (11) Pulmonary infection (37) Grade A/B pancreatic fistula (46) Duodenum leakage (13)	Wound infection (1) Incomplete Ileus (0) Pulmonary infection (4) Grade A/B pancreatic fistula (1) Duodenum leakage (0)	/
Grades III–IV	Intraabdominal bleeding (49) Residual necrotic tissue or abscess (80) Complete ileus (2) Colonic fistula (67) Alimentary tract bleeding (12) Sepsis (40) Grade C pancreatic fistula (11)	Intraabdominal bleeding (1) Residual necrotic tissue or abscess (5) Complete ileus (0) Colonic fistula (1) Alimentary tract bleeding (1) Sepsis (3) Grade C pancreatic fistula (0)	/
Grade V (Mortality)	Death (52/18.2%)	Death (1/2.1%)	<0.05

Table 8
Comparisons of the outcomes of the patients with early MOF and late MOF within the two groups.

Variables	Patients with MOF in Group 1 ($n = 81$)			Patients with MOF in Group 2 ($n = 3$)		
	Early MOF ($n = 44$)	Late MOF ($n = 37$)	P	Case 1[a]	Case 2[a]	Case 3[b]
Age (years)	47.5 ± 12.7[a]	45.1 ± 14.3[a]	0.405	48	42	51
Gender (M/F)	14/30	11/26	0.839	F	F	M
ASA* (II/III)	25/19	20/17	0.826	III	III	II
Etiology (gallstone/alcohol/others)	20/8/16	22/3/12	0.309	Others	Gallstones	Others
Persistent SIRS* in the first week, n (%)	34 (77.3%)	21 (56.8%)	<0.05	Yes	Yes	Yes
APACHE-II* score on admission	8.0 (6.5–11.0)[b]	7.0 (5.0–10.5)[b]	<0.05	11.0	12.0	8.0
ICU* utility before any intervention, n (%)	44 (100.0%)	37 (100.0%)	1.000	Yes	Yes	Yes
Infected necrosis, n (%)	21 (47.7%)	19 (51.4%)	0.745	Yes	Yes	No
Mortality, n (%)	18 (40.9%)	7 (18.9%)	<0.05	Yes	No	No

ASA*: American Society of Anesthesiologists.
SIRS*: Systemic inflammatory response syndrome.
APACHE-II*: Acute Physiology and Chronic Health Examination-II.
ICU*: Intensive care unit.
Cases 1[a] and 2[a]: Early MOF.
Case 3[b]: Late MOF.
[a] The data are expressed as the means ± the standard deviations.
[b] The data are expressed as the medians and the interquartile ranges (IQRs).

First, in combined necrosis, the necrosis involves the pancreatic parenchyma in which the activation of trypsin leads to autodigestion and local inflammation and the subsequent occurrence of severe systemic inflammatory response syndrome, which in turn lead to organ failure [35]. This progression does not seem to occur in patients with EPN alone because the pancreatic parenchyma is preserved. Second, necrosis of the pancreatic parenchyma increases the release of inflammatory mediators into the circulation, which causes a more severe systemic inflammatory response and organ failure [36]. Third, pancreatic ductal disruption and pancreatic fistula are associated with the increases in the rates of serious complications including infection, intraabdominal abscesses, postoperative bleeding, and multiple organ failure [37].

Admittedly, our study is limited by the fact that the number of patients with EPN alone was lower compared with the number of patients with combined necrosis and the number of patients with interstitial pancreatitis. Additionally, the long-term results of the included patients were not available, and this study was retrospective in nature. Furthermore, it is now recognized that a significant portion of the morbidity and perhaps mortality of patients with infected necrotizing pancreatitis results from open necrosectomy; therefore, the outcomes of this study may be largely dependent on a somewhat outdated intervention strategy. We hope that in the near future, a well-designed trial involving the optimal intervention strategy (i.e., the step-up approach) will be performed to support our conclusions.

In summary, based on this comparative study, patients with EPN alone exhibit significantly better prognoses than patients with combined necrosis, and EPN alone should be regarded as a separate acute necrotizing pancreatitis entity.

Disclosure statement

No competing financial interests exist.

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References

[1] Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–61.
[2] Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med 2006;354:2142–50.
[3] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al., Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
[4] Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010;139:813–20.
[5] Babu RY, Gupta R, Kang M, Bhasin DK, Rana SS, Singh R. Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. Ann Surg 2013;257:737–50.

