The Role of Organ Failure and Infection in Necrotizing Pancreatitis

A Prospective Study

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Objective: To clarify the roles of organ failure and infection in the outcome of necrotizing pancreatitis.

Background: Results of previous cohort studies that focused on the roles of infection and organ failure in acute pancreatitis are controversial.

Methods: In this study, we collected the medical records of 447 patients with necrotizing pancreatitis from January 2009 to June 2012. Data associated with organ failure and infection were analyzed.

Results: The overall mortality rate was 13% (58/447). Intervention was performed in 223 of 447 patients. Among these 223 patients, 134 were confirmed to be with infected necrosis by a positive culture. The mortality rate was 15% (13/89) in the sterile necrosis group and 18% (24/134) in the infected necrosis group ($P = 0.52$). A multivariate analysis of death predictors indicated that bacteremia (odds ratio [OR] = 2.76, 95% confidence interval [CI], 1.23–5.46, $P < 0.001$), age (OR = 1.07, 95% CI, 1.03–1.11, $P < 0.001$), American Society of Anesthesiologists class (OR = 3.56, 95% CI, 1.65–7.18, $P = 0.001$), persistent organ failure in the first week (OR = 16.72, 95% CI, 7.04–32.56, $P < 0.001$), and pancreatic necrosis (OR = 1.73, 95% CI, 1.14–2.98, $P = 0.008$) were significant factors.

Conclusions: Among patients with necrotizing pancreatitis, the effects of organ failure on mortality are more critical than those of infection. Bacteremia, age, American Society of Anesthesiologists class, persistent organ failure in the first week, and pancreatic necrosis were identified as the predictors of mortality.

Keywords: acute pancreatitis, infection, organ failure

(*Ann Surg* 2014;259:1201–1207)

Acute pancreatitis is a common disease with a very varied outcome.[1] In the United States, acute pancreatitis is the most common reason for hospitalization because of gastrointestinal diseases.[2] Approximately 5% to 10% of patients with acute pancreatitis develop necrosis of the pancreatic parenchyma, peripancreatic tissue, or both.[3] Patients with necrotizing pancreatitis have worse outcomes than those with interstitial edematous pancreatitis.[4] Both organ failure and infection are considered as 2 major reasons for death in the patients with necrotizing pancreatitis.[5]

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Disclosure: The authors declare no conflicts of interest and financial funding.

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ISSN: 0003-4932/13/25906-1201
DOI: 10.1097/SLA.0000000000000264

The clinical course of necrotizing pancreatitis process has 2 phases: early and late. The early phase, usually lasting during the first week, is characterized by the systemic inflammatory response syndrome (SIRS) as a result of the release of inflammatory mediators. This syndrome is often accompanied with organ failure and general derangements, including hypovolemia, hyperdynamic circulatory regulation, fluid loss from the intravascular space, and increased capillary permeability.[6,7] Although necroses can be identified during the early phase, they are not the predominant determinants of mortality. The definition of acute pancreatitis severity in the early phase depends on the presence of organ failure rather than necrosis.[3] In some patients, necrotizing pancreatitis is completely resolved after a noninterventional treatment, and the necrosis eventually disappears. However, others become infected or persist for a long time. The later phase, which can last from a few weeks to months, always has persistent systemic inflammations accompanied with the presence of the local complications mentioned previously.[7,8] Thus, the definition of acute pancreatitis severity in the late phase depends on the presence of organ failure and morphologic features.[3]

Several cohort studies concentrated on the roles of infection and organ failure in acute pancreatitis.[9–16] Most of these studies indicated that the presence of organ failure, particularly persistent organ failure, is significantly associated with mortality.[9,10] However, results of the studies that examined the relationship between pancreatic infection and mortality are controversial. Some of these studies demonstrated an association between pancreatic necrosis infection and mortality,[11–13] whereas others failed to prove this relationship.[14–16] Most of these studies are outdated and have a few inadequacies, particularly because the definitions and classifications of acute pancreatitis have been updated and the treatment for necrotizing pancreatitis has changed.[17–20]

Considering the developments in the pathophysiology of organ failure and necrotizing pancreatitis, and their outcomes, we conducted a prospective observational cohort study to implement the consensus on recent changes. In this study, the characteristics of organ failure and infection in patients with necrotizing pancreatitis were investigated to clarify the roles of organ failure and infection in the outcome of necrotizing pancreatitis and to identify the clinical predictors of mortality for necrotizing pancreatitis.

PATIENTS AND METHODS

Patient Identification and Definition

Patients with a first diagnosis of acute pancreatitis were hospitalized at West China Hospital after an initial consultation in the emergency department. During the study period from January 2009 to June 2012, adult patients identified with signs of pancreatic necrosis or peripancreatic necrosis using contrast-enhanced computed tomography (CECT) were prospectively registered. Readmission within 7 days after being discharged from admission was considered a

prolonged admission. Acute pancreatitis was diagnosed using a combination of clinical (ie, the sudden onset of upper abdominal pain), laboratory (more than 3 times the upper normal limit for amylase or lipase levels), and imaging test (abdominal ultrasound, abdominal computed tomography [CT], and magnetic resonance imaging) findings based on the revised Atlanta Classification.[3] The definition of necrotizing pancreatitis included both pancreatic parenchymal necrosis with or without peripancreatic necrosis and only peripancreatic necrosis. Pancreatic necrosis was assigned with a CT severity index greater than 4, and peripancreatic necrosis was given a CT severity index of 3 or 4.

Treatment Protocol and Data Collection

After admission, full laboratory tests, except interleukin-6 (IL-6) and procalcitonin measurements, were conducted to evaluate the severity of the disease. However, CECT was not routinely conducted on the day of admission. All components of the modified Marshall scoring system and all signs of SIRS were also recorded every day in the first week of onset.[3] All components of the Acute Physiology and Chronic Health Examination (APACHE) II scoring system were recorded upon admission. Body temperature was measured at least 3 times daily; when the temperature was higher than 38.0°C, a blood culture was drawn. Sputum samples of the patients with or without mechanical ventilation were cultured. Routine fine-needle aspiration was not performed on patients with pancreatic necrosis. The definitions of bacteremia, pneumonia, persistent SIRS, and organ failure are listed in Table 1.

All patients initially received noninterventional treatment. After admission, antibiotics were administered to patients for not more than 7 days, unless they had persistent clinical manifestations of sepsis. Parenteral nutrition was initiated, and after the gastrointestinal tract function recovered from paralysis, the patients were fed by both enteral nutrition and parenteral nutrition. During the noninterventional treatment, CECT was performed 7 to 10 days after onset, and the CT severity index was recorded. A professional radiologist and experienced surgeons evaluated the CECT results for pancreatic necrosis or peripancreatic necrosis. On the basis of the evaluation, patients were prospectively included. Patients who developed organ failure were treated in an intensive care unit (ICU). In the ICU department, IL-6 and procalcitonin were routinely measured to evaluate the severity of the disease.

When abdominal pain, severe clinical deterioration, or development of clinical signs of sepsis persisted or recurred, a second CECT was performed. The CT severity index was also recorded. Patients with confirmed or suspected infected necrosis were advised to receive surgical intervention. Experienced surgeons were then provided with a case description to discuss the case with the radiologist, after which they would decide on the type (open pancreatic necrosectomy, retroperitoneal pancreatic necrosectomy,[21] or primary percutaneous catheter drainage with pigtail plastic stents) and time for surgery. Whenever possible, intervention was postponed until approximately 4 weeks after the onset of disease. Cultures were taken during all primary procedures to confirm the diagnosis of infected necrosis. In this study, abdominal compartment syndrome occurring early in the course of the disease was not an indication for emergency laparotomy, unless a perforation or bleeding of a visceral organ occurs. Although the minimally invasive step-up approach has been proved to be a remarkable success,[19] we did not perform percutaneous or endoscopic transgastric drainage routinely. Here are our reasons. First, if the fluid collection was not close to the abdominal wall, it is easy to result in gastrointestinal perforation. Second, large amount of pancreatic necrosis might lead to obstruction of the tube and repeated procedures. We only performed primary percutaneous catheter drainage on the patients with fluid collection that was close to the abdominal wall, and at the same time, the extent of pancreatic necrosis less than 30% based on CECT. We call this strategy "selective percutaneous catheter drainage." We also performed a retroperitoneal pancreatic necrosectomy approach on the patients with fluid collection that was close to the lateral abdominal wall, and at the same time, the extent of pancreatic necrosis was greater than 30%.