[6] Howard JM, Wagner SM. Pancreatography after recovery from massive pancreatic necrosis. Ann Surg 1989;209:31–5.
[7] Sakorafas GH, Tsiotos GG, Sarr MG. Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. J Am Coll Surg 1999;188:643–8.
[8] Bakker OJ, van Santvoort H, Besselink MG, Boermeester MA, van Eijck C, Dejong K, et al., Dutch Pancreatitis Study Group. Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? Gut 2013;62:1475–80.
[9] Traverso LW, Kozarek RA. Pancreatic necrosectomy: definitions and technique. J Gastrointest Surg 2005;9:436–9.
[10] Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15.
[11] Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al., Espen. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009;28:387–400.
[12] Lytras D, Manes K, Triantopoulou C, Paraskeva C, Delis S, Avgerinos C, et al. Persistent early organ failure: defining the high-risk group of patients with severe acute pancreatitis? Pancreas 2008;36:249–54.
[13] Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006;93:738–44.
[14] Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004;53:1340–4.
[15] Rana SS, Sharma V, Sharma RK, Chhabra P, Gupta R, Bhasin DK. Clinical significance of presence and extent of extra pancreatic necrosis in acute pancreatitis. J Gastroenterol Hepatol 2015;30:794–8.
[16] Vege SS, Fletcher JG, Talukdar R, Sarr MG. Peripancreatic collections in acute pancreatitis: correlation between computerized tomography and operative findings. World J Gastroenterol 2010;16:4291–6.
[17] Gambiez LP, Denimal FA, Porte HL, Saudemont A, Chambon JP, Quandalle PA. Retroperitoneal approach and endoscopic management of peripancreatic necrosis collections. Arch Surg 1998;133:66–72.
[18] Kloppel G. Acute pancreatitis. Semin Diagn Pathol 2004;21:221–6.
[19] Singh VK, Bollen TL, Wu BU, Repas K, Maurer R, Yu S, et al. An assessment of the severity of interstitial pancreatitis. Clin Gastroenterol Hepatol 2011;9:1098–103.
[20] Larvin M, Chalmers AG, McMahon MJ. Dynamic contrast enhanced computed tomography: a precise technique for identifying and localising pancreatic necrosis. BMJ 1990;300:1425–8.
[21] Garg PK, Madan K, Pande GK, Khanna S, Sathyanarayan G, Bohidar NP, et al. Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. Clin Gastroenterol Hepatol 2005;3:159–66.
[22] Makhija R, Kingsnorth AN. Cytokine storm in acute pancreatitis. J Hepatobiliary Pancreat Surg 2002;9:401–10.
[23] Lankisch PG, Pflichthofer D, Lehnick D. No strict correlation between necrosis and organ failure in acute pancreatitis. Pancreas 2000;20:319–22.
[24] Tenner S, Sica G, Hughes M, Noordhoek E, Feng S, Zinner M, et al. Relationship of necrosis to organ failure in severe acute pancreatitis. Gastroenterology 1997;113:899–903.
[25] Skouras C, Hayes AJ, Williams L, Garden OJ, Parks RW, Mole DJ. Early organ dysfunction affects long-term survival in acute pancreatitis patients. HPB (Oxf) 2014;16:789–96.
[26] Isenmann R, Rau B, Beger HG. Early severe acute pancreatitis: characteristics of a new subgroup. Pancreas 2001;22:274–8.
[27] Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg 2006;23:336–44 [Discussion 344–5].
[28] Petrov MS, Whelan K. Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. Br J Nutr 2010;103:1287–95.
[29] van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al., Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491–502.
[30] Bakker OJ, Issa Y, van Santvoort HC, Besselink MG, Schepers NJ, Bruno MJ, et al. Treatment options for acute pancreatitis. Nat Rev Gastroenterol Hepatol 2014;11:462–9.
[31] Freeman ML, Werner J, van Santvoort HC, Baron TH, Besselink MG, Windsor JA, et al., International Multidisciplinary Panel of Speakers and Moderators. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas 2012;41:1176–94.
[32] Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al., Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053–61.
[33] Connor S, Alexakis N, Raraty MG, Ghaneh P, Evans J, Hughes M, et al. Early and late complications after pancreatic necrosectomy. Surgery 2005;137:499–505.
[34] Howard TJ, Patel JB, Zyromski N, Sandrasegaran K, Yu J, Nakeeb A, et al. Declining morbidity and mortality rates in the surgical management of pancreatic necrosis. J Gastrointest Surg 2007;11:43–9.
[35] Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371:143–52.
[36] Malmstrom ML, Hansen MB, Andersen AM, Ersboll AK, Nielsen OH, Jorgensen LN, et al. Cytokines and organ failure in acute pancreatitis: inflammatory response in acute pancreatitis. Pancreas 2012;41:271–7.
[37] Sell NM, Pucci MJ, Gabale S, Leiby BE, Rosato EL, Winter JM, et al. The influence of transection site on the development of pancreatic fistula in patients undergoing distal pancreatectomy: a review of 294 consecutive cases. Surgery 2015;157:1080–7.