Referred patients without a primary surgical intervention were also included and prospectively registered. Detailed data, which included patient history, laboratory tests, and imaging tests, were obtained by contacting the referring hospitals. For these patients, no strict treatment protocol was established. Data of all the patients included in the study were recorded and entered into a database for analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients or their legal representatives provided written informed consent. The ethics review board of West China Hospital approved the study.

TABLE 1. Definitions

Infected necrosis
A positive culture of pancreatic necrosis or peripancreatic necrosis obtained by fine-needle aspiration or from the first operation, or the presence of gas in the peripancreatic collection on contrast-enhanced computed tomography.
Suspected infected necrosis
Persistent clinical manifestations of sepsis without the presence of gas in the peripancreatic collection on contrast-enhanced computed tomography.
Extrapancreatic infectious complications
Bacteremia
Positive blood culture.
Pneumonia
Coughing, dyspnoea, and chest film indicating infiltrative abnormalities or a positive sputum culture
Persistent systemic inflammatory response syndrome
Occurrence of 2 or more of the following criteria for >48 h: pulse > 90 beats/min; rectal temperature <36°C or >38°C; white blood cell count < 4000 or >12 000/mL; and respirations > 20/min or pCO_2 <32 mm Hg
Organ failure
Pulmonary failure
Pa_{O_2} <60 mm Hg, despite Fi_{O_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
Failure of at least 2 organ systems on the same day
Persistent organ failure
Presence of organ failure lasting for more than 48 h

Statistical Analysis

Mortality rate was the primary result. Patients with organ failure were subdivided into different types. Results of the different types of organ failure were calculated. Patients who received intervention were divided into the sterile necrosis and infected necrosis groups. The impact of infection was expressed by comparing the mortality rate with that of the sterile necrosis group. Multivariate analysis was used to determine the effect of the different predictors of mortality. The results were analyzed using standard tests (Mann–Whitney U test, χ^2 test, and linear-by-linear association). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 447 patients with pancreatic necrosis or only peripancreatic necrosis were included, and 126 of these patients were transferred from other hospitals. Intervention was performed in 223 of the 447 patients. Among the 223 patients, 134 were confirmed to be with infected necrosis by a positive culture. Patient characteristics upon admission and details from the CECTs before any intervention are given in Table 2, which includes data for the sterile necrosis and infected necrosis groups. The overall mortality rate was 13% (58/447). The mortality rate in the sterile necrosis group and the infected necrosis group was 11% (34/313) and 18% (24/134), respectively.

Organ Failure

Organ failure during admission occurred in 175 of the 447 patients, among which most were persistent organ failures (158/175) (Table 3). More deaths occurred among patients with organ failure during admission compared with patients without organ failure (56/58 vs 2/58; $P < 0.001$). About 68% (107/158) of the persistent organ failures occurred within the first week of onset. In the infected

TABLE 3. Mortality in the Patients With Organ Failure

	Total	Mortality Rate (%)
Organ failure		
At any time during admission	175	56/175 (32)
Persistent organ failure at any time during admission	158	52/158 (33)
Persistent organ failure started in the first week	107	39/107 (36)
Multiple organ failure		
At any time during admission	104	54/104 (52)
Persistent organ failure at any time during admission	87	51/87 (59)
Persistent organ failure started in the first week	59	33/59 (56)
Different types of organ		
Pulmonary failure at any time during admission	156	41/156 (26)
Renal failure at any time during admission	84	51/84 (61)
Circulatory failure at any time during admission	45	36/45 (80)

TABLE 2. Characteristics of the Patients With Necrotizing Pancreatitis

Characteristic	All Patients (N = 447)	Sterile Necrosis (N = 313)	Infected Necrosis (N = 134)	*P*
Age, median (range), yr	45 (22–75)	44 (22–75)	48 (27–72)	0.08
Male, n (%)	268 (60)	185 (59)	83 (62)	0.48
Etiology, n (%)				
Biliary	228 (51)	165 (53)	63 (47)	0.27
Alcohol abuse	45 (10)	30 (10)	15 (11)	0.68
Others	174 (39)	118 (38)	56 (42)	0.42
BMI on admission, median (range)*	28 (20–34)	27 (20–33)	29 (22–34)	0.13
ASA class on admission, n (%)				0.18
I—healthy status	161 (36)	116 (37)	45 (34)	
II—mild systemic disease	237 (53)	169 (54)	68 (50)	
III—severe systemic disease	49 (11)	28 (9)	21 (16)	
APACHE II score on admission, median (range)†	8 (2–32)	7 (2–32)	8 (2–30)	0.14
Persistent SIRS in the first week of onset, n (%)	248 (55)	145 (46)	10 3 (77)	<0.001
Organ failure				
Persistent organ failure started in the first week of onset, n (%)	107 (24)	59 (19)	48 (36)	<0.001
Persistent MOF started in the first week of onset, n (%)	59 (13)	31 (10)	28 (21)	0.002
Highest modified Marshall score in the first week of onset, median (range)	2 (0–12)	1 (0–12)	3 (0–10)	<0.001
Intensive care unit admission, n (%)	208 (47)	107 (32)	101 (75)	<0.001
Intubated	149 (33)	80 (26)	69 (51)	<0.001
Requiring renal replacement therapy	52 (12)	28 (9)	24 (18)	<0.001
Computed tomography				
CT severity index, median (range)	5 (3–10)	4 (3–10)	8 (4–10)	<0.001
Pancreatic necrosis, n (%)	214 (48)	119 (38)	95 (71)	<0.001
Peripancreatic necrosis alone, n (%)	233 (52)	194 (62)	39 (29)	<0.001
Extent of pancreatic necrosis, n (%)				<0.001
<30%	280 (63)	225 (72)	55 (41)	
30%–50%	76 (17)	44 (14)	32 (24)	
>50%	91 (20)	44 (14)	47 (35)	
Laboratory tests within 72 h of onset				
White blood cell count, median (range), 10^9/L	13.5 (2.3–35.9)	13.2 (2.8–35.9)	14.2 (2.3–30.1)	0.21
C-reactive protein, median (range), mg/L‡	195 (34–433)	192 (34–407)	202 (36–433)	0.35
Extrapancreatic infectious complications				
Bacteremia, n (%)	80 (18)	37 (12)	43 (32)	<0.001
Pneumonia, n (%)	168 (38)	125 (40)	43 (32)	0.12

*BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

†Data were not available for 126 patients because these patients were transferred from other hospitals.

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APACHE indicates Acute Physiology and Chronic Health Examination; ASA, American Society of Anesthesiologists; BMI, body mass index; CT, computed tomography; MOF, multiple organ failure; SIRS, systemic inflammatory response syndrome.

necrosis group, 48 out of 134 patients had organ failures within the first week of onset, whereas in the sterile necrosis group, only 59 of 313 patients had organ failure within the first week ($P < 0.001$). Mortality rates were not significantly higher in patients with organ failure that started in the first week of onset than in the patients with organ failure after the first week (39/107 vs 13/51; $P = 0.17$).

Multiple organ failure (MOF) occurred in 104 of the 447 patients (23%), and persistent MOF occurred in 87 of the 447 patients (19%). Compared with the infected necrosis group, fewer patients in the sterile necrosis group had MOF within the first week of onset (28/107 vs 31/313; $P = 0.002$). The median modified Marshall score in the first week was 2, and the infected necrosis group had a higher score than the sterile necrosis group (1 vs 3, $P < 0.001$).

Distribution of the different types of organ failures in this study was varied. Pulmonary failure occurred in 156 of the 447 patients (35%), and the median time onset of diagnosis for pulmonary failure was 3 days. Renal failure occurred in 84 of the 447 patients (19%), and the median time onset of diagnosis for renal failure was 5 days. Circulatory failure occurred in 45 of the 447 patients (10%), and the median time onset of diagnosis for circulatory failure was 4 days. The death rates of the patients with pulmonary failure, renal failure, and circulatory failure were 26% (41/156), 61% (51/84), and 80% (36/45), respectively.

Infectious Complications

Bacteremia occurred in 80 patients, and the median time onset was 8 days. Pneumonia was found in 168 patients and the median time onset was 9 days. Patients previously afflicted with bacteremia were associated with higher risk of developing infected necrosis (43/80) than those with pneumonia (43/168). The most common pathogens cultured from the first intervention were *Escherichia coli* (43/134) and *Enterococcus* (37/134). However, among the 43 patients with both initial positive cultures of pancreatic or peripancreatic fluid collections and blood samples, only 16 patients had the same pathogens, most of which were *E. coli* (9/16). Among the 43 patients with both initial positive cultures of pancreatic or peripancreatic fluid collections and sputum samples, only 2 patients had the same pathogens of *Acinetobacter baumannii*. Among the 134 patients with confirmed infected necrosis, 22 had drug resistance to carbapenems, 38 had drug resistance to cephalosporins, and 92 had drug resistance to quinolones.

From Table 2, compared with the patients with infected necrosis, patients in the sterile necrosis group had lower modified Marshall score, CT severity index, and extent of pancreatic necrosis. Most of the patients with sterile necrosis did not receive any intervention (224/313). Thus, to compare the results between infected necrosis and sterile necrosis, we analyzed the characteristics of the patients who underwent intervention.

Table 4 shows the baseline and the results for the patients who underwent intervention, subdivided into the 2 groups. The baselines were similar between the 2 groups (age, sex, body mass index, American Society of Anesthesiologists [ASA] class, morphological feature on CT, organ failure, laboratory tests). The mortality rate was 15% in the sterile necrosis group and 18% in the infected necrosis group ($P = 0.52$).

Predictors of Mortality

Table 5 lists the potential parameters that can be used to predict death in the patients with necrotizing pancreatitis. Age greater than 60 years, ASA class II or III, APACHE II score greater than 8, SIRS, organ failure, CT severity index greater than 8, pancreatic necrosis, infected necrosis, procalcitonin greater than 1 ng/mL, prolonged surgical time to 28 days later, and bacteremia were all associated with high mortality rates. Bacteremia, age, ASA class, persistent organ failure in the first week, infected necrosis, and pancreatic necrosis were entered into a multivariate analysis of the predictors of death. Bacteremia (odds ratio [OR] = 2.76, 95% confidence interval [CI], 1.23–5.46, $P < 0.001$), age (OR = 1.07, 95% CI, 1.03–1.11, $P < 0.001$), ASA class (OR = 3.56, 95% CI, 1.65–7.18, $P = 0.001$), persistent organ failure in the first week (OR = 16.72, 95% CI, 7.04–32.56, $P < 0.001$), and pancreatic necrosis (OR = 1.73, 95% CI, 1.14–2.98, $P = 0.008$) were identified as significant factors.

DISCUSSION

This prospective study investigated the characteristics and the roles of organ failure and infection in patients with necrotizing pancreatitis. This study considered a large number of patients to determine the predictors of mortality for necrotizing pancreatitis. Our results indicate that organ failure, rather than infection, has a primary role in the necrotizing pancreatitis outcome. By comparing the outcomes of the patients with sterile necrosis and conducting a multivariate analysis, we confirmed that infection has a weak effect on mortality.

At the start of the natural course of acute pancreatitis, cytokines are massively released, possibly causing SIRS. When SIRS is persistent, the risk of developing organ failure increases.[22,23] In our study, persistent SIRS that started in the first week of onset is associated with a high risk of infection (77% vs 46%) and high mortality rate (19% vs 6%). Another prospective study demonstrated that organ failure that persists longer than 48 hours, even if not initially progressive, has grave prognoses.[9] Our results also confirmed that more deaths occurred among patients with organ failure during admission compared with patients without organ failure (56/58 vs 2/58, $P < 0.001$), and that the majority of persistent organ failures (107/158) occurred within the first week of onset. Persistent organ failure and MOF that started in the first week of onset are associated with high mortality rates (36% vs 6%, 56% vs 6%) and high risks of infection (36% vs 19%, 21% vs 10%). As a simple and practical clinical scoring system, a modified Marshall scoring system is recommended to stratify the severity of acute pancreatitis.[3,24] We recorded modified Marshall scores daily during the first week of onset; when the highest modified Marshall score was higher than 3 in the first week of onset, patients had a higher risk of death than those who had lower scores. To the best of our knowledge, this work is the first study that used this system to predict the necrotizing pancreatitis outcome.

For the different types of organ failures, most of the patients with organ failure had pulmonary failure (156/175), followed by those with renal failure (84/175) and circulatory failure (45/175). Previous studies also presented the difference in incidence; however, they did not investigate onset time and mortality rates.[9,11] In our result, the death rates of the patients with pulmonary failure, renal failure, and circulatory failure were 26% (41/156), 61% (51/84), and 80% (36/45), respectively. The onset time was 3, 5, and 4 days. The use of mechanical ventilation in the ICU may account for the better pulmonary failure outcome.

By contrast, a meta-analysis concluded that in patients with acute pancreatitis, the effects of organ failure and infected pancreatic necrosis on mortality are comparable.[5] The authors analyzed the effect of pancreatic infection on mortality in patients with organ failure and the effect of organ failure on mortality in patients with infected pancreatic necrosis. However, this conclusion is questionable. First, these cohort studies covered a long period, wherein the definitions of organ failure and the treatments varied. Some studies considered the timing of organ failure as any time during admission; some regarded it as within 5 days. Second, those studies did not compare the baselines between sterile necrosis and infected necrosis. In fact, in a well-designed prospective study with a large sample size, patients in the sterile necrosis group had lower CT severity index, more systemic complications, and smaller extent of pancreatic necrosis than patients with infected necrosis.[25] This result is similar to ours. Mortality rate

TABLE 4. Characteristics of the Patients Who Received Interventional Treatment

Characteristic	Sterile Necrosis (N = 89)	Infected Necrosis (N = 134)	*P*
Age, median (range), yr	46 (22–74)	48 (27–72)	0.48
Male, n (%)	53 (60)	83 (62)	0.20
Etiology, n (%)			
Biliary	45 (51)	63 (47)	0.60
Alcohol abuse	9 (10)	15 (11)	0.80
Others	35 (39)	56 (42)	0.71
BMI on admission, median (range)	28 (22–33)	29 (22–34)	0.56
ASA class on admission, n (%)			0.78
I—healthy status	32 (36)	45 (34)	
II—mild systemic disease	44 (49)	68 (50)	
III—severe systemic disease	13 (15)	21 (16)	
APACHE II score on admission	8 (2–32)	8 (2–30)	0.44
Computed tomography			
CT severity index, median (range)	8 (4–10)	8 (4–10)	0.78
Pancreatic necrosis, n (%)	61 (68)	95 (71)	0.71
Peripancreatic necrosis alone, n (%)	28 (32)	39 (29)	0.71
Extent of pancreatic necrosis, n (%)			0.26
<30%	34 (38)	55 (41)	
30%-50%	26 (29)	32 (24)	
>50%	29 (33)	47 (35)	
Persistent SIRS in the first week of onset, n (%)	71 (80)	103 (77)	0.61
Organ failure			
Highest modified Marshall score in the first week of onset, median (range)	3 (0–10)	3 (0–10)	0.64
Persistent organ failure started in the first week of onset, n (%)	34 (38)	48 (36)	0.82
Persistent MOF started in the first week of onset, n (%)	20 (22)	28 (21)	0.78
Nutritional support at any time before surgery			
Parenteral nutrition only, n (%)	22 (25)	31 (23)	0.79
Enteral and parenteral nutrition, n (%)	67 (75)	103 (77)	0.79
Laboratory tests within 72 h of onset			
White blood cell count, median (range), 10^9/L	14.0 (2.8–35.9)	14.2 (2.3–30.1)	0.32
C-reactive protein, median (range), mg/L	199 (34–407)	202 (36–433)	0.43
Procalcitonin, median (range), ng/mL*	10.2 (0.09–48.38)	11.1 (0.09–48.38)	0.08
IL-6, median (range), pg/mL†	213 (6–786)	221 (23–1312)	0.12
Extrapancreatic infectious complications			
Bacteremia, n (%)	24 (27)	43 (32)	0.41
Pneumonia, n (%)	35 (39)	43 (32)	0.27
Mortality, n (%)	13 (15)	24 (18)	0.52

*Data are available for 103 patients.
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APACHE indicates Acute Physiology and Chronic Health Examination; ASA, American Society of Anesthesiologists; BMI, body mass index; CT, computed tomography; IL, interleukin; MOF, multiple organ failure.

obviously rises when a study group is more severe than the others. Infected necrosis always has a larger extent of necrosis; thus, the outcome is worse than that of sterile necrosis.[26,27] Thus, we analyzed the characteristics of the patients who underwent intervention and subdivided them into 2 groups. Baselines were similar in the 2 groups (age, sex, body mass index, ASA class, morphologic feature on CT scan, organ failure, and laboratory tests). Mortality rates were also similar (15% for the sterile necrosis group and 18% for the infected necrosis group; $P = 0.52$). Third, after a multivariable analysis of the predictors of death, infection was not identified as a significant factor. Another study also proved that infection is not a predictor.[28] Fourth, given that infection always occurs later than organ failure, and that organ failure can persist during the entire clinical course,[28] concluding that both organ failure and infection are determinants of mortality is valid. Fifth, for patients with severe acute pancreatitis, the use of antibiotic prophylaxis was not associated with a statistically significant reduction in mortality rate.[29] Among the 134 patients with confirmed infected necrosis in our study, 22 had drug resistance to carbapenems, 38 had drug resistance to cephalosporins, and 92 had drug resistance to quinolones. Antibiotics seem useless for infected necrosis. These results might change our views of prophylactic strategies. Thus, future studies in necrotizing pancreatitis should pay more attention on organ failure rather than infection.

The pathways for pancreatic infection have drawn considerable attention. Several hypothetical mechanisms by which bacteria may enter pancreatic and peripancreatic necrosis exist: the hematogenous route via circulation; transmural migration through the colonic bowel wall to the pancreas; via the lymphatic circulation; via the biliary duct system; and from the duodenum via the main pancreatic duct.[8] The theory of bacterial translocation seems most acceptable, and the small bowel seems to be the major source of enteral bacteria in infected pancreatic necrosis.[30] This theory is supported by the microbiological findings from fluid collections: most of the pathogens are common in the intestinal tract.[28] In our study, among the 43 patients with both initial positive cultures of pancreatic or peripancreatic fluid collections and blood samples, only 16 patients had the

TABLE 5. Predictors of Mortality for Necrotizing Pancreatitis

Characteristic	Survived	Died	*P*
All patients	389/447 (87)	58/447 (13)	
Age > 60, yr	39/60 (65)	21/60 (35)	<0.001
Male	235/268 (88)	33/268 (12)	0.61
Biliary cause	197/228 (86)	31/228 (14)	0.56
BMI > 30 on admission	61/72 (85)	11/72 (15)	0.53
ASA class II or III on admission	241/286 (84)	45/286 (16)	0.023
APACHE II score > 8 on admission	153/177 (86)	34/177 (14)	0.047
Persistent SIRS in the first week of onset	201/248 (81)	47/248 (19)	<0.001
Organ failure			
Persistent organ failure in the first week of onset	68/107 (64)	39/107 (36)	<0.001
Persistent MOF in the first week of onset	26/59 (44)	33/59 (56)	<0.001
Highest modified Marshall score > 3 in the first week of onset	42/78 (54)	36/78 (46)	<0.001
Computed tomography			
CT severity index > 8	62/91 (68)	29/91 (32)	<0.001
Pancreatic necrosis	179/214 (84)	35/214 (16)	0.04
Laboratory tests within 72 h of onset			
White blood cell count > 15, 10^9/L	131/152 (86)	21/152 (14)	0.70
C-reactive protein > 200, mg/L	114/136 (84)	22/136 (16)	0.68
Procalcitonin > 1, ng/mL	28/56 (50)	28/56 (50)	0.006
IL-6 >100, pg/mL	31/53 (58)	22/53 (42)	0.43
Infected necrosis	106/134 (79)	24/134 (21)	0.04
Extrapancreatic infectious complications			
Bacteremia	60/80 (75)	20/80 (25)	<0.001
Pneumonia	144/168 (86)	24/168 (14)	0.52
Time from onset to intervention >28, days	80/96 (83)	16/96 (17)	0.006

APACHE indicates Acute Physiology and Chronic Health Examination; ASA, American Society of Anesthesiologists; BMI, body mass index; CT, computed tomography; IL, interleukin; MOF, multiple organ failure; SIRS, systemic inflammatory response syndrome.

same pathogens. Among the 43 patients with both initial positive cultures of pancreatic or peripancreatic fluid collections and sputum samples, only 2 patients had the same pathogens. Infection via circulation and pneumonia is apparently rare.

Bacteremia, age, ASA class, persistent organ failure in the first week, and pancreatic necrosis were identified as significant predictors of death by multivariate analysis. An increase in the serum levels of C-reactive protein, IL-6, and procalcitonin precede acute inflammatory response and predict the severity of acute pancreatitis.[31–33] However, we did not enter these variables into the multivariate analysis because the data are incomplete. A previous study also identified bacteremia as a risk factor for pancreatic necrosis infection and death.[28] The authors did not provide an explanation; thus, further research on this subject is needed. Considering that extrapancreatic fat necrosis causes fewer complications than pancreatic parenchymal necrosis, it is suggested to be considered as a separate entity in necrotizing pancreatitis.[34] Our results also proved this characteristic.

This study has some possible limitations. As a clinical scoring system that has been utilized for decades, APACHE II is important in predicting acute pancreatitis outcomes. However, we were not able to complete all the APACHE II scores because of the complexity of this system and the difficulty of obtaining the data of all the system components from the referring hospitals. For the patients from the referring hospitals, C-reactive protein, procalcitonin, and IL-6 data were also incomplete and no strict treatment protocol was established. We also evaluated only 1 outcome, namely, mortality. Other outcomes such as the length of hospital stay or the length of ICU stay were not considered because we believe that an intervention will obviously prolong the length of hospital and ICU stays. These outcomes cannot provide additional information for our purpose. Besides, during the study period, a first CECT was performed 7 to 10 days after onset. Thus, the patients who developed sterile necrosis and died within 7 days may have been missed for inclusion, and the difference between the baselines might change when compared with the patients who developed infected necrosis. Nevertheless, in fact, within the first week of the disease, it is difficult to define a pancreatic parenchymal necrosis on CECT because nonenhancing area of pancreatic parenchyma was always found after several days, and that is why we performed CECT after 1 week of onset.[3] Furthermore, the therapeutic schedule regarding the use of antibiotics and nutrition was conducted before 2009 and might be outdated. A meta-analysis indicated that enteral nutrition is associated with a more significant reduction in both infectious complications and mortality in patients with acute pancreatitis compared with parenteral nutrition.[35] Another meta-analysis also suggested that in patients with severe acute pancreatitis, the use of antibiotic prophylaxis is not associated with a statistically significant reduction in mortality.[29] Nevertheless, in this study, a conservative principle for sterile necrosis was applied; the indication and timing for intervention were adopted from updated worldwide consensus.

In summary, this study demonstrated that compared with infection, organ failure is a more critical determinant of mortality in patients with necrotizing pancreatitis. Renal failure and circulatory failure are associated with high mortality rates. Bacteremia, age, ASA class, persistent organ failure in the first week, and pancreatic necrosis are the predictors of mortality.

ACKNOWLEDGMENTS

All of the authors contributed to the collection and analysis of the data and to the preparation of the report. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors have seen and approved the final version of the manuscript.

